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The Use of Lymphocyte Stimulation Test in Severe Nabumetone-Induced Stevens-Johnson Syndrome: A Case Report

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Abstract

The plausible causative role of nabumetone in severe Stevens-Johnson syndrome in a 27-year old healthy female was shown by the Lymphocyte Stimulation Test (LST). In 2 healthy controls, LST was negative, and nabumetone did not prevent lymphocyte stimulation by phytohemagglutinin. The positive LST is somewhat surprising, because the patient had not been exposed by the drug previously and already the first 2 tablets induced the reaction.

The results suggest that LST can be useful in the diagnostics of severe life-threatening drug reaction, but the use of multiple drug dilutions is necessary in the case of suspected antigen that possesses anti-inflammatory properties. It can be possible that the positive LST and clinical reaction are related to crossreactivity between anti-inflammatory analgesic drugs. Also it may be possible that even a short transient time of nabumetone in blood before biotransformation may trigger a severe drug reaction.

Keywords: Lymphocyte stimulation test • Nabumetone • Phytohemagglutinin

Introduction

Nabumetone (4-(6'-methoxy-2'-naphthalenyl)-2-butanone) is used as a nonsteroidal, anti-inflammatory, anti-pyretic and analgesic prodrug in the inhibition of cyclooxygenase-2. Occasionally, it may cause a variety of adverse skin eruptions, including erythematous rash, erythema fixum, erythema multiforme and its severe forms, i.e., Stevens-Johnson syndrome and Lyell syndrome [1]. It's elimination half-life is 22.5 ± 3.7 hours. Nabumetone itself is not detected in the plasma, because, after absorption, it undergoes a rapid biotransformation by the liver to the principal active metabolite, 6-Methoxy-2-Naphthylacetic Acid (6-MNA) with plasma concentration of about 40-70 µg/ml with also inactive metabolites. According to Drug Information Sheet and Lexicom, about 35% of 6-MNA is formed. It is not known for certainty, whether the adverse reaction is caused by the transiently present nabumetone molecule or by its metabolite 6-MNA, but likely so by 6-MNA, because this metabolite is the major form in the blood circulation. To our knowledge, there are no previous reports on the use of Lymphocyte Stimulation Test (LST) in nabumetone-induced severe cutaneous drug eruptions.

Case Presentation

A 27-year-old healthy female with no known allergy or hypersensitivity used nabumetone 500 mg effervescent tablets (Relifex, Meda Oy, Finland) prescribed in 1998 to be used bid as an anti-inflammatory analgesic for her tension neck syndrome. After the very first tablet at about 6 p.m., she experienced slight itch and redness on both lateral sites of lips in about 6 hours. After the second tablet in the following morning at about 7 a.m., blisters developed in the mouth cavity followed by fever (38°C), and skin eruption within a few hours. The patient had previously used occasionally only paracetamol (acetaminophen) and one tablet of acetylsalicylic acid (350 mg) about 1 month before the onset of nabumetone-induced reaction.

The patient was first treated in a primary health care center with one dose of intravenous infusion of 60 mg hydrocortisone sodium succinate (Solu-Cortef) followed by discharge to home with oral prednisolone (Prednisolon) 30 mg/day for 3 days. Nabumetone was immediately discontinued after the second tablet. However, the skin condition exacerbated, and the patient was transferred to a

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University Hospital Emergency Unit, where the corticosteroid dose was increased to 180 mg, i.e., methylprednisolone (Depo-Medrol) per day due to severe erosions in the mouth, eye and genital mucosa. During the following days, the dose was decreased to 60 mg/day, and a central nutritional catheter was installed, and the patient was transferred to a Dermatological in-patient ward. After 9 days, i.v. dosing was changed to oral prednisolone. The diagnosis of severe Stevens-Johnson syndrome was set. The patient was treated in the in-patient ward using prednisolone with slowly decreasing dose for 3 weeks. An H2-receptor antagonist, famotidin (Pepcidin) 20 mg bid was used for gastrointestinal protection. For mouth erosions, triamsinolone solution was used 2-3 times a day, and class II-III corticosteroid creams topically on the skin. The diagnostic tests were carried out about 6-9 months later after the cessation of corticosteroid treatment.

Afterwards, the patient suffered from strictures in the genital mucosal area leading to surgical operations. The patient experienced also changes of fingernails and toenails that remained permanent; the fingernails III and V in the right, and V in the left hand, are completely missing. Similarly, toenails IV and V in the right and III and IV in the left foot are missing, as verified years later. Also, many other nails show dystrophic appearance. Post-inflammatory hyperpigmentation on the trunk and extremities has almost disappeared.

