Terapia antalgica topica: solo effetto placebo?

Simone Franzoni

GRG   ICCB
Bimbo in coma per cerotto antidolorifico a Torino. Applicato per sbaglio dalla nonna

16 aprile 2012

Il piccolo di 3 anni è ricoverato in gravissime condizioni all'ospedale Regina Margherita. Per errore la signora 80enne lo ha applicato al nipotino che si era fatto male giocando.

La farmacologia: "Non sono approvati per l'uso pediatrico"
Topical therapy was defined as including treatments intended to act locally with little systemic effect and excluding therapies applied transdermally but intended to act systemically, such as opioids (e.g. transdermal fentanyl or buprenorphine, clonidine, nicotine, nitroglycerin, scopolamine, testosterone).
DUBBIO DEL MEDICO
NON MUTUABILITA’
MERCATO OTC IN CRESCITA

Agenti topici rappresentano fetta crescente del mercato di analgesici da banco (fascia C), ma al medico spesso resta il dubbio sulla loro efficacia, sebbene circa 43% dei pazienti rispondano favorevolmente al trattamento, solo 27% essi vengono consigliati dal medico.
Guideline: recommendations

American Association of Orthopedic Surgeons
Patients with symptomatic OA of the knee and increased GI risk may receive one of the following analgesics for pain: paracetamol (<4 g/day), topical NSAIDs, nonselective oral NSAIDs plus gastroprotective agent, or COX-2 inhibitor

American Geriatric Society
All patients with localized non-neuropathic persistent pain may be candidates for topical NSAIDs

European League Against Rheumatism (hand)
Local treatments are preferred over systemic treatments, especially for mild to moderate pain and when only a few joints are affected. Topical NSAIDs and capsaicin are effective and safe treatments for hand OA

National Institute for Health and Clinical Excellence
Topical NSAIDs for pain relief in addition to core treatment for people with knee or hand OA. Topical NSAIDs or paracetamol should be considered ahead of oral NSAIDs, COX-2i or opioids

Osteoarthritis Research Society International
Topical NSAIDs and capsaicin may be considered as adjuncitives or alternatives to oral analgesics/anti-inflammatory agents in patients with knee OA
VANTAGGI ANALGESICI TOPICI

Evita 1° passaggio tratto gastrointestinale (pH gastrico, metabolismo)
Riduzione effetti collaterali e picchi concentrazione plasmatici
Facilità interrompere somministrazione in caso di effetti indesiderati
Somministrazione mantenuta e controllata per un lungo periodo
Accesso diretto al sito di azione
Somministrazione non traumatica e facile
Utile quando impossibile somministrazione orale
LIMITI ANALGESICI TOPICI

Diffusione attraverso strato corneo solo per molecole < 500 Da
Devono essere idro / liposolubili
Assorbimento dipende da integrità della cute
Enzimi cutanei possono metabolizzare il farmaco
Irritazione cutanea
CATEGORIES OF TOPICAL ANALGESICS

1) analgesics: NSAIDs
   salicylates

2) counterirritants: capsaicin
   menthol
   canfora

3) anesthetics: lidocaine
   EMLA

4) others: opioid (?)
   .......

Delivery Methods for Topical and Transdermal Medications

- Electrical: iontophoresis, electroporation
- Heat: thermophoresis
- Mechanical: microneedle/puncture/perforation, abrasion, needle-less injection, suction, stretching
- Miscellaneous: ultrasound, magnetophoresis, radio frequency, laser and photomechanical waves

American Pain Society

Why are several analgesics sometimes prescribed for a pain condition? They are used because they are better for some patients.

Prescription drug use should be the goal of analgesics, not treatments.

Topical Therapies for Osteoarthritis

Roy D. Altman¹ and H. Richard Barthel²
Topical NSAIDs provide analgesia by the same mechanism of action as oral NSAIDs, but effective activity is intended to be confined to the application site, systemic NSAID exposure with either a gel or a patch formulation is substantially lower than with oral NSAIDs.

