



## Drug Generalized Hypersensitivity Reactions to Tolperisone (Mydocalm)

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### Abstract

Tolperizol (Mydocalm) is a widely used drug as a skeletal muscle relaxant and is often additionally prescribed by family doctors in the course of lumbar discopathy. Among its adverse event, the possibility of a hypersensitivity reaction to anaphylactic shock is also mentioned. Few cases of severe hypersensitivity to this drug in the literature as now have been reported. Two cases of anaphylactic hypersensitivity and its confirmation using an oral challenge test are presented. These cases should draw the attention of GP doctors to the possibility of hypersensitivity to tolperizol. They also emphasize the need to pay particular attention to the patients' medical history of prodromal symptoms such as pruritis and urticaria, which may predict the occurrence of more severe general reactions.

**Keywords:** Tolperisone; Drugs; Hypersensitivity reaction; Anaphylactic shock

### Case Presentation

Tolperisone (dimethyl-2-4-piperidino-3-propiofenone), (Tolperisone hydrochloridum) - centrally acting muscle relaxant is a popular agent which has been widely used as a spasmolytics drug for acute and especially chronic pain with spasticity of neurological and orthopedic origin [1]. In the mechanism of its action it exhibits membrane stabilizing potency, which is characteristic of antiarrhythmic and local anesthetic agents. Without concomitant sedation or withdrawal phenomena Being a centrally acting muscle relaxant, it acts at the level of spinal cord by blocking sodium and calcium channels and inhibits spinal reflex via a presynaptic blockade of the release of neurotransmitters from the different endings of neuromuscular plaque [2,3]. Tolperisone increases the blood supply to skeletal muscles; this action is noteworthy since the muscle contracture may compress the small blood vessels and induce an ischemia leading to release of pain stimulating compounds. It also leads to membrane stabilization & has analgesic activity. The muscle relaxation is a dose dependent manner. This agent is common administered orally, intramuscularly and intravenously, but additional (intraarterial, intraspinal, intraperitoneal, intranasal inhalation form) can be used [4].

Therapeutically effective dosage of tolperisone ranges from approximately 75 mg/day to 1500 mg/day. No drug interactions have been reported with the concomitant intake of benzodiazepines, Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), analgesics and alcohol. In some cases it may cause systemic side effects which include: sweating, urticaria, erythema and gastrointestinal effects with abdominal pain, nausea, vomiting and diarrhea. Its good tolerability, minimum contraindications and safety makes tolperisone a suitable choice of muscle relaxant for a broad range of patients including elderly patients with concomitant diseases [4].

The efficacy of tolperisone has been demonstrated in patients with post stroke spasticity and it is still controversial in the treatment of patients with increased muscle tone due to musculo – skeletal system diseases other than post stroke spasticity [5]. Hypersensitivity to tolperisone is often manifesting as urticaria and/or angioedema but. Especially anaphylactic shock is very rare [6]. Because of its frequent use by patients with spinal pain, one should remember about this possibility. The following 2 cases illustrate the problems associated with the diagnosis of tolperisone hypersensitivity.

#### Patient 1

A 60 year old man with hypertension, spinal degeneration, after right knee arthroscopy and an episode of generalized anaphylactic reaction was admitted to the Department of Infectious Disease and Allergology to have additional examinations made and determine the cause of the anaphylaxis

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episode.

Because of the spinal degeneration he was staying in the sanatorium before admission to the hospital. He suffered from severe pain in the lower back of the sacrolumbar spine and diclofenac (Diclofenacum Natrium) (Naklofen) was intravenously injected in a single dose and diclofenac (Aglan) was administered orally. After the treatment the symptoms did not stop and for this reason, he again received the previously used drugs and additionally tolperisone was taken orally (Mydocalm forte 150 mg - Gedeon Richter). Approximately 40 minutes after taking the drug there appeared a severe skin pruritus, angioedema, generalized urticaria, shortness of breath, hypotonia with loss of consciousness (retrospectively rated Mueller's grade IV) [7]. Rescue medication was offered, including epinephrine and gradually the symptoms disappeared after about 60 minutes. During 24-hour follow-up, anaphylaxis was not reported.

