Nicolau syndrome caused by non-steroidal anti-inflammatory drugs: systematic literature review

Running title: Nicolau syndrome caused by NSAIDs

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Abstract

Aim: Intramuscular or, more rarely, local drug injection is occasionally followed by immediate local pain, livedoid skin lesions and, some days later, the development of ischemic lesions. This very uncommon but potentially severe reaction, termed Nicolau syndrome, is traditionally associated with bismuth and β-lactam antimicrobials. The aim of this report was to review the literature associating Nicolau syndrome with the administration of non-steroidal anti-inflammatory drugs.

Methods: The National Library, Excerpta Medica, Web of Science and Cochrane library databases were used.

Results: Sixty-two cases (40 females and 22 males aged from 13 to 81, median 57 years) of Nicolau syndrome were published after 1992. Fifty-three cases occurred after diclofenac. The remaining nine cases were associated with ketoprofen (N=2), ketorolac (N=2), phenylbutazone (N=2), etofenamate (N=1), ibuprofen (N=1) and piroxicam (N=1).

Conclusion: Although Nicolau syndrome is extremely uncommon, physicians must be aware of this complication after intramuscular administration of non-steroidal anti-inflammatory drugs and should avoid unnecessary injections.

Keywords: embolia cutis medicamentosa, injection site reaction, livedoid dermatitis, Nicolau syndrome, non-steroidal anti-inflammatory drugs

How did you gather the information you considered in your review

- Four online databases (Cochrane, EMBASE, Library MEDLINE and Web of Science) were searched. Papers published after 1992 in Dutch, English, French, German, Italian, Portuguese or Spanish. The following search terms were used: (Nicolau[’s] syndrome OR embolia cutis medicamentosa OR livedoid dermatitis) AND non-steroidal anti-inflammatory drug.
- Pre-defined inclusion and exclusion criteria were applied. Cases were eligible if the clinical features of Nicolau syndrome occurred immediately after intramuscular or local injection of a non-steroidal anti-inflammatory drug. Data were extracted using piloted forms and transcribed into a predefined dedicated database.

What is the ‘take-home’ message for the clinician

- Healthcare providers must be aware that Nicolau syndrome may develop after injection of non-steroidal anti-inflammatory drugs.

Introduction

A peculiar and impressive reaction at the site of intramuscular drug injection occasionally occurs.[1] Abruptly after injection, local severe pain occurs and the overlying skin blanches. Within minutes to hours, the site develops an erythematous macule that evolves into a livedoid violaceous patch. This becomes hemorrhagic and subsequently ulcerates. Finally, over weeks to months, the ulcer heals with an atrophic scar. It is held that the German dermatologist Walter Freudenthal in 1924[2] and especially the Romanian dermatologist Ștefan G. Nicolau (1874-1970) in 1925[3] first reported on this uncommon injection site reaction, which is currently termed livedoid dermatitis, embolia cutis medicamentosa or Nicolau syndrome, after intramuscular administration of bismuth. However, some data suggest that the first report was made in 1898.[1]

Nicolau syndrome has been traditionally associated with the intramuscular administration of bismuth and, more recently, β-lactam antimicrobials.[1] More recently, Nicolau has also been observed after local injection of drugs such as corticosteroids, lidocaine or hyaluronic acid soft tissue fillers.[1]
In 1992, the possible occurrence of symptoms and signs resembling Nicolau syndrome following intramuscular injection of a non-steroidal anti-inflammatory drug was first suggested in the Netherlands.[4] To our knowledge, no published studies systematically evaluated the occurrence of Nicolau syndrome following administration of a non-steroidal anti-inflammatory drug. The aim of this report was to review the literature associating this injection site reaction with these widely prescribed agents.

Methods

Data source

A systematic literature review was conducted by two of us (P.F.L. and M.G.B.) in accordance with the Preferred Reporting of Systematic Reviews and Meta-Analyses guidelines, using the

National Library of Medicine, Excerpta Medica and Web of Science databases.[5] The Cochrane Library was also searched. Following subject headings terms were used: (Nicolau[’s] syndrome OR embolia cutis medicamentosa OR livedoid dermatitis) AND non-steroidal anti-inflammatory drug. Articles and letters published in Dutch, English, French, German, Italian, Portuguese or Spanish after 1992 were retained. The list of finally included publications was decided on by discussion between authors based on predefined eligibility criteria (see below).

Eligibility criteria – data extraction

Cases were considered eligible for inclusion if the distinctive local clinical features of Nicolau syndrome occurred abruptly (≤30 seconds) after intramuscular or local injection of a non-steroidal anti-inflammatory drug. Data were extracted using piloted forms and transcribed into a predefined dedicated database. The data extracted from each case meeting study criteria included demographics, drug name and site of injection, possible co-administration of further drugs, local lesion size, both pharmacological and surgical treatment, and final outcome. Authors of original articles were sometimes contacted to provide missing data or verify the accurateness of reported information.

Analysis

Results are presented as frequency or as median and interquartile range, as appropriate. The kappa index was used to assess the agreement between investigators, the Fisher test was used to compare dichotomous variables and the Mann-Whitney-Wilcoxon rank-sum test to compare continuous variables. Statistical significance was assigned at $P<0.05$.

Results

Search results

The literature search process is depicted in Figure 1. The chance-adjusted agreement between the two investigators on the

application of the inclusion and exclusion criteria was 0.88. A total of 45 eligible reports[6-50] published between 1996 and 2019 in English (N=44) or Spanish (N=1) were identified. The reports were primarily (N=41, 91%) from Europe (Turkey, N=17; Italy, N=4; Belgium, N=1; Germany, N=1; Switzerland, N=1) and Asia (India, N=9; South Korea, N=5; China, N=1; Israel, N=1; Qatar, N=1). Africa and America accounted for the remaining four (9%) reports (Cameroon, N=1; Jamaica, N=1; Mexico, N=1; United States, N=1).

