

Nightmares and dizziness during treatment with thiocolchicoside – case report

Koszmary nocne i zawroty głowy podczas terapii tiokolchikozydem – opis przypadku

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Summary

Background. Thiocolchicoside (TCC) is a muscle relaxant used as an adjunct in the treatment of painful muscle contractures in acute spine diseases in adults and adolescents from 16 years of age. The pharmacokinetics and pharmacodynamics of TCC remain not fully understood. This drug can exert side effects such as seizures, hallucinations and hypersensitivity reactions. **Material and methods.** We describe a case report of a 72-year-old man who experienced an adverse reaction of nightmares and dizziness during the therapy with thiocolchicoside. **Results.** Symptoms resolved after discontinuation of thiocolchicoside. **Conclusions.** Described case confirms the risk of adverse reactions as a consequence of thiocolchicoside therapy. (*Farm Współ 2020; 13: 223-227*)

Key words: *thiocolchicoside, analgesic therapy, sleep disorders*

Streszczenie

Wstęp. Tiokolchikozyd (TCC) jest lekiem zmniejszającym napięcie mięśni, stosowanym wspomagająco w leczeniu bolesnych przykurczów mięśni w ostrych chorobach kręgosłupa, u dorosłych i młodzieży w wieku od 16 lat. Farmakokinetyka i farmakodynamika TCC nie są w pełni poznane. Lek może wywołać takie działania niepożądane jak: napady padaczkowe, halucynacje i reakcje nadwrażliwości. **Materiał i metody.** Przedstawiamy przypadek 72-letniego mężczyzny leczonego tiokolchikozydem, u którego wystąpiły koszmary senne i zawroty głowy. **Wyniki.** Objawy ustąpiły po odstawieniu tiokolchikozydu. **Wnioski.** Opisany przypadek potwierdza ryzyko wystąpienia działań niepożądanych jako następstw terapii tiokolchikozydem. (*Farm Współ 2020; 13: 223-227*)

Słowa kluczowe: *tiokolchikozyd, terapia przeciwbólowa, zaburzenia snu*

Introduction

Spinal pain syndromes may appear in various forms, depending on the mechanisms of their formation. They are frequently classified into pains of osteoarticular origin, muscle pains and pains resulting from compression of the spinal nerve structures [1]. In the elderly population, where pain may be underreported because of the belief that pain is a normal process of aging, the prevailing types of pain are low back or neck pain (65%), musculoskeletal pain (40%), peripheral neuropathic pain (40%), and chronic joint pain (20%) [2]. Back pains are often accompanied by increased muscle tension, which often worsen the symptoms. For that reason, the pharmacotherapy of spinal pains associates anesthetics with myorelaxants- agents that reduce the tone of striated

muscles [1]. One of these drugs is thiocolchicoside, indicated for the adjunctive treatment of painful muscle contractures in acute spine diseases in adults and adolescents from 16 years of age [3]. Thiocolchicoside (3,10-di (demethoxy)-3-glucopyrosyloxy-10-methyl thiocolchicine, TCC), a sulfurated semisynthetic derivative of colchicoside, naturally present in *Gloriosa superba*. It is known to act as a muscle relaxant, and thus, it is applied for acute muscular spasms, contractures, myofascial pain syndrome, chronic osteoarticular, rheumatic, and neurologic disorders [4,5].

Case report

A 72-year-old patient reported to the family doctor (an online consultation) complaining about

pain involving the sacral and lumbar sections of the spine, which appeared after physical effort, 3 weeks before the consultation. The patient's medical history includes arterial hypertension (from 10 years), type 2 diabetes (from 5 years), and dyslipidemia. The applied pharmacotherapy (amlodipine 5 mg/day, ramipril 10 mg/day, metformin xr 1000 mg/day, atorvastatin 20 mg/day) assessed during periodic outpatient and laboratory examinations achieves the therapeutic goal. For 2 years, the patient has also been taking alprazolam 0.25 mg/day due to sleep disorder. The pharmacotherapy is well tolerated by the patient – it does not cause any complications. In addition, the patient periodically uses vitamin and magnesium preparations. The patient initially treated the back pain with a topical gel preparation of diclofenac and acetaminophen (2 g/day). The lack of effectiveness of the ointment prompted the patient to consult a doctor, who recommended the following therapy: thiocolchicoside 16 mg/day (p.o.); diclofenac 75 mg/day (i.m.), and combination preparation consisting of thiamini hydrochloridum 100 mg, pyridoxini hydrochloridum 100 mg, cyanocobalaminum 1 mg (i.m.). On the 3rd day of the modified analgesic therapy, the patient developed nightmares and dizziness. On the 6th day of treatment, after a telephone contact with the doctor, thiocolchicoside was discontinued, which resulted in clinical improvement and resolution of the reported problems.