On admission to the Department his general condition was good. The complaints concerned only problems of osteoarthritis of the joints because of his suffering for many years. Anamnesis in allergic disease was negative, especially as regards food allergy, lactose intolerance and lignocaine allergy, which was used in the past with no adverse effects. No changes in mouth cavity mucosa or skin and non-enlarged available peripheral lymph nodes were reported in the subject physical examination. Thyroid gland was smooth, not enlarged and painless. Respiratory and cardiovascular systems were normal: HR 80 beats/min, RR 130/80 mmHg, No abnormalities in the abdominal structures were found. Also there was not seen a peripheral edema.

During hospitalization the following tests were made [8]

1. Prick skin tests with standard inhalant allergens: dust mites (D1, D2), cat hair, dog skin, mold, hazel pollen, alder, birch, grass and mugwort whose results were negative.
2. Prick skin tests with food allergen panel: meat I, meat II, citrus, apple, banana, strawberry, peanut, hazelnut, tomato, rye flour, wheat flour, cow's milk, egg white and cocoa – all of them were also negative.
3. An autologous serum test - the result was negative.
4. A blind oral placebo trial (lactose closed into gel capsules) - negative result.
5. A blinded oral acetylsalicylic acid trial (doses of 1, 10, 50, 100 and 300 mg of aspirin in gel capsules) - negative result at a cumulative dose of 461 mg.
6. A blind tolperisone challenge (150 mg Mydocalm forte - Gedeon Richter tablets were divided into 4 parts and located in gel drug capsules).

Fifteen minutes after taking the first dose of 37.5 mg, head skin itching occurred, in upper and lower limbs later, general anxiety, generalized urticaria and facial edema, sinus tachycardia about 140 beats/minute and blood pressure decreased to the value 60/45 mmHg.

Anaphylaxis with life-threatening anaphylactic shock was diagnosed and the treatment for anaphylaxis in accordance with the guidelines of the Polish Society of Allergology and the European Academy of Allergy and Clinical Immunology was implemented [9,10], administering 0.5 mg of epinephrine into intramuscular injection. It had to be repeated after 15 minutes because of incomplete improvement. Dexamethasone 8 mg (Dexaven, Jelfa SA)

and 2 mg clemastine (Clemastinum Polfa SA) were administered intravenously additionally, oxygen (6 l/min to 10 l/min) through the nasal cannula, intravenous 500 ml 0.9% NaCl, resulting in about 60 minutes after the onset of the episode, total symptoms disappeared. ECG examination and blood pressure was monitored for 6 hours after the anaphylaxis episode with no recurrence. An oral test with Mydocalm was considered positive. The patient was discharged home with the recommendation not to use any drug containing the active substance tolperisone (Tolperisone hydrochloridum). The patient was provided with a set of medicines containing epinephrine.

## Patient 2

Forty five year old woman with the pain in the because of spinal osteoarthritis, otherwise without any symptoms was admitted to the clinic to widen the diagnosis of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) hypersensitivity. In an anamnesis it was known, that in 2008, after a week of taking painkillers: Ketoprofen, 100 mg/day and tolperisone (Mydocalm forte) 150 mg/day orally, the whole body erythema appeared accompanied by head dizziness. For this reason she was diagnosed in local health services but she had no documentation about diagnostic procedures which were carried out. In June 2016 she received Tolperis 50 mg (Tolperis VP, ICN Polfa) orally. After 15 minutes generalized anaphylactic reaction to urticaria, angioneurotic edema, dyspnoea, and hypotension (retrospectively Mueller's level IV) was assessed [7]. Occasionally, Paracetamol and Ibuprofen were used because of spinal pain without any abnormal reactions. In her young age she had swollen lips and tongue in the spring after eating tomatoes. Moreover, she was allergic to nickel, and not showed lactose intolerance and lignocaine allergy, because the two substances were repeatedly used without negative consequences. In addition, in an anamnesis asymptomatic cholecystolithiasis. On admission to the department her general condition was good. In the physical examination, except for minor obesity, no significant deviations from normal were observed.

