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REVIEW

Review of the pharmaceutical properties and clinical effects of the topical NSAID formulation, diclofenac epolamine

K. D. Rainsford[a], W. F. Kean[b] and G. E. Ehrlich[c],

[a]*Biomedical Research Centre, Sheffield Hallam University, Sheffield, UK*

[b]*Department of Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario, Canada*

[c]*Section of Rheumatology, Department of Medicine, The University of Pennsylvania Health Sciences Center, Philadelphia, PA, USA*

Address for correspondence: **Professor K. D. Rainsford, Biomedical Research Centre, Faculty of Health & Wellbeing, Howard Street, Sheffield, S1 1WB, UK. Tel.: +44-114-225-3006; Fax: +44-114-225-3064; k.d.rainsford@shu.ac.uk**

Key words: **Diclofenac – Musculoskeletal pain – Percutaneous – Pharmacokinetics – Sports injuries – Topical NSAIDs**

ABSTRACT

Background: Topical formulations of non-steroidal anti-inflammatory drugs (NSAIDs), in particular diclofenac (DI), have become popular for treating various acute and chronic painful inflammatory conditions.

Objective: To perform a literature review of (1) the use of topical NSAIDs; (2) the pharmaceutical, pharmacokinetic and pharmacodynamic properties of a medicated plaster (patch) containing diclofenac epolamine (DI-EP, Flector Tissugel, Flector patch*) compared with other formulations of topical NSAIDs; and (3) evaluation of the clinical findings from studies with this novel DI-EP patch.

Outcomes: (1) Pharmacokinetic studies involved determination of DI from DI-EP and separately epolamine (EP) and the epoxide metabolite (*N*-oxide-EP) in laboratory animals and humans; the latter being the major metabolite in humans. About 2% of DI is absorbed by the skin in humans and is excreted in the urine. Maximum plasma concentrations of 17.4 ng/mL DI are reached at 5.4 hours (approximate steady state conditions); the plasma elimination half-time ($t_{½}$) being 26.4 hours. Low systemic levels of DI and EP are produced from DI-EP. Pronounced accumulation of DI occurs in the muscle layers and in synovial fluids of arthritic patients; (2) No significant toxicity occurs from EP nor *N*-oxide-EP, while that of oral DI-EP was similar to that from DI; and (3) In acute musculoskeletal conditions (sprains, tendonitis and sports injuries) and osteoarthritis DI-EP patches control pain and signs of joint or physical injury compared with placebo controls by 3–5 days with almost complete pain relief at 14 days. DI-EP was shown to have equivalent therapeutic effect to another DI diethylammonium gel formulation (Voltaren Emulgel†).

There were no reports of serious adverse events in the gastro-intestinal (GI) tract, kidneys or liver from DI-EP. Mild GI symptoms and skin reactions occur in 2 and10% of patients, respectively.

Conclusions: The patch delivery of DI in DI-EP affords controlled delivery of the active drug in contrast to that from application of gels or ointments of NSAIDs.

*Flector Tissugel, Flector patch are the registered trade marks for diclofenac epolamine (DI-EP) of Institut Biochimique SA, Lugano, Switzerland

†Voltaren Emulgel is the registered trade mark for diclofenac diethylammonium (DI-DEA) of Novartis AG, Basel, Switzerland

Introduction

Topically-administered non-steroidal anti-inflammatory drugs (NSAIDs) have become popular in recent years for the local treatment of acute and chronic musculoskeletal and other painful conditions as well as skin and ocular inflammatory conditions[1–8]. These formulations are useful adjuncts with oral analgesics or other pain-relieving drugs or physical therapies for treating chronic pain[4,7]. Topical NSAIDs are invaluable for elderly patients who are at risk for taking oral NSAIDs because of systemic toxicity and adverse reactions especially in the gastro-intestinal (GI) tract[6]. These drug formulations also have wide applications in treating acute conditions such as sports injuries (see review by Bolin[2]) where they are especially effective in local injuries to joints or muscles.

Arguably, local application of NSAIDs leads to lower circulating levels of these drugs and thus less likelihood of developing serious GI adverse drug reactions (ADRs) compared with orally ingested forms of these drugs. This suggestion has been confirmed in randomized controlled clinical trials in which topical NSAIDs have relatively low rates of reporting of ADRs[9]. However, some evidence suggests from case-control linkage studies that risks of upper GI bleeding or GI perforation might be lower from topical NSAIDs than with orally-administered drugs; these risks being increased with prolonged usage (see review by Evans *et al.*[10]). Also, individual topical NSAIDs vary considerably in their risks of GI events[10].

Historically, salicylate esters such as oil of wintergreen or methyl salicylate were probably the first topical analgesics employed for treating pain and inflammation[11]. However, meta-analysis and analytical review of their efficacy in clinical trials has shown that they may be less efficacious than conventional NSAIDs[12]. Among the topical NSAIDs, diclofenac (DI) gel has been found to be particularly effective although there are reasons to suggest that the efficacy of these preparations may vary considerably[12]. Thus, in any consideration of the therapeutic benefits of topical NSAIDs it is important to assess the relative efficacy and safety of (1) the properties of the drug, (2) their pharmacokinetics (PKs) and actions and (3) the GI and other ADRs of these drugs.

Objectives and methodology

The purpose of this review is to examine the mode of action and to critically evaluate the evidence for the comparative efficacy and safety of a topical diclofenac epolamine (DI-EP) gel preparation formulated in a plaster (Flector Tissugel, Flector patch, Institut Biochimique SA, Lugano, Switzerland) that can be applied to specific body regions where the drug is required for the relief of pain and inflammation. The rationale for the use of this DI impregnated dressing is that it (1) provides sustained and controlled delivery of the drug such that it achieved consistently high local concentrations that are prolonged in the skin and surrounding connective tissues so obtaining good local relief of pain and inflammation, (2) comprises an active drug with relatively high potency as an anti-inflammatory/analgesic agent with potent prostaglandin synthesis inhibitory effects and (3) produces negligible systemic concentrations of the drug so reducing the risks of GI and other ADRs.

This review provides information on the pharmaceutical, PK and pharmacological properties of topical DI formulations including DI-EP patch system. Background information on the rationale for using topical formulations of NSAIDs in treating musculoskeletal conditions is briefly reviewed as a basis for establishing the clinical needs for topical formations. The clinical evaluation and safety assessments of DI-EP are considered in comparison with placebo or comparative topical formulations of DI in treating various inflammatory pain conditions.

Literature sources searched include PubMed/Medline and ISI World of Knowledge, supplemented with some publications on pharmaceutical and chemical aspects cited in Chemical Abstracts. Some reports and unpublished investigations performed on DI-EP were provided at the request of the authors from IBSA Institut Biochimique SA (Lugano, Switzerland). All the studies on DI-EP provided by IBSA as well as those published under this company's auspices were performed according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH Guidelines). The data in these unpublished reports was critically evaluated by the authors before inclusion in this report.

Rationale for topical application of diclofenac

Diclofenac and its salts

DI (2-[(2,6-dichlorophenyl)amino]-benzene acetic acid; GP45840, Ciba Geigy AG, Basel, Switzerland) is a member of the aniline phenyl acetate class of acidic non-steroidal anti-inflammatory drugs. It was first synthesized by Dr. Alfred Sallmann and introduced in 1974. DI was discovered on the basis of an hypothesis that two structural features were essential

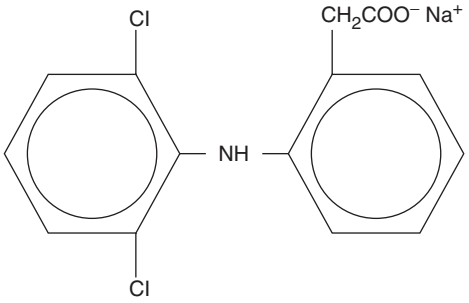


Figure 1. *Structure of diclofenac sodium*

Table 1. *Physico-chemical properties of diclofenac sodium (from Sengupta* et al.*[13])*

Molecular weight	318.15
Melting point	280–281°C
*p*Ka (water, 25°C)	3.9 ± 0.2
Solubility in water	2.0 g/100 mL (pH 8.0)
Partition coefficient	28.4 (pH 7.4, 23*C)
Log P	1.45

Table 2. *Ratio of synovial fluid to plasma concentrations of diclofenac sodium following oral administration of 75 mg enteric-coated tablets twice daily to rheumatic patients (modified from Liauw* et al.*[15].)*

Day	Hour	Synovial fluid (mg/mL)	Plasma (mg/mL)	Ratio synovial/ plasma concentration
1	0	0 ± 0	0 ± 0	0
	2	34 ± 12	1004 ± 29	0.03
	4	258 ± 27	138 ± 29	1.68
	8	138 ± 19	31 ± 5	4.45
	12	50 ± 9	9 ± 3	5.56
	24	138 ± 48	57 ± 22	2.42
2	0	188 ± 30	32 ± 15	5.88
	2	215 ± 39	661 ± 260	0.33
	4	275 ± 48	84 ± 24	3.27
	8	158 ± 19	21 ± 3	7.52
	12	89 ± 30	18 ± 11	4.94
	24	114 ± 28	58 ± 16	1.96

Data from 7–16 patient samples

for good anti-inflammatory activity – (1) an acidic function with pH 6 and (2) two aromatic nuclei whose substitution (with chloro-groups) inhibits coplanarity, making the two aromatic structures out of plane with one another by almost 70°, enabling a fit with anti-inflammatory receptors – proposed by Scherrer and Shen in the 1960s[13,14]. For a number of pharmaceutical reasons it was developed as a sodium salt (Figure 1) and it was this property that gave it a high degree of water solubility. Thus, the combination of lipid solubility of the phenylacetic acid drug moiety (Table 1) with its solubility in alkaline and other salts gives DI highly desirable physico-chemical properties for penetrating through membranes especially those lining the GI tract, synovial lining of diarthroidal joints and the skin.

DI when taken orally shows striking penetration into the synovial fluid of patients with rheumatic conditions (Table 2)[15]. It is probably one of the few NSAIDs to achieve such high concentrations in synovial fluids that persist in this compartment long after the decline in plasma concentrations. As shown in Table 2 the ratio of synovial/plasma drug concentration is fivefold after 1 day and sevenfold under steady state conditions at Day 8. Clearly, this property along with the persistence of the drug in the synovial compartment gives DI very desirable PK properties for achieving control of joint pain and inflammation in arthritic diseases. Aspects concerning the favourable properties of DI for skin penetration and retention are considered later in this section.

DI was also found to have potent anti-inflammatory and analgesic activities and was among the most potent of the prostaglandin synthesis inhibitors that were developed in the 1960–1970s[13,16]. It has been shown in extensive clinical trials to be a highly effective and widely accepted drug for treating a wide range of acute and chronic musculoskeletal and other painful inflammatory conditions[16]. This drug has distinct advantages as an anti-inflammatory/analgesic agent arising from its potent anti-inflammatory activities, especially related to inhibitory effects on the synthesis of those prostaglandins involved in inflammation and pain[13,16]. DI has only a modest degree of cyclooxygenase (COX)-2 selectivity (the average ratio of COX-2/COX-1 being ≈ 2), but it is a potent inhibitor of prostaglandin E_2 (PGE_2) *in vivo*[17], so it would be expected to have profound local anti-inflammatory activity when applied topically. As low concentrations are found in the plasma after topical administration relative to those after oral administration the risks of systemic effects contributing to the development of GI and other adverse reactions would be low.

DI taken orally has been found in various pharmacoepidemiological and pharmacovigilance studies to have a relatively low GI and other adverse reaction profile[18,19]. While animal studies show that DI sodium is ulcerogenic in the stomach and intestinal tract, the sustained-release enteric coated tablet formulation comprising sodium or potassium salts, that are normally rapidly absorbed from the upper GI tract, probably accounts for more controlled GI absorption

extending over several hours thus spreading the contact area of the GI mucosa and reducing the potential for GI irritancy.

Topical formulations of diclofenac

DI has been successfully formulated in a variety of pharmaceutical preparations using ion-pairing systems comprising amines as cations, or salts complexed with the acidic anionic drug. These complexes are particularly useful for uptake by skin which, with its complex structure and composition, along with associated vasculature, has been described as an 'organ'. The key features relating to drug absorption[20–23] can be summarized as follows (see also Figures 2A to 2C):

(1) Comprised of a multi-layered epithelium of squamous cells, the outer layer or stratum corneum is impermeable to chemical and physical agents. This is an effective barrier that has to be 'overcome' to favour skin uptake of drugs. This layer of enucleated cells evolves from basal keratinocytes. Corneocytes have abundant filaments of the structured disulphide linked α-keratin and these cells are surrounded by a thick intermediate filament protein, involucrin, and the intracellular spaces are filled with highly hydrophobic lamellar lipids. Thus, this structure of hydrophilic 'bricks' in a hydrophobic 'mortar' is effectively a barrier to both hydrophobic and hydrophilic substances. The characteristics of DI as a drug containing the polar moiety (carboxylic acid) linked to a highly lipophilic aniline-phenyl ring structure offers potential as a consequence of its combined lipophilic and aquasoluble properties for penetrating through the stratum corneum. As shown later the ion pairing of DI further aids penetration through this barrier. Unfortunately, the relative skin penetrability offers advantages and disadvantages since systemic absorption of drugs topically-applied is both slow and incomplete. However, there are advantages in the transcutaneous route in that first-pass hepatic metabolism can be largely avoided. For DI, which exhibits extensive biotransformation by this route, percutaneous administration can be particularly advantageous in that relatively high concentrations of the active parent drug can be obtained at or around the local sites of application.

