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Carbadox Intoxication in Pigs

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Abstract: The aim of this study is to present the clinical and pathological findings occurring in a natural outbreak of Carbadox poisoning in pigs. Carbadox was administrated as much as four times the recommended dose (210 ppm) at least during the fattening period. Clinical signs included emaciation, dry feces, pica, ataxia, tremor and nervousness in some animals. Postmortem examination showed dehydration, gastric ulcers, bronchopneumonia, hydrothorax and hydropericadium. Microscopically, the most significant lesions were atrophy of glomerulosa zone in the adrenals with hydropic degeneration and necrosis of the remaining cells. Diagnosis was based on clinical history and lesions in the adrenal cortex, which are considered characteristics.

Key words: Carbadox, intoxication, pigs, poisoning, diagnosis, dysentery

INTRODUCTION

The current demand in today's animal production systems have made additives common use in diets of animals destined for human consumption (Straw *et al*., 1999). Carbadox (methyl (2E)-2-[(1,4-dioxidoquinoxalin-2-yl) methylene]hydrazinecarboxylate)* is a synthetic antibacterial used as additive in pig's feeds. It was originally used as a growth promoter and more recently has been considered as a prophylactic agent very effective for porcine dysentery prevention (Straw *et al*., 1999). However, given that Carbadox and its metabolites are toxic, its use must be restricted and always monitored considering its potential risk (Jager and Vromeen, 1990). There have been previous references of intoxication cases when Carbadox has been administrated in doses superior to the recommended for prolonged periods of time. In these reports, it is mentioned that medicated feeds had 2, 3 or even 7 times the recommended dose and were administrated for >4 weeks. In every case, the most significant lesions presented themselves in the adrenal gland where, there were different states of atrophy of the zona glomerulosa (Van Der Molen *et al*., 1985; Power *et al*., 1989). In experiments, it has been demonstrated that even the prophylactic dose of 50 ppm if administrated during 5 weeks can provoke lesions in the adrenal gland (Van Der Molen, 1988). Even, if these lesions are reversible after the additive is removed, when the administration surpasses 2 or 3 times the recommended dose, lesions persist for >11 weeks (Van Der Molen *et al*., 1989). The pathophysiology of the Carbadox intoxication has been attributed to a estate of hypoaldosteronism (Nabuurs and Van Der Molen, 1989; Nabuurs *et al*., 1990).

MATERIALS AND METHODS

The objective of this report is to describe the clinic manifestations and the pathologic findings in a case of Cabadox overdose intoxication in pigs.

A general mortality problem and lack of growth was informed in a pig farm located in the Municipality of General Zuazua, Nuevo Leon. Other problems referred previously include ear and tail biting and pica, which was interpreted as a mineral deficiency indicative. Also, it was referred that the pigs had been through an illness characterized by diarrhea attributed to pig dysentery. For this reason, the animal received a bigger dose of Carbadox

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in feeds. Given that there wasn't a favorable response the dose was heightened and also Dimetridazole and Tylosin phosphate were administrated.

When, the ingredients used in feeds preparation were reviewed it was noted that pigs in the introduction were administrated at least 140 ppm of Carbadox and that when the animals passed to fattening phase, they were given 70 ppm more. It was estimated that pigs in fattening were given at least 210 ppm. In the same matter, it was proved that this diet lasted 8 months. With base in this, it was categorically established that the animal were exposed to toxic levels during the whole of the introduction and fattening phases.

During the visit to the farm there were observed retarded and pallid pigs with shaggy hair, retracted belly, weakness, uncoordination and paralysis of the hind legs and muscular tremors. Other manifestations were hard excrement, drinking of urine and pica. In some animals there was also perceived an estate of agitation and irritability. The clinic signs were varied but were observed with more notoriety in pigs in fattening. Complete necropsy was done to 4 animals representative of the problem. The most relevant aspect was the marked dehydration, cachexia, muscular atrophy, hydrothorax and hydropericardium. Also, the animals showed lesions of bites in the tail and ears and flank traumatism. Other lesions of significance were gastric ulcer, bronchopneumonia suppurativa, valvular endocarditis and suppurative arthritis. Microscopically, the lesions were variable. It stands out the presence of multifocal necrosis with Kupffer cell hyperplasia in the liver, lymphoid and interstitial pneumonia and bronchopneumonia suppurativa, as well as adenomatoid proliferative enteritis. However, the most constant lesion was a marked atrophy in the adrenal cortex. This lesion was characterized by a loss of the zona glomerulosa to the point of observing an almost absolute replacement for fibrous tissue (Fig. 1). The scarce cells of the glomerulosa that were still present showed a marked hydropic degeneration (Fig. 2). Is worth mention that there were also detected some cells with prominent cytoplasm PAS-positives infiltrating zones of the capsule or just beneath it (Fig. 3). Meanwhile, the zona fasciculata and reticularis didn't show changes, except for scarce polimorfonuclears occluding the sinusoids.

