

Inflammation, Infiltration, Necrosis, Abscess and Nicolau Syndrome After Injection of Nonsteroidal Anti-inflammatory Drugs: What is the Reason?

Abstract:

It has been established that some nonsteroidal anti-inflammatory drugs (NSAIDs) ~~in the dosage form of when administered through "injectable preparations"~~ ~~Solution for injection~~ have ~~have~~ a locally irritating effect, ~~despite the fact that even though~~ the ~~drugs preparations~~ are considered high-quality. It ~~seems is shown~~ that ~~the this mechanism of~~ local irritant action is not related to ~~the any~~ specific pharmacological action ~~but with the of the basis ingredients included in the preparations of this group~~. It turned out that the chemical and physico-chemical properties of the ~~dosage form "Solution for injection", preparation that~~ ~~which~~ grossly violate the "ecology" homeostasis of the tissues, ~~have a local irritating effect~~. It ~~has been shown seems~~ that the local complications at injection sites can be caused by the ~~nonspecific local irritating effect of the following nonspecific properties of nonsteroidal anti-inflammatory drugs in the "Solution for injection the injectable preparations"~~: denaturing (cauterizing), hypertonic and acidic activity. Each such property ~~ys~~, or their combination, has a locally irritating effect, which can cause ~~abscess, necrosis, and~~ acute aseptic inflammation of ~~a reversible or and irreversible nature, necrosis and abscess, that follows that occurs~~ immediately after subcutaneous ~~or~~ intramuscular ~~administration, a condition named and other injections and is known as~~ "Nicolau Syndrome". Conversely, ~~injectable preparations of nonsteroidal anti-inflammatory drugs in the dosage form "Solution for injection", NSAIDs~~ having isotonic or hypotonic ~~activity osmolarity associated with a~~ neutral or weakly alkaline pH ~~ity~~ (about pH 7.4), ~~have produce a~~ minimal, short-term ~~reversible local~~ inflammatory effect ~~of a reversible nature and~~ do not cause Nicolau Syndrome after ~~administration injection~~.

Keywords: NSAIDs, injection, local complications, abscess, Nicolau syndrome, nonsteroidal anti-inflammatory drugs.

Nonsteroidal anti-inflammatory drugs (NSAIDs) firmly hold ~~the~~ leadership in medicine in terms of the frequency of prescriptions both in solid dosage forms and in solutions for injections [1]. The mechanism of action of drugs of this group has long attracted researchers and many aspects of the action of tablets and solutions of these medicines have been thoroughly studied [2,3]. However, the mechanism of development of post-injection complications occurring at injection sites of NSAIDs has not yet been fully studied [4]. Among such complications, local aseptic inflammations, ~~infiltrate, s and~~ soreness, ~~and including~~ neuralgia, are ~~more the most~~ common. Local aseptic necrosis and abscesses are less common. At the same time, the most severe local complication of injections of NSAIDs is acute aseptic post-injection necrosis of the muscles, subcutaneous fat, skin, and other tissues, which has been known for about 100 years under the name "Nicolau syndrome" [5]. It is known that a complication after injection, called "Nicolau syndrome", is manifested by immediate severe pain at the injection site, followed by erythema and a hemorrhagic spot on the skin at the injection site, after a few hours necrosis develops in this place, then an abscess and after a few days, a scar appears on the skin.

Nicolau syndrome was first described in the early 1920s by Freudenthal and Nicolai as a local complication that occurs after intramuscular injections of bismuth salts in the treatment of syphilis [6]. Since then, several reports have appeared in the literature about this disease occurring after intramuscular, intra-articular, intravenous, and subcutaneous injections associated with various drugs, such as NSAIDs, (for example, diclofenac sodium), vitamin K, antibiotics, (such as penicillin), antihistamines, corticosteroids, (for example triamcinolone acetonide), local anesthetics, vaccines, antiepileptics, ~~polydocanol polidocanol~~, and pegylated ~~alpha~~-interferon ~~alpha~~. The pathogenesis of Nicolau syndrome is unknown [7-10].

However, since 2002, reports have begun to appear that the cause of such post-injection complications may not be the drug, which is the main ingredient, but the ~~special~~ chemical and physico-chemical properties of the ~~excipients of the dosage form "Solution for Injection"~~ injectable preparation in which this medicine is ~~located~~ diluted. It has been shown that irritation and damage to the tissues of the human body and piglets after injection occurs due to the aggressive environment created by the ~~excipient compounds "Solution for injection" added to the containing~~ anti-inflammatory agents. It turned out that some ~~injectable preparations of NSAIDs-nonsteroidal anti-inflammatory drugs in the dosage form "Solution for injection" have excessively have~~ high hypertonic osmolarity, ~~urine and/or acidic activity, or have~~ alcohols, aldehydes, strong acids, and/or some other denaturing ingredients in their composition. Therefore, some ~~injectable preparations of~~ NSAIDs in the dosage form of "Solution for injection" ~~disrupt the homeostasis worsen the "ecology"~~ of tissues to an extent incompatible with their vital activity. And that is why after the injection of such drugs, aseptic inflammation develops, similar in all signs to the inflammation that occurs when injecting a hypertonic solution of 10% sodium chloride, a disinfectant solution of formaldehyde, and ~~anthe~~ antiseptic 96% ethyl alcohol [11-14].

