Comparison of analgesic effect of three topically applied preparations containing indometacin – a pilot, double-blind clinical and experimental study

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Background: Results of our previous published studies indicate that substantial differences in analgesic efficacy might exist between individual preparations containing the same topical non-steroidal anti-inflammatory drug. The aim of this pilot, double--blind, placebo-controlled clinical study was to compare the analgesic efficacy of a single-dose application of three indometacin containing preparations for topical administration (Elmetacin® spray, Indobene® gel, Indometacin 1% gel) in patients with active gonarthrosis and also in an experiment on animals.

Material and method: The analgesic effect of the tested preparations in patients with bilateral active gonarthrosis was evaluated in comparison with relevant placebos eight hours after administration to one knee joint. The following criteria were used: effectiveness on spontaneous pain, pain relieve (4-point arbitrary scale) and measurement of pressure pain threshold (P_{min}) and pressure pain tolerance (P_{max}) as objective parameters. Randall-Selitto model of yeast inflammation was used for measuring pressure-induced hyperalgesia of inflamed rat paw.

Results and conclusion: Only Indobene® gel was demonstrated to be efficacious in influencing all evaluating tests both in patients and in animals (efficacy 5/5). Elmetacin® spray manufactured by the Hospital Pharmacy of the University Hospital Olomouc (UHO) was effective in patients; it decreased significantly the pressure-induced knee hyperalgesia (P_{min} and P_{max}) but not the subjective criteria of the pain (efficacy 2/5). Elmetacin® spray decreased significantly the pressure pain threshold in patients only and produced significant relief of the spontaneous pain (efficacy 2/5). Neither Indometacin 1% gel nor Elmetacin® spray were effective in the Randall-Selitto.

Key words: indometacin for topical administration, different preparations, analgesic effect, clinical and experimental study.

SROVNÁNÍ ANALGETICKÉHO ÚČINKU TŘÍ LOKÁLNĚ APLIKOVANÝCH PŘÍPRAVKŮ S OBSAHEM INDOMETACINU – PILOTNÍ, DVOJITĚ SLEPÁ KLINICKÁ A EXPERIMENTÁLNÍ STUDIE

Úvod: Výsledky našich dřívějších studií ukazují, že různé přípravky s obsahem totožného nesteroidního antiflogistika pro lokální aplikaci mohou mít rozdílný analgetický účinek. Cílem této dvojitě slepé, placebem kontrolované klinické studie bylo ověřit analgetickou účinnost tří přípravků s obsahem indometacinu ve formě roztoku (Elmetacin® spray) a gelu (Indometacin 1% gel, Indobene® gel). Analgetická účinnost těchto přípravků byla hodnocena po jednorázové aplikaci u pacientů s aktivní gonartrózou a též v pokuse na zvířeti.

Materiál a metody: Analgetický účinek uvedených přípravků byl hodnocen po aplikaci na jeden kolenní kloub u pacientů s aktivní oboustrannou gonartrózou v porovnání s odpovídajícím placebem v průběhu osmi hodin po aplikaci podle těchto kritérií: ovlivnění klidové bolesti, stupně úlevy této bolesti a podle prahu a maximální tolerance tlakové hyperalgezie kolenních kloubů. Hodnoty objektivních parametrů (práh tlakové citlivosti – P_{min} a práh tlakové tolerance – P_{max}) byly získány měřením tlaku vzduchu v manžetě tonometru, omotané kolem kloubu, při kterém dochází k pocitu bolesti. Subjektivní kritéria (klidová bolest a úleva od bolesti) byla hodnocena 4bodovou stupnicí. V pokuse na zvířeti byla analgetická účinnost testovaných přípravků hodnocena podle ovlivnění zánětlivé hyperalgezie tlapky potkana vyvolané kvasnicovým zánětem (metoda podle Randalla a Selitta).

