Short communication

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 in the dosage form of "Solution for injection" have a locally irritating effect, despite the fact that the drugs are considered high-quality. It is shown that the mechanism of local irritant action is not related to the specific pharmacological action 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", which grossly violate the "ecology" of tissues, have a local irritating effect. It has been shown that local complications at injection sites can be caused by the nonspecific local irritating effect of the following properties of nonsteroidal anti-inflammatory drugs in the " Solution for injection ": denaturing (cauterizing), hypertonic and acidic activity. Each such property or their combination has a locally irritating effect, which can cause acute aseptic inflammation of a reversible and irreversible nature, necrosis and abscess that occurs immediately after subcutaneous, intramuscular and other injections and is known as Nicolau syndrome. Conversely, nonsteroidal anti-inflammatory drugs in the dosage form "Solution for injection", having isotonic or hypotonic activity, neutral or weak alkalinity (about pH 7.4), have a minimal, short-term inflammatory effect of a reversible nature and do not cause Nicolau syndrome after 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, infiltrates and soreness, including neuralgia, are more 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 and pegylated 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 dosage form "Solution for Injection" in which this medicine is located. 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 " Solution for injection " containing anti-inflammatory agents. It turned out that some nonsteroidal anti-inflammatory drugs in the dosage form "Solution for injection" have excessively high hypertщтшс and/ or acidic activity, or have alcohols, aldehydes, strong acids and some other denaturing ingredients in their composition. Therefore, some NSAIDs in the dosage form of "Solution for injection" 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 an antiseptic 96% ethyl alcohol [11-14].

In experimental and clinical conditions, the condition of 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 caused aseptic inflammation, necrosis and abscess. At the same time, a solution of 50% sodium metamizole had an osmotic activity of 4638 ± 12.5 mosm/l of water. At the same time, preliminary dilution of this solution 10 times with water for injection prevented 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 and after subcutaneous injection cause 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, 5% Ketoprofen® injection solution (Sintez OJSC, Kurgan, Russia) and 3% Ketorol® injection solution (Dr. Reddis Laboratories Ltd., Hyderabad, Andhra Pradesh, India) cause 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 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 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 occur after injections of NSAIDs may be hypertonic activity and the content of excipients in solutions that have 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 is proved 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 chemical castration of male cats, dogs and other animals achieved by intra-testicular injection of 5, 10 or 20% calcium chloride solution [17].

In addition, solutions of metallibur, dexamethasone, metopyron, niridazole, α-chlorohydrin or danazole, 3.5% formalin in phosphate-salt buffer, 1.5% chlorhexidine gluconate in 50% dimethylsulfoxide of formalin, a solution of10% silver nitrate, 3.6% formaldehyde in ethanol, 5% potassium permaganate, 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 necrosis, does not prevent sterilization, that is, necrosis. Consequently, local anesthetics are able to 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 the reasons of local post-injection complications of NSAIDs and indicate a way to improve their safety.

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