Diclofenac in the treatment of pain in patients with rheumatic diseases

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Abstract

Diclofenac, a phenylacetic acid derivative, is a drug demonstrating high efficacy after oral administration in the treatment of pain and physical disability in rheumatic diseases. In view of the adverse effects associated with using diclofenac, it is necessary to consider all known drug safety information before the drug is selected for therapy and the dosage regimen is set for individual patients. Selecting an oral dosage form with specific properties determined by excipients is a method to improve the availability of the drug substance and, at the same time, minimize adverse drug reactions. An alternative to tablet or capsule dosage forms is diclofenac application to the skin. The proven efficacy of this method is further improved through the use of transdermal penetration enhancers and vehicle ingredients which provide dosage forms with specific physical properties.

Key words: diclofenac, efficacy, adverse effects, dosage form technology.

Introduction

Diseases of the musculo-skeletal system affect 70% of the population over the age of 50 years. Pain caused by rheumatic diseases decreases or resolves during remission-inducing treatment. Drugs used in the therapy of rheumatic diseases usually have a late onset of action. Consequently, in addition to the treatment of the underlying disease analgesics are indicated as adjunct therapy. At all stages of pain treatment, analgesics can be used in combination with co-analgesics including sedatives, antidepressants and anti-epileptics which may contribute to a reduction in doses of analgesic drugs. Patients with chronic pain evaluated at a minimum of 50% percent on the visual analogue scale (VAS: 0–100 mm) are eligible for therapy with high-potency opioids [1].

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a pharmacokinetically and pharmacodynamically diverse group of drug substances which have an effect on different forms of cyclooxygenase (COX) and vary in their mechanism of action, distribution to the inflammation site and half-life. Pharmaceutical products available on the market also exhibit technological differences (dosage form modifications). Intense pharmacological and formulation research is currently being conducted to obtain more effective and safer products [2].

NSAIDs are effective in multiple indications. In rheumatology, they are used in the treatment of a range of diseases including rheumatoid arthritis, lupus erythematosus, psoriatic arthritis, ankylosing spondylitis, gout and rheumatic fever [3–5].

Efficacy of diclofenac after oral administration

In 2017 Costa et al. [6] published the findings of a study evaluating the efficacy of different drugs and their doses in the treatment of pain secondary to osteoarthritis based on a search of the Cochrane Central Register of Controlled Trials. The researchers reviewed published studies from the period from January 1980 to February 2015 in which the study group included at least 100 patients. Overall, the review encompassed 8,973 publications based on studies conducted in a total of 58,451 patients. The results of efficacy comparisons

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Submitted: 22.05.2018; Accepted: 21.06.20.

between paracetamol and NSAIDs (including naproxen, ibuprofen, diclofenac, celecoxib, lumiracoxib, rofecoxib, etoricoxib used at different therapeutic doses) were analyzed in this cited review. The drugs were compared with each other and with placebo. The authors of the study concluded that diclofenac at a dose of 150 mg per day is currently the most effective drug in the treatment of pain and physical disability caused by osteoarthritis (OA), and superior to widely used NSAIDs (including ibuprofen, naproxen and celecoxib) at maximum doses. Etoricoxib at a maximum dose of 60 mg per day exhibits comparable efficacy to diclofenac at a dose of 150 mg per day in the therapy of pain, but its effect on the treatment of physical disability is undetermined. The authors of the review assert that in view of the diclofenac safety profile all available information should be considered when diclofenac treatment is selected and its dose is determined for individual patients [6].

Pavelka [7] presented randomized well-controlled clinical trials, excluding reviews, meta-analyses and n = 1 trials. A number of databases were searched including Embase, Ovid Medline, and Ovid Medline In-Process & Other Non Indexed Citations. The review encompassed a total of 263 articles published after 1999. The studies focused on comparing the therapeutic efficacy of diclofenac with other drugs including etoricoxib, celecoxib, lumiracoxib, rofecoxib, aceclofenac, dexketoprofen, etodolac, lornoxicam, meloxicam, nabumetone, nimesulide, acetaminophen, tramadol, diacerein and oxaceprol. The authors found that in the majority of studies diclofenac at therapeutic doses exhibited similar efficacy to the other drugs listed above. Thus, diclofenac confirmed its status as the reference drug of choice in the therapy of OA. Based on the studies, the efficacy of diclofenac is not inferior to newer analgesic medications used in the treatment of OA [7].