DSG = diclofenac sodium 1% gel

D-DMSO = diclofenac sodium 1.5% in 45.5% dimethylsulfoxide solution

Diclofenac gel, solution, and patch have similar efficacy
PLASMA CONCENTRATIONS

Peak plasma concentrations with oral diclofenac were 40-fold higher than with high dose DSG 150-fold higher than with low dose DSG
PLATELET FUNCTION

Usually altered when COX-1 is inhibited at least 95%
Mean COX-1 inhibition with oral diclofenac was 76% which means that some patients met or exceeded the 95% threshold required for the development of bleeding or renal complications.

Mean COX-1 inhibition with DSG was
8% when applied to a single knee
31% when both knees and hands
(COX-1 inhibition did not meet the threshold for clinically meaningful AEs)
SYNOVIAL FLUID

KNEE
Analgesic effects of DSG are probably a product of enhanced concentrations in skin and subcutaneous tissues at the application site. Therapeutic concentrations in synovial tissue and fluid of the knee are not achieved with DSG or patch.

HAND
DSG applied topically to the hand penetrates into synovial tissue. Diclofenac concentrations in synovial tissue excised from patients undergoing hand surgery were 18 to 52 fold higher than those in plasma.
HAND OSTEOARTHRITIS
TOPICAL DICLOFENAC

Topical diclofenac was at least as effective as oral ibuprofen

Double-blind, randomized trial, 321 patients with symptomatic hand OA applied topical diclofenac diethylamine 1.16% gel 4 times daily or took oral ibuprofen 400 mg 3 times daily for 3 w

Equivalent reductions in pain intensity (measured on a 100-mm VAS)
-25 mm vs -21 mm

clinical response (40% improvement in VAS pain intensity over baseline)
44% vs 34%

Similarly equivalent results on secondary outcome measures: measures of disease activity, pain at rest, pain on movement, morning stiffness, grip strength and QoL

HAND OSTEOARTHRITIS
TOPICAL IBUPROFEN VS ARNICA

Double-blind, randomized trial, 204 patients with mild to moderate OA of the hand applied topical ibuprofen 5% gel or topical arnica gel (dosages not specified) 3 times daily for 3 w

Topical ibuprofen and arnica were associated with 35% and 40% reductions in intensity of pain (VAS), respectively

Each treatment was associated with a 38% reduction in functional impairment

(Widrig 2007)
KNEE OSTEOARTHRITIS
TOPICAL DICLOFENAC

Double-blind, randomized, vehicle (placebo) controlled trial, 492 patients with symptomatic knee OA applied DSG 4g 4 times daily to a single knee for 12 w

DSG was accompanied by a
42% reduction compared with baseline in WOMAC pain (Western Ontario and McMaster Universities Osteoarthritis Index pain subscale score)
39% improvement in WOMAC physical function

2/3 of DSG-treated patients met OARSI response criteria
(>50% improvement in WOMAC pain or pain on movement)

KNEE OSTEOARTHRITIS
TOPICAL IBUPROFEN

TOIB (Topical or Oral Ibuprofen for Chronic Knee Pain in Older People) study compared topical ibuprofen 5% cream (1.5 g/day) with oral ibuprofen (1.2 g/day) for up to 2 y

N.585 patients with mild to moderate OA of the knee

Topical and oral ibuprofen each failed to relieve symptoms, but the topical route was generally preferred to oral NSAID therapy

(Underwood 2008)
KNEE OSTEOARTHRITIS
TOPICAL KETOPROFEN

In a 6 w multicentre, randomized, double-blind, active comparator and placebo-controlled trial, ketoprofen gel 4.8 g (110 mg ketoprofen) twice daily was compared with oral celecoxib 100 mg twice daily
N.397 patients with mild to moderate OA of the knee

Improvements in
WOMAC index pain subscale scores (100-mm VAS) were significant for ketoprofen gel (-18; p < .05) and oral celecoxib (-20; p < .01) compared with placebo
WOMAC physical function were significant for oral celecoxib (-17 mm; p < 0.05) but not for ketoprofen gel (-15 mm)

(Rother 2007)
KNEE OSTEOARTHRITIS
TOPICAL PIROXICAM

In a double-blind, randomized trial, 235 patients with mild OA of the knee applied 1 g of piroxicam 0.5% gel (5 mg of piroxicam) or took oral ibuprofen 400mg 3 times daily for 4 w

Both treatments were associated with 30–50% improvements in pain experienced during passive motion, overall pain during the night and overall pain during the day, the ability to stand up straight from a chair, walk on flat ground, climb stairs and perform specified tasks.

