Evidence for Self-Medication
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Evidence for the treatment of acute joint pain with topical diclofenac gels

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An ex-vivo study on human skin samples showed that topical diclofenac not only penetrates the skin but also forms a reservoir of the drug in the epidermis. Confirmation that the drug reaches the site of action was provided by a double-blind Phase 1 study in which repeated topical application led to the presence of diclofenac in the joint space – irrespective of the patient's BMI.

Both national and international guidelines advise that topical non-steroidal anti-inflammatory drugs (NSAIDs) such as diclofenac gel should be used as first-line treatment for acute joint pain before oral therapy is started [1–4]. Topical application has several advantages: the NSAID is applied directly to the site of pain, it avoids a first-pass effect and, if used in combination with oral NSAIDs, it may enable dosage of the latter to be reduced. This is of particular benefit to elderly patients, because they are more frequently affected by acute joint pain and the lower systemic availability reduces the probability that side effects or interactions will occur. In a preference study, almost three times as many patients with osteoarthritis opted for topical instead of oral treatment with NSAIDs [5, 6].

In order for topical treatment to be effective, adequate amounts of the active agent must reach the site of action. In two recently published studies, GlaxoSmithKline in collaboration with well-known scientists investigated the skin penetration of diclofenac and whether relevant concentrations of the drug are achieved in and around the affected joint.

Topically applied diclofenac forms a drug depot in the skin

An ex-vivo study examined the distribution of diclofenac in the skin and used Raman spectroscopy to visualise the location of a drug reservoir in transversally microtomed sections [7]. The authors based their work on published studies that had already confirmed the formation of a reservoir in the skin, but had not demonstrated its exact location.

The following three commercial products were tested on skin samples from eight patients:

- A: Voltaren® (US formulation with diclofenac sodium 1%),
- B: Voltaren® Pain Gel (diclofenac diethylamine 1.16%),
- C: Voltaren® Pain Gel forte (diclofenac diethylamine 2.32% with permeation enhancer oleyl alcohol).

The above-mentioned products were applied according to their maximum recommended daily doses to the surface of full-thickness, abdominal, human skin samples from six female and two male donors.

A heterogeneous spatial distribution of diclofenac was clearly visible both in the epidermis and in the dermis of all samples, with a markedly higher proportion of diclofenac in the epidermis compared to the dermis. To avoid a false positive identification of diclofenac, detection limits were set to ensure that only diclofenac-specific signals above the limit of statistical significance were mapped in the Raman images.

Figure 1 illustrates the structure of skin and formation of a diclofenac reservoir in the epidermis, as can be seen in the Raman images of the skin samples in **Figure 2**.

The Raman images demonstrate that the topical diclofenac gels investigated penetrated the stratum corneum skin barrier and formed drug depots located in the epidermis. A quantitative comparison of the size of the reservoir for the three formulations was not a subject of this investigation, partly because of the low number of skin samples.

Topical diclofenac is detectable 12 hours after application to the target site

The therapeutic effectiveness of topical diclofenac gel is not only associated with its ability to penetrate the skin, but also with the achievement of pharmacodynamically

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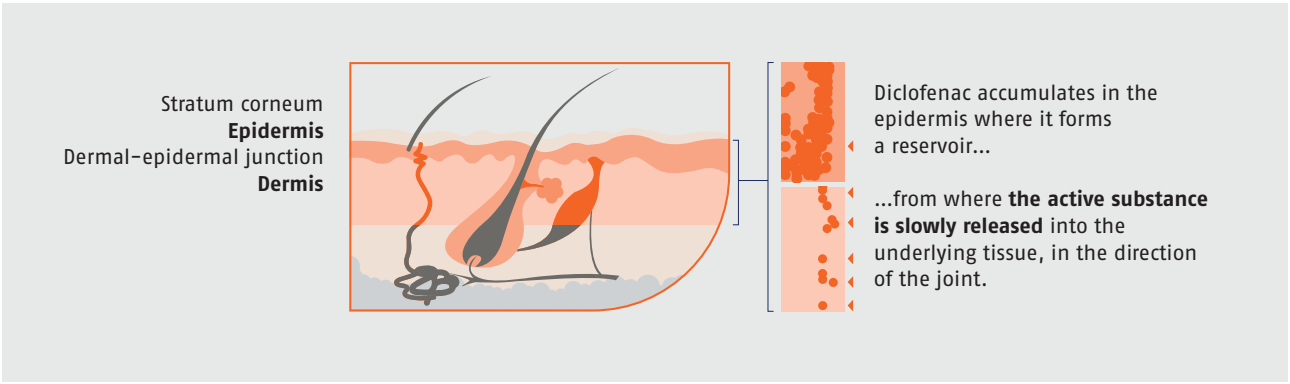

Fig. 1. Simplified diagram to show the results of Raman spectroscopy.

