FARMACI *OFF-LABEL* IN CURE PALLIATIVE (CP) PER LA POPOLAZIONE PEDIATRICA

Proposta di immissione nell'elenco dei medicinali istituito con la L. 648/96 di farmaci utilizzati ***off-label*** nell'ambito delle **Cure Palliative** (CP)

Tavolo Tecnico di Lavoro sull'uso dei farmaci per le Cure Palliative *off-label*

composto

dalla **Società Italiana di Cure Palliative (SICP)**

e dall'Agenzia Italiana del Farmaco (AIFA)

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Sommario

1. INTRODUZIONE

1.1. Utilizzo *off-label* dei farmaci in Pediatria

Il 26 Gennaio 2007 è entrato in vigore in tutti i Paesi dell'EU il Regolamento Europeo relativo ai medicinali ad uso pediatrico (Regulation (EC) No 1901/2006). L'obiettivo del Regolamento Pediatrico è di agevolare lo sviluppo e l'accessibilità di farmaci appositamente studiati per i bambini da 0 a 18 anni di età, garantire che i medicinali utilizzati nella popolazione pediatrica siano oggetto di una ricerca etica di qualità elevata e di un'autorizzazione specifica per l'uso pediatrico, nonché di aumentare la disponibilità delle informazioni sull'uso dei medicinali per i bambini.

Tuttavia nonostante il Regolamento Europeo e le iniziative messe in campo in questo ambito dall'Agenzia Italiana del Farmaco (AIFA), ancora oggi solo un terzo dei farmaci disponibili per la fascia adulta arriva al paziente pediatrico e talvolta con molti anni di ritardo. Dall'analisi della situazione attuale emerge, infatti, che molti nuovi farmaci e la maggior parte delle molecole da tempo in commercio, non sono registrati per l'uso in età pediatrica.

Ne consegue che, nella pratica clinica, i bambini sono spesso trattati con farmaci studiati e sperimentati solo nell'adulto, secondo modalità e indicazioni né previste né registrate per l'età pediatrica (uso *off-label* del farmaco).

Usare un farmaco *off-label* significa infatti prescriverlo in condizioni che differiscono da quelle per cui è stato autorizzato in termini di età, posologia (dose o frequenza di somministrazione), indicazione terapeutica, via di somministrazione e formulazione.

L'uso di farmaci *off-label* in età pediatrica varia dall'11 all'80%, a seconda dei diversi setting clinici: è tra l'11 e il 37% in ambito ambulatoriale, va dal 16 al 62% nei reparti di pediatria generale e supera l'80% nelle terapie intensive pediatriche e neonatologiche.

Diverse le motivazioni che condizionano la "non registrazione del farmaco" per questa fascia di popolazione.

- Vi sono problemi di numerosità ed eterogeneità di pazienti e situazioni cliniche: tra gli 0 e i 18 anni si individuano infatti almeno tre diverse sotto-popolazioni (neonati, bambini e adolescenti) che presentano caratteristiche biologiche e metaboliche particolari e sensibilmente differenti fra loro e che quindi richiedono studi e sperimentazioni specifici.

- Vi sono problematiche di natura etica: vi è infatti una sorta di pregiudizio etico ad esporre i bambini alle sperimentazioni cliniche, benché, al contrario, ciò vada a ledere i loro stessi interessi, perché preclude la possibilità di sviluppare farmaci adatti alle loro specifiche esigenze.

- Ci sono inoltre motivazioni di tipo economico determinate dagli alti costi della sperimentazione e dal limitato ritorno economico: situazione questa che scoraggia gli investimenti da parte dell'industria farmaceutica.

Ne consegue che sono pochi i farmaci creati *ad hoc* per il paziente pediatrico e che molti sono utilizzati in maniera *off-label*.

Del resto l'uso *off-label* rappresenta in molte situazioni l'unica alternativa terapeutica disponibile. Tale impiego ha nella pratica clinica un ruolo "fondamentale" e in molte situazioni non differibile e che, seppur non autorizzato, ha frequentemente alle spalle lunghi periodi di utilizzo in ambito pediatrico (pratica clinica consolidata), nonché lavori/segnalazioni nella letteratura scientifica che ne supportano efficacia e sicurezza.

Non va però dimenticato che la prescrizione di farmaci *off-label* ha dei risvolti clinici, legali ed etici che vanno considerati: è maggiore la possibilità di incorrere in errori nella definizione di un trattamento, implica l'assunzione diretta di responsabilità da parte del medico prescrittore all'utilizzo del farmaco (sia in ambito di efficacia che di eventuali effetti avversi), richiede l'assenso informato da parte di chi esercita la patria potestà e ha delle ricadute sulla rimborsabilità del farmaco stesso.

Il problema dell'utilizzo *off-label* dei farmaci in pediatria si amplifica ulteriormente in alcuni ambiti, dove ancora maggiori sono le problematiche relative alla sperimentazione clinica per tipologia del paziente, peculiarità della situazione e/o novità del problema.

Per esempio, le criticità diventano maggiori in ambito neonatale, nelle malattie e/o situazioni rare e complesse, nei bambini con patologia inguaribile e/o in fase di terminalità, dove studi clinici controllati e randomizzati sono condotti molto raramente sia per la bassa numerosità e l'eteregeneità della popolazione, sia per motivi etici e a volte per la scarsa disponibilità di risorse economiche.

Il risultato è che l'utilizzo di farmaci *off-label* in queste situazioni/patologie è praticamente l'unico possibile e rappresenta la "normalità" consolidata nella gestione clinica del piccolo paziente. In questi ambiti le scelte terapeutiche sono fatte sulla base di una pratica consolidata (spesso dedotta da esperienze/studi maturati nell'ambito dell'adulto) e di poche segnalazioni/studi/evidenze scientifiche.

È quanto per esempio succede nell'ambito delle Cure Palliative rivolte al paziente pediatrico.

1.2. Cure palliative pediatriche

In questi ultimi anni si è assistito ad un lento ma continuo cambiamento dei bisogni assistenziali del neonato/bambino/adolescente malato: nuove tipologie di pazienti, nuove situazioni e nuovi obiettivi di "salute". Certamente una di queste "novità" è rappresentata dai bisogni di Cure Palliative nella popolazione pediatrica (CPP).

Le Cure Palliative Pediatriche sono quella parte della medicina pediatrica che si occupa dei bambini portatori di malattia inguaribile e/o disabilità grave: hanno come obiettivo la qualità della vita del piccolo paziente e il controllo dei sintomi. Il domicilio rappresenta, nella stragrande maggioranza dei casi, il luogo scelto e ideale per assistenza e cura. Eterogeneo e ampio lo spettro di patologie potenzialmente eleggibili alle CPP (malattie neurologiche, muscolari, oncologiche, respiratorie, cardiologiche, metaboliche, cromosomiche, malformative, infettive, post anossiche..), ed eterogeneo ed ampio anche

lo spettro dei bisogni, clinici e non, che queste innescano, e delle modalità di presa in carico necessarie. Si stima che in Italia siano circa 30.000 i minori eleggibili alle CPP.

L'obiettivo principale per tutti questi bambini è alleviare la sofferenza, il dolore e controllare tutti gli altri sintomi stressanti e invasivi.

In questi contesti le evidenze scientifiche sono molto carenti e per ottenere degli obiettivi assistenziali coerenti alla situazione, la prescrizione dei farmaci è *off-label* nella stragrande maggioranza dei casi per indicazione d'uso e/o per età e/o per modalità di somministrazione e/o formulazione.

I minori eleggibili alle CPP sono pazienti ad alta complessità assistenziale, portatori di patologie multiple che innescano sintomi complessi che richiedono programmi di politerapia, frequentemente anche per periodi di tempo lunghi.

Sono pazienti con deficit funzionali che compromettono frequentemente la possibilità di somministrazione dei farmaci attraverso le vie di somministrazione normalmente proposte e/o registrate.

Spesso presentano deficit cognitivi e/o relazionali che limitano la possibilità di condivisione e/o partecipazione attiva alla gestione/accettazione di un programma terapeutico.

Nella stragrande maggioranza dei casi la gestione di questi neonati/bambini/adolescenti avviene a domicilio e quindi anche la gestione dei farmaci viene calata in una realtà ben diversa da quella ospedaliera o ambulatoriale, dove le deroghe a quanto registrato diventano irrinunciabili e dovute.

1.3. Farmaci *off-label* e Legge 648/96

In Italia, per alcuni farmaci, l'utilizzo *off-label* è disciplinato dalla Legge 648/96 che ha permesso di identificare una lista di farmaci con un'indicazione terapeutica diversa da quella autorizzata, ma impiegati nella pratica clinica in ragione dell'uso consolidato e sulla base di dati di letteratura scientifica. Questi farmaci, una volta inseriti nell'elenco dei medicinali istituito con la Legge 648/96, vengono somministrati sempre sotto diretta responsabilità del medico e possono essere rimborsati dal Servizio Sanitario Nazionale.

In questo elenco vi sono farmaci, che coprono parzialmente i bisogni prescrittivi delle diverse aree della medicina pediatrica (*Lista farmaci per oncologia pediatrica, cardiovascolari, antinfettivi, anestetici, gastrointestinali, farmaci pediatrici sangue e organi eritropoietici, dermatologici, farmaci dell' apparato genito-urinario e ormoni sessuali*).

Nell'analisi dell'elenco mancano peraltro alcuni medicinali usati frequentemente per il controllo del dolore e degli altri sintomi nelle CPP.

Data la peculiarità delle situazioni e gli obiettivi di cura che le CPP si propongono, abbiamo individuato una lista di farmaci usati nelle CPP per i quali l'inclusione nell'elenco dell' Agenzia Italiana del Farmaco (AIFA) istituito con la Legge 648/96, rappresenta per i pazienti, gli operatori e per tutto il sistema salute un obiettivo di efficacia, sicurezza ed equità.

Per tali farmaci resta necessario raccogliere, da parte dei legali rappresentanti del minore, il consenso informato all'utilizzo. E' inoltre importante informare il minore, con strumenti e modalità adeguate a età, situazione clinica e capacità di discernimento, sul farmaco e sulle strategie di somministrazione, nell'ottica della condivisione e dell'aderenza al programma terapeutico.

1.4. Bibliografia

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3. European Medicines Agency. Updated priority list (revised) for studies into off-patent paediatric medicinal products. Doc. Ref. EMA/197972/2007. London: EMA, 2007.
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5. Working Group Pediatrico dell' AIFA. The first list of cardiovascular drugs authorized in paediatrics - Medico e Bambino 2010;29:172-176
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13. Mir AN,Geer MI. Off-label use of medicines in children. Int J Pharm Sci Res 2016; 7(5)1820-28
14. Bonati M, Jacqz-Aigrain E, Choonara I. Licensed medicines, off-label use or evidence-based. Which is most important? Arch Dis Child. 2017;102(1):53-54.
15. Jamieson L, Wong IC, Craig F, Christiansen N, Brombley K, Tuleu C, Harrop E. Palliative medicines for children - a new frontier in paediatric research. J Pharm Pharmacol. 2017;69(4):377-383

2. OBIETTIVO DEL LAVORO

Con questo documento sottoponiamo all'attenzione dell'AIFA un elenco di farmaci utilizzati *off-label* nelle cure palliative pediatriche (CPP) e nella terapia del dolore (TD) e ritenuti essenziali per risolvere, almeno in parte, la scarsa disponibilità di medicinali studiati ed approvati in età pediatrica.

Sono stati individuati 10 farmaci che routinariamente, per specifiche indicazioni, nella pratica clinica delle CPP vengono utilizzati *off-label* con modalità che differiscono da quelle per cui sono stati autorizzati in termini di età, posologia, indicazione terapeutica, via di somministrazione e formulazione.

I farmaci individuati sono:

- BUTILBROMURO DI JOSCINA
- DESMEDETOMIDINA
- FENTANILE
- GABAPENTIN
- KETAMINA
- KETOROLAC
- LIDOCAINA
- MIDAZOLAM
- ONDANSETRON
- SCOPOLAMINA.

Alcune indicazioni oggetto della richiesta di inserimento nell'elenco ai sensi della Legge 648/96, sono riferite a terapie utilizzate per periodi di tempo brevi, in corso di riacutizzazioni e/o fine vita. Altre richieste invece, pongono indicazioni di uso prolungato (mesi, anni), durante il percorso di presa in carico in cure palliative del minore con patologia inguaribile.

3. METODOLOGIA

Al fine di derivarne una proposta di inserimento nella lista dei farmaci erogabili ai sensi della Legge 648/96, il lavoro svolto comprende informazioni circa l'evidenza scientifica a supporto dell'uso *off-label* (dati di letteratura, RCT, eventuali studi clinici in corso) e l'utilizzo del principio attivo nell'indicazione *off-label* in altri Stati membri (Inghilterra, con riferimento al Prontuario *British National Formulary, BNF for children, edizione 2016-17*).

È stato inoltre analizzato lo stato dell'arte relativo a precedenti richieste di inserimento nell'elenco AIFA.

La lista ha la finalità di indicare i principi attivi, per ciascuna classe ATC, che possano essere utilizzati nel bambino nell'ambito delle CPP, anche se il loro uso non è autorizzato in età pediatrica. Per alcuni di essi si tratta di un utilizzo razionale in quanto supportato dalle evidenze disponibili, anche se non esistono a supporto del loro impiego formali studi registrativi, perché si tratta di molecole vecchie o per difficoltà oggettive nella conduzione di trial clinici pediatrici.

Per ciascun principio attivo individuato è stata formalizzata una scheda in cui è indicata la specifica indicazione di richiesta di autorizzazione nella pratica clinica, il razionale della richiesta, le evidenze a supporto della richiesta (con l'*abstract* dei singoli lavori), eventuali note aggiuntive.

In allegato le tabelle riassuntive dei dieci farmaci per i quali viene chiesto l'inserimento nell'elenco 648/96.

4. SCHEDE DEI SINGOLI FARMACI

4.1. BUTILSCOPOLAMINA – IOSCINA BUTILBROMURO

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Somministrazione EV per ostruzione intestinale da peritonite in pazienti pediatrici oncologici.
2. Somministrazione EV per riduzione delle secrezioni e del rantolo nella terminalità.

RAZIONALE DELLA RICHIESTA:

1. Le lesioni neoplastiche peritoneali primitive e/o secondarie sono la causa nei pazienti pediatrici in CPP, soprattutto in fase di terminalità, di problemi di ostruzione intestinale con vomito incoercibile e dolore viscerale, che rispondono poco alla terapia analgesica convenzionale. La butilscopolamina in queste situazioni, somministrata EV, è il farmaco di scelta nella limitazione della sintomatologia algica e gastrointestinale.

2. Sempre in fase di fine vita, il deficit della deglutizione e la difficoltà nella gestione delle secrezioni delle alte vie respiratorie, sono alla base dell'insorgenza del rantolo agonico. L'impatto che il rantolo del bambino morente ha sui familiari è notevole sia durante il periodo di fine vita che dopo; viene, infatti, interpretato come fatica respiratoria e difficoltà "del morire" con una ricaduta negativa sia nella gestione dell'evento morte che nella fase di elaborazione del lutto. La butilscopolamina con la sua azione anticolinergica, limita/annulla l'impatto secretivo e tutti gli effetti clinici e psicologici che questo determina nella fase di fine vita.

SITUAZIONE ATTUALE APPROVATA:

Compresse rivestite_ **paziente** > 14 anni: manifestazioni spastico-dolorose del tratto gastroenterico e genito-urinario.

Supposte_ **paziente** > 6 anni: manifestazioni spastico-dolorose del tratto gastroenterico e genito-urinario.

RICERCA BIBLIOGRAFICA RICHIESTA 1:

Parole chiave: Hyoscine butylbromide, bowel obstruction, cancer

Lavori evidenziati:

1. Tytgat GN. Hyoscine butylbromide: a review of its use in the treatment of abdominal cramping and pain. Drugs. 2007;67(9):1343-57.PMID 17547475

Commento: la *review* supporta l'uso nel dolore addominale crampiforme nel paziente adulto.

2. Mercadante S, Casuccio A, Mangione S. Medical treatment for inoperable malignant bowel obstruction: a qualitative systematic review. J Pain Symptom Manage. 2007 Feb;33(2):217-23.PMID 17280927
   Commento: l'articolo indica che octreotide (maggiore efficacia) e ioscina butilbromuro sono i farmaci di scelta per il trattamento dell'ostruzione intestinale da patologie neoplastiche nel paziente adulto.
3. Miller M and Karwacki M: Management of the gastrointestinal tract in paediatric palliative medicine. OXFORD TEXBOOK OF PALLIATIVE CARE FOR CHILDREN . Oxford University press 2nd edition 2012.
   Commento: l'elaborato indica l'uso del farmaco per via im/ev/sottocute in ic in bambini affetti da patologia neoplastica con dolore addominale (gastrointestinale o genito-urinario) in cure palliative.

RCT DISPONIBILI:

Nessuno

RICERCA BIBLIOGRAFICA RICHIESTA 2:

Parole chiave: Hyoscine butylbromide, death rattle

Lavori evidenziati:

1. Albert RH. End-of-Life Care: Managing Common Symptoms. Am Fam Physician. 2017 Mar 15;95(6):356-361.PMID 28318209
   Commento: l'articolo supporta l'uso del farmaco per la gestione del rantolo terminale in pazienti adulti.
2. Miller M and Karwacki M: Management of the gastrointestinal tract in paediatric palliative medicine. OXFORD TEXBOOK OF PALLIATIVE CARE FOR CHILDREN . Oxford University press 2nd edition 2012.
   Commento: l'elaborato indica l'uso del farmaco per via im/ev/sottocute in ic nella gestione del rantolo terminale in età pediatrica.

RCT DISPONIBILI:

Nessuno

COMMENTO E CONCLUSIONI:

I dati a disposizione sono limitati e per lo più in ambito del paziente adulto. Tuttavia le segnalazioni presenti propongono l'utilizzo della butilscopolamina in CPP come farmaco

adiuvante in situazioni quali l'ostruzione intestinale da peritonite e la gestione dell'eccesso di secrezioni in fase di terminalità, che non presentano alternative terapeutiche.

ABSTRACT RICHIESTA 1:

1. Tytgat GN

Abdominal cramping and pain is a frequent problem in the adult population of Western countries, with an estimated prevalence of < or =30%. Hyoscine butylbromide (scopolamine butylbromide) [Buscopan/Buscapina] is an antispasmodic drug indicated for the treatment of abdominal pain associated with cramps induced by gastrointestinal (GI) spasms. It was first registered in Germany in 1951 and marketed in 1952, and has since become available worldwide both as a prescription drug and as an over-the-counter medicine in many countries. This article reviews the pharmacology and pharmacokinetic profile of hyoscine butylbromide, and summarises efficacy and safety data from clinical trials of this drug for abdominal cramping and pain. Pharmacological studies have revealed that hyoscine butylbromide is an anticholinergic drug with high affinity for muscarinic receptors located on the smooth-muscle cells of the GI tract. Its anticholinergic action exerts a smooth-muscle relaxing/spasmolytic effect. Blockade of the muscarinic receptors in the GI tract is the basis for its use in the treatment of abdominal pain secondary to cramping. Hyoscine butylbromide also binds to nicotinic receptors, which induces a ganglion-blocking effect. Several pharmacokinetic studies in humans have consistently demonstrated the low systemic availability of hyoscine butylbromide after oral administration, with plasma concentrations of the drug generally being below the limit of quantitation. The bioavailability of hyoscine butylbromide, estimated from renal excretion, was generally <1%. However, because of its high tissue affinity for muscarinic receptors, hyoscine butylbromide remains available at the site of action in the intestine and exerts a local spasmolytic effect. Ten placebo-controlled studies have evaluated the efficacy and safety of oral or rectal hyoscine butylbromide. Hyoscine butylbromide was considered beneficial in all of these trials, which supports its use in the treatment of abdominal pain caused by cramping. Hyoscine butylbromide is barely absorbed and detectable in the blood and does not penetrate the blood-brain barrier, and is, therefore, generally well tolerated. Few adverse events have been reported; in particular, no significant increases in the incidence of anticholinergic-related adverse effects have been observed. In summary, hyoscine butylbromide appears to be a valuable treatment option for patients with symptoms of abdominal pain or discomfort associated with cramping.

