Diclofenac solution (Pennsaid) in the management of osteoarthritis of the knee : patient implications.

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Abstract: Topical diclofenac sodium (pennsaid) is a non-steroidal-anti- inflammatory drug that is used to manage the recurrent pain and symptoms of osteoarthritis of the knee. Pennsaid is applied topically, absorbed cutaneously and concentrates locally at the site of application. Tugwell et al. [54] has shown that pennsaid is as efficacious as oral diclofenac as a mode of pain relief without systemic effects. The most common side effect induced by pennsaid is the development of dry skin at the site of application. This is caused by dimethyl sulfoxide which is the vehicle used in the pennsaid formulation. Dimethyl sulfoxide dissolves the natural oils in the skin causing dryness.

Introduction to management issues in the treatment of osteoarthritis knee

Osteoarthritis (OA) is a common condition that is associated with degeneration of joints. It is estimated that between 21 and 40 million people suffer from OA often involving at least one joint [1, 2, 3]. It is postulated that OA will become a global cause of disability by the year 2020 [4] OA is a disorder of middle aged people, predominantly women and is a disease that progresses with advancing age [2,5,6]. Although it is common for radiographic evidence of OA to be present in individuals over 65 years [7], the severity of symptoms may correlate poorly with radiographic pathogenic alterations [8]. OA was once referred to as a 'wear and tear' disorder due to the progressive loss of articular cartilage from joints and underlying bone [8] which can lead to joint inflammation. Common sites for OA sites include the weight bearing joints such as the hip and knee [9]. These changes can be debilitating and painful [8]. In OA of the knee the characteristic symptoms which can be used to diagnose the condition include: joint pain in and around the knee joint site which may vary on severity from a constant dull ache to a sharp pain with motion; joint instability; crepitus (irregularity of opposing cartilage surfaces) on motion and limitation of range of motions leading to possible immobility; potential alterations to the gait; bony enlargement in affected joints; osteophytes on X ray, loss of ; function; morning stiffness lasting up to 30 minutes and age over 50 years [2, 5]. The onset of symptoms can be insidious. Pain may be worse during motion and can be alleviated by rest. These defining characteristics are required because pathogenic changes on X ray may occur without the patient demonstrating symptoms of pain.

In terms of the pathogenesis of OA of the knee, the central features include degenerative changes to the articular cartilage of joints, osteophyte (new bone) formation, progressive narrowing of the joint space between bone endings, subchondral sclerosis, chrondrocalcinosis and bone deformity [10]. OA develops when cartilage catabolism exceeds the process of cartilage synthesis. The proteolytic digestion of cartilage has also been associated with numerous cytokines; Interleukin-1 and tumour necrosis factor β [11]. It is proposed that insulin growth factor 1 and tissue growth factor β may be involved in cartilage synthesis and repair processes [12].These inflammatory changes are responsible for the destruction of the joint capsule. As the articular cartilage gradually erodes nociceptors become sensitized causing pain [13]. Pain can develop from the subchrondral bone, periosteum, joint capsule, synovial membrane, peri-articular muscles and ligaments and can result from the stretching of the adjacent periosteum, growth of osteophytes, impact of microfractures, intraosseous pressure and synovitis [14] . These changes can lead to limitations in movement and disability [15, 16].

Pain is a complex sensory process which is related to specific tissue damage. In traumatic situations, inflammatory mediators such as prostaglandins, neuropeptides like substance P and calictonin-gene related peptide are released from blood vessels where they act as a stimulus and cause peripheral nociceptor C and Aδ fibers to depolarize. This leads to the transmission of signals (signal transduction) via the dorsal horn to the cerebrum. During inflammation, signal transmission to the dorsal horn does not require a stimulus therefore a hyperresponsive response exists. This hyperresponsive response can be controlled by Non Steroidal Anti-Inflammatory Drugs (NSAIDs) [17].