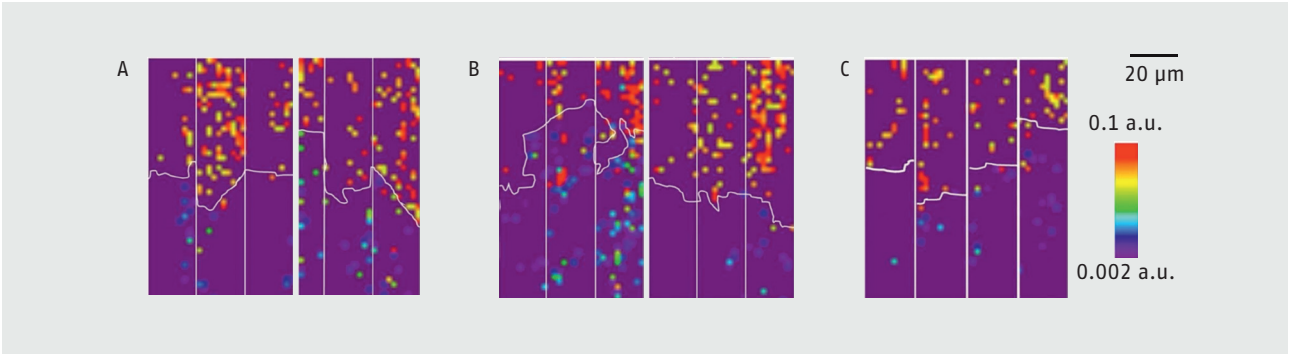

Fig. 2. A to C show Raman images of the relative diclofenac concentration in the epidermis (top) and dermis (bottom), obtained from skin treated with diclofenac gels. The white line shows the dermal-epidermal junction. (Modified from [7]) A: Diclofenac sodium 1% (US formulation of Voltaren), B: Voltaren Pain Gel 1.16% diclofenac diethylamine and C: Voltaren Pain Gel forte 2.32% diclofenac diethylamine with permeation enhancer oleyl alcohol. A and B each show images from two different skin donors (three images per donor) and C shows images from four different skin donors (one image per donor).

active concentrations at the underlying site of pain and inflammation.

The primary objective of a double-blind, multicentre Phase 1 study was to determine whether diclofenac penetrates the knee joint after repeated topical use [8]. A post hoc analysis of the primary endpoint was undertaken to demonstrate whether the body mass index (BMI) affected the penetration of diclofenac. The secondary objective was to compare the relative concentrations of diclofenac in the knee joint and plasma.

29 patients received 4 g diclofenac diethylamine 2.32% w/w gel (= 74.4 mg diclofenac/application) and 16 patients were given placebo. Active treatment and placebo gels were applied by a trained professional every 12 hours for about 7 days (average value across all participants was 7.27 days). The final dose was applied 12 to 15 hours before planned knee surgery.

There was some variability between the concentrations measured in synovial tissue (mean 1.57 ng/g, 95% confidence interval [CI] 1.12, 2.20) and also those measured in synovial fluid [mean 2.27 ng/ml, 95% CI 1.87, 2.76). However, in all participants – even in those who were overweight or obese – , diclofenac penetrated the knee joint, where measurable concentrations were present for 12 hours after the last application.

The ratio of diclofenac concentration in synovial tissue to that in the plasma was 0.32 (95% CI 0.23, 0.45) and that of synovial fluid to plasma was 0.46 (95% CI 0.40, 0.54), indicating that concentrations of diclofenac in plasma were higher than those in the joint. This result differs from earlier studies where generally a higher concentration was found in the joint. The authors speculate whether diclofenac diethylamine 2.32% w/w gel might be a fast-acting topical formulation. In this case, the peak concentration of drug in synovial tissue and fluid would occur soon after application and then would decrease, but to levels still measurable 12 hours after the last application.

The rate of adverse events was similar with diclofenac (55.2%) and placebo (58.8%). In the opinion of the investigators, they were not related to the treatment.

The study was designed to assess the pharmacokinetics and contains no results about efficacy. The investigation of any direct correlation between diclofenac concentrations in the joint and therapeutic effectiveness remains reserved for further clinical studies.

Summary

The authors of the ex-vivo study conclude that topically applied diclofenac penetrates the stratum corneum skin barrier and forms a reservoir of drug in the epidermis.

From there, the drug undergoes sustained release into the underlying tissue.

Local concentrations of NSAID in the joint are considered important for their therapeutic effect in the treatment of acute joint pain, because inflammation in the joint is a critical element of the pathogenesis. The pharmacokinetic study on the penetration of diclofenac to the site of action showed that after twice daily application of diclofenac diethylamine 2.32% w/w gel for 7 days, the drug had penetrated into the target tissue. Diclofenac was detected in synovial tissue and synovial fluid 12–15 h after the last application in all participants, thereby confirming the appropriateness of the current, twice-daily dosing scheme. Since the BMI did not affect penetration of the drug into the joint, even overweight patients can benefit from the topical use of a pain gel. According to the study investigators, no medication-related adverse events occurred. Elderly patients in particular benefit from the reduced systemic availability and the associated low probability of interactions or undesirable effects.

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