A CASE OF CLOSANTEL TOXICITY IN CROSSBRED LAMBS

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INTRODUCTION

The differential diagnosis of blindness or apparent blindness in sheep on the Central Tablelands of NSW includes polioencephalomalacia, vitamin A deficiency, infectious keratoconjunctivitis, focal symmetrical encephalomalacia and intoxication by Stypandra glauca (nodding blue lily or blind grass) or closantel (and rafoxanide). Ewes with pregnancy toxaemia can also appear to be blind.

Anecdotally, closantel intoxication causing a low prevalence of death and blindness is occasionally encountered by sheep producers on the central tablelands of New South Wales and elsewhere. Several cases of closantel intoxication have been seen at the State Veterinary Diagnostic Laboratory at EMAI Menangle in recent years.

HISTORY

In mid-March 2015 approximately 400 September 2014 drop Dorset cross Merino lambs from a property near Hill End on the central tablelands of NSW were shorn and drenched with 10 ml of a commercial closantel and abamectin mix (Genesis Xtra, Ancare containing 1g/L abamectin and 50g/L closantel, recommended dose 1 ml/5kg bodyweight, equivalent to 10mg closantel/kg). Two weeks later, several lambs were noticed blind, 2-3 of which died.

CLINICAL FINDINGS

Two affected lambs were examined. Both weighed approximately 20 kg. They were observed bumping into objects and had fixed dilated pupils. Menace and pupillary light reflexes were absent, but the palpebral reflex was present. The corneal reflex could not be determined accurately.
Figure 1. Two affected lambs. Both appear to be blind with marked pupillary dilation. Photograph: Bruce Watt.

Figure 2. Eye of blind lamb showing pupillary dilation (left) and eye of normal lamb (right) showing normal pupils (but some entropion and epiphora). Photographs: Bruce Watt

NECROPSY FINDINGS
One young affected Dorset Merino cross lamb was necropsied. The lamb was in fat score 1.5. On necropsy the liver appeared normal except for several small indentations on the diaphragmatic surface, suggestive of previous larval fluke migration.

Paddock Inspection

The paddock that the lambs had grazed was inspected for other causes on blindness (and in particular for the locally endemic species *Stypandra glauca*). The pasture had been heavily grazed with less than 500 kg/ha dry matter of pasture but had abundant Sifton bush (*Cassinia arcuata*). No *Stypandra glauca* was seen.

![Stypandra glauca growing beside the road within 10 km of the affected property. Photograph: Bruce Watt.](image-url)
Figure 4. *Stypandra glauca* in flower. Photograph: Bruce Watt

CLINICAL PATHOLOGY

Liver enzyme and protein levels were within normal limits. The faecal egg count was negative.

HISTOPATHOLOGY

Standard Haematoxylin & Eosin-stained sections were examined.

In the eye, there was extensive loss of retinal layers, particularly the photoreceptor and outer nuclear layers. In some areas all layers were affected, while in other areas, layers were maintained. Pigmented cells had migrated into the depleted retinal layers (*Figure* 8, 9).

The intra-orbital part of optic nerve had mild to moderate vacuolation, this being most prominent in the peripheral parts of the nerve. Some vacuoles contained degenerate phagocytic cells or axonal debris (Wallerian degeneration) (*Figure* 9, 10).

The optic tract in the cranial brainstem showed diffuse hypercellularity (astrocytosis), with moderate diffuse vacuolation. Some vacuoles contained axonal debris or phagocytic cells (Wallerian degeneration) (*Figure* 11, 12).

There were no significant findings in midbrain, cerebrum, liver or kidney.
Figure 5. Eye from a 2 day old lamb with normal retinal layers (left, detaching from underlying choroid and sclera which is a common artefact) and optic nerve (right) entering (20x). Photograph: Erika Bunker

Figure 6. Closer view of normal retina layers with inner layer of ganglions and nerve fibres, inner plexiform layer, inner nuclear layer, outer plexiform layer, outer nuclear layer, layer of rods and cones, pigment epithelium, vascular layer (choroid) with melanocytes, sclera (200x). Photograph: Erika Bunker
Figure 7. Retina (artefactual detachment from underlying layers) with extensive loss of outer layers in centre of image. To the left and right of centre, retinal layers are better maintained (20x). Photograph: Erika Bunker