Management of OA and patient considerations

Currently there is no cure for OA. Historically, pain management options include both non-pharmacological and pharmacological approaches. Non-pharmacological management includes: dietary advice and exercise to encourage weight loss, social support, assistive devices for ambulation, appropriate footwear, occupational therapy, joint protection and devices to assist activities of daily living [2]. The efficacy of these approaches is limited because pain restricts mobility and willingness and ability to undertake any form of physical activity. Inactivity can hasten disability and exacerbate joint pain. For these reasons pharmacological treatment is viewed as the mainstay of treatment. Pharmacological approaches include the use of regular analgesics such as paracetamol to control pain. In patients with uncontrolled pain and symptom control the recent EULAR recommendations [18] suggest that NSAIDs can be used as part of pain management or patients with OA of the knee.

NSAIDs are a large range of drugs that includes; acetic acid derivates such as indomethacin and diclofenac, salicylates and commonly used propionic acid substitutes such as ibuprofen and naproxen. These oral forms of NSAIDs are commonly used for patients with moderate to severe OA related pain. However they are not without their drawbacks; NSAIDs are associated with the risk of gastrointestinal disturbance, gastrointestinal bleeding, gastric ulceration and renal disease complications and toxicity even at low doses [19]. The risk of gastrointestinal toxicity is increased in patients over the age of 65 years, those with a history of gastric ulcer, gastrointestinal bleeding particularly in patients who are prescribed multiple doses of NSAIDs [20]. In patients it is advisable to prescribe NSAIDs at the lowest possible dose possible and increase the dose as tolerance develops [21].

Cyclooxygenase -2-(COX-2) specific inhibitor such as celecoxib have also been used to manage the pain and symptom control in patients with moderate to severe pain associated with OA of the knee. Although studies show that COX -2 inhibitors are efficacious in the management of osteoarthritic symptoms [22, 23] can produce equivalent pain relief to the NSAID diclofenac [24, 25, 26], 27, 28] and are less likely to produce gastrointestinal disturbances but there is the increased risk of cardiovascular complications such as stroke and cardiac arrest. This problem led to the withdrawal of 2 widely used COX-2-specific inhibitors, rofecoxib and valdecoxib from the market.

Topical NSAIDs are a safer option as the formulation allows the drug to be absorbed cutaneously in to the dermis, reaches its target site, the synovial membrane, peripheral nerves and soft tissues local to the site of application [29] and has low systemic availability [30]. The topical formulation improves tolerability with fewer reported fewer side effects, particularly reduced gastrointestinal side effects [31,32].. Numerous topical NSAIDs are now available of these, topical diclofenac is reported to be as efficacious as oral formulations without the risk of systemic side effects [33] .Additional reports indicate the added benefit of using topical diclofenac in terms of its ability to quickly relieve symptoms of morning stiffness, control pain and physical mobility [34, 35, 36]. Oral forms of diclofenac have been compared with paracetamol [37, 38, 39], leech therapy [40], enzymic anti-inflammatory compounds [41]. In all studies, diclofenac produced greater pain control and improved mobility in patients with OA.

Since its development topical diclofenac has been used as an anti-inflammatory drug to alleviate the pain symptoms in patients with OA and researched in short-term, 2 week studies [42] and compared to ketoprofen [43] and placebo [44]. This time duration is too short to measure therapeutic effectiveness particularly as OA is a long-term chronic disease that

requires treatment over long periods of time. In order to assess the efficacy and safety of topical NSAIDS, studies should be conducted over periods longer than two weeks. Studies of short duration are unlikely to capture important long-term safety information which will be of importance for ongoing applications of gels, creams or sprays in chronic conditions.

