Experimental oleander (*Nerium oleander*) poisoning in goats: a clinical and pathological study

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Summary

Dried oleander leaves at single lethal dose of 110 mg/kg body weight were administered orally to five native female goats. Clinical signs of toxicosis in goats began to appear about 1 hr after receiving the oleander and included abdominal pain, ruminal atony and tympany, frequent urination, bradycardia, tachycardia, tachyarrhythmia, depression, weakness and convulsive movement and death at the end stage. Electrocardiography revealed sinus bradycardia, sinus tachycardia, A-V dissociation, ventricular premature beats, depression of S-T segment, ventricular tachycardia and ventricular fibrillation. Four goats died within 4 to 84 hrs and one survived. Haemorrhages in varying degrees in internal organs were observed at necropsy. Histopathology revealed extensive tubular necrosis in kidneys with haemosiderin pigment in the cytoplasm of convoluted tubular cells, varying degrees of coagulative necrosis of cardiac muscle cells associated with haemorrhage and infiltration of mononuclear inflammatory cells, scattered necrosis of hepatocytes, perivascular and perineural oedema, haemorrhagic foci and ischemic cell changes in brain, congestion and oedema in lungs. Severe hyperaemia and infiltration of inflammatory cells were also observed in tissue sections of forestomachs, abomasum and different parts of the intestines.

Key words: Oleander poisoning, Goat, Arrhythmia

Introduction

Oleander (*Nerium oleander*) is a drought-tolerant, evergreen flowering shrub that belongs to the Dogbane family, Apocynaceae. It is frequently grown as an ornamental plant in gardens and parks as well as highway median divider or hedge around yards or orchards. Oleander is originally a Mediterranean and Asian plant and is widely distributed in the world, especially in tropical and subtropical regions. The plant is grown throughout Iran and is more common in eastern and southern provinces (Aslani, 2004).

Oleander has long been known to be poisonous to animals and human beings (Frohn and Pfander, 1983). All parts of the plant either fresh or dried are toxic and contain cardiac glycosides, the roots and seeds having the highest concentrations. The most prominent of those glycosides are oleandrin and neriin (Knight, 1988; Galey *et al*., 1996). The toxicity of oleander cardiac glycosides is related to their ability in inhibition of plasmalemmal sodium, potassium adenosine triphosphatase (Na^+, K^+–ATPase) and is similar to that of digitalis glycosides (Pearn, 1987; Langford and Boor, 1996)

Oleander poisoning is not infrequent in man and domestic animals. Cases of accidental toxicosis have been reported in adults and children (Henning, 1932; Shaw and Pearn, 1979; Haynes *et al*., 1985). The plant has also been used for suicidal or homicidal intent (Pearn, 1987; Lim *et al*., 1999). Accidental and/or experimental oleander toxicosis have been described in cattle (Mahin *et al*., 1984; Rezakhani and Maham, 1992; Aslani and Rezakhani, 2000), horses (Henning, 1932; Catton and

Smithcore, 1972; Hughes *et al*., 2002), sheep (Aslani *et al*., 2004), goats (Panisset, 1923; Bazargani, 1971), donkeys (Rezakhani and Maham, 1994; Smith *et al*., 2003), camels (Vashishta and Singh, 1977), cats (Burton *et al*., 1965), dogs (Szabuniewicz *et al*., 1971, 1972; Humphreys, 1988), monkeys (Schwartz *et al*., 1974), budgerigars (Shropshire *et al*., 1992), canaries (Arai *et al*., 1992), geese (Alfonsa and San Chez, 1994), ducks (Bardosi, 1963), turkeys (Shlosberg *et al*., 2004), toed sloth (Miller, 1973) and bears (Ratigan, 1921).

The purpose of this study was to determine the acute toxic effects of oleander and its clinical and pathological features in goats.

Materials and Methods

Five clinically healthy female native breed goats, 2-3 years of age and weighing between 25-30 kg were used for the study. The animals were purchased from a farm in suburb of Mashhad. Fifteen days before commencement of the experiment the goats were dewormed with albendazole (Razak Co, Iran) and rafoxined (Damloran Co, Iran).

Leaves from mature varieties of a pink oleander were collected in August and then cleaned and dried at room temperature. The dried leaves were finely ground to powder. The powder of oleander leaf was administered orally to the goats as an aqueous suspension in a single lethal dose of 110 mg/kg body weight (Fowler, 1993), using a stomach tube.

The baseline electrocardiograms (ECG) (Fukuda-Japan) were recorded using a base-apex lead (Robertson, 1990). ECG and clinical signs were recorded repeatedly at 30-min intervals after oleander administration.

