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# The use of topical diclofenac in the pain management of osteoarthritis of the knee

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## Abstract

Osteoarthritis (OA) is a common complaint that affects millions of people worldwide. As there is no cure for OA, drug treatment is the main form of management. This can be achieved through the use of analgesics and anti-inflammatory drugs such as the NSAID diclofenac sodium. The chronic use of diclofenac sodium can lead to adverse gastrointestinal problems. The use of a topical formulation of diclofenac sodium aims to reduce this problem. Evidence from four randomized controlled trails of the efficacy and safety of topical diclofenac sodium as a method of pain relief for the treatment of OA of the knee is presented and discussed. Findings imply that topical diclofenac sodium is an efficacious and safe method of pain control in patients with OA of the knee.

## Introduction

Osteoarthritis (OA) is a common degenerative joint disorder that affects people from third decade of life and progresses with advancing age (Altman, 2004, Hillaire, 2006). In the US, it is estimated that between 21 and 40 million people suffer from OA with at least 70% to 90% of the population suffering from degenerative changes involving at least one joint (Arthritis Foundation, 1999, Hillaire 2006, Oddis, 1996). The prevalence of OA increases with the ageing process (Lawrence & Hochberg, 1989). Gender appears to influence the onset of OA, where women are twice as likely to develop OA in the hands and knees compared to age-matched men (Solomon, 2001).

OA was once referred to as the 'wear and tear' disorder due to the progressive loss of articular cartilage from joints and underlying bone (Felson et al., 2000), often leading to joint inflammation. Weight bearing joints are commonly affected (Health Notes, 2005) but the hands, spine, ankles, wrists, elbows and shoulders can also be affected (Hillaire, 2006). The characteristic symptoms include; joint pain, joint instability, loss of function, morning stiffness lasting up to 30 minutes, pain with motion and limitation of range of motions, crepitus with motion and bony enlargement in affected joints (Hillaire, 2006).

Currently there is no cure for OA. Management options involve both non-pharmacological and pharmacological treatment forms. Non-pharmacological management includes the following; patient education about diet, encouraging weight loss and exercise, social support, assistive devices for ambulation, appropriate footwear, occupational therapy, joint protection and devices to assist activities of

daily living (Hillaire, 2006). Even though these forms of treatment are available, it is established that 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. Analgesics such as paracetamol and tramadol and antinflammatory agents such as Non-Steroidal Anti-inflammatory agents (NSAIDs), cyclooxygenase -2-(COX-2) specific inhibitors such as celecoxib, intra-articular glucocorticoids and hyaluronate are the main forms of treatment. The NSAIDs represent the largest range of drugs that includes; salicylates, propionic acid substitutes such as ibuprofen and naproxen, acetic acid derivates such as diclofenac and indomethacin. Oral forms of NSAIDs are used for patients with moderate to severe OA related pain they carry the risk of gastrointestinal disturbance and toxicity even at low doses (DeAngleo & Gordin, 2004). The risk of gastrointestinal toxicity is increased in patients over the age of 65 years, those with a history of gastrointestinal bleeding or gastric ulcer, patients concomitantly prescribed oral corticosteroids, anticoagulants or multiple doses of NSAIDs (Lichtenstein et al., 1995). Due to the added risk of developing gastrointestinal toxicity, patients are prescribed NSAIDs at the lowest dose possible and increasing the dose as tolerance develops (ACR, 2000).

Oral forms of diclofenac have been compared with paracetamol (Case et al., 2003, Pincus et al., 2001, Pincus et al.,2005) novel anti-inflammatory compounds (Lung et al., 2004), leech therapy (Michalsen et al., 2003), enzymic anti-inflammatory compounds (Akhtar et al., 2004). In all studies, diclofenac produced greater pain control and improved mobility in patients with OA.

COX-2-specific inhibitors are appropriate for patients with moderate to severe pain associated with OA of the knee and hip. Numerous studies have demonstrated that COX-2 inhibitors are efficacious in the management of osteoarthritic symptoms (Fleischmann et al., 2006, McKenna et al., 2001) and can produce equivalent pain relief to the NSAID diclofenac (Alvarez-Soria et al., 2006,Gottesdiener et al.,2003, Liang & Hsu, 2003, Schnitzer et al., 2004, Zacher et al., 2003). COX-2 inhibitors are less likely to produce gastrointestinal disturbances but unfortunately run the 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. This problem was the stimulus for the development of a topical formulation of the NSAIDs diclofenac sodium. This formulation is absorbed via the dermis and has low systemic availability (Brunner et al., 2005) and has markedly reduced gastrointestinal side effects (Evans et al., 1995).

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 (Cooper et al., 2004, Grace et al., 1999, Lin, et al., 2004) and compared to ketoprofen (Waikakul et al., 1997) and placebo (Dreiser & Tisne-Camus, 1993). This time duration is too short to measure therapeutic effectivness 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 use of topical NSAIDS, it was necessary to conduct studies over periods longer than two weeks. Studies of short duration were not included as they 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. This paper aims to explore the use of the topical NSAID diclofenac sodium in the pain management of treatment of OA of the knee.

