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

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Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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Short Communication

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ABSTRACT

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

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1. INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) firmly hold 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, soreness, and neuralgia are 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 [6,7].

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 [8]. 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, polidocanol, and pegylated alpha-interferon. The pathogenesis of Nicolau syndrome is unknown [9-12].

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 chemical and physicochemical properties of the excipients of the injectable preparation in which the medicine is 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 added to the anti-inflammatory agents. It turned out that some injectable preparations of NSAIDs have high hypertonic osmolarity, alcohols, aldehydes, strong acids, and/or some other denaturing ingredients in their composition. Therefore, some injectable preparations of NSAIDs disrupt the homeostasis of tissues to an extent incompatible with their vital activity. 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 the antiseptic 96% ethyl alcohol [13-16].

When studying, in experimental and clinical situations, the condition of the tissues after intramuscular and subcutaneous injections of high-quality NSAIDs, it was found that solutions of 50% metamizole sodium had an aggressive local irritant effect after intramuscular or subcutaneous injection, which caused aseptic inflammation, necrosis, and abscess. An aqueous solution of 50% sodium metamizole has an osmotic activity of 4638 ± 12.5 mosm/l. A preliminary 10-times dilution of this solution 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. 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. 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% [17]. 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 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 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 after injections of NSAIDs may be due to the hypertonic osmolarity of the excipients 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 [18]. This hypothesis is 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 intra-testicular injection of 5, 10, or 20% calcium chloride solution [19]. In addition, solutions of methallibure, dexamethasone, metopirone, niridazole, α-chlorohydrin or danazol, 3.5% formalin in phosphate-salt buffer, 1.5% chlorhexidine gluconate in 50% 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 [19]. 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 but does not prevent necrosis. Consequently, local anesthetics 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 study the reasons for local post-injection complications of NSAIDs and indicate a way to improve their safety.