Výsledky: Pouze Indobene® gel byl průkazně analgeticky účinný podle čtyř sledovaných kritérií u pacientů s aktivní gonartrózou i v pokuse na zvířeti (účinnost 5/5). Indometacin 1% gel snížil významně P_{min} i P_{max} kolenních kloubů, subjektivní kritéria neovlivnil, ani nebyl průkazně účinný v pokuse na zvířeti (účinnost 2/5). Elmetacin® spray snížil významně pouze P_{min} kolenních kloubů a vyvolal subjektivní úlevu bolesti a nebyl analgeticky účinný v pokuse na zvířeti (účinnost 2/5).

Závěr: Výsledky ukazují, že mezi jednotlivými přípravky indometacinu pro lokální aplikaci může být značný rozdíl v jejich analgetické účinnosti.

Klíčová slova: indometacin v lokální aplikaci, různé přípravky, analgetický účinek, klinická a experimentální studie.

Introduction

During past ten years, Czech pharmaceutical market was literally "inundated" with a lot of **n**on-steroidal **a**nti--**i**nflammatory **d**rugs (NSAIDs) for local application. Nowadays, about 35 preparations containing twelve basic substances (alone or in combination with other adjuvant components) are registered in the Czech Republic[(1)]. For the introduction of a new topical NSAID preparation to

the market as well as for its quality recommendations to consumers, an objective evaluation of its real analgesic effect would be appropriate, especially in comparison with a standard preparation. However, such a type of study is not obligatory for registration and therefore is not regularly performed. The Institute of Pharmacology and the Department of Geriatrics of the University Hospital Olomouc (UHO) have co-operated in this field since 1988 and developed for this purpose their own methodology[2, 3]. The principle of this method is based on the measurement of inflammatory hyperalgesia in patients with bilateral active gonarthrosis, which is suppressed after administration of locally applied preparations containing different anti-inflammatory drugs. The first pain sensation (pressure pain threshold) appears at the pressure values of 40–100 mmHg, pressure pain tolerance at those of 80–180 mmHg. Control individuals manifest much higher values (P_{min} 200 mmHg, P_{max} 280 mmHg). Results of our previously published studies indicate significant differences in analgesic efficacy of different locally applied preparations containing the same NSAID in comparable concentrations[2, 3, 4, 5]. The aim of this pilot, double-blind, placebo-controlled clinical study was to compare the analgesic efficacy of three preparations containing indometacin – one in liquid and two in gel form. The principle method used for evaluation of analgesic activity of those indometacin-containing preparations was measurement of changes of inflammatory hyperalgesia of arthrotic knee joints in patients suffering from bilateral gonarthrosis. Subjective criteria of pain intensity and pain relief of both arthrotic knee joints in those patients were also assessed. Results of the clinical testing were compared with the efficacy of the tested preparations on inflammatory hyperalgesia of the rat paw.

Both experimental and clinical parts of the study have been approved by the Ethical Committee of the UHO and of the Medical Faculty of Palacký University in Olomouc and comply with all relevant regulations. All patients participating in the study obtained both written and oral information about the study and have signed informed consent.

This study should bring answers to the following questions:

1. Is the analgesic effect of the drug decisive compared to that of a relevant placebo?
2. Are all indometacin-containing drug formulations comparable to each in their analgesic effect?
3. Is there any evidence of an analgesic effect on hyperalgesia of the non-applied arthrotic knee (what would indicate the analgesic effect following the systemic drug resorption from the applied contralateral knee)?

Material

A. Evaluated preparations

- *Elmetacin® spray*, LUITPOLD PHARMA München, Germany, 50 ml of solution in a plastic bottle with mechanical pump sprayer as a dosing machine; 1 ml of solution contains 8 mg of indometacin in solution base (70 % isopropylalcohol).
- *Indobene® gel*, Merckle GMBH, Blauberen, Germany, 50 g of gel in a metal tube; 1 g of the gel contains 10 mg of indometacin in gel base.
- *Indometacin 1 % gel*, manufactured by the Hospital Pharmacy of the UHO, 40 g of gel in a metal tube; 1 g of the gel contains 10 mg of indometacin in gel base (4 % carboxymethylcellulose).
- *Elmetacin® placebo:* Spitaderm®, Farmakon, Olomouc, CR, licensed product (Henkel GV) 500 ml of solution in a plastic bottle contain isopropylalcohol 70 %, chlorhexidingluconate 0,5 %, hydrogen peroxide 0,45 %). For the reasons of application route and blinding, placebo was put into an empty original Elmetacin® plastic bottle.
- *Gel placebo:* Carbopol 4 % gel, manufactured by the Hospital Pharmacy of the UHO.

