Peer reviewed article

Anaphylactic reactions to tolperisone (Mydocalm®)

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Summary

Four patients with anaphylaxis attributed to the intake of the centrally acting muscle relaxant tolperisone hydrochloride (Mydocalm®) were observed at the Emergency Department of the Geneva University Hospital between November 2001 and March 2003. All patients were middle-aged women who took tolperisone for chronic muscular pain. All reactions occurred within an hour after oral intake of this drug frequently prescribed in Switzerland. The severity of anaphylaxis ranged from urticarial reactions to shock with arterial hypotension. Prick-to-prick skin testing performed in one patient with a tablet of tolperisone diluted in water was negative. Its globally restricted commercialisation may explain the lack of reports on such adverse effects in the MedLine database. Anaphylactic reactions to this drug, however, are mentioned in other sources such as the Swiss Drug Compendium and the WHO drug reaction database. Together, these findings suggest that anaphylaxis to tolperisone is not uncommon and should be known to physicians in countries where this drug is available.

Key words: hypersensitivity; drug; tolperisone

Introduction

Allergic reactions to drugs are among the most frequent complications of pharmacotherapy. Anaphylaxis, a potentially life threatening immediate type reaction, has been well studied for drugs such as the penicillins. Other drugs causing anaphylaxis are more rarely found in publications and textbooks specialized in drug reactions, as well as in databases such as MedLine. A search by these means may fail if drugs have a restricted distribution. Here, we report 4 cases presenting anaphylaxis to tolperisone observed at the Geneva University Hospital between November 2001 and March 2003. This drug is frequently prescribed in Switzerland. We were unable to find any report of anaphylaxis or other allergic reactions to tolperisone referenced by MedLine.

Case reports

Case 1

A 45-year old woman with lower back pain, but otherwise in good health, experienced two anaphylactic episodes with generalized urticaria and angio-oedema of the face, dyspnoea and hypotension (grade IV according to H.L. Mueller [1]).[1] The first episode occurred half an hour after taking one tablet of tolperisone hydrochloride (Mydocalm®). She had been taking this drug occasionally over several years without side effects. Despite the severity of the symptoms, she did not seek medical attention. The symptoms faded spontaneously in reclined position. The second episode occurred one month later, 20 minutes after intake of one tablet of Mydocalm®. She had taken ibuprofen in a slow release preparation twelve hours earlier. On admission, the patient was pale and arterial pressure was not measurable. She responded well to administration of epinephrine, corticosteroids and clemastine. Further intake of Mydocalm® was proscribed. The patient was lost to follow up.

Case 2

A 59-year old woman with history of allergy to penicillin, hypothyroidism and chronic back pain experienced palmar and facial erythema as well as angio-oedema of the face and tongue (grade II) 20 minutes after ingestion of one tablet of Mydocalm®. She had no respiratory distress. Other medication included levothyroxine and estradiol/norethisterone. Tolperisone was believed to be the culprit drug, and was stopped. She had taken tolperisone in the past without side effects. The two other drugs were continued without problems. She did not show up for the follow up appointment.

1 The author has established a classification of the severity of anaphylactic symptoms. Reactions range from grade I to grade IV (grade I – urticaria, pruritus, malaise; grade II – angio-oedema, chest tightness, dizziness and digestive symptoms like vomiting, diarrhoea and abdominal pain; grade III – dyspnoea, wheeze, stridor, hoarseness and dysphagia; grade IV – hypotension, collapse, loss of consciousness, incontinence, cyanosis. This classification has been initially described in hymenoptera sting allergy but is also helpful to assess the severity of other immediate-type reactions.

Case 3

A 48-year old woman with allergic rhinitis and asthma to cat dander, dust mites and pollens experienced a severe anaphylactic episode with urticaria, angio-oedema, malaise and hypotension (grade IV) 2 hours after eating a soup with various vegetables, and half an hour after taking a tablet of tolperisone hydrochloride (Mydocalm®). She had been taking this medication since 3 days without any problems. Prick tests with tolperisone (one crushed tablet dissolved in water) and all the consumed vegetables were negative. The patient refused to undergo an oral provocation test. All the vegetables, except celery (the patient's initiative), were ingested subsequently without any reaction.

Case 4

A 55-year old woman with migraine and chronic rhinitis experienced three anaphylactic episodes of increasing severity, all within one hour after the intake of tolperisone (Mydocalm®). She had experienced a first episode three weeks previously; at that time under treatment with rofecoxib, taken several hours before the reaction. She developed itching and intense palmar erythema within one hour after taking one tablet of tolperisone, drug she denied having ever taken before this incident. The itching resolved under levocetirizine within 48 hours. She took another tablet of tolperisone three days later and experienced generalized erythema, pruritus and malaise within one hour but did not seek medical attention. One hour after the third intake of tolperisone without other concomitant medication, she was brought to the Emergency Department with generalized urticaria, facial angio-oedema, dyspnoea and dysphonia but without hypotension (grade III). Skin tests and oral challenge with tolperisone could not be performed.