Materials

Nabumetone 500 mg effervescent tablets were dissolved in 0.9% saline at the stock concentration of 50 mg/ml, filtered through a 0.22 µm filter, and then used in assays. Phytohemagglutinin (PHA) was obtained from Sigma (St. Louis, MO, USA).

The Nabumetone tablet constituents were as follows: sodium starch glycolate (type A), sodium lauryl sulfate, hypromellosis, micro-chrystalline cellulose, saccharin sodium (E954), Makrogol 6000, titanium oxide (E171) and toffee aroma.

The Lymphocyte Stimulation Test (LST)

The heparinized blood sample was taken from the antecubital fossa, and Peripheral Blood Mononuclear Cells (PBMCs) were isolated as described [2]. The LST test was performed in triplicate using a 3-day or 6-day incubation, ^{3}H-labeled thymidine incorporation technique, various concentrations of the test compound (final concentrations 0.1-50 µg/ml), and liquid scintillation counter with quench correction. The LST index is defined as the ratio of DPM (antigen) to DPM (control), and the index of over 2.5 is considered positive [3]. Nabumetone was used as a diluted series at the final concentrations of 0.033 µg/ml to 10 mg/ml in LST. To study the effect of the ability of nabumetone to inhibit PHA-stimulated lymphocyte proliferation, PHA was used at the concentration of 200 µg/ml, and both compounds were added to the PBMC suspension simultaneously. Also, a 41-year-old-male (with nasal allergy to rat) and a 25-year-old healthy female participated in this experiment as controls.

Whole blood histamine liberation test

Whole blood histamine liberation test was performed using heparinized blood as described [4]. For this, nabumetone was used at the final concentrations of 0.033 µg/ml to 3.3 mg/ml. The incubation time was 30 minutes and the liberated histamine was analyzed by radio enzyme assay using ^{3}H-labeled S - adenosylmethionine as the methyl donor [5].

Epicutaneus test

Nabumetone was used at the concentration ranging from 5 µg/ml to 5 mg/ml in 0.9% saline solution using standard epicutaneous testing on previously affected right brachial skin area of the patient.

Results

The LST test was positive at the nabumetone concentration of 0.033 µg/ml (index 4.5) and at 0.1 µg/ml (index 3.8), but at higher concentrations the stimulation index was between 0.9-2.1, when the 6-day incubation was used (Table 1).

In 2 healthy controls, the LST index remained within 0.9 to 1.4, but the positive control PHA produced an index of 128.

To study the possible inhibitory effect of 0.033 µg/ml to 3.3 mg/ml nabumetone on the lymphocyte stimulation induced by the positive control PHA, the PBMC cells from both control subjects were used. However, nabumetone did not show any inhibitory effect on the lymphocyte stimulation induced by PHA in 3-and 6-day incubations.

In the whole blood histamine release experiment, there was no liberation of histamine after incubation with nabumetone for 30 min.

The epicutaneus test with nabumetone solutions on the previously affected skin site was negative.

Table 1. Effect of nabumetone on lymphocyte stimulation.

Concentration (µg/ml) of nabumetone	Patient	Control person
0.000	1.0	1.0
0.033	4.5	0.9
0.100	3.8	1.0
0.330	1.6	1.1
1.000	2.1	1.3
3.300	1.9	1.1
10.000	1.3	1.1
33.000	0.9	1.0
100.000	2.0	1.2
330.000	1.7	1.0
1000.000	1.5	1.2
3300.000	1.2	1.1
10000.000	1.7	1.4

Note: As representative control person a 41-year old male, 0,000 µg/ml concentrattion of nabumetone was considered as zero baseline with value of 1,0

Discussion

Here we describe a 27-year-old healthy female hospitalized for severe erosions in the mouth, eye and genital mucosa following with nabumetone treatment showed clinical signs of Stevens-Johnson syndrome. Suspicion of nabumetone-related adverse reaction was confirmed by LST-test.

A previous case report describes two females with immediate reaction to nabumetone [6], even though both patients had tolerated earlier this drug. Skin prick tests (10 and 100 mg/ml) were negative and oral challenges with other NSAIDs, and even of the same group as nabumetone, were negative.

There is also a case report of a 15-year-old boy experiencing Stevens-Johnson syndrome after taking nabumetone for 4 days, which suggests a possibility to proceed to severe skin reaction within a short medication time [7]. A nabumetone-induced erythroderma with high fever was reported in a 81-old-male after about an 1-2 week use of the drug [8].