(2) The dermal component of skin along with the extended vasculature comprises the model for facilitated distribution of topically-applied drugs[22] (Figure 2A). The dermis has abundant collagen and reticulum fibres, the former of which is continually replaced, and is interspersed with ground substances which comprise sulphated or non-sulphated glycosaminoglycans or acidic mucopolysaccharides covalently linked to peptides to form high molecular weight proteoglycans[24]. To these are added elastin fibres to give skin its characteristic plasticity. The proteoglycan components are generally hydrophobic and allow for appreciable uptake of water and aquasoluble drugs. To this dynamic structure of the dermis should be added the capacity for perfusion, exchange of drugs through skin capillaries, lymphatic drainage (particularly of lipophilic agents) and the local distribution to deeper tissues some of which may have subcutaneous fatty tissue[22]. Here lipophilic drugs like DI may accumulate to serve as depot reservoirs. This may have both advantages (as store), or disadvantages where fat is in abundance in mopping-up appreciable quantities of percutaneously-applied lipophilic drugs.

(3) The rate of transfer of drugs into the systemic circulation will be governed by the extent of perfusion dynamics as shown in Figure 2A. The physicochemical properties that govern overall permeability through the skin (Figure 2B) are (1) liposolubility, as defined by the log of the partition coefficient (Log P), (2) molecular weight (MWt), (3) partial charge of the molecule, (4) aqueous solubility and (5) the presence of certain functional groups on the drug molecule[25–28]. Quantitative studies of the permeation of drugs in skin permeation models and *in vivo* has confirmed the importance of these parameters (especially Log P, MWt and molecular charge)[29–31]. Kinetic parameters governing the penetration characteristics from the pharmaceutical system through the different layers of the skin are shown in Figure 2C. The kinetics of blood flow through the skin and relative anatomic vascularity also govern the dynamic movement of drugs and their transport into the circulation[31–33].

Skin absorption and effects of diclofenac gel formulations

The first topical gel formulation of DI was Voltaren Emulgel (Novartis AG, Basel, Switzerland). This preparation was developed by Ciba Geigy AG (Basel, Switzerland). It comprises diethylammonium complexed with DI as a 1.16% w/w (DI-DEA) as an ion-pair salt having 1 g DI sodium (CAS 15307-86-5) in 100 g gel (Novartis Consumer Health). This formulation has been extensively investigated for its PK properties[32,33] since the initial studies in guinea pigs, rabbits and humans by Riess *et al.*[34]. They observed that ^{14}C-DI in DI-DEA applied to the skin of guinea pigs resulted in plateau levels of the drug after 1.5 hours.

Steady state deposits of the drug were evident in skin with three times the amount of drug in muscle tissue proximal to the site of application. Topical application of DI-DEA to the knee joints of rabbits resulted in penetration of synovial fluids, adjacent adipose tissue and patellar ligaments. In humans 6% of the dose of DI from DI-DEA was absorbed. The pattern of DI metabolites in the urine following application of

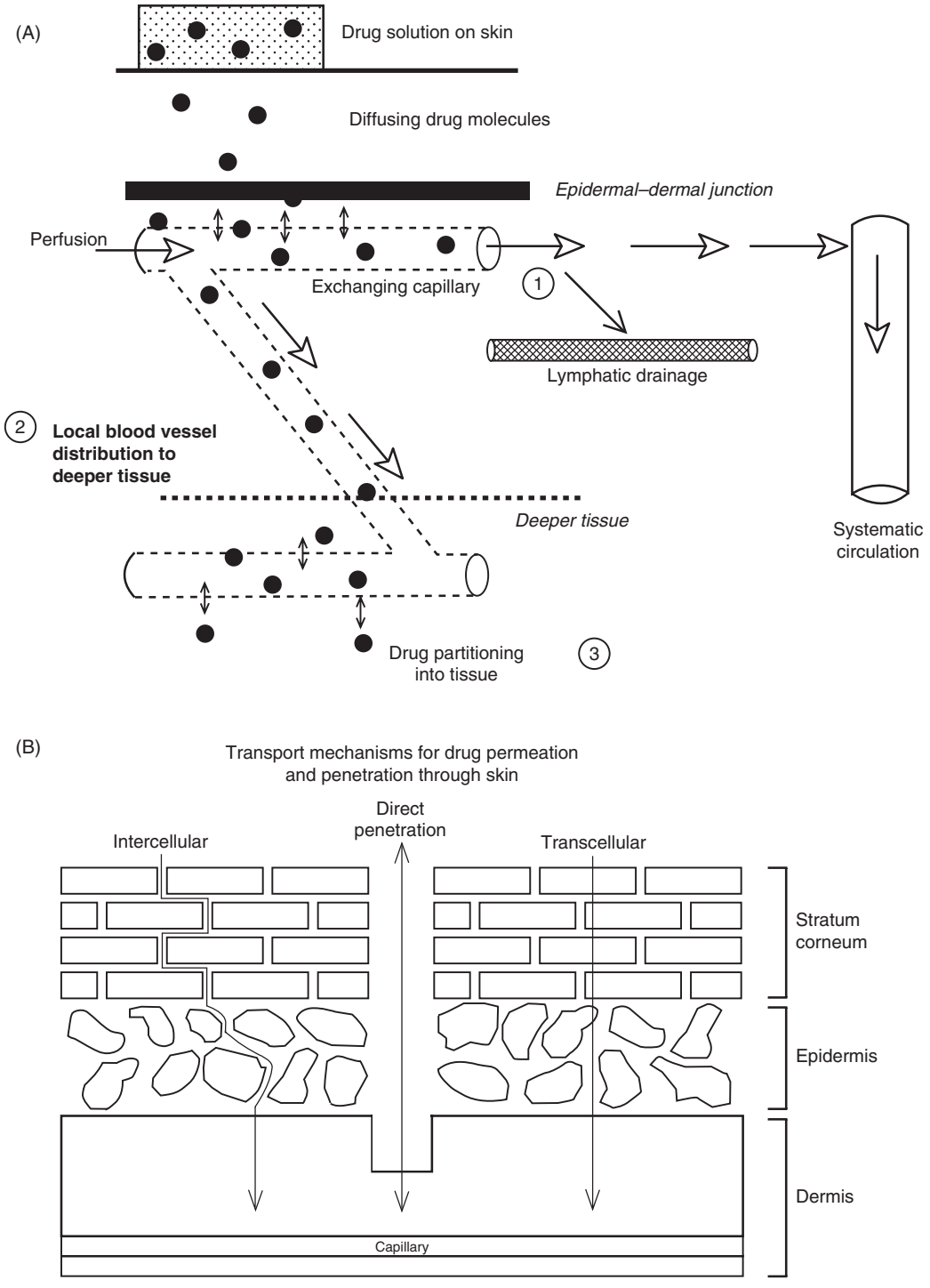


Figure 2. *Factors affecting the skin penetration of drugs. (A) Diagrammatic representation of a facilitated pathway for deep tissue penetration of topically applied solutes from dermal exchanging capillaries or lymphatics (1) through inter-connecting vessels into deeper tissue (2) and subsequent partitioning out of the deeper vessels into surrounding tissues (3) (from Roberts and Cross[22], with permission). (B) Transport mechanisms involved in drug and solute transport through the skin. The drug penetration process involving transcellular, intercellular and direct access through the layers of the stratum corneum, epidermis and dermis of the skin (reproduced with permission of Institut Biochimique SA, Lugano, Switzerland). (C) Total transport of drugs applied to the skin into the surrounding tissues and circulation showing the individual kinetic processes (from Banakar[21], reproduced with permission)*

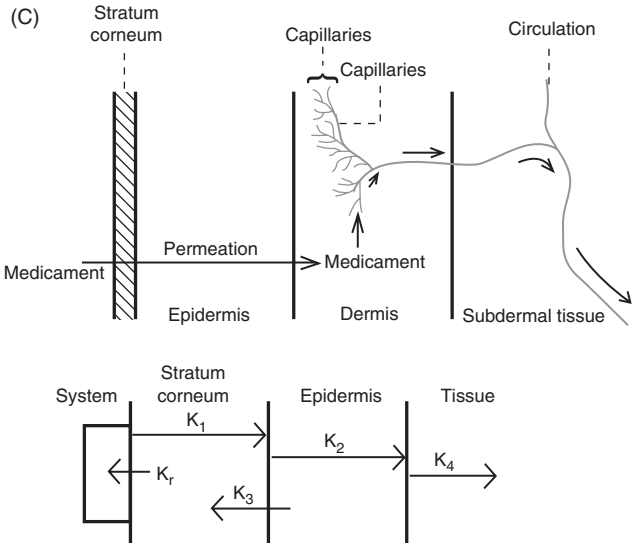


Figure 2. *Continued*

DI-DEA was the same as that observed following oral ingestion of DI tablets.

Properties of diclofenac gel topical formulations

A wide variety of salts of DI have been examined for their skin absorptive properties in topical formulations[30,35–60]. Among the key features of formulations which have been shown to be important in skin penetration are the inclusion of percutaneous enhancers[40] (e.g. *d*-limonene[46,50], oleic acid[50], menthol[44], lecithin[48,51]), solvent compositions[60] and rheological properties[53]. Various microemulsion formulations[47], as well as the dimethyl sulfoxide (DMSO) liquid preparation (Pennsaid [Dimethaid (UK) Ltd, London], described later) have also been developed to enable penetration of DI. However, among the most successful formulations to date have been those that are gel based[31,35,36,53].

Studies of skin penetration through human skin *in vitro* of a range of NSAIDs (many of them used as topically-applied formulations, e.g. ketorolac, ketoprofen, piroxicam) by Cordero *et al.*[29] showed that DI had the highest value of transdermal penetration. In a related study by the same group[30] it was found that DI showed the greatest potency for inhibition of phorbol-ester induced PGE_2 production (reflecting inflammation induced COX-2 activity) compared with a similar range of NSAIDs in human fibroblasts *in vitro*. These results suggest that, among the NSAIDs, DI has optimal properties for skin penetration and biological functions.

Penetration to the muscle layer below the sites of application on skin can vary considerably among the NSAIDs and may in part be related to the free (non-protein bound) concentration of the drug as well as its physicochemical properties as a skin penetrant[33]. Thus, the muscle disposition of DI is almost directly as a consequence of its direct skin penetration (90.8%) whereas, for example, that of felbinac is a consequence of being derived from the systemic circulation (>50%)[33]. It, therefore, appears that among the topical NSAIDs, DI has optimal characteristics for penetration and uptake into local sites where it is desirable to have therapeutic actions.

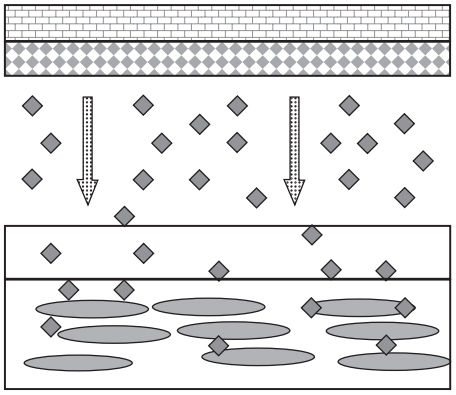
A number of reports have appeared showing that some topical NSAIDs, including DI-DEA are associated with upper GI haemorrhage (even if at lower rates than observed from the oral preparation)[10,61,62]. Cutaneous reactions though reported, are rare[62]. Thus, in any assessments of risk/benefits it is important to obtain evidence of any of these or other adverse effects.

Composition of DI-EP (Flector Tissugel) patches

The DI-EP patches described in the papers that have been reviewed in this article were developed and patented by Institut Biochimique SA (Lugano, Switzerland). They are 10 × 14 cm in size and comprise a non-woven polyester felt backing to which a hydrophilic adhesive material has been applied before covering with a polyethylene terephthalate (PET) film. The adhesive material contains 182 mg of DI-EP (1.3% w/w; equivalent to 1.0% DI free acid) in addition to a number of other ingredients including 1,3-butylene glycol, dihydroxy-aluminum aminoacetate, disodium edentate, d-sorbitol, gelatin, kaolin, methyl paraben, polysorbate 80, polyvinyl pyrrolidone, propylene glycol, propyl paraben, sodium carboxymethylcellulose, sodium polyacrylate, tartaric acid, titanium dioxide and water[63].

Appendix A contains details of the countries where 1.3% DI-EP is approved for sale and the estimated patient exposures.

