Accidental and experimental salinomycin poisoning in rabbits

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An outbreak of salinomycin poisoning in rabbits is described. At least 27 out of 2,000 rabbits reared on a farm died after the coccidiostatic drug sulfaquinoxaline was substituted by salinomycin in the feed. An average of 26.9ppm salinomycin was detected in the ration given to the rabbits. Clinical signs included anorexia, apathy and bradykinesia, which progressed to incoordination and recumbency. Gross lesions consisted of pale areas in the skeletal muscles. The histopathological findings showed severe necrotic degenerative myopathy in association with infiltration of neutrophils and macrophages. One rabbit exhibited similar alterations in the myocardium. Mineralization was observed in the affected skeletal muscles in some cases. In order to verify if the poisoning was due to salinomycin, 20 rabbits were divided into five groups and a ration containing the drug at doses of 10, 25, 50, 75 and 100ppm was given. The administration of doses higher than 50ppm resulted in manifestation of the clinical signs seen in the outbreak of poisoning. It was concluded, that probably an error related to the mixture of salinomycin in the feed was the cause of deaths in the spontaneous outbreak of poisoning on the rabbit farm.

INDEX TERMS: Salinomycin, poisoning, toxic myopathy, rabbits.

INTRODUCTION

Salinomycin, an antibiotic of the ionophore group, is used to control coccidiosis and also to promote weight gain in poultry, rabbits, cattle and swine (Novilla 1992). Ionophores modify the cell membrane permeability, facilitate the influx...
of ions, but may cause severe functional and morphological disturbances in cells (Novilla 1992, Kawazoe 2000). Poisoning by ionophore antibiotics can occur as a consequence of excessive ingestion due to improper mixing of the drug with the feed (Ganter et al. 1989), mistakes in the calculation of dosages (Rollinson et al. 1987), administration to more susceptible species (Griffiths et al. 1989, Salles et al. 1994), or use in combination with other drugs that potentiate their effects (Ganter et al. 1995). Salinomycin poisoning has been reported to occur in horses, cattle, broiler chickens, cats, turkeys and swine (Frigg et al. 1983, Wanner 1984, Amstel & Guthrie 1986, Potter et al. 1986, Gava et al. 1997, Van der Linde-Sipman et al. 1999). High mortality of rabbits that received the ionophore narasin has been described in Brazil (Salles et al. 1994). We are unaware of any report describing salinomycin poisoning in rabbits. The objective of this paper was to describe the clinical, anatomical and histopathological aspects of unintentional and experimental poisonings by salinomycin in rabbits.

MATERIALS AND METHODS

Accidental poisoning. Twenty-seven rabbits of a total of 2,000 animals from a farm located in the county of Mendes, RJ, Brazil, were received at the Veterinary Pathology Section of Projeto Sanidade Animal Embrapa / Universidade Federal Rural do Rio de Janeiro, Seropédica, in midst 1989. Information concerning the medical history of the rabbits was obtained from the owner, who visited the institution several times. Samples of the feed used in the farm were sent to Pfizer laboratory in the city of São Paulo, where they were qualitatively and quantitatively analyzed by high performance liquid chromatography (HPLC).

Experimental poisoning. The experiments were performed at the above mentioned Veterinary Pathology Section, and at the Veterinary Pathology Section of Universidade Federal de Santa Maria, RS. Twenty New Zealand rabbits in finishing phase weighing 2 to 3 kg were kept in individual cages and received water ad libitum, Brachiaria and coccidiostatic-free feed. Two animals were used as controls. The rabbits were divided into five groups (I to V) of four animals. Each group received salinomycin at a dose of 10, 25, 50, 75 or 100ppm through the oral route by means of a feeding tube. The dosages were chosen with basis on the daily feed intake of rabbits in finishing phase, i.e., around 150g/day. The rabbits that exhibited alterations were subjected to a detailed clinical examination. The rabbits which had received the doses of 50 and 75ppm were euthanized (diethyl ether) on the 9th day of the experiment.

The animals from the accidental poisoning outbreak and those submitted to experimental poisoning were necropsied. Fragments of the muscles and diverse organs were collected, fixed in 10% formalin, processed for histology, and stained with hematoxylin and eosin. The Masson’s technique was used to stain muscle sections.