Figure 8. Closer view of retina, with loss of layers of rods and cones and outer nuclear layer, part of inner nuclear layer and nerve cell layer still maintained, with severe infiltration by pigment cells migrating in from the underlying choroid (400x). Photograph: Erika Bunker
Figure 9. Affected peripheral part of the optic nerve has vacuoles with degenerate phagocytes (400x). Photograph: Erika Bunker

Figure 10. Less affected central part of the nerve (400x). Photograph: Erika Bunker
Figure 11. Vacuolated optic tract (right part of image) and normal cranial brainstem white matter (left part of image) (100x). Photograph: Erika Bunker

Figure 12. Closer view of optic tract showing Wallerian degeneration and astrocytosis (400x). Photograph: Erika Bunker
DISCUSSION

About two weeks before sampling, the lambs received about 2.5 times the recommended dose of closantel, a halogenated salicylanilide.

The lesions in the eye (retinal degeneration, atrophy and pigment cell infiltration) and optic nerve and tract (Wallerian degeneration and astrocytosis) are suggestive of subacute to chronic closantel intoxication. The early stage changes, myelinic oedema of optic nerve and tract and white matter of the brain, were not seen here. In the more chronic stage, lesions progress to fibrosis of the optic nerve and tract.

Optic neuropathy and retinopathy associated with halogenated salicylanilide intoxication has been reported in sheep and goats in Australia and worldwide (South Africa, South America, Europe).

Gill et al (1999) reported cases on several properties in Australia. The lesions seen in this case are consistent with those described in 1999 that were sampled more than 11 days after treatment. The intracanalicular part of the optic nerve was also examined in the 1999 cases, and the lesions there, which included focal necrosis, were more severe than in the intraorbital part, and were also grossly visible as narrowed segments.

Van der Lugt et al (2007) described progressive development of lesions. The early lesions of vacuolation of the brain white matter, optic tract and optic nerve represent myelinic oedema . While the pathogenesis of these initial lesions is not determined, subsequent degeneration of the optic nerve is secondary to compression of the nerve in the optic canal due to swelling caused by oedema. The retinopathy is not secondary to the optic neuropathy but is a separate toxic effect, and it is assumed that a common toxic mechanism is responsible for the initial lesions in brain, optic nerve and retina. The Merck Veterinary Manual suggests uncoupled phosphorylation as a mechanism. The severity of myelinic oedema decreases over time and is followed by degeneration, fibrosis and atrophy.

Several other cases of closantel intoxication have been seen at NSW DPI’s State Veterinary Diagnostic Laboratory at EMAI Menangle in recent years, including the subacute lesions of optic nerve and optic tract Wallerian degeneration. At least two cases had more acute lesions of brain white matter oedema, with an interesting distribution pattern of oedema affecting white matter parenchyma surrounding blood vessels. The transition from the early oedema to subsequent degeneration was nicely demonstrated in a subacute case which showed Wallerian degeneration in optic nerve and tract but which also had some remnant/ regressing mild oedema in the cranial brainstem white matter, again centered around blood vessels. Early lesions in the retina could sometimes be difficult to define in clinical cases submitted to the laboratory due to artefactual separation and damage to the retina particularly affecting the outer layers.
The time from treatment to onset of clinical signs can vary (Gill et al 1999), as can doses at which toxicity is reported. Crilly et al report toxicity at doses not exceeding 14.5 mg/kg which is less than 1.5 recommended dose. In another case submitted to SVDL Menangle, three times the recommended dose was given. According to Jubb, Kennedy (2016) the response appears to be inconsistent and unknown predisposing factors are possibly involved. Merck Vet Manual suggests adverse effects are most commonly seen in animals that are severely stressed, in poor condition, nutritionally or metabolically, or have severe parasitic infections.

Closantel is a valuable anthelmintic providing long-acting *Haemonchus* control and is also effective against *Fasciola hepatica*. It is critical that closantel is administered at the recommended dose rate, according to weight of the animal, especially if using newer products with a dose rate of 10mk/kg, as opposed to 7.5 mg/kg. As Gill et al (1999) warned, 'calculating dosage based on the heaviest animal in the group, ... may have increased the risk of closantel toxicosis in the lighter animals.'

Plant intoxications with *Stypandra glauca* in NSW and *Stypandra imbricata* in Western Australia, and *Helichrysum argyrosphaerum* in South Africa can cause similar lesions, with a similar sequence of histopathological changes (Jubb, Kennedy 2016; Gill et al, 1999).

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REFERENCES