Drug Profile

Diclofenac sodium is an arylacanoic acid and NSAID with analgesic properties. Consistent with other NSAIDs, diclofenac sodium interacts exerts its actions by inhibiting the cycloxygenase (COX) group of enzymes. Two forms of the COX enzyme exist; COX-1 is associated with gastric epithelium; COX-2 is responsible for prostaglandin synthesis. Inhibition of COX-2 reduces the production of inflammatory mediators such as prostaglandins [45, 46], substance P and interleukin-6. Diclofenac also alters G-protein mediated signal transduction pathways [29] and interacts with nociceceptors by exerting an enhanced effect on hyperalgic muscle [47].

Diclofenac sodium is formulated as a lotion with the absorption enhancer dimethyl sulfoxide (DMSO). DMSO aids absorption of Diclofenac sodium particularly following repeated dosing [48, 49]. The absorption of diclofenac sodium can be altered by the integrity of the skin and impact of dehydration [50] DMSO is absorbed locally and distributed with plasma levels of 0.48 μg/mL detected after 8 hours. The mean whole blood level of DMSO was 647±659.3 ng/mL 6 hours after the last application. The mean elimination $t_{½}$ was 8.4 hours [50].

Following a single application of diclofenac sodium the mean peak plasma diclofenac sodium concentration (Cmax) was 9.7±4.7 ng/ mL after 24 to 48 hours. After multiple applications, 4 times per day for 84 days, the mean plasma level of diclofenac sodium as was 8.95±9.17ng/mL [50]. In open label studies, patients administered 40 drops of diclofenac sodium to both knees for 8 days. Steady state was reached by day 6 and on day 8 and the mean plasma Cmax was 19.4 ng/mL with a mean Tmax of 4 hours. Values for the terminal $t_{½}$ was 79.0 hours.

Diclofenac is metabolized by cytochome P450 (CYP2C) and undergoes hydroxylation during phase 1 to form hydroxylated derivatives which then undergo methylation followed by conjugation with glucuronic acid to form metabolites either as conjugates or sulfates during phase 2. The enhancer DMSO is either oxidized during phase 1 to form dimethyl sulfone or reduced to form dimethyl sulfide with no trace amounts detected following multiple dosing [49, 50].

In terms of the drug elimination of diclofenac sodium, the plasma clearance is 263±56mL/ min. Up to 60-70% of metabolites are excreted in the urine [51] and 30% of metabolites are excreted in the faeces [50].

Efficacy studies

Several studies have examined the effects of pennsaid on pain control and the associated symptoms of OA using the validated Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC) [52].. The WOMAC index examines pain, morning stiffness and physical function using a questionnaire in patients with OA of the knee. The questionnaire has 24 questions (5 pain related; 17 related to physical function; 2 on morning stiffness), patients respond to each question using a likert scale of mild to extreme measured on a scale of 1-5. The WOMAC questionnaire has a reported cronbach's alpha of 0.93 and a test-retest reliability of 0.86 [52]. Four randomized controlled trials (RCTS) examined the efficacy of topical diclofenac compared to either a vehicle containing the absorption enhancer DMSO or oral formulations of diclofenac [33, 34, 35, 36]. See Table 1.

The efficacy of topical diclofenac was assessed in patients aged 40-85 years, predominantly female, with a history of OA of the knee defined by one key characteristic, e.g. radiological evidence of abrasion, deterioration of articular cartilage, osteophyte formation at the surface of the knee or flare of pain after removal of analgesic therapy. Patients with evidence of OA knee were randomized to topical diclofenac or DMSO for periods of 4-12 weeks [34, 35, 36]. Salient findings indicate that patients receiving topical diclofenac reported significant pain relief, improved physical function and morning stiffness compared to patients administering a vehicle control solution [34., 35, 36]. In the longest duration study (12 weeks) reported improvements in pain control ($p=0.01$), physical function ($p= 0.02$), morning stiffness ($p=0.05$) [36] Additional parameters pain on walking was favourably assessed by patients ($p=0.04$) and patient global assessment ($p=0.03$). Patient global assessment (PGA) is based on OMERACT-OARSI responder criteria [53]. A responder is defined as a patient with >50% improvement in pain or function that was graded as $\geq$ 20% of the scale or $\geq$ 20% improvement in at least two areas; pain and physical function or a PGA that was $\geq$ 10% of the scale. Baer et al., [34] reported PGA of (-1.3 vs 0.7, $p=0.001$) wheras Bookman et al. [35] reported a PGA ($p=0.039$).

