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Original article

Thiocolchicoside: A review

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Abstract

Thiocolchicoside is a commonly used muscle relaxant in the treatment of acute painful muscle spasms. It exhibits a selective affinity for the inhibitory gamma-aminobutyric acid and glycinergic receptors, although, the exact mechanism for muscle relaxant property is not known. It has a proconvulsant action and hence should be avoided in patients predisposed to seizures. The recent drug warning from the European medicines agency regarding potential for aneuploidy limits the long term use of thiocolchicoside which was until now considered relatively safe. Aneuploidy is a common chromosome abnormality in humans, and is the leading genetic cause of miscarriage, congenital birth defects and reduced fertility in men. The drug is contraindicated in children less than 16 years of age, during pregnancy, breast feeding and patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed.

Keywords: Thiocolchicoside, muscle spasm, seizures, aneuploidy

Introduction

Thiocolchicoside, is a natural derivative of colchicine and a semisynthetic derivative of the naturally occurring colchicoside extracted from the seeds of Gloriosa superba (Liliaceae). This medicinal plant has been used for a long time as a traditional medicinal herb to cure various diseases in Africa and Southeast Asia. The tuberous roots of Gloriosa superba are commonly used to cure snakebites, skin diseases and ulcers, or to treat inflammation. Its seeds are used for relieving rheumatic and muscle pains [1]. It is used clinically as a centrally acting muscle relaxant. In addition, it also has anti-inflammatory and analgesic action [2]. While the compound has been in use since many years in the european countries, the first formulation containing thiocolchicoside was approved in India in the year 2008 [3]. Being less sedating than other centrally acting muscle relaxants, thiocolchicoside is commonly used in the treatment of symptomatic spasms and contractures in muscular, rheumatic and neurologic disorders

[4,5]. The recent drug warning from the Euuropean medicines agency regarding potential for aneuploidy limits the long term use of thiocolchicoside which was until now considered relatively safe [6]. The present review describes the pharmacology of thiocolchicoside based on available literature till date.

Mechanism of action

Thiocolchicoside exhibits a selective affinity for the inhibitory gamma-aminobutyric acid and glycinergic receptors. It has an agonistic action at the spinal-strychnine-sensitive receptors that could mediate its myorelaxant effect [7]. However, experimental and clinical evidence strongly suggest a proconvulsant action for thiocolchicoside [7, 8]. Interaction with glycine receptors does not explain the convulsant action of the molecule. It has been suggested that thiocolchicoside might preferentially interact with a cortical subtype of the gamma-aminobutyric acid type A ($GABA_A$) receptor that expresses low-affinity binding sites for GABA. The low-affinity recognition site seems to be an antagonist-binding site. This explains the proconvulsant effect of thiocolchicoside. This is in contrast to earlier studies that suggested a GABA mimetic effect which would explain its muscle relaxant property. $GABA_B$ receptors are largely unaffected by thiocolchicoside and hence do not contribute to its muscle relaxation action [7, 8]. Hence, the exact mechanism for muscle relaxation is yet to be known, although from available evidence, inhibition of glycine receptors is a possible mechanism.

Therapeutic Uses

Centrally acting muscle relaxants have been used in the treatment of painful muscle spasm associated with local tissue trauma or muscle strains, neurological disorders such as multiple sclerosis, cerebral palsy and stroke [9]. Thiocolchicoside is indicated for the symptomatic treatment of painful muscle spasms. However, with the recent evidence of development of aneuploidy, the European Medicines Agency's Committee on Human Medicinal Products has recommended that the authorized uses for thiocolchicoside containing medicines for use by mouth or injection should be restricted [6]. Thiocolchicoside and other formulations containing the drug are now recommended only as an add-on treatment for painful muscle contractures (permanent tightening of the muscle tissue) resulting from spinal conditions in adults and adolescents 16 years of age or older. In addition, the dose of thiocolchicoside by mouth or injection should be restricted.

Oral, parenteral and topical formulations of thiocolchicoside are available in India. The maximum recommended oral dose is 8 mg every 12 hours for no more than 7 consecutive days. The maximum intramuscular dose should be 4 mg every 12 hours, for up to 5 days [6]. These safety restrictions are not

applicable for the topical formulation as their application does not produce substantial levels of the metabolite responsible for aneuploidy [6].

The efficacy of thiocolchicoside in comparison to tizanidine has been evaluated in a randomized trial of 60 Indian patients aged between 18 and 65 years with clinical diagnosis of muscle spasm associated with low back pain [10]. Visual analogue scale (VAS) for pain at rest and VAS for tiredness, drowsiness, dizziness and alertness was used as the self-rated primary efficacy and safety variable. Pain was also assessed by mobility assessment, muscle spasm assessment and analgesic consumption. While both the groups showed sustained symptom relief, thiocolchicoside group showed significantly better scores for the seven days treatment duration. Two multicenter, randomized, placebo controlled studies have evaluated and confirmed the efficacy and safety of thiocolchicoside [11, 12]. Thiocolchicoside has also been evaluated in the treatment of myofascial pain syndrome. The ointment form has been shown to be a good alternative, particularly in patients who cannot receive injections [13]. Myofascial pain syndrome is a disorder characterized by hypersensitive sites called trigger points at one or more muscles and/or connective tissue, leading to pain, muscle spasm, sensitivity, rigor, limitation of movement, weakness, and rarely, autonomic dysfunction. Thiocolchicoside, along with other muscle relaxants, has also been evaluated in a pilot study as an adjuvant therapy in the routine protocol of treatment of oral submucosal fibrosis [14]. It has been shown to improve the muscle spasm and inflammation which also inadvertently contribute to the restricted mouth opening. A possible novel use of thiocolchicoside is in the treatment of bone loss. This is based on the data which showed that thiocolchicoside suppressed osteoclastogenesis induced by receptor activator of nuclear factor kappa-B ligand, breast cancer and multiple myeloma cells through inhibition of inflammatory pathways [15]. However, the results of all these studies have to be interpreted in the light of current knowledge of possible safety issue, particularly with long term use. Although currently there are no specific recommendations from the Indian drug regulatory body, the accumulated evidence, absence of adequate pharmacovigilance data and the relatively short duration of the drug in the market necessitates cautious use of the drug as per the European recommendations.

