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Successful therapeutic management of acute oxyclozanide-levamisole toxicity in a jersey crossbred cow with multiple infections

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Abstract
A Jersey crossbred cow with a swollen udder and reduced feed intake for the past four days was presented to the Veterinary Clinical Complex, Veterinary College and Research Institute, Orathanadu. On physical examination, the animal had hyperthermia and swollen udder indicative of mastitis. Fecal examination revealed the presence of amphistome eggs. The animal was positive for both theileriosis and anaplasmosis on peripheral blood smear examination. The animal was treated for mastitis and haemoprotozoal infection with parenteral administration of antibiotics and advised the owner to give 100 mL of Oxyclozanide-Levamisole suspension for amphistomiasis. But the owner accidentally drenched 3 times the actual dose. The animal developed toxicity symptoms like salivation, diarrhea, tenesmus, tachypnea, arched back and colic pain which mimicked cholinergic symptoms. The animal was treated with Inj. Normal Saline, Inj. Atropine Sulphate, Inj. Chlorpheniramine maleate, Inj. Vitamin B complex, Inj. Pantoprazole, Inj. Flunixin meglumine. After administration of atropine, the cholinergic symptoms reduced but there were colic signs. On 2nd day, the animal had mild salivation, tenesmus, and mucoid diarrhea with mild dyspnea. The same treatment protocol was followed along with ascorbic acid, dicyclomine, activated charcoal and egg white. On the third day, the same treatment protocol was followed, and the animal showed an uneventful recovery from the effects of oxyclozanide-levamisole toxicity.

Keywords: Crossbred jersey cow, oxyclozanide-levamisole toxicity

1. Introduction
Helminths have seriously threatened farm productivity, affecting dietary intake, growth rate, carcass weight, milk yield, fertility, wool quality and other production values of animals (Charlier *et al.*, 2014; Rather *et al.*, 2020) [2, 11]. To overcome this challenge, anthelmintics are widely used in veterinary practices. Livestock producers largely depend on these anthelmintics due to their significant advancements in efficacy, safety, spectrum of activity and continued affordability (Waller, 2006) [18]. The reports of toxicity due to anthelmintics are occasional (Jadhav *et al.*, 2017) [6]. However, accidental administration or ingestion of an excess quantity of drugs is a common cause of poisoning in farm animals (Muntener *et al.*, 2010) [9]. Oxyclozanide and levamisole are routinely used in veterinary medicine to treat internal parasitism in animals, especially for amphistomiasis and nematodiasis. Improper dosing of these anthelmintics can lead to the development of resistance while overdosing leads to toxicity. The present report documents an instance of acute oxyclozanide-levamisole poisoning in a Jersey crossbred cow and its successful therapeutic management.

2. Case history and observations
A Jersey crossbred cow with a swollen udder and reduced feed intake over the past four days was presented to the Veterinary Clinical Complex, Veterinary College and Research Institute, Orathanadu. On clinical examination, the animal had its right hindquarters of the udder hard and swollen up to the level of the umbilicus. Fecal examination revealed the presence of amphistome eggs. As the animal had increased rectal temperature and pale conjunctival mucus membrane, a peripheral blood smear examination was done, and it was found to be positive for

both theileriosis and anaplasmosis. The complete blood count revealed that the animal had anemia (Hb: 6 mg/dL, PCV: 18.8%, RBC: 4 million cells/µL). The serum biochemistry results were as follows: Total bilirubin - 0.68 mg/dL, Glucose - 32 mg/dL, Total protein - 4.43 g/dL, Albumin - 2.69 g/dL, AST 77.5 U/L, Calcium - 9.1 mg/dL and Phosphorous - 3.21 mg/dL. Hence the animal had a concurrent infection of theileriosis, anaplasmosis, amphistomiasis and mastitis.