In all three studies, the main reported side effect of topical diclofenac was dryness of the skin around the site of application. This effect was reported in 36% of patients [35], 39% of

patients [34] and 41% of patients [36]. In all studies this side effect led to less than 6% of patients discontinuing treatment (34, 35, 36]. In the study by Roth et al., [36] patients complained that the solution used in topical diclofenac and in control caused halitosis or garlic breath. This is due to the metabolism of DMSO to dimethyl sulfide and dimethyl sulfone [54].

It was also reported that 1 patient treated with topical diclofenac showed minor elevations in serum alanine aminotransferase and aspartate aminotransferase. [35] This elevation was 1.2 times the upper limit of normal when both levels were elevated. This effect was not repeated in the DMSO only group. More recently, Tugwell et al., [33] reported elevated serum alanine aminotransferase and aspartate aminotransferase in 2-5% of patients receiving topical diclofenac and 10%-17% of patients administering oral diclofenac [33].

Tugwell et al. [33] also found no clinically significant differences between topical diclofenac compared to an oral diclofenac formulation. In both drug groups, patients developed symptoms of dyspepsia, diarrhea, nausea, flatulence and abdominal pain. However, these gastric symptoms were more common in patients receiving oral diclofenac. Up to patients (27%) administering topical diclofenac reported symptoms of minor skin irritation or pruritis. The development of drug-induced pruritis concurs with reported studies [34, 35, 36]. In addition, some patients developed a vesiculobullous rash, of these 5% discontinued their treatment [33] which concur with published findings [35]. Following discontinuation of treatment, the symptoms of rash resolved.

Following an assessment of RCTs it was reported that pennsaid is a safe and effective alternative NSAID for patients with OA knee [33]. The main drawback of treatment is the development of dry skin.

Safety and tolerability

Historically NSAIDs have been associated with serious gastrointestinal and renal disorders such as peptic ulceration, ulcer perforation, gastrointestinal bleeding, anaemia [33], acute renal failure and small bowel injury [55]. The use of topical diclofenac markedly reduces the incidence of these adverse effects due to systematic exposure without loss of efficacy. [56]. Dyspepsia is a common side effect of NSAIDs, should patients experience symptoms of dyspepsia, they should be instructed to notify the prescriber immediately. Prescribers need to be pharmacovigliant to respond quickly to gastric symptoms as gastrointestinal bleeding or ulceration can occur quickly and in such conditions pennsaid should be discontinued. Patients need to be educated about the need for follow-up if gastric symptoms occur. In patients with a

history of peptic ulceration, inflammatory conditions of the bowel such as Crohn's disease or ulcerative colitis, pennsaid should be prescribed under close supervision. Furthermore, in older people, pennsaid should be prescribed under close supervision due to increased susceptibility to adverse drug reactions and risk of lower esophageal ulceration and bleeding [50].

The long-term safety of pennsaid is unknown, because of this, the drug should be used as a treatment regimen for OA knee for no longer than three months either as a continuous or intermittent therapy. Pennsaid should not be prescribed for lactating women due to deficient safety data. In addition to this, pennsaid should not be administered concurrently with other NSAIDs because of the risk of additive side effects or applied directly to open wounds, abraded or infected skin [50]. Due to the risk of anaphylaxis, pennsaid should not be used in patients with a history of asthma, urticaria/ angioedema, or nasal polyps.

Pennsaid causes a dose-dependent reduction in prostaglandins which can lead to overt renal decompensation. As a result of this, patients with a history of impaired renal function, heart failure particularly older people may be susceptible to renal toxicity. If these types of patients are prescribed Pennsaid, they need to be monitored carefully [50] .