The concepts of the skin permeation of DI-EP are shown in Figure 3. The initial studies leading to understanding of the properties of the DI-EP system were undertaken by Fini *et al.*[64–66] and have been further examined by these authors[67–69]. As an organic acid DI has pronounced lipophilic properties (reflected by the Log P values) favouring membrane permeation while its salts are all very water soluble. While many



The plaster: the outer layer is made of a semipermeable tissue that avoids drying of the gel while allowing transpiration of the cutis. The inner layer is made of a polymeric gel keeping DI-EP in water solution

Release: controlled release of DI-EP

Activity: due to its enhanced hydro- and lypo-solubility DI-EP diffuses through the skin and reaches the target tissue in the muscle layer.

Figure 3. *Diagrammatic representation of the diclofenac epolamine (DI-EP) patch system (reproduced with permission of Institut Biochimique SA, Lugano, Switzerland)*

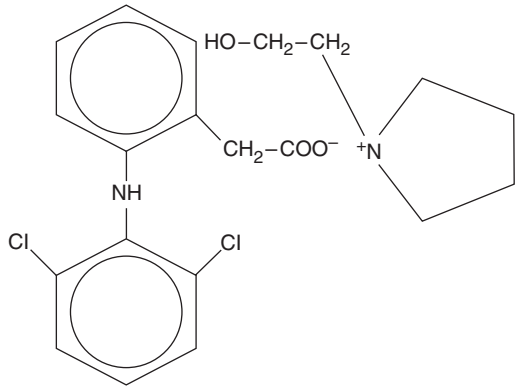


Figure 4. *Chemical structure of the diclofenac epolamine ion pair. These show the complexation of diclofenac carboxylic acid moiety (anion) with the charged nitrogen (N^+) of the pyrrole ring of the 2-hydroxy-ethyl-pyrrolidine (epolamine) cation (from Fini and Fazio[67], with permission)*

of the alkaline salts (Na^+, K^+) and bases that are employed in various DI formulations afford solubility in water, the EP salt has the most favourable solubility in both organic solvents as well as in water[64]. Thus, the EP salt of DI has about twice the solubility in water and the organic solvent, n-octanol (1.8 and 8.3 g%, respectively) compared with that of the sodium salt (0.96 and 0.43 g% respectively), and even more so than that of the potassium salt[63,67].

The unique complexation of DI with EP probably accounts for the favourable permeation characteristics and this may be related to its structure as an ion pair (Figure 4) and crystal structure (Figure 5)[70].

Fini *et al.*[67,68] have observed that the ion-pairing of DI with EP gives this unprecedented detergent-like action and this may be a factor accounting for the unique skin penetrating-properties of this complex. The molecular energy required for the interaction of DI with EP would be expected to be considerable and would thus favour the permeation of the intact complex through skin[33,55,56,63].

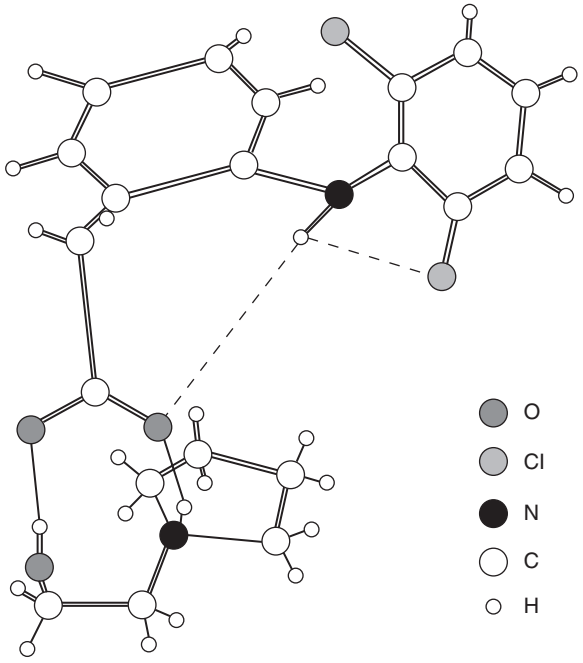


Figure 5. *Crystal structure of the complex of diclofenac with epolamine (adapted from figures and data of Castellari and Sabatino[70], with permission)*

Pharmacokinetics of DI-EP in animal models

The percutaneous absorption of DI from DI-EP patch (which had equivalent to 20.9 mg DI) was studied in depilated skin areas of rats[63]. The plasma concentrations of DI were variable. The maximum plasma concentration (C_{max}) values were 0.18–0.32 µg/mL with a time to maximum or peak concentration (t_{max}) of approximately 3.5 hours. The plasma elimination half-time ($t_{½}$) ranged from 3–16 hours. The results suggest there is sustained-release absorption of DI to the extent of about 5–6% of the dose; this being comparable with that of DI-DEA.

Pharmacokinetics of diclofenac and epolamine

Pre-clinical investigations

As discussed above, the physico-chemical properties of DI-EP give it unique PKs that favour percutaneous absorption.

The skin and systemic PKs of DI sodium and other alkaline salts have been well-described in both humans and in animal models. When orally-administered DI sodium is well absorbed from the GI tract, it undergoes extensive first-pass metabolism in the liver, while only about 50–60% of DI is found in the systemic circulation as unchanged drug. DI also is absorbed into systemic circulation after topical application to the skin[33–36,52,55].

Since the combination of DI with EP may give rise to different PKs of the former it is important to know if EP in any way affects both the absorption and disposition of DI. Moreover, EP would be expected to have PK properties that could be of significance for its toxicological properties as well as those of DI when in combination. Because of the potential for EP to form an *N*-epoxide, unpublished investigations were undertaken by IBSA to determine the formation of this metabolite as well as its toxicological properties and that of EP in rats, rabbits and dogs *in vivo*.

Accordingly, PK studies with EP were conducted (1) in rats following single oral and epicutaneous administration, (2) in dogs after single oral and repeated dosing and (3) in pregnant rabbits by the intravenous (IV) and oral (*per os*) routes. The kinetics of EP was determined using ^{14}C-labelled pyrrolidine nucleus (stable metabolic position). Large doses of EP were used, comprising 100 mg/kg *per os* in rats; 100 mg/kg *per os* and IV in rabbits and 50 mg/kg in dogs. In relation to DI-EP, these doses would be considerable since EP represents about 36.5% of the initial molecule.

The radioactive plasma PK in all species was characterized by a rapid absorption of EP after oral administration (0.5–1.17 hours depending on the species). Slow terminal elimination was noted in all three species with a mean $t_{½}$ of 91–102 hours being observed in rabbits, while in dogs this was 95 hours after single dose and 165 hours after repeated doses.

Percutaneous administration to rats resulted in a kinetic profile indicating a pseudo plateau over 0.5–48 hours with an average C_{max} ranging between 1.67 and 2.25 µg eq/mL; the slow absorption was the consequence of the application of the occlusive patch.

In rats, the metabolism of EP was evaluated after an oral dose of 100 mg/kg, while in dogs, the urinary metabolites of EP were detected after single and repeated doses for 7 days. In both species, *N*-pyrrolidine acetaldehyde was found in urine (which can re-arrange into *N*-[2-formyl]-methylpyrrolidine). In dogs, besides this ubiquitous component, there was a small amount of unchanged EP.

In humans, the main metabolites present in the urine are the *N*-oxide derivative of EP in equilibrium with the *N*-hydroxy-derivative. Moreover, there are also traces of unchanged EP. Thus, animal metabolism involves a somewhat different pattern of oxidation of the molecule, than in humans.

Orally administered ^{14}C-EP was primarily eliminated through the urine in rat and in dog, while about 2–4% of the dose was eliminated in the faeces. After repeated doses in dogs, the average quantity eliminated was close to the elimination results for a single dose.

The elimination results in man are comparable to those of the rat, but the kinetics are faster than in animals. After 24 hours, following single and repeated doses, renal clearance has not changed; the cumulated percentage for excretion of EP and its single metabolite, EP-*N*-oxide reaches, on average, 95% of the administered dose. Biliary elimination was less than 1% and thus is negligible.

The distribution of ^{14}C-EP was studied in rats given 100 mg/kg EP (0.61 MBq/kg). After 1 hour the radioactivity was distributed rapidly in all organs and tissues. The liver and kidneys were the target organs, but the absorption of the administered radioactivity on the stomach and intestine walls (small and large) was also noticeable, and accounts, cumulatively, for about 9% of the dose.

With the exception of the gastric mucosa where there are relatively high concentrations, the radioactivity although variable is lower in tissues than in plasma during the first 102 hours. Thus, the tissue/plasma ratio varied in the range 85:1 (liver) and 2.6:1 (prostate). At 8 hours the radioactivity levels in tissues had slowly declined. By 48 hours the radioactivity had decreased in most organs and tissues; the concentration in the liver was about 10 times lower than that measured at the 8-hour sampling time. In the other tissues, including the kidneys, a five-fold decline of the labelled compound was observed. The decay of ^{14}C in plasma was faster than in tissues, the tissue to plasma ratios were still higher and ranged between 30:1 and 2:1. This confirms the high tissue distribution of radioactivity and the slower elimination from tissues than from plasma.

The distribution of ^{14}C-EP was also examined by whole body autoradiography in rats at 0.5 and 24 hours; the former corresponding to the plasma t_{max} of EP. At 0.5 hour the radioactivity was distributed mainly in the stomach and small intestine contents, but also the liver and the kidneys showed noticeable radioactivity levels. Less radioactivity was observed in

the spleen, bone marrow and salivary glands, while traces of radioactivity were observed in the heart and lungs. At 24 hours the radioactivity was evident in the liver and in the kidneys (medulla), with relatively little in the other organs and only traces of radioactivity being observed in the GI tract.

From comparison of the data when EP was given by the oral and IV routes, it emerged that the results were comparable, confirmed by the absolute bioavailability of the oral treatment that resulted in rapid absorption of the drug in animals.

Pharmacological and toxicological studies

Acute anti-inflammatory effects

DI-EP 1.3% gel was compared for anti-inflammatory activity with 1% DI gel (of the same formulation as that used in the plaster), placebo plaster and no treatment in rats in which hind paw swelling had been induced by sub-plantar injection of carrageenan in sterile saline[63]. Prior application of both preparations resulted in reduction of paw swellings at 2–4 hours after application. The percentage reduction in swelling averaged 27–35% over this period. Maximal reduction occurred at 3 hours and was 31.9% with DI-EP and 35.6% with the gel. There were no significant differences in swellings between the two preparations over the time period of the experiment but both were significantly different from plaster placebo or control (no treatment). These results show that DI-EP shows acute anti-inflammatory effects which are comparable with those of the gel formulation of DI. Similar acute and chronic anti-inflammatory properties of DI gel have been observed in rat models[71].

Toxicology

There are two issues to be considered in the toxicity of DI-EP; (1) toxicity of EP especially in relation to the formation of EP-*N*-oxide, and (2) the influence of EP on the toxic effects of DI and *vice versa*. Toxicity studies in conventional animal models are complicated by the fact that only EP-*N*-oxide is formed from EP in humans, whereas in rats, rabbits and dogs EP is predominantly metabolized to *N*-pyrrolidine acetaldehyde which undergoes re-arrangement to form *N*-(2-formyl)-methyl-pyrrolidine, with EP-*N*-oxide formed, to a lesser extent[63]. Studies in rats for 4–13 weeks with orally administered DI-EP or EP-*N*-oxide did not reveal any significant toxic reactions with EP-*N*-oxide. Oral DI-EP produced intestinal perforations, GI lesions and haematological effects typical of those attributed to high doses of DI, which were present in the doses of DI-EP that were employed[63].

There were no unexpected toxic reactions in genotoxicity, fetotoxicity or mutagenicity studies from DI-EP, EP-*N*-oxide or EP. Local tolerability studies in rabbits using the plaster or gel 1% formulations did not reveal any signs of skin toxicity when observed over 28 days[63].

Overall, these toxicological studies indicate that neither EP nor EP-*N*-oxide have any appreciable toxic effects that would be of significance for humans.

Human pharmacokinetics

DI has been found to accumulate in regions adjacent to the sites of application most especially in the adjacent muscle layers[33,52,55,56,72]. Gallacchi and Marcolongo[72] showed that there was pronounced penetration of DI into the synovial fluids of patients with knee osteoarthritis following application of DI-EP. The synovial fluid concentrations on Day 5 after twice daily application each day of these patches ranged from 0.38–1.02 ng/mL whereas the plasma concentrations in these patients at the same time (4th hour after last application) were 3.62 ± 1.05 ng/mL (standard error of the mean [SEM]). At these concentrations in the synovial fluids, DI would be expected to have partially inhibited COX-2 and COX-1 activities based on data in various *in vitro* test systems[16].

The PKs of both DI and EP were investigated in human volunteers. The data from studies in which the PKs of DI were determined after percutaneous application of patches of DI-EP and the equivalent concentration of the 1% gel formulation are shown in Table 3[35]. These data show that there is comparable bioequivalence of both preparations as reflected by values of the area under the curve at 0–12 hours (AUC_{0-12}). The $t_{½}$ of DI was also comparable ($\approx$26 hours) but it appeared that the absorption of DI was more prolonged from the patch formulations. Thus, the PK parameters from the two treatments appear similar but there is evidence of progressively slow absorption from the patches compared with those from the applied gel, since the t_{max} from the patches is 5.4 hours and that from the gel is 3.1 hours; the AUC_{0-12} values are comparable (Table 3).