~~When studying, in~~ experimental and clinical ~~conditionssituations~~, the condition of the tissues after intramuscular and subcutaneous injections of high-quality NSAIDs, ~~in the dosage form "Solution for injection" was studied. It~~ was found that solutions of 50% metamizole sodium had an aggressive local irritant effect ~~and~~ after intramuscular or subcutaneous injection, ~~which caused~~ aseptic inflammation, necrosis, and abscess. ~~At the same time, An aqueous~~ solution of 50% sodium metamizole had ~~s~~ an osmotic activity of 4638 ± 12.5 mosm/l ~~of water~~. ~~At the same time,~~ preliminary 10-times dilution of this solution ~~10-times~~ with water for injection prevented both local inflammation and necrosis by intramuscular and subcutaneous injections. Naturally, this solution had a concentration of 5% sodium metamizole and osmotic activity of about 460 mosm/l ~~of water~~. It has also been shown that 5% Ketoprofen® injection solution (OAO Sintez, Kurgan, Russia) and 3% Ketorol® injection solution (Dr. Reddis Laboratories Ltd., Hyderabad, Andhra Pradesh, India) also have a strong local aggressive effect. ~~A~~ and after subcutaneous injection, ~~these preparations~~ caused acute inflammation and necrosis, despite the low concentration of the main ingredients in solutions, compared with a solution of 50% sodium metamizole. However, a study of the formulations of these nonsteroidal anti-inflammatory drugs has shown that solutions for injection of these NSAIDs contain, in addition to the main ingredients indicated on the labels, auxiliary ingredients, including propylene glycol at a concentration of 40% [15].

~~Consequently~~ Additionally, 5% Ketoprofen® injection solution (Sintez OJSC, Kurgan, Russia) and 3% Ketorol® injection solution (Dr. Reddis Laboratories Ltd., Hyderabad, Andhra Pradesh, India) caused acute aseptic inflammation after injection, infiltration, necrosis, and abscess due to the high concentration of propylene glycol in the drugs. It ~~is~~ propylene glycol that has a cauterizing effect. This statement has been proven in experiments on live piglets.

It ~~is~~ was reported that an antidote against propylene glycol was found. In the role of such an antidote, it was proposed to use a drug - a solution of 10% calcium gluconate. To prevent post-injection inflammation, necrosis, and abscess (Nikolau syndrome), it was proposed to immediately inject a solution of 10% calcium gluconate into the area of the drug infiltrate. It was shown that the volume of the injected solution should be 1/3 of the volume of the injected ~~diclofena~~ diclofenac. It has also been shown that for the prevention of necrosis, it is necessary to inactivate propylene glycol very quickly. Therefore, the injection of the antidote should be timely - no later than 6 minutes after the injection of diclofenac (RU Patent No. 2326662, 20.06.2008).

Consequently, one of the causes of acute local aseptic inflammation, necrosis, abscess, and Nicolau syndrome that occurred ~~red~~ after injections of NSAIDs may be ~~due to the~~ hypertonic ~~osmolarityactivity and of the the content of~~ excipients ~~in solutions that have~~ producing a cauterizing effect. In particular, it was found that with a total concentration of dissolved ingredients of less than 1%, solutions are hypoosmotic and relatively safe, in the range of 1-10% have moderate local toxicity and, as a rule, hyperosmotic activity, and in the range of 10-76% have high hyperosmotic and necrotizing activity [16].

~~This conclusion hypothesis is proved corroborated~~ not only by the results of experiments carried out by pharmacologists on awake piglets, but also by the results of veterinary practice. The most convincing veterinary evidence is ~~the~~ chemical castration of male cats, dogs, and other animals achieved by intratesticular injection of 5, 10, or 20% calcium chloride solution [17].

In addition, solutions of methalibure, dexamethasone, ~~metopirone~~ niridazole, α -chlorohydrin or danazole, 3.5% formalin in phosphate-salt buffer, 1.5% chlorhexidine gluconate in 50%

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dimethylsulfoxide of formalin, a solution of 10% silver nitrate, 3.6% formaldehyde in ethanol, 5% potassium permanganate, 100% ethanol or 3.6% are also used for cauterizing action in veterinary medicine formaldehyde. In all cases, veterinarians add local anesthetics to injection solutions containing all of the above substances (from calcium chloride to formaldehyde). The presence of local anesthetics reliably prevents the soreness of necrosbutis, does not prevent sterilization, that is, necrosis. Consequently, local anesthetics are able to can reduce soreness in the necrosis site after injection, but this is not a guarantee of preserving the viability of the tissue.

Thus, additional research is needed to put an end to the history of studying study, the reasons of for local post-injection complications of NSAIDs and indicate a way to improve their safety.

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