(Dickson 1991)
SAFETY AND TOLERABILITY
NSAIDS

Short-Term Safety
In 1 to 12 w placebo-controlled trials of topical NSAIDs, the most common treatment-related AEs have been application-site reactions

Long-Term Safety
D-DMSO was examined in a 1 y, open-label study enrolling 793 patients, including 259 patients aged >65 y
Most common AEs were application site reactions (contact dermatitis 13%). GI and other systemic AEs are infrequent and typically unrelated to treatment

(Shainhouse 2010)
Adverse Effects of Topical NSAIDs in Older Adults with Osteoarthritis: a Systematic Review of the Literature


N.953 articles of which 19 met eligibility criteria.
Subjects receiving topical NSAIDs reported up to 39% application site AEs
up to 17% systemic AEs (5 cases of warfarin potentiation; 1 gastrointestinal bleeding)

Withdrawal rate from AEs was the same in the topical agents and in the oral NSAIDs (double than placebo group)
TOPICAL NSAIDS IN ELDERLY

DSG is well tolerated for up to 1 y for the relief of OA pain in patients both <65 y and ≥65 y (N.575 <65 y N.372 ≥65 y)

4g of DSG or placebo gel to 1 or both knees 4 times daily
Duration of therapy: 1y
Rescue medication: acetaminophen (≤4g/day) was allowed.

Application-site dermatitis occurred less frequently in patients <65 y (9%) compared with patients ≥65 y (13%)
Patients <65 y experienced more gastrointestinal (9%) and cardiovascular events (4%) than p ≥65y (7% and 3% respectively)

DSG provided slightly greater pain relief in patients <65 y, but remained effective for both age groups

(Wieman and Peniston  American Pain Society's 31st Annual Scientific Meeting)
DICLOFENAC

- DICLOFENAC DOROM GEL 1% 50gr 6 EUR
- SOLARAZE GEL 3% 25gr 38
- TRAULEN GEL 4% 25gr 12
- DICLOFENAC RAT.IT 140 mg n.10 cer 17
- FLECTOR 180 mg n.10 cer 20
- VOLTAGAN schiuma 3% 50gr -
- DOLAUT GEL 4% SPRAY 25gr 13
KETOPROFENE

- ARTROSILENE GEL 5% 50gr  8 EUR
- KETOPROFENE Sandoz Crema 50gr 5%  6
- FASTUM GEL 2.5% 50gr  8
- LASONIL GEL 2.5% 50gr  8
- KEPLAT 20 mg n.7 cer  20
SALICYLATES

No studies reported superior efficacy of a salicylate compared with placebo

Methyl salicylate has been associated with
- severe toxicity after topical application, and either accidental or deliberate ingestion
- potentiate the anticoagulant effects of warfarin, increasing the risk of bleeding events
**SALICYLATES**

Nonacetylated salicylates are derived from aspirin (acetylsalicylic acid) but do not share the same mechanism of action as NSAIDs.

Nonacetylated salicylates inhibit COX-2 approximately 100-fold less than does acetylsalicylic acid.

Although the precise mechanisms underlying nonacetylated salicylate-mediated analgesia remain unclear, these agents appear to provide analgesia in part through counterirritation, creating mild irritation of pain receptors to desensitize them.
NSAIDS ANALGESIC EFFECT

Data support the analgesic efficacy of topical diclofenac, ketoprofen formulations in patients with OA affecting 1 or more superficial joints such as those of the knees or hands.