Necropsy of four animals was performed immediately after death and gross pathology of organs were recorded. To examine microscopic lesions, tissue samples of forestomachs, abomasum, intestines, liver, heart, kidneys, lungs and different parts of the brain were collected, fixed in 10% neutral buffered formalin, and processed for routine histology. Tissue sections were stained with haematoxylin and eosin.

The experiment was approved by the animal welfare committee of the School of Veterinary Medicine of Mashhad.

Results

Clinical and ECG findings

Abdominal pain, manifested by restlessness, teeth grinding, pawing the ground, looking at the flank, frequent lying down and getting up, and humped posture about 1 hr after oleander administration. Auscultation of the heart revealed bradycardia with strength beats at this time. The heart sounds were also audible in thoracic area and left flank. The bradycardia replaced by sinus tachycardia and tachyarrhythmia at the late stages. Other signs of toxicosis were ruminal atony with moderate to severe tympany, polakiuria, diarrhoea, salivation with foam in the mouth, depression, weakness, incoordination of movements, tachypnea and convulsion and death at the end stage. Body temperature of the animals remained within normal limits during the experiment. Four goats, numbered 1, 2, 4 and 5 died in 25, 4, 84 and 13 hrs after receiving the oleander, respectively and one survived.

ECG tracing of intoxicated animals

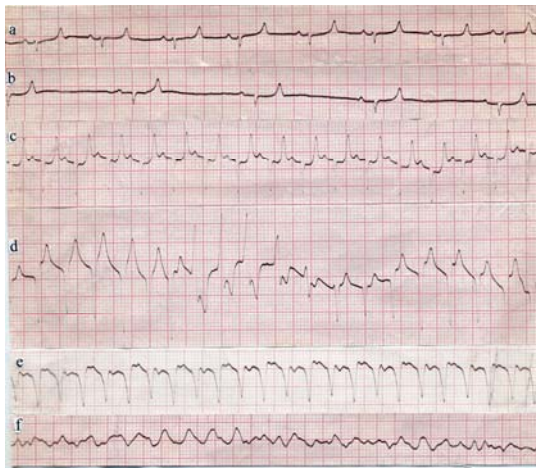

Fig. 1: a. Normal sinus rhythm in a goat before oleander administration. b. Sinus bradycardia 1.5 hrs after receiving of the oleander. c. Sinus tachycardia after 4 hrs. d. Multifocal ventricular premature beats after 10.5 hrs. e. Ventricular tachycardia after 12 hrs. f. Ventricular fibrillation after 13 hrs. (Base-apex lead, 25 m/s)

revealed sinus bradycardia, sinus tachycardia, A-V dissociation, ventricular premature beats, depression of S-T segment, ventricular tachycardia and ventricular fibrillation (Fig. 1). Ventricular arrhythmia was not observed in one goat which survived from toxicosis.

Pathology

At gross, congestion of visceral organs including liver, kidney, lungs, abomasum and intestines and haemorrhages in the left ventricular endocard were observed. Histopathological examination revealed severe congestion and extensive tubular epithelial necrosis in all kidneys. There were haemorrhage and also frequent haemosiderin pigment in the cytoplasm of renal convoluted tubules in two goats. The hearts in all goats showed congestion and severe haemorrhage especially in the subendocardial regions. There were also varying degrees of coagulative necrosis of cardiac muscle cells associated with infiltration of mononuclear inflammatory cells. In some instances, there was mononuclear cell infiltration into the endoneurium of nerve fascicles of conductive system.

Lesions in the liver were fatty change and infiltration of inflammatory cells into the portal spaces with scattered necrosis of hepatocytes. There was also mild bile duct hyperplasia in 2 goats. The central nervous system showed congestion, perivascular and perineuronal oedema, haemorrhagic foci and varying degrees of ischaemic cell changes. Severe congestion and oedema were observed in the lungs. There was interstitial haemorrhage in the lung of 1 goat.

Severe hyperaemia and infiltration of inflammatory cells were observed in tissue sections of the forestomachs, abomasum and different parts of the intestines.

Discussion

Clinical, ECG and pathological findings of oleander intoxication in goats reported in this study are generally consisted with those reported in sheep and cattle (Oryan *et al*., 1996; Aslani *et al*., 2004). The main clinical signs observed were related to gastrointestinal and cardiac systems disturbances. The malignant and lethal effects of oleander were cardiac arrhythmias especially ventricular arrhythmias which finally led to ventricular fibrillation and death of animals.