2. Mercadante S

The use of symptomatic agents has greatly improved the medical treatment of advanced cancer patients with inoperable bowel obstruction. A systematic review of studies of the most popular drugs used in the medical management of inoperable malignant bowel obstruction was performed to assess the effectiveness of these treatments and provide some lines of evidence. Randomized trials that involved patients with a clinical diagnosis of intestinal obstruction due to advanced cancer treated with these drugs were reviewed. Five reports fulfilled inclusion criteria. Three studies compared octreotide (OC) and

hyoscine butylbromide (HB), and two studies compared corticosteroids (CSs) and placebo. Globally, 52 patients received OC, 51 patients received HB, 37 patients received CSs, 15 patients received placebo, and 37 patients received both placebo and CSs. On the basis of these few data, the superiority of OC over HB in relieving gastrointestinal symptoms was evidenced in a total of 103 patients. The latter studies had samples more defined in terms of stage and inoperability, and had a shorter survival in comparison with studies of CSs (less than 61 days, most of them less than 20 days). Data on CSs are less convincing, due to the methodological weakness of existing studies. This review confirms the difficulties in conducting randomized controlled trials in this population.

ABSTRACT RICHIESTA 2:

1. Albert RH

Physicians should be proficient at managing symptoms as patients progress through the dying process. When possible, proactive regimens that prevent symptoms should be used, because it is generally easier to prevent than to treat an acute symptom. As swallowing function diminishes, medications are typically administered sublingually, transdermally, or via rectal suppository. Opiates are the medication of choice for the control of pain and dyspnea, which are common symptoms in the dying process. Delirium and agitation may be caused by reversible etiologies, which should be identified and treated when feasible. When medications are required, haloperidol and risperidone are effective options for delirium. Nausea and vomiting should be treated with medications targeting the etiology. Constipation may be caused by low oral intake or opiate use. Preventive regimens to avoid constipation should include a stimulant laxative with a stool softener. Oropharyngeal secretions may lead to noisy breathing, sometimes referred to as a death rattle, which is common at the end of life. Providing anticipatory guidance helps families and caregivers normalize this symptom. Anticholinergic medications can modestly help reduce these secretions. Effective symptom control in end-of-life care can allow patients to progress through the dying process in a safe, dignified, and comfortable manner.

4.2. DESMEDETOMIDINA

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Controllo dei sintomi stressanti da patologia o procedura e difficoltà di addormentamento al di fuori della terapia intensiva in pazienti in cure palliative, come trattamento in situazioni non rispondenti alle terapie convenzionali.

2. Via di somministrazione endonasale.

RAZIONALE DELLA RICHIESTA:

1. La desmedetomidina è un alfa-2 agonista selettivo e differisce perciò dagli altri sedativi comuni, come propofol e le benzodiazepine, che hanno invece come *target* il recettore dell'acido gamma-aminobutirrico (GABA). Il meccanismo d'azione della desmedetomidina fa sì che questo agente possa alleviare l'ansia e fornire analgesia senza gli effetti avversi respiratori o amnesici osservati con i GABA-agonisti.

Ansia, dolore, difficoltà all'addormentamento sono sintomi stressanti frequenti in CPP, sintomi che, data la complessità della situazione clinica di questi bambini, pongono frequentemente problematiche di scelta e valutazione rischio/beneficio nella scelta del farmaco, anche a discapito del controllo dei sintomi stessi.

2. La desmedetomidina si propone come un'alternativa efficace e sicura sia somministrata ev, sia, in caso di mancanza di accesso vascolare, per via nasale, in grado di controllare (da sola o in associazione) sintomi stressanti che talvolta non hanno altre possibilità d'intervento.

SITUAZIONE ATTUALE APPROVATA:

Analgosedazione procedurale al di fuori della Sala Operatoria (Not Operating Room Anestesia NORA) nel bambino con gestione difficile delle vie aeree e non, bambino con disturbi convulsivi che deve essere sottoposto a studi diagnostici per localizzare i foci epilettogeni.

Analgosedazione del neonato e del bambino critico ricoverati in terapia intensiva, ventilati meccanicamente e scarsamente responsivi al trattamento analgosedativo convenzionale.

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 1:

Parole chiave: dexmedetomidine, paediatric

Lavori evidenziati:

1. Mahmoud M, Mason KP. Dexmedetomidine: review, update, and future considerations of paediatric perioperative and periprocedural applications and limitations. Br J Anaesth. 2015 Aug;115(2):171-82. doi: 10.1093/bja/aev226. Review.

   Commento: lo sudio sostiene l'uso della desmedetomidina in pazienti pediatrici, in particolare con funzionalità respiratoria compromessa, in alternativa ad altri farmaci (benzodiazepine, propofol, oppioidi).

2. Sulton C, McCracken C, Simon HK, Hebbar K, Reynolds J, Cravero J, Mallory M, Kamat P. Pediatric Procedural Sedation Using Dexmedetomidine: A Report From the Pediatric Sedation Research Consortium. Hosp Pediatr. 2016 Sep;6(9):536-44. doi: 10.1542/hpeds.2015-0280. Epub 2016 Aug 11.

   Commento: la desmedetomidina utilizzata per la sedazione procedurale in età pediatrica si dimostra efficace e sicura.

3. Ni J, Wei J, Yao Y, Jiang X, Luo L, Luo D. Effect of dexmedetomidine on preventing postoperative agitation in children: a meta-analysis. PLoS One. 2015 May 21;10(5):e0128450. doi: 10.1371/journal.pone.0128450. eCollection 2015.

   Commento: la *review* analizza 19 studi (>1000 pazienti pediatrici), dimostrando che la desmedetomidina è efficace nel prevenire l'agitazione post-operatoria, riduce il dolore severo e la necessità di ricorrere a farmaci *rescue*.

4. Weerink MAS, Struys MMRF, Hannivoort LN, Barends CRM, Absalom AR, Colin P. Clinical Pharmacokinetics and Pharmacodynamics of Dexmedetomidine. Clin Pharmacokinet 2017 Aug;56(8):893-913.

   Commento: la *review*, focalizzata su farmacocinetica e farmacodinamica della desmedetomidina, evidenzia il profilo di sicurezza in neonati e bambini.

5. Alexopoulou C, Kondili Ea, Diamantaki E, Psarologakis C, Kokkini Sa, Bolaki M, Georgopoulos D. Effects of Dexmedetomidine on Sleep Quality in Critically Ill Patients. Anesthesiology 2014 Oct;121(4):801-807.

   Commento: lo studio, condotto su pazienti adulti critici, riporta la capacità di desmedetomidina di migliorare la qualità del sonno.

RCT DISPONIBILI:

Nessuno

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 2:

Parole chiave: dexmedetomidine, children, intranasal

Lavori evidenziati:

1. Cozzi G, Norbedo S, Barbi E. Intranasal Dexmedetomidine for Procedural Sedation in Children, a Suitable Alternative to Chloral Hydrate. Paediatr Drugs. 2017 Apr;19(2):107-111. doi: 10.1007/s40272-017-0217-5.

   Commento: lo studio suggerisce l'uso della desmedetomidina per via intranasale per la sedazione in procedure diagnostiche in età pediatrica, evidenziandone la sicurezza in particolare nella gestione delle vie aeree.

RCT DISPONIBILI:

Nessuno

NOTE:

La potenza analgesica è limitata, pertanto, in caso di dolore severo la desemdetomidina va utilizzata in associazione ad altro farmaco analgesico.

COMMENTO E CONCLUSIONI:

I lavori a disposizione per l'età pediatrica sono riferiti per lo più all'ambito della sedazione procedurale e alla gestione dei sintomi stressanti in ambito critico. La letteratura supporta l'utilizzo per via nasale per la sedazione procedurale. I dati a disposizione supportano le richieste di inserimento nell'elenco 648/96 .

ABSTRACT PER LA RICHIESTA 1:

1. Mahmoud M

Despite lack of paediatric labelling, contributions to the literature on paediatric applications of dexmedetomidine have increased over recent years. Dexmedetomidine possesses many properties that are advantageous for a sedative and anaesthetic; it has been reported to provide sedation that parallels natural sleep, anxiolysis, analgesia, sympatholysis, and an anaesthetic-sparing effect with minimal respiratory depression. In addition, there is increasing evidence supporting its organ- protective effects against ischaemic and hypoxic injury. These favourable physiological effects combined with a limited adverse effect profile make dexmedetomidine an attractive adjunct to anaesthesia (general and regional) for a variety of procedures in paediatric operating rooms. A comprehensive understanding of the pharmacological, pharmacokinetic, and pharmacodynamic effects of dexmedetomidine is critical to maximize its safe, efficacious, and efficient paediatric perioperative applications. This review focuses on the current paediatric perioperative and periprocedural applications of dexmedetomidine and its limitations, with a consideration for the future. In conclusion, data regarding the perioperative off-label use of DEX in the paediatric population are promising but still

limited, and further studies are required. The adverse event profile of benzodiazepines, propofol, and opioids, alone and in combination, leaves a window of opportunity to consider alternative agents that may improve outcome and minimize risk. Particularly in patients with respiratory compromise, for whom the preservation of spontaneous ventilation and airway tone is preferable, or those for whom the preservation of neuromonitoring with or without patient responsiveness is the goal, DEX should be seriously considered. An indepth understanding of the pharmacological, pharmacokinetic, and pharmacodynamic effects of DEX is critical to maximize its safe use in paediatric perioperative applications.

2. Sulton C

OBJECTIVES: Dexmedetomidine (DEX) is widely used in pediatric procedural sedation (PPS) by a variety of pediatric subspecialists. The objective of our study was to describe the overall rates of adverse events and serious adverse events (SAEs) when DEX is used by various pediatric subspecialists. METHODS: Patients from the Pediatric Sedation Research Consortium (PSRC) database were retrospectively reviewed and children that received DEX as their primary sedation agent for elective PPS were identified. Demographic and clinical data, provider subspecialty, and sedation-related complications were abstracted. SAEs were defined as death, cardiac arrest, upper airway obstruction, laryngospasm, emergent airway intervention, unplanned hospital admission/increased level of care, aspiration, or emergency anesthesia consult. Event rates and 95% confidence intervals (CIs) were calculated. RESULTS: During the study period, 13 072 children were sedated using DEX, accounting for 5.3% of all sedation cases entered into the PSRC. Of the sedated patients, 73% were American Society of Anesthesiologists Physical Status class 1 or 2. The pediatric providers responsible for patients sedated with DEX were anesthesiologists (35%), intensivists (34%), emergency medicine physicians (12.7%), hospitalists (1.1%), and others (17%). The overall AE rate was 466/13 072 (3.6%, 95% CI 3.3% to 3.9%). The overall SAE rate was 45/13 072 (0.34%, 95% CI 0.19% to 0.037%). Airway obstruction was the most common SAE: 35/13 072 (0.27%, 95% CI 0.19% to 0.37%). Sedations were successful in 99.7% of cases. CONCLUSIONS: We report the largest series of PPS using DEX outside the operating room. Within the PSRC, PPS performed using DEX has a very high success rate and is unlikely to yield a high rate of SAEs.

3. Ni J

BACKGROUND: Emergence agitation (EA) is one of the most common postoperative complications in children. The purpose of this meta-analysis is to assess the effect of dexmedetomidine for preventing postoperative agitation in children. METHODS: We searched the Cochrane Central Register of Controlled Trails, MEDLINE, and EMBASE. Randomized controlled trials were included. The following outcome measures were evaluated: incidence of EA, number of patients requiring rescue, time to eye-open, time to extubation, time to discharge from the postanesthesia care unit (PACU). RESULTS: We analyzed 19 trials (1608 patients) that met the inclusion criteria. Compared with placebo, intravenous dexmedetomidinesignificantly reduced the incidence of EA [risk ratio (RR) 0.34, 95% confidence interval (CI) 0.25-0.44, P<0.00001). Dexmedetomidinealso decreased the incidence of severe pain (RR 0.41, 95% CI 0.27-0.62, P<0.0001) and

requirement of a rescue drug (RR 0.31, 95% CI 0.18-0.53, P<0.0001). However, compared with placebo, dexmedetomidine increased the time to eye-open by 0.98 min (P = 0.01) and the time to PACU discharge by 4.63 min (P = 0.02). Dexmedetomidine was also compared with midazolam, propofol, ketamine, and fentanyl, among others. No significant difference was found in the incidence of EA for most of these comparisons, with the exception of fentanyl and propofol, where dexmedetomidine was more beneficial. CONCLUSIONS: Dexmedetomidine was proved effective for preventing EA and for reducing severe pain and the requirement of rescue drugs. It slightly increased the time to eye-open and the time to PACU discharge. Dexmedetomidine was also more beneficial than propofol or fentanyl in preventing EA.

3. Weerink MAS

Dexmedetomidine is an a_2-adrenoceptor agonist with sedative, anxiolytic, sympatholytic, and analgesic- sparing effects, and minimal depression of respiratory function. It is potent and highly selective for a_2-receptors with an a_2:a_1 ratio of 1620:1. Hemodynamic effects, which include transient hypertension, bradycardia, and hypotension, result from the drug's peripheral vasoconstrictive and sympatholytic properties. Dexmedetomidine exerts its hypnotic action through activation of central pre- and postsynaptic a-receptors in the locus coeruleus, thereby inducting a state of unconsciousness similar to natural sleep, with the unique aspect that patients remain easily rousable and cooperative. Dexmedetomidine is rapidly distributed and is mainly hepatically metabolized into inactive metabolites by glucuronidation and hydroxylation. A high inter-individual variability in dexmedetomidine pharmacokinetics has been described, especially in the intensive care unit population. In recent years, multiple pharmacokinetic non-compartmental analyses as well as population pharmacokinetic studies have been performed. Body size, hepatic impairment, and presumably plasma albumin and cardiac output have a significant impact on dexmedetomidine pharmacokinetics. Results regarding other covariates remain inconclusive and warrant further research. Although initially approved for intravenous use for up to 24 h in the adult intensive care unit population only, applications of dexmedetomidine in clinical practice have been widened over the past few years. Procedural sedation with dexmedetomidine was additionally approved by the US Food and Drug Administration in 2003 and dexmedetomidine has appeared useful in multiple off-label applications such as pediatric sedation, intranasal or buccal administration, and use as an adjuvant to local analgesia techniques.

4. Alexopoulou C

BACKGROUND: Dexmedetomidine, a potent α-2-adrenergic agonist, is widely used as sedative in critically ill patients. This pilot study was designed to assess the effect of dexmedetomidine administration on sleep quality in critically ill patient. METHODS: Polysomnography was performed on hemodynamically stable critically ill patients for 57 consecutive hours, divided into three night-time (9:00 PM to 6:00 AM) and two daytime (6:00 AM to 9:00 PM) periods. On the second night, dexmedetomidine was given by a continuous infusion targeting a sedation level -1 to -2 on the Richmond Agitation Sedation Scale. Other sedatives were not permitted. RESULTS: Thirteen patients were studied. Dexmedetomidine was given in a dose of 0.6 μg kg(-1) h(-1) (0.4 to 0.7) (median [interquartile range]). Compared to first and third nights (without dexmedetomidine), sleep

efficiency was significantly higher during the second night (first: 9.7% [1.6 to 45.1], second: 64.8% [51.4 to 79.9], third: 6.9% [0.0 to 17.1], P < 0.002). Without dexmedetomidine, night-time sleep fragmentation index (7.6 events per hour [4.8 to 14.2]) and stage 1 of sleep (48.0% [30.1 to 66.4]) were significantly higher (P = 0.023 and P = 0.006, respectively), and stage 2 (47.0% [27.5 to 61.2]) showed values lower (P = 0.006) than the corresponding values (2.7 events per hour [1.6 to 4.9], 13.1% [6.2 to 23.6], 80.2% [68.9 to 92.8]) observed with dexmedetomidine. Without sedation, sleep was equally distributed between day and night, a pattern that was modified significantly (P = 0.032) by night-time dexmedetomidine infusion, with more than three quarters of sleep occurring during the night (79% [66 to 87]). CONCLUSIONS: In highly selected critically ill patients, dexmedetomidine infusion during the night to achieve light sedation improves sleep by increasing sleep efficiency and stage 2 and modifies the 24-h sleep pattern by shifting sleep mainly to the night.

ABSTRACT PER LA RICHIESTA 2:

1. Cozzi G

Sedation is often required for children undergoing diagnostic procedures. Chloral hydrate has been one of the sedative drugs most used in children over the last 3 decades, with supporting evidence for its efficacy and safety. Recently, chloral hydrate was banned in Italy and France, in consideration of evidence of its carcinogenicity and genotoxicity. Dexmedetomidine is a sedative with unique properties that has been increasingly used for procedural sedation in children. Several studies demonstrated its efficacy and safety for sedation in non-painful diagnostic procedures. Dexmedetomidine's impact on respiratory drive and airway patency and tone is much less when compared to the majority of other sedative agents. Administration via the intranasal route allows satisfactory procedural success rates. Studies that specifically compared intranasal dexmedetomidine and chloral hydrate for children undergoing non-painful procedures showed that dexmedetomidine was as effective as and safer than chloral hydrate. For these reasons, we suggest that intranasal dexmedetomidine could be a suitable alternative to chloral hydrate.

4.3. FENTANIL

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Uso per via transcutanea, EV per la gestione del dolore acuto e/o cronico da patologia oncologica e non, in minori in CPP.
2. Uso transmucoso per dolore incidente/breakthroug pain/dolore procedurale nei minori in CPP.

RAZIONALE DELLA RICHIESTA:

1. Le patologie eleggibili alle CCP, presentano nella stragrande maggioranza dei casi dolore (fino nel 90% per alcune malattie). Il dolore (cronico, acuto, procedurale, *breakthroug pain*) è il sintomo che fra tutti maggiormente mina la storia di malattia e la qualità della vita del paziente e della sua famiglia.

   Le cause sono molteplici, frequentemente condizionate e condizionanti gli altri sintomi stressanti (dispnea, insonnia, ansia, anoressia) e nella maggior parte dei casi sono cause ineliminabili. La terapia antalgica quindi rappresenta uno strumento essenziale nelle CPP.

   Il Fentanil è un oppioide forte (100 volte la potenza della morfina): farmaco essenziale e di scelta in talune situazioni, perchè efficace sia nella gestione del dolore severo acuto o cronico, che nel controllo del dolore incidente, procedurale e nel *breakthrough pain.*

   È un farmaco molto utile sia come scelta alternativa in caso di scarsa efficacia di un altro oppioide, sia come molecola da proporre in corso di trattamento cronico nella rotazione di oppiodi per evitare situazioni di eccessiva tolleranza e ritardare la dipendenza. La via di somministrazione EV per infusione continua e/o boli è indicata nella gestione del dolore nocicettivo/misto acuto, cronico o procedurale.

2. Le somministrazioni transdermica (dolore cronico), transmucosa (dolore incidente e *breakthrough pain*) e nasale (dolore procedurale, incidente e *breakthrough pain*) permettono una gestione del dolore efficace anche nei bambini che non hanno accessi vascolari e permettono al bambino di essere assistito a domicilio o in setting divesi da quello ospedaliero e ambulatoriale, senza invasività, né limitazione delle proprie attività residue.

   Il fentanil, nelle diverse modalità di somministrazione, rappresenta quindi un farmaco essenziale nella gestione del dolore del bambino in CP.