B. Trial subjects

Total number of fifteen multimorbid patients (12 females, 3 males; age 68–91, average 75.2 years) long-term hospitalised at the Dept. of Geriatrics of the UHO for different basic illnesses were enrolled into the study.

Inclusion criteria were:

1. Diagnosed bilateral active gonarthrosis with positive X-ray signs (grade II.–III.).
2. Permanent both spontaneous pain and pressure-induced hyperalgesia of both knee joints.
3. Pressure pain threshold lower than 80 mm of Hg.
4. Pressure pain tolerance lower than 100–150 mm of Hg.
5. Signed agreement with participation in the study.

Exclusion criteria were:

1. Incapability of cooperation during the study (e. g. dementia).
2. Permanent pain of other etiology (cancer pain, etc.) requiring uninterrupted administration of analgesics.
3. Hypersensitivity to any component of the locally administered preparations.

C. Experimental animals

Laboratory rats (males, n=25, average weight 235 g), Wistar conventional breed (Konárovice farm, Czech Rep.). Animals were housed in plastic boxes (five in a group), fed with a standard laboratory diet (type LzŽ Mohelský, Brno, CR). Feeding was discontinued 18 hours prior to the onset of the experiment, the amount of water remained continuously ad libitum.

Fig. 1. Calculation of pressure-pain quotients

$$Q_{min} = \frac{P_{min}n}{P_{min}0} \qquad Q_{max} = \frac{P_{max}n}{P_{max}0}$$

$P_{min}n$ pain threshold in given time interval of measurement
$P_{min}0$ pain threshold before local application of samples
$P_{max}n$ pain tolerance in a given time interval of measurement
$P_{max}0$ pain tolerance before local application of samples
n time interval of measurement after application of tested drugs (i. e. 1, 2, 4, 6 and 8 h)

Methods

A. Clinical study

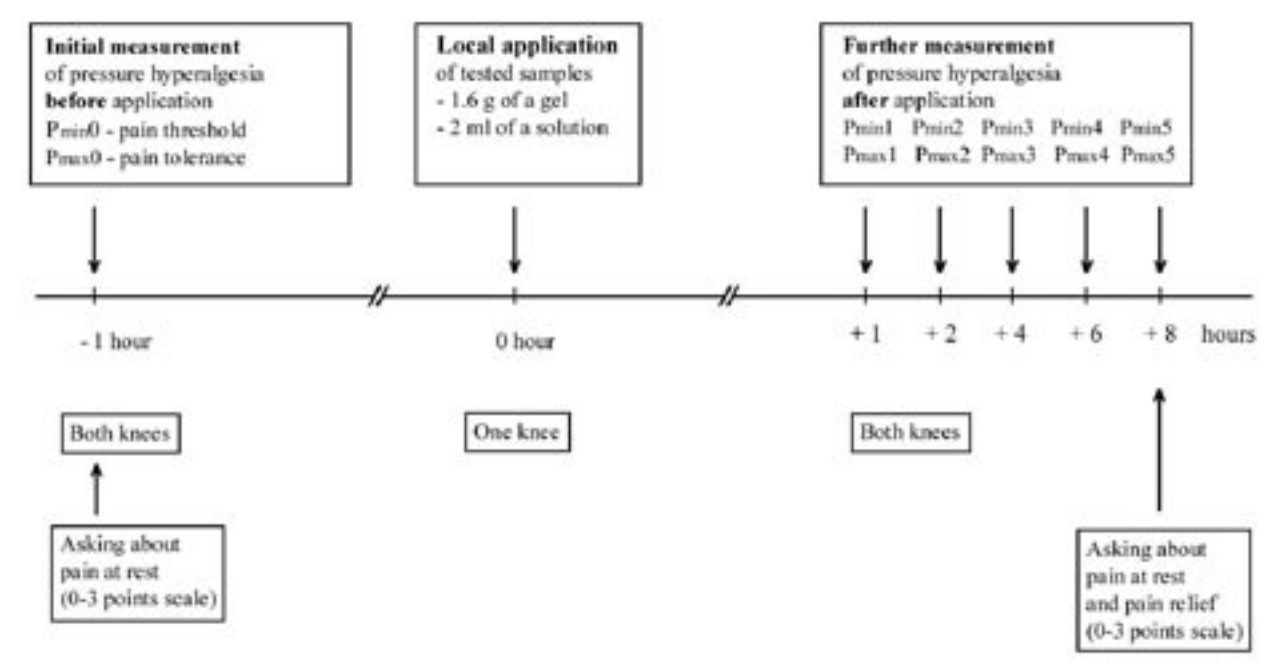
Adjustment, dosing and application of tested preparations