Oleandrin, the principal cardiac glycoside of oleander and its derivatives are structurally similar to digoxin and other digitalis glycosides, which are widely used for treatment of congestive heart failure in human and domestic animals. These glycosides at the molecular level are powerful inhibitor of Na^+, K^+–ATPase. Inhibition of Na^+, K^+–ATPase ultimately resulted in increasing of intracellular Ca^{2+} levels which is responsible for inotropic effect of cardiac glycosides (Joubert, 1989; Jortani *et al*., 1996; Langford and Boor, 1996).

Higher degrees of inhibition of Na^+, K^+–ATPase caused by toxic doses of cardiac glycosides in cardiac muscle fibers. In such condition the sympathetic outflow is also increased, which sensitize the myocardium and exaggerate all toxic effects of the glycosides. This toxic course causes reduction in normal electrical conductivity of the myocardium that results to conduction blocks, ventricular arrhythmias and eventually complete loss of myocardial contractility or systole (Katzung and Parmley, 1998; Panwar and Garg, 2000).

The histopathological findings of the present study in goats as well as our previous study on sheep (Aslani *et al*., 2004) showed some degrees of cardiomyopathy in intoxicated animals. The lesions of the myocardium may also have a rule in development of cardiac arrhythmias. Mechanism of cardiomyopathy is not determined in cardiac glycosides toxicosis. However, as general, elevation of cytosolic Ca^{2+} leads to phospholipase and protease activation which in turn causes phospholipid degradation and cytoskeletal damage, respectively (Cotran *et al*., 1999).

The intoxicated goats in the present study showed various extracardiac signs including gastrointestinal and renal disturbances. Extracardiac lesions were also observed in the kidneys, forestomachs, liver and brain of intoxicated goats. Vomiting and diarrhoea are common signs of oleander and digitalis toxicosis in human and small

animals and are related to central nervous system (Shaw and Pearn, 1979; Pearn, 1987; Adams, 1995). Ruminal atony accompanied by mild to moderate tympany is a frequent clinical signs of oleander toxicosis in ruminants which observes in the early stages of the intoxication (Aslani *et al*., 2004).

Effects of oleander glycosides on the kidneys of goats manifested clinically by frequent urination and tubular necrosis in pathology. Diuretic effect of digitalis glycosides is also known and induced event by subtrapeutic dose. The diuretic effect is interpreted as evidence that Na^+, K^{+-} ATPase is involved in urine concentration mechanism and by inhibiting this enzyme, cardiac glycosides could evoke a direct diuretic effect on the kidneys. On the other hand, in congestive heart failure patients, circulatory effect of cardiac glycosides increases the renal blood flow and glomerular infiltration (Adams, 1995).

The cause of renal tubular necrosis in oleander toxicosis is unidetified. Tubular cells of kidneys are probably exposed to much amounts of oleander toxins due to their excretion from this organ. Intracellular Ca^{2+} elevation following inhibition of Na^+, K^+-ATPase may also be involved in tubular cell degeneration and necrosis.

Uptake of oleandrin in brain after intraperitoneum injection of oleandrin or oleander extract has been reported in mice. It has also been shown that the component within oleander extract enhances transport of oleandrin across the blood brain barrier (Ni *et al*., 2002). The oleander toxins may cross the blood brain barrier in goats, however, the brain lesions are caused secondary to vascular endothelial damage and acute heart failure, and direct effect of the toxins on the cells. Pulmonary lesions may also be produced by vascular endothelial damage and acute left heart failure.

All classes of livestock are susceptible to oleander toxicosis (Henning, 1932; Galey *et al*., 1996). However, because of unpalatable nature of the plant and selective feeding habit of the goat, poisoning in this species is infrequent. Although when it does occur it is often acute with high fatality rates (Bazargani, 1971; Smith and Sherman, 1994). Among different species of domestic animals, cattle are more prone to eat oleander leaves. Housing of cattle indoors and non-selective feeding predispose them to intoxication (Joubert, 1989; Galey *et al*., 1996).

The median lethal dose (LD50) of oleander as well as biological half life of its cardiac glycosides has not been determined in ruminants. The present report and also our previous experiments in sheep and calves (Aslani, 1995; Aslani *et al*., 2004) show that the dose of 110 mg/kg body weight of dried oleander leaves is lethal for ruminants. Very high doses of oleander (250 and 1000 mg/kg) has also been used for experimental induction of acute toxicosis in sheep (Adam, 2001).

Based on the findings of the present study, it is concluded that goat is susceptible to oleander toxicosis just like other domestic ruminants. Laboratory animals of rodent species because of very low susceptibility are not useful for experimental studies on cardiac glycosides (Joubert, 1989; Langford and Boor, 1996). Therefore, sheep and goats are convenient animals for this object and using them in the experimental studies of poisoning with oleander or other sources of cardiac glycosides will help to elucidate unknown aspects of the toxicosis with these compounds.

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