SITUAZIONE ATTUALE APPROVATA:

Premedicazione per qualunque tipo di anestesia (anche locale), sia nel decorso postoperatorio, sia durante l'intervento.

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 1:

Parole chiave: fentanyl, transdermal, intravenous, pain

Lavori evidenziati:

1. Collins JJ, Dunkel IJ, et al. Transdermal Fentanyl in children with cancer pain: feasibility, tolerability and pharmacokineic correlates. J pediatr 1999;134:319-23. PMID 10064669

   Commento: lo studio conferma che il farmaco, pur con evidenze ormai datate sull'efficacia e sicurezza dell'uso transdermico in età pediatrica, non ha ancora un'indicazione pediatrica *in label*.

2. Finkel JC, Finley A, Greco C, Wieisman SJ, Zeltzer L. Trasdermal Fentanyl in the management of children with chronic severe pain. Cancer 2005:104(12):2847-857. PMID 16284992.

   Commento: lo studio evidenzia come l'uso trasndermico del farmaco sia sicuro e ben tollerato nei bambini, sia con patologia oncologica che non oncologica, con ottimo impatto sulla qualità di vita.

3. Zernikow B, Michel E, Anderson B. Transdermal Fentanyl in childhood and adolescence: a comprensive Literature review. J Pain 2007; 8(3):187-192.PMID 17350554.

   Commento: il farmaco per via trasndermica presenta minor effetti collaterali, in particolare la stipsi (effetto collaterale molto limitante in CPP).

4. Drake R et al. Pharmacological approaches to pain: Simple analgesics and opioids. OXFORD TEXBOOK OF PALLIATIVE CARE FOR CHILDREN. Oxford University press 2nd edition 2012.

   Commento: l'elaborato indica l'uso transdermico ed endovenoso in CPP per la gestione del dolore acuto/cronico.

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 2:

Parole chiave: fentanyl, transmucosal, breakthrough cancer pain

Lavori evidenziati:

1. Zernikow B, Michel E, Craig F, Anderson BJ. Pediatric palliative care: use of opioids for the management of pain. Paediatr Drugs. 2009;11(2):129-51. doi: 10.2165/00148581-200911020-00004.

   Commento: lo studio riporta l'efficacia del fentanil nella gestione del *breakthrough pain*, per quanto riguarda la formulazione sia transmucosa che nasale.

2. Mystakidou K, Katsouda E, Parpa E, Vlahos L, Tsiatas ML. Oral transmucosal fentanyl citrate: overview of pharmacological and clinical characteristics. Drug Deliv. 2006 Jul-Aug;13(4):269-76.PMID 16766468.

   Commento: l'*overview* farmacologica indica l'uso del fentanil per via intramucosale anche in situazioni non oncologiche.

3. Friedrichsdorf SJ, Postier A. Management of breakthrough pain in children with cancer, J Pain Research, 2014; 7: 117–123. doi: 10.2147/JPR.S58862

Commento: lo studio riporta l'uso del fentanil iv/sc/sl/transdermico e buccale nel *breakthrough pain* in bambini affetti da patologia oncologica.

4. Zeppetella G, Davies AN. : Opioids for the management of breakthrough pain in cancer patients. Cochrane Database Syst Rev. 2013 Oct 21;(10):CD004311. doi: 10.1002/14651858.CD004311.pub3.

Commento: la *review* riguarda l' uso nell'adulto; pur non essendo inclusi dati sul paziente pediatrico, è riportato un livello di efficacia alto, che è comunque importante da considerare.

5. Drake R et al. Pharmacological approaches to pain: Simple analgesics and opioids. OXFORD TEXBOOK OF PALLIATIVE CARE FOR CHILDREN . Oxford University 2nd edition 2012.

Commento: l'elaborato indica l'uso intranasale e transmucoso nel *breakthrough pain* e nel dolore procedurale in età pediatrica in CP.

RCT DISPONIBILI:

Sono presenti 81 RCT che riguardano pazienti da 0-18 anni (fonte: Fontiguerra et al Arch Dis Child 2010; 95:749-753).

NOTE:

Per la somministrazione transdermica si raccomanda di non manipolare il cerotto.

COMMENTO E CONCLUSIONI:

I dati a disposizione per le somministrazioni transdermica e transmucosa del fentanil, per la gestione del dolore in CPP supportano le richieste di inserimento nell'elenco 648/96.

ABSTRACT RICHIESTA 1:

1. Collins JJ

OBJECTIVES: To assess the feasibility and tolerability of the therapeutic transdermal fentanyl system (TTS-fentanyl) by using a clinical protocol developed for children with cancer pain. (2) To estimate the pediatric pharmacokinetic parameters of TTS-fentanyl. METHODS: The drug was administered in open-label fashion; and measures of analgesia, side effects, and skin changes were obtained for a minimum of 2 doses (6 treatment days). Blood specimens were analyzed for plasma fentanyl concentrations. The

pharmacokinetics of TTS-fentanyl were estimated by using a mixed effect modeling approach. RESULTS: Treatment was well tolerated. Ten of the 11 patients who completed the 2 doses continued treatment with TTS-fentanyl. The duration of treatment ranged from 6 to 275 days. The time to reach peak plasma concentration ranged from 18 hours to >66 hours in patients receiving the 25 microg/h patch. Compared with published pharmacokinetic data from adults, the mean clearance and volume of distribution of transdermal fentanyl were the same, but the variability was less. CONCLUSIONS: Treatment of children with TTS-fentanyl is feasible and well tolerated and yields fentanyl pharmacokinetic parameter estimates similar to those for adults. A larger study is required to confirm these findings and further test the clinical protocol.

2. Finkel JC

BACKGROUND: The current study was conducted to assess the safety and tolerability of a transdermal fentanyl delivery system for the relief of chronic pain in a pediatric population, and also to validate titration recommendations and conversion to transdermal fentanyl from oral opioid therapy. METHODS: This 15-day (with 3-month extension), single-arm, open-label trial was conducted at 66 sites in 10 countries. A total of 199 pediatric patients (ages 2-16 years) with both malignant and nonmalignant conditions who were receiving oral or parenteral opioids for moderate to severe chronic pain were enrolled. Transdermal fentanyl doses were titrated upward according to the rescue medication consumed during the previous application period. Degree of pain was assessed by patients and parents/guardians using visual and numeric scales. Level of play and quality of life were assessed using the Play Performance Scale (PPS) and the Child Health Questionnaire (CHQ). Adverse events were monitored on Days 1-15. Hypoventilation and sedation were monitored every 4 hours during the first 72 hours of the study. RESULTS: A total of 173 patients completed the primary treatment period and 130 entered the extension phase. The average daily pain intensity scores were reported to have decreased by Day 16 and improvements in the mean PPS scores were observed to the end of the extension period. The CHQ scores demonstrated improvements in 11 of 12 domains after Month 1 of the extension period. CONCLUSIONS: Transdermal fentanyl was found to be a safe and well tolerated alternative to oral opioid treatment for children ages 2-16 years who were previously exposed to opioid therapy.

3. Zernikow B.

The recently introduced fentanyl transdermal therapeutic system (TTS) with a drug release rate of 12.5 microg/h matches the lower dosing requirements of cancer pain control in children. It is likely that fentanyl TTS will be used in pediatrics with increasing frequency. We compiled the published evidence on pediatric applications of this drug formulation to help physicians get the most benefit from its use. Within this systematic review, a total of 11 observational clinical or pharmacokinetic studies were identified. There are no pediatric randomized or controlled cohort studies. Pharmacokinetic studies poorly described time-concentration profiles after application. The time to reach steady-state serum drug concentrations seems to be longer, clearance (expressed as liters per kilogram per hour) higher, and elimination half-life shorter in children than in adults. There are no fundamental differences in effect or profile of adverse effects compared with adults. Fentanyl TTS may be associated with less constipation compared with morphine use. Frequently, pediatric

patients need supplemental mechanical fixation of the fentanyl TTS by means of medical tape. Younger patients tend to have a higher fentanyl requirement when referenced to body weight. Both parents and medical professionals are satisfied with fentanyl TTS to a higher degree than with individual analgesic pretreatment regimens. Fentanyl TTS is a promising option for chronic pain control in children. An approximate conversion factor of 45 mg/day oral morphine to 12.5 microg/h fentanyl TTS is used for initial therapy dose estimation in children receiving long-term morphine therapy. This is conservatively low to avoid respiratory depression. Daily oral morphine equivalent dose should be at least 30 mg/d before fentanyl TTS therapy is started with 12.5 microg/h. Evidence for superiority of fentanyl TTS treatment above conventional opioid administration is both scarce and of low quality. PERSPECTIVE: The article gives a comprehensive overview of all pediatric data concerning the fentanyl TTS. Children may take longer to reach steady-state fentanyl serum concentrations than adults, and younger children may require higher doses referenced to body weight than older children or adults. Consequently, there is a need to provide sufficient medication in the phase of therapy initiation to prevent breakthrough pain. The 72-hour dosing schedule recommended by the manufacturers may not be applicable to children because of poor patch adhesiveness. The authors suggest to ensure firm fixation of the fentanyl TTS with additional medical tape if necessary and to change the fentanyl TTS after 48 hours. Transdermal fentanyl in children may exhibit fewer side effects when compared with other opioids, especially constipation. Randomized studies are urgently needed to definitively answer this question.

ABSTRACT RICHIESTA 2:

1. Zernikow B

Pediatric palliative care (PPC) is provided to children experiencing life-limiting diseases (LLD) or life-threatening diseases (LTD). Sixty to 90% of children with LLD/LTD undergoing PPC receive opioids at the end of life. Analgesia is often insufficient. Reasons include a lack of knowledge concerning opioid prescribing and adjustment of opioid dose to changing requirements. The choice of first-line opioid is based on scientific evidence, pain pathophysiology, and available administration modes. Doses are calculated on a bodyweight basis up to a maximum absolute starting dose. Morphine remains the gold standard starting opioid in PPC. Long-term opioid choice and dose administration is determined by the pathology, analgesic effectiveness, and adverse effect profile. Slow-release oral morphine remains the dominant formulation for long-term use in PPC with hydromorphone slow-release preparations being the first rotation opioid when morphine shows severe adverse effects. The recently introduced fentanyl transdermal therapeutic system with a drug-release rate of 12.5 microg/hour matches the lower dose requirements of pediatric cancer pain control. Its use may be associated with less constipation compared with morphine use. Though oral transmucosal fentanyl citrate has reduced bioavailability (25%), it inherits potential for breakthrough pain management. However, the gold standard breakthrough opioid remains immediate-release morphine. Buprenorphine is of special clinical interest as a result of its different administration routes, long duration of action, and metabolism largely independent of renal function. Antihyperalgesic effects, induced through antagonism at the kappa-receptor, may contribute to its effectiveness in neuropathic pain. Methadone also has a long elimination half-life (19 [SD 14] hours) and NMDA receptor activity although dose administration is complicated by highly variable morphine equianalgesic equivalence (1 : 2.5-20). Opioid rotation to methadone requires special protocols that take this into account. Strategies to minimize adverse effects of long-

term opioid treatment include dose reduction, symptomatic therapy, opioid rotation, and administration route change. Patient- or nurse-controlled analgesia devices are useful when pain is rapidly changing, or in terminal care where analgesic requirements may escalate. In this article, we present detailed pediatric pharmacokinetic and pharmacodynamic data for opioids, their indications and contraindications, as well as dose-administration regimens that include practical strategies for opioid switching and dose reduction. Additionally, we discuss the problem of hyperalgesia and the use of adjuvant drugs to support opioid therapy.

2. Mystakidou K

Oral transmucosal fentanyl citrate (OTFC; brand name Actiq, Cephalon, UT) is a new opioid formulation that incorporates fentanyl into a lozenge and allows drug delivery through the buccal mucosa. This kind of absorption avoids first-pass metabolism, yielding a bioavailability substantially greater than oral administration. OTFC has a rapid onset of action and a short duration of effect. These characteristics, which resemble the course of a typical breakthrough pain episode, resulted in making OTFC the first opioid analgesic formulation specifically developed and approved for control of breakthrough pain in cancer patients. Apart from that, OTFC has been used in a variety of clinical situations of noncancer pain. This review article presents the synthesis; clinical pharmacology; pharmacokinetic and pharmacodynamic properties, toxicity, and clinical efficacy of this novel agent.

3. Friedrichsdorf SJ

Breakthrough pain in children with cancer is an exacerbation of severe pain that occurs over a background of otherwise controlled pain. There are no randomized controlled trials in the management of breakthrough pain in children with cancer, and limited data and considerable experience indicate that breakthrough pain in this pediatric patient group is common, underassessed, and undertreated. An ideal therapeutic agent would be rapid in onset, have a relatively short duration, and would be easy to administer. A less effective pharmacologic strategy would be increasing a patient's dose of scheduled opioids, because this may increase the risk of oversedation. The most common and effective strategy seems to be multimodal analgesia that includes an immediate-release opioid (eg, morphine, fentanyl, hydromorphone, or diamorphine) administered intravenously by a patient-controlled analgesia pump, ensuring an onset of analgesic action within minutes. Intranasal fentanyl (or hydromorphone) may be an alternative, but no pediatric data have been published yet for commercially available fentanyl transmucosal application systems (ie, sublingual tablets/spray, buccal lozenge/tablet/film, and nasal spray), and these products cannot yet be recommended for use with children with cancer and breakthrough pain. The aim of this paper was to emphasize the dearth of available information on treatment of breakthrough pain in pediatric cancer patients, to describe the treatment protocols we currently recommend based on clinical experience, and to suggest future research on this very important and under-researched topic.

4. Zeppetella G

BACKGROUND: This review is an update of a previously published review in the Cochrane Database of Systematic Reviews (Issue 1, 2006). Breakthrough pain is a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger despite relative stable and adequately controlled background pain. Breakthrough pain usually related to background pain and is typically of rapid onset, severe in intensity and generally self limiting with a mean duration of 30 minutes. Breakthrough pain has traditionally been managed by the administration of supplemental oral analgesia (rescue medication) at a dose proportional to the total around-the-clock (ATC) opioid dose. OBJECTIVES: To determine the efficacy of opioid analgesics given by any route, used for the management of breakthrough pain in patients with cancer, and to identify and quantify, if data permitted, any adverse effects of this treatment.SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and trial registries in January 2005 for the original review, and again on 6 February 2013 for this update. SELECTION CRITERIA: We included randomised controlled trials (RCTs) of opioids used as rescue medication against active or placebo comparator in patients with cancer pain. Outcome measures sought were reduction in pain intensity measured by an appropriate scale, adverse effects, attrition, patient satisfaction and quality of life. We applied no language restrictions. DATA COLLECTION AND ANALYSIS: Two review authors independently selected and examined eligible studies. We retrieved full text if any uncertainty about eligibility remained. We screened non-English texts. We conducted quality assessment and data extraction using standardised data forms. We compared drug and placebo dose, titration, route and formulation and recorded details of all outcome measures (if available).MAIN RESULTS: The original review included four studies (393 participants), all concerned with the use of oral transmucosal fentanyl citrate (OTFC) in the management of breakthrough pain. Two studies examined the titration of OTFC, one study compared OTFC versus normal-release morphine and one study compared OTFC versus placebo. Fifteen studies (1699 participants) met the inclusion criteria for this update. All studies reported on the utility of seven different transmucosal fentanyl formulations, five of which were administered orally and two nasally. Eight studies compared the transmucosal fentanyl formulations versus placebo, four studies compared them with another opioid, one study was a comparison of different doses of the same formulation and two were randomised titration studies. Oral and nasal transmucosal fentanyl formulations were an effective treatment for breakthrough pain. When compared with placebo or oral morphine, participants gave lower pain intensity and higher pain relief scores for transmucosal fentanyl formulations at all time points. Global assessment scores also favoured transmucosal fentanyl preparations. One study compared intravenous with the transmucosal route and both were effective. CONCLUSIONS: Oral and nasal transmucosal fentanyl is an effective treatment in the management of breakthrough pain. The RCT literature for the management of breakthrough pain is relatively small. Given the importance of this subject, more trials, including head-to-head comparisons of the available transmucosal fentanyl formulations are required.

4.4. GABAPENTIN

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

Dolore neuropatico o misto in bambini in cure palliative, di età superiore a 2 anni.

RAZIONALE DELLA RICHIESTA:

Il dolore neuropatico è molto frequente nelle cure palliative del bambino e dell'adolescente; tuttavia, spesso il sintomo è poco riconosciuto e come tale sotto diagnosticato Un recente studio osservazionale evidenzia che il dolore neuropatico è particolarmente presente nel bambino in cure palliative, che presenta un quadro di comorbidità rilevante e che circa la metà dei casi non sono adeguatamente diagnosticati e trattati (Friedrichsdorf SJ, J Pain Res 2017).

Il trattamento del dolore neuropatico in età pediatrica non è stato adeguatamente codificato e si avvale dell'uso di analgesici minori, degli oppiodi e del gabapentin (Friedrichsdorf SJ, J Pain Res 2017). Il gabapentin non ha specifica indicazione di uso per il dolore neuropatico in età pediatrica, mentre nel paziente adulto il suo uso è consolidato alla luce dei risultati di studi clinici controllati e randomizzati.

SITUAZIONE ATTUALE APPROVATA:

Paziente> 6 anni: terapia aggiuntiva nel trattamento di attacchi epilettici parziali in presenza o in assenza di generalizzazione secondaria.

Paziente> 12 anni: monoterapia nel trattamento delle convulsioni parziali in presenza o in assenza di generalizzazione secondaria.

RICERCA BIBLIOGRAFICA:

Parole chiave: gabapentin, pain, children

Lavori evidenziati:

1. Friedrichsdorf SJ, Postier AC, Andrews GS, Hamre KE, Steele R, Siden H. Pain reporting and analgesia management in 270 children with a progressive neurologic, metabolic or chromosomally based condition with impairment of the central nervous system: cross-sectional, baseline results from an observational, longitudinal study. J Pain Res. 2017;10:1841-1852. Doi: 10.2147/JPR.S138153. eCollection 2017.

   Commento: lo studio osservazionale, pur non fornendo dati di efficacia, attesta il largo uso del gabapentin, in caso di dolore neuropatico in età pediatrica.

2. Brown SC, Johnston BC, Amaria K, Watkins J, Campbell F, Pehora C, et al. A randomized controlled trial of amitriptyline versus gabapentin for complex regional pain syndrome type I and neuropathic pain in children. Scandinavian Journal of Pain 2016; 13:156–63. doi.org/10.1016/j.sjpain.2016.05.039

   Commento: il RCT, condotto in età pediatrica, ha comparato l'efficacia del gabapentin a quella dell'amitriptilina. Lo studio non ha previsto un gruppo di controllo trattato con *placebo*. I risultati sono dichiarati dagli Autori come positivi per entrambi i trattamenti.

3. Cooper TE Antiepileptic drugs for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev. 2017 Aug 5;8:CD012536. Doi: 10.1002/14651858.CD012536.pub2. [Epub ahead of print].

   Commento: la recente revisione della Cochrane ha valutato l'efficacia dei farmaci antiepilettici (tra cui il gabapentin) per il dolore cronico in bambini e adolescenti. La revisione riporta due studi di cui uno è quello di Brown (vedi sopra), citato sull'uso del gabapentin. I revisori concludono che non ci sono evidenze che possono dimostrare con sicurezza l'efficacia o l'inefficacia del trattamento.

4. Kaul I, Amin A, Rosenberg M, Rosenberg L, Meyer WJ 3rd. Use of gabapentin and pregabalin for pruritus and neuropathic pain associated with major burn injury: A retrospective chart review. Burns. 2017 Aug 16. Pii: S0305-4179(17)30406-0. Doi: 10.1016/j.burns.2017.07.018. [Epub ahead of print]

   Commento: il recente lavoro retrospettivo ha valutato su una coorte di 136 pazienti in età pediatrica e adolescenziale l'efficacia del gabapentin sul dolore neuropatico e sul prurito dopo ustione. Il farmaco risulterebbe efficace in merito a scale del dolore individuali nel controllo sia del prurito che del dolore neuropatico (condizioni a volte difficilmente distinguibili l'una rispetto all'altra).

