

Metoclopramide Toxicity in Cattle

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Abstract: Adverse effects have been reported in human and are potentially possible in animals. Following treatment with to metoclopramidem, but adverse effects to metoclopramide administration have not been reported in cattle. Five crossbred Holstein cattle with abomasal displacement, was referred to the veterinary clinic of Lorestan and Shiraz University. Right flank laparotomy and abomesopexy was performed. For stimulation of the abomasum motility and try to emptying of abomasum, Metoclopramide hydrochloride was administered (0.1 mg/kg) in 1 liter normal saline. At end of infusion, cattle showed particular drug toxicity. Treatment was performed by intravenous administration of normal saline and Ringer's solution. Treatment of metoclopramide toxicity in this cases involved supportive care and relief of signs.

Key words: Cattle · Metoclopramide · Toxicity · Abomasal displacement

INTRODUCTION

Metoclopramide(4-amino-5-chloro-2-methoxy-N-[2-diethylaminoethyl] benzamide) is a relatively nonpolar, lipophilic drug that has multiple actions [1, 2]. It is a dopamine (D₂) antagonist, serotonin (5-HT₄) agonist and serotonin (5-HT₃) antagonist [1-3]. Among the proposed mechanisms of metoclopramide is an increase in the release of acetylcholine in the gastrointestinal tract, possibly via a prejunctional mechanism [1-3]. It also may increase motility of gastric smooth muscle by increasing sensitivity of the cholinergic response [1-3]. Since it also is a dopamine antagonist, it may antagonize dopamine's (D₂) inhibitory action on GI motility [1-3].

Metoclopramide increases gastric emptying, increases the tone of the esophageal sphincter and stimulates motility of the duodenum [1-3]. It has less effect on distal segments of the intestine [1-3]. Metoclopramide acts centrally to inhibit dopamine in the CRTZ, which is responsible for antiemetic effects [1-3]. In human, metoclopramide also has been used to treat hiccups and lactation deficiency [1-3]. There are also endocrine effects: There is a transient increase in prolactin and aldosterone [1-3].

In dogs, metoclopramide has been used as an antiemetic more commonly than other drugs [1-4]. Although it has been used to promote GI motility as well, this effect is less established than previously thought

[1-4]. It also has been used to stimulate normal upper motility following surgery (e.g., corrective surgery for gastric dilatation), but one study showed that metoclopramide did not change gastric motor activity to promote gastric emptying in dogs with gastric dilatation volvulus (GDV) [4]. In another study, it reduced, but did not prevent gastroesophageal reflux in anesthetized dogs at a dose of 1 mg/kg [5]. Doses are in the range of 0.25 to 0.5 mg/kg, q8-12h, but they have been increased to 1-2 mg/kg [1-3]. The clinical use of metoclopramide in large animals has not been as common as in small animals [6]. Metoclopramide has little usefulness in cattle, although it may increase the motility of the rumen in cattle and sheep [6-7]. It has been successfully used in some cattle with functional pyloric stenosis [8], but was not effective in calves (0.1 mg/kg IM) [9]. Metoclopramide, has been shown to be useful in the antagonism of fescue toxicosis in grazing steers [1,7].

Some equine surgeons have used infusions of metoclopramide (0.125-0.25 mg/kg/hr) added to IV fluids to reduce postoperative ileus in horses [10]. It may stimulate small intestine-but not large bowel motility, but this has little benefit for horses with intestinal ileus [11]. Since this drug transiently increases prolactin secretion, there has been interest in using this drug for treating agalactia in animals, but efficacy has not been determine. Side effects of metoclopramide have been reported in dogs, cats, horses and humans [1-4,12].

Cases History and Clinical Signs: Five 3-5 year-old crossbred Holstein cattle were referred to the clinic of veterinary college of Lorestan and Shiraz University from different private herds in Khorramabad and Shiraz suburb. History of anorexia and loss of weight was present. The cattle refused grain but continue to eat little hay. The cattle had a history of inappetence and a little soft, dark defecation. It is occurred 31±0.5 day post parturition and milk production dropped one-third to one-fifth of that expected. The animals showed a mild depression and physical examination revealed normal to subnormal temperature (38.1±0.4°C), pulse (66±3 Beat/min) and respiratory rate (18±3 Movement/min). Ruminal movement was reduced to one movement per two minute. Ping sound and splashing sound was heard in auscultation in right (3 cattle) and left (2 cattle) side of flank. Surgical treatment was performed by right flank laparotomy and abomasopexy with carefully manipulation of the abomasum.