Discussion

Thiocolchicoside is a semi-synthetic derivate of colchicine, used clinically for its muscle relaxant and analgesic properties. Surveys performed in in cell culture and animal model also revealed other therapeutic properties of TCC, i.e. anticancer properties and attenuation of cerebral vasospasm after subarachnoid hemorrhage [4,6,7]. This substance, available in oral, parenteral, and topical preparations, is less sedating than other centrally acting muscle relaxants. TCC biological half-life is up to 5 hours [8]. Peak plasma concentrations are observed after 30 minutes when administered intramuscularly or after 50 minutes in case of oral administration [5]. In general, thiocolchicoside is a relatively safe drug. Nevertheless, TCC therapy may entail the risk of some adverse effects such as liver injury, severe cutaneous disorder, pancreatitis, rhabdomyolysis, reproductive disorders, and seizures [4,9]. Pharmacokinetics and pharmacodynamics of TCC still remain unclear. Its muscle relaxant and

analgesic effects may result from an agonist interaction of this drug spinal-strychnine-sensitive glycine receptors (GlyRs). However, another study indicated, that TCC therapeutic effect is due to interaction with a cortical subtype of the γ -aminobutyric acid type A (GABA_A) receptor. GABA_A receptor is known to expresses low-affinity binding sites for γ -aminobutyric acid (GABA – the primary inhibitory neurotransmitter in the human cortex; GABAergic neurons are involved in myorelaxation, anxiolytic treatment, sedation, and anesthetics) that seem to be antagonist-binding sites. The knowledge about thiocolchicoside is limited; however, it is a relatively safe drug with few known side effects [4].

Adverse reactions

Epileptic seizures. Thiocolchicoside, commonly used as a muscle relaxant, is known to cause convulsive effects in humans and animals. TCC-induced epileptic seizures have been observed in a small number of patients, often suffering from acute brain injury and epilepsy. In case of rats, epileptic seizures after TCC administration were reported at the total dose of 6-12 mg/kg. In a case report, described by Yilmaz et. al, a 67-year-old man patient received a cumulative dose (64 mg) of TCC and as a result, he developed epileptic seizures. The patient suffered from end-stage renal disease and was taking sodium polystyrene sulfonate (25 g/day) for hyperkalemia and benidipine (4 mg/day) and doxazosin mesylate (4 mg/day) for hypertension. He had undergone an operation for cervical disc herniation three months earlier. Due to painful myofascial spasm in face and neck muscles, the patient had taken TCC 8 mg capsules twice a day for four days and he had a sudden generalized tonic-clonic seizures (no previous history of epileptic seizures and cerebrovascular disease). Systemic and neurological examination (EEG, brain CT, MRI) was normal. The TCC was discontinued and epileptic seizure was treated with sodium valproate- this therapy was continued for three months, and the patient had no recurrence of epileptic seizures during the following year [4]. Another case described by Giavina-Bianchi et al., reports a sudden epileptic seizure connected with the intake of thiocolchicoside for muscle contracture and pain. The patient developed partial motor seizures of the right upper limb and face with speech arrest. He had three episodes of acute symptomatic seizures during 12 hours which occurred after taking thiocolchicoside (4 mg twice

a day, in a total dose of 20 mg) for 3 days- seizures started 6 hours after the final dose. The intake of TCC along with the presence of cerebral microhemorrhages related to cerebral amyloid angiopathy were apparently the cause of the seizures [10]. The central nervous system pathologies notably increase the risk of epileptic seizures in patients treated with thiocolchicoside. Thiocolchicoside convulsant potential apparently involves the vast effect of drug antagonism at a subset of GABAA receptors in comparison with its inhibitory effect of allosteric activation of GlyRs. Another research proved that thiocolchicoside epileptogenic activity might be a result of inhibition of the function of inhibitory receptors in the central nervous system [10,11].

Visual hallucinations. There is one report presenting a case of visual hallucinations resulting from the therapy with thiocolchicoside. The 75-year-old male was given a combination of acetaminophen 500 mg and thiocolchicoside 2 mg 3 times daily for the treatment of neck pain. The first night after completing 2 administrations of the drugs, the patient had started experiencing hallucinations (he reported unusual images in his left visual field for 3 days). The patient had no other symptoms, such as headaches, confusion, fever, hyperthermia or lower consciousness. Moreover, he had no similar symptoms previously. He did have diminished visual acuity (he sees 0.1 in the right eye and 0.2 in the left eye) but the examination at the ophthalmology department indicated retinopathy deterioration. He was recommended to discontinue the medications. The patient underwent examinations- the bloodwork showed no anomalies, CT revealed only moderate cortico-subcortical atrophy with no acute changes and no suggestion of recent functional decline. The observations made by the psychiatrist did not show any abnormalities. However, the hallucinations continued 4 days after withdrawal of thiocolchicoside. For that reason, the patient was treated with oxazepam 15 mg 3 times daily and melperone 12.5 mg at bedtime but due to excessive sedation caused by 2 administrations of oxazepam, he did not proceed with the treatment plan. Nevertheless, the hallucinations had stopped. The patient underwent EEG, which showed no epileptogenic activity but slower basal rhythm due to an intermittent and diffuse slow activity in both temporal lobes was reported. This phenomenon may be explained by the hypothesis, that people with visual damage resulting from the impairment of the visual pathway, may be prone to develop a state of cortical hyperexcitability,