During hospitalization we carried out:

1. Serum C3 complement concentration test - result - 181 mg/dl (norm 90 ng/dl to 180 ng/dl) and C4 complement concentration test - 39 mg/dl (norm 10 mg/dl to 40 mg/dl).
2. Qualitative study of serum C1 inhibitor of complement esterase activity – score >110% - in the norm.
3. Serum IgE allergen specificity test (food panel) - crab 3 grade (7.8 kU/l), other were negative.
4. The autologous serum test was negative.
5. A blind oral placebo trial (lactose) - negative result.
6. A blinded acetylsalicylic acid test (doses of 1, 10, 50, 100 and 300 mg of aspirin in gelatin capsules) - a negative result at a cumulative dose of 461 mg.
7. Tolperisone challenge test (150 mg Mydocalm forte) with tablets divided into 4 parts and sealed in gel drug capsules). Forty minutes after the first capsule dose of 37.5 mg, generalized urticaria, tachycardia about 100 beats/min appeared. The blood pressure was normal. Dexamethasone 8 mg (Dexaven, Jelfa S.A.) and 2 mg clemastine (Clemastinum Polfa S.A.) were administered intravenously and a gradual complete disappearance of urticaria and tachycardia after about 30 minutes was observed. The Mydocalm test was considered positive.

The patient was discharged home with the recommendation not to use any drugs containing the active substance tolperisone (Tolperisone hydrochloridum). The patient was provided with a set of medicines containing Adrenaline.

## Discussion

Tolperisone is a centrally acting muscle relaxant agent, also extends peripheral vessels and improves vascular blood supply. It has high affinity for nervous tissue reaching the highest concentrations in the brain stem, spinal cord, and peripheral nerves. The most important therapeutic effect of tolperisone is its inhibitory effect on spinal cord reflex activity, which together with the inhibition effect on the descending tract of the spinal cord determines the clinical effects most commonly used in practice [11].

Tolperisone is used in treatment of sclerosis multiple, cerebrovascular disease, posttraumatic disease, intensified muscle tone as a response to pain, and as an adjuvant in extrapyramidal symptoms (post drugs Parkinsonism). It reduces the intensity of transverse striated muscle tension, so it is recommended to reduce stiffness and pain caused by tension and contractures of skeletal muscles of various origins (pyramidal lesions, spinal cord disease, multiple sclerosis, adjunctive therapy in rheumatic diseases) [2,4]. In general tolperisone is well tolerated in clinical use and little side effects or none were reported. The list of possible side effects associated with Tolperisone is extensive and includes: anorexia, sleep disturbances, insomnia, drowsiness, head pain and dizziness, hypotension, gastrointestinal disorders, weakness and muscle aches, discomfort, fatigue, decreased activity, depression, attention deficit, tremor, epilepsy, reduced reaction to stimulation, paraesthesia, lethargy, blurred vision, tinnitus, vertigo, angina pectoris, tachycardia, heart arrhythmia, heartburn, bloating, dyspnea, abdominal pain, constipation, bloating, vomiting, mild hepatic injury, excessive sweating, proteinuria, hot feeling, excitation, thirst, hypotension, decreased liver function, thrombocytopenia, leukocytosis, anemia, lymphadenopathy, elevated retention rates nitrogen in blood. These cases illustrate that hypersensitivity to tolperisone may be different. This includes many factors associated with oral drugs administration. In the tolperisone leaflet for the patient added to the medicine pack, there is information about the possibility of allergic reactions ranging from mild skin reactions (redness, urticaria) to severe systemic reactions (including anaphylactic shock). Generalized anaphylactic reactions with an anaphylactic shock have been published only in a few well documented cases so far.

