CASE REPORT

Harmful Use of Veterinary Drugs: Blindness Following Closantel Poisoning in a 5-Year-Old Girl

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Abstract

Background: Closantel is a veterinary drug used as anthelmintic for ruminants while it is contraindicated for humans. This report describes a rare case of blindness, increased liver enzymes and coagulopathy following closantel poisoning.
Case report: A 5-year-old girl was presented with acute blindness following closantel poisoning. She was given mistakenly a dose of 500 mg/day (25mg/kg/day) for 8 days. Clinical examination revealed a well-appearing child with bilateral mydriasis, loss of pupillary light reflex and absence of blinking to threat. Fundoscopic exam revealed bilateral pre-atrophic papilledema. Electroretinogram showed a highly significant decrease in retinal activity. Laboratory examinations revealed 52% increase in prothrombin time, prolongation of activated partial thromboplastin time to 1.3 times the normal and rise of aspartate aminotransferase to 120 IU/L. In addition, creatine kinase peaked at 904 IU/L. Moreover, normocytic normochromic anemia with hemoglobin at 10.7 mg/L and leukocytosis with lymphocytic predominance was noted. The patient received glucocorticoids, vitamin B12 and vitamin K and was discharged after correction of blood and coagulation parameters and normalization of liver enzymes. Partial recovery in visual acuity was found two months after ingestion of the last dose.
Discussion: Closantel can cause significant spongiform change (intra-myelin vacuolation) in the white matter of the cerebrum and the cerebellum. It can also induce optic nerve damage as a result of Wallerian degeneration, fibrosis and atrophy. On the retina, closantel leads to papilledema, necrosis of the outer layers, and retinal detachment. It can also cause fatty change and hydropic degeneration in the liver and hepatocellular degeneration.
Conclusion: Closantel is a toxic drug for humans causing blindness, hematologic and hepatic disorders. Public awareness should be raised regarding the risks of use of unapproved drugs for human.

Keywords: Acute Liver Failure; Blindness; Closantel; Poisoning; Salicylanilides

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INTRODUCTION

The halogenated salicylanilides are a large class of medications developed mainly for their anti-parasitic effects for animals (1). Closantel, which is the most well-known drug in the class, is widely used for the control of *Haemonchus spp*. and *Fasciola spp*. infestations in sheep and cattle, and *Oestrus ovis* in sheep and goat in many parts of the world (1,2). It is contraindicated to be used for humans and in high doses for milk producing animals (3,4). In this report, a rare case of blindness, acute increase in hepatic enzymes and coagulopathy following closantel poisoning is described.

CASE REPORT

A 5-year-old girl, living in rural area, was admitted to our department with acute blindness approximately four days after ingestion of closantel. This veterinary drug was given mistakenly by her mother. She had ingested closantel with the dose of 500 mg/day (25 mg/kg/day) for 8 days. Clinical examination at the time of admission showed a well-appearing child. Eye examination yielded bilateral mydriasis with loss of pupillary light reflex and absence of blinking to threat. Fundoscopic exam revealed bilateral pre-atrophic papilledema.

The electroretinogram showed a highly significant decrease in retinal activity. Visual evoked potential testing was also performed and showed delayed latency and decreasing amplitude in both eyes. Laboratory examinations revealed 52% increase in prothrombin time, prolongation of activated partial thromboplastin time to 1.3 times the normal and rise of aspartate aminotransferase to 120 IU/L. In addition, creatine kinase peaked at 904 IU/L. We also noted normocytic normochromic anemia with hemoglobin at 10.7 mg/L and leukocytosis with lymphocytic predominance.

The patient received glucocorticoids, vitamin B12 and vitamin K and was discharged after correction of blood and coagulation parameters and normalization of liver enzymes. The patient was advised for visual re-evaluation and on the follow-up visit, partial recovery of visual acuity was found two months after last dose of closantel. The patient was

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referred to a pedopsychiatric consultation and was advised to a school for visually impaired children.

DISCUSSION

Closantel is widely used against a large number of veterinary parasitic diseases, especially for the prevention and treatment of blood-feeding helminthes such as *Fasciolla hepatica* and *Haemonchus contortus* infestation in sheep and cattle (1,2). In this case report, a little girl with blindness, coagulopathy, increased hepatic enzymes, leucocytosis and anemia due to closantel toxicity was presented.