Patnaik et al. [8] published the findings of a study comparing the efficacy of lornoxicam and aceclofenac and diclofenac in patients with musculoskeletal disorders. The subjects were randomized into three groups of 50. The patients in the three groups were treated with lornoxicam (dose 4 mg), aceclofenac (dose 100 mg) and diclofenac (dose 50 mg). The drugs were applied twice a day after meals. A comparative assessment of analgesic efficacy achieved with the three products was performed by evaluating the level of pain on the VAS scale [9] on day 0 and then every week for 3 weeks in total. It was found that lornoxicam, aceclofenac and diclofenac were equally effective as analgesic agents. The findings are listed in Table I.

The drug substance which is most commonly compared with diclofenac is aceclofenac, which is related to similarities in the structure and mechanism of action of both drug substances [10]. In their studies, Hinz et al. [11] assessed whether the biotransformation of aceclofenac to metabolites including 4'-hydroxyaceclofenac, diclofenac and 4'-hydroxydiclofenac contributes to the inhibitory effect on cyclooxygenase isoenzymes in vitro and ex vivo. Short-term in vitro tests based on human whole blood and monocytes showed that neither aceclofenac nor 4'-hydroxyaceclofenac affected COX-1 and COX-2, whereas diclofenac and 4'-hydroxydiclofenac were found to inhibit both isoforms. In long-term in vitro tests both aceclofenac and 4'-hydroxyaceclofenac inhibited both isoforms of COX, but the inhibition occurred in parallel to the conversion to diclofenac and 4'-hydroxydiclofenac, respectively. Comparative studies of aceclofenac and diclofenac found the maximum plasma concentration of diclofenac after application of both aceclofenac and diclofenac (0.39 µmol/l and 1.28 µmol/l, respectively). The obtained concentrations were recognized as sufficient to achieve over 97% inhibition of COX-2 (50% inhibitory concentration: 0.024 µmol/l). Studies show unambiguously that the inhibition of COX isoenzymes by aceclofenac requires its conversion to diclofenac. Table II shows the potency of the inhibitory effect produced by the studied drugs and their metabolites on cyclooxygenases both in short- and long-term tests [11].

Yamazaki et al. [12] also studied the mechanisms underlying the effect of aceclofenac in primary cultured synovial cells obtained from 10 patients with rheumatoid arthritis. The research showed that aceclofenac and 4'-hydroxyaceclofenac, the main chemical compounds found in human blood, have no inhibitory effect on the activity of cyclooxygenase (COX) or the expression of COX in rheumatoid synovial cells. It was also observed that aceclofenac and 4'-hydroxyaceclofenac were hydrolyzed in rheumatoid synovial cells to COX inhibitors

 Table I. Comparison of analgesic efficacy of lornoxicam, aceclofenac and diclofenac [9]

Treatment	Mean VAS ±SD						
	n	Baseline value	n	First week	n	Second week	Percentage reduction
Lornoxicam	50	4.16 ±1.63	50	2.15 ±1.46	41	1.42 ±1.25	48
Aceclofenac	50	4.34 ±1.67	50	1.91 ±1.24	39	1.03 ±0.94	56
Diclofenac	50	4.48 ±1.35	50	2.07 ±1.14	38	1.03 ±0.97	62

Substance	Short-te	erm test	Long-term test		
or metabolite	COX-1 IC50 (µmol/l)	COX-2 IC50 (µmol/l)	COX-1 IC50 (µmol/l)	COX-2 IC50 (µmol/l)	
Aceclofenac	no inhibition*	no inhibition*	3.59 ±0.54	1.65 ±0.46	
4'-hydroxyaceclofenac	no inhibition*	no inhibition*	12.73 ±3.53	25.35 ±7.98	
Diclofenac	0.43 ±0.13	0.0054 ±0.0028	0.16 ±0.03	0.024 ±0.007	
4'-hydroxydiclofenac	8.28 ±0.93	0.72 ±0.40	1.63 ±0.56	0.76 ±0.03	

Table II. Potency of inhibitory effect of aceclofenac, 4'-hydroxyaceclofenac, diclofenac and 4'-hydroxydiclofenac on COX-1 and COX-2 in short- and long-term *in vitro* tests [11]