DMSO is a relatively safe compound with no reported nephrotoxicity or mutagenicity. However, DMSO is metabolized to form dimethyl sulfide which is a volatile gas that can either be excreted via the skin or through the breath and cause a garlic-like odour/ taste which can be unpleasant for patients [54]. DMSO dissolves the fat cells in skin causing dryness of the skin which can be unpleasant for patients. In recent trials, pennsaid caused skin irritation in up to 39% of patients this is rather high and can possibly led to discontinuation of treatment [34, 35, 36].

There is a paucity of evidence that has examined patient's views on the treatment of pennsaid. Patient considerations tend to be reflected in accounts of RCTs with regard to symptoms encountered or data on drop out from studies, e.g. lack of effect from drugs used [35]. It is important that authors report patient considerations, albeit, the short duration of studies may be a prohibiting factor in such exploration.

Conclusions

Pennsaid is a topical NSAID which has been shown to be an effective and safe alternative for patients with OA of the knee. Four RCTS have demonstrated that pennsaid can significantly

improve WOMAC criteria; pain control, physical function and morning stiffness as well as improving OMERACT-OARSI responder criteria patient global assessment. Tugwell et al., [332004) found that pennsaid produced equivalent efficacy to oral diclofenac in patients with OA knee. In the remaining three RCTS, pennsaid was more efficacious then control in terms of WOMAC criteria. The most common side effect specific to pennsaid was the development of dry skin; in the majority of patients this was not severe enough to cause patients to discontinue therapy. In a small number of patients, gastric symptoms and elevated liver enzymes were reported however these changes were not significant enough to discontinue therapy. Data on patient experiences of using pennsaid are limited to the reporting of symptoms. Additional studies are needed to explore in depth how patients respond and potentially benefit from using pennsaid. Overall the data from RCTs indicate support the use of pennsaid as a topical NSAID to be used continuously in patients with OA of the knee for periods of up to 12 weeks.

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Table 1. Characteristics of RCTs and meta-analyses involving OA of the knee

PARAMETERS	BAER	BOOKMAN	ROTH	TUGWELL
Study	RCT	RCT	RCT	RCT
Duration	6 weeks	4 weeks	12weeks	12 weeks

Sample	216	248	326	622
Drug	1.5% dic. Na	1.5% dic Na	1.5% dic Na	1.5% dic Na versus oral dic.
Pain relief reduction	-5.2vs 3.3. p= 0.002	-3.9 vs -2.5 p=0.023	-7.1 vs -5.6. p=0.02	44% dic na versus 49 % oral dic.
Physical function Improvement	-13.4vs -6.9 p= 0.01	-11.6vs -8.4, p=0.023	-18.5 vs -14.3 p=0.04	39% dic na versus 46 % oral dic.3
Stiffness Improvement	-1.8 vs -0.9 p=0.002	-1.5 vs -0.7 p=0.003	-2.3 vs -1.6 p=0.02	39% dic na versus 45 % oral dic.
PGA improvement	-1.3 vs -0.7 p=0.001	-6.7vs 7.8 p0.039	-1.5 vs -1.2 p=0.06	43% dic na versus 49 % oral dic.
Side effects	Dry skin in 39% of cases	Dry skin in 36% of cases	Dry skin in 36.6% of cases	Dry skin in 27% of 1.5% Dic Na cases

Dic Na refers to diclofenac sodium solution.

Oral dic. Refers to 50 mg oral diclofenac capsules

Pain, physical function and stiffness were assessed using the WOMAC LK3.1 OA index criteria measured on a 5 –point likert scale where 0 indicates none, 1 indicates mild, 2 indicates moderate, 3 indicates severe and 4 indicates extreme.

PGA refers to physical general assessment measured using a visual analogue scale from very good (0) to extreme (4).