A summary of the oral PKs of EP and its principle *N*-oxide metabolite (in humans) is shown in Table 4[63]. The important information of relevance to potential toxicities of the agents is the plasma levels and retention. Both EP and *N*-oxide-EP have a $t_{½}$ of about 5–6 hours which is slightly prolonged after repeated administration to about 8 hours. Since it is unlikely that concentrations from percutaneous application of DI-EP would approach those from oral

Table 3. *Plasma pharmacokinetics of diclofenac following application of diclofenac epolamine (DI-EP) patches or gel formulation to healthy volunteers. Data from Assandri* et al.[35]

	Mean	SD	%CV	Min int	Max int
DI-EP patch (A)*					
C_{max}, ng/mL	17.4	13.5	77.7	7.6	40.0
t_{max}, h	5.4	3.7	69.4	2.0	12.0
C_{12}, ng/mL	2.8	2.4	86.8	1.0	7.4
t_n, h	26.4	12.4	46.9	12.0	48.0
AUC_n, ng/mL.h	176.1	107.5	61.1	69.2	394.6
$AUC_{0–12}$, ng/mL.h	119.3	75.7	63.5	47.0	269.8
FA/B (0–12)	0.29	0.10	36.0	0.14	0.43
FA/B (n)	0.33	0.14	41.2	0.13	0.51
DI-EP 1% Gel (B)†					
C_{max}, ng/mL	28.1	13.2	46.9	11.6	47.8
t_{max}, h	3.1	0.7	23.8	2.0	4.0
C_{12}, ng/mL	2.0	0.9	46.4	1.0	3.4
t_n, h	26.4	12.4	46.9	12.0	48.0
$AUC_{0–12}$, ng/mL.h	104.7	35.7	34.2	68.8	168.1

Ten healthy male volunteers (18–45 years) participated in an open, randomized, cross-over study with a washout period of 14d between treatments

*The subjects who received DI-EP patches (treatment A; 140 cm^2; Flector patch A) applied the patch to their back every 12 hours for 8 days. These patches had the equivalent of 139.5 mg of diclofenac sodium and the area of application was approximately 1 mg/cm^2

†Those subjects that received DI-EP 1% Gel (Treatment B) applied 5 g diclofenac epolamine gel comprising an equivalent of 400 cm^2 of 38.75 mg diclofenac sodium (approximately 0.1 mg/cm^2). Plasma and urine samples were collected on Days 5 and 8. Plasma and urinary concentrations of diclofenac were determined (after extraction and derivatization) using GC-MS. The pharmacokinetic parameters were calculated using model-independent procedures. As the period of sampling was 5 and 8 days it was reasonable to expect these were at steady-state conditions. The AUC and values were not extrapolated to zero because at 48 hours the diclofenac concentrations in plasma were unquantifiable, so these AUC values are approximations

AUC = area under the curve; C_{12} = concentration at 12 h; C_{max} = maximum plasma concentration; CV = coefficient of variation; FA/B = fractional clearance; SD = standard deviation; t_{max} = time to maximum or peak concentration; t_n = last sampling time with quantifiable (measurable) level of diclofenac; C_n = the diclofenac plasma concentration value obtained at t_n; FA/B (0-12) = the relative bioavailability of treatment A (patch) vs. treatment B (gel) up to sampling time 12h (i.e. during the 12-hour period following last patch application); FA/B (n) = the relative bioavailability of treatment A (patch) vs treatment B (gel)up to sampling time t_n (i.e. during the period from last patch application to when the last measurable diclofenac level was obtained for each subject)

Table 4. *Single dose (D1) and multiple dose (D8) pharmacokinetics of epolamine in healthy human volunteers given DI-EP 50 mg three times daily. Data from IBSA (1999) internal report no. CRO-PK-98-14*

Treatment		D1	D8
Epolamine	C_{max}, ng/mL	11.7 ± 3.66	19.07 ± 9.22
	t_{max}, h	0.34 ± 0.12	0.37 ± 0.13
	AUC_{ss}	–	109.98 ± 30.88
	AUC_∞, ng/mL.h	53.16 ± 14.47	–
	$t_{½}$	6	8.7
Epolamine *N*-oxide (EPNO)	C_{max}, ng/mL	637.6 ± 119.58	753.67 ± 33.85
	t_{max}, h	0.56 ± 0.17	0.68 ± 0.26
	AUC_{ss}	–	3442.0 ± 1210.4
	AUC_∞, ng/mL.h	2055 ± 661.1	–
	$t_{½}$	5.61 ± 2.06	8.22 ± 1.40

D1 and D8 denote the days of oral treatment with DI-EP

AUC_{ss} = steady state area under the curve; C_{max} = maximum plasma concentration; $t_{½}$ = plasma elimination half-time; t_{max} = time to maximum or peak concentration

absorption of DI-EP (as in the toxicological studies) it is reasonable to assume these are data at the extreme. Thus, accumulation of EP and its metabolites would be expected to be unlikely when DI-EP is applied topically.

Therapeutic applications of topical NSAIDs

In order to present the case for using topical NSAIDs in the treatment of acute and chronic musculoskeletal and other painful conditions it is necessary to show the limitations of existing therapies and how specific topical drugs can usefully be employed. First, we consider the current status of treatments for these conditions and how these may be more effectively treated with topical drugs.

Burdens in the use of analgesic and anti-inflammatory medication

Almost all patients with musculoskeletal disorders will need treatment with analgesic agents, NSAIDs or steroids[73,74]. The incidence of musculoskeletal disorders increases with age[75], in parallel to the increased risk of adverse effects to the NSAIDs[76]. The major therapeutic limitations to the successful management of musculoskeletal disease and disability are the side effects from the medications, especially the NSAIDs including aspirin[73]. The oral and sometimes systemic versions of these medications can cause injury or other complications to the gastrointestinal tract[77], the kidney[78], the cardiovascular homeostatic mechanisms[74,79], the liver and the skin[73]. While concomitant physiological failure results in an increase in renal, cardiovascular and other NSAID adverse responses, especially with age, the most serious side effects are due to GI toxicity[80–83,74]. The majority of GI effects are symptomatic responses such as bloating, cramping, pain, diarrhoea, constipation and acid reflux, but the most dangerous are erosions, gastric and duodenal ulcers, perforations and bleeds[80,84,85].

Thus, the treatment of osteoarthritis, the inflammatory arthritides and general musculoskeletal pain disorders with analgesics, oral NSAIDs, narcotics and steroid therapy provides pain relief, but carries a substantial risk of adverse effects. Topical NSAID therapy offers an alternative to oral treatment, with the potential for a reduced risk of side effects. The clinical trial methodology[86,87], the efficacy and toxicity[88–90] and the physiological properties[91] of topical nonsteroidal anti-inflammatory drugs (tNSAIDs) have been extensively reviewed. tNSAIDs have been shown to be superior to placebo, and equal to oral NSAIDs in the treatment of osteoarthritis and in acute and chronic musculoskeletal pain disorders[9,13,92–96]. Clinical studies have included, among others, the use of NSAIDs such as topical indomethacin[1,12], felbinac[92], flurbiprofen[96], piroxicam[97] ketoprofen[98,99] and DI, together with various delivery systems.

Grace *et al.*[94] performed a double blind, randomized, placebo controlled, parallel group design 2-week clinical trial on the efficacy and safety of a topical formulation of 2% DI in lecithin organogel in 70 patients with mild to moderate osteoarthritis (OA) of the knee. Patient responses to disease-specific (Western Ontario and McMaster [WOMAC] VA3.0 Osteoarthritis Index) and quality of life (Medical Outcome Survey SF-36) health status measures were assessed. Global assessments were recorded at baseline and post-treatment. The physician conducted a global assessment and range of motion of the knee at baseline and post-treatment. The aggregated WOMAC total score and aggregated subscale scores revealed significant improvement ($p < 0.05$) on the aggregated total score and the pain, stiffness and physical function subscales from baseline to post-treatment for the active treatment group versus the placebo group. Analysis of pain scores from the aggregated WOMAC total score and aggregated subscale scores also revealed that this improvement was significantly greater than the improvement recorded by the placebo treatment group on the aggregated total and the pain and physical function subscale scores. Other efficacy measures exhibited no significant differences between or within treatment groups. The authors concluded that the topical formulation of 2% DI in lecithin organogel appeared to have therapeutic value in patients with mild to moderate OA of the knee as determined by responses from the WOMAC (VA3.0) osteoarthritis health status measure.

Mason *et al.*[100] reviewed randomized, double blind trials comparing topical NSAID with either placebo or another active treatment, in adults with acute pain from strains, sprains or sports injuries and identified information approximating to a 50% reduction in pain at 1 week, together with details of adverse events and withdrawals. The relative benefit and number-needed-to-treat (NNT), and relative risk and number-needed-to-harm (NNH) were calculated, with sensitivity analyses where appropriate to investigate differences between individual drugs and aspects of trial design. There were 26 double blind placebo controlled trials with 2853 patients for evaluation of efficacy. Topical NSAID was significantly better than placebo in 19 of the 26 trials, with a pooled relative benefit of 1.6 (95% confidence interval [CI] 1.4 to

1.7), and NNT of 3.8 (95% CI 3.4 to 4.4) compared with placebo for the outcome of 50% pain relief at seven days. The results were not affected by outcome reported, or condition treated. Three trials, with 433 patients, compared topical with oral NSAID (two trials compared the same drug, one compared different drugs) and found no difference in efficacy. Local adverse events, systemic adverse events, or withdrawals due to an adverse event were rare, and no different between topical NSAID and placebo. The authors thus concluded that topical NSAIDs were effective and safe in treating acute painful conditions over a 1-week period.

Mason *et al.*[9] also reviewed randomized, double blind trials comparing topical NSAID with either placebo or another active treatment, in adults with chronic pain. The primary outcome was a reduction in pain of approximately 50% at 2 weeks, and secondary outcomes were local and systemic adverse events and adverse event-related withdrawals. The relative benefit and NNT, and relative harm and NNH were calculated, and the effects of trial quality, validity and size, outcome reported and condition treated, were examined by sensitivity analyses. They explored the results of 25 trials. Fourteen double blind placebo-controlled trials had information from almost 1500 patients. It was shown that topical NSAID was significantly better than placebo with relative benefit 1.9 (95% CI 1.7 to 2.2), NNT 4.6 (95% CI 3.8 to 5.9). The results were not affected by trial quality, validity or size, outcome reported, or condition treated. Three trials with 764 patients comparing a topical with an oral NSAID found no difference in efficacy. Local adverse events (6%), systemic adverse events (3%) and the numbers of withdrawals due to an adverse event were the same for topical NSAID and placebo. The authors concluded that topical NSAIDs were effective and safe in treating chronic musculoskeletal conditions over a 2 week period.

Topical applied salicylate preparations have been reported to cause toxicity, especially rash and urticaria[101,102] and may have an effect on warfarin anticoagulation[103]. Mason *et al.*[12] investigated randomized double blind trials to assess the efficacy and safety of topical rubefacients containing salicylates compared to placebo or another active treatment in the management of acute and chronic pain. Three double blind placebo controlled trials had information on 182 patients with acute conditions. Topical salicylate was significantly better than placebo (relative benefit 3.6, 95% CI 2.4 to 5.6; number needed to treat 2.1, 1.7 to 2.8). Six double blind placebo controlled trials had information on 429 patients with chronic conditions. Topical salicylate was significantly better than placebo (relative benefit 1.5, 1.3 to 1.9; number needed to treat 5.3, 3.6 to 10.2). Local adverse events and withdrawals were generally rare in trials that reported them. They concluded that based on limited information, topically applied rubefacients containing salicylates may be efficacious in the treatment of acute pain, but trials of musculoskeletal and arthritic pain suggested moderate to poor efficacy. Adverse events were rare in studies of acute pain and poorly reported in those of chronic pain.

Renal complications have also been reported with the tNSAIDs[104]. The majority of adverse effects of tNSAIDs are skin related. There is evidence that topically applied capsaicin cream provides modest pain relief[105,106] especially in small joint disease[107], but some elderly patients complain of a burning sensation after application even with the low concentration (0.025%) cream.

Recently, Zacher *et al.*[108] reported an evidenced-based review of trials in which topical DI was examined in double-blind, randomized, placebo- or active-controlled (RCT) trials in soft-tissue injuries or soft-tissue rheumatic disorders and osteoarthritis. Of the studies selected (19 RCTs were examined in a population totalling more than 3000 patients) topical DI was found to effectively reduce pain and inflammatory reactions in various acute and chronic conditions with minimal skin irritation and fewer GI reactions compared with oral NSAIDs. There was a considerable degree of heterogeneity in the trials examined and as with all meta-analyses there are concerns about the potential of biasing data in which trials have been initially selected for analysis.

