REVIEWING OF MELOXICAM CONCENTRATION APPLIED PERORALY AND BY ELECTROPHORESIS ON INJURIED KNEE ANKLE OF PARACHUTISTS

(Original scientific paper)

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Abstract
The research goal was to qualify concentration of meloxicam (M), applied oral and by electrophoresis (EF) in meniscus and synovial liquid of the damaged knee ankle, because of sport injuries within the parachutists. Research sample included 8 sport male parachutists, age 28-48, divided into 2 groups with 4 examinees each. For the first group 0.015 g M, was per oral (1 tablet per day) applied during 5 days, and the second group of 4 parachutists for same drug dosage equally by electrophoresis (EF). Meniscus and synovial liquid samples were taken afterwards by menisectomy. By methods of liquid-mass spectrometry (HPCL) the drug concentration was quantified in micrograms of medicament per g of tissue, applied within the both ways. The research results were tested by Student t-test for small pairs of samples, and high significant concentration of drug was noted p<0.001, applied in one term EF in meniscus and synovial liquid in comparison to five day per oral drug application. By Eliminating, the local applied systems effects, and maximal concentration of drug, by longer maintaining in the targeted tissue, EF can be recommended as a method of choice in clinical praxis for sport injuries. Electrophoresis application of Meloxicam in targeting the knee joint provides significant saturation and better effectiveness of the drug compared to the per oral application.

Keywords: sport injuries, synovial liquid, liquid-mass spectrometry, t-test for dependent small samples

INTRODUCTION
Knee ankle as significant hypomochlion of biodynamic lower extremity lever is exposed in parachutes by strong forces of dynamic strike and micro-trauma, which are caused by inappropriate grounding, caused by it’s chronically inflammation of the damaged meniscus structures, and therefore anatomic remodeling and lowered functionality. According to that, a profound way for lowering this symptoms and significance is of great importance in biomedical, anthropological and martial sports aspect (Leopold et al. 2003.).

Iontophoresis and electrophoresis (EF) represents painless and efficient way for application of the drug locally in tissue by using the galvanic electricity, by which we avoid the systemic and side effects of the drug. In this way, we accomplish a higher concentration of the drug in the target tissue, which is also more reactive because of the ionic state, so it stays longer time within the tissue, in comparison with the per oral and parenteral way of application (Kalia Naik, Garrison, & Guy, 2004.).

By influence of a potential-voltage, a directed movement of ions and dipol molecules is applied, among which there are therapeutic ones, according to counter electrified electrode, by which drug is attached toward the tissue, accomplishing faster and longer therapeutic effect. Effects of electrophoretically applied drug is maintained in duration of up to four days. Because of that, this kind of applying drug is especially convenient in the reumatology, sport injuries, traumatology, neurology, dermatovenerology, gynecology, as well as within a wide span of the clinical practise. As a pre-requ-
isition for a drug to be applied by iontophoresis is that the drug should be hydrosoluble, with lower molecular mass, and to be easily dissuasive in ions (Kostić, 2000.).

Meloxicam belongs to a group of selective inhibitors of cycloxygenase-2 (COX-2), which has specific pharmacokinetic effect on reparation of the damaged cartilage, improving its remodeling and preventing the process of chondral destruction. Therefore, this modern and powerful drug is used mostly per oral, and parenteral in later days for treatment of sport injuries, but also for curing pathological conditions of cartilage in rheumatology, traumatology and sports medicine. (Jezdimirović, 2002.; Demirtas & Oner, 1998.). This drug meets noted prerequisites for an iontophoretic application.

METHODS

The research has been realized on 8 patients, sport male parachutists, with age varying from 28 to 48, who have accomplished over 200 parachute jumps and who had knee meniscus damaged diagnosed by clinical methods, by ultrasonography and by 64.-slice scanner, and afterwards histopathological according to orthopedic intervention by an arthroscopy. The examinees were divided into two groups. First group contained 4 examinees, and per oral applied meloxicam in one stage by daily dosage of 0,015g, during 5 days successively, while for the secondary group of containing 4 examinees, also with damaged and inflamed meniscus cartilage, one-stage by electrophoresis, electricity of strength X=7mA and application duration of 20 min., applied meloxicam from and anode 0,015g in 5 ml of water solution. All examinees were of mesomorph constitution by Scheldon, with a BMI lower than 24 and they had inflammation symptoms, functionless with expressed algesic sensation, limited mobility and per completed conservative and physiotherapeutic treatment without satisfactory results.