5. Butkovic D, Toljan S, Mihovilovic-Novak B. Experience with gabapentin for neuropathic pain in adolescents: report of five cases. Paediatr Anaesth. 2006;16(3):325-9. PMID16490100.

   Commento: il *case report* dimostra l'efficacia del gabapentin nel dolore neuropatico intrattabile.

6. Mc Cullock R. Pharmacological approaches to pain. 3: Adjuvants for neuropathic and bone pain. OXFORD TEXBOOK OF PALLIATIVE CARE FOR CHILDREN . Oxford University press 2nd edition 2012.

   Commento: lo studio indica l'utilizzo del gabapentin per la gestione del dolore neuropatico, anche post-chemioterapia, nel bambino oncologico.

RCT DISPONIBILI:

Brown SC et al, Scandinavian Journal of Pain 2016; 13:156–63

COMMENTO E CONCLUSIONI:

È disponibile un RCT condotto in età pediatrica che ha comparato l'efficacia del gabapentin a quella dell'amitriptilina. Lo studio non ha previsto un gruppo di controllo

trattato con *placebo*. I risultati sono dichiarati dagli Autori come positivi per entrambi i trattamenti (Brown SC et al).

Una revisione recente della Cochrane ha valutato l'efficacia dei farmaci antiepilettici per il dolore cronico in bambini ed adolescenti (Cooper TE). La revisione riporta due studi di cui uno è quello di Brown citato sull'uso del gabapentin. I revisori concludono che non ci sono evidenze che possano dimostrare con sicurezza l'efficacia o l'inefficacia del trattamento. Inoltre, un recente lavoro retrospettivo ha valutato su una coorte di 136 pazienti in età pediatrica e adolescenziale l'efficacia del gabapentin sul dolore neuropatico e su parestesie a tipo prurito dopo ustione (Kaul I et al). Il farmaco risulterebbe efficace in merito a scale del dolore individuali nel controllo sia del prurito che del dolore neuropatico (condizioni a volte difficilmente distinguibili l'una rispetto all'altra).

Diversi *case report* presenti in letteratura dimostrerebbero l'efficacia del gabapentin nel dolore neuropatico intrattabile (Butkovic D et al).

In conclusione, il dolore neuropatico è frequente nel bambino e nell'adolescente in cure palliative ed è difficile da riconoscere e soprattutto da trattare. Nell'adulto l'efficacia del gabapentin è dimostrata. Nel paziente pediatrico le evidenze a supporto dell'efficacia del gabapentin nel dolore neuropatico derivano da un singolo RCT, da alcuni studi di coorte e da singoli *case report*. Non sono riportati importanti effetti collaterali.

ABSTRACT:

1. Friedrichsdorf S

Little is known about the prevalence, characterization and treatment of pain in children with progressive neurologic, metabolic or chromosomal conditions with impairment of the central nervous system. The primary aims of this study were to explore the differences between parental and clinical pain reporting in children with life-limiting conditions at the time of enrollment into an observational, longitudinal study and to determine if differences in pain experiences were associated with patient- or treatment-related factors. Pain was common, under-recognized and undertreated among the 270 children who enrolled into the "Charting the Territory" study. Children identified by their parents as experiencing pain (n=149, 55%) were older, had more comorbidities such as dyspnea/feeding difficulties, were less mobile with lower functional skills and used analgesic medications more often, compared to pain-free children. Forty-one percent of children with parent-reported pain (21.8% of all patients) experienced pain most of the time. The majority of clinicians (60%) did not document pain assessment or analgesic treatment in the medical records of patients who were experiencing pain. Documentation of pain in the medical record was positively correlated with children receiving palliative care services and being prescribed analgesics, such as acetaminophen, nonsteroidal anti-inflammatory drugs and opioids, as well as the adjuvant analgesics gabapentin and amitriptyline.

2. Brown SC

BACKGROUND: Treatment of neuropathic pain in children is challenging, and requires a multimodal approach of pharmacologic, physical, and psychological therapies; however there is little evidence to guide practice. Amitriptyline and gabapentin are first-line drugs for treating neuropathic pain in adults, yet no studies have examined their efficacy, or compared them directly, to determine which might be better for pain relief and sleep disturbance in children. METHODS: After informed consent was obtained, 34 patients aged 7–18 years diagnosed with complex regional pain syndrome type I (CRPS I) or a neuropathic pain condition were randomly allocated to receive either amitriptyline or gabapentin. Patients were followed for 6 weeks and assessed for pain intensity, sleep quality and adverse events. We blinded study personnel, including health-care providers, participants, parents, the research coordinator and the data analyst. Patients then completed quantitative sensory testing (QST) and a psychosocial pain assessment with the team psychologist, within 1–3 days of the start of the trial. RESULTS: At the end of the 6-week trial, patients on both drugs had important reductions in pain, having surpassed the minimally important difference (MID) of 1. The difference between the groups however was not statistically significant. For the secondary outcomes, we found no statistically significant difference between the two drugs in sleep score or adverse events suggesting that both drugs improve sleep score to a similar degree and are equally safe. CONCLUSIONS: Amitriptyline and gabapentin significantly decreased pain intensity scores and improved sleep. There were no significant differences between the two drugs in their effects on pain reduction or sleep disability.IMPLICATIONS: Although larger, multi-centred trials are needed to confirm our findings, including long-term follow-up, both drugs appear to be safe and effective in treating paediatric patients in the first-line treatment of CRPS I and neuropathic pain over 6-weeks.

3. Cooper TE

Pain is a common feature of childhood and adolescence around the world, and for many young people, that pain is chronic. The World Health Organization (WHO) guidelines for pharmacological treatments for children's persisting pain acknowledge that pain in children is a major public health concern of high significance in most parts of the world. While in the past, pain was largely dismissed and was frequently left untreated, views on children's pain have changed over time, and relief of pain is now seen as importantWe designed a suite of seven reviews on chronic non-cancer pain and cancer pain (looking at antidepressants, antiepileptic drugs, non-steroidal anti-inflammatory drugs, opioids, and paracetamol) in order to review the evidence for children's pain utilising pharmacological interventions in children and adolescents.As the leading cause of morbidity in the world today, chronic disease (and its associated pain) is a major health concern. Chronic pain (that is pain lasting three months or longer) can occur in the paediatric population in a variety of pathophysiological classifications (nociceptive, neuropathic, or idiopathic) relating to genetic conditions, nerve damage pain, chronic musculoskeletal pain, and chronic abdominal pain, and for other unknown reasons. Antiepileptic (anticonvulsant) drugs, which were originally developed to treat convulsions in people with epilepsy, have in recent years been used to provide pain relief in adults for many chronic painful conditions and are now recommended for the treatment of chronic pain in the WHO list of essential medicines. Known side effects of antiepileptic drugs range from sweating, headache, elevated temperature, nausea, and abdominal pain to more serious effects including mental or motor function impairment.

OBJECTIVES: To assess the analgesic efficacy and adverse events of antiepileptic drugs used to treat chronic non-cancer pain in children and adolescents aged between birth and 17 years, in any setting. SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online, MEDLINE via Ovid, and Embase via Ovid from inception to 6 September 2016. We also searched the reference lists of retrieved studies and reviews as well as online clinical trial registries. SELECTION CRITERIA: Randomised controlled trials, with or without blinding, by any route, treating chronic non-cancer pain in children and adolescents, comparing any antiepileptic drug with placebo or an active comparator. DATA COLLECTION AND ANALYSIS: Two review authors independently assessed studies for eligibility. We planned to use dichotomous data to calculate risk ratio and number needed to treat for one additional event, using standard methods if data were available. We assessed the evidence using GRADE and created two 'Summary of findings' tables. MAIN RESULTS: We included two studies with a total of 141 participants (aged 7 to 18 years) with chronic neuropathic pain, complex regional pain syndrome type 1 (CRPS-I), or fibromyalgia. One study investigated pregabalin versus placebo in participants with fibromyalgia (107 participants), and the other study investigated gabapentin versus amitriptyline in participants with CRPS-I or neuropathic pain (34 participants). We were unable to perform any quantitative analysis. Risk of bias for the two included studies varied, due to issues with randomisation (low to unclear risk), blinding of outcome assessors (low to unclear risk), reporting bias (low to unclear risk), the size of the study populations (high risk), and industry funding in the 'other' domain (low to unclear risk). We judged the remaining domains of sequence generation, blinding of participants and personnel, and attrition as low risk of bias. Primary outcomesOne study (gabapentin 900 mg/day versus amitriptyline 10 mg/day, 34 participants, for 6 weeks) did not report our primary outcomes (very low-quality evidence).The second study (pregabalin 75 to 450 mg/day versus placebo 75 to 450 mg/day, 107 participants, for 15 weeks) reported no significant change in pain scores for pain relief of 30% or greater between pregabalin 18/54 (33.3%), and placebo 16/51 (31.4%), P = 0.83 (very low-quality evidence). This study also reported Patient Global Impression of Change, with the percentage of participants feeling "much or very much improved" with pregabalin 53.1%, and placebo 29.5% (very low-quality evidence).We downgraded the evidence by three levels to very low for one of two reasons: due to the fact that there was no evidence to support or refute the use of the intervention, or that there were too few data and the number of events was too small to be meaningful. Secondary outcomesIn one small study, adverse events were uncommon: gabapentin 2 participants (2 adverse events); amitriptyline 1 participant (1 adverse event) (6-week trial). The second study reported a higher number of adverse events: pregabalin 38 participants (167 adverse events); placebo 34 participants (132 adverse events) (15-week trial) (very low-quality evidence). Withdrawals due to adverse events were infrequent in both studies: pregabalin (4 participants), placebo (4 participants), gabapentin (2 participants), and amitriptyline (1 participant) (very low-quality evidence).Serious adverse events were reported in both studies. One study reported only one serious adverse event (cholelithiasis and major depression resulting in hospitalisation in the pregabalin group) and the other study reported no serious adverse events (very low-quality evidence). There were few or no data for our remaining secondary outcomes (very low-quality evidence).We downgraded the evidence by three levels to very low due to too few data and the fact that the number of events was too small to be meaningful.AUTHORS' CONCLUSIONS: This review identified only two small studies, with insufficient data for analysis. As we could undertake no meta-analysis, we were unable to comment about efficacy or harm from the use of antiepileptic drugs to treat chronic non-cancer pain in children and adolescents. Similarly, we could not comment on our remaining secondary outcomes: Carer Global Impression of Change; requirement for rescue analgesia; sleep duration and quality;

acceptability of treatment; physical functioning; and quality of life. We know from adult randomised controlled trials that some antiepileptics, such as gabapentin and pregabalin, can be effective in certain chronic pain conditions.We found no evidence to support or refute the use of antiepileptic drugs to treat chronic non-cancer pain in children and adolescents.

4. Kaul I

INTRODUCTION: Pruritis after burn is one of the most common chronic complaints in burn survivors. Pruritus is often indistinguishable from neuropathic pain. There is a paucity of studies reporting the use of gabapentin and pregabalin to treat both pruritus and neuropathic pain. The purpose of this current study is to explore and document the effect of gabapentin and pregabalin in children and adolescent burn survivors. METHODS: A retrospective review of charts and pharmacy records of gabapentin and pregabalin dispensed to control pruritus and/or pain was conducted for burn survivors up to 20 years of age. Data collected included medication doses, age and weight of patients, presence of neuropathic pain and pruritus, reported response to medication, and side effects of these medications. 136 individuals who received gabapentin, pregabalin, or both medications are included in the study. 112 received only gabapentin, none received only pregabalin, and 24 received both. All results are documented in mean±standard deviation (s.d.) dose/kg/day. 104 individuals experienced pruritus exclusively, two experienced neuropathic pain exclusively, and 30 experienced both. Use of medications was considered effective if the individuals reported pruritus or pain relief from the medication. The medication was considered safe if the individuals did not experience adverse side effects warranting discontinuation of the drugs. Medications were continued with dose adjustments if an individual reported minor side effects such as sedation or hyperactivity. RESULTS: The average effective dose mg/kg/day for gabapentin and pregabalin was calculated for each of the three age groups (≤5years, 6-12 years, and >12years). The average effective dose of gabapentin was 23.9±10.3mg/kg/day for children ≤5years, 27.0±15.3mg/kg/day for children 6-12 years, and 34.1±15.7mg/kg/day for children >12years. The average effective dose of pregabalin was 6.5±3.5mg/kg/day for children 6-12 years and 4.7±1.6mg/kg/day for children >12years. One 5-year-old child received 3.7mg/kg/day of pregabalin. Note that for all patients in this study, pregabalin was added after an inadequate response to gabapentin. For individuals receiving both gabapentin and pregabalin, the maximum gabapentin failure dose for pruritus was 32.8±18.0mg/kg/day and for both pain and pruritus was 28.1±18.3mg/kg/day. For individuals treated with only gabapentin, 91.4% had an adequate response for pruritus, 100% for neuropathic pain, and 43.3% for both pruritus and pain. 100% of individuals treated with both gabapentin and pregabalin had an adequate response for pruritus and 88.2% had an adequate response for both pruritus and pain. Gabapentin was associated with hyperactivity in two individuals, and sedation in one individual. One individual reported nausea, vomiting, and headaches when taking both medications; this resolved when gabapentin was discontinued. One individual reported sedation while taking both medications. CONCLUSION: Gabapentin and pregabalin are effective in relieving pruritus and neuropathic pain in most burn survivors. In some instances, these medications can be given together. Few individuals reported side effects.

5. Butkovic D

SUMMARY: Gabapentin is an antiepileptic drug indicated for the treatment of partial seizures in children. Many studies have proved its analgesic action in the treatment of neuropathic pain in adults and we have noticed an analgesic action of gabapentinin neuropathic pain in children. Five patients treated in the Children's Hospital Pain Control Service for intractable neuropathic pain were included in gabapentin treatment. Four were cancer patients and one suffered from neuropathic pain in the neck (C3). The visual analog scale (VAS) scores of pain were compared before and during treatment with gabapentin. We noticed a rapid improvement, in 1 week, of our patients' VAS scores (from 9 or 10 to 4 or 3) with minimal adverse effects. In the follow-up period of 6 months we gradually reduced the dose of gabapentin. Our findings are that gabapentin should be included earlier in the treatment of neuropathic pain in adolescents, because it rapidly improves analgesia and has minimal side effects.

4.5. KETAMINA

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Utilizzo in pazienti in CPP per la gestione di dolore procedurale o neuropatico/misto non rispondente ad altra terapia, da solo o in associazione/sostituzione ad analgesici oppioidi.
2. Somministrazione per via endonasale.

RAZIONALE DELLA RICHIESTA:

1. Nell'ambito delle CPP, la ketamina rappresenta, in alcune situazioni, l'unica alternativa terapeutica possibile per la gestione del dolore procedurale (per es posizionamento di catetere vescicale, sondino naso-gastrico, medicazione) e per la gestione, in associazione con altri farmaci, del dolore neuropatico o misto.

Le caratteristiche farmacocinetiche e farmacodinamiche della ketamina EV, ne permettono infatti l'utilizzo in sicurezza per la gestione del dolore da procedura in bambini in CPP ad alta complessità, con deficit funzionali multipli e in politerapia: situazioni che per il rischio di effetti collaterali importanti, limitano l'utilizzo di altri farmaci analgesici e sedativi.

La ketamina inoltre rappresenta il farmaco di scelta nel dolore neuropatico o misto (in associazione con altri farmaci).

2. La somministrazione endonasale, inoltre, permette di offrire queste stesse possibilità di analgesia anche in bambini in CPP che non abbiano accessi vascolari.

SITUAZIONE ATTUALE APPROVATA:

Utilizzo per somministrazione EV, IM, e per infusione continua.

Utilizzo per induzione e mantenimento dell'anestesia generale dall'età neonatale e in premedicazione sopra 1 mese di vita come unico anestetico per manovre chirurgiche e diagnostiche o come supplemento ad altri anestetici.

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 1:

Parole chiave: ketamine, pain, children

Lavori evidenziati:

1. Bredlau AL, McDermott MP, Adams HR, Dworkin RH, Venuto C, Fisher SG, Dolan JG, Korones DN. Oral ketamine for children with chronic pain: a pilot phase 1 study. J Pediatr. 2013 Jul;163(1):194-200.e1. doi: 10.1016/j.jpeds.2012.12.077.

Commento: il *clinical trial* coinvolge bambini, anche se in numero non elevato, con dolore cronico sia in CPP, sia in altri ambiti (es. chirurgico, reumatologico); dimostra l'efficacia e la sicurezza della ketamina orale nel controllo del dolore cronico.

2. Bredlau AL, Thakur R, Korones DN, Dworkin RH. Ketamine for pain in adults and children with cancer: a systematic review and synthesis of the literature. Pain Med. 2013 Oct;14(10):1505-17. doi: 10.1111/pme.12182. Epub 2013 Aug 5. Review.

   Commento: lo studio consiglia la ketamina come valida opzione nel trattamento del dolore refrattario in patologie oncologiche sia negli adulti che nei bambini, sommnistrata per via EV/SC/OS.
3. Tawfic QA A review of the use of ketamine in pain management. J Opioid Manag. 2013 Sep-Oct;9(5):379-88. doi: 10.5055/jom.2013.0180.

   Commento: lo studio riporta l'uso della ketamina nel dolore neuropatico severo.

4. Grunwell JR, Travers C, Stormorken AG, Scherrer PD, Chumpitazi CE, Stockwell JA, Roback MG, Cravero J, Kamat PP. Pediatric Procedural Sedation Using the Combination of Ketamine and Propofol Outside of the Emergency Department: A Report From the Pediatric Sedation Research Consortium. Pediatr Crit Care Med. 2017 Aug;18(8):e356-e363. doi: 10.1097/PCC.0000000000001246.

   Commento: lo studio è riferito a una ampia casistica (>7000 pazienti pediatrici) sottoposti a sedazione per dolore procedurale con profol e ketamina.

RCT DISPONIBILI:

Bredlau 2013 J Pediatr, 2013 Jul;163(1):194-200

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 2:

Parole chiave: ketamine, pain, intranasal, children

Lavori evidenziati:

1. Poonai N, Canton K, Ali S, Hendrikx S, Shah A, Miller M, Joubert G, Rieder M, Hartling L. Intranasal ketamine for procedural sedation and analgesia in children: A systematic review. PLoS One. 2017 Mar 20;12(3):e0173253. doi:10.1371/journal.pone.0173253. eCollection 2017

   Commento: la revisione valuta 7 studi dedicati all'età pediatrica sull'utilizzo della ketamina intranasale nella sedazione procedurale e nella analgesia con evidenza di buona tolleranza e sicurezza.

2. Mehran M, Tavassoli-Hojjati S, Ameli N, Zeinabadi MS. Effect of Intranasal Sedation Using Ketamine and Midazolam on Behavior of 3-6 Year-Old Uncooperative Children in Dental Office: A Clinical Trial. J Dent (Tehran). 2017 Jan;14(1):1-6. PMID 28828011.

   Commento: lo studio compara la ketamina intranasale vs il midazolam durante procedure odontoiatriche in età pediatrica, dimostrando come entrambi siano efficaci.

3. Scheier E, Siman A, Balla U. Intranasal ketamine proved feasible for pain control in paediatric care and parental support was high. Acta Paediatr. 2017 Jun 24. doi: 10.1111/apa.13965. [Epub ahead of print]

   Commento: lo studio dimostra che la ketaminina intranasale riduce il dolore e l'ansia da venopuntura o incannulazione di vena periferica nei bambini.