Bookman *et al.*[109] studied the safety and efficacy of a topical DI solution for relief of moderate pain symptoms of primary osteoarthritis of the knee in 248 men and women from southern Ontario. The patients were randomly assigned to apply one of three solutions to their painful knee for 4 weeks: a topical DI solution (1.5% wt/wt DI sodium in a carrier containing DMSO (Pennsaid); a vehicle-control solution (the carrier containing DMSO but no DI); and a placebo solution (a modified carrier with a token amount of DMSO for blinding purposes but no DI). The primary efficacy end point was pain relief, measured by the WOMAC LK3.0 Osteoarthritis Index pain subscale. Secondary end points were improved physical function and reduced stiffness (measured by the WOMAC subscales), reduced pain on walking and patient global assessment (PGA). Safety was evaluated with clinical and laboratory assessments. The study results showed that in the intent-to-treat (ITT) group the mean change (with 95% CI) in pain scores from baseline to final assessment while modest was significantly greater for the patients who applied the topical DI solution (−3.9 [−4.8 to −2.9]) than for those who applied the vehicle-

control solution (−2.5 [−3.3 to −1.7]; $p=0.023$) or the placebo solution (−2.5 [−3.3 to −1.7]; $p=0.016$). For the secondary variables, the topical DI solution also revealed superiority to the vehicle-control and placebo solutions, leading to mean changes (and 95% CI's) of −11.6 (−14.7 to −8.4; $p=0.002$ and 0.014, respectively) in physical function, −1.5 (−1.9 to −1.1; $p=0.015$ and 0.002, respectively) in stiffness and −0.8 (−1.1 to −0.6; $p=0.003$ and 0.015, respectively) in pain on walking. The PGA scores were significantly better for the patients who applied the topical DI solution than for those who applied the other two solutions ($p=0.039$ and 0.025, respectively). The topical DI solution caused some skin irritation, mostly minor local skin dryness, in 30 (36%) of the 84 patients, but this led to discontinuation of treatment in only five (6%) of the cases. The incidence of gastrointestinal events did not differ between the treatment groups. No serious gastrointestinal or renal adverse events were reported or detected by means of laboratory testing. The authors concluded that this topical DI solution can provide safe, site-specific treatment for osteoarthritic pain, with only minor local skin irritation and minimal systemic side effects.

Baer *et al.*[110] studied topical NSAIDs for the efficacy and safety of a topical DI solution over a 6-week treatment course in symptomatic primary OA of the knee. Two hundred and sixteen men and women, age 40–85 years, with radiologically confirmed primary OA of the knee and a flare of pain at baseline following discontinuation of prior therapy were enrolled into a double-blind study. Participants applied either a topical DI + DMSO solution (Pennsaid) or vehicle control solution (carrier with no DI); 40 drops four times daily directly to the painful knee(s), without massage, for 6 weeks. Pre-planned primary efficacy outcome measures included the core continuous variables pain relief and improved physical function measured by the WOMAC LK3.1 OA Index, and improved patient global assessment (PGA). Secondary efficacy measure was reduced stiffness. Safety assessments included adverse events and vital signs. They found that the topical DI group had a significantly greater mean change in score (final minus baseline) compared to the vehicle control group for pain (−5.2 vs. −3.3, $p=0.003$), physical function (−13.4 vs. −6.9, $p=0.001$), PGA (−1.3 vs. −0.7, $p=0.0001$) and stiffness (−1.8 vs. −0.9, $p=0.002$). The mean difference between treatment arms (95% CI) was 1.9 (0.7 to 3.2), 6.5 (2.5 to 10.5), 0.6 (0.2 to 0.9) and 0.9 (0.3 to 1.4), respectively. Safety analyses showed that topical DI caused skin irritation, mostly minor local skin dryness, in 42/107 (39%), leading to discontinuation of treatment in 5/107 (5%) participants. The authors concluded that the topical DI solution demonstrated relief of the symptoms of primary osteoarthritis of the knee at 6 weeks.

Niethard *et al.*[111] assessed the efficacy and safety of topical DI diethylamine gel, 1.16%, 4 g versus placebo applied qid for 3 weeks to relieve the symptoms of osteoarthritis (OA) of the knee. Paracetamol (up to 2 g/day) was supplied as rescue medication. Patients recorded compliance to dosing, use of rescue medication, and assessed daily pain on movement, spontaneous pain and pain relief, in a diary. At weekly site visits, patients completed the WOMAC Osteoarthritis Index Questionnaire, which included assessment of pain, stiffness and physical function, and assessed pain intensity 'right now'. At the final visit, a global assessment of treatment efficacy was completed. Of the 238 randomized patients, 237 were included in the ITT efficacy analysis. Treatments differed significantly for daily pain on movement at Day 5, and continued on most days through end of study. Peak differences were achieved in the second week. On the primary outcome, average pain on movement over Days 1–14, DI gel was significantly superior to placebo gel. Scores for all 3 WOMAC indices for DI gel treatment were significantly superior to placebo at Weeks 2 and 3. A significant difference was achieved on pain intensity 'right now' at 3 weeks. At the end of the study, patients rated DI gel as significantly more effective in treating the pain of OA of the knee ($p=0.03$) compared to placebo. There were no safety issues concerning adverse events or laboratory values. The authors concluded that DI gel was effective and safe for relief of symptoms of OA of the knee over 3 weeks of dosing.

The use of a fixed dosage patch would appear to be the preferred type of application for topical NSAIDs. The patch can be applied exactly to the painful site and the dosage is always standard. Reproducible placement on the exact site following application of a liquid, gel or cream can be difficult for the patient to judge. Moreover, the exact reproducibility of repeat dosages can also be especially difficult with the use of these preparations. This problem can be compounded for a patient with impaired eyesight, or hand pain or impaired fine motor action of the hands. Liquids, creams and gels are more easily accidentally washed off, or removed following excess perspiration.

Clinical studies with DI-EP 1.3%

Analgesic effects of DI-EP

Affaitati *et al.*[112] investigated the effects of DI-EP compared with placebo plasters on pain thresholds following electrical stimulation of the quadriceps muscle (vastus

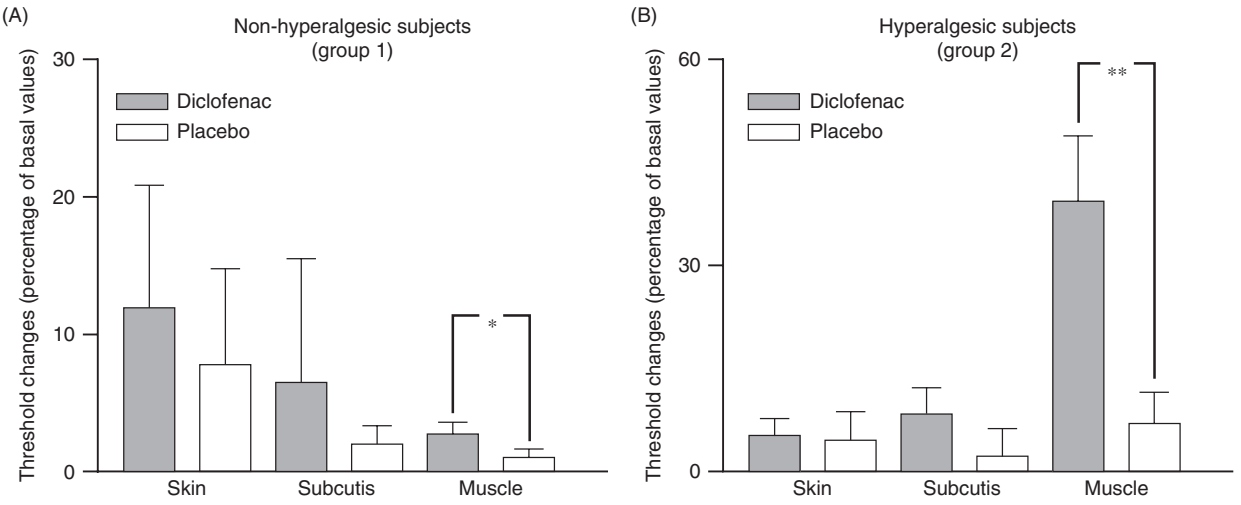


Figure 6. *Changes in skin, subcutis and muscle thresholds after either DI-EP (Diclofenac) or placebo patch application (difference between second and first evaluations), expressed as a percentage of basal values (first evaluation) in: (A) non-hyperalgesic subjects* (n = *9) (means* ± *SEM).* *p < *0.05; Student's* t*-test; (B) hyperalgesic subjects* (n = *11) (means* ± *SEM).* **p < *0.01; Student's* t*-test. (Both figures from Affaitati* et al.[112]*, with permission.) DI-EP = diclofenac epolamine; SEM = standard error of the mean*

lateralis) and overlying subcutis and skin in a double-blind study in which the DI-EP was applied to one leg and placebo to the other. Following a training period and recording of baseline pain thresholds, the subjects were required to alternate the plasters at 12 hour intervals. Nine of the subjects showed a normal range of pain threshold and were classed as non-hyperalgesic subjects (Figure 6A) while 11 others had pain thresholds below controls (Figure 6B). The most striking effects of DI-EP versus controls were observed in the muscle 30 minutes after removal of the second patch where the DI treatment significantly increased the muscle pain thresholds in both groups (Figures 6A and 6B); the increase in pain threshold from DI was several-fold greater in the hyperalgesic group (as a reflection of greater pain threshold overall versus the non-hyperalgesic group) compared with placebo.

Thus, although this maybe considered a preliminary investigation it appears that DI-EP exerts greater analgesia in subjects with lower pain threshold. The greater effects of DI in hyperalgesia have been attributed to its direct actions on tissue nociceptors as well as inhibitory effects on the production of prostaglandins in the hyperalgesic compared with non-hyperalgesic state[49,113] which may be due to increased expression of the COX-2 isoenzyme which can occur upon muscle stimulation[114], or in rheumatic conditions affecting muscle[115].

Clinical studies in musculoskeletal diseases

Osteoarthritis

Dreiser and Tisne-Camus[116] performed a double-blind placebo-controlled parallel group study in 155 elderly patients with osteoarthritis of the knee (gonarthrosis). DI-EP treatment was applied by 78 patients while 77 received placebo of identical appearance on a twice daily regime (morning and evening) for 15 days. Criteria for inclusion in this study was that the knee osteoarthritis was diagnosed by femoropatellar and/or femorotibial radiology with the presence of pain >40 mm using the Huskisson visual analogue scale (VAS). The primary efficacy parameter was the relief of spontaneous pain at rest assessed on the Huskisson VAS. The secondary efficacy parameters included (1) the extent and duration of improvement using the Lequesne Functional index, (2) the physician's and patient's independent assessment of efficacy and tolerability, (3) the intake of 'rescue medication' (paracetamol) from Day 4 and (4) the number of nocturnal awakenings.

Statistically-significant differences in the Huskisson VAS scores were observed between DI-EP treated patients compared with those that received placebo on Days 4, 7 and 15 (Figure 7). The improvement in VAS score was progressive with time. Joint functional improvement as determined by the values of the Lequesne index paralleled the improvement in pain-relief (Table 5). Consumption of rescue medication progressively increased in the placebo group at Day 7 and Day 15 (Figure 8). In comparison there was much lower consumption of paracetamol in patients that received DI-EP (Figure 8).

This study showed that there are marked benefits in both relief of painful symptoms and joint parameters from twice daily application of DI-EP compared with placebo. The difference between DI-EP and placebo was about equal over the time of treatment and by

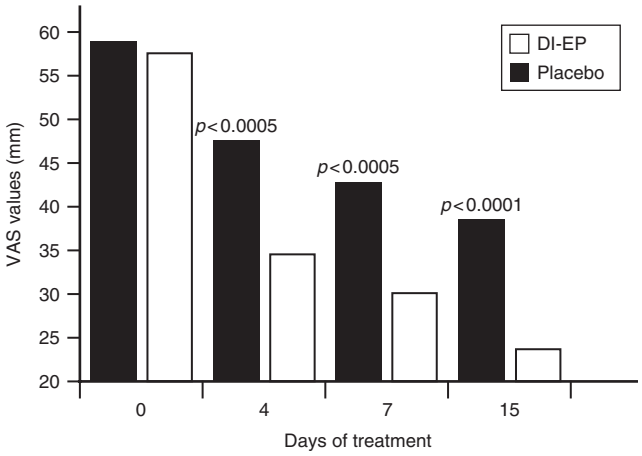


Figure 7. *Mean values of Huskisson visual analogue scale (VAS) scores (intent-to-treat analysis) in patients with knee osteoarthritis who received DI-EP compared with those that received control (placebo) patches of identical appearance for 15 days. The* p*-values derived from application of the Kruskal-Wallis test. (From Dreiser and Tisne-Camus[116], with permission.) DI-EP = diclofenac epolamine*

15 days placebo values were about half those at the beginning on Day 0. A placebo effect is expected and the extent of this is in the range observed in most pain studies with NSAIDs in rheumatic patients[87].