NSAIDS have different analgesia effect and improvement of motion in patients with OA of the knees or hands. Piroxicam and ibuprofen resulted lesser efficacy.
NSAIDS ANALGESIC EFFECT

NSAIDs may be
- suitable primarily for individuals with OA affecting only a few joints
- preferred option for mono-therapy in patients with OA in 1 or several superficial joints, particularly those with an increased risk of NSAID-related systemic AEs

Adjunctive therapy in patients taking a non-NSAID analgesic (opioid). Potential reductions in the cost of monitoring and treating adverse events

Greatly reduced frequency of cardiovascular and GI AEs with topical NSAIDs compared with oral NSAIDs
Per il dolore cronico si ottiene un miglioramento solo nelle prime 2 settimane di trattamento e mai, neanche nella prima settimana, gli agenti topici si rivelavano superiori alla terapia orale né per la loro azione sul dolore né per il miglioramento funzionale

Non si evidenzia nessun beneficio nel trattamento topico di situazioni croniche e che pertanto debbano essere riviste le linee guida sulla terapia dell’osteoartrite che ne suggeriscono l’uso
CAPSAICIN IS RECOMMENDED IN RECENT OA GUIDELINES

However, prescription may best be reserved for use as adjunctive therapy in patients with pain that does not respond sufficiently to other therapies.

STATUS, TOPICAL CAPSAICIN:
Use when individuals are unresponsive to, or intolerant of, other treatments. Regarded as a third-line medication in treatment algorithms for neuropathic pain.

REVIEW ARTICLE

Topical capsaicin for pain management: therapeutic potential and mechanisms of action of the new high-concentration capsaicin 8% patch

P. Anand¹* and K. Bley²
Fig 6 Alterations in skin innervation can be used to categorize neuropathic pain syndromes of diverse aetiologies. (A) Innervation of the skin serves to protect organisms through normal nociception. Growth factors (e.g. NGF and GDNF) are constantly produced in the skin and transported retrogradely to sensory neurone cell bodies. (a) When cell bodies are lost or nerves cut and cannot regrow (‘static’ denervation neuropathies), reduced cutaneous innervation results in intact sensory fibres being exposed to abnormally high levels of neurotrophins; this hypertrophic microenvironment is known to enhance excitability and promote sprouting. (c) In ‘dynamic’ denervation neuropathies, cyclic metabolic or other types of stress render cell bodies unable to maintain their longest axons. During cycles of retraction and regrowth, pro-inflammatory cytokines or other mediators may produce axonal excitation. In addition, intact nerve terminals are subject to a hypertrophic environment. (o) In a class of neuropathies or ‘dynias’ best exemplified by vulvodynia or Gullian–Barré syndrome (GBS), immune system activation (or perhaps other factors) have caused local regions of hyperinnervation by cutaneous nociceptors and these nerve terminals display hyperexcitability.
ATC: N01BX04  6-nonenamide, N-[(4-idrossi-3-metossifenil) metil]-8-metile

Patch di capsaicina (piante del genere Capsicum)
Misura 14 cm x 20 cm (280 cm2) e contiene alte dosi (8%)

Indicata per dolore neuropatico periferico negli adulti non diabetici, da solo o in associazione ad altri antalgici
(non indicata nella neuropatia diabetica: non ancora studiato)

Efficace usato da solo o in associazione a medicinali sistemici per dolore neuropatico
(poor to moderate efficacy in chronic musculoskeletal pain)
CAPSAICIN

Activity was limited to nerve fibres at the skin surface, with nerve bundles in the dermal-epidermal baseline showing less effect.

Nerve fibres reinnervated after discontinuation of capsaicin, returning to 83% of baseline levels over a 6 w period.

APPLICAZIONE CEROTTO CAPSAICINA

Tagliare e adattare alla forma e dimensioni dell’area da trattare: minimizza esposizione ad alte concentrazioni di capsaicina, proteggendo sia paziente che operatore

Cerotto deve rimanere posizionato sulla sede del dolore per 30 min. nel caso dei piedi (neuropatia HIV) e di 60 min. per altre sedi (nevralgia post erpetica)

Non si devono usare più di 4 cerotti contemporaneamente

Applicato esclusivamente dal medico o infermiere sotto il controllo medico

Marcare zone più dolorose sulla pelle con pennarello

Prima di applicare lavare con acqua e sapone e asciugate, rasare i peli.