4. Carr DB, Goudas LC, Denman WT, Brookoo D, Staats PS, Brennen L, Green G, Albin R, Hamilton D, Rogers MC, Firestone L, Lavin PT, Mermelstein F.Safety and efficacy of intranasal ketamine for the treatment of breakthrough pain in patients with chronic pain: a randomized, double-blind, placebo-controlled, crossover study. Pain. 2004 Mar;108(1-2):17-27. PMID15288418.

   Commento: il RCT, condotto sugli adulti, dimostra la sicurezza e l'efficacia della ketamina intranasale per il trattamento del *breaìkthrough cancer pain*.

RCT DISPONIBILI:

Nessuno

COMMENTO E CONCLUSIONI:

Sono stati evidenziati studio di buona qualità che dimostrano l'utilità, l'efficacia e la sicurezza dell'uso intranasale per il trattamento del dolore neuropatico/cronico, anche da cancro.

ABSTRACT RICHIESTA 1:

1. Bredlau 2013 J Pediatr

OBJECTIVE: To assess whether oral ketamine is safe at higher dosages for sedating children and whether it may be an option for the control of chronic pain in children. STUDY DESIGN: A prospective study was performed on 12 children with chronic pain to identify the maximum tolerated dosage of oral ketamine. Participants were given 14 days of oral ketamine, 3 times daily, at dosages ranging from 0.25-1.5 mg/kg/dose. Participants were assessed for toxicity and for pain severity at baseline and on day 14 of treatment. RESULTS: Two participants, both treated at 1.5 mg/kg/dose, experienced dose-limiting toxicities (sedation and anorexia). One participant, treated at 1 mg/kg/dose, opted to stop ketamine treatment due to new pain on treatment. Nine participants completed their course of ketamine treatment. Of these 12 children, 5 experienced improvement in their pain scores, 2 with complete resolution of pain, lasting >4 weeks off ketamine treatment. CONCLUSIONS: Oral ketamine at dosages of 0.25-1 mg/kg/dose appears to be safe when given for 14 days to children with chronic pain.

2. Bredlau 2013 Pain Med

OBJECTIVE: Chronic cancer pain is often refractory and difficult to treat. Ketamine is a medication with evidence of efficacy in the treatment of chronic pain. DESIGN: This article presents a synthesis of the data on ketamine for refractory cancer pain in adults and children. RESULTS: There are five randomized, double-blind, controlled trials of ketamine use in cancer pain that demonstrate improvement in pain for some patients. There are six prospective, uncontrolled trials in cancer pain that also demonstrate improvement in pain scores for some patients. There are no randomized, controlled trials in children with cancer pain, although there are a few studies reflecting improved pain control with ketamine for children with cancer pain. Adverse events for adults on ketamine are most commonly somnolence, feelings of insobriety, nausea/vomiting, hallucinations, depersonalization/derealization, and drowsiness. However, when ketamine is combined with benzodiazepines, feelings of insobriety, hallucinations, and depersonalization/derealization are not reported. Children on ketamine have had few reported adverse effects, which include sedation, anorexia, urinary retention, and myoclonic movements. Recommended ketamine infusion dosages are from 0.05 to 0.5 mg/kg/h (intravenous or subcutaneous). Recommended oral dosages of ketamine are 0.2-0.5 mg/kg/dose two to three times daily with a maximum of 50 mg/dose three times daily. CONCLUSIONS: Despite limitations in the breadth and depth of data available, there is evidence that ketamine may be a viable option for treatment-refractory cancer pain.

3. Tawfic QA

Ketamine is a noncompetitive antagonist of N-methyl-d-aspartate receptor. It has been widely used in anesthesia and pain management. Ketamine has been administered via the intravenous, intramuscular, subcutaneous, oral, rectal, topical, intranasal, sublingual, epidural, and caudal routes. Ketamine improves postoperative and posttrauma pain scores and reduces opioid consumption. It has special indication for patients with opioid tolerance, acute hyperalgesia, and neuropathic pain. It also has a role in the management of chronic pain including both cancer and noncancer pain. Recreational use of ketamine is increasing as well through different routes of administration like inhalation, smoking, or intravenous injection. Long-time exposure to ketamine, especially in the abusers, may lead to serious side effects. This review is trying to define the role of ketamine in pain management.

4. Grunwell JR

OBJECTIVES: Outcomes associated with a sedative regimen comprised ketamine + propofol for pediatric proceduralsedation outside of both the pediatric emergency department and operating room are underreported. We used the Pediatric Sedation Research Consortium database to describe a multicenter experience with ketamine + propofol by pediatric sedation providers. DESIGN: Prospective observational study of children receiving IV ketamine + propofol for procedural sedation outside of the operating room and emergency department using data abstracted from the Pediatric Sedation Research Consortium during 2007-2015. SETTING: Procedural sedation services from academic, community, free-standing children's hospitals, and pediatric wards within general hospitals. PATIENTS: Children from birth to less than or equal to 21

years old. INTERVENTIONS: None. MEASUREMENTS AND MAIN RESULTS: A total of 7,313 pediatric procedural sedations were performed using IV ketamine + propofol as the primary sedative regimen. Median age was 84 months (range, < 1 mo to ≤ 21 yr; interquartile range, 36-144); 80.6% were American Society of Anesthesiologists-Physical Status less than III. The majority of sedation was performed in dedicated sedation or radiology units (76.1%). Procedures were successfully completed in 99.8% of patients. Anticholinergics (glycopyrrolate and atropine) or benzodiazepines (midazolam and lorazepam) were used in 14.2% and 41.3%, respectively. The overall adverse event and serious adverse event rates were 9.79% (95% CI, 9.12-10.49%) and 3.47% (95% CI, 3.07-3.92%), respectively. No deaths occurred. Risk factors associated with an increase in odds of adverse event included ASA status greater than or equal to III, dental suite, cardiac catheterization laboratory or radiology/sedation suite location, a primary diagnosis of having a gastrointestinal illness, and the coadministration of an anticholinergic. CONCLUSIONS: Using Pediatric Sedation Research Consortium data, we describe the diverse use of IV ketamine + propofol for procedural sedation in the largest reported cohort of children to date. Data from this study may be used to design sufficiently powered prospective randomized, double-blind studies comparing outcomes of sedation between commonly administered sedative and analgesic medication regimens.

ABSTRACT RICHIESTA 2:

1. Poonai N

BACKGROUND: Ketamine is commonly used for procedural sedation and analgesia (PSA) in children. Evidence suggests it can be administered intranasally (IN). We sought to review the evidence for IN ketamine for PSA in children. METHODS: We performed a systematic review of randomized trials of IN ketamine in PSA that reported any sedation-related outcome in children 0 to 19 years. Trials were identified through electronic searches of MEDLINE (1946–2016), EMBASE (1947–2016), Google Scholar (2016), CINAHL (1981–2016), The Cochrane Library (2016), Web of Science (2016), Scopus (2016), clinical trial registries, and conference proceedings (2000–2016) without language restrictions. The methodological qualities of studies and the overall quality of evidence were evaluated using the *Cochrane Collaboration's Risk of Bias* tool, and the *Grading of Recom- mendations Assessment*, *Development*, *and Evaluation (GRADE)* system, respectively. RESULTS: The review included 7 studies (n = 264) of children ranging from 0 to 14 years. Heterogeneity in study design precluded meta-analysis. Most studies were associated with a *low* or *unclear* risk of bias and outcome-specific ratings for quality of evidence were *low* or *very low*. In four of seven studies, IN ketamine provided superior sedation to comparators and resulted in adequate sedation for 148/175 (85%) of participants. Vomiting was the most common adverse effect; reported by 9/91 (10%) of participants. CONCLUSIONS: IN ketamine administration is well tolerated and without serious adverse effects. Although most participants were deemed adequately sedated with IN ketamine, effectiveness of sedation with respect to superiority over comparators was inconsistent, precluding a recommendation for PSA in children.

2. Mehran M

OBJECTIVES: The aim of the present study was to compare the effects of intranasal ketamine and midazolam on behavior of 3-6 year-old children during dental treatments. MATERIALS AND METHODS: In this randomized cross-over clinical trial, 17 uncooperative children requiring at least two dental treatments were selected and randomly received ketamine (0.5mg/kg) or midazolam (0.2mg/kg) prior to treatment. The other medication was used in the next visit. The children's behavioral pattern was determined according to the Houpt's scale regarding sleep, movement, crying and overall behavior. Physiological parameters were also measured at different time intervals. The data were subjected to Wilcoxon Signed Rank test and two-way repeated measures ANOVA. RESULTS: The frequency of crying decreased significantly following ketamine administration compared to midazolam (P=0.002); movement of children decreased with fewer incidence of treatment interruption (P=0.001) while their sleepiness increased (P=0.003). Despite higher success of sedation with ketamine compared to midazolam, no significant differences were found between the two regarding patients' overall behavior (P>0.05). The patients had higher heart rate and blood pressure with ketamine; however, no significant difference was found regarding respiratory rate and oxygen saturation (P>0.05). CONCLUSIONS: Ketamine (0.5mg/kg) led to fewer movements, less crying and more sleepiness compared to midazolam (0.2mg/kg). No significant differences were found between the two drugs regarding children's overall behavior and sedation efficiency. Both drugs demonstrated positive efficacy for sedation of children during dental treatments.

3. Scheier E

Our results add to the existing literature by showing that a 1 mg/kg dose of intranasal ketamine was safe and appeared to be effective in reducing pain and anxiety in children age 1-12 years undergoing intravenous placement or venipuncture.

4. Carr DB

Few placebo-controlled trials have investigated the treatment of breakthrough pain (BTP) in patients with chronic pain.

We evaluated the efficacy and safety of intranasal ketamine for BTP in a randomized, double-blind, placebo-controlled, crossover trial. Twenty patients with chronic pain and at least two spontaneous BTP episodes daily self-administered up to five doses of intranasal ketamine or placebo at the onset of a spontaneous BTP episode (pain intensity > or =5 on a 0-10 scale).

Two BTP episodes at least 48 h apart were treated with either ketamine or placebo. Patients reported significantly lower BTP intensity following intranasal ketamine than after placebo (P < 0.0001) with pain relief within 10 min of dosing and lasting for up to 60 min. No patient in the ketamine group required his/her usual rescue medication to treat the BTP episode, while seven out of 20 (35%) patients in placebo group did (P = 0.0135). Intranasal ketaminewas well tolerated with no serious adverse events. After ketamine administration, four patients reported a transient change in taste, one

patient reported rhinorrhea, one patient reported nasal passage irritation, and two patients experienced transient elevation in blood pressure. A side effect questionnaire administered 60 min and 24 h after drug or placebo administration elicited no reports of auditory or visual hallucinations. These data suggest that intranasal administration of ketamine provides rapid, safe and effective relief for BTP.

4.6. KETOROLAC

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

Utilizzo per os e sublinguale, in età 4-15 anni e per un periodo massimo di 5 gg, in pazienti senza accesso vascolare, per gestione di dolore acuto nocicettivo episodico moderato/severo, quale integrazione di altra analgesia se non efficace, in corso di patologia eleggibile alle CPP sia in fase di terminalità.

RAZIONALE DELLA RICHIESTA:

I bambini in CPP presentano situazioni complesse da un punto di vista sia clinico-assistenziale che etico-decisionale.

In alcune situazioni, per motivi relativi a diversi fattori, quali tempo a disposizione, età, tipologia di patologia, situazione clinica, diventa complesso, talvolta impossibile e/o non "giustificato", sottoporre il paziente alla procedura di posizionamento di un accesso vascolare. Il controllo dei sintomi pertanto deve essere assicurato per vie diverse da quella EV, vie che peraltro devono assicurare comunque efficacia e velocità d'azione.

In caso di dolore nocicettivo, il ketorolac per via orale permette di ottenere un efficace ed immediato controllo del dolore nei bambini in CPP che non hanno/possono avere un accesso vascolare per la somministrazione EV.

SITUAZIONE ATTUALE APPROVATA:

Utilizzo per il trattamento del dolore acuto per OS e IM a partire da 16 anni di vita, EV a partire da 6 mesi.

RICERCA BIBLIOGRAFICA:

Parole chiave: ketorolac, sublingual, oral

Lavori evidenziati:

1. Dancel R, Liles EA, Fiore D Acute Pain Management in Hospitalized Chidren.Rev Recent Clin Trials. 2017 Aug 16.doi:10.2174/1574887112666170816151232.

   Commento: lo studio suggerisce l'uso del ketorolac sublinguale nella gestione del dolore nel bambino.

2. Plapler PG, Scheinberg MA, Ecclissato Cda C, Bocchi de Oliveira MF, Amazonas RB. Double-blind, randomized, double-dummy clinical trial comparing the efficacy of ketorolac trometamol and naproxen for acute low back pain. Drug Des Devel Ther. 2016 Jun 17;10:1987-93. doi: 10.2147/DDDT.S97756. eCollection 2016.

Commento: il *trial* clinico confronta l'uso di ketorolac sublinguale con quello del naprossene per *os* nel dolore dorsale acuto, dimostrando che il ketorolac è efficace e controlla più rapidamente il dolore.

3. Neri E, Maestro A, Minen F, Montico M, Ronfani L, Zanon D, et al. Sublingual ketorolac versus sublingual tramadol for moderate to severe post-traumatic bone pain in children: a double-blind, randomised, controlled trial. Arch Dis Child 2013; 98: 721–4. doi: 10.1136/archdischild-2012-303527.

   Commento: il *trial* clinico, che confronta ketorolac sublinguale vs tramadolo sublinguale nel controllo del dolore acuto da frattura ossea in età pediatrica (età 4-17anni), dimostra l'efficacia di entrambi.

4. Di Massa A, Scardigli M, Bruni L, Valentino L. Ketorolac for paediatric postoperative pain. A review. Minerva Anestesiol. 2000 Oct;66(10):749-56. PMID 11194983.

   Commento: la *review* segnala il ketorolac come farmaco particolarmente efficace nella gestione del dolore post-operatorio in età pediatrica.

5. Marzuillo P, Calligaris L, Amoroso S, Barbi E. Narrative review shows that the short-term use of ketorolac is safe and effective in the management of moderate-to-severe pain in children. Acta Paediatr 2017 Dec 16. doi: 10.1111/apa.14189.

   Commento: la *review* evidenzia la sicurezza d'uso del ketorolac in età pediatrica.

RCT DISPONIBILI:

Neri E, Maestro A, Minen F, Montico M, Ronfani L, Zanon D, et al. Sublingual ketorolac versus sublingual tramadol for moderate to severe post-traumatic bone pain in children: a double-blind, randomised, controlled trial. Arch Dis Child 2013; 98: 721–4. doi: 10.1136/archdischild-2012-303527.

NOTE:

Si suggerisce di assicurare idratazione adeguata e di associare un inibitore di pompa, vista la situazione stressante e la probabile politerapia del paziente.

(Yang M, He M, Zhao M, et al. Proton pump inhibitors for preventing non-steroidal anti-inflammatory drug induced gastrointestinal toxicity: a systematic review. Curr Med Res Opin. 2017 Jun;33(6):973-980. doi: 10.1080/03007995.2017.1281110. Epub 2017 Jan 25.)

COMMENTO E CONCLUSIONI:

La letteratura esistente è molto carente per quanto riguarda il ketorolac per via orale e/o sublinguale sia per l'adulto che per il bambino. Vi sono, invece, molti lavori che valutano

efficacia e sicurezza nell'uso endovenoso anche in lattanti < 6 mesi, senza segnalazione di particolari eventi avversi.

A conclusione, consapevoli della scarsità di lavori pubblicati, si chiede ugualmente l'inserimento nell'elenco di cui la Legge 648/96, data l'utilità e la frequenza d'uso, in casi selezionati, di questo farmaco mediante la via di somministrazione per *os*/sublinguale.

ABSTRACT:

1. Dancel R

BACKGROUND: Acute pain in hospitalized pediatric patients is prevalent. Recent shifts in the paradigm of pediatric acute pain management focus less on reliance on opioids, due to their adverse side effects and risk of dependence, and more on multimodal pain management. OBJECTIVE: We sought to review the most recent studies on acute pain management in hospitalized pediatric patients. METHODS: We searched the Cochrane Database and PubMed for articles published in the past five years regarding the treatment of acute pain in pediatric patients focusing on large randomized or quasi-randomized control trials, cohort trials, and meta-analyses. RESULTS: We categorized results into non-pharmacological, localized, non-opiate pharmacological, and opiate based therapies. Recent studies show that environmental and non-pharmacological methods of pain management are efficacious in infants. School aged children benefit from active distraction more than passive distraction. Needleless methods of introducing lidocaine locally alleviate the pain associated with many procedures to which hospitalized children are exposed. The shift towards use of nonopiate pharmacology focuses on novel means of utilizing older medications, such as intravenous parecoxib, inhaled methoxyflurane, and sublingual ketorolac or tramadol and the avoidance of codeine. CONCLUSION: Acute pediatric pain management has changed to emphasize multimodal and multidisciplinary therapy. In all children, non-pharmacological therapies should be employed routinely. Given the myriad tools available, pediatric acute pain services have developed in order to integrate more advanced treatments such as nerve blocks and infusions of centrally acting pain modulators.

2. Plapler PG

BACKGROUND: Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most common type of medication used in the treatment of acute pain. Ketorolac trometamol (KT) is a nonnarcotic, peripherally acting nonsteroidal anti-inflammatory drug with analgesic effects comparable to certain opioids. OBJECTIVE: The aim of this study was to compare the efficacy of KT and naproxen (NA) in the treatment of acute low back pain (LBP) of moderate-to-severe intensity. PATIENTS AND METHODS: In this 10-day, Phase III, randomized, double-blind, double-dummy, noninferiority trial, participants with acute LBP of moderate-to-severe intensity as determined through a visual analog scale (VAS) were randomly assigned in a 1:1 ratio to receive sublingual KT 10 mg three times daily or oral NA 250 mg three times daily. From the second to the fifth day of treatment, if patient had VAS >40 mm, increased dosage to four times per day was allowed. The primary end point was the reduction in LBP as measured by VAS. We also performed a post hoc superiority analysis. RESULTS: KT was not inferior to NA for the reduction in LBP over 5 days of use

as measured by VAS scores (*P*=0.608 for equality of variance; *P*=0.321 for equality of means) and by the Roland–Morris Disability Questionnaire (*P*=0.180 for equality of variance test; *P*=0.446 for equality of means) using 95% confidence intervals. The percentage of participants with improved pain relief 60 minutes after receiving the first dose was higher in the KT group (24.2%) than in the NA group (6.5%; *P*=0.049). The most common adverse effects were heartburn, nausea, and vomiting. CONCLUSION: KT is not inferior in efficacy and delivers faster pain relief than NA.

3. Neri E

OBJECTIVES: To assess the effectiveness of sublingual ketorolac versus sublingual tramadol in reducing the pain associated with fracture or dislocation of extremities in children. PATIENTS AND METHODS: A double-blind, randomised, controlled, non-inferiority trial was conducted in the paediatric emergency department of a research institute. One hundred and thirty-one children aged 4-17 years with suspected bone fracture or dislocation were enrolled. Eligible children were randomised to ketorolac (0.5 mg/kg) and placebo, or to tramadol (2 mg/kg) and placebo by sublingual administration, using a double-dummy technique. Pain was assessed by the patients every 20 min, for a maximum period of 2 h, using the McGrath scale for patients up to 6 years of age, and the Visual Analogue Scale for those older than 6 years of age. RESULTS: The mean pain scores fell significantly from eight to four and five in the ketorolac and tramadol groups, respectively, by 100 min (Wilcoxon sign rank test, p<0.001). The mean pain scores for ketorolac were lower than those for tramadol, but these differences were not significant at any time point (Mann-Whitney U Test, p values: 0-20 min: 0.167; 20-40 min: 0.314; 40-60 min: 0.223; 60-80 min: 0.348; 80-100 min: 0.166; 100-120 min: 0.08). The rescue dose of paracetamol-codeine was administered in 2/60 children in the ketorolac group versus 8/65 in the tramadol group (Fisher exact test, p=0.098). There were no statistically significant differences between the two groups in the frequency of adverse effects. CONCLUSIONS: Both sublingual ketorolac and tramadol were equally effective for pain management in children with suspected fractures or dislocations.