This study is of particular interest in as much as it was analyzed by Mason *et al.*[9] and McQuay and Moore[87] in their evidence-based comparison of topical NSAIDs. It was rated 4 in the quality assessment of the design and conduct of the trial which is relatively high (5 being the highest which is rarely achieved, and a score of 4 is considered relatively good). In two such studies with plasters they were equal to or better than DI gel and most other NSAIDs (with the exception of the combination of flufenamate and salicylate (which was comparable with DI plasters) or pooled data for all NSAIDs (Figure 9).

In another study by Brühlmann and Michel[117], 103 patients with mono- or bilateral femorotibial and/or femoropatellar radiologically-confirmed osteoarthritis of the knee were included in a randomized, placebo-controlled, double-blind parallel group trial performed under GCP conditions using the same design and test materials as employed in the previous study; the duration of treatment being 14 days. DI-EP was applied by 51 patients while 52 received placebo patches twice daily. Pain was assessed on a numerical scale from 0 = no pain to 10 = severe pain. The primary efficacy parameters were (1) spontaneous pain, and (2) Lequesne Index. Secondary efficacy parameters were (1) pain on pressure, extension and flexion, (2) degree of extension/flexion, (3) walking time, (4) amount of rescue medication (paracetamol intake) and (5) overall assessment of efficacy.

Table 5. *Determination of functional improvement assessed by Lequesne index values at Day 0, Day 4, Day 7 and Day 15. Data from Dreiser and Tisne-Camus[116]*

Lequesne Index on (days)	Treatment		*p*-value*
	Flector-plaster ($n = 78$) mean (SEM)	Placebo ($n = 77$) mean (SEM)	
D0	12.0 (0.43)	12.6 (0.37)	NS
D4	10.0 (0.44)	11.3 (0.41)	<0.0005
D7	8.9 (0.40)	10.6 (0.47)	<0.0005
D15	7.0 (0.43)	10.3 (0.51)	<0.0001

*Kruskal-Wallis Test
SEM = standard error of the mean; NS = not statistically different

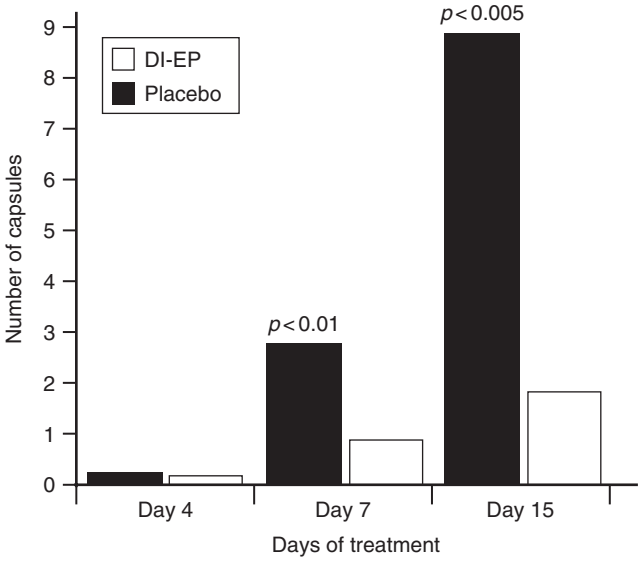


Figure 8. *Mean value of daily consumption of capsules of paracetamol rescue medication in patients with knee osteoarthritis who received DI-EP plasters compared with control (placebo) plasters of identical appearance. Statistical significance was determined by Fisher's exact probability test (*p*-values). (From Dreiser and Tisne-Camus[116], with permission.) DI-EP = diclofenac epolamine*

As shown in Figure 10 statistically significant reduction in pain scores compared with Day 0 were observed in patients that received DI-EP by Day 4 and progressively improved to almost zero values compared with placebo by Day 14. The values of Lequesne Index between the two treatments were statistically significant from placebo at Days 7 and 14. This suggests pain relief from DI-EP proceeded in advance of improvements in joint function. There were also improvements in secondary parameters in the DI-EP group versus placebo, among them knee flexion but not walking time.

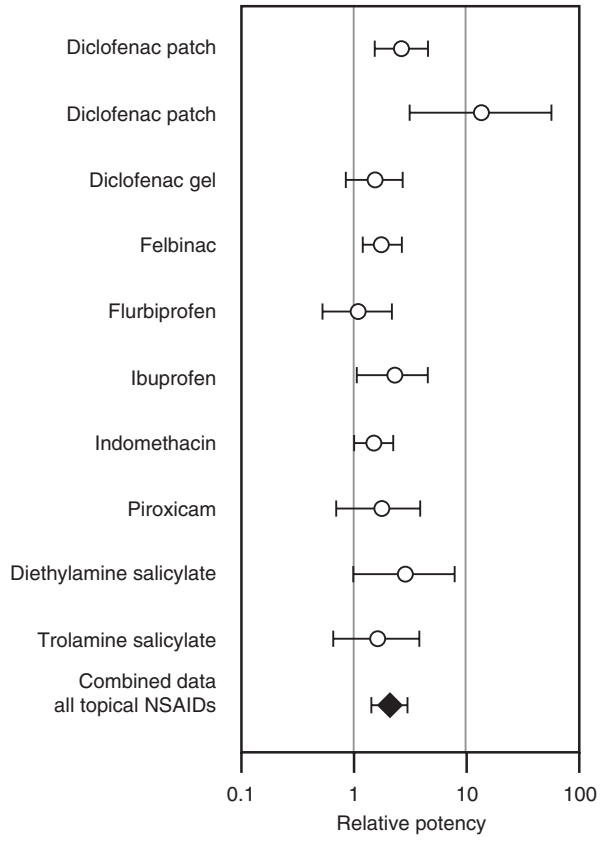


Figure 9. *Comparison of relative benefits of placebo-controlled trials of topically-administered NSAIDs (modified and redrawn from McQuay and Moore[87], reproduced with permission of the authors). NSAIDs = non-steroidal anti-inflammatory drugs*

In a subsequent pooled analysis, Brühlmann *et al.*[118] combined data from the two abovementioned trials[116,117]. The baseline parameters for the Huskisson VAS pain scale, the Lequesne index as well as demographic characteristics from both these two trials, were very similar and each overlapped the other indicating a high degree of homogeneity among the data from the two groups. In the ITT analysis of 235 patients that completed 14 days treatment (23 patients had dropped out) the results showed that both sets of parameters of pain and joint function progressively improved with time of DI-EP patch treatment compared with placebo. At the end of the treatment periods the decrease in Lequesne index was about 35% in the DI-EP group and only about 15% in the placebo group. The ANOVA analysis of spontaneous pain was similar to those of the Lequesne index, the major finding being evidence of appreciable efficacy of the DI-EP treatment. There was 30% difference in the pain intensity between Days 0 and 14 in the DI-EP group compared with the placebo group. The relative benefit increase (RBI) of treatment for 50% pain reduction in patients that received DI-EP was 98% while the NNT for 50% pain reduction over the two week period was 3.

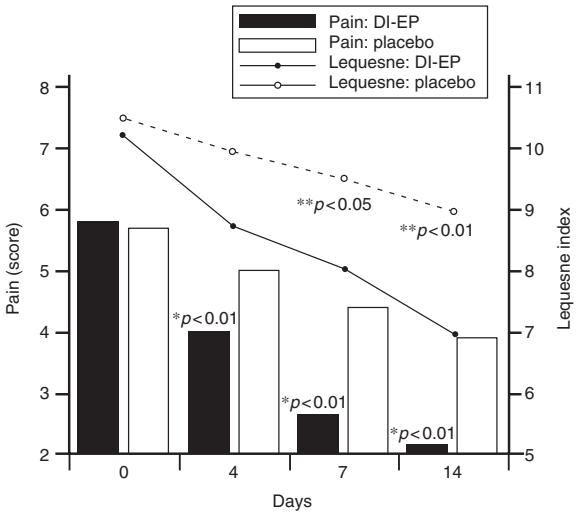


Figure 10. *Primary efficacy parameters determined from use of DI-EP compared with a plaster placebo patches (of identical appearance to Flector) applied twice daily for 2 weeks by patients with osteoarthritis of the knee. Mean pain scores (recorded on a numerical scale of 0–10) are shown on the left hand scale and mean values of Lequesne's index on the right hand scale. Statistically significant differences in * spontaneous pain (Mann–Whitney U-test, p-values) and ** Lequesne Index (ANOVA, p-values). (From Brühlmann and Michel[117], with permission.) DI-EP = diclofenac epolamine*

The RBI for 75% pain reduction after 2 weeks treatment with DI-EP was 138% and an NNT of 5.

Thus these studies are consistent in showing that the overall reduction in pain with DI-EP patches appears to be greater and proceeds at an early time period than the parameters of joint functions.

Miscellaneous musculoskeletal conditions

A randomized double-blind, multi-centre study in 100 patients with mild-moderate post-traumatic injuries involving ankles, knees and adjacent muscle by Mahler *et al.*[119] compared the time-course of effects of DI-EP alone and in combination with lecithin, the addition of which was presumably designed to aid absorption of the DI-EP gel. The ITT analysis showed that both preparations showed within-group improvement by 3 days and progressively improved to 10 days; the addition of lecithin had a small added effect. The results of this study suggest that there may be little or no benefit conferred by addition of lecithin compared with DI-EP patches.

Tendonitis

Arroyo and colleagues (unpublished, see Dreiser[63]) performed a randomized placebo-controlled, double-blind, cross-over study in 80 geriatric patients

(average age 83 ≤ 7 years) with periarticular painful inflammation of the shoulder or knee. The patients served as their own control using a 6 day and 6 day crossover sequence. An issue with this type of study is that there maybe appreciable carry-over effect following treatment with the active preparation. Statistically significant reduction in pain on motion (VAS) but not pain at rest (VAS) was observed with DI-EP bid, compared with the placebo patches. Functional impact (recorded on a five-point categorical scale) assessed by patients and doctors as well as pain assessed by physicians all improved significantly with DI-EP patches compared with placebo. There was no difference in consumption of the rescue analgesic (paracetamol) between these treatments. Thus, for geriatric patients DI-EP patches are a particularly useful therapy since they act relatively quickly (6 days) and have good tolerability. Two patients dropped out of the study because of allergic dermatitis and intense pruritus during the placebo treatment period.

Sport and acute injuries

Saillant *et al.*[120] undertook a randomized, double-blind, multicentre, placebo-controlled study in 140 patients with mild ankle sprains of less that 48 hours duration in which DI-EP 1 patch/daily was compared with identical placebo 1 patch/day for 7 days. Pain measured by Huskisson's VAS was the primary outcome measure with secondary criteria involving pain on movement and application of pressure; pain on standing singularly on foot; joint oedema; paracetamol intake; and global assessment of efficacy.

Figure 11 shows that there was significant reduction in values of percentage decrease in VAS assessment of pain in the periods of 0–3 and 0–7 days with DI-EP versus placebo plasters and joint oedema were also reduced significantly and patients' and physicians' global efficacy judgement was in favour of the DI-EP patch treatment. The tolerability of DI-EP patch was judged to be 'good' or 'very good' and there were no adverse effects observed.

In another similarly designed study, the effects of DI-EP patches were compared with placebo in 134 patients with ankle sprains of about 48 hour's duration[121]. DI-EP patches or placebo patches were applied 1 patch each/day for 7 days and the VAS scores of pain which were determined once hourly for 6 hours then at Days 1, 2, 3 and 7 thereafter, showed statistically significant reduction with DI-EP patch treatments from 4 hours to Day 7. The maximum reduction in pain VAS scores occurred with the DI-EP patches at 7 days although the maximum difference compared with placebo patches occurred between Days 2 and 3. Home diary measurements of pain relief and functional improvement in secondary pain measures with the treatments paralleled VAS scores and were statistically significant at Day 7 of treatment.

In two studies[122,123] performed under identical conditions, the first of which was in 222 and the second in 411 subjects, Galer *et al.* compared the effects of DI-EP patches with placebo patches applied at 12 hourly intervals in patients who had experienced a variety of minor sports injuries within 72 hours of enrolment for treatment. These were both large multicentre studies based in USA which were in patients with a wide variety of injuries and thus could be considered as representative of 'real-world' sports injuries.

The primary outcome measure in the first study was the Summed Pain Intensity Differences (SPID) from baseline[122], the difference of the pain on application of pressure determined using an algometer were additionally recorded. The secondary outcome measures were the Total Spontaneous Pain Relief (TOTPAR), Total Pressure and Movement Pain Relief (TOTMPR) and Summed Functional Improvement Scores (SFIS).