Adverse effects

The following undesirable effects have been described in the product literature [16, 17]: anaphylactic reactions, such as pruritus, urticaria, angioneurotic oedema; anaphylactic shock following intramuscular injection, somnolence, vasovagal syncope, usually occurring in the minutes following the intramuscular injection; diarrhoea, gastralgia, nausea, vomiting and allergic skin reaction. Most of the above reactions

are uncommon or rare. In a multicenter, randomized, comparative clinical trial thiocolchicoside was associated with more adverse events as compared to tolperisone, another centrally acting muscle relaxant with less sedative property [18]. The adverse events included loose motion, giddiness, nausea, skin rash. All the adverse events were of mild intensity and resolved without any intervention. Although rare, thiocolchicoside may cause hepatotoxicity [5].

Seizures have been reported in association with use of thiocolchicoside [8]. The experimental evidence of drug antagonistic effect at the $GABA_A$ receptor sites may explain these clinical findings. Hence, thiocolchicoside can precipitate seizures in predisposed patients and should be avoided in patients with lower seizure thresholds or blood–brain barrier disruption [8].

Development of localised skin atrophy following intramuscular injections of thiocolchicoside has been reported [19]. Also, Embolia cutis medicamentosa or Nicolau syndrome has been reported following thiocolchicoside injection [20]. Nicolau syndrome consists of immediate excruciating pain, early pallor, erythema, oedema at the site of intramuscular injection of drugs, followed by cutaneous, subcutaneous and even muscular aseptic necrosis in a livedoid pattern.

The effect of thiocolchicoside on psychomotor performance has been evaluated in patients with acute low back pain in comparison to tizanidine. Thiocolchicoside was found to be atleast as effective as tizanidine while devoid of any sedative effect [4]. The psychomotor performances were assessed by a VAS of tiredness, drowsiness, dizziness, alertness and by psychometric tests.

Recent safety alert: The recent safety alert follows experimental evidence of aneuploidy that could be caused by a metabolite of thiocolchicoside. Aneuploidy is a chromosomal abnormality wherein the individual organism has a chromosome number more or less than the wild type. It is a common chromosome abnormality in humans, and is the leading genetic cause of miscarriage, congenital birth defects and reduced fertility in men [21]. Aneuploidy is a remarkably common characteristic of solid tumors and haematopoeitic cancers and hence has been proposed to initiate tumorigenesis [22]. M2 or SL59.0955, a metabolite of thiocolchicoside, has the potential to damage dividing cells and cause aneuploidy. M2 is formed in significant amounts in the body as the aglycone derivative obtained after de-glycosylation of thiocolchicoside. The major circulating metabolite is 3-O-glucuronidated aglycone (M1 or SL18.0740) obtained after glucuronide conjugation of M2 [23]. From a pharmacokinetic aspect, after oral administration, no thiocolchicoside is detected in plasma. This is because of the intestinal metabolism of thiocolchicoside to the aglycon 3-demethylthiocolchicine , M2 metabolite, explaining the lack of circulating unchanged thiocolchicoside by this route of administration. The glucuronide conjugate

of M2, the M1metabolite, has equipotent pharmacological activity to thiocolchicoside and thus supports the pharmacological activity after oral administration of thiocolchicoside [24]. Following oral administration, M1 metabolite is eliminated with an apparent $t_{1/2}$ ranging from 3.2 to 7 hours and the M2 metabolite has a $t_{1/2}$ averaging 0.8 hours [24]. The Committee on Human Medicinal Products concluded that aneuploidy could occur with M2 at levels not much greater than those seen after recommended doses of thiocolchicoside taken by mouth. Therefore, a restriction has been imposed on the maximum dose and number of days of treatment when given by mouth or injection to ensure safe use of the drug [6]. The drug is contraindicated during pregnancy, breast feeding and patients should be carefully informed about the potential risk of a possible pregnancy and about effective contraception measures to be followed. The drug is also contraindicated in children less than 16 years of age [24].

Conclusion

Thiocolchicoside, a centrally acting muscle relaxant, is commonly used for treating acute painful muscle spasms. While its mechanism of action is not completely understood, the relatively lesser side effects and absence of sedation has made it an attractive treatment option. However, with the recent concern of possibility of development of chromosomal abnormalities at therapeutic doses of the drug, a more restricted use of the drug is necessary.

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