IC50 – 50% inhibitory concentration; *lack of inhibitory effect at concentrations of up to 100 µmol/l

– diclofenac and 4'-hydroxydiclofenac, respectively. Since the potency of the effect exerted by aceclofenac and 4'-hydroxyaceclofenac on prostaglandin E2 (PGE2) production was correlated proportionally with hydrolytic activity in rheumatoid synovial cell preparations, the authors of the study suggested that the inhibitory effect of aceclofenac and 4'-hydroxyaceclofenac on the production of PGE2 is facilitated by hydrolysis in rheumatoid synovial cells.

The studies showed that the inhibitory activity of aceclofenac and 4'-hydroxyaceclofenac, its main metabolite in human blood, towards PGE2 production was not attributable to the inhibition of COX expression and activity by the two substances, but rather their hydrolysis to active metabolites (diclofenac and 4'-hydroxydiclofenac) in rheumatoid synovial cells. The hydrolytic activity was strongly correlated with the potency of the inhibitory effect of aceclofenac and 4'-hydroxyaceclofenac on PGE2 production. The study findings indicate that aceclofenac is a type of NSAID inhibiting PGE2 production, and its inhibitory effect is further enhanced by hydrolytic activity in the inflammation site [12].

Adverse effects of diclofenac

NSAIDs have a distinct mechanism of action which makes them highly effective therapeutically but also causes side effects that are particularly common after oral administration. It is estimated that approximately 21–25% of known cases of adverse drug reactions (ADR) are caused by NSAIDs. The most frequent side effects associated with NSAID treatment, especially when used on a long-term basis, are functional disorders of the gastrointestinal tract, kidneys, cardiovascular and central nervous systems. Nonsteroidal anti-inflammatory drugs have been shown to vary considerably in terms of adverse effects, contraindications and use restrictions [13–17].

The toxicity of NSAIDs in the upper gastrointestinal tract is currently well documented. They may also cause injury to the small and large intestines, and other digestive organs. NSAIDs induce perforations, ulcerations and strictures of the small intestine requiring operative treatment, and may cause enteropathy, i.e. inflammation accompanied by blood and protein loss from the intestine. In addition, drugs from this class may exacerbate the underlying large-bowel disease, lead to reactivation of previously inactive disease or induce the primary episode of inflammatory bowel diseases.

Liver damage is possible and it may develop after treatment with any NSAID, although usually this condition is induced by diclofenac and sulindac [18]. Sriuttha et al. [19] presented a systematic review of 18 randomized controlled trials (RCTs) which assessed the risk of hepatotoxicity of NSAIDs. These authors found that from 18 only 8 studies with NSAIDs (celecoxib, etoricoxib, diclofenac) confirmed clinically significant hepatotoxicity. In these 8 studies, diclofenac was shown to have the highest hepatotoxicity but was not associated with an increase in hospitalization for this reason. A contrary review based on population epidemiological studies by Rubenstein [20] did not show significant hepatotoxicity from diclofenac. It should be noted that the two cited works were based on different inclusion criteria - from damage to the liver causing the increase of enzymes [19] to severe damage which is the reason for hospitalization and death [20].

In their studies, Kellner et al. [21] compared the efficacy of diclofenac in combination with omeprazole versus celecoxib in patients with OA and RA, at high gastrointestinal risk. The studies had a randomized double-blind design. A total of 4,484 patients were randomized to treatment: 2,238 of the subjects were treated with celecoxib at a dose of 200 mg twice a day, and 2,246 with diclofenac SR (delayed release) at a dose of 75 mg, used twice a day in combination with a proton pump inhibitor administered at a dose of 20 mg once daily. The follow-up period was 6 months. The authors concluded that celecoxib and diclofenac combined with omeprazole had similar efficacy in patients with OA and RA, at high gastrointestinal risk. The same study also assessed the effect of diclofenac combined with omeprazole and celecoxib on the risk of gastrointestinal complications in treated patients [22]. The assessment comprised a range of gastrointestinal complications including bleeding, stricture or perforation of the upper gastrointestinal tract, small and large intestine, and clinically significant anaemia [23]. Complications developed in 0.9% of patients treated with celecoxib and in 3.8% of patients taking diclofenac and omeprazole.