The bacteriological studies gave positive in a case on the isolation of *Salmonella* sp. The results of the hematic biometry showed hemoconcentration, in two cases, meanwhile, one of them showed discrete leucocytosis. In two animals, in which urinalysis was practiced there was hypostenuria.

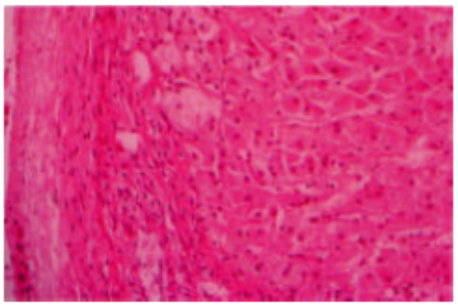

Fig. 1: Adrenal Gland, cortex. The loss of zona glomerulosa can be appreciated with connective fibrous tissue replacing it (PAS 200x)

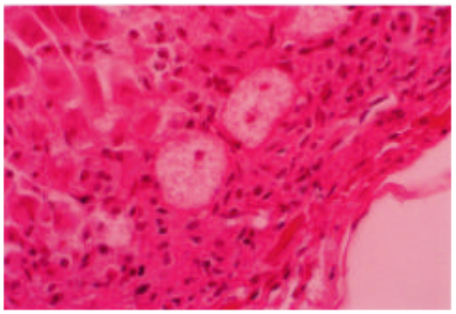

Fig. 2: Adrenal gland, cortex. Two granulosa cells, one of them binucleated, probably duo to a previous mitosis, with a marked vacuolization of its cytoplasm. The Nuclei are picnotic (PAS 400x)

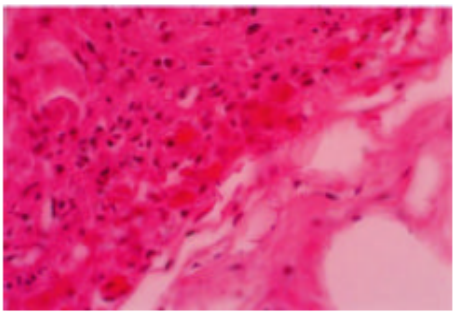

Fig. 3: Adrenal gland, cortex. Several cells PAS-positives infiltrated in the capsule and in the zona glomerulosa that was replaced with connective fibrous tissue (PAS 400x)

RESULTS AND DISCUSSION

Considering the antecedents, in which it was confirmed the additive Carbadox was administrated in a concentration 4 times the recommended and verified that it was done during the whole introduction and fattening phases, the suspicion of intoxication was completely

ustified. The period of exposure and the high doses are compatible with maximum doses used in experiment destined to induce the intoxication with the additive (Van Der Molen *et al*., 1985; Van Der Molen, 1988; Van Der Molen *et al*., 1989). Also the clinic signs that were registered in this case, such as dry feces, drinking urine, emaciation, dehydration, pica, ataxia and in some animals agitation and irritability are similar to those described in natural (Van Der Molen *et al*., 1985; Power *et al*., 1989) and provoked (Van Der Molen, 1988; Van Der Molen *et al*., 1989; Nabuurs and Van Der Molen, 1989; Nabuurs *et al*., 1990) intoxications. In the same manner, the atrophy in the zona glomerulosa of the adrenal gland consistently recognized in the current case is considered a conclusive lesion agreeing with the previous reports of this intoxication (Van Der Molen *et al*., 1985, 1989; Power *et al*., 1989; Van Der Molen, 1988; Nabuurs and Van Der Molen, 1989; Nabuurs *et al*., 1990). It is important to also mention the presence of some abundant cytoplasm PAS positive infiltrated in the capsule. Even though, this finding is consistent with Carbadox intoxication (Jager and Vromeen, 1990; Van Der Molen, 1988; Van Der Molen *et al*., 1989), the nature of this cells hasn't been determined and it only has been suggested their probable role in the stimulation of glomerulosa cells, probably in response of the damage (Van Der Molen *et al*., 1989).

CONCLUSION

Carbadox is an additive with notable prophylactic effects in the prevention of porcine dysentery; however, the toxic effects should always be considered when administrated in doses higher than recommended and for a long period of time and even in a mixture with some other drugs that may share detoxification pathways bringing it up to saturation of the catabolic cell capacity.

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