Poi applicare gel o crema anestetici per ridurre la sensazione di puntura

Di solito pelle punge o si arrossa e brucia durante e dopo il trattamento per breve tempo

Se molto dolore, applicare raffreddamento locale o antalgico

Calzini monouso sopra i cerotti se il trattamento viene effettuato sui piedi (kit)

Al termine del trattamento pulire cute trattata con del gel detergente (kit), lasciato sulla pelle per 1 minuto e poi tolto per eliminare eventuali residui di medicinale rimasti sulla pelle dopo il trattamento. Dopo aver rimosso il gel detergente, la zona viene lavata delicatamente con acqua e sapone.

♦ PRECAUZIONI: No parti della testa, faccia, cute lesa o ferite aperte. A causa del dolore, la pressione arteriosa potrebbe aumentare
FARMACOCINETICA CAPSAICINA

Assorbimento circa 1% nello strato epidermico e dermico della cute durante applicazioni di 1 h

Quantità rilasciata dal cerotto per ogni h è proporzionale alla superficie di applicazione, questo equivale ad una possibile dose max totale stimata per area di applicazione 1000 cm2 di circa 7 mg (MAX 4 cerotti)

Non si osservavano livelli rilevabili di metaboliti in nessun soggetto

PLASMA: livelli molto bassi, picco circa 20 min. dopo averlo tolto e scendono molto rapidamente (t/2 eliminazione media 130 min)
Scomparsa entro 3-6 h dopo rimozione
MECCANISMO AZIONE CAPSAICINA

Anni ’90: uso ripetuto nel tempo porta deplezione della sostanza P. Per ottenere una risposta, veniva somministrata a basse dosi, in pluri-somministrazioni giornaliere (3-4 volte/die) e per periodi prolungati (circa 1 mese)

Recentemente identificato recettore Transient Receptor Potential Vanilloid-1 (TRPV1 o recettore della capsaicina), ampiamente espresso nelle fibre sensoriali di piccolo diametro (C e Aδ), ma è presente anche a livello di altre membrane fisiologiche

TRPV1 sensibili a stimoli: calore, pH acido e agenti chimici endogeni o esogeni (capsaicina)
Stimolato il recettore, canale si apre, passaggio ioni Ca e Na, depolarizzazione membrana neuronale, formazione/propagazione potenziale azione che viaggia lungo il nervo fino al cervello, dove viene percepito come una sensazione dolorosa urette. **Attivazione terminazioni nervose nocicettive già iperattive** (sensazione di puntura ed eritema dovuti al rilascio di neuropeptidi vasoattivini)

“**Desensibilizzazione**”: stimolazione continua TRPV1, aumenta in modo massivo concentrazione intracellulare Ca che attiva proteasi Ca-sensibili e modifica le forze osmotiche all’interno neurone (risposta adattativa della soglia)

Degenerazione neuriti che regrediscono dall’epidermide verso gli strati interni
Fig 4 The site of action of topical capsaicin is in the skin, and pain relief is not mediated by transdermal systemic delivery. Owing to near insolubility in water, capsaicin is not readily absorbed into the microvasculature. When cutaneous nociceptors are hypersensitive and sometimes spontaneously active, localized defunctionalization of capsaicin-responsive nerve fibre terminals in the epidermis and dermis can reduce the afferent barrage which may drive pain syndromes. Inset shows how mitochondrial dysfunction leads to nerve terminal retraction.
Fig 5  Topical capsaicin treatment leads to a reversible loss of ENFs. Human leg (calf) skin biopsies pre-capsaicin treatment (baseline; A, PGP 9.5; D, TRPV1), 1 day post (B, PGP 9.5; E, TRPV1), and 54 days post (C, PGP 9.5; F, TRPV1) capsaicin treatment. Biopsies were immunostained with antibodies to structural nerve marker PGP 9.5, and heat and capsaicin receptor TRPV1. There was a marked loss of ENFs and sub-ENFs after capsaicin treatment for 3 days (day 1 biopsy), with regeneration of a majority of ENFs by day 54. Magnification ×40.
Solo cambiamenti nei segmenti distali delle fibre nervose lasciando intatto gran parte assone e corpo cellulare del ganglio della radice dorsale, anche dopo applicazioni ripetute del principio attivo.