RESULTS

Accidental poisoning

In November 1989, rabbits of a farm located in the county of Mendes, RJ, Brazil, developed a disease characterized by diarrhea after the commercial feed formulation was changed. The owner had requested the feed manufacturer to modify the ration for a better control of coccidiosis, which caused significant economical losses at that time. Consequently, the coccidiostatic sulfadiazine was substituted by salinomycin. Clinically, the animals showed anorexia, apathy, incapacity to raise the head and bradykinesia that progressed to incoordination. Later, the rabbits became recumbent at/bizarre positions (Fig.1a,b). Generalized loss of muscle tone was also evident. Some rabbits showed extreme muscular flaccidity, to the point that they were unable to make any movement and remained in the position they were left when placed on the floor. There were dirty, with matted hair in the posterior region, and semi-liquid feces in the perianal region. Finally, the animals were unable to make any movement and died within 48 to 72 hours. The macroscopic examination of the 27 rabbits revealed a lighter color of the muscles throughout the body in several cases. One rabbit exhibited dark urine. In two animals, part of the small intestine was filled with a mucous-gelatinous substance,

![Image](Fig.1a. Incoordination of the pelvic limbs, weakness, flaccid paralysis of the skeletal musculature, inability to make movements, and sternal/abdominal decubitus.)

![Image](Fig.1b. Animal with difficulty to move and unable to stand or raise the head because of the lesions in the cervical muscle.)

Three animals of the group given 100ppm salinomycin died euthanized (diethyl ether) on the 9th day of the experiment. Apathy and marked weight loss. Both groups fed containing 75ppm of the drug showed moderate anorexia and apathy; those that ingested experimental salinomycin revealed the presence of alterations similar to those found in the animals that died due to accidental poisoning. The lesions were conspicuous in the thigh, cervical, longissimus dorsi, and abdominal muscles; they were characterized by degeneration, hyaline and floccular necrosis, presence of inflammatory infiltrates composed mainly of macrophages and neutrophils, and satellite cell proliferation. The cardiac muscle and the smooth musculature of the esophagus, bladder and digestive tract did not exhibit noteworthy alterations. Similar lesions were observed in the animals of group IV (75ppm); however, their intensity was moderate.Few necrotic muscle fibers were found in the rabbits that ingested feed containing 50ppm salinomycin. The histopathological evaluation of the animals belonging to group I (10ppm) and II (25ppm) did not reveal any alterations. Some animals exhibited pulmonary edema, congestion of the kidneys, spleen and lungs, and liver with nutmeg appearance.

DISCUSSION

The diagnosis of poisoning by salinomycin as the cause of the mortality observed in the rabbit farm in Rio de Janeiro was based on epidemiological, clinical, anatomical and pathological findings, and was confirmed by the presence of salinomycin in the feed given to the rabbits. The amount of salinomycin detected in the feed submitted for analysis was 26.9ppm. Even though we were unable to experimentally reproduce the poisoning using similar amounts of salinomycin, the evidence indicates that the outbreak occurred due to improper mixing of the drug with the feed, as frequently described (Whitlock et al. 1978, Rollinson et al. 1987, Novilla 1992). The possible presence of an ionophore antibiotic potentiator in the feed cannot, however, be excluded. According to the National Research Council Committee on Animal, feed containing salinomycin doses above 50ppm can cause negative effects on performance, such as growth depression and decrease in food ingestion. Salinomycin at a concentration of 50ppm in the feed did not cause the death of the animals in group III; on the other hand, it caused only mild anorexia and apathy. This reinforces the possibility that the poisoning outbreak occurred due to the presence of non-homogeneous concentrations of the drug in the feed as a...
or microscopic alterations in the myocardium. It is possible with a nutmeg appearance, in spite of the absence of gross
showed signs of heart failure such as pulmonary edema, narasin (Salles et al. 1994). In this study, some rabbits
myocardium were mild or absent in rabbits poisoned by
lesions in the intercostal muscles and in the diaphragm
 muscles. We believe that respiratory failure caused by
the cells, and the metabolism of cardiac and skeletal
ionophore antibiotics compromise energy production by
smooth musculature were not found, probably because

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