what applies mainly to the visual cortex- this state is considered to disinhibit and incite visual regions, thereby leading to the occurrence of hallucinations. Regarding this particular case of the patient with visual impairment and an already hyperexcitable cortex, thiocolchicoside, acting as an antagonist of GABA receptors (whereas GABA is the primary inhibitory neurotransmitter in the brain) might have triggered the occurrence of visual hallucinations. This is supported by the fact, that benzodiazepines administered to the patient helped to resolve the hallucinations [12].

Hypersensitivity. Thiocolchicoside can cause an immediate hypersensitivity reactions, such as anaphylactic reactions, urticaria, and angioedema (after intramuscular injection) but these are rather rare cases. The literature describes few cases of Nicolau syndrome (*Embolia cutis medicamentosa*) after administration of thiocolchicoside via injection [13]. In the reports, there are also cases of delayed hypersensitivity reactions, such as contact dermatitis, and photosensitivity reactions subsequent to TCC injection [14,15]. Amaral et al. reported two cases of anaphylactic reactions after intramuscular injection with thiocolchicoside and diclofenac- a 56-year-old woman who reported palmar and plantar erythema, generalized pruritus, wheezing, dyspnea and abdominal cramps (grade 3 anaphylaxis—Mueller) 5 minutes after intramuscular (IM) and the second case- a 52-year-old man who reported hypotension (systolic blood pressure < 90 mm Hg), dizziness and malaise (grade 4 anaphylaxis—Mueller) 40 minutes after IM administration [5]. Mancuso described a case of a 27-year-old non-atopic woman who developed an itching eruption (dermatitis had first started on the right thigh and lesions mainly affected this area) immediately after the first application of a cream containing 0.25% TCC for sciatica pain relief. Skin test showed, that TCC can induce an immediate reaction (in case of a damaged epidermal barrier) when applied epicutaneously. Moreover, it can also cause a delayed-type reaction, which is not restrained by skin integrity [9]. An important fact is that TCC is frequently prescribed together with nonsteroidal anti-inflammatory drugs, which increases the likelihood of drug hypersensitivity [5].

Liver injury. Efe et al. reported a rare case of liver injury induced by thiocolchicoside. A 58-year-old man with abdominal discomfort, nausea and yellowish discoloration of the sclera was admitted to the emer-

gency clinic. Complete blood count results were typical, but hepatic and cholestatic enzyme levels were elevated. Except for thiocolchicoside, the patient was taking no other drugs. He was not consuming alcohol at the time. After discontinuation of thiocolchicoside, the levels of hepatic and cholestatic enzyme returned to normal and resolution of the hepatotoxicity was observed [16].

Reproduction. Despite many years of use, data regarding thiocolchicoside use in pregnancy is deficient. According to the European Medicines Agency (EMA) 2014 report this drug application by mouth or the injection should be restricted in the EU. The report suggested that, after oral administration of the therapeutic dose of TCC, the levels of its metabolite M2 (SL59.0955) may reach the threshold for the occurrence of aneuploidy, which is a risk factor for reduced fertility, fetal development disorders, and cancer. Thus, the use of TCC was contraindicated in children, and women who are pregnant, lactating and even in those who are in reproductive age and not using contraception [17].

Conclusion

Thiocolchicoside is used as an adjuvant treatment of painful muscle contractures in acute spinal pathology in adults and adolescents. The therapy with this drug may result in the occurrence of side effects such as

epileptic seizures, so precautions should be taken in case of predisposed patients, and the drug should be avoided in patients with brain diseases or blood-brain barrier disruption. There is also need for caution with prescribing thiocolchicoside in visually impaired individuals as it may cause visual hallucinations. TCC may also cause hypersensitivity reactions, and as it is frequently prescribed concomitantly with NSAIDs (a common cause of drug hypersensitivity on its own), the probability of hypersensitivity reactions is even higher. The occurrence of such adverse reactions highlights the significance of information all the coadministered drugs and medical history of diseases in patients before starting the treatment with thiocolchicoside.

Conflict of interest

None

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