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THE BENEFITS OF THE COMBINED TOPICAL ADMINISTRATION OF KETOPROFEN AND GLUCOSAMINE HYDROCHLORIDE TO BACK PAIN TREATMENT

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Abstract: The article presents research data on analgesic activity of different samples of combinations with glucosamine and ketoprofen in topical dosage forms. The study showed significant analgesic activity (55.1%) of glucosamine hydrochloride 5.0% / ketoprofen 2.0% cream-gel combination with the indices significantly higher than in ketoprofen 2.5% cream-gel and glucosamine hydrochloride 2.5% / ketoprofen 2.0 % cream-gel. The findings showed that glucosamine hydrochloride 5.0% / ketoprofen 2.0% cream-gel combination offers challenge for further study and implementation into wide clinical practice, including for the treatment of spinal osteoarthritis and back pain.

KeyWords: glucosamine hydrochloride, ketoprofen, back pain, spinal osteoarthritis, cream-gel, analgesic activity.

INTRODUCTION

Spinal disorders include trauma, mechanical injury, spinal cord injury, inflammation, infection, and tumors. Low back pain, the most common spinal disorder, affects over 80.0% of patients at some point in their life, and from 4.0-33.0% of the population at any one time. Back pain is the most common cause of disability among young adults. Many factors, physical, psychological and occupational, contribute to the development of back pain. Spinal osteoarthritis is one of the common causes of back pain. Spinal osteoarthritis is the mechanical breakdown of the cartilage between the aligning facet joints in the back portion (posterior) of the spine that quite often leads to mechanically induced pain [8].

Osteophytes (small bony growths also known as bone spurs) form on facet joints and around vertebrae recompensing the lost stability of the joint. Gradually, the spine stiffens and loses flexibility. Osteophytes sometimes become large enough to cause narrowing of the spinal canal or foramen, irritating or entrapping nerves passing through them (spinal stenosis and foraminal stenosis).

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Stenosis, while related to osteoarthritis, is a separate medical condition. Osteoarthritis can also be confused with degenerative disk disease, a gradual deterioration of disks between the vertebrae, but is considered to be a separate medical condition [1].

Therefore, effective treatment of back pain requires not only administration of analgesic drugs (analgesics and NSAIDs), but also drugs with chondroprotective effect. The most efficient method involves administration of combinations of the above drugs, including topical dosage forms.

2 PURPOSES, SUBJECTS AND METHODS:

2.1 Purpose

The aim of our study was to investigate the analgesic properties for the perspective of combined use of NSAIDs and chondroprotector glucosamine (GA) hydrochloride, at different doses in the dosage form of a cream-gel.

2.2 Subjects & Methods

The study of analgesic properties of different topical combinations with GA hydrochloride and ketoprofen was conducted under the conditions of induced pain reaction [3, 5]. The study involved a model of inflammatory hyperalgesia in rats [5], in which the intensity of pain was

measured by Randall-Selitto method [6]. Assessment comprised Analgesy-meter Ugo Basile 37215 (Ugo Basile, Italy) [2, 4], which gives a possibility to provide a very accurate determination of threshold pain sensitivity (THPS) by changing the mechanical pressure on the limb of the animal. The trial was conducted on 70 white nonlinear rats of both sexes, with the body mass of 150-180 g. We also evaluated topical drugs of ketoprofen in 2.5% and 2.0% concentrations and combinations of ketoprofen in 2.5% concentration and glucosamine hydrochloride in 2.5%, 5.0% and 10.0% concentration. At the beginning of the trial the rats were subjected to the procedure of determining initial indicators THPS using Analgesy-meter Ugo Basile 37215 by stimulating pain reaction on the right rear paw [2, 4]. Then, at least in 30 minutes, inflammatory hyperalgesia on the right rear paw of animals was reproduced by subplantar injection of 0.1 ml of 1.0% λ-carrageenan solution («Sigma», USA) into the paw [3, 5]. In 2 hours after injection we conducted a single application of the gels under investigation (except for the control pathology group) on the right rear paw through the skin in equivalent therapeutic doses of 50 mg (or 25 mg /cm2).

The study drugs were applied onto the area of the paw below the ankle joint of approximately 2×2 cm, with careful rubbing excluding the possibility of topical medical forms leaking from the skin of animals. THPS was determined in 3 hours after carrageenan administration for all the animals [6]. Further analgesic properties were evaluated according to analgesic activity (AA) and the ability of investigated drugs to reduce the degree of hyperalgesia in the animals [3, 5]. Thus, AA was calculated in terms of increasing the THPS in animals compared to the control pathology group and expressed as a percentage by Formula 1:

$$AA = \frac{\Delta THPSc - \Delta THPSr}{\Delta THPSc} \times 100\%$$

AA – analgesic activity%
ΔTHPSr – the percentage difference in the levels of pain sensitivity in a group of experimental animals before and after inflammatory hyperalgesia and application of the drug under investigation;
ΔTHPSc – the percentage difference in the levels of pain sensitivity in the control pathology group before and after inflammatory hyperalgesia.

Conflict of interests
There is no conflict of interests.