Administration of any analgesics was stopped twenty-four hours before the test, and renewed, if necessary, immediately after the end of the measurement procedure. During one testing procedure, one of five preparations was applied on the surface of one arthrotic knee (300–400 cm^2) – gels in the amount of 1.6 g, solutions in the amount of 2 ml. Each applied amount of tested samples contained 16 mg of indometacin. Using randomized double-blind study scheme each dose of gel was adjusted into a single-use plastic syringe and labelled (name of the respondent, date of application). Bottles with Elmetacin® or placebo solution sample were labelled in the same way as syringes with gels. The dose of solution (2 ml) was reached by 25 pressings of the bottle sprayer. Both solutions and gels were spread uniformly over the whole knee surface. All data obtained from each patient were recorded onto special procedure protocol form. The decoding of the tested preparation was recorded there immediately after the filled form was returned to the co-ordinator of the study. During the study, five single doses of the tested preparations were prepared for administration to each patient. Wash-out period between individual measurement procedures was five days.

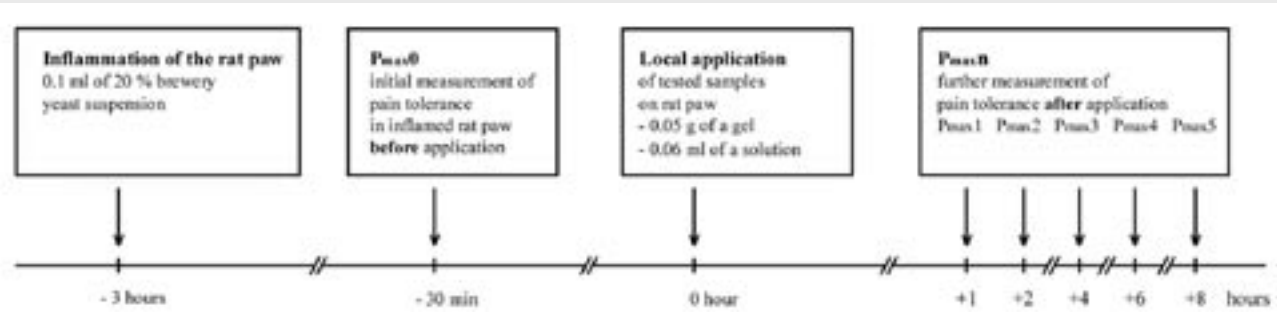
Study procedure (see Scheme 1)

I. At first, respondents were asked about pain at rest in both knees (each knee separately) one hour before local application of the drug or placebo. Subjective level of pain at rest was expressed using the four-point pain intensity-scale (0 – no pain, 1 – mild pain, 2 – moderate pain, 3 – severe pain). This parameter was followed-up also in the eighth hour after local administration of the tested preparation to one knee. In addition, pain relief in this eighth hour compared with pain sensation one hour before testing was evaluated and expressed by the respondent also by the four-point pain relief-scale (0 – no relief, 1 – slight relief, 2 – distinct relief, 3 – full relief).