Recent studies in rodents show that proton pump inhibitors (PPIs) not only fail to bring any therapeutic benefits but, in fact, may exacerbate NSAID-induced enteropathy [24]. Rats treated with PPIs (omeprazole or lansoprazole) had a higher incidence of intestinal ulceration and bleeding than animals treated concomitantly with NSAIDs (naproxen or celecoxib) compared with the control group receiving just the vehicle and NSAIDs.

The studies thus confirmed that the regimen consisting of NSAIDs used in combination with PPIs to prevent NSAID-induced damage fails to bring significant effects in the small intestine. Recent video capsule endoscopy (VCE) studies demonstrated a high incidence (55–75%) of small intestinal injuries in healthy volunteers taking NSAIDs in combination with PPIs for 2 weeks [25].

NSAID therapy is also limited by adverse effects, and use of coxibs, diclofenac and high-dose ibuprofen should be avoided in patients at cardiovascular risk [26]. All NSAIDs, with the exception of acetylsalicylic acid, may cause cardiovascular complications [27]. A review of 138 randomized clinical studies involving a total of 145,373 patients showed that high doses of coxibs, similarly to diclofenac, were associated with an increased risk of cardiovascular complications, particularly myocardial infarction. No similar observation was made in patients treated with naproxen [28].

The largest meta-analysis investigating cardiovascular risk associated with NSAIDs published to date included a total of 280 comparative placebo-controlled studies (124,513 patients) and 474 studies with other NSAIDs in the control group (229,296 patients). The findings indicated that diclofenac and high doses of ibuprofen increase cardiovascular risk to a degree comparable to coxibs, whereas naproxen is relatively safe in this respect [29]. A meta-analysis comprising 21 studies involving over 2.7 million patients treated with various NSAIDs and 30 control group studies revealed a total of 184,946 recorded cardiovascular complications. Findings of the meta-analysis show that coxibs and diclofenac increase the risk of such complications, and therapy with ibuprofen and naproxen is associated with the lowest risk. The risk was found to increase both in patients with a history of circulatory system diseases and in individuals with no previous cardiovascular complications. The same meta-analysis also showed NSAIDs to elevate the risk of atrial fibrillation [30].

However, patients with coronary heart disease taking small doses of acetylsalicylic acid (ASA) sometimes require concomitant NSAID treatment on account of coexisting rheumatic disorders. Concomitant use of two different NSAIDs is thus a therapeutic exception, and caution must be exercised to ensure a minimum interval of 2 hours between the administration of ASA and another NSAID [4, 31].

The majority of NSAIDs reduce the effectiveness of acetylsalicylic acid in cardiac doses, which results from reversible blocking of cyclooxygenase receptor sites. The mechanism prevents irreversible blockage of receptor sites by acetylsalicylic acid. Some NSAIDs have been shown to interfere with the antiplatelet activity of acetylsalicylic acid, while others exhibit no such effect. The former group comprises ibuprofen, naproxen, nimesulide and piroxicam, while the lowest risk of interactions with acetylsalicylic acid is associated with diclofenac and ketoprofen [1, 32].

The relationship between acute kidney injury and NSAIDs is well documented. However, little is known about the risk associated with individual NSAIDs including specific COX-2 inhibitors. A meta-analysis of studies included in the Medline, Embase and Cochrane databases and published before September 2014 was performed to evaluate the safety of using traditional NSAIDs and two specific COX inhibitors. Overall, studies investigating indomethacin, piroxicam, ibuprofen, naproxen, sulindac, diclofenac, meloxicam, rofecoxib and celecoxib were reviewed. No significant differences were found in the assessment of the risk ratio for acute kidney injury associated with using traditional NSAIDs included in the study. The pooled risk ratios were relatively consistent and ranged from 1.58 to 2.11. Differences between risk ratios did not reach statistical significance ($p \ge 0.19$ for each comparison). An elevated risk of acute kidney injury was noted in diclofenac, meloxicam, rofecoxib and celecoxib users, but it failed to achieve statistical significance [33].

However, a review of results obtained in 3,789 studies found by searching the Medline and Embase databases, published before June 2016, demonstrated an elevated risk of acute nephritis in the elderly and patients with chronic kidney diseases [34].