It has been reported to the European Union Registry of the European Medicines Agency since 2012 (https://www.adrreports.eu/fi/) a total of 18 Stevens-Johnson syndrome cases by April 2022. In the age group of 18-64 years, there were 3 women and 3 men, so the ratio is equal, whereas in the age group of 64-85 years all 9 cases were women. Age was not specified in one male, one male was in the age-group of 12-16 years, and one female in the age group of more than 85 years.

In the case of acetylsalicylic acid, there are 332 reports on Stevens-Johnson syndrome, 133 subjects in the age group of 18-64 years with 68 women and 65 men; whereas in the older age group of 123 patients, 75 were women and 48 were men.

In the case of diclofenac, there are 368 reports on Stevens-Johnson syndrome, 234 patients in the age group of 18-64 years with an almost equal sex ratio consisting of 122 women and 115 men; whereas in the older age group of 73 patients, 43 were women and 30 were men.

Finnish Xreactbase Database classifies almost all anti-inflammatory analgesics to marked over 10% cross-reactivity group. Thus, similarities in molecular structures, that is, between diclofenac and acetylsalicylic acid, may theoretically act as pre-triggers for nabumetone-induced Stevens-Johnson syndrome.

The mechanism for the present severe nabumetone-induced Stevens-Johnson syndrome is not clear, because the patient had not been used the drug previously and the drug induced some facial skin symptoms already after the first tablet followed by severe eruption after the second tablet.

There can be at least 2 possibilities, i.e., a previous delayed-type sensitization by a NSAID drug with similar molecular structure, i.e., acetylsalicylic acid, in the present patient. This hypothesis is supported by the case report of fixed drug eruption due to nabumetone in a patient with previous fixed drug eruptions due to naproxen [9] and hypersensitivity to nabumetone due to cross-reactivity with naproxen [10].

Another mechanism for Stevens-Johnson syndrome might be a non-specific activation of the FAS/FADD/caspase-8 pathway [11] leading to death of the epidermis. However, the positive index in LST favors the first possibility.

Nabumetone is transformed in human hepatic cells to 6-MNA by Cytochrome P450 enzymes, predominantly by CYP1A2 [12,13] and this enzyme is also present in leucocytes [14]. Thus, theoretically it is possible that during experimental conditions in LST, 6-MNA could have been formed from nabumetone. This hypothesis needs, however, further studies and the use of 6-MNA together with the prodrug. However, the fast reaction of the symptoms experienced by the patient favors for the unmetabolized nabumetone, but the exacerbation of skin reaction by 6-MNA cannot be excluded.

It may also be possible that even a short and transient exposure to nabumetone in blood before biotransformation can trigger a drug eruption at a low concentration as detected by positive lymphocyte stimulation at 0.033-0.1 μg/ml concentration. However, at higher concentrations this stimulation was not detected, and thus, it is possible that it may have also an inhibitory effect.

The negative epicutaneous test result may be explained by the low penetration, or concentration of nabumetone through the skin, although the test concentration was at least 10,000-fold higher than the blood concentration.

There was no histamine liberation from the whole blood by nabumetone suggesting no marked involvement of the immediate-type reaction from blood basophils within 30 minutes. Serum tryptase assay was not used to detect mast cell involvement, since it was not available at the time of the nabumetone-induced reaction.

In mild reactions, a direct exposure with the culprit drug may be used to confirm the diagnosis. However, in severe reactions, that is, Lyell syndrome or Stevens-Johnson syndrome, an exposure may be life-threatening even in small doses. Therefore, in vitro experiments are safe in diagnostics, like the use of PBMC cells isolated from patients' blood. To the best of our knowledge, there are no descriptions in the literature on the use of LST in nabumetone-induced skin eruptions. The LST test produced a clearly positive index for the culprit prodrug, but several dilutions should be used in the test.

Conclusion

In mild reactions, a direct exposure with the culprit drug may be used to confirm the diagnosis. However, in severe reactions, that is, Lyell syndrome or Stevens-Johnson syndrome, an exposure may be life-threatening even in small doses. Therefore, in vitro experiments are safe in diagnostics, like the use of PBMC cells isolated from patients' blood. To the best of our knowledge, there are no descriptions in the literature on the use of LST in nabumetone-induced skin eruptions. The LST test produced a clearly positive index for the culprit prodrug, but several dilutions should be used in the test.

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Conflict of Interest

All authors declare that there are no conflicts of interests.

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