Schema 1. Single-dose application of tested preparations on one arthrotic knee in patients with bilateral gonarthrosis



Schema 2. Single-dose application of tested preparations on the dorsal surface of inflamed rat raw – Randall-Selitto test



II. The pressure-induced pain of the arthrotic knee – pressure-induced inflammatory hyperalgesia – was measured using an ordinary mercury sphygmomannometer for measurement of blood pressure. The cuff of the mercury sphygmomannometer (width – 15 cm, length of cuff – 100 cm) was wreathed around the knee and the air pressure was slowly increased (10 mm of Hg/sec.). The level of the pressure when first (minimal) pain sensation occurred was marked as pressure pain threshold (P_{min}). The pressure was increased until the maximum tolerable pain sensation appeared. This level was marked as pressure pain tolerance (P_{max}). Both P_{min} and P_{max} were measured one hour before and in given time intervals (1, 2, 4, 6, 8 hours) after local application of tested preparations or placebos (Scheme 1).

Even though the preparations were applied to one knee, P_{min} and P_{max} were followed-up in both knees to study eventual resorptive effects of the indometacin released from the tested drug formulations. Local tolerability of the preparation was also evaluated.

Calculations

Variance in the pressure sensitivity of arthrotic knees in each hour of measurement compared to that in time 0 was expressed as a comparative pressure-pain quotient (Q). These quotients were calculated for both P_{min} and P_{max} for each interval of measurement (Fig. 1). A pressure pain quotient greater than 1 means that there was some degree of pain relief.

These quotients were used for statistical analysis of the analgesic effect of the tested preparations and are presented in tables 1, 2, and 4. Data obtained for gels and solutions were compared to those of the relevant placebo. Results were evaluated by pair t-test using statistical PC software Statgraphics.

B. Experimental study (see Scheme 2)

0.1 ml of 20 % brewery yeast suspension prepared from tablets (Pangamin® tbl, Prague Brewery, CR) was injected subplantarly into a rat's left hind paw. The inflammation with hyperalgesia of the paw developed within 2.5 hours after injection. Thirty minutes before local application of the tested preparations, $P_{max}0$ was measured using Randall-Selitto method[6]. The value of pressure pain tolerance equalled to that of piston pressure causing the animal to struggle. All of the five tested preparations (two placebos and three indometacin-containing preparations) were administered locally in a random order to five animals. Gels were applied onto the dorsal surface of the inflamed paw in the dose of 0.05 ml and solutions in the dose of 0.06 ml respectively (to reach the same dose of indometacin in the applied volume). $P_{max}1$ – $P_{max}5$ were measured in 1, 2, 4, 6, and 8 hours after administration of the tested preparations. After the experiment, the animals were overdosed with pentobarbital.

Calculations

Only the pressure-pain tolerance $P_{max}n$ could be measured in the Randall-Selitto test and $Q_{max}n$ was calculated in the same way as in the clinical study (Fig. 1).

Results

The average values of the pressure pain threshold (P_{min}) in patients with active gonarthrosis before administration of the tested preparations ranged between 47.7–57.3 mmHg and the pressure pain tolerance (P_{max}) in the same knee joint ranged

Table 1. Clinical study: An average values (arithmetic mean ± SD) and statistical significance changes in pressure pain threshold (Qmin) of the applied arthrotic knee (n = 15) after single-dose application

evaluated preparation	Q min in time intervals after application				
	+1 h	+2 h	+4 h	+6 h	+8 h
Gel placebo (C1)	1.09 ± 0.174	1.20 ± 0.287	1.13 ± 0.174	1.08 ± 0.151	1.06 ± 0.155
Indometacin 1 % gel versus C1	1.09 ± 0.052 n. s.	1.15 ± 0.078 n. s.	1.21 ± 0.108 n. s.	1.25 ± 0.121 n. s.	1.29 ± 0.141 p < 0.05
Indobene® gel versus C1	1.15 ± 0.075 n. s.	1.28 ± 0.207 n. s.	1.39 ± 0.235 n. s.	1.40 ± 0.216 p < 0.01	1.42 ± 0.207 p < 0.01
Elmetacin® spray versus C2	1.04 ± 0.061 n. s.	1.18 ± 0.072 p < 0.05	1.32 ± 0.213 p < 0.02	1.35 ± 0.324 n.vs.	1.38 ± 0.351 p < 0.05
Placebo of Elmetacin® spray (C2)	1.03 ± 0.065	1.06 ± 0.094	1.03 ± 0.092	1.10 ± 0.140	1.05 ± 0.119