Transversal flexible gummed carbon electrodes were fixed on prepared skin of inflamed joint, coated with four layers of saturated gaze by using physiological solution of NaCl. A 0,015 ml solution of meloxicam was applied to the anode, within surface of 150 cm² dissolved in re-distilled water. The cathode surface was 100 cm². Biological dose of galvanic electricity was 140 mAmin (7mA x 20 min). (Djurdjević, 2001.).

After finished EF, punction of synovial liquid was performed; therefore a biopsy sample of the hyaline meniscus cartilage, per orthopedic intervention of arthroscopic meniscectomy has been performed. The tissue samples of the meniscus cartilage are first converted into a gel by using hydrolysis and after that into a solid state. Afterwards, by using methods of High-performance liquid chromatography (HPLC), concentration of drug in synovial liquid of knee rapture has been determined, also on cartilage of the meniscus, in articulator tissues, which is expressed in µg/g tissue measurement. (Batheja, Thakur, & Michaniak, 2006.).

For the HPLC analysis method, it was used the HPLC WATERS 2695 Alliance system, connected to ZQ mass detector WATERS-Single quadropole. The

<table>
<thead>
<tr>
<th>Variable</th>
<th>X±SD</th>
<th>t-test</th>
<th>p</th>
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<tbody>
<tr>
<td>Per os</td>
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<tr>
<td>Concentration of meloxicam-a in synovial fluid (µg/g)</td>
<td>4.95±0.32</td>
<td>51.12±0.32</td>
<td>12.45</td>
</tr>
<tr>
<td>Amplitude of knee flexion in° 10. days after arthroscopy</td>
<td>114, 12°±0.24</td>
<td>124,50°±0.58</td>
<td>3.45</td>
</tr>
</tbody>
</table>

Diagram 1. Compared concentration of meloxicam in synovial liquid and cartilage application
process of inflammation was reviewed pathohystologically (colouring sample by hematoxilin-eozinom).

RESULTS
Within the statistical processing of data, it was used the Student t-test for small uneven samples (DOS statistic package), as well as the regression analysis with a correlation analysis. A statistic significance of concentration of medicament existed only if p<0,001, and anthropometric parameters: volume of the knee and movement amplitude (in degree) in case of p<0,005.

Concentration of meloxicam in synovial liquid and patient cartilage, who applied drug per oral on several day basis in order to saturate within the target tissues, was compared with the concentration of meloxicam applied in one term, by using iontophoresis in knee joint. Arthroscopic menisectomy tissues samples were taken in order to quantify containing of the medicament inside the synovial liquid (samle within 2ml) and cartilage of meniscus (per 10g of biopsic debridman) and determined by HPLC method, afterwards compared the concentration of applied drug within the both ways (Djurđević, Milenković, & Đurović, 2006.). After that there was measuring of the drug concentration significance difference. In Table 1., the concentration of medicament was compared in the synovial liquid and the damaged meniscus knee cartilage of patients on whom drug is applied by EF.

DISCUSSION
Meloxicam applicated by iontophoresis penetrates the skin very quickly, toward the sub tissue and the synovial liquid of the damaged knee joints, compared to system-per oral applied drug.

Found differences in concentration of meloxicam in synovial liquid and cartilage of inflamed joints can be explained by terms of cartilaginous structure of peri-epiphyseal cartilage being deeper positioned from cuts and synovial liquid, higher specific density, it is of a higher consistency of the surface level of cartilage according to the densely interlaced collagen, mineralized matrix which contains mucopolysaccharides and appearance of chondrocytes. Therefore penetration of meloxicam in cartilage is significantly lower than in the skin, sub skin tissue and synovial liquid of inflamed joint (Leopold et al. 2003.).