3 RESULTS AND DISCUSSION

The findings of the trial are presented in Table 1 and show a significant induction of pain in animals following the development of inflammatory hyperalgesia, as evidenced by the probable THPS decline in control pathology group by 2.9 times (Table 1).

Table 1.

The study of the analgesic activity of different combinations of glucosamine hydrochloride and ketoprofen in topical dosage forms (n = 60)

Conditions of the trial	THPS, conv. units.		Δ THPS, %	AA, %
	Initial indices	One hour after application of the drug		
Control pathology group	217.1 ±12.3	73.8 ±5.5	66.1 ±1.2	–
Control pathology group + ketoprofen 2.5 % cream-gel	233.0 ±16.8	149.4 ±10.7	35.8 ±2.2[1]	45.8 ±2.7
Control pathology group + ketoprofen 2.0% cream-gel	230.0 ±17.3	142.0 ±9.7	38.2 ±2.2[1]	42.2 ±3.3
Control pathology group +GA hydrochloride 2.5 % / ketoprofen 2.0 % cream-gel	234.0 ±16.7	150.3 ±12.2	35.6 ±2.0[1]	46.1 ±3.1
Control pathology group + GA hydrochloride 5.0 % / ketoprofen 2.0% cream-gel	235.0 ±23.2	166.0 ±18.5	29.6 ±2.0[1,2,3,4]	55.1 ±2.9 [2,3,4]
Control pathology group + GA hydrochloride 10.0 % / ketoprofen 2.0 % cream-gel	239.0 ±22.0	173.0 ±19.3	28.6 ±2.2[1,2,3,4]	56.8 ±3.3 [2,3,4]

Notes:
1. – p <0.05 relative to the control pathology group;
2. – p <0.05 relative to animals treated with 2.5% ketoprofen cream-gel;
3. – p <0.05 relative to animals treated with 2.0% ketoprofen cream-gel;
4. – p <0.05 relative to animals treated with GA hydrochloride 2.5% / 2.0% ketoprofen cream-gel;
5. n – total number of animals in the study.

Administration of ketoprofen 2.5% cream-gel showed a decrease in THPS by 1.6 times as compared to the initial indices and the percentage was significantly lower than in the control pathology group. Analgesic activity of this drug amounted to 45.8 ± 2.7%. NSAID-treated group was found to have a range of side effects, becoming more severe with an increase in dosage. To obtain the optimal dose NSAIDs were used in combination with ketoprofen cream-gel 2.0%. Its THPS indicator was 1.6 times lower than in the initial findings, the percentage was not significantly different from the previous drug, but higher than the THPS indicator in the control pathology group. Its AA was 42.2 ± 3.3%, which was not significantly different from the AA of ketoprofen 2.5% gel. According to the scientific literature, R. J. Tallarida provided evidence that combined use of NSAIDs and chondroprotectors caused analgesic synergism of NSAIDs properties and allowed to reduce the dosage of NSAIDs without disrupting the pharmacological effectiveness [7]. Our study design involved pharmaceutical combinations in cream-gel form which contained ketoprofen in 2.0% concentrations, GA hydrochloride in 2.5%, 5.0% and 10.0% concentrations. Another objective was to assess the effectiveness of GA hydrochloride 2.5% / ketoprofen 2.0% cream-gel combination. Its THPS decreased by 1.6 times, and AA was 46.1 ± 3.1%, which was on the level of 2.5% ketoprofen cream-gel. We also investigated the potential of GA hydrochloride 5.0% / ketoprofen 2.0% cream-gel combination. Its THPS, which decreased only by 1.4 times according to the initial indices and the AA was 55.1 ± 2.9%. The data exceeded all previous values and demonstrated the positive impact of glucosamine on the analgesic properties of NSAIDs.

Furthermore, we determined the effectiveness of GA hydrochloride 10.0% / ketoprofen 2.0% cream-gel combination. Its THPS decreased by 1.3 times as compared to the initial indices and the AA was 56.8 ± 3.3%. The results of latter combination in the percentage ratio by AA and THPS indices did not significantly differ from the abovementioned combination, although GA hydrochloride concentration was 2 times higher.

Taking the above into account, it is advisable to choose GA hydrochloride 5.0% / ketoprofen 2.0% cream-gel combination for further research, as it showed a higher AA indicator, which was 55.1%, that was significantly higher than the indices of the two other objects. Though the research indices of GA hydrochloride 5.0% / ketoprofen 2.0% cream-gel combination were lower than the latter object of the study, this difference was not significant and was only 1.0% for THPS and 1.7% for AA.

4 CONCLUSIONS

1. Spinal osteoarthritis is one of the common causes of back pain. Efficient treatment of spinal osteoarthritis requires the usage of combination of NSAIDs and chondroprotectors in different dosage forms.

2. The study showed that GA hydrochloride 5.0% / ketoprofen 2.0% cream-gel combination had a distinct analgesic activity (55.1%) as compared to ketoprofen 2.5% cream-gel (45.8%) and GA hydrochloride 2.5% / ketoprofen 2.0% cream-gel (46.1%). GA hydrochloride 5.0% / ketoprofen 2.0% cream-gel combination is perspective offers the challenge for further study and wide

implementation into clinical practice, including for the treatment of spinal osteoarthritis and back pain.

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