n. s. non-significant value

Table 2. Clinical study: An average values (arithmetic mean ± SD) and statistical significance changes in pressure pain tolerance, Qmax, of the applied arthrotic knee (n = 15) after single-dose application

Evaluated preparation	Q max in time intervals after application				
	+1 h	+2 h	+4 h	+6 h	+8 h
Gel placebo (C1)	1.03 ± 0.060	1.09 ±v0.121	1.09 ± 0.111	1.02 ± 0.063	1.03 ± 0.072
Indometacin 1 % gel versus C1	1.06 ± 0.028 n. s.	1.12 ± 0.066 n. s.	1.15 ± 0.092 n. s.	1.15 ±v0.089 p < 0.05	1.17 ± 0.083 p < 0.01
Indobene® gel versus C1	1.11 ± 0.060 n. s.	1.20 ± 0.121 n. s.	1.25 ± 0.136 n. s.	1.28 ± 0.157 p < 0.01	1.27 ± 0.146 p < 0.01
Elmetacin® spray versus C2	1.04 ± 0.030 n. s.	1.08 ± 0.037 n. s.	1.13 ± 0.048 n. s.	1.10 ± 0.062 n. s.	1.10 ± 0.059 n. s.
placebo of Elmetacin® spray (C2)	1.06 ± 0.062	1.10 ± 0.076	1.06 ± 0.055	1.07 ± 0.082	1.08 ± 0.062

n. s. – non-significant value

between 107.7–110.7 mmHg. The average values of P_{min} and P_{max} in measured contralateral knee joints of the same patients range between 60.7–71.0 mmHg and 116–127 mmHg under the same conditions. These values of pressure-induced hyperalgesia of knee joints serve as initial values (denominator in the formula) for calculation of the pressure-pain quotients (Fig. 1). The average values of pressure pain tolerance measured three hours after induction of the rat paw inflammation range between 100–160 mmHg, normal values of non-inflamed paw are higher than 350 mmHg. Also these values of pressure pain tolerance were used for the calculation of pressure-pain quotients after administration of the tested preparations (Tab. 4).

A) Topical administration of tested preparations on arthrotic knee and inflamed rat paw

1. Indobene® gel significantly decreased the inflammatory hyperalgesia of the applied arthrotic knee joint of patients with bilateral gonarthrosis in both P_{min} and P_{max} at 6 and 8 hours after administration as compared to the corresponding placebo (Tab. 1 and Tab. 2). Indobene® gel also significantly decreased the intensity of pain at rest and produced significant pain relief 8 hours after its local administration on arthrotic knee joint (Tab. 3). Hyperalgesia of the inflamed rat paw in Randall-Selitto test was significantly decreased by this preparation in intervals 1, 2, 6 and 8 hours after its topical application (Tab. 4). Indobene® gel was the only preparation tested that demonstrated a significant analgesic effect in all five analgesic tests (Tab. 5).
2. Indometacin 1% gel influenced only the inflammatory hyperalgesia of the applied knee joint: pressure pain threshold was increased in 8 hour and pressure pain tolerance in 6 and 8 hour after application (Tab. 1 and Tab. 2). Neither pain at rest nor the intensity of pain relief was changed significantly by this preparation. Results of the animal experiment showed no statistically significant analgesic effect of the preparation (Tab. 4). Indometacin 1 % gel was significantly effective in two of five evaluated parameters (see Tab. 5).
3. Elmetacin® spray increased only pressure pain threshold of the applied arthrotic knee joint (Q_{min}) in 2, 4, and 8 hour after application (Tab. 1). Pressure pain tolerance (Q_{max}), was not increased significantly (Tab. 2). The pain relief was increased significantly by this preparation as compared to the corresponding placebo (Tab. 3). No significant analgesic effectiveness of Elmetacin spray was demonstrated in the animal study (Tab. 4). The analgesic efficacy of Elmetacin® spray was demonstrated in two of five evaluated parameters.