The animal was treated for mastitis and haemo-protozoan diseases initially with Inj. Normal Saline 500 mL IV, Inj. Dextrose Normal Saline 1000 mL IV, Inj. Oxytetracycline @ 10 mg/Kg IV, Inj. Enrofloxacin @ 5 mg/Kg IM, Inj. Sodium bicarbonate 50 mL IV, Inj. Meloxicam @ 0.5 mg/Kg IV and advised the owner to give Susp. Oxyclozanide 6% and Levamisole 3% 100 mL PO for amphistomiasis and supplemented with Bol. Serratiopeptidase, Powder Trisomast®, Gel. Maxxtol®.

The owner accidentally drenched about 300 mL of oxyclozanide-levamisole suspension which is three times the actual dose. On the same day, the animal was brought back to clinics with cholinergic symptoms like salivation, diarrhea, and colic pain. Dullness, tachypnea, severe straining during defecation, and arched-back posture were also observed during the examination. Based on circumstantial evidence and clinical signs the condition was diagnosed as acute oxyclozanide-levamisole toxicity.

3. Treatment

The animal was treated for oxyclozanide-levamisole toxicity symptomatically with Inj. Normal Saline 1000 mL IV, Inj. Atropine Sulphate @ 0.2 mg/Kg (12.5 mg slow IV, 37.5 mg SC). Inj. Pantoprazole @ 1.0 mg/Kg IV and Inj. Flunixin meglumine @ 1.1 mg/Kg IV, After the initial treatment, the cholinergic symptoms reduced because of atropine administration but there were persistent colic signs. After 4-6 hrs, the treatment was continued with Inj. Normal Saline 1000 mL IV, Inj. Atropine Sulphate @ 0.1 mg/Kg (6.25 mg slow IV, 18.5 mg SC), Inj. Chlorpheniramine maleate IM, Inj. Vitamin B-complex (Methylcobalamine, pyridoxine and nicotinamide) 15 mL IV and Inj. Vit. AD_3E 10 mL IM. On 2nd day, the animal had mild salivation, mucoid diarrhea with slight tenesmus, and mild dyspnea with normal rectal temperature, heart rate, and rhythm. The same treatment protocol was followed along with Inj. Ascorbic acid 15 mL IV, Inj. Dicyclomine hydrochloride 10 mL IV, Suspension activated charcoal 300 mg, and egg white 100 g orally and on the third day also the same treatment protocol was followed.

The clinical signs such as colic, anal straining, and arched back posture were partially subsided on the first day post-treatment and completely subsided on the second day while the feed and water intake and normal defecation processes were resumed on the third day. After three days of treatment, the animal regained its normal health condition and recovered totally from toxicity.

4. Case Discussion

In veterinary medicine, drugs are routinely administered to treat various disease conditions in farm animals. However, accidental overdose or unintended ingestion of these drugs frequently leads to poisoning. Reports of drug poisoning in farm animals are rare, but antibiotics, antiparasitics, and non-steroidal anti-inflammatory drugs are often the culprits. Anthelmintics, commonly used for routine deworming, are associated with very few cases of poisoning or toxicity in animals (Muntener *et al.*, 2010) [9]. Amphistomiasis or Paramphistomosis is a trematode infection commonly encountered in ruminants. Oxyclozanide is routinely used for deworming animals with amphistomiasis. Oxyclozanide is used in combination with levamisole for a broader spectrum of action (Sandhu, 2013) [13] and as an immunostimulant in concurrent infections like mastitis (Sarfaraz *et al.*, 2009) [15]. This combination is both pharmacologically and economically effective for farmers in managing most of the helminthic infestations in ruminants, thereby reducing production costs. However, these drugs have a narrow therapeutic index where improper dosage can lead to therapeutic failures and potentially fatal adverse drug reactions (Marais, 2003) [7].