Closantel mechanism of action is believed to be based on interference with energy metabolism of the parasite by uncoupling oxidative phosphorylation (5,6). However, other potential mechanisms such as disturbing glycolysis and so drop in ATP levels may also contribute to the overall drug efficacy (7,8). The recommended oral dose of closantel for sheep is 7.5-10 mg/kg and for cattle is 10-15 mg/kg. For humans acceptable daily intake of closantel is 0-0.03 mg/kg, while recommended maximum residue limit of closantel on food products in edible tissues of sheep is 1.5 mg/kg, and in bovine tissues is 0.5 mg/kg for muscles, 2 mg/kg for kidneys and 1 mg/kg for liver (3). Our patient had taken 25 mg/kg/day of closantel which was about 800 times the permissible daily dose of closantel for humans.

Closantel is well absorbed after oral or parenteral administration and its oral bioavailability is 50% in sheep and cattle (8). Peak plasma concentrations of this drug are reached within 24 to 48 hours. It is highly albumin bound and is metabolized only to a very small extent. It is mainly (80%) excreted in the bile and feces in unchanged form. Its elimination half-life is 2 to 3 weeks in sheep and 1 to 3 weeks in cattle (6,8). These unique pharmacokinetic characteristics of closantel including rapid parenteral absorption and long half-life appear to play important roles in its efficacy and toxicity.

Several cases of toxicity and mortality due to closantel ingestion in animals especially sheep and goats have been reported, so far (9-15). The toxic dose is estimated to be 4 times the recommended dose in sheep and 7 times the recommended dose in cattle. Clinical features of poisoning with this substance include anorexia, depression, loss of proprioception, incoordination, asthenia and decreased or absent skin sensitivity (6,9-15). The ocular complications of closantel poisoning include mydriasis, loss of pupillary reflexes and bilateral blindness due to optic neuropathy, fibrosis of the optic nerve and retinal degeneration (10-16).

The histopathological changes induced by closantel poisoning are mainly localized in the central nervous system. They are represented by a significant spongiform change (intra-myelin vacuolation) in the white matter of the cerebrum and the cerebellum (11). Optic nerve damage is due to the development of edema and vacuolization of the myelin sheaths followed by compression of the nerve within osseous part of nerve canal resulting in Wallerian degeneration, fibrosis and atrophy (11-14). On the retina, poisoning with closantel leads to papilledema, necrosis of the outer layers in general and the photoreceptive cells in particular, and retinal detachment (11-15). There is still no specific treatment or antidote against closantel poisoning.

Low dose closantel has been claimed to be well-tolerated in humans (3). Closantel poisoning in humans can occur either by accident, misuse, medication error or as a result of consumption of milk from cows or sheep treated with high dose closantel. In Lithuania, blindness occurred in 11 women who were mistakenly treated with closantel for gynecological problems as a result of poorly labeled donated drugs (16). In Germany also, complete blindness in a middle aged man due to ingestion of closantel was reported which was relatively responsive to symptomatic treatments and plasmapheresis as he regained 60% of his vision (17). In Morocco, the packaging of oral form of closantel is diverse: 4.5 L container, 2.25 L container, 900 mL bottle and 225 mL bottle. Morrocan poison control and pharmacovigilance center has reported three cases of blindness related to closantel poisoning in humans and issued a warning about the risk of blindness associated with the use of this veterinary drug in August 2008 (18). Blindness was partially reversible after two months in one of the cases while in the other two the outcome could not be evaluated as they were lost to follow-up (18). Likewise, in our patient, partial recovery of visual acuity was observed two months after ingestion of the drug. It seems that improvement in vision is likely to be related to the dose of closantel ingested per body weight as the eyesight recovery was greater in animals which were exposed to lower doses of the drug (10-13,15).

In the present report, beside blindness that was the main problem of our patient; increased liver enzyme was also observed. The impact of closantel on hepatic function has not been reported in literature, so far. Nevertheless, it seems that the drug can cause microscopic damages on hepatic tissue as Sakhaee and Derakhshanfar found fatty change and hydropic degeneration in the liver and hepatocellular degeneration caused by closantel toxicity in a goat (19). Subsequent to liver damage, coagulopathy is an expected complication similar to what occurred in our patient.

LIMITATIONS

The value of our findings can be limited by the fact that we could not provide an objective evidence of drug exposure (drug levels). The electroretionogram profile of the patient was not available to be presented in this paper.

CONCLUSION

Closantel is a toxic drug for humans causing blindness, hematologic and hepatic disorders. Public awareness should be raised about the risks of use of drugs unapproved for human use.

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