Findings

The aforementioned 45 reports included 62 previously healthy subjects (40 females and 22 males aged from 13 to 81, median 57 years) with Nicolau syndrome occurring after intramuscular[6-11,13-50] or local[12] injection of a non-steroidal anti-inflammatory drug, as shown in table 1. The vast majority of cases (N=53; 85%) occurred following administration of diclofenac. The remaining nine cases were associated with the administration of ketoprofen (N=2), ketorolac (N=2), phenylbutazone (N=2), etofenamate (N=1), ibuprofen (N=1) and piroxicam (N=1).

Four patients had been concomitantly administered by intramuscular injection diclofenac and a further drug: dexamethasone, gentamicin, metoclopramide or thiocolchicoside, respectively.[7,35,36,46] Finally, phenylbutazone was administered intramuscularly together with dexamethasone, lidocaine and salicylamide in a patient of Nicolau syndrome reported by Ruffieux.[6]

In most cases (N=50, 81%), Nicolau syndrome occurred after intramuscular gluteal injection and was characterized by a local lesion averaging 10 centimeters in long-axis and 6 centimeters in short-axis diameter.

Systemic or topical antimicrobials, anticoagulants (either heparins or an oral vitamin K antagonist) or corticosteroids were prescribed in many cases (table 2). Pentoxifylline, a methylxanthine derivative that has been used for decades in the symptomatic management of intermittent claudication, was also prescribed in some cases (table 2). Forty-three cases underwent

debridement of necrotic tissue, skin graft or both debridement and skin graft.

Permanent sequelae (table 2) were observed in 42 (68%) cases, including a permanent scar and, less frequently, a permanent local muscle wasting causing reduced muscle power, joint stiffness or abnormal gait. A sciatic nerve injury, a severe limb ischemia and a fatal large muscle necrosis were observed in each one case.

Discussion

Nicolau syndrome is an injection site reaction, which is easily identifiable based on history, clinical findings and course.[3] This literature reviews points out that Nicolau syndrome and severe sequalae may occur after intramuscular or local administration of a non-steroidal anti-inflammatory drug. The vast majority of cases followed the administration of diclofenac, a widely prescribed non-steroidal anti-inflammatory drug worldwide.[51]

The very acute and distinctive presentation and histologic data support the notion, already suggested by Ștefan Nicolau, that this condition results from arterial damage.[3] Histologic examination of a few cases revealed thrombosis of medium- and small-sized vessels without vessel inflammation.[1,15,52] Three main mechanisms have been suggested.[1,15,52] First, direct intravascular injection may cause thromboembolic arterial occlusion. Second, perivascular or perinervous injection may produce a vasospasm owing to sympathetic nerve stimulation. Finally, vascular or perivascular injection may produce marked vascular inflammation, leading to destruction of the whole arterial wall (however, this hypothesis is not supported by the above presented histologic features).

The results of the present analysis point out that Nicolau syndrome associated to non-steroidal anti-inflammatory drug injection is a potentially severe condition.[3] Furthermore, our data and the literature indicate that there is no effective therapy available. Anecdotal observations suggest that hyperbaric oxygen, which increases the dissolved plasma oxygen level but is not

universally available and may not be well tolerated in childhood, could be an adjunct in the treatment of this uncommon condition.

Since there is no therapy once injury has occurred, prevention is the cornerstone of care. First, the indication for intramuscular administration should be carefully weighted. Second, it is usually advised to perform intramuscular injections after aspirating the syringe to ensure extra-vascular injection. Furthermore, the preferred injection site is the upper outer gluteal quadrant, which has few large blood vessels. Finally, it has been speculated that drug leakage into the subcutaneous tissue might cause irritation or pain and subsequently predispose the development of Nicolau syndrome. To prevent drug leakage, the Z-track technique is recommended that involves the displacement of the skin and subcutaneous tissue prior to intramuscular injection.[53] However, it is doubtful as to whether these strategies may prevent Nicolau syndrome.

Non-steroidal anti-inflammatory drugs are prescribed for various conditions including among others intense pain. Since the latter symptom often occurs together with nausea and vomiting[54], the intramuscular route is still sometimes preferred. Furthermore, it is customarily held that the intramuscular administration has a more rapid onset of action than the oral administration. Formulations of non-steroidal anti-inflammatory drugs are available that can be given as intravenous bolus. Maybe even more relevant is that tablets, powders for oral solution and liquid-filled soft gelatin capsules of non-steroidal anti-inflammatory drugs are also currently available, which are characterized by a very prompt onset of pain relief. Hence, in our opinion, avoidance of intramuscular injection of non-steroidal anti-inflammatory drugs is the best option in preventing this form of Nicolau syndrome.

Conclusion

Although Nicolau syndrome is extremely uncommon, physicians must be aware of this complication also after administration of non-

steroidal anti-inflammatory drugs and should avoid unnecessary injections.

Data availability statement

The data that support the findings of this study are derived from the National Library, Excerpta Medica and Web of Science databases, as stated in the Methods section. The analysis that supports the findings of this study is available from the corresponding author upon reasonable request.

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Figure 1 – Legend

Nicolau syndrome following administration of non-steroidal anti-inflammatory drugs. Flowchart of the literature search process. No further, potentially pertinent study was found in the Cochrane library database.