Table 3. Clinical study – arbitrary pain-scale (0–3 points): An average values pain at rest and pain relief eight hour after topical administration on the gonarthrotic knee joint (n=15)

Evaluated preparation	Subjective criteria (0-3 points arbitrary pain-scale)		
	pain at rest		pain relief
	0 h	8 h	8 h
Indobene® gel	1.47 ± 0.36	1.00 ± 0.30 •	1.13 ± 0.29 •
Indometacin 1 % gel	1.20 ± 0.30	1.00 ± 0.00	0.73 ± 0.25
Elmetacin® spray	1.33 ± 0.27	1.20 ± 0.23	0.93 ± 0.25 •
Gel placebo	1.27 ± 0.25	1.20 ± 0.23	0.67 ± 0.34
Elmetacin® spray placebo	1.20 ± 0.23	1.07 ± 0.25	0.40 ± 0.28

• statistically significant difference ($p < 0,05$)

Table 4. Randall-Selitto test in rats: An average values (arithmetic mean ± SD) and statistical significance changes in pressure pain tolerance of the inflamed rat paw after single-dose application (five in a treated group)

Evaluated preparation	Q max in time intervals after application				
	+ 1 h	+ 2 h	+ 4 h	+ 6 h	+ 8 h
Gel placebo (C1)	0.78 ± 0.19	1.10 ± 0.13	1.03 ± 0.25	1.10 ± 0.38	1.21 ± 0.18
Indometacin 1 % gel versus C1	1.03 ± 0.29 n. s.	1.15 ± 0.48 n. s.	1.32 ± 0.27 n. s.	1.40 ± 0.41 n. s.	1.39 ± 0.37 n. s.
Indobene® gel versus C1	1.05 ± 0.16 **p < 0.02**	1.38 ± 0.25 **p < 0.05**	1.35 ± 0.44 n. s.	1.49 ± 0.21 **p < 0.05**	1.66 ± 0.36 **p < 0.05**
Elmetacin® spray versus C2	1.21 ± 0.48 n. s.	1.30 ± 0.52 n. s.	1.42 ± 0.37 n.vs.	1.20 ± 0.23 n. s.	1.30 ± 0.13 n. s.
placebo of Elmetacin® spray (C2)	1.04 ± 0.25	1.35 ± 0.36	1.34 ± 0.52	1.32 ± 0.49	1.57 ± 0.27

n. s. non-significant value

Table 5. Study outcomes: An overview of topical NSAIDs analgesic activities: subjective and objective criteria, clinical and experimental study

Evaluated preparation	Respondents with gonarthrosis				Rat yeast inflammation
	Pressure hyperalgesia		pain at rest ↓ in 8th hour	pain relief in 8th hour	test Randall-Selitto Pmax
	Pmin	Pmax			
Indobene® gel	+	+	+	+	+
Indometacin 1 % gel	+	+	–	–	–
Gel placebo	–	–	–	–	–
Elmetacin® spray	+	–	–	+	–
placebo of Elmetacin® spray	–	–	–	–	–

+ statistically significant analgesic effect; – without analgesic effect

Table 6. Possible resorptive effect of indometacin from tested preparations

Evaluated preparation	Respondents with gonarthrosis: contralateral non-applied knee joint			
	Pressure hyperalgesia		pain at rest ↓ in 8th hour	pain relief in 8th hour
	Pmin	Pmax		
Indobene® gel	–	–	–	–
Indometacin 1 % gel	+	–	–	–
Gel placebo ®	–	–	–	–
Elmetacin® spray	–	–	–	–
placebo of Elmetacin® spray	–	–	–	–

+ statistically significant analgesic effect; – without analgesic effect

B) Resorptive effect of indometacin

The results of measurement of pressure hyperalgesia of the contralateral knee joints without application of the tested preparations as well as follow-up of subjective criteria showed no significant resorptive analgesic efficacy of Indobene® gel and Elmetacin® spray. Only Indometacin 1 % gel increased significantly the pressure pain threshold of the contralateral knee joint 8 hours after local administration (Tab. 6). The possible resorptive effect of the tested preparations after application on contralateral rat paw was unfortunately not tested.