According to the fact that hyaline perry physis acid of joint is minimally fed over low developed periosteal vasculature, and by higher mean of osmotic perfusion from the synovial liquid conditioned by a gradient of concentration, over which is used the metabolic conversion, and therefore the concentration of meloxicam in cartilage grows over the time per disclosing of electrophoresis drug application because of it’s high concentration in synovial liquid (Kalia et al.2004.).

After the EF application of meloxicam, the drug concentration is significantly higher in the joint structures, if the therapeutic dose are applied systemically (per oral or parenteral), according to which the drug is contained for longer and connects to the targeted tissue better, because of higher ionic-reactive structure. Taking this into consideration, the side effects are avoided along with the systemic effect, and a better saving of the total quantity of the active substance, which is significant in medical and economic term, as in sports as well as in clinical medicine (Kanikkannan, 2004; Osborne & Allison, 2006.).

CONCLUSIONS
Concentration of meloxicam applied by electrophoresis in synovial liquid meniscepathic knee of injured parachutists is of higher statistical significance and in higher degree than the concentration of meloxicam in synovial liquid of inflamed joint applied per oral. Concentration of mediament will grow in cartilage in time, due to nivelation of drug concentration gradient, because the cartilage feeds mostly from the synovial liquid.

Amplitude of knee movement, as well as flexy, as a valid anthropometric and biomechanic pararemeter, was of statistically higher significant in group of examinees with the electrophoretic application of medicament during the 10 days per endoscopic intervention compared to those with per oral application.

This method of electrophoretic application of the medicament can be recommended as a method of choice for sportsman cartilage injuries and inflamed cartilage in clinical praxis, due to which the degree of deformity would be significantly lowered, and a higher degree of functional prevention in kinesiological biomecine and clinical term, will be accomplished.

REFERENCES
СОГЛЕДУВАЊЕ НА КОНЦЕНТРАЦИЈАТА НА МЕЛАСИКАМОТ КОЈ СЕ ВНЕСУВА ПЕРОЛАЛНО И СО ЕЛЕКТРОФОРЕЗА ВО ПОВРЕДЕН КОЛЕНСКИ ЗГЛОБ КАЈ ПОДОБРАНЦИТЕ

(Оригинален научен јаву)

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Апстракт

Целта на трудот беше да се квантификува концентрација на мелоксикамот (М), внесен перорално и со електрофореза (EF), во менискозитот и синовијалната течност на општен зглоб на коленото, поради спортичките повреди кај подобранците. Примерокот на испитници беше составен со 8 спортски подобранци од машки пол, во возраст од 28 до 48 години. Примерокот беше поделен во две групи од по 4 испитници. Во првата група аплициран е 0,015 гр. М, перорално (1 таблета дневно) 5 денови, а во втората група, исто така од 4 испитници, истата количина на лекот е внесена еднократно со електрофореза (EF). Потоа, при менисцотомија е земен со биопсиса примерок од менискозитот и синовијалната течност. Со методата на течномасената спектротомија (HPCL) е квантификувана концентрацијата на лекот во микрограми на медикаментот по грам на ткивото, кој беше внесен на два начини. Резултатите од истражувањето се тестирали со студентовиот t-тест за мали зависни примероци, при што е забележана статистичка значајна концентрација на лекот на нивото P<0,01 кој беше внесен еднократно со EF во менискозитот и синовијалната течност во споредба со петдневото перорално внесување на лекот. Елиминирајќи ги системските и несаканите ефекти на локалната апликација, со придружната концентрација на лекот, подолгото заджување во таргетот на ткивото, EF може да се предложи како избрана метода во киничката практика на спортичките повреди. Електрофоретската апликација на Мелоксикамот во повреденот зглоб на коленото, обезбедува посигнфикантна сатурација и поголема делотворност на лекот во споредба со пероралното внесување.

КЛУЧНИ ЗБРОВИ: спортички повреди, синовијална течност, высоко перформанси јачна хроматохромографија, t-тест за мали зависни примероци

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