Statistically significant reductions of SPID scores (Figure 12) at Days 3 and 14 were observed in 213 patients ITT analysis who received DI-EP patches compared with placebo patches (two-way ANOVA). TOTPAR and SFIS scores were statistically different on Days 7 and 14 in favour of DI-EP patches. In the assessment of 365 patients who completed the treatment in the second, larger Galer study, the time to pain resolution was found to progress more quickly with the DI-EP patches compared with placebo patches (Figure 13). The median time for 188 patients treated

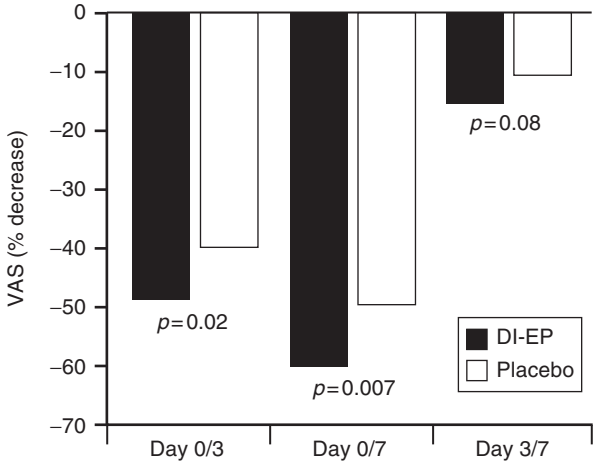


Figure 11. *Percentage decrease in the visual analogue scale (VAS) measures of pain in 140 patients with minor ankle sprains treated with DI-EP or placebo patches applied once daily for 7 days. Results are expressed as per cent decrease between Day 0 and 3 (Day 0/3), Day 0 and 7 (Day 0/7) and between Day 3 and 7 (Day 3/7). (From Saillant* et al.[120]*, with permission.) DI-EP = diclofenac epolamine*

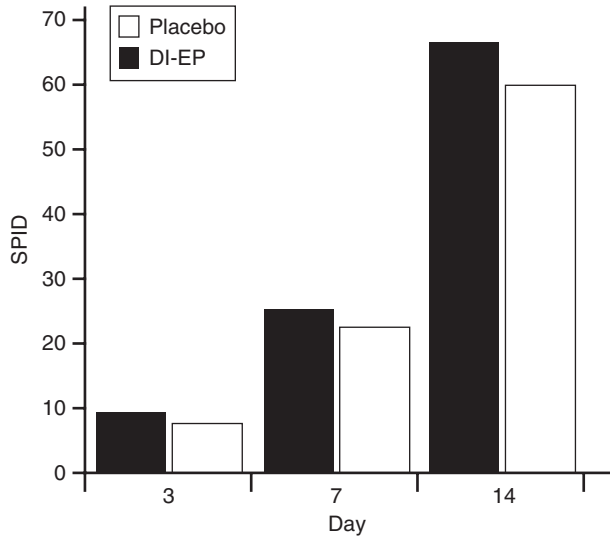


Figure 12. *Effects of the treatments with DI-EP or placebo patches on values of SPID in 213 patients with minor sports injuries (sprain, strain, contusion). There were statistically significant differences between the treatment groups on all days of the pain assessments ($p < 0.05$). (From Galer et al.[122], with permission.) DI-EP = diclofenac epolamine; SPID = summed pain intensity difference*

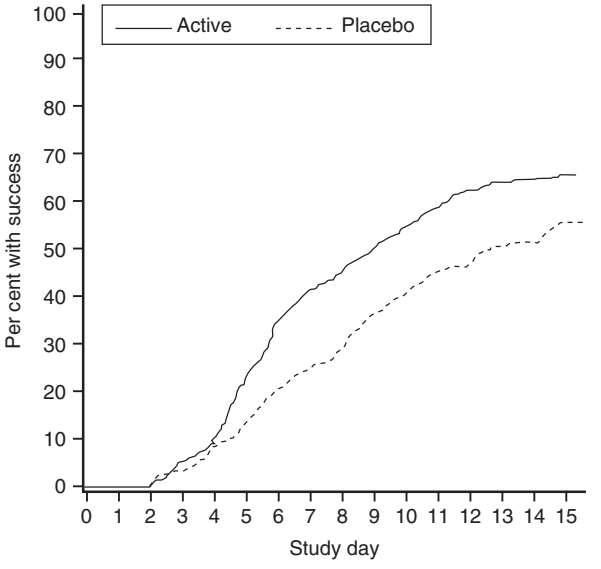


Figure 13. *Time to pain resolution with DI-EP (Flector Tissugel) or placebo patch bid. for 14 days in the larger Galer study of 365 patients (per protocol analysis) with minor sports injury[123]. The results are shown as the per cent of patients without pain. (From Rowbotham[123], with permission.) DI-EP = diclofenac epolamine*

with DI-EP patches was 8.8 days (95% CI 7.5 to 10.3) and 12.4 days (95% CI 10.3 to 15) with the placebo patches ($p = 0.009$).

Symptomatic relief of spontaneous pain (VAS) with DI-EP patches was found to be greater than placebo in an unpublished trial by Camarri[124] in 61 patients with

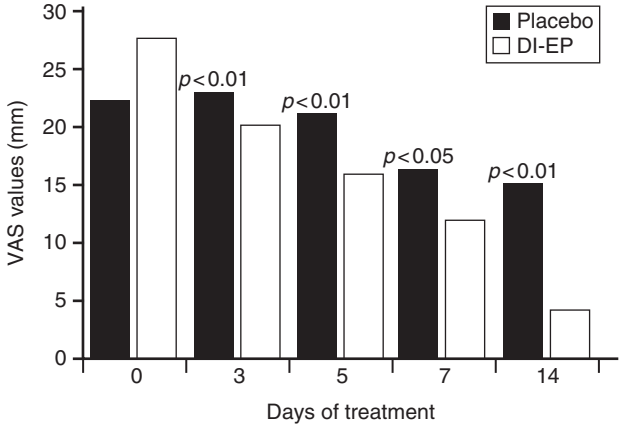


Figure 14. *Effects of DI-EP and placebo patches applied bid for 2 weeks in 61 patients with periarticular rheumatism (i.e. tendonitis, epicondylitis, bursitis) using the visual analogue scale (VAS) of pain for patients with periarticular inflammation (from Camarri[124], with permission). DI-EP = diclofenac epolamine*

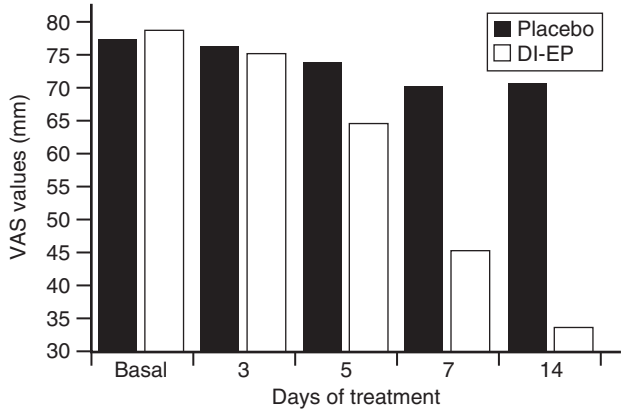


Figure 15. *Effects on spontaneous pain visual analogue scale (VAS) of DI-EP and placebo patches applied bid. for 2 weeks in 60 patients with periarticular rheumatism (from Galeazzi and Marcolongo[125], with permission). DI-EP = diclofenac epolamine*

various tendinopathies (Figure 14). Significant differences in favour of DI-EP patches were observed after 3 days treatment and the VAS scores progressively declined and were accompanied by progressively increasing differences in 14 days (Figure 14). By this time the VAS scores with DI-EP patches were almost negligible while placebo values had only declined by about 25%.

A similarly designed study was performed by Galeazzi and Marcolongo[125] with spontaneous pain and pain on movement measured by VAS scores. As shown in Figure 15 differences in VAS scores between DI-EP patches and placebo treatment were only evident at Day 5 but the former treatment did lead to negligible scores by Day 14 as observed in the study by Camarri[124]. These data suggest that DI-EP patch

treatment leads to almost complete resolution of pain (and associated swelling) of injured tendons by about 2 weeks treatment.

Local inflammation was determined in this study by thermography and statistically significant improvement was evident at 3 days treatment with DI-EP patches and became progressively greater compared with placebo patches over the 14 days treatment. Global judgement of efficacy assessed by both physicians and patients was more favourable with DI-EP patch treatment by Day 7 with assessments being good to excellent in 60–80% of patients who received DI-EP patches and 0–10% of those that had placebo patches. There was good tolerability and patient compliance in the active treatment group and no clinically relevant alterations in liver biochemistries.

An unblinded study performed by Rosenthal and Bahous[126] in 190 patients with various rheumatic conditions showed that treatment with DI-EP plasters for 10 days led to symptom relief. Another study by the same group[127] in 100 patients with various musculoskeletal conditions showed that although DI-EP plasters bid and DI-DEA qid gel treatments both gave significant reduction in pain at 7 and 14 days determined by the Huskisson VAS scores, there was a statistically significant difference in favour of DI-EP treatment at both time intervals. The global efficacy assessed by both physicians and patients in symptom-relief was significantly better for those patients that had treatments DI-EP plasters compared with patients that had DI-DEA gel.

Jenoure *et al.*[128] showed in an open-label study in 101 patients that treatment with DI-EP plasters reduced pain and joint symptoms from sports injuries progressively from 7 days to 14 days. By the latter time, pain at rest or with pressure application was reduced by 60% and 61% respectively compared with that at the start of treatment. Tolerability was favourable, being assessed as 'good' or 'excellent' overall by all the subjects. In another study in sports injuries from Jenoure *et al.*[129] 85 patients with humerocondylar tendinopathy pain arising from sports injuries (principally from tennis) participated in a multi-centre, double-blind study comparing the effects of 14 day treatments with DI-EP compared with placebo plasters, with observations being also extended for a further 14 day non-treatment period. Pain relief determined by Huskisson's VAS scale was significantly reduced at 7 days by DI-EP compared with placebo plasters and was further reduced by 14 days (Figure 16). Interestingly, pain relief further improved with DI-EP treatment compared with placebo over the 14 day follow-up period. Pain upon application of pressure also paralleled the VAS scores and showed that

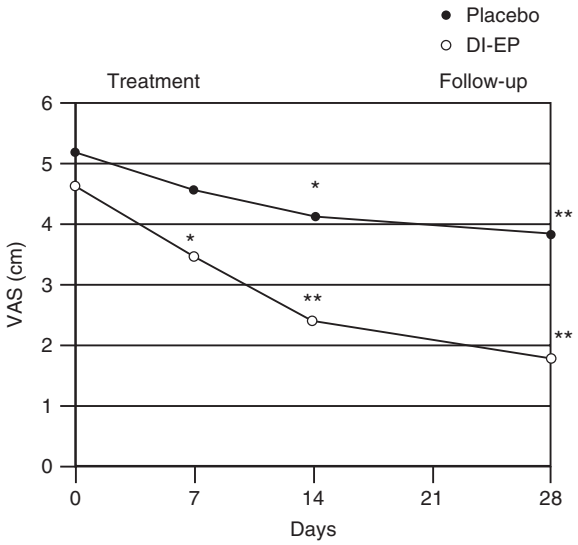


Figure 16. *Effects of DI-EP and placebo patches applied bid for 14 days in 85 patients with epicondylitis on spontaneous pain visual analogue scale (VAS). The follow-up from 14–28 days shows the persistence of therapeutic benefits of DI-EP patches compared with placebo.* *$p < (vs. baseline)$, **$p < 0.01$ *(vs. baseline). (From Jenoure* et al.[129]*, with permission.) DI-EP = diclofenac epolamine*

DI-EP was appreciably better in pain relief than placebo.

Polieri and Saponati[130] performed an open-label study in children (aged 8–15 years) to determine the effects of DI-EP for the treatment of articular injuries. A total of 187 events were studied in 176 young males most of whom (92%) had experienced motor injury to lower limbs (73%) while playing soccer. Treatment involved application of one DI-EP plaster for periods ranging from 3 to 14 days with most having 7 days. The authors asserted that the DI-EP treatment was effective, but no quantitative data or qualitative information was provided. It is assumed that the period of treatment reflected the need for therapy and so the mean treatment period of 7 days probably reflects the possible therapeutic response by this period which is in agreement with abovementioned observations[120–124,128] in which significant pain relief has been observed by this time or earlier.