4. Di Massa A

Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID) largely used in adults, deserves particular attention for postoperative pain therapy in children, even if it is not officially approved for paediatric use. We have examined a lot of studies about the use of ketorolac for paediatric postoperative pain, pointing out pharmacological and pharmacokinetic properties and side effects. There are significant differences in pharmacokinetic parameters, doses, routes of administration, length of treatment, side effects, usage precautions and pharmacological interactions between children and adults. Amongst the many drugs available, ketorolac seems to be particularly efficient for postoperative pain therapy in children too.

5. Marzuillo P

In June 2013, the European Medicine Agency recommended limiting codeine use in paediatric patients, creating a void in managing moderate pain. We reviewed the literature published in English (1985-June 2017) on the pharmacokinetic, pharmacodynamic and safety profile of ketorolac, a possible substitute for codeine and opioids, for treating moderate-to-severe pain. We found that gastrointestinal side effects were mainly reported with prolonged use, significant bleeding was reported in adenotonsillectomy, and adverse renal effects appeared to be limited to patients with specific coexisting risk factors.

Conclusions:The short-term use of ketorolac appears to be safe for children in many situations

4.7. LIDOCAINA

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Uso in aerosol per il trattamento della tosse refrattaria ad altre terapie, in caso di metastasi polmonari.
2. Uso endovenoso per il trattamento del dolore neuropatico in pazienti in CPP non rispondenti alle terapie convenzionali.

RAZIONALE DELLA RICHIESTA:

1. La tosse refrattaria a qualsiasi trattamento convenzionale, è un sintomo non infrequente in minori con lesioni pleuropolmonari primitive e/o secondarie in CPP. E' un sintomo destruente, limita il sonno, l'alimentazione, il movimento e le relazioni, con ricaduta drammatica sulla qualità della vita del piccolo paziente e della sua famiglia. I farmaci a disposizione sono pochi e quasi del tutto inefficaci.

L'uso della Lidocaina aerosolica si propone come strumento alternativo per la gestione della tosse refrattaria.

2. Il dolore è il sintomo destruente che accompagna molteplici patologie eleggibili alle CPP (oncologiche e non oncologiche) e nel paziente pediatrico è un sintomo complesso sia a livello diagnostico che terapeutico.

In particolare il dolore neuropatico è il dolore "più difficile" da trattare (presenta infatti una ricaduta clinica, sociale drammatica con un livello di insuccesso al trattamento ancora elevato).

Come per l'adulto, anche in ambito pediatrico non esiste un farmaco efficace in assoluto in tutte le situazioni di dolore neuropatico e le molecole a disposizione sono poche e con efficacia variabile nelle diverse situazioni eziopatogenetiche.

La lidocaina si propone come farmaco alternativo nella gestione del dolore neuropatico nelle CPP.

SITUAZIONE ATTUALE APPROVATA:

Iniettabile: anestesie periferiche e loco regionali, interventi conservativi e chirurgici in odontostomatologia

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 1:

Parole chiave: lidocaine, nebulized, cancer

Lavori evidenziati:

1. Slaton RM, Thomas RH, Mbathi JW. Evidence for therapeutic uses of nebulized lidocaine in the treatment of intractable cough and asthma. Ann Pharmacother. 2013 Apr;47(4):578-85. doi: 10.1345/aph.1R573. Epub 2013 Apr 2.

   Commento: la revisione della letteratura valuta l'uso della lidocaina in aerosol per la gestione della tosse intrattabile e dell'asma negli adulti. Conclude proponendo la lidocaina in aerosol come trattamento in pazienti che non hanno risposto o non hanno tollerato altre terapie standard.

2. Decco ML, Neeno TA, Hunt LW, O'Connell EJ, Yunginger JW, Sachs MI. Nebulized lidocaine in the treatment of severe asthma in children: a pilot study. Ann Allergy Asthma Immunol. 1999 Jan;82(1):29-32. doi:10.1016/S1081-1206(10)62656-7.

   Commento: lo studio evidenzia come la lidocaina in aerosol possa essere usata in alternativa agli steroidi in pazienti pediatrici affetti da asma grave steroide-dipendente.

3. Truesdale K, Jurdi A. Nebulized lidocaine in the treatment of intractable cough. Am J Hosp Palliat Care. 2013 Sep;30(6):587-9. doi: 10.1177/1049909112458577. Epub 2012 Sep 9.

   Commento: lo studio indica che la lidocaina in aerosol è ben tollerata nei pazienti oncologici con minimi effetti collaterali.

4. Molassiotis A, Smith JA, Mazzone P, Blackhall F, Irwin RS; CHEST Ex pert Cough Panel. Symptomatic Treatment of Cough Among Adult Patients With Lung Cancer: CHEST Guideline and Expert Panel Report. Chest. 2017 Apr;151(4):861-874. doi: 10.1016/j.chest.2016.12.028. Epub 2017 Jan 17.

   Commento: la revisione della letteratura sostiene l'uso della lidocaina in aerosol in per la gestione della tosse in pazienti oncologici.

RCT DISPONIBILI:

Nessuno

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 2:

Parole chiave: lidocaine, intravenous, neuropathic pain

Lavori evidenziati:

1. Hutson P, Backonja M, Knurr H. Intravenous lidocaine for neuropathic pain: a retrospective analysis of tolerability and efficacy. Pain Med. 2015 Mar;16(3):531-6. doi: 10.1111/pme.12642. Epub 2014 Dec 19.

Commento: lo studio indica che l'uso della lidocaina EV per la gestione del dolore neuropatico negli adulti non mostra particolari effetti collaterali/eventi avversi, arrivando a suggerire l'uso di dosi più alte rispetto a quella utilizzata nello studio stesso (500 mg in 30 minuti).

2. Kajiume T, Sera Y, Nakanuno R, Ogura T, Karakawa S, Kobayakawa M, Taguchi S, Oshita K, Kawaguchi H, Sato T, Kobayashi M. Continuous intravenous infusion of ketamine and lidocaine as adjuvant analgesics in a 5-year-old patient with neuropathic cancer pain. J Palliat Med. 2012 Jun;15(6):719-22. doi: 10.1089/jpm.2011.0097. Epub 2012 Mar 8.

   Commento: il *case report* riguarda l'uso di lidocaina EV per la gestione del dolore neuropatico in una bambina di 5 anni, affetta da patologia oncologica non responsiva a oppioidi maggiori.

RCT DISPONIBILI:

Nessuno

COMMENTO E CONCLUSIONI:

Vi è un solo studio che valuta l'uso della lidocaina in aerosol per l'età pediatrica, in bambini affetti da asma. Gli altri lavori sono relativi all'adulto in ambito oncologico.

ABSTRACT RICHIESTA 1:

1. Slaton RM

OBJECTIVES: To summarize the efficacy and safety data for use of nebulized lidocaine in intractable cough and asthma. DATA SOURCES: A literature search was conducted using PubMed (through November 2012), International Pharmaceutical Abstracts (1970-December 2012), and Cochrane Library (up to 2012) with the search terms nebulization, nebulized or nebulised; administration, inhalation; cough; asthma; and lidocaine. Results were limited to human studies published in the English language. Referenced citations from relevant publications were also reviewed. STUDY SELECTIONE AND DATA EXTRACTION: All articles identified from the data sources were reviewed for inclusion. Clinical trials and descriptive studies that discussed use of nebulized lidocaine for treatment of intractable cough and asthma were included in the review. DATA SYNTHESIS: Seventeen studies were identified for review. Seven studies (6 descriptive studies and 1 clinical trial) evaluating the use of nebulized lidocaine in intractable cough reported efficacy in doses ranging from 10 mg to 400 mg. Five clinical trials in asthma showed conflicting results regarding improvement in pulmonary function and glucocorticoid-sparing effects. General improvements in pulmonary function as well as the initial bronchoconstriction induced by nebulized lidocaine in subjects with baseline bronchial hyperreactivity were investigated in 5 studies. Overall, the available evidence does not appear to preclude the use of lidocaine as a treatment option for intractable cough after failure of traditional cough suppressants. Data on its use for short-term glucocorticoid-sparing effects in asthma are conflicting. Study limitations, including design, small sample size, and inconsistencies in method and adjunctive therapies, should be considered. Nebulized lidocaine is well tolerated; however, reports of initial

bronchoconstriction have occurred. CONCLUSIONS: Although nebulized lidocaine is not first-line therapy in intractable cough and asthma, it may provide an alternative treatment option in patients who cannot tolerate or are unresponsive to other treatments. Appropriate monitoring precautions should be used to ensure patient safety.

2. Decco ML

BACKGROUND: Glucocorticoids have been used to treat asthma since the 1950s; however, their adverse systemic effects have limited their duration of use and dosage. Unfortunately, many patients with severe asthma often require oral glucocorticoids in addition to inhaled glucocorticoids. Alternatives to glucocorticoids have been sought with mixed success. Recently, lidocaine has been added to the list of potent glucocorticoid sparing agents for the treatment of severe asthma. OBJECTIVES: We report the first group of pediatric patients with severe asthma treated with nebulized lidocaine. METHODS: The study was performed in an open manner with 6 severely asthmatic patients followed in the Pediatric Allergy and Immunology Section, Mayo Clinic. The only intervention was the institution of nebulized lidocaine (0.8 mg/kg/dose to 2.5 mg/kg/dose t.i.d to q.i.d). The average daily steroid requirement was followed during the administration of the nebulized lidocaine. RESULTS: During a mean of 11.2 months of therapy (range 7 to 16 months) 5 of the 6 patients completely discontinued their oral glucocorticoids within an average time of 3.4 months (range 1 to 7 months). CONCLUSIONS: After further study, lidocaine may prove to be the first non-toxic, steroid alternative to patients with severe steroid-dependent asthma.

3. Truesdale K

Cough is one of the most common symptoms prompting patients to be seen by health care providers in the United States. Persistent cough can disrupt daily activities such as conversation, eating, breathing, and sleeping, and it can become extremely debilitating both physically and mentally. Pharmacological treatments include dextramethorphan, opioid cough suppressants, benzonatate, inhaled ipratropium, and guaifenesin. Successful cough suppression has also been demonstrated in several studies with the use of nebulizedlidocaine. Nebulized lidocaine also appears to be well tolerated by patients with minimal side effects including dysphonia, oropharyngeal numbness, and bitter taste. Studies conducted thus far have been small, so larger randomized control trials comparing nebulizedlidocaine to placebo need to be conducted in the future.

4. Molassiotis 2017

BACKGROUND: Cough among patients with lung cancer is a common but often undertreated symptom. We used a 2015 Cochrane systematic review, among other sources of evidence, to update the recommendations and suggestions of the American College of Chest Physicians (CHEST) 2006 guideline on this topic. METHODS: The CHEST methodologic guidelines and the Grading of Recommendations, Assessment, Development, and Evaluation framework were used. The Expert Cough Panel based their recommendations on data from the Cochrane systematic review on the topic, uncontrolled

studies, case studies, and the clinical context. Final grading was reached by consensus according to the Delphi method. RESULTS: The Cochrane systematic review identified 17 trials of primarily low-quality evidence. Such evidence was related to both nonpharmacologic (cough suppression) and pharmacologic (demulcents, opioids, peripherally acting antitussives, or local anesthetics) treatments, as well as endobronchial brachytherapy. CONCLUSIONS: Compared with the 2006 CHEST Cough Guideline, the current recommendations and suggestions are more specific and follow a step-up approach to the management of cough among patients with lung cancer, acknowledging the low-quality evidence in the field and the urgent need to develop more effective, evidence-based interventions through high-quality research.

ABSTRACT RICHIESTA 2:

1. Hutson P

OBJECTIVES: This study was designed to describe the efficacy and toxicity of intravenous (i.v.) lidocaine infusions for the treatment of neuropathic pain initially administered at a flat-rate trial dose of 500 mg over 30 minutes. SETTING: Academic, tertiary care hospital and infusion center. METHODS: Data were retrospectively collected and analyzed for efficacy, correlations between infusion rates with adverse effects, patterns of infusion rate adjustments, and infusion frequencies. RESULTS: The average rate for all infusions was 9.1 mg/min. Efficacy was seen in 45 patients (65%), and all but eight patients (12%) required infusion rate reductions from the initial test rate of 16.7 mg/min due to adverse effects. Fifty-five patients experienced adverse effects, with light-headedness as the most frequently reported side effect. CONCLUSION: The flat-dose trial used under the University of Wisconsin Health protocol for i.v. lidocaine administration did not cause serious adverse events, but few patients who responded to this trial dose tolerated subsequent infusions at the trial rate. Due to the lack of serious adverse events, administering an aggressive trial dose to elicit an analgesic response appears to be rational. If patients show a benefit from the trial dose, the need for reductions in infusion rate of subsequent doses should be anticipated.

2. Kajiume T

For difficult to treat neuropathic pain from cancer, adjuvant analgesics are often used with opioids. We present the case of a 5-year-old girl who was diagnosed with meningitis caused by malignant T-cell lymphoma. She had severe neuropathic pain not relieved by increasing doses of a fentanyl infusion. Intravenous administration of ketamine and lidocaine in combination with fentanyl provided excellent analgesia without significant side effects. Ketamine and lidocaine can be safely infused together with concomitant opioids for the treatment of refractory neuropathic pain caused by cancer.

4.8. MIDAZOLAM

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

1. Uso intranasale per minore invasività e rapidità di somministrazione in assenza di accesso venoso, anche in caso di urgenza in pazienti in CPP di età > 1 mese
2. Uso endovenoso per la gestione dei sintomi da distress non doloroso nella fase di terminalità.

RAZIONALE DELLA RICHIESTA:

1. Il midazolam è tra i principali farmaci in uso in età pediatrica per tutte le procedure diagnostiche o terapeutiche che richiedono necessariamente la sedazione. E' inoltre il farmaco di prima scelta per il trattamento delle convulsioni.

L'uso orale ed endovenoso è formalmente autorizzato in età pediatrica.

La via di somministrazione nasale, con gli stessi obiettivi terapeutici, è largamente utilizzata nella pratica, per l'efficacia, la sicurezza, la rapidità di azione e la facilità di somministrazione. E' oltremodo fondamentale nei casi di mancato accesso venoso (pratica di per sè dolorosa e non sempre necessaria, oltre che a volte difficile).

2. Il midazolam è inoltre previsto nelle linee guida per le cure palliative dell'adulto e del bambino, come farmaco di prima scelta per uso endovenoso per la gestione del distress non doloroso nella fase di terminalità, pratica che viene spesso inevasa e che non ha valide alternative terapeutiche.

SITUAZIONE ATTUALE APPROVATA:

F: Sedazione conscia prima e durante procedure diagnostiche o terapeutiche con o senza anestesia locale; anestesia: premedicazione prima dell'induzione dell'anestesia, sedazione in terapia intensiva. **SOL**: per pazienti di 3 mesi-18 anni, trattamento di crisi convulsive acute prolungate.

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 1:

Parole chiave: Intranasal, midazolam, children.

Lavori evidenziati:

Sono state identificate 245 voci bibliografiche, di cui 106 "clinical trial".

Si riportano i lavori più significativi, tra cui alcune revisioni sistematiche degli studi clinici controllati.

1. Tsze DS, Ieni M, Fenster DB, Babineau J, Kriger J, Levin B, Dayan PS. Optimal Volume of Administration of Intranasal Midazolam in Children: A Randomized Clinical Trial. Ann Emerg Med. 2017 May;69(5):600-609. doi: 10.1016/j.annemergmed.2016.08.450. Epub 2016 Nov 4.

   Commento: il *clinical trial* valuta il volume di somministrazione del midazolam intranasale (0,2-0,5-1 ml) per indurre sedazione in corso di sutura di ferita.

2. Nemeth M, Jacobsen N, Bantel C, Fieler M, Sümpelmann R, Eich C.Intranasal Analgesia and Sedation in Pediatric Emergency Care-A Prospective Observational Study on the Implementation of an Institutional Protocol in a Tertiary Children's Hospital. Pediatr Emerg Care. 2017 Jan 24. doi: 10.1097/PEC.0000000000001017. [Epub ahead of print]

   Commento: lo studio prospettico osservazionale valuta l'uso di midazolam, fentanil e ketamina intranasale in età pediatrica per la gestione del dolore acuto e di sedazione urgente. Ne dimostra efficacia e sostiene l'utilizzo quando non sia possibile o inappropriato l'accesso venoso.

3. Jain P, Sharma S, Dua T, Barbui C, Das RR, Aneja S. Efficacy and safety of anti-epileptic drugs in patients with active convulsive seizures when no IV access is available: Systematic review and meta-analysis. Epilepsy Res. 2016 May;122:47-55. doi: 10.1016/j.eplepsyres.2016.02.006. Epub 2016 Feb 16.

   Commento: la revisione della letteratura valuta l'uso di benzodiazepine intranasali vs altre vie di sommnistrazione per la gestione delle crisi convulsive quando non vi sia accesso venoso.

4. Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, Bare M[1], Bleck T, Dodson WE , Garrity L, Jagoda A, Lowenstein D, Pellock J[11], Riviello J, Sloan E, Treiman DM. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016 Jan-Feb;16(1):48-61. doi: 10.5698/1535-7597-16.1.48.

   Commento: la revisione della letteratura valuta la gestione delle crisi convulsive utilizzando anche midazolam intranasale sia negli adulti che nei bambini.

5. Chiaretti A, Barone G, Rigante D, Ruggiero A, Pierri F, Barbi E, Barone G, Riccardi R. Intranasal lidocaine and midazolam for procedural sedation in children. Arch Dis Child. 2011 Feb;96(2):160-3. doi: 10.1136/adc.2010.188433. Epub 2010 Oct 27.

   Commento: lo studio dimostra la sicurezza e l'efficacia di lidocaina spray e midazolam intranasale nella sedazione di bambini per procedure diagnostiche minori o poco dolorosa (incannualzione vena periferica, prelievo venoso, iniezione Intramuscolare,..).

RCT DISPONIBILI:

Tsze DS, Ieni M, Fenster DB, Babineau J, Kriger J, Levin B, Dayan PS. Optimal Volume of Administration of Intranasal Midazolam in Children: A Randomized Clinical Trial. Ann Emerg Med. 2017 May;69(5):600-609. doi: 10.1016/j.annemergmed.2016.08.450. Epub 2016 Nov 4.

RICERCA BIBLIOGRAFICA PER LA RICHIESTA 2:

Parole chiave: midazolam, end of life, children.

Lavori evidenziati:

1. Korzeniewska-Eksterowicz A, Przysło Ł, Fendler W, Stolarska M, Młynarski W. Palliative sedation at home for terminally ill children with cancer. J Pain Symptom Manage. 2014 Nov;48(5):968-74. doi: 10.1016/j.jpainsymman.2014.01.012. Epub 2014 Apr 18.

   Commento: lo studio descrive la gestione della sedazione palliativa a domicilio in età pediatrica, utilizzando midazolam EV e morfina.

2. Postovsky S, Moaed B, Krivoy E, Ofir R, Ben Arush MW. Practice of palliative sedation in children with brain tumors and sarcomas at the end of life. Pediatr Hematol Oncol. 2007 Sep;24(6):409-15.

   Commento: l'analisi retrospettiva valuta la gestione della sedazione palliativa in età pediatrica.