**Method**

Papers were selected that were published from 1999 to 2006 commensurate with current developments in drug formulation and drug availability. Search strategy used included; Cochrane Library, EMBA, Pub Med., Medline, Pre-Medline to include access to both UK and International Research. The following web-based journals were also reviewed; J. Rheumatology, BMC, Muscloskeletal Journal, Canadian MA Journal, J. Clinical Rhuematology, Br, J. Clinical Pharmacology, Archives of Internal Medicine and the American J. of Medicine. Drug based information was located from relevant websites; virtual rheumatology centre, mayoclinic, creative consultants, yahoo health, medscape and wikipedia. Papers were selected that were written in English, studies that were of longer than 2 weeks duration were preferentially selected as OA is a chronic disease which involves the prolonged use of NSAIDs, safety and efficacy could not be assessed in periods of less than 2 weeks (Mason et al., 2004), so studies of short duration, less than three weeks were excluded. Studies were preferentially selected that used a randomized controlled trial research design approach with double blinding with identified selection and exclusion criteria for the selection of the sample. This was to ensure that the studies selected accurately assessed and compared treatment modalities and carefully selected their patients particularly those that may be sensitive to the actions of NSAIDs as this could lead to false results.

Studies were excluded that did not use a validated pain and physical status research tool such as the Western Ontario and McMaster (WOMAC) osteoarthritis Index

questionnaire. WOMAC is a 24-item questionnaire which uses a likert subscale to assess pain, physical function, stiffness and assessed pain intensity.

**Results**

In total 5 clinical trials were identified. Each study used a randomized sampling approach to select patients using strict exclusion and inclusion criteria. In each study patients were excluded that were sensitive to NSAIDs. All studies used the validated Western Ontario and MacMaster Universities (WOMAC) LK3. OA index (Bellamy et al. 1988). The Patient Global Assessment (PGA) questionnaire was also included, this focuses on "how has the osteoarthritis in your study joint been over the last 48 hours" and is also scored using a likert scale (Bellamy et al., 1988).

Baer et al, (2005) used mean and standard deviation measurements to assess baseline flare of pain using both the WOMAC and PGA assessment questionnaires. Findings suggest that patients in the drug group had a 50% reduction in pain and improvements in responses to walking, morning stiffness and physical function and overall adequate pain relief compared to the control group. This response was not significantly different from the control group. Baer et al.,(2005) suggest that the lack of significant response to pain in the drug treatment group patients compared to control may be due to the definition of clinical success, as the mathematical assessments and the number-needed-to-treat assessment used to see a clinical effect were equivalent to published studies (Osiri et al., 2003). The data suggest that the lack of therapeutic effectiveness to NSAIDS as a whole may result from the fact that patients who are intolerant to the effects of NSAIDs may not respond to topical diclofenac sodium.

In Baer et al, (2005) study 39% of the drug treatment group and 21% of control group developed dry skin. Both groups administered solutions that contained dimethyl sulfoxide, this compound dissolves the natural oils found in the epithelium and leads to dry skin. Dimethyl sulfoxide is used as the control solution and is also present in the drug solution where it acts as a carrier for diclofenac sodium. The safety of diclofenac sodium was verified by the negligible incidence (3.7%) of gastrointestinal side effects such as dyspepsia and abdominal pain and is lower than published findings with oral NSAIDs and COX-2-specific inhibitors (Tugwell et al., 2004) and with that of Bookman et al., (2004).

In contrast, Niethard et al., (2005) found that in a short term 3 week study topical diclofenac was more effective than placebo in relieving the symptoms of OA of the knee in 238 randomly selected patients. Treatment with topical diclofenac was not associated with any adverse side effects. More recent, equivalent studies that examined the therapeutic effectiveness of topical diclofenac over a 12 week period reported similar findings ( Towheed, 2006).

Tugwell et al. (2004) compared the use of topical diclofenac to oral diclofenac in a randomized sample of 622 patients with OA of the knee over a 12 week period. Topical diclofenac was as efficacious as the oral formulation in relieving pain, and did not cause any significant abnormalities in liver function, haemoglobin or creatinine clearance. These findings concur with those of Towheed, (2006). Similarly, Roth et al., (2004) found that patients that received topical diclofenac experienced a 45.7% improvement in pain control. This was accompanied by improvements in physical function (36.7%), morning stiffness (35.1%) and pain on walking (45%). A minority

of patients experienced minor skin irritation; pruritus and a vesiculobullous rash were found. No other adverse effects were found. These findings also concur with those of Bookman et al., (2004).

**Conclusion**

The evidence from the six clinical trials illustrates the therapeutic benefits that can be achieved using topical diclofenac sodium as a key method of pain control for patients with OA. Cumulatively the evidence presented by Baer et al, (2005), Roth et al, (2004) and Tugwell et al., (2004) convinced the Canadian Arthritis and Rheumatology CNW group (2006) to recommend topical diclofenac as the primary choice of medication for the management of OA of the knee in patients who are either intolerant or sensitive to the actions of oral NSAIDs, or are classified as high risk users of oral NSAIDs. Topical diclofenac provides a safe alternative to this select group of patients and replaces the use of selective COX-2 inhibitors due to their propensity to produce risky side effects such as cardiac arrest and stroke. Topical diclofenac is as effective as the maximum daily dose of NSAID and as effective in relieving joint stiffness, arthritic pain without the problems of renal, gastric or hepatic side effects (Tugwell et al., 2004, Baer et al., 2005, Roth, et al., 2004, Niethard et al., 2005, Towheed, 2006). Collectively, these studies provide evidence to support the chronic use of topical diclofenac sodium in the pain management of OA of the knee.

District nurses with an interest in rheumatology who have non-medical prescribing roles should consider the use of topical diclofenac sodium in the pain management of patients with OS of the knee.

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