Diclofenac in the chemical forms of acid, potassium salt or sodium salt is available on the pharmaceutical market in a large number of medicinal products in various dosage forms and with different routes of administration [35, 36]. They include oral dosage forms (tablets, capsules), usually with modified release, rectal dosage forms, injections, products applied or sprayed on the skin, mucoadhesive dosage forms and eye drops [37]. Pharmaceutical forms most typically contain diclofenac in the form of sodium salt.

Dosage form technology and its impact on the efficacy of diclofenac oral dosage forms

In addition to the dose, chemical form and administration route, one of the most important elements affecting the clinical efficacy of every biologically active substance is the drug dosage form containing carefully selected excipients which, according to the definition of the Pharmaceutical Excipients Council, are used to aid the manufacturing process, increase stability, obtain optimum pharmaceutical and biological availability parameters and shelf-life, and reduce the occurrence of potential adverse reactions. An interesting example among formulations is a modified-release hard capsule containing micropellets with diverse functionalities in terms of technology and application. The medicinal product contains 75 mg of diclofenac sodium salt: 25 mg of this dose is in an enteric form and the remaining 50 mg is in an extended-release form. The formulation is characterized by a high content of excipients in order to achieve a double application profile (Table III).

Another type of diclofenac sodium formulation comes in the form of a hard capsule containing one type of pellets exhibiting extended- and delayed-release properties at the same time. The form consists of a hard gelatin capsule and its filling, i.e. enteric-coated homogeneous micropellets (microspheres) containing diclofenac sodium at a dose of 100 mg. The dosage forms are not characterized by division into initial and maintenance doses with varying release mechanisms. Instead, the entire dose of diclofenac sodium is released in a delayed manner starting in the duodenum and continuing towards the small intestine. Such dosage forms (formulations) often contain the minimum required quantity of excipients. These technologies are aimed at delivering the full dose of diclofenac sodium to the patient during an extended period of time, while reducing gastric adverse effects to a minimum. Commercially available formulations, despite being equivalent in form, vary in the type of excipients used (Table IV).

Diclofenac tablets are most commonly modified-release products [38, 39] with relatively complex formulations. Their commercial names often additionally include the acronym "SR" (slow release). A possible example is an extended-release tablet containing 75 mg of diclofenac sodium, but not possessing enteric properties. The tablet core formulation contains high-viscosity hypromellose ensuring slow release of the drug substance (Table V).

A quite distinct variant of the above formulation comes in the form of multi-layered tablets. They are modified-release tablets containing diclofenac sodium both at doses of 75 mg and 150 mg. A specific property of tablets of this type is that they are usually composed of two layers containing varying doses of diclofenac sodium. The layers perform different functions, releasing diclofenac sodium in different sections of the gastrointestinal tract at different time intervals. The commercial names of such products contain a distinguishing acronym, for example "Duo". In bi-layer tablets, one layer is like a conventional non-modified release tablet containing a smaller amount of diclofenac sodium, and the other extended-release layer contains more of the active

Table III. Formulation details for hard capsuleof diclofenac sodium salt at a total dose of 7	containing micropellets with enteric properties and extended release 5 mg
Formulation of enteric pellets	Formulation of extended-release nellets

Formulation of enteric pellets	Formulation of extended-release pellets		
25 mg of diclofenac sodium salt	50 mg of diclofenac sodium salt		
microcrystalline cellulose povidone K-25 anhydrous colloidal silica methacrylic acid and ethyl acrylate copolymer (1 : 1) sodium hydroxide 1N propylene glycol talc	microcrystalline cellulose povidone K-25 anhydrous colloidal silica ammonium methacrylate copolymer, type B (Eudragit RS 100) ammonium methacrylate copolymer, type A (Eudragit RL 100) dibutyl phthalate talc		
Ingredients of gelatin capsule	Ingredients of colouring ink capsule coating		
gelatin titanium dioxide E 171 indigotin E 132	shellac soy lecithin antifoam DC1510 titanium dioxide E 171		