Oxyclozanide is a potential oral flukicide that belongs to the category of salicylanilides. It has a narrow spectrum of action being effective only against some trematodes. It has a shorter half-life of 6.4 days. They are metabolized by glucuronide conjugation and excreted in bile (Riviere *et al.*, 2009) [12]. The mechanism of action is by uncoupling oxidative phosphorylation, interfering with mitochondrial reactions thus depleting ATP in the susceptible parasites and killing them. The dose of oxyclozanide in cattle and sheep is 10-15 mg/Kg, PO (Sandhu, 2013) [13]. Salicylanilides are relatively safe compounds, with safety margins of about 3 to 6 times the recommended dosage levels (Swan and Schroder, 1981) [16]. The toxicity is also due to the uncoupling oxidative phosphorylation characterized by the toxicity signs include inappetence, depression and frequent defecation with soft feces (McKellar, 1991; Garg, 2014) [8, 4]. Typical indicators of salicylanilide toxicity include blindness (not a constant sign in cattle), paresis and death. There may be increased body temperature and heart rate, hyperventilation and convulsions along with neutrophilia and lymphopenia. Focal necrosis in the lymphoid tissues and liver leads to increased SGOT and ALP (Swan, 1999) [16].

Levamisole is a broad-spectrum antinematodal drug that belongs to the category of synthetic imidazothiazole derivatives which also has an immunomodulator activity by stimulating T-cell differentiation. It is an autonomic ganglionic stimulant and stimulates both the sympathetic and the parasympathetic nervous systems of parasites (Sandhu, 2013) [13]. Ishikawa *et al.* (1982) [5] stated that levamisole acts as an immunotherapeutic agent for bovine sub-clinical mastitis by boosting immunoglobulin levels and enhancing the activity of macrophages and polymorphonuclear cells, key defensive cells in the mammary gland's immune system. In the present case, the animal was presented with mastitis along with other infections, so the animal was treated with levamisole too. It is not indicated for use in weak and debilitated animals, lactating ones, animals in breeding age and animals with renal or hepatic issues. Levamisole has inhibitory action on fumarate reductase and succinate oxidase enzymes which in turn inhibits the carbohydrate metabolism of the parasites. This paralyzes the worm and is expelled alive in the feces and the ova remains unaffected. (Rang *et al.*, 2011; Budde and McCluskey, 2023) [10, 1]. These effects are observed as actions similar to nicotine. The dose of levamisole in cattle and sheep is 7.5 mg/Kg, single dose, SC or PO. It has a half-life of about 4 hours and a narrow therapeutic index of 5 to 6 (Sandhu and Brar, 2009) [14]. The toxicity is due to the action of levamisole as acetylcholine receptor agonist, causing muscle contraction, ataxia and paralysis (Dar *et al.*, 2020; Rather *et al.*, 2020) [3, 11]. The signs of toxicity resemble those of OPC poisoning. The signs manifest due to the extended antiparasitic action which encompasses both muscarinic and nicotinic cholinergic signs

like salivation, urination, diarrhea, pupillary constriction, hyperaesthesia, clonic seizures, CNS depression, colic, dyspnea and respiratory paralysis leading to collapse of the animal. In some cases, cardiac arrhythmias are noticed. (Sandhu and Brar, 2009; Budde and McCluskey, 2023) [14, 1]. Severe anal straining with abdominal pain had been reported in Red Kandhari bullocks overdosed with oxyclozanide and levamisole (Jadhav *et al.*, 2017) [6]. In the present case also, several of these signs like salivation, pupillary constriction, diarrhea and colic pain, dullness, tachypnea, severe straining during defecation and arched back posture were noticed which were in concordance with the findings of Jadhav *et al.* (2017) [6].

There is no specific antidote for both oxyclozanide and levamisole toxicity. The management of the poisoning is supportive and symptomatic. Activated charcoal can be used within 2 hrs of ingestion for adsorption of excess drugs. GI decontamination can also be done with emetics, gastric lavage or cathartics. Atropine sulphate proved effective in mitigating the cholinergic signs. To inhibit the actions of levamisole, hexamethonium, a non-depolarizing ganglionic blocker that inhibits both sympathetic and parasympathetic activities can also be used. Intravenous fluid therapy is recommended. Adequate oxygenation is required in case of respiratory distress (Sandhu and Brar, 2009) [14]. In this case, the toxicity was effectively managed by administering atropine sulfate, which counteracted the cholinergic symptoms which was very much predominant in this animal. Additionally, using activated charcoal helped prevent further drug absorption, enabling the animal to recover more quickly from the toxicity.