Discussion

We have seen four patients with anaphylaxis within less than 18 months as consultant allergists at the Emergency Department of the University Hospital of Geneva. All patients were middle-aged women with chronic muscular pain. All reactions occurred within an hour after the intake of tolperisone. The severity of anaphylactic reactions according to the classification of H. L. Mueller ranged from grade II (urticaria and angio-oedema) in one patient to grade III (urticaria, angio-oedema and dyspnoea) in another patient, and grade IV (including hypotension) in two patients. Three patients had previously been exposed to this drug. Remarkably, one patient experienced symptoms without admitted prior exposure.

On the basis of the medical history, three cases were considered as certainly (case 1, 2 and 4) and one as probably caused by tolperisone hydrochloride. We performed prick-to-prick testing in one patient. Because an injectable preparation of tolperisone hydrochloride is not available in Switzerland, we used crushed tablets dissolved in water. As the skin test was negative we found no argument for an IgE-mediated reaction to the drug itself. Such skin testing is however not standardised and cannot rule out an IgE-mediated hypersensitivity to the drug or to its metabolites. Double-blinded challenge with the suspected drug and with placebo in a hospital setting is considered to be the most reliable assessment of drug hypersensitivity. It is contraindicated in patients with severe reactions and only performed after informed consent. None of the patients were submitted to an oral double-blinded placebo-controlled challenge with tolperisone hydrochloride. Two patients had already performed a challenge test, reexposing themselves inadvertently to the drug and experiencing anaphylactic symptoms. Those cases have therefore the strongest evidence of hypersensitivity to this drug. The personnel of the Emergency Department failed to follow our recommendation to have serum tryptase levels determined in the patients with grade IV reactions. Increased serum tryptase levels could have confirmed the diagnosis of anaphylaxis [2].

Tolperisone hydrochloride (dimethyl-2,4'-piperidino-3-propiophenone) is a muscle relaxant introduced in 1959. It is a beta-aminopropiophenone derivative and closely related to eperisone, another centrally acting muscle relaxant. Although the exact mechanism is still unknown, it is believed that its action as centrally acting muscle relaxant is principally based on the inhibition of voltage gated sodium channels in the brain stem [3]. Another effect is arterial vasodilatation [4] used to treat peripheral arterial insufficiency [5]. It can be hypothesized that the intrinsic vasodilator activity of the drug contributed to the immediate type hypersensitivity reaction. According to the WHO, this drug is available only in a few countries, including Japan, the Netherlands and Switzerland.

In Switzerland, tolperisone hydrochloride is commonly used to treat back pain associated with paravertebral muscle spasm. It is available under the brand names Mydocalm® and Mydocalm mite®, corresponding to tablets containing 150 mg and 50 mg of tolperisone hydrochloride, respectively. The usually prescribed dose is 150 mg t.i.d. It is only available on medical prescription and usually associated with non-steroidal anti-inflammatory agents.

To our knowledge, there is no publication in MedLine reporting allergic or allergic-like reactions to this drug. The restricted global commercialisation may be related to this fact. Immediate adverse effects of anaphylactic nature to tolperisone hydrochloride, ranging from urticaria/angio-oedema to anaphylactic shock, are mentioned, however, in the Swiss Drug Compendium [6]. Anaphylactic reactions to tolperisone have also been reported to the WHO. We performed a search in the WHO drug reaction database in April

2002. From a total of 711 reported adverse effects to tolperisone, almost half (344 cases, 48.3%) can be considered to represent immediate type hypersensitivity reactions (e.g. urticaria, angio-oedema, dyspnoea, anaphylactic shock).

Physicians in countries where tolperisone is available should be aware of the risk of anaphylactic reactions to this drug. Intake of tolperisone without medical prescription should be discouraged. Patients should be advised to immediately withdraw the drug if reactions such as pruritus and urticaria occur, as mentioned in the Swiss Drug Compendium. Despite alarming symptoms within an hour after the intake, two of our patients repeated the administration of the offending drug without seeking medical attention.

Conclusion

Our case histories and the frequency of the anaphylactic events reported to the WHO suggest that anaphylaxis to tolperisone is not rare, ranging from urticaria and angio-oedema to more serious reactions with dyspnoea and hypotension. The mechanism of these allergic-like reactions remains unclear.

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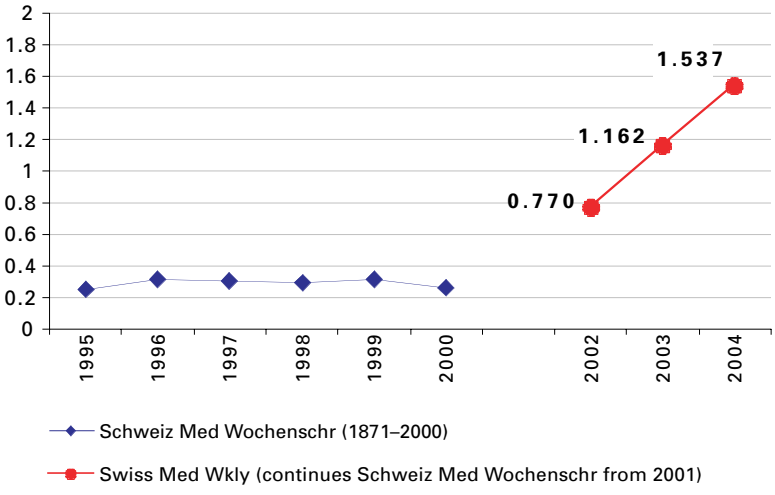

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