Hard capsules with micropellets containing 100 mg of diclofenac sodium			
Formulation 1	Formulation 2		
saccharose corn starch shellac talc ammonium methacrylate copolymer, type A (Eudragit RL PO) gelatin titanium dioxide E 171	lactose monohydrate microcrystalline cellulose PH102 microcrystalline cellulose + sodium croscarmellose glycerol trimyristate titanium dioxide E 171 triethyl citrate hydrated colloidal silica ammonium methacrylate copolymer, type B gelatin titanium dioxide E 171 red iron oxide E 172 black iron oxide E 172 erythrosine E 127		

Table IV. Different formulations of diclofenac sodium 100 mg in the form of pellets enclosed in a hard capsule

Table V. 75 mg of diclofenac sodium in extended-release film-coated tablet

Tablet core	Tablet coating	
lactose monohydrate	hypromellose	
microcrystalline cellulose	titanium dioxide E 171	
(high-viscosity) hypromellose	red iron oxide (E 172)	
talc	macrogol 6000	
magnesium stearate	-	

Table VI. Characteristics of multi-layered tablets with modified-release diclofenac sodium

Modified-release multi-layered ta	blets containing 75 mg or 150 mg of sodium diclofenac	
Non-modified release layer	Extended release layer	
12.5 mg or 25 mg of diclofenac sodium	62.5 mg or 125 mg of diclofenac sodium	
lactose monohydrate calcium hydrophosphate dihydrate microcrystalline cellulose magnesium stearate sodium carboxymethyl starch (type A) anhydrous colloidal silica corn starch red iron oxide (E 172)	lactose monohydrate hypromellose magnesium stearate	

ingredient. The formulations are divided into initial and maintenance doses (Table VI).

Topical application of diclofenac

NSAID therapy based on dosage forms applied on the skin is an alternative to the oral and parenteral administration routes. Topical dosage forms reduce the systemic exposure of drug substances and hence lower the risk of gastrointestinal and cardiovascular complications and renal dysfunction. Adverse effects accompanying topical application of NSAIDs affect only 10–15% of treated patients, and they usually present as mild rash and itching on the application site [40]. Low incidence of adverse reactions after the topical administration of a drug substance is a particularly important factor in the therapy of chronic conditions. Application on the skin is convenient to the patient and, at the same time, it constitutes the least invasive method of delivering the drug substance.

Factors influencing drug substance absorption into the skin include properties of the drug substance itself, such as lipophilicity, molecular mass and charge, as well as characteristics of the vehicle and dosage form, method of application and condition of the skin [41]. As a consequence, the rate of transdermal penetration of diclofenac may vary [42]. Different diclofenac salts have been studied with a focus on their penetration into deep-lying tissues. The incorporation of transdermal penetration enhancers, selection of excipients and rheological parameters of the drug vehicle have been shown to play a role in pharmaceutical and biological

availability of the drug substance. Detailed studies were conducted to investigate drugs containing penetration-enhancing excipients including dimethyl sulphoxide (DMSO) to promote the topical absorption of diclofenac [43, 44]. Penetration enhancers, such as DMSO, change the permeability of the stratum corneum for a specified time, thus increasing the absorption of the drug substance. They work by facilitating the diffusion of the drug substance through inducing a change in the structural arrangement in intercellular lipid layers in the stratum corneum [41]. One of the methods to increase the penetration of the active substance through the skin is iontophoresis. Studies conducted with model organisms found that iontophoresis combined with geraniol was an effective system for delivering diclofenac transdermally into the deep tissues [45].

Also, studies were carried out to evaluate the penetration of diclofenac sodium in 4% gel into the synovial membrane, synovial fluid and blood plasma in subjects with knee joint effusions due to osteoarthritis, and planned total knee arthroplasty. A total of 39 patients applied the gel to the knees 2 or 3 times daily for a period of 3 days. Within 8 hours after the last application, surgical interventions were performed, and diclofenac concentrations were measured by liquid chromatography. The gel was found to penetrate the skin locally in substantial amounts and thus reach the desired target tissue. The concentration of the drug substance was shown to be dose-independent and approximately 10–20 times higher in the synovial membrane than in the synovial fluid or plasma. The gel was well tolerated in 97.4% of the patients. Adverse effects were observed in only two cases and were limited to skin reactions [46].