5. Conclusion

Thus, the present study reports the toxicity of oxyclozanide-levamisole toxicity, and its successful clinical management was established. The oxyclozanide-levamisole suspension has been highly effective both in terms of action and cost, thus helping out the farmers in dealing with internal parasitism and increasing production. Given the fatal consequences and the absence of a specific antidote for this toxicity, the likelihood of economic losses is high. In conclusion, administering the correct dose of any deworming drug should always be guided by a veterinarian's advice to minimize the risk of adverse or toxic effects, particularly when the drug has a low safety margin. Prompt and emergency veterinary care, combined with continuous patient monitoring, played a crucial role in achieving a successful recovery from the toxic condition in this case.

6. References

1. Budde JA, McCluskey DM. Plumb's Veterinary Drug Handbook. Tenth edition, Wiley, United Kingdom. c2023. p.743-745
2. Charlier J, Van der Voort M, Kenyon F, Skuce P, Vercruysse J. Chasing helminths and their economic impact on farmed ruminants. Trends in Parasitology. 2014;30(7):361-367.
3. Dar PA, Ahanger SA, Mehrajudin M, Rather MA, Shah MM. Levamisole toxicity in Sheep: A case study. Anim Sci Quart. c2020. p. 36-37.
4. Garg SK. Veterinary Toxicology. First edition, CBS Publishers and Distributors, India. c2014. p. 205.
5. Ishikawa H, Shimizu T, Hirano H, Saito N, Nakano T. Protein Composition of Whey from Subclinical Mastitis and Effect of Treatment with Levamisole. Journal of Dairy Science. 1982;65(4):653-658.
6. Jadhav RK, Bhikane AU, Bhosale AA, Shaikh HA, Jadhav AS. Acute oxyclozanide-levamisole poisoning in red kandhari bullocks. Journal of Advanced Veterinary Research. 2017;7(1):16-17.
7. Marais JF. The formulation of different dosage forms with the anthelmintics: Levamisole, Niclosamide and Oxyclozanide (Doctoral dissertation, North-West University). c2003.
8. McKellar QA, Kinabo LD. The pharmacology of flukicidal drugs. British Veterinary Journal. 1991;147(4):306-321.
9. Muntener CR, Bruckner L, Sturer A, Althaus FR, Caduff-Janosa P. Vigilance for Veterinary Medicinal products: Declarations of adverse reactions in the year 2009 (in German). Schweizer Archiv Fur Tierheilkunde. 2010;152:575-583
10. Rang HP, Dale MM, Ritter JM, Flower RJ, Henderson Rang G, Dale's. Pharmacology. Seventh edition. United Kingdom: Elsevier Health Sciences UK. c2011.
11. Rather MA, Dar MA, Dar TA, Hameed A, Ahmad M, Munawar F, *et al*. Acute levamisole-fenbendazole (LEVOB) poisoning in a sheep flock. Animal Science Quarterly. 2020;1(1):31-33.
12. Riviere JE, Riviere JE, Papich MG. Veterinary Pharmacology and Therapeutics. Ninth edition. Wiley, United States; c2009. p. 1107
13. Sandhu HS. Essentials of Veterinary Pharmacology and Therapeutics. Second edition. Kalyani Publishers. India; c2013. p.1057.
14. Sandhu HS, Brar RS. Textbook of Veterinary Toxicology. Second edition. Kalyani Publishers. India. c2009, p.393.
15. Sarfaraz I, Yousaf A, Muhammad G, Abbas ZR, Zafar MA, Ahmad T, *et al*. Evaluation of tri-sodium citrate alone and in combination with Levamisole Hcl. in the treatment of sub-clinical mastitis in dairy buffaloes. Pak. J Zool. Sup. 2009;9:839-843.
16. Swan GE, Schröder J. A Safety trial with Rafoxanide in Sheep. Journal of South African Veterinary Association. 1981;2:123-125.
17. Swan GE. The Pharmacology of halogenated salicylanilides and their anthelmintic use in animals. Journal of the South African Veterinary Association. 1999;70(2):61-70.
18. Waller PJ. Sustainable nematode parasite control strategies for ruminant livestock by grazing management and biological control. Animal feed science and technology. 2006;126(3-4):277-289.

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