The first case was described in 1974 in a Russian journal but did not attract much attention [12]. Ribí et al. [13] described 4 patients who were hospitalized in the University of Geneva in 2001-2003 years for generalized anaphylactic reactions (II to IV degree according to Mueller scale) that occurred within 60 minutes after tolperisone. There was a general finding of highly likely drug hypersensitivity, and none of these cases confirmed the cause of drug-induced hypersensitivity by challenge in hospital settings [13]. Kwasniewski et al. [14] described the case of a 49-year-old man suspected of causing anaphylactic shock after giving tolperisone (Mydocalm). Another skin anaphylactic shock developed during the skin test. Porębski et al. [6] described also the case of an anaphylactic reaction after application of tolperisone (Mydocalm) manifested by redness of the face and hands, accompanied by increasing itching, tendency to generalized skin symptoms and the appearance of ever more potent abdominal pain and progressive weakness. The oral challenge test with tolperisone

followed by an oral dose of 12.5 mg had the same effect as in the previously described hypersensitivity reaction, but without feeling weak and with stable blood pressure. This is one of the few publications in which an aggravating anamnesis was verified via a drug challenge test [6]. This subject, also in the aspect of casuistry, was also undertaken by others. Anaphylactic reactions to these drugs are also mentioned in the WHO drug reaction database (<http://www.who-umc.org>). Taken together, these findings suggest that anaphylaxis to tolperisone is not uncommon and should be known to physicians. Very little is known about the mechanism of hypersensitivity to tolperisone. Nagai et al. [15] studies in mice suggested that tolperisone (2,4'-dimethyl-3-piperidino propiophenone hydrochloride) may have antagonizing properties of slow-acting anaphylaxis. Due to a similar chemical structure, cross-reactivity of tolperisone with lidocaine is possible. There are no reports of such reactions with drugs that can currently be used instead of tolperisone: baclofen and tizanidine.

## Summary

The descriptions of 2 cases of hypersensitivity to tolperisone supplement a few references on this topic. They are also one of the few instances in which an aggravating anamnesis has been verified with a drug challenging test, which should be a gold diagnostic standard. The clinical manifestations of hypersensitivity have evolved after a small 37.5 mg tolperisone dose, which represents one-fourth of the typical single dose. Porębski et al. [6] confirmed the occurrence of hypersensitivity to the drug at an even lower 12.5 mg dose, which is 1/12 of a single dose [6]. We did not make drug skin testing, because as reported by Gluck et al. [16] the sensitivity of skin tests is limited in drug hypersensitivity and in certain cases, hypersensitivity can only be confirmed via drug challenge tests [17]. The symptoms developed within minutes, indicating either a specific immunological IgE-dependent mechanism of drug hypersensitivity reaction or a non-IgE dependent reaction (i.e., direct histamine release from mast cells was probably involved).

These cases highlight also the potential for different severity of anaphylactic reactions, including a life-threatening anaphylactic shock after the use of tolperisone, a commonly used drug and referred to as relatively safe. Although in many cases the very circumstances of hypersensitivity are indicative of tolperisone as a highly probable cause, it is important to point out that this drug is often used as a complement to the multi-drug treatment of very common pain not only in the course of musculo-skeletal system. In such situations, all groups of medications, especially NSAIDs, may be the cause of hypersensitivity symptoms, so it may be necessary to determine precisely the drug responsible for the symptoms. The oral challenge test is, in such cases, a test of the choice [6]. Literature review and our experience suggest that this test is highly sensitive and specific (in our current study we do not discuss patients with a negative outcome for such trials). We believe that when tolperisone is suspected of causing a severe hypersensitivity reaction, an oral challenge should be initiated by administering less than the doses used in the presented cases (depending on the assessment of a previous episode of 5 mg to 10 mg tolperisone). Due to the need for proper administration (first time the placebo and next examined drug), high risk of anaphylaxis, and the fact that the causative agent administered orally can stimulate the body for an extended period of time, the trial should be performed at specialized allergy centers with the possibility of monitoring important life functions such as cardiac function, saturation, arterial blood pressure, and the ability to perform a spirometry test

and observe the patient over at least 12 hours after the end of the challenge test within a 2 to 3 day hospitalization [6]. Occasionally, other medicines used by the patient are also needed.

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