

THE TOXICITY OF BERENIL IN DONKEYS

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We presented a dissertation entitled "Berenil Toxicity" at a previous congress. The paper might as well have been called "The toxicity of Berenil in Dogs", for it was with that species that we were concerned at that time. Boyt and MacKenzie had however attempted to produce Berenil poisoning in cattle and rats with no success. A grade Africander cow was dosed with the drug at 7.5 mgs/kg weekly for 5 weeks and it showed no signs of ill health and lost no weight compared with a control group of similar cattle.

In similar manner a group of rats was dosed at 10 mgs/kg body weight weekly for six weeks and they did not lose weight compared with controls.

Berenil has been used in cattle of all ages and varying condition for more than 15 years and no accounts of toxicity have been recorded. In Rhodesia alone during the 1968-69 agricultural year, in the control of Trypanosomiasis, 47,577 doses were dispensed and not one report of toxicity was recorded. One report of an allergic (urticarial) reaction was mentioned some years earlier. Under certain circumstances however the administration of Berenil after isometamidium, up to 14 days later, may produce fatalities with gross fatty change in the liver. (Report of the Assistant Director Veterinary Services, (Tsetse and Trypanosomiasis Control) 1966-67). Little has been written of the use or side effects of Berenil in the equid group but the makers indicate that it may be used at doses of 7 mgs/kg in the treatment of nagana due to Trypanosoma brucei. It has certainly been used on a small scale in Rhodesia in the treatment of donkeys and there has been only one vague unconfirmed report of 18 deaths in the Mtoko district following its use during 1961. It is emphasised however that not more than 200 doses have been given in the official control of trypanosomiasis over the last 9 years. The dosage rate used has usually been the lower one recommended (3.5 mgs/kg) but a number of donkeys were repeatedly dosed in the early sixties at the higher rate of 7.0 mgs/kg.

DETAIL OF INCIDENT

The present incident occurred at the end of June 1970 at Lusulu Trypanosomiasis Research Station in the Binga District of Rhodesia. Some 154 donkeys of varying ages and both sexes are employed by the Tsetse Control Branch of the Veterinary Department as pack animals and they are required to patrol constantly, often in areas of heavy trypanosome risk. They are protected by the regular application of the drug * isometamidium at a dosage rate of 0.5 mgs/kg administered every three months. Under normal circumstances

* Samorin Messrs. May & Baker Ltd., Dagenham, England

this regimen serves to maintain the animals free of trypanosomiasis but the incident to be described below was an exception. Two animals returned blood films positive for T. brucei towards the end of a twelve week period. These were members of a group of 31 animals, and as the reason for the breakthrough was not clear, on the 19th June the whole group was treated with Berenil at approximately 7 mgs/kg as recommended by the makers. Twice the lower curative dose is mentioned for the elimination of T. brucei. On the morning of the 21st, 48 hrs later, 4 animals were reported sick with signs described as weakness trembling and staggering. One animal, a yearling foal, was recumbent and when lifted attempted to walk, but collapsed again. The other three were affected to a lesser degree and were permitted to walk to the nearby grazing grounds. On the same afternoon one of them collapsed in the veld and had to be transported back to the kraal. By the next morning a further 14 were affected in varying degree and by the 96th hour a further two making 20 in all of the whole herd of 31 head. Over the next 39 days six animals died as indicated.

<u>Animal</u>	<u>Day of death</u>
1. Aged Jack	3
2. Aged Jack	5
3. Yearling Jenny	3
4. Aged Jenny	slaughtered in extremis day 3
5. 8 months Jenny foal	day 18. (inanition and pneumonia)
6. aged Jenny	day 42 (" " ")

The remaining 14 mildly affected ones recovered, some being quite normal in a week or less, others over a protracted period of up to one month, the residual nervous signs gradually abating. Cases Nos. 5 and 6 might have eventually recovered but the prolonged convalescence was affected by cold frosty nights and a lack of good quality hay and succulent forage.

There was a rapid loss of condition in the affected animals but they attempted to eat and drink until becoming comatose.

The main sign was ataxia with coarse tremors of groups of muscles especially when the animal was lifted. There was evidence of dis-orientation and affected balance as evinced by staggering, a wide spread stance and a high stepping gait. In two cases the animals tended to bore forward with the head against attendants or the wall of the kraal and one adopted a staggering circling movement. There was a lack of accommodation with a contracted pupil, a tendency to lacrimation and a bright pink colour to the visible mucous membranes. Breathing and heart rate except in terminal stages was little affected. Empirical treatment was aimed at avoiding fluid loss together with the use of sedatives and stimulants as indicated. Post mortem lesions were.

inanimation. Blood examination showed no parasites. No biochemical examinations were carried out other than serum protein estimations at a later date which showed little change. In two cases there appeared to be macroscopic haemorrhages in the cerebellum.