3. Cowan JD, Walsh D. Terminal sedation in palliative medicine--definition and review of the literature. Support Care Cancer. 2001 Sep;9(6):403-7.

   Commento: l'analisi retrospettiva valuta i farmaci utilizzati nella sedazione palliativa, segnalando il midazolam come il farmaco più utilizzato.

4. Wolfe J, Hinds PS, Sourkes BM. Palliative sedation. Textbook of interdisciplinary pediatric palliative care. Elsevier Saunders 2011.

   Commento: l'elaborato indica il midazolam come il farmaco di scelta e il più utilizzato nella sedazione palliativa.

RCT DISPONIBILI:

Nessuno

NOTE:

Si raccomanda l'uso del dispositivo per le reazioni locali della mucosa.

COMMENTO E CONCLUSIONI:

I dati a disposizione per quanto riguarda l'uso del farmaco somministrato per via sia intranasale che endovenosa, per la gestione dei sintomi nella fase di fine vita, supportano le richieste di inserimento nell'elenco 648/96.

ABSTRACT RICHIESTA 1:

1. Tsze DS

STUDY OBJECTIVE: The optimal intranasal volume of administration for achieving timely and effective sedation in children is unclear. We aimed to compare clinical outcomes relevant to procedural sedation associated with using escalating volumes of administration to administer intranasal midazolam. METHODS: We conducted a randomized, single-blinded, 3-arm, superiority clinical trial. Children aged 1 to 7 years and undergoing laceration repair requiring 0.5 mg/kg intranasal midazolam (5 mg/mL) were block-randomized to receive midazolam using 1 of 3 volumes of administration: 0.2, 0.5, or 1 mL. Procedures were videotaped, with outcome assessors blinded to volume of administration. Primary outcome was time to onset of minimal sedation (ie, score of 1 on the University of Michigan Sedation Scale). Secondary outcomes included procedural distress, time to procedure start, deepest level of sedation achieved, adverse events, and clinician and caregiver satisfaction. RESULTS: Ninety-nine children were enrolled; 96 were analyzed for the primary outcome and secondary outcomes, except for the outcome of procedural distress, for which only 90 were analyzed. Time to onset of minimal sedation for each escalating volume of administration was 4.7 minutes (95% confidence interval [CI] 3.8 to 5.4 minutes), 4.3 minutes (95% CI 3.9 to 4.9 minutes), and 5.2 minutes (95% CI 4.6 to 7.0 minutes), respectively. There were no differences in secondary outcomes except for clinician satisfaction with ease of administration: fewer clinicians were satisfied when using a volume of administration of 0.2 mL. CONCLUSIONS: There was a slightly shorter time to onset of minimal sedation when a volume of administration of 0.5 mL was used compared with 1 mL, but all 3 volumes of administration produced comparable clinical outcomes. Fewer clinicians were satisfied with ease of administration with a volume of administration of 0.2 m

2. Nemeth M

OBJECTIVES: Children presenting with acute traumatic pain or in need of therapeutic or diagnostic procedures require rapid and effective analgesia and/or sedation. Intranasal administration (INA) promises to be a reliable, minimally invasive delivery route. However, INA is still underused in Germany. We hence developed a protocol for acute pain therapy (APT) and urgent analgesia and/or sedation (UAS). Our aim was to evaluate the effectiveness and safety of our protocol. METHODS: We performed a prospective observational study in a tertiary children's hospital in Germany. Pediatric patients aged 0 to 17 years requiring APT or UAS were included. Fentanyl, s-ketamine, midazolam, or combinations were delivered according to protocol. Primary outcome variables included quality of analgesia and/or sedation as measured on age-appropriate scales and time to onset of drug action. Secondary outcomes were adverse events and serious adverse events. RESULTS: One hundred pediatric patients aged 0.3 to 16 years were enrolled, 34 for APT and 66 for UAS. The median time onset of drug action was 5 minutes (ranging from 2 to 15 minutes). Fentanyl was most frequently used for APT (n = 19). Pain scores decreased by a median of 4 points (range, 0-10; P < 0.0001). For UAS, s-ketamine/midazolam was most frequently used (n = 25). Sedation score indicated minimal sedation in most cases. Overall success rate after the first attempt was 82%. Adverse events consisted of nasal burning (n = 2) and vomiting (n = 2). No serious adverse events were recorded. CONCLUSIONS: A fentanyl-, s-ketamine-,

and midazolam-based INA protocol was effective and safe for APT and UAS. It should then be considered where intravenous access is impossible or inappropriate.

3. Jain P

OBJECTIVES: To explore the existing evidence for anti-convulsant drugs and their routes of administration in treating acute seizures in children and adults when intravenous access is not available. METHODS: All major databases including Medline via Ovid, PubMed, Cochrane CENTRAL, Embase, and Google Scholar were searched till May 2015. Randomized and quasi-randomized controlled trials comparing two anti-convulsant drugs (at least one comparator being administered through non-intravenous route) for treatment of acute seizures were included. OUTCOME MEASURES: Primary outcome measure was proportion of children with clinical seizure cessation within 10min of drug administration. Secondary outcome measures were time taken to clinical seizure cessation from the time of admission and from the time of drug administration, and incidence of significant adverse effects. RESULTS: Out of the 19,165 citations, 26 studies were finally included. Regarding the primary outcome measure, the quality of evidence was 'moderate' for following 3 comparisons: buccal midazolam being superior to per-rectal diazepam (RR 1.14; 95% CI, 1.06-1.24), intra-nasal lorazepam being same as intravenous lorazepam (RR 1.04; 95% CI, 0.89-1.22) and intramuscular paraldehyde (RR 1.22; 95% CI, 0.99-1.52). The quality of evidence was “very-low” for 1 comparison: per-rectal lorazepam being superior to per-rectal diazepam (RR 3.17; 95% CI, 1.63-6.14). The quality of evidence was 'low' for following 2 comparisons: sub-lingual lorazepam being inferior to rectal diazepam (RR 0.71; 95% CI, 0.62-0.81), and intranasal midazolambeing superior to per-rectal diazepam (RR 1.14; 95% CI, 1.05-1.25). The rest of the comparisons did not show any difference, but the quality of evidence was 'low' to 'very low'. The time to seizure cessation after drug administration was lower in the intravenous group. However, time to seizure cessation after presentation (includes time for drug administration) was lower in the non-intravenous group. Significant adverse effects were infrequently reported and when present, were similar in both the groups. CONCLUSIONS: When intravenous access is not available, non-intravenous routes of administration of benzodiazepines should be considered for the control of acute seizures in children/adults. The preference may be guided by availability, expertise and social preference.

4. Glauser T

CONTEXT: The optimal pharmacologic treatment for early convulsive status epilepticus is unclear. OBJECTIVE: To analyze efficacy, tolerability and safety data for anticonvulsant treatment of children and adults with convulsive status epilepticus and use this analysis to develop an evidence-based treatment algorithm. DATA SOURCES: Structured literature review using MEDLINE, Embase, Current Contents, and Cochrane library supplemented with article reference lists. STUDY SELECTION: Randomized controlled trials of anticonvulsant treatment for seizures lasting longer than 5 minutes. DATA EXTRACTION: Individual studies were rated using predefined criteria and these results were used to form recommendations, conclusions, and an evidence-based treatment algorithm. RESULTS: A total of 38 randomized controlled trials were identified, rated and contributed to the assessment. Only four trials were considered to have class I evidence of efficacy. Two studies were rated as class II and the remaining 32 were judged to have class III evidence.

In adults with convulsive status epilepticus, intramuscular midazolam, intravenous lorazepam, intravenous diazepam and intravenous phenobarbital are established as efficacious as initial therapy (Level A). Intramuscular midazolamhas superior effectiveness compared to intravenous lorazepam in adults with convulsive status epilepticus without established intravenous access (Level A). In children, intravenous lorazepam and intravenous diazepam are established as efficacious at stopping seizures lasting at least 5 minutes (Level A) while rectal diazepam, intramuscular midazolam, intranasal midazolam, and buccal midazolam are probably effective (Level B). No significant difference in effectiveness has been demonstrated between intravenous lorazepam and intravenous diazepam in adults or children with convulsive status epilepticus (Level A). Respiratory and cardiac symptoms are the most commonly encountered treatment-emergent adverse events associated with intravenous anticonvulsant drug administration in adults with convulsive status epilepticus (Level A). The rate of respiratory depression in patients with convulsive status epilepticus treated with benzodiazepines is lower than in patients with convulsive status epilepticus treated with placebo indicating that respiratory problems are an important consequence of untreated convulsive status epilepticus (Level A). When both are available, fosphenytoin is preferred over phenytoin based on tolerability but phenytoin is an acceptable alternative (Level A). In adults, compared to the first therapy, the second therapy is less effective while the third therapy is substantially less effective (Level A). In children, the second therapy appears less effective and there are no data about third therapy efficacy (Level C). The evidence was synthesized into a treatment algorithm. CONCLUSIONS: Despite the paucity of well-designed randomized controlled trials, practical conclusions and an integrated treatment algorithm for the treatment of convulsive status epilepticus across the age spectrum (infants through adults) can be constructed. Multicenter, multinational efforts are needed to design, conduct and analyze additional randomized controlled trials that can answer the many outstanding clinically relevant questions identified in this guideline.

5. Chiaretti A

OBJECTIVE: To evaluate the safety and efficacy of a sedation protocol based on intranasal lidocaine spray and midazolam (INM) in childrenwho are anxious and uncooperative when undergoing minor painful or diagnostic procedures, such as peripheral line insertion, venipuncture, intramuscular injection, echocardiogram, CT scan, audiometry testing and dental examination and extractions. PATIENTS AND DESIGN: 46 children, aged 5-50 months, received INM (0.5 mg/kg) via a mucosal atomiser device. To avoid any nasal discomfort a puff of lidocaine spray (10 mg/puff) was administered before INM. The child's degree of sedation was scored using a modified Ramsay sedation scale. A questionnaire was designed to evaluate the parents' and doctors' opinions on the efficacy of the sedation. Statistical analysis was used to compare sedation times with children's age and weight. RESULTS: The degree of sedation achieved by INM enabled all procedures to be completed without additional drugs. Premedication with lidocaine spray prevented any nasal discomfort related to the INM. The mean duration of sedation was 23.1 min. The depth of sedation was 1 on the modified Ramsay scale. The questionnaire revealed high levels of satisfaction by both doctors and parents. Sedation start and end times were significantly correlated with age only. No side effects were recorded in the cohort of children studied. CONCLUSIONS: This study has shown that the combined use of lidocaine spray and atomised INM appears to be a safe and effective method to achieve short-term sedation in children to facilitate medical care and procedures.

ABSTRACT RICHIESTA 2:

1. Korzeniewska-Eksterowicz A

CONTEXT: The presence of symptoms that are difficult to control always requires adjustment of treatment, and palliative sedation (PS) should be considered. OBJECTIVES: We analyzed our experience in conducting PS at home for terminally ill children with cancer during a seven-year period. METHODS: We performed a retrospective analysis of medical records of children with cancer treated at home between the years 2005 and 2011. RESULTS: We analyzed the data of 42 cancer patients (18% of all patients); in 21 cases, PS was initiated (solid tumors n = 11, brain tumors [5], bone tumors [4], leukemia [1]). Sedation was introduced because of pain (n = 13), dyspnea (9), anxiety (5), or two of those symptoms (6). The main drug used for sedation was midazolam; all patients received morphine. There were no significant differences in the dose of morphine or midazolam depending on the patient's sex; age was correlated with an increase of midazolam dose (R = 0.68; P = 0.005). Duration of sedation (R = 0.61; P = 0.003) and its later initiation (R = 0.43; P = 0.05) were correlated with an increase of the morphine dose. All patients received adjuvant treatment; in patients who required a morphine dose increase, metoclopramide was used more often (P = 0.0002). Patients did not experience any adverse reactions. Later introduction of sedation was associated with a marginally higher number of intervention visits and a significantly higher number of planned visits (R = 0.53; P = 0.013). CONCLUSION: Sedation may be safely used at home. It requires close monitoring and full cooperation between the family and hospice team. Because of the limited data on home PS in pediatric populations, further studies are needed.

2. Postovsky S

Despite progress in the treatment of pediatric cancer, approximately 25% of these children will die of the disease. The last period of lifeis characterized by profound physical and psychological suffering, both of the children and their loved ones. Adequate alleviation of this suffering becomes the priority in the management of these patients. The authors retrospectively evaluated the indications, incidence, and characteristics of palliative sedation (PS) in 19 children with brain tumors (BT) and 18 with sarcomas (S) at the end of life. Twelve of the 18 S patients received PS, as did 13 of the 19 BT patients. Indications for initiation of PS for those with BT were seizures and/or pain, for those with S were pain and/or respiratory insufficiency. It was concluded that PS may be the only efficacious and safe treatment for the alleviation of suffering in these children at the end of life, despite differing indications.

3. Cowan JD

This paper reviews the reported use of nonopioid medications for terminal sedation. To provide a summary of the available literature, an electronic database search was performed. Thirteen series and 1 4 case reports were identified. Various symptoms, including agitation, pain, and confusion, required terminal sedation. Eleven drugs were used in 342 patients. Most patients were also treated with concurrent opioids and received terminal sedation in an inpatient hospice unit. Midazolam was the most common sedative employed. A good response--defined as adequate sedation--ranged between 75% and

100%. The median time to death following the introduction of terminal sedation was greater than 1 day. No agent appears to have superior efficacy or limiting toxicity.

4.9. ONDANSETRON

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

Controllo della nausea e del vomito in corso di terapia con oppioidi in pazienti in cure palliative in età >6 mesi.

RAZIONALE DELLA RICHIESTA:

La nausea e il vomito sono un effetto collaterale relativamente frequente e notevolmente disturbante degli oppioidi somministrati in cronico nell'ambito delle cure palliative. Le linee guida consigliano per il controllo di tali sintomi nel paziente adulto l'utilizzo della metoclopramide, delle fenotiazine e dell'ondansetron.

In età pediatrica l'uso della metoclopramide e delle fenotiazine sono gravati da possibili e rilevanti effetti collaterali. L'ondansetron ha un profilo di sicurezza sufficientemente documentato.

L'ondansetron attraverso il controllo dei sintomi gastroitestinali (nausea e vomito) provocati dalla terapia oppioide, permette di proseguire nel tempo il programma analgesico efficace impostato, facilitandone l'accettazione da parte del paziente e della sua famiglia.

SITUAZIONE ATTUALE APPROVATA:

Autorizzato l'uso in due condizioni:

a) vomito da chemioterapia (CINV)

b) vomito post operatorio (PONV)

RICERCA BIBLIOGRAFICA:

Parole chiave: ondansetron, opioid-induced nausea and vomiting, children.

Lavori evidenziati:

1. Jitpakdee T and Mandee S. Strategies for preventing side effects of systemic opioid in postoperative pediatric patients. Paediatr Anaesth 2014 Jun;24(6):561-8. doi: 10.1111/pan.12420.

   Commento: ondansetron è il farmaco di scelta per prevenire la nausea e il vomito indotti da oppioidi.

2. Engelman E, Salengros JC, Barvais L. How much does pharmacologic prophylaxis reduce postoperative vomiting in children? Calculation of prophylaxis effectiveness and expected

incidence of vomiting under treatment using Bayesian meta-analysis. Anesthesiology 2008; 109:1023-1035.

Commento: ondansetron da solo è in grado di ridurre significativamente nausea e vomito indotti da oppioidi, ancora di più se in associazione a desametasone.

3. Gomez-Arnau JI, Aguilar JL, Bovaira P et al. Postoperative nausea and vomiting and opioid-induced nausea and vomiting guidelines for prevention and treatment. Rev Exp Anestesiol Reanim 2010; 57:508-524.

   Commento: ondansetron è il farmaco più efficace per il trattamento di nausea e vomito indotti da oppioidi.

4. Culy CR, Bhana N, Plosker GL. Ondansetron: a review of its use as an antiemetic in children. Paediatr Drugs 2001; 3:441-79.

   Commento: onsansetron è un farmaco antiemetico efficace e sicuro in età pediatrica.

5. Binstock W, Rubin R, Bachman C et al. The effect of premedication with OTFC, with or without ondansetron, on postoperative agitation, and nausea and vomiting in pediatric ambulaotry patients. Pediatr Anesthesia 2004; 14:759-767.

   Commento: ondansetron può essere utile per il trattamento di nausea e vomito da oppioidi in interventi chirurgici ambulatoriali.

RCT DISPONIBILI:

Binstock W. . Pediatr Anesthesia 2004; 14:759-767.

NOTE:

Il farmaco deve essere utilizzato con cautela in caso di documentate cardiopatie aritmogene e di concomitante uso di farmaci che allungano l'intervallo Q-T. E' documentato che in un uso in cronico l'ondansetron può ridurre l'efficacia analgesica del tramadolo.

(https://www.ncbi.nlm.nih.gov/pubmed/25490944)

COMMENTO E CONCLUSIONI:

I lavori evidenziati dimostrano che ondansetron è eleggibile per la profilassi di nausea e vomito, indotti da oppioidi nei bambini, efficace e bel tollerato con pochi effetti collaterali.

ABSTRACT

1. Jitpakdee T

BACKGROUND AND OBJECTIVES: Opioid is the gold standard for treating moderate-to-severe pain in pediatric patients. However, its undesirable side effects lead to unsatisfied postoperative pain management outcome (Pediatr Anesth, 17, 2007, 756). The most commonly reported opioid-related side effects are vomiting (40%), pruritus (20-60%) (Anesthesiology, 77, 1992, 162; Drugs, 67, 2007, 2323), and constipation (15-90%) (Int J Clin Pract, 61, 2007, 1181). The potential life-threatening adverse event, respiratory depression, is less common (0.0013%) (Pediatr Anesth, 20, 2010, 119). The aim of this review was to evaluate prevention strategies that have been shown to decrease opioid side effects in pediatric patients during the postoperative period. METHODS: Literature searches were conducted from 1984 to February 2013. Meta-analysis, systematic review, and randomized, placebo-controlled studies were obtained from PubMed and the Cochrane Library. The medical subject heading (MeSH) terms were opioid analgesics, adverse effects, pediatrics, children, side effects, and postoperative pain. RESULTS AND CONCLUSIONS: Data from 62 studies were reviewed. The strategies that could effectively prevent and reduce opioid side effects in pediatric patients during the postoperative period included minimizing the amount of opioid consumption by a multimodal approach, opioid titration, using local anesthetic techniques and providing the specific prophylaxis for each side effect.

2. Engelman E

BACKGROUND: The authors calculated the effect size for treatments recommended for the pediatric population in the new Guidelines for the Management of Postoperative Nausea and Vomiting that should be implemented with the help of a new risk scale developed for children. METHODS: Six single-drug therapies and five combination treatments were subjected to a Bayesian analysis, with respect to the outcome reported, in a sequence that parallels their dates of publication. Based on the Bayes theorem, a posterior probability was calculated after inclusion of the data from the successive studies, to update a prior probability existing before inclusion of that study. The posterior for the preceding group of trials served as the prior for the subsequent trial. The final odds ratio with its 95% credibility interval compared with placebo is considered as the results for that treatment, and was transformed into a relative risk whose 95% credibility interval allows the calculation of a most pessimistic and a most optimistic incidence of postoperative vomiting. RESULTS: The most pessimistic expectations with the 5-hydroxytryptamine receptor antagonists and dexamethasone result in a 50-60% relative risk reduction. The results with droperidol offer a decrease of only approximately 40%. With the combinations of a 5-hydroxytryptamine receptor antagonist and dexamethasone, a relative risk reduction of approximately 80% is expected. CONCLUSIONS: The authors' tables list the expected incidence of postoperative vomiting with each treatment for each risk category, and the expected relative risks that can be used with baseline risk values from any source.