A randomized, multicentre study[131] designed to compare the efficacy and safety of DI-EP compared with placebo patches was recently performed in a total of 418 patients, involving centres in Germany (eight centres) and the UK (six centres). Patients having incurred a minor soft tissue injury (sprain, strain, or contusion) and having spontaneous pain of at least 5 on the 0–10 categorical pain scale were included. At inclusion, time to injury was a mean 1.4 days. The primary efficacy variable was post-treatment pain assessed by the patient twice a day for 14 days or pain resolution,

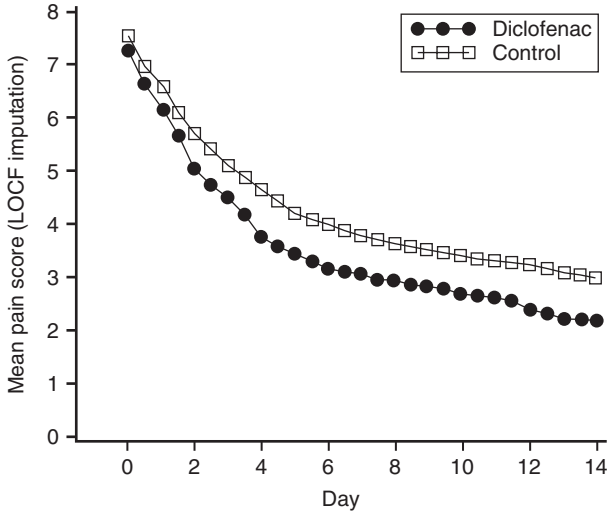


Figure 17. *Time-course of mean scores of pain relief in DI-EP (Diclofenac) and placebo (Control) treated patients (total N = 418) in a multi-centre study performed in UK and Germany. Statistically significant changes between the treatments were evident after 1 day treatment and then progressively improved. (From Jones[131], with permission.) LOCF = last observation carried forward*

and expressed as a proportion of the baseline pain score. Investigator's assessments of the global response to therapy, change from baseline in the range of motion and in the degree of swelling at the injury site and time to pain resolution were considered as secondary parameters.

The results showed overall that pain levels were reduced by the DI-EP patches to 15% compared with placebo ($p = 0.009$). Daily pain score comparisons reached significance by the time the second patch was removed on Day 1, always remaining below 0.05 over the 14 day observation period (Figure 17).

Favourable responses to DI-EP were noted by investigators and shown to be statistically significant. A higher percentage of DI-EP patients with restricted mobility at baseline was able to move freely at the end of treatment (70.3% vs. 59.9%, $p = 0.058$), but a similar effect was not observed for baseline/post-baseline swelling. Pain resolution occurred in average 2 days in advance in the active treatment group as compared with placebo (5.5 vs. 7.5 days; $p = 0.007$), indicating a significant benefit of DI-EP therapy.

Since, from a methodological viewpoint, this study was similar to those previously conducted in US by Galer *et al.*[122] (with data in Ref[123]) in minor sports injuries, the results of these three studies were pooled (also a 4th study, the French study on ankle sprain, was added), analysed and used to support the registration of the product in USA, based on specific requirements of the US Food and Drug Administration. While there were variations in the period of recruitment at entry into the trials after injury (48 hour or 72 hour) and some differences in procedures for primary efficacy by pain scores and secondary measures all the patients essentially received the same treatments randomly allocated comprising active or placebo patches applied twice daily each day for 14 days, with the exception being 7 days with an option to extend this to 14 days in France.

The analysis was performed on a total of 1185 patients, recruited and randomly assigned to treatment with the DI-EP patch (590 patients), or a placebo patch identical to DI-EP minus the active ingredient (595 patients). A major feature of this analysis was the screening for adverse events which were categorized according to COSTART (in the US studies) and MedDRA (in the German and UK studies); the French reports were not coded because of there being few in number.

The efficacy analysis was based on pain as recorded by the patient on a VAS scale, twice daily for 14 days. Missing data were imputed using a two-stage process. In the first stage, 20 imputations were performed using the Markov Chain Monte Carlo (MCMC) method to produce a monotone missing dataset for the 29 pain scores from Day 0 to Day 14. In the second stage, the remaining missing data were imputed using the regression method. No other variables were used in the model and imputed values were not allowed to exceed the 0–10 limits of the VAS. The primary efficacy variable was the mean pain score over the entire 14-day post-treatment period.

The results showed overall that pain levels were reduced by DI-EP patches to 12.3–15.4% in the US and UK/German trials whereas those in the French trial were greater being 38.4% compared with placebo. Subgroup analysis indicated, however, that although most injury categories will benefit from DI-EP topical application, certain types of injuries may be more responsive to treatment with DI-EP than others: a particularly higher mean pain reduction occurred for shoulder (16.7%), lower leg (26.7%), elbow (29.5%) and back (39.5%) injuries.

Favourable responses to DI-EP were noted by investigators in the UK/German and French studies and shown to be statistically significant. However, in the two US studies there was only a trend but this was not statistically significant. With analysis of all the studies combined the difference between groups for Investigator's assessment of global treatment efficacy was found to be statistically significant in favour of DI-EP ($p < 0.001$).

The author's report on this study suggested that the results from the treatment with DI-EP overall though modest were likely to be underestimated. It is also

Table 6. *Demographics and duration of exposure of the patients enrolled in the clinical trials and evaluated for safety. Data from Dreiser (2002) IBSA Internal Report*

	Placebo patch	DI-EP patch	DI-DEA*	Subtotal
Demographic characteristics of the patients				
Male	470	666	34	1170
Female	466	876	60	1402
Unknown	9	9	–	18
Subtotal/total	945	1551	94	2590
n of volunteers/patients for duration of treatment				
1 day	–	20	–	20
6 days	80	80	–	160†
7 days	136	138	–	274
9 days	211	207		418
10 days	–	306	–	306
14 days	518	728	94	1340
21 days	–	72		72
Subtotal/total	945	1551	94	2590

*Diclofenac diethylamine gel was used in one study as reference control treatment
†80 patients with periarticular rheumatism were treated in cross-over both with placebo and DI-EP (Flector Tissugel®)
DI-DEA = diclofenac diethylammonium; DI-EP = diclofenac epolamine

likely that there was such a wide variety of patients that were recruited in the US studies with variable sports injuries that this contributed to the variable outcomes.

Safety and adverse events

The demographic features and exposure of patients in the abovementioned multicentre trials are shown in Table 6.

In the above investigations about 10% of patients experienced adverse reactions (Table 7). These were all minor and mostly involved skin reactions. There were 14 (1.4%) GI reactions and these were all symptomatic. Of importance regarding the GI events is that none appeared to involve GI ulceration and bleeding. There were no differences between the two treatments in the numbers of ADRs that were reported.

Combined assessment of ADRs in all the trials that have been discussed above in the published reports has been evaluated. Most of the reports involved reactions in the skin and appendages (Table 8) with pruritus being the most common; there appears to be no differences in the incidence of these events between DI-EP and placebo patches. Withdrawal of the plaster would no doubt lead to reduction in the itching so observed.

Table 7. *Treatment-related adverse events in the Diclofenac Epolamine Patch Studies. Data from IBSA internal report*

Adverse event*	DI-EP patch Total	Placebo patch Total	*p*-values†
Number of patients	967	851	–
Any adverse event, *n* (%)	103 (10.7)	117 (13.7)	0.04
Application site conditions, *n* (%)	72 (7.5)	78 (9.2)	0.21
Atrophy	1 (0.1)	0 (0.0)	0.35
Burning	2 (0.2)	8 (0.9)	0.04
Cold feeling	1 (0.1)	0 (0.0)	0.35
Dermatitis	8 (0.8)	4 (0.5)	0.35
Dermatitis exfoliative	2 (0.2)	3 (0.4)	0.55
Discoloration	1 (0.1)	1 (0.1)	0.93
Dryness	4 (0.4)	0 (0.0)	0.06
Erythema	8 (0.8)	7 (0.8)	0.99
Hyperhidrosis	1 (0.1)	0 (0.0)	0.35
Irritation	4 (0.4)	6 (0.7)	0.40
Pruritus	36 (3.7)	43 (5.1)	0.17
Reaction	3 (0.3)	4 (0.5)	0.58
Application site warmth	0 (0.0)	1 (0.1)	0.29
Vesicles	1 (0.1)	0 (0.0)	0.35
Oedema	0 (0.0)	1 (0.1)	0.29
Eye disorders, *n* (%)			
Conjunctivitis	0 (0.0)	1 (0.1)	0.29
Gastrointestinal disorders, *n* (%)			
All	14 (1.4)	16 (1.9)	0.47
Abdominal pain	1 (0.1)	1 (0.1)	0.93
Constipation	1 (0.1)	0 (0.0)	0.35
Dysgeusia	5 (0.5)	4 (0.5)	0.89
Dyspepsia	2 (0.2)	2 (0.2)	0.90
Nausea	5 (0.5)	6 (0.7)	0.61
Vomiting	0 (0.0)	3 (0.4)	0.07
General disorders, *n* (%)			
Fatigue	1 (0.1)	1 (0.1)	0.93
Swelling	0 (0.0)	1 (0.1)	0.47
Injury/procedural complications, *n* (%)			
Pain increased	0 (0.0)	1 (0.1)	0.29
Musculoskeletal/ connective tissue, *n* (%)			
Joint stiffness	0 (0.0)	1 (0.1)	0.29
Pain	1 (0.1)	4 (0.5)	0.14
Nervous system disorders, *n* (%)			
All	11 (1.1)	10 (1.2)	0.94

(*continued*)

Table 7. *Continued*

Adverse event*	DI-EP patch Total	Placebo patch Total	*p*-values†
Headache	5 (0.5)	2 (0.2)	0.33
Hypoesthesia	1 (0.1)	0 (0.0)	0.35
Paraesthesia	3 (0.3)	6 (0.7)	0.23
Somnolence	2 (0.2)	2 (0.2)	0.90
Psychiatric disorders, *n* (%)			
Agitation	0 (0.0)	1 (0.1)	0.29
Anxiety	1 (0.1)	0 (0.0)	0.35
Respiratory/thoracic disorders, *n* (%)			
Respiratory distress	1 (0.1)	0 (0.0)	0.35
Skin/subcutaneous disorders, *n* (%)			
Acne	1 (0.1)	0 (0.0)	0.35
Vascular disorders, *n* (%)			
Ecchymosis	0 (0.0)	1 (0.1)	0.29
Vasodilatation	0 (0.0)	2 (0.2)	0.13

*Number of patients with an adverse event possibly or probably related to treatment provided, with percentages of total patient number in parenthesis. Open non-placebo-controlled studies, where practically no adverse reaction was reported, are not included, to allow for a more correct comparison
†The *p*-values were determined using the Cochrane–Mantel–Haenszel test for treatment effects. Tests for homogeneity across centres participating in the studies did not result in any significant differences among the groups
DI-EP = diclofenac epolamine

It is noteworthy that review of all the safety data from the published and unpublished studies with DI-EP has not revealed any reports of elevated liver enzymes or other liver reactions as observed with oral DI[132]. Overall, the DI-EP patch has good tolerance and is not associated with any severe adverse reactions especially when compared with the oral formulation of the drug.

Conclusions

This review presents evidence for the effectiveness of the patch containing DI-EP in comparison with placebo and shows there is clinically significant benefit from DI-EP patches and no differences in the pattern or number of ADRs. In comparative studies similar therapeutic effects were observed with the marketed diethylammonium gel DI preparation although the DI-EP formulation has more sustained actions. While some of the earlier studies have been performed in small groups of patients the data overall are consistent in showing effects of DI-EP compared with placebo and comparable effects with comparator topical DI preparations.

The adverse reactions experienced by patients in the trials that were reviewed here were all minor and did not involve serious GI or hepatic reactions that are experienced by patients taking oral DI[13,15,132]. Moreover, there were no serious GI events as reported

Table 8. *Number and type of 'possibly-related' adverse events by COSTART body system observed in the experimental groups during all studies. Data from Dreiser (2002) IBSA internal report*

Body system	Flector	Placebo	DI-DEA
Number of patients treated	1344	736	94
Number of possible related adverse events recorded	43	44	3
Number of patients reporting AEs possibly related to treatment	42 (3.1%)	43 (5.8%)	3 (3.2%)
Body as a whole, general	1	0	0
Allergic reaction	1		
Hematologic and lymphatic systems, general	2	0	0
Petechiae	2		
Skin and appendages, general	40	44	3
Pruritus	22	24	3
Application site reaction	4	6	
Dry skin	2	2	
Dermatoses			
Erythema	8	2	
Rash	4	10	

AE = adverse event; DI-DEA = diclofenac diethylammonium

previously with topical NSAIDs[10]. It should be noted, however, that the studies from which these data on GI events were recorded are not specifically designed to establish GI safety nor were they sufficiently powered to enable definitive estimations of rare events such as GI bleeding or ulceration.

The advantages of a controlled delivery of drug from the patch formulation and evidence of patient acceptability afford this preparation considerable value in the therapeutic armamentarium for treating musculoskeletal conditions. The patch preparations enable penetration of the NSAID to the site of inflammatory pain for therapeutic effects while minimizing burdens on drug metabolism and elimination systems with reduction in systemic toxicity compared with the conventional orally-administered drugs.

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Appendix A

Countries where 1.3% diclofenac epolamine (Flector Tissugel, Flector patch) is approved for sale and estimated patient exposures

The diclofenac epolamine patch (DI-EP) has been approved for sale in more than 40 countries throughout the world, including the USA, Western Europe (15 countries) and/or the European Union including the UK, Germany, France and Italy. Since its initial approval by the Swiss Regulatory Authority in 1993, approximately 175 000 000 patches have been sold worldwide, representing 6 250 000 patient exposures, if it is assumed that each patient applied two patches per day for a maximum 14 day treatment period as allowed for the various indications for which the product has been approved (i.e. local symptomatic treatment of pain in ankle sprain, epicondylitis, muscle contusion/sprain and periarthropathies, including osteoarthritis).

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