The signs resembled those seen in cases of organic chlorinated pesticide poisoning and fresh samples of liver, gut wall and gut contents were frozen and submitted to the public analyst. The highest levels were that of dieldrin in the liver, 0.50 ppm a concentration described as being of no toxicological significance. Serum Choline-esterase levels were demonstrated to be within the normal range thus eliminating the possibility of organo-phosphate poisoning.

The nervous signs were quite different from those characteristically seen in Berenil poisoning in the dog Boyt, Lawrence and MacKenzie (1968) loc.cit. but because of the history of the onset 48 hours after treatment, the haemorrhages in the brain, albeit in a different area, and the absence of evidence incriminating other agents, it was decided to carry out another experiment.

An aged gelding which, at the time of the original incident had shown only mild incoordination which rapidly and apparently completely resolved, was on the 31st July retreated with Berenil at 7 mgs/kg by sub-cutaneous injection. Twenty-four hours later it showed nervous signs which progressed in a similar manner until the animal became comatose and died during the night of the 4th August.

The post mortem indicated, as in several other cases, pneumonia and a clearly defined haemorrhage in the cerebellar cortex.

This experiment was undertaken at Lusulu Trypanosomiasis Experimental Station where there were no facilities for sophisticated biochemical analysis. An attempt was made in Salisbury to reproduce the condition in an old blind jenny in which blood pyruvate levels had been established prior to the application of the berenil. The animal was treated at 7 mgs/kg twice at weekly intervals with no resulting departure from normal health and no significant changes in serum pyruvate level.

The brains of four donkeys were examined histologically, three of which died in the acute stage of the disease, including the test donkey, and one which showed residual nervous signs and died later.

Of the acute cases two, including the test animal, had lesions confined to a small segment of the cerebellar cortex. The lesions were clearly visible macroscopically as a group of small punctate haemorrhages. Histologically in addition to the haemorrhage there was evidence of degeneration in the form of a spongy appearance of the tissue, and the presence of occasional necrotic cells and rare infiltrating neutrophils. These animals also showed a mild sub-acute meningitis over the cerebrum.

In the third acute case there was no haemorrhagic

an area of degeneration was visible macroscopically. Histologically the lesion resembled that of the other two animals, without the haemorrhage. The sub-acute case also showed slight degenerative changes in the same position.

No other abnormalities were detected in the brains, and no significant lesions were seen in liver, kidney, heart or spleen of the same four animals.

Discussion

The incidents described provide strong presumptive evidence of the toxicity of Berenil in the donkey despite the failure of the final experiment. Indeed the failure to produce typical signs bears a striking resemblance to the unpredictable condition as seen in dogs. (Boyt et al loc.cit.) Such failures must constantly bedevil experimentation until the nature of the precipitating factor has been established and this will not be easy without reproducing the syndrome. It is clear that these facts apply in donkeys as well as dogs.

The lesions in donkeys are similar in appearance to those described previously in dogs, consisting as they do of degeneration or necrosis, often associated with intense hyperaemia and haemorrhage. The degenerative changes in the donkey are less obvious histologically than in the dog, but it is likely that the functional disturbance is no less severe. The striking difference between the two species is in the site of the lesions, which are confined to the cerebellum in the donkey but are variably distributed in the mid-brain of the dog, from thalamus to medulla oblongata, without involvement of the cerebellum.

Since the 1968 paper we have been reminded of certain nervous conditions attendant upon disorders of carbohydrate metabolism resulting from thiamine deficiency as seen in Chastek paralysis in mink and foxes. The failure to metabolise pyruvic acid results in its accumulation in brain and serum and the production of haemorrhages and necrosis.

Edwin and his associates (1968), discussing the aetiology of a specific condition, Cerebro cortical Necrosis, suggest the possibility of a conditioned thiamine deficiency. In the absence of any other clues we have attempted to follow this line by establishing serum pyruvate levels in suspected cases but again with little success because of our inability to reproduce the condition.

The donkey is relatively unimportant economically speaking but the facts related above must raise the question of the advisability of using Berenil in other members of the equid group.

REFERENCES:

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