Vitalità tronchi nervosi subdermali e nucleo evidente in quanto interruzione trattamento coincide con rigenerazione terminazioni nervose.

Sensazioni che dipendono dai nervi cutanei che non esprimono TRPV1 restano inalterate (stimoli meccanici e vibratori).

Alterazioni indotte da capsaicina nei nocicettori cutanei sono reversibili: percezione di sensazioni nocive si ripristina in alcune settimane.
EFFICACIA CAPSAICINA

Di solito certo sollievo dal dolore 1° g di applicazione
Possono essere necessari 1-14 g prima che si manifesti tutto effetto analgesico
Può essere ripetuta ad intervalli 90 g

Efficacia di una singola applicazione di
30 min ai piedi è stata dimostrata per neuropatia HIV
60 min in sedi diverse dai piedi è stata dimostrata per PHN
EFFETTI INDESIDERATI CAPSAICINA

Molto comuni:
arrossamento, dolore nella zona applicazione

Comuni:
prurito, bozzi, bolle, gonfiore, secchezza zona applicazione

Non comuni:
ponfi, formicolio, infiammazione, aumento sensibilità, irritazione, ematoma
ipertensione, riduzione sensibilità arti, sensazione di brucio, irritazione agli occhi, tosse, irritazione gola, nausea, prurito, dolore arti, spasmi muscolari
COUNTERIRRITANTS or
TOPICAL RUBEFACIENTS

Canfora (TRPV1, TRPV3), mentolo ed eucaliptolo (TRPM8) appartengono ad una categoria di analgesici topici che eccitano e di conseguenza desensibilizzano i neuroni sensori nocicettivi; modificano flusso ematico

Pochi studi clinici

Principi attivi:
• Canfora 4%
• Mentolo 10%
• Metilsalicilato 30%
STATUS, TOPICAL LIDOCAINE:
Topical lidocaine patch 5% is considered a first-line treatment for localized neuropathic pain (but not for central NP). Lidocaine gel 5% can be used when patch is not available or cost precludes use.

Lidocaine has varied absorption depending on the duration of application and the surface area over which it is applied. Only 3% of the applied dose is expected to be systemically absorbed.

Approximately 70% protein bound. Metabolism in the skin is unknown. Metabolized rapidly by the liver to a number of metabolites which are then renally excreted.

Caution in patients receiving Class I antiarrhythmic drugs (tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.
5% lidocaine vs pregabalin in post-herpetic neuropathy and diabetic painful neuropathy  

Baron (2009) Clin Drug Invest

• 4 w comparison trial: 55 PHN, 91 DPN

• **4 lidocaine patches** up to 12 h/day vs **pregabalin** (150 mg/d w1, 300 mg/d w2; increased to 600 mg/d if needed w 3/4)

OUTCOMES

• 65% vs 62% respond to treatment

• 4% vs 39% AEs

• 1% vs 20% discontinued due to AEs

• similar pain relief in PHN and DPN but fewer AEs
Areas of peripheral nerve injury have been associated with an abnormally elevated expression of Na channels, which may contribute to the hyperexcitability of nerves.

Block abnormal activity of Na channels, providing analgesia to a local area.

Without substantial systemic absorption, the most common AEs are mild local reactions.

Lack of systemic AEs and drug interactions can be particularly advantageous in older patients or patients with complex NP.
Patch 5% lidocaine has shown efficacy and excellent tolerability in RCTs involving patients with PHN and allodynia and in patients with allodynia due to different types of peripheral NP.

Lidocaine gel (5%), which is less expensive than the patch, has also shown efficacy in patients with PHN and allodynia.

Topical lidocaine is most appropriate in well-localized NP, and it is unlikely to be of benefit in patients with central NP. Unfortunately, attempts to predict which patients are most likely to respond to treatment with topical lidocaine have been generally unsuccessful.
LIDOCAIN ANDnociceptive pain

Effectiveness of lidocaine 5% is also being investigated in painful diabetic neuropathy, low back pain, and OA, but controlled trial data are not yet available in these pain states.
**LIDOCAINA**

- EMLA crema 2,5% (+prilocaina) 5gr  12 EUR
- LIDOCAINA spray 50gr 15%  23
- LIDOCAINA crema 5% 30gr  12
- LUAN pomata 2,5% 15gr  7
TOPICAL ANESTHETICS

Topical analgesics differ from topical anesthetics, which result in local pain relief by causing a reversible loss of sensation.