3. Gomez-Arnau JI

Postoperative nausea and vomiting (PONV) causes patient discomfort, lowers patient satisfaction, and increases care requirements. Opioid-induced nausea and vomiting (OINV) may also occur if opioids are used to treat postoperative pain. These guidelines aim to provide recommendations for the prevention and treatment of both problems. A working group was established in accordance with the charter of the Sociedad Española de Anestesiología y Reanimación. The group undertook the critical appraisal of articles relevant to the management of PONV and OINV in adults and children early and late in the perioperative period. Discussions led to recommendations, summarized as follows: 1) Risk for PONV should be assessed in all patients undergoing surgery; 2 easy-to-use scales are useful for risk assessment: the Apfel scale for adults and the Eberhart scale for children. 2) Measures to reduce baseline risk should be used for adults at moderate or high risk and all children. 3) Pharmacologic prophylaxis with 1 drug is useful for patients at low risk (Apfel or Eberhart 1) who are to receive general anesthesia; patients with higher levels of risk should receive prophylaxis with 2 or more drugs and baseline risk should be reduced (multimodal approach). 4) Dexamethasone, droperidol, and ondansetron (or other setrons) have similar levels of efficacy; drug choice should be made based on individual patient factors. 5) The drug prescribed for treating PONV should preferably be different from the one used for prophylaxis; ondansetron is the most effective drug for treating PONV. 6) Risk for PONV should be assessed before discharge after outpatient surgery or on the ward for hospitalized patients; there is no evidence that late preventive strategies are effective. 7) The drug of choice for preventing OINV is droperidol.

4. Culy CR

Ondansetron, a selective serotonin (5-hydroxytryptamine; 5-HT) 5-HT3 receptor antagonist, is an antiemetic agent available for use in adults and children. In children receiving ondansetron (multiple 5 mg/m2 or 0.15 mg/kg intravenous and/or oral doses) in addition to chemotherapy in 2 large (n > 100) non-comparative analyses, < or =2 emetic episodes were observed in 33 and 40% of cisplatin recipients, 48 and 68% of ifosfamide recipients, and 70 and 72% of patients receiving other chemotherapeutic regimens. In comparative trials, ondansetron was significantly more effective at reducing nausea and vomiting than metoclopramide or chlorpromazine (both combined with dexamethasone), although the incidence of delayed symptoms were similar between children receiving ondansetron and metoclopramide. In addition, dexamethasone significantly improved the antiemetic efficacy of ondansetron in 1 randomised trial. When used in children undergoing conditioning therapy (including total body irradiation) prior to bone marrow transplantation, ondansetron was significantly better at controlling nausea and vomiting than combined perphenazine and diphenhydramine therapy. In dose-ranging and large placebo-controlled trials, intravenous (0.075 to 0.15 mg/kg) or oral (0.1 mg/kg) ondansetron was significantly more effective than placebo in preventing emesis in children undergoing surgery associated with a high risk of postoperative nausea and vomiting (PONV) including tonsillectomy or strabismus repair. In comparative studies, intravenous administration of ondansetron 0.1 to 0.15 mg/kg was significantly superior to droperidol 0.02 to 0.075 mg/kg or metoclopramide 0.2 to 0.25 mg/kg in preventing emesis in children undergoing various surgical procedures. In comparison with other antiemetics, including prochlorperazine and dimenhydrinate, ondansetron generally showed greater prophylactic antiemetic efficacy. Ondansetron combined with dexamethasone was significantly more effective than ondansetron or dexamethasone alone, as was the combination of ondansetron with a propofol-based anaesthetic compared with either agent alone. Ondansetron is generally well tolerated in children, rarely necessitating treatment

withdrawal. The most frequently reported adverse events were mild to moderate headache, constipation and diarrhoea in patients receiving chemotherapy. Wound problems, anxiety, headache, drowsiness and pyrexia were reported most frequently in patients postsurgery. CONCLUSIONS: Ondansetron has shown good efficacy in the prevention of acute nausea and vomiting in children receiving moderately or highly emetogenic chemotherapy and/or irradiation, particularly when combined with dexamethasone. In the chemotherapy setting, ondansetron is significantly better than metoclopramide and chlorpromazine and has a more favourable tolerability profile. In children undergoing surgery, ondansetron demonstrated superior prophylactic antiemetic efficacy compared with placebo, droperidol and metoclopramide, and was relatively free of adverse events. Ondansetron is thus an effective first-line antiemetic in children undergoing chemotherapy, radiotherapy and surgery.

5. Binstock W

BACKGROUND: The purpose of this study was to evaluate, in the pediatric ambulatory surgical population, the efficacy of: (i) oral transmucosal fentanyl citrate (OTFC), when given preoperatively, to reduce postoperative excitement associated with sevoflurane, and (ii) intravenous ondansetron to reduce postoperative nausea and vomiting (PONV) associated with OTFC. METHODS: This randomized, double-blinded, placebo controlled study evaluated the efficacy of OTFC [normal dose (ND) = 10-15 microg x kg(-1) or low dose = 100 microg] compared with placebo in the prevention of postoperative agitation; and the efficacy of ondansetron (0.1 mg x kg(-1) to 4 mg) compared with placebo to reduce PONV associated with OTFC. RESULTS: There were 125 patients evaluated (2-10 years old, ASA class I or II and weight 10-40 kg). Preoperatively OTFC was associated with an increased likelihood of cooperation at baseline (P = 0.018). Postoperatively there was a higher incidence of vomiting in children that received OTFC. The anxiety/agitation of patients entering the PACU was significantly less in children who received OTFC ND (P < 0.001). This effect decreased over time. Patients with respiratory adverse events related to the study drug were significantly higher in groups who received OTFC, however, they were not of clinical significance. OTFC was associated with delays in time for eligibility to PACU discharge (P = 0.003). CONCLUSIONS: Even though OTFC reduced early postoperative agitation the increase in side effects, namely PONV and prolonged recovery times, limits its clinical usefulness. The study demonstrates the tradeoffs between anxiety and agitation vs vomiting, respiratory events and prolonged recovery times. Ambulatory pediatric patients undergoing procedures in which opioids would be routinely used might benefit the most from OTFC combined with ondansetron as part of the anesthetic technique.

4.10. SCOPOLAMINA – IOSCINA IDROBROMURO

USO *OFF-LABEL* CHE SI VUOLE AUTORIZZARE:

Trattamento della scialorrea in pazienti in cure palliative e in fine vita.

RAZIONALE DELLA RICHIESTA:

La scialorrea è un sintomo molto frequente nei bambini con patologie neurologiche, muscolari, metaboliche, genetiche, cromosomiche e anche oncologiche, eleggibili alle CPP. Le problematiche innescate da questo sintomo sono molteplici, sia a livello clinico che psicologico e relazionale. I bambini hanno un rischio sensibilmente maggiore di inalazione sia di saliva che di liquidi o cibo, con possibile secondaria polmonite *ab-ingestis*. Inoltre, la scialorrea si accompagna spesso a lesioni locali della cute attorno alla bocca e a infezioni recidivanti; non di rado, si sommano problemi di disidratazione. A ciò si aggiunge il frequente isolamento sociale a cui questi bambini sono sottoposti (sia per l'impatto visivo determinato dalla scialorrea che per il cattivo odore che a questa si accompagna) e il notevole impatto sulla gestione della *care*, sia in termini di tempo che di complessità assistenziale.

Un adeguato controllo della scialorrea, ha una ricaduta importante in termini di qualità della vita sia del minore che della sua famiglia e, non infrequentemente, rappresenta un bisogno prioritario nella gestione del bambino in CPP.

La scopolamina transdermica, per efficacia e facilità d'uso, rappresenta nella stragrande maggioranza dei casi uno strumento insostituibile nella gestione di questi pazienti.

SITUAZIONE ATTUALE APPROVATA:

Nessuna

RICERCA BIBLIOGRAFICA:

Parole chiave: scopolamine, drooling, children

Lavori evidenziati:

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   Commento: la *review* non è specifica per l'età pediatrica, ma pone la scopolamina transdermica come farmaco di prima scelta nella gestione dell'ipersalivazione.

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4. Táboas-Pereira MA, Paredes-Mercado C, Alonso-Curcó X, Badosa-Pagès J, Muchart J, Póo P. Drooling therapy in children with neurological disorders Rev Neurol. 2015 Jul 16;61(2):66-70

   Commento: l'articolo evidenzia l'efficacia della scopolamina nel trattamento della scialorrea.

5. Jongerius PH, van den Hoogen FJ, van Limbeek J, Gabreëls FJ, van Hulst K, Rotteveel JJ. Effect of botulinum toxin in the treatment of drooling: a controlled clinical trial. Pediatrics. 2004 Sep;114(3):620-7. doi: 10.1542/peds.2003-1104-L

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   Commento: il *case report* segnala alcuni effetti collaterali.

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RCT DISPONIBILI:

SI (Táboas-Pereira MA et al, Rev Neurol. 2015 Jul 16;61(2):66-70)

COMMENTO E CONCLUSIONI:

I lavori riportati evidenziano come la scopolamina transdermica sia il farmaco di prima scelta nella gestione dell'ipersalivazione, pur non scevra da effetti collaterali dei quali sia gli operatori che i familiari devono essere adeguatamente istruiti.

ABSTRACT:

1. Bavikatte G

Drooling, also known as ptyalism or sialorrhea can be defined as salivary incontinence or the involuntary spillage of saliva over the lower lip. Drooling could be caused by excessive production of saliva, inability to retain saliva within the mouth, or problems with swallowing. Drooling can lead to functional and clinical consequences for patients, families, and caregivers. Physical and psychosocial complication includes maceration of skin around the mouth, secondary bacterial infection, bad odour, dehydration and social stigmatisation. People with drooling problems are also at increased risk of inhaling saliva, food, or fluids into the lungs especially when body's normal reflex mechanisms, such as gagging and coughing are also impaired. Successful management of sialorrhea can alleviate the associated hygienic problems, improve appearance, enhance self-esteem, and significantly reduce the nursing care time of these sufferers.Chronic drooling can be difficult to manage; this article gives overview of the causes, effects and management of drooling of saliva in general practice.

2. Mato A

AIM: To evaluate the efficacy of scopolamine administered transdermally for the treatment of drooling in severely disabled patients. METHODS: A prospective, randomized, double-blind, crossover, placebo-controlled clinical trial was designed. The study group consisted of 30 handicapped patients with persistent drooling. The exclusion criteria were the specific contra-indications of scopolamine. Severity of drooling was quantified using a modified Thomas-Stonell and Greenberg visual scale simplified into three grades: 1 = dry; 2 = mild/moderate; 3 = severe/fulsome. The frequency of drooling was estimated using the number of bibs used each day. The baseline observational phase was followed by the application of a 1.5 mg scopolamine (Scopoderm TTS; Novartis Consumer Healthcare, UK) or placebo patch every 72 h for a fortnight. This was followed by a 1 week washout period and then crossover of assignments for 2 weeks. RESULTS: At baseline, 77% of patients showed grade 3 of drooling. The placebo administration showed no significant reduction in drooling. We found a significant drooling reduction ($P < 0.005$) in the scopolamine group in the 1 and 2 week controls (69% and 80% respectively <or= grade 3). The mean number of bibs/day decreased during the scopolamine phase from 6/day at baseline to 3/day at the 2 week control. Four patients (13.3%) dropped out because of scopolamine side effects and minor adverse reactions were observed in three other patients. No blood alterations were found during the study period. CONCLUSIONS: Scopolamine can be useful to control drooling in severely disabled patients although it requires appropriate patient selection and is not free from adverse effects.

3. Little SA

BACKGROUND: Drooling is a common dysfunction in children with cerebral palsy and may also affect neurologically unimpaired children. It causes significant social handicap to both children and their families. METHODS: The data in this article are supported by a Medline search (November 2008) utilising the keywords drooling, sialorrhea, botulinum toxin, salivary duct ligation and also by the use of the personal bibliographies of the senior authors. RESULTS: The majority of the published literature for drooling is of level III/IV evidence. CONCLUSIONS: Multiple therapeutic interventions are available for paediatric drooling. These are most appropriately introduced in a stepwise progression from behaviour therapy, to pharmacotherapy to surgical procedures.

4. Táboas-Pereira MA,

INTRODUCTION: Drooling is the inability to retain saliva in the mouth and its progression to the digestive tract, being a common problem in pediatric patients with neurological disorders. Three different treatment options are available. AIM: To assess the effectiveness and safety of trihexyphenidyl, scopolamine and botulinum toxin infiltration in the treatment of drooling in children with neurological disorders. PATIENTS AND METHODS: This is an open and prospective type study. We include patients treated in the Neurology Service that present excessive drooling, affecting their quality of life, between 2009 and 2013. RESULTS: We enrolled 46 patients in the study. The treatment with oral trihexyphenidyl was indicated in 46, obtaining good result in 15 (32.6%), three with temporary effect and the rest with lasting effect. Three patients presented side effects (6.5%). Four out of 11 (36.36%) patients treated with scopolamine patch had beneficial effects. One was withdrawn due to lack of efficacy and six due to side effects. Twenty-five patients were infiltrated with botulinum toxin, with a significant decrease of drooling in 16 patients (64%) after the first injection. We observed no significant changes in nine patients. Only one out of 25 showed side effects (mild dysphagia). CONCLUSIONS: Currently there is not a fully effective therapeutic option for drooling. We recommend starting treatment with trihexyphenidyl. A second option could be the scopolamine patch and botulinum toxin as a third option. Botulinum toxin infiltration in salivary glands is shown as an effective and safe alternative in our study.

5. Jongerius PH

OBJECTIVE: To investigate the clinical effectiveness of botulinum neurotoxin type A (BoNT) to reduce drooling in children with cerebral palsy (CP). METHODS: A controlled clinical trial was performed in which the results of single-dose BoNT injections in the submandibular glands were compared with treatment with scopolamine. Forty-five children who had CP and experienced severe drooling were enrolled. Drooling severity was measured at baseline, during application of scopolamine, and at different intervals after BoNT injections up to 24 weeks, using the Drooling Quotient (DQ), the Teacher Drooling Scale (TDS), and Visual Analog Scales (VAS). RESULTS: Drooling was reduced during scopolamine application as well as after BoNT injections. Compared with baseline, the mean DQ showed a significant decrease throughout the study. Greatest reductions were

achieved 2 to 8 weeks after BoNT injection. No significant differences were found between scopolamine measurements and those up to 24 months after BoNT injection. Using VAS, parents recorded the effect on drooling in which significant differences were found between baseline VAS score and all follow-up assessments. According to our definition of "success to therapy," demanding a 2-point decrease on the TDS, 61.5% of patients responded to BoNT injections. Analysis of the DQ demonstrated a response rate of 53% of the patients to scopolamine and 48.7% to BoNT until 24 weeks after BoNT injections, the actual duration of this study. As a reaction to scopolamine, 71.1% of the patients had moderate to severe side effects. Only nonsevere, incidental side effects were reported after BoNT injections. CONCLUSIONS: During scopolamine application as well as after intraglandular BoNT injections, a clinically relevant reduction in drooling was achieved in children with CP, demonstrating maximum effect 2 to 8 weeks after injections. This is the first controlled clinical trial that confirmed a significant effect of BoNT injections in the treatment of drooling. General anesthesia was needed for all children. BoNT injections show fewer and less serious side effects than transdermal scopolamine treatment.

6. Walshe M

BACKGROUND: Drooling is a common problem for children with cerebral palsy (CP). This can be distressing for these children as well as for their parents and caregivers. The consequences of drooling include risk of social rejection, damp and soiled clothing, unpleasant odour, irritated chapped skin, mouth infections, dehydration, interference with speech, damage to books, communication aids, computers, and the risk of social isolation (Blasco 1992; Van der Burg 2006). A range of interventions exist that aim to reduce or eliminate drooling. There is a lack of consensus regarding which interventions are most effective for children with CP. OBJECTIVES: (1) To evaluate the effectiveness and safety of interventions aimed at reducing or eliminating drooling in children with cerebral palsy. (2) To provide the best available evidence to inform clinical practice. (3) To assist with future research planning. SEARCH METHODS: We searched the following databases from inception to December 2010 : Cochrane Central Register of Controlled Trials (CENTRAL); Medline via Ovid; EMBASE; CINAHL; ERIC; Psych INFO; Web of Science; Web of Knowledge; AMED; SCOPUS; Dissertation Abstracts.We searched for ongoing clinical trials in the Clinical Trials web site (http://clinicaltrials.gov.) and in the Current Controlled Trials web site (http://www.controlled-trials.com/). We hand searched a range of relevant journals and conference proceeding abstracts. SELECTION CRITERIA: Only randomised controlled trials (RCTs) and controlled clinical trials (CCTs) were included. DATA COLLECTION AND ANALYSIS: Data were extracted independently by MW, MS and LP and differences resolved through discussion. MAIN RESULTS: Six studies were eligible for inclusion in the review. Four of these studies were trials using botulinum toxin-A (BoNT-A) and two were trials on the pharmacological interventions, benztropine and glycopyrrolate. No RCTs or CCTs were retrieved on surgery, physical, oro-motor and oro-sensory therapies, behavioural interventions, intra-oral appliances or acupuncture. In the studies eligible for review, there was considerable heterogeneity within and across interventions and a meta-analysis was not possible. A descriptive summary of each study is provided. All studies showed some statistically significant change for treatment groups up to 1 month post intervention. However, there were methodological flaws associated with all six studies. AUTHORS' CONCLUSIONS: It was not possible to reach a conclusion on the effectiveness and safety of either BoNT-A or the pharmaceutical interventions, benztropine and glycopyrrolate. There is insufficient evidence to inform clinical practice on interventions for drooling in children with CP. Directions for future research are provided.

7. Chowdhury NA

Scialorrhea in children with cerebral palsy (CP) results in aspiration, decreased social integration, and poor quality of life. Managementoptions include transdermal anticholinergics such as the scopolamine patch. A controlled clinical trial has proven botulinum toxin (BTX) injections into the salivary glands are an effective alternative to transdermal anticholinergics with a safer side effect profile. Multiple studies of the injections in diverse populations demonstrate reduction in saliva production with improvement in quality of life and decrease in hospitalization-associated costs. The authors describe a 15-year-old boy with spastic quadriplegic CP who developed emesis, nausea, and lethargy 1 day after the first injection of botulinum toxin A (BTX-A) to his salivary glands for sialorrheamanagement. The authors ascribed his symptoms to scopolamine withdrawal. Given the lack of exposure in the medical literature, there is minimal awareness of the withdrawal syndrome from transdermal scopolamine in children with or without CP, resulting in delayed diagnosis and potential complications. Treatment of the withdrawal syndrome has been successful with meclizine though safety and efficacy has not been established in children younger than 12 despite frequent clinical and over-the-counter use. Prompt diagnosis of the transdermal scopolamine withdrawal syndrome can result in quicker treatment and a shorter hospital stay.

8. Delgado-Charro MB

Transdermal administration offers a non-invasive and convenient method for paediatric drug delivery. The competent skin barrier function in term infants and older children limits both water loss and the percutaneous entry of chemicals including drugs; but the smaller doses required by children eases the attainment of therapeutic concentrations. Transdermal patches used in paediatrics include fentanyl, buprenorphine, clonidine, scopolamine, methylphenidate, oestrogens, nicotine and tulobuterol. Some patches have paediatric labelling supported by clinical trials whereas others are used unlicensed. Innovative drug delivery methods, such as microneedles and sonophoresis are being tested for their safety and efficacy; needleless injectors are primarily used to administer growth hormone; and two iontophoretic devices were approved for paediatrics. In contrast, the immature and rapidly evolving skin barrier function in premature neonates represents a significant formulation challenge. Unfortunately, this population group suffers from an absence of approved transdermal formulations, a shortcoming exacerbated by the significant risk of excessive drug exposure via the incompletely formed skin barrier.