Metoclopramide hydrochloride (Ampule 10mg/2 mL) was administered at 0.1 mg/kg for stimulating motility of abomasum and reduces postoperative ileus. Metoclopramide was added in 1 liter of Dextrose 5% and normal saline. At the end of serum infusion, cattle were appeared a particular drug toxicity. Sign of toxicity were started by anxiety (5/5), involuntary muscle movements (4/5), falling saliva from mouth (5/5), lip licking (5/5), head shaking(5/5), then progressed to slight convulsion signs (3/5), nervousness (2/5) and finally restlessness (5/5), listlessness (5/5), depression (5/5), ataxia(5/5) and recumbency (3/5). Further examination showed increased heart rates (86±8 beat/Min) and respiratory rates (58±4 movement/Min) and decreased body temperature (37.5±0.2°C). They were not blind and responded bilaterally to the menace test. Saline and Ringer's solution were administered intravenously accompanying calcium magnesium phosphorus solution (250 mL) in 15 liters in all cases. Recovery was not achieved by these treatments on the same day. Two cases were recovered on next day but incoordination and ataxia were seen. Three other cases were shown ataxia, contraction of neck and mandible muscles, dry mouth, tremor of the limbs, incoordination of the limbs, wandering, myoclonus, myotonia and recumbency on next day. On third day post treatment, two cases (left displacement of abomasum) were completely recovered and return to eat and production but others have some tremor in limbs, ataxia and incoordination. Signs of right displacement of abomasum were appeared in two unrecovered cases again and submitted to slaughterhouse. Last case was recovered completely 5 day after metoclopramide administration.

DISCUSSION

Side effects following treatment with metoclopramide in dogs and cats are rare and CNS side-effects may include either sedation or hyperactivity in dogs and cats may experience hyperactivity or disorientation [1-3]. Signs of neurotoxicity may occur in both dogs and cats at therapeutic levels [1-3]. These signs usually will resolve within a few days of discontinuing the metoclopramide [1-3]. Constipation may occur in both species [1-3]. Side effects in adult horses are CNS side-effects (alternating both sedation and excitement) and colic may occur with IV administration [1, 2, 6, 11]. Side effects are less common in foals [1, 2, 6]. In ponies, IV infusion of metoclopramide at 0.5 mg/kg/hr produced alternating periods of sedation and excitement [11]. In adult horses, IV administration of doses as low as 0.02 mg/kg has been associated with severe CNS side effects (i.e., alternating periods of sedation and excitement) [14].

In experiments for detection of pharmacokinetic and pharmacodynamic of metoclopramide in goats, several goats showed transient restlessness following intravenous administration of metoclopramide at 5 mg/kg [15,16]. Nervous signs such as lip licking, head shaking, or head pressing occurred in two goats during this period, which lasted less than 5 min [15]. This was followed by a somnolent period, which lasted for approximately an hour [15]. Nervous signs did not accompany intramuscular administration of metoclopramide at 0.5 mg/kg in any goat; however, somnolence was evident in most of the goats over the duration of the recording period [15,16]. Side-effects associated with the use of metoclopramide in these goats were minimal [15,16]. The goats of both IV and IM groups exhibited prolonged somnolence, the duration of which was longer for those receiving IM metoclopramide [15, 16]. Excitement followed by depression and somnolence has been observed in cattle and goats after administration of metoclopramide at doses ≥ 0.3 mg/kg in some pharmacological experiments [15-17].

Hypotension has been reported to occur after intravenous use [2,12]. Reported side effects are restlessness, excitement and somnolence [12]. Metoclopramide has been shown to be a safe drug in humans when administered in the usual therapeutic dose (30-40 mg daily) [12]. Akathisia, a feeling of unease and restlessness in the lower limbs, has been related to plasma concentrations over 100 ng/ml in human

subjects [13]. Other CNS effects have been commonly reported in humans and include nervousness, somnolence and dystonic reactions [18]. These effects have been attributed to central dopamine receptor blockade [1, 12]. In humans, it is also a neuroleptic agent that induces extrapyramidal activity (including torticollis, opisthotonus, trismus and facial spasms), which is more likely to occur in children [12]. Acute dystonic reactions occur in approximately 0.2% of patients (1 in 500) treated with 30 to 40 mg of metoclopramide per day [12].

Authors examined 34 cattle with right and left abomasal displacement that received metoclopramide IM or SC at 0.1 mg/kg, but none of them showed any toxicity signs. Authors suggested two mechanisms for these sign in cattle; one is hypotension that may cause some of side effects and other is extrapyramidal effect and block of central dopamine receptors. Blood pressure was not measured in these cases but fall in body temperature may show hypotension. The Upper Motor Neuron (UMN) system is divided into the pyramidal and extrapyramidal systems [7]. The pyramidal system allows animals to perform finely skilled movements but is not necessary for initiation of gait in animals [7]. The extrapyramidal system allows animals to gait and to initiate voluntary movement [7]. Neurons are located in nuclei in all divisions of the brain [7]. If metoclopramide affect extrapyramidal system and block dopamine receptors in this part of brain, major toxicity signs are justifiable [1, 2, 12].

Hypokalemia and hypochloremia in abomasal displacement are evident and these may alter sensitivity of blood-brain barrier of cattle to metoclopramide and cause further toxicity signs. There is no specific antidote thus treatment of metoclopramide toxicity in this case involved supportive care. Authors suggest metoclopramide should be used at recommended dose (0.1 to 0.5 mg/kg) in ruminants only SC or IM.

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