1) **Eutectic mixture of local anesthetics (EMLA) cream** *(an oil-in-water emulsion in which the oil phase is a combination of 2.5% lidocaine and 2.5% prilocaine)*

2) **L.M.X.4**: 4% lidocaine employing a liposomal delivery system to allow better penetration of the skin

3) **Lidocaine-tetracaine combination (S-Caine)** available as a cream or patch (Synera)
Not recommended for the control of chronic pain

Application reserved for transient pain relief due to **minor dermatologic procedures or venipuncture**
OTHER TOPICAL AGENTS

GTN (glyceryl trinitrate) ointment, patch
• releases NO, acts on vascular endothelium and sensory nerve endings
• analgesia in tendonitis, osteoarthritis

Doxepin 3-5% (+/- capsaicin)
• Analgesia in neuropathic pain (2 trials)
• Also oral rinse for mucositis (1 trial)

Amitriptyline (0.5-2%) + Ketamine (1-4%)
AMI= inhibits NA/5-HT uptake; blocks Na+ channels and H1, mACH, Î±-ARs...
KET= blocks NMDA-Rs; inhibits Na/5-HT uptake, blocks Na+ channels
In addition to opioid receptors in CNS, peripheral neurons, neuroendocrine (pituitary, adrenals), immune, and ectodermal cells also express opioid receptors. *These peripheral opioid receptors (μ, δ, κ) play a critical role in modulating pain and inflammation.*

_Peripheral mechanisms of opioid analgesia?_
Immune cells migrate to sites of tissue inflammation, and release opioid peptides in response to stress, or release agents such as corticotrophin-releasing factor, chemokines, cytokines, and norepinephrine.

Opioid peptides bind to peripheral opioid receptors expressed on sensory nerve fiber terminal endings, activate and produce analgesia by inhibiting the excitability of sensory nerves, and /or inhibit the release of pro-inflammatory neuropeptides (substance P, calcitonin gene related peptide)
Clinically significant analgesia is obtained from this neuro-immune interaction without the accompanying side effects commonly associated with centrally mediated opioid analgesia.

Endogenous immune cell derived opioids do not readily produce cross-tolerance to morphine, but rather prevent development of tolerance at peripheral opioid receptors.

Strategies and treatments that selectively attract opioid producing immune cells, increase expression of opioid receptors in damaged tissues in the periphery, and selectively activate peripheral opioid receptors appear to have immense therapeutic potential.
Experimental and clinical research has demonstrated that opioids can produce potent and receptor specific analgesic effects outside the central nervous system.

Mechanisms of endogenous pain inhibition by opioid peptide-producing immune cells may be important for understanding pain in immune compromised states such as cancer, diabetes, and acquired immunodeficiency syndrome (AIDS).
TOPICAL OPIOIDS IN PALLIATIVE CARE

• Used for painful skin and mucosal lesions
• Case reports and some trials report favorable outcomes
• Need for primary studies to inform practice guidelines

• Preclinical studies indicate opioids act peripherally in inflammatory and in NeP models

THE FUTURE

- Knowledge of peripheral pain mechanisms reveals new drug targets

- Novel topical analgesic formulations will be developed for both inflammatory and neuropathic pain conditions (proof-of-concept, efficacy, safety data)

- Topical formulations will consist of new targets (e.g. TRPV1 receptor antagonists, cannabinoids) and novel combinations
CONCLUSIONI

- Diclofenac e ketoprofene per dolori osteoartrosici (nocicettivi = infiammatori) delle mani e ginocchia
- Capsaicina 8% solo per dolore neuropatico posterpetico e HIV
- Lidocana 5% per dolore neuropatico (e osteortrosico ?)

- Dolore lieve-moderato
- Prima scelta o terapia antidolorifica complementare
- Applicazione laboriosa (3-4 volte / die)
- Costi ?

- Nuove molecole per terapia topica (oppioidi, cannabinoidi)
grazie

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