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A microdialysis study of topically applied diclofenac to healthy humans: Passive versus iontophoretic delivery

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ABSTRACT

Topical application of NSAIDs is an alternative route to systemic administration when a local anti-inflammatory effect of the underlying tissue is a treatment option. The aim of the present microdialysis study was to assess and compare plasma and tissue levels of diclofenac when topically applied with or without iontophoresis in healthy adults. Fourteen healthy adults (26 ± 9.4 years) were randomized to diclofenac applied by iontophoresis, or by a gel, in a crossover design. Diclofenac concentrations were measured in plasma and in microdialysis perfusates from the underlying tissues. Iontophoretic application resulted in the highest plasma concentration of 3.4 ± 0.5 ng/ml (SEM given) compared to 0.4 ng/ml (at the detection limit) with gel, whereas no differences were observed between tissue concentrations for the two application methods, both being very low, below or around the detection limit. Iontophoresis caused skin reactions in 25% of the participants. Iontophoresis of diclofenac as compared to traditional topical application was not superior in order to increase the NSAID concentration locally and appears to have a higher frequency of skin reactions.

1. Introduction

Topical or systemic applications of NSAIDs are frequently used in management of musculoskeletal pain [30,13,7].

Oral intake of NSAIDs over an extended period of time can cause ulcers, cardio-vascular events, and nephrotoxicity [12], and hence long-term oral administration of NSAIDs for management of e.g. osteoarthritis is not recommended [31]. Topical administration of some NSAIDs (e.g. ibuprofen) is shown to give drug concentrations in subcutaneous layers and underlying muscle comparable to the orally administered drug [27]. Topical application penetrates the skin slowly [30] and hence the onset of effect is slower and may vary according to the pharmacokinetics of the particular molecule to a higher degree than after systemic administration [22,10].

Acute pain after acute traumatic injury responds to topical application of diclofenac [23], but the efficacy is dependent on skin area covered, and type of application [13,1,16]. It is not always clear how much and how fast the NSAID penetrates into the tissue [30,10] since the absorption kinetics depends on the actual formulation [10]. Degree of skin dryness and differences in thickness of the skin layers will also affect the penetration [20,11]. To speed up transport, and thereby increase the NSAID available in the tissue, the charged NSAID molecule may be driven iontophoretically into the tissue [9,25,4,15,5,6,3], a method also used for analgetics [26].

The aims of this study were to test (1) if diclofenac applied together with iontophoresis leads to a faster transdermal transport than standard topical application, (2) if drug concentration in the subcutaneous layer and plasma differed between the two application paradigms, and finally (3) compare the adverse effect profiles.

2. Methods

2.1. Subjects and treatments

Sixteen healthy subjects (5 men and 9 women, mean age 26.6 ± 9.4 years, mean BMI 22.2 kg/m^2 ± 2.1 kg/m^2) participated in the study. All participants were Caucasians.

The study was carried out as a pilot trial for GlaxoSmithKline Consumer Healthcare (GSKCH) according to protocol A2410337. GSKCH participated in the writing of the protocol, but had no further connection to or possibility of influencing the study.

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Exclusion criteria were BMI < 18 kg/m^2 or BMI > 27 kg/m^2, pregnancy, or being female and not using one of following birth control methods: intra-uterine device or hormonal contraceptives, or being breast-feeding, hepatitis, renal insufficiency, congestive heart failure, history of gastro-intestinal bleeding, presence of any skin disorder, drug abuse (tested at enrolment), or measurable alcohol breath.

Intake of any NSAIDs, topically or orally, during the whole study period was furthermore prohibited, and the participants had to abstain from exercise for at least three hours prior to participating in the experiment.

The subjects were, following enrolment and screening, given a physical examination by a clinician with recording of found abnormalities prior to randomisation. The randomisation was carried out by The Biostatics and Data Management Department, GlaxoSmithKline Consumer Healthcare, Weybridge, UK, using a computer programme and applying a Latin-square design. The study was an open-label, two-period, crossover, active-comparator design, where each participant would be exposed to both treatment methods in the order they were randomised into, receiving either 2.00 ml diclofenac potassium (2%) solution delivered via a iontophoretic patch with an area of 13 cm^2, equivalent to an amount of 35.44 mg diclofenac base, or to receive 4.00 g Voltarol Emulgel P® 1.16% diclofenac diethylammonium gel on a skin area of 13 cm^2, the amount of active substance being equivalent to 37.22 mg diclofenac base. The dose 4.00 g of this Voltarol Emulgel P is the maximum single dose recommended for the marketed product. For iontophoresis a voltage of 4 V was applied with a current density of 0.3–0.5 mA/cm^2. The patch was specifically produced for the study by GlaxoSmithKline, Weybridge, UK, as a single-use iontophoretic patch, batch number 34905A-500 and 08706A-500, and quality assured for research and development purposes prior to use. The two methods were applied with a wash-out period of minimum four days, and the two methods were applied on different shoulders and on the skin over the trapezius muscle. The application of either patch or Emulgel P was four hours, where after remaining gel or the patch was removed. If the drug penetrates the skin, four hours is plenty diffusion time to reach the underlying tissue [28,2].