C) No signs of ***local dermal irritation*** *of any of the tested preparation were registered.*

Discussion

Local drug formulations of NSAIDs belong among the most frequently administered OTC drugs. Differences among them – in respect to their analgesic efficacy – are usually not tested. The introduction of a new preparation of this group to the market does not require any comparison of its analgesic efficacy to the corresponding standard and the adequate tests are not regularly performed. Published clinical studies are almost exclusively aimed at the evidence of the analgesic activity of the preparation in comparison with placebo[7, 8, 9]. The comparison of the analgesic efficacy of several NSAIDs-containing preparations is very rare as well as experimental studies dealing with this problem[10].

In our two previous pilot clinical studies the same method of measurement of knee hyperalgesia in patients with active gonarthrosis as in the present study was used[2, 5]. In those studies we have demonstrated that substantial significant differences in analgesic efficacy between three diclofenac-containing gel preparations and between three indometacin-containing preparations exist. Voltaren emulgel® was significantly superior in the analgesic efficacy of three diclofenac-containing preparations (Veral® gel showed medium analgesic effect and Olfen® gel showed no analgesic effect). In a group of indometacin-containing gels, Indobene® gel was also significantly superior.

The main objective of the present study was to compare the analgesic efficacy of two drug formulations containing indometacin – two in the form of gel and one in the form of solution. Results of the present study indicate distinctly that indometacin if applied locally to the arthrotic knee joint as well as to the dorsal surface of inflamed rat paw in the form of isopropylalcohol solution (Elmetacin®) is substantially less active with respect to its analgesic effectiveness as compared with the same dose of indometacin administered in the form of commercial gel form (Indobene® gel). In our opinion, isopropylalcohol in Elmetacin® is evaporated after its application on the warm surface of the skin and thus it cannot contribute to the transdermal penetration of the active substance (i. e. indometacin) into the subcutaneous tissue. On the contrary, commercial gel base is not evaporated and contains certain penetration enhancers, which substantially participate in the transdermal penetration of the active substance from this drug formulation[13]. This is probably also the reason why Indometacin 1 % gel manufactured in the hospital pharmacy, which contains simple non-commercial gel base, exerts lower analgesic effect compared with the commercial Indobene® gel. The resorptive effect of indometacin from the locally-applied drug formulations has been followed in this communication indirectly according to the influencing of the hyperalgesia of the contralateral knee joint. It must be evaluated very carefully with respect to the fact, that the total dose of locally applied indometacin is relatively very low (i. e. 16 mg) in comparison with the its usual therapeutic dose (25–50 mg p. o.). Nevertheless some degree of resorptive effect of indometacin administered locally in the simple gel base (Indometacin 1 % gel) has been demonstrated. It seems that there doesn't necessary have to be a direct relation between deep tissue penetration and its resorptive effect.

Conclusions

Our results demonstrate that in locally applied NSAIDs drug formulations not only the active drug and its concentration but also the drug formulation itself – which might contain some effective permeability enhancers – might contribute substantially to the final therapeutic effect of such locally administered therapeutics. This is the reason why – in our opinion – any newly registered NSAIDs preparations for topical use should be tested from the point of view of their analgesic activity in comparison with a proper original standard preparation. Such testing might be regarded as an indirect evidence of bioavailability of the active drug from its formulation as compared with a standard because the direct bioavailability of locally applied NSAIDs to the target tissues is not possible. The procedures we have described in this communication might be useful for this purpose.

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