Kienzler et al. [47] conducted a comparative study of biological availability of diclofenac in the form of a topical gel containing 1% of sodium salt of this NSAID, and an oral dosage form with the same drug substance, in healthy volunteers. The study found that systemic absorption associated with the topically applied medication was 5- to 17-fold lower than with the oral drug. In addition, topical application was shown to induce higher concentrations in the adjacent adipose tissue and skeletal muscles than oral medications [48]. However, the concentration of diclofenac in the synovial fluid was lower after the topical application of diclofenac compared to the oral administration [49].

The analgesic effect produced by topically applied diclofenac is not fully understood. At high tissue concentrations diclofenac appears to be able to act as a sodium channel blocker, mediating local anaesthetic effects [50]. Findings from animal studies indicate that the antagonism of the *N*-methyl-D-aspartate receptor may contribute to the analgesic effect associated with the topical application of diclofenac [51]. There is also evidence suggesting that diclofenac may inhibit L-type calcium channels, which play a role in the perception of pain [52].

Derry et al. [53] conducted a review of studies evaluating NSAIDs in the form of topical formulations including cream, gel, patch and solution, used in the therapy of chronic musculoskeletal pain. Topical NSAIDs were clearly superior to placebo in reducing pain caused by chronic diseases of the musculoskeletal system. The greatest therapeutic benefits were demonstrated for diclofenac and ketoprofen. Used topically, the two drugs provide benefits in the treatment of acute pain and have a conveniently low NNT (number needed to treat) index [54].

Based on a meta-analysis encompassing 14 clinical trials involving a total of 1500 patients, topically applied NSAIDs were also shown to be highly effective in the therapy of chronic diseases of the musculoskeletal system. After a two-week treatment with NSAIDs a reduction in pain, with a statistically significant improvement versus placebo, was noted in approximately 50% of patients. Also, there were no statistically significant differences in the efficacy of NSAIDs after oral and topical applications [55].

In their studies, Baraf et al. [56] evaluated the safety and efficacy of topical application of diclofenac sodium 1% gel versus drug vehicle alone in patients between the ages of 25 and 64, and over the age of 65 years, who had been diagnosed with knee osteoarthritis. The patients applied 4 g of the gel or placebo four times a day for a total of 12 weeks. The study relied on the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scale, which is designed for subjective assessment based on patient-completed questionnaires. The patients rated pain (0-20 scale), physical activity (0-68 scale) and pain on movement (100-mm VAS scale), and provided a global assessment of the disease (100 mm VAS scale). The study found that diclofenac sodium 1% gel was effective and well tolerated in adult patients irrespective of age.

Hsieh et al. [57] assessed myofascial pain syndrome of the upper trapezius muscle in 153 patients using diclofenac patches for 8 days, compared to control patches containing menthol. An improvement in terms of pain relief and recovery of the range of motion was noted in the group using diclofenac patches in comparison to the control group.

Conclusions

The treatment of pain in patients with rheumatic diseases is most typically based on non-opioid analgesics including paracetamol and nonsteroidal anti-inflammatory drugs. Diclofenac is a phenylacetic acid derivative non-selectively inhibiting cyclooxygenases COX-1 and COX-2. A number of meta-analyses have shown that diclofenac at therapeutic doses is highly effective in the treatment of pain and physical disability in rheumatic diseases. However, taking into account the safety profile of diclofenac, all available drug safety information should be considered when diclofenac treatment is selected and its dose is determined for individual patients.

The therapeutic efficacy of oral dosage forms with diclofenac is determined not only by the dose of the drug substance, but also by the type of drug formulation and appropriate selection of excipients. Technologically advanced modified-release tablets, multi-layered tablets or hard capsules containing micropellets belong to pharmaceutical forms developed in order to achieve optimum pharmaceutical and biological availability of diclofenac, improve its stability and reduce adverse effects.

Another method of limiting the systemic exposure of diclofenac and its adverse reactions is application of the drug substance in topical dosage forms. Based on meta-analyses, topical diclofenac was found to be highly effective in the therapy of acute pain and chronic musculoskeletal diseases. The transdermal penetration rate of diclofenac may vary, depending on a range of factors such as the dosage form (cream, gel, patch, solution), transdermal penetration enhancers and excipients used in the formulation, and physical properties of the drug vehicle.

The publication was prepared under the statutory grant of the Medical University of Lodz No. 503/3-021-02/503-31-001-17.

The authors declare no conflict of interest.

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