2.2. Microdialysis system and assessment of penetration through skin

Penetration of diclofenac was determined with microdialysis. The system was prior to this study validated by GlaxoSmithKline, Weybridge, UK. Custom-made microdialysis catheters composed of a single plasmaphoresis hollow fibre (0.3 mm in diameter, molecular mass cut-off 100 kDa) from CMA Microdialysis (North Chelmsford, MA 01863, USA) were used. A suture thread (Johnson & Johnson, Brussels, Belgium) was glued to the membrane to improve the mechanical stability of the catheter. Each catheter was glued to a gas-tight nylon inlet and outlet tube (Portex Autoclavable Nylon Tubing, Portex Limited, Smiths Industries, Kent, England) and came in a sterile packing. Prior to use syringes were sterilised with ethylene oxide.

Before inserting the microdialysis catheters, the skin and subcutaneous tissues where the catheters entered were anaesthetised with a local injection of Xylocaine (20 mg/ml) without adrenalin. Care was taken not to anaesthetise the underlying fascia and muscle.

Determination of the location as well as the insertion of the microdialysis tubes were carried out with ultrasound guidance (General Electric, Logiq9™, General Electric, Milwaukee, I1, USA), using the M12L transducer to give a precise location of the microdialysis tube. One tube was located in the centre of the subcutaneous layer of the skin to follow the direct penetration over the skin barrier. Another tube was located in a position which was at one cm depth into the trapezius muscle to follow penetration of drug into the tissue it was aimed for. Both tubes were directly underneath the iontophoretic patch or the skin area covered with gel. The exit sites were covered with a sterile plaster (Tegaderm, 3 M, St. Paul, MN, USA) to prevent any direct penetration of diclofenac. Extracellular fluid was collected from both positions. The microdialysis catheters were perfused via a high-precision syringe pump (CMA 100; Carnegie Medicine, Solna, Sweden) at a rate of 2 ml min^{-1} with a perfusate (Intralipid 20%®, Fresenius Kabi, Uppsala, Sweden) containing purified egg phospholipids of the type used in parenteral nutrition. Sampling times were half an hour prior to application of diclofenac, and then at times 0 and every half hour thereafter, up to four hours from time 0. The dialysates were frozen at -80 °C and stored until end of the sample collection.

Blood tests were taken at time 0 and after 1, 2, and 4 h into heparinised tubes, spun down, and plasma was stored at 80 °C until end of the sample collection.

The plasma and dialysate samples were sent frozen to Medeval Ltd., Manchester, UK, for measurements. Concentration of diclofenac in the dialysates and the plasma samples was measured by Medeval Ltd. with a validated liquid chromatography–Mass Spectroscopy (LCMS-MS) method.

As efficacy of a method of drug application, time for reaching the muscle (dialysate) and/or total concentration reaching the muscle was used. As a secondary measure, skin and plasma concentrations of the drug were considered. Efficacy of penetration into the sampling compartment was expressed by $AUC_{(0\rightarrow t)}$, C_{max} and T_{max}, i.e. the area under the concentration versus time curve, the maximal concentration, and the time elapsed until the maximal concentration was reached, in subcutaneous tissue, muscle, and plasma. In these calculations it was assumed that concentration equilibrium between the perfusion medium in the microdialysis tube and its surrounding tissue is instantaneous, which is the case with a fair approximation.

2.3. Ethics and safety

The study was approved by The Copenhagen and Frederiksberg Municipality Ethics Committee (KF 02-286972) and The Danish Medicine Agency, registered in the EUDRACT Database (EUDRACT no. 2005-002791-15), and was carried out in accordance with the guidelines given in the Helsinki Declaration of 1975, as revised in 1983. All participants gave their informed consent.

Tolerance and safety of the treatments applied in the study was determined by a clinician assessing withdrawal and other adverse events.

2.4. Possible bias

The study was carried out as a pilot trial for GlaxoSmithKline Consumer Healthcare (GSKCH) according to protocol A2410337. GSKCH participated in the writing of the protocol, but had no possibility of influencing the data.

2.5. Data handling and statistics

Plasma concentration pharmacokinetic parameters, total drug transport during the study period, and maximal drug concentration achieved were log-transformed and analysed using a linear mixed-effects analysis of variance (ANOVA) with factors for subject (as a random effect), period, and treatment. The residual mean square from the ANOVA was used to construct confidence intervals for the difference between treatments and then expressed as a ratio.