2. CONCLUSION

Thus, NSAID injections can sometimes cause an acute local postinjection complication known as Nicolaou syndrome, which includes acute local soreness, acute aseptic inflammation, necrosis, and then abscess. One of the causes of Nicolau syndrome is the excessive physicochemical aggressiveness of the NSAID solution due to its hypertonic and/or strong acidic activity. In addition, in some cases, the NSAID solution causes Nicolaou syndrome because the solvent of the drug is not water, but 40% propylene glycol solution. The fact is that 40% propylene glycol solution has a cauterizing effect. It has been proven that pre-dilution of NSAIDs with water 10 times (before injection) completely prevents the development of Nicolau syndrome.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical Pharmacology. 2020;180:114147. DOI:https://doi.org/10.1016/j.bcp.2020.114147.
2. Vane JR, Botting RM. Mechanism of action of nonsteroidal anti-inflammatory drugs. The American Journal of Medicine. 1998; 104(3A):2S–22S. DOI:https://doi.org/10.1016/s0002-9343(97)00203-9.
3. Sinniah A, Yazid S, Flower RJ. From NSAIDs to glucocorticoids and beyond. Cells. 2021;10(12):3524. DOI:https://doi.org/10.3390/cells10123524.
4. Mojarrad P, Barikbin B, Oghazian MB. Can betamethasone prevent Nicolau syndrome when coadministered with penicillin? A case report. Clinical Case Reports. 2021;9(12):e05187. DOI:https://doi.org/10.1002/ccr3.5187
5. Adil M, Amin SS, Arif T. Nicolau's syndrome: A rare but preventable iatrogenic disease. Acta Dermatovenerologica Croatica: ADC. 2017;25(3):251–253.
6. Ibrahim A, Ali MM, Abou-Khalil NS, Ali MF. Evaluation of chemical castration with calcium chloride versus surgical castration in donkeys: testosterone as an endpoint marker. BMC Veterinary Research. 2016;12:46. DOI:https://doi.org/10.1186/s12917-016-0670-3
7. Kutzler MA. Intratesticular and intraepididymal injections to sterilize male cats: From calcium chloride to zinc gluconate and beyond. Journal of Feline Medicine and Surgery. 2015;17(9):772–776. DOI:https://doi.org/10.1177/1098612X15594991
8. Nicolau S. Dermite livédoïdeetgangréneuse de la fesse, consécutive aux injections intra-musculaires, dans la syphilis: à propos d'un casd'emboliearteriellebismuthique. Ann Mal Vener. 1925;11:321–339.
9. Kılıç İ, Kaya F, Özdemir AT, Demirel T, Çelik İ. Nicolau syndrome due to diclofenac sodium (Voltaren®) injection: a case report. Journal of Medical Case Reports. 2014;8:404. DOI:https://doi.org/10.1186/1752-1947-8-404.
10. Senel E, Ada S, Güleç AT, Cağlar B. Nicolau syndrome aggravated by cold application after i.m. diclofenac. The Journal of Dermatology. 2008;35(1):18–20. DOI:https://doi.org/10.1111/j.1346-8138.2007.00404.x
11. Sasmal PK, Sahoo A, Singh PK, Vs V. Nicolau Syndrome: An Unforeseen Yet Evadable Consequence of Intramuscular Injection. Surgery Journal (New York, N.Y.). 2021;7(2):e62–e65. DOI:https://doi.org/10.1055/s-0041-1728652
12. Lardelli PF, Jermini L, Milani GP, Peeters G, Ramelli GP, Zgraggen L, Terrani I, Bianchetti MG, Vanoni F, Faré PB, Lava S. Nicolau syndrome caused by non-steroidal anti-inflammatory drugs: Systematic literature review. International Journal of Clinical Practice. 2020;74(10): e13567. DOI:https://doi.org/10.1111/ijcp.13567.
13. Корепанова МВ, Коровяков АП, Уракова НА, Ураков АЛ. Осмотическая активность готовых растворов лекарственных средств как показатель их качества. Успехи современного естествознания (Россия). 2002;2:95-95; Available;https://natural-sciences.ru/ru/article/view?id=14080.
14. Urakov AL, Dementyev VB, Urakova NA, Sadilova PYu, Mikhajlova NA, Suslonova SV, Ivanova LB. Clinical significance of physical-chemical processes determining qualitative and quantitative characteristics of post-injection diffusion of drug solutions in patient's soft tissues. Chemical Physics and Mesoscopy (Russia). 2007;9(2):105 – 111. Available:https://cyberleninka.ru/article/n/clinical-significance-of-physical-chemical-processes-determining-oualitative-and-quanita-tive-characteristics-of-post-injection/viewer.
15. Уракова НА, Ураков АЛ. Инъекционная болезнь кожи. Современные проблемы науки и образования (Россия). 2013;1. Available:https://science-education.ru/ru/article/view?id=8171.
16. Urakov AL, Strelkov NS, Urakova NA, Benderskaya EYu. Physico-chemical and biophysical factors of post-injection aggression of the drug solutions in infiltrated tissues and methods of necrosis prevention. Pathological physiology and

experimental therapy (Russia). 2010;1:20-24.
17. Urarov AL, Urakova NA, Reshetnikov AP, Kasatkin AA, Nikityuk DB. Drug concentration and activity. Международный журнал прикладных и фундаментальных исследований. (Russia). 2014;12(1):106-108. Available:https://applied-research.ru/ru/article/view?id=6273
18. Urakov A. and Urakova N. Osmotic activity of drugs is an important factor of their local action at their Injection site: What we don't use to prevent post-injection abscesses. Journal of Pharmaceutical Research International. 2021;33(59B):647-650. DOI:10.9734/jpri/2021/v33i59B34428
19. Jana K, Samanta PK. Clinical evaluation of non-surgical sterilization of male cats with single intra-testicular injection of calcium chloride. BMC Veterinary Research. 2011;7:39. DOI:https://doi.org/10.1186/1746-6148-7-39.

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