Commentary: Closantel – A lesser-known evil

Closantel is an antiparasitic agent routinely used in veterinary practice against some parasites of livestock. It is not used against agricultural and household pests. Recently, it has been discovered that closantel also acts against Onchocerca volvulus, a filarial nematode causing river blindness in humans.[1] Closantel belongs to the chemical class of the salicylanilides, which acts as an uncoupler of oxidative phosphorylation in the cell mitochondria and disturbs ATP production. This impairs the parasite's motility and probably other processes as well. Closantel also disturbs the liquid and ion transport mechanisms in the parasite's membranes.

Closantel is a narrow-spectrum anti-helminthic effective against a few roundworms (mainly blood-sucking species), against flukes (e.g., Fasciola hepatica) and also against certain myiasis. It is ineffective against tapeworms or most external parasites. It is not used in swine, poultry, horses, or pets. It is used moderately in ruminants both as an injectable or a drench, often mixed with other anti-helminthics.

After oral administration, closantel is readily absorbed into the bloodstream. Four days after treatment up to 60% of the injected and 30% of the drenched closantel is absorbed to blood. In the blood, >99% of the unchanged closantel binds strongly to plasma albumins. Peak plasma levels are reached between 10 and 48 h after administration, both after oral or intramuscular administration. Half-life in plasma is 3 to 4 weeks. Owing to the strong binding to plasma albumins, closantel residues in the tissues are rather low. Closantel is poorly metabolized. Approximately, 80% of the administered dose is excreted through the feces, of which >98% in the parent molecule form. Excretion 48 h after oral administration reaches ~45% of the administered dose, but only ~10% after intramuscular injection. Excretion half-life in the organism is 2 to 3 weeks. In dairy cows, about 1% of the administered dose is excreted unchanged through the milk.

The routinely used safe-dose for the anti-helminthic action of closantel varies from 3 to 10 mg/kg depending upon the type of parasite and the animal affected. The established lethal dose limit for oral closantel in rats is 342 mg/kg, and for subcutaneous administration is 67 mg/kg of the active ingredient. Closantel intoxication has been reported in animals such as sheep, cattle, goats, and dogs.[2-5] Closantel intoxication often presents with neurological and ocular features. The central nervous system, retina, and optic nerve are commonly affected. Histopathological changes noted are spongiosis in the brain white matter and spinal cord. These changes are symmetrical and affect periventricular white matter, optic radiation, brain stem, thalamic nuclei, and cerebellar peduncles. The induced histopathological changes in optic nerve following closantel overdosage include significant spongiform change, edema, and myelin vacuolization resulting in optic disc atrophy.[6] This results in edema in the intracanalicular portion of the optic nerve, which being in the osseous part gets compressed, resulting loss of myelinated axons.[6] In retina, there is destruction and apoptosis of the outer retinal layers, especially photoreceptors.

The most frequent symptoms following closantel intoxication include loss of appetite, ataxia or uncoordinated movements, weakness, visual disturbances, and blindness. Other symptoms reported in sheep include depression, prostration, colic, reduced skin sensitivity, opisthotonos, nystagmus, mydriasis, loss of pupillary reflex, and blindness. Mortalities can also happen. The use of closantel in humans and milk-producing animals is strongly avoided. However, accidental ingestion of closantel leading to overdose and adverse effects in humans has been reported in literature.[7-10] In humans, ocular symptoms following closantel overdosage range from sudden onset blurring of vision to total blindness. The onset of symptoms has been reported to occur from as early as 3 days to 22 years following closantel intake.[9,10] Depending upon the severity of damage, ocular features show optic nerve involvement ranging from blurring of disc margins and disc edema in acute stage to optic atrophy in the late stages. There is outer retinal layer thinning with spicule like hyper-pigmentation owing to the involvement of photoreceptor and retinal pigment epithelium layer. Destruction in outer retinal layers and visual pathway leads to changes in electroretinography and visual evoked potential (VEP) test. On electro-retinography, there is a reduction in both a- and b-wave amplitudes, whereas VEP shows a reduction in amplitude and delay in latency. The effects of closantel intoxication are often permanent and irreversible. There is no specific antidote for closantel. Treatment consists of supportive and symptomatic measures. Partial visual recovery with plasma exchange has

been reported in a man who ingested closantel because of helminthiasis fearing.[8]

To conclude, accidental closantel intake can lead to blinding visual symptoms due to outer retinal degeneration and optic atrophy.

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