

The effect of magnesium sulfate in treatment of experimental oleander (*Nerium oleander*) poisoning in sheep

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Abstract: The purpose of this study was evaluation of magnesium sulfate effect in treatment of acute oleander intoxication in sheep. Eleven young native sheep randomly divided into 2 groups, 6 sheep being allocated to the treatment group and 5 served as controls. Sheep of both groups were dosed with a lethal dose of 110mg/kg body weight of dried oleander leaves. In sheep of treatment group, following development of ventricular arrhythmias, magnesium sulfate was slowly administered intravenously with dose rate of 100mg/kg body weight. Clinical signs of toxicosis were developed within 30 -40 minutes after dosing of the plant. Serial electrocardiography revealed various abnormalities and arrhythmias of cardiac rhythm in sheep of control group. Animals of control group died within 4.5 to 12 hours (median 8.5 hours) after receiving the toxic material. Administration of magnesium sulfate in sheep of treatment group suppressed ventricular arrhythmias to benign ones or normal sinus rhythm but its effect was transient and persisted for 3 to 3.5 hours. Second injection of magnesium had same effect but there was no considerable therapeutic effect after third injection of the drug. Sheep of treatment group died within 18 to 34 hours (median 24.5 hours) after receiving the oleander. Statistical analysis revealed a highly significant difference in survival time between the control and the treatment groups ($p < 0.004$). The results suggested that magnesium sulfate can be used as a complementary therapeutic agent for treatment of acute oleander toxicosis in farm animals.

Key words: *Nerium oleander*, sheep, cardiac glycosides, magnesium sulfate, arrhythmias.

Introduction

Oleander (*Nerium oleander*) is an evergreen flowering shrub that belongs to the Dogbane family, Apocynaceae. The plant is also known as roselaurel, adelfa, and rosenlorbeer and grow ubiquitously throughout tropical and subtropical regions of the world. Oleander is an extremely toxic plant and its ingestion has caused poisoning and death among humans (Hynes *et al.*, 1985) as well as pet and farm animals (Galey *et al.*, 1996, Aslani and Rezakhani, 2000), poultry (Alfonsa *et al.*, 1994) and wild animals (Ratigan, 1921).

Cardiac glycosides are the most important toxic compounds of the oleander. The more known cardiac

glycosides of the plant are oleandrin, folinerin and digitoxigenin (Langford and Boor, 1996). Seeds and roots of the plant contain the highest measurable levels of total cardiac glycosides while the leaves contain the highest concentration of the oleandrin (Karawya *et al.*, 1973). The glycosides contained within oleander can effect the cardiovascular, neurological and gastrointestinal system (Joubert, 1989).

The cardiac effects of the glycosides are due to direct cardiotoxicity and also to an indirect effect via the vagal nerve. The mechanism of action is well established and it involves the inhibition of the plasma membrane sodium-potassium adenosine 3-phosphatase (ATPase), which leads to alteration in the intracellular potassium, sodium and calcium

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levels (Joubert, 1989, Adams, 1995).

There is no specific treatment of oleander poisoning in farm animals once a toxic dose of the plant has been eaten. Symptomatic treatments are often attempted but are usually unsuccessful. When oleander toxicosis is established, the treatment procedure has to control cardiac arrhythmias particularly ventricular ones.

Magnesium has an important role in protecting the myocardium against damaging effect of intracellular accumulation of calcium (Shakerinia *et al.*, 1996). Because the main part of pathogenesis of cardiac glycosides poisoning is performed by accumulation of calcium in cardiac muscle cells as well as cellular depletion of potassium, which in turn causes cardiac excitability and development of arrhythmias, magnesium administration to intoxicated animals may be beneficial to suppress or abolish of the cardiac arrhythmias.

Materials and Methods

Eleven native 8 to 12 months old sheep with 25-30 kg weight were randomly divided into 2 groups. Six sheep were allocated to the treatment group and 5 sheep served as control one. Oleander leaves were collected from a local pink flowered bush, dried at room temperature and then were grounded. Sheep of both groups were dosed via gastric tube with a lethal dose, 110mg/kg body weight (Aslani *et al.*, 2004), of oleander. Cardiac rhythm of animals was recorded by electrocardiography using base apex lead system (Radostits *et al.*, 2000) at 10 to 15 minute intervals. In sheep of treatment group, following development of ventricular arrhythmias, magnesium sulfate (Magnesium sulfate 20%-Nasr-Iran) was slowly administered intravenously with dose rate of 100mg/kg body weight. Administration of magnesium sulfate with same rout and dose rate was repeated at 3 to 4 hours intervals following reappearing of ventricular arrhythmias.

Time of death of in control and treatment group compared using non-parametric Mann-Whitney test $p < 0.5$ considered as significant.

Results



Sheep of both groups developed clinical signs of oleander toxicosis within 30 to 40 minutes after dosing of the plant. Monitoring of the cardiac rhythm in animals of control group revealed various arrhythmias and abnormalities including bradycardia, second degree A-V block, A-V dissociation, S-T segment depression, ventricular premature beats, ventricular tachycardia and ventricular fibrillation. These sheep died within 4.5 to 12 hours (median 8.5 hours) after receiving the toxic material (Table 1).

About 15-30 minutes after administration of the magnesium sulfate in sheep of treatment group, there was an improvement in cardiac rhythm, so that the ventricular arrhythmias converted to sinus tachycardia, normal rhythm or benign arrhythmias such as second degree A-V blocks.

This condition persisted for 3-3.5 hours and then the ventricular arrhythmias reappeared in electrocardiograms. Following second injection of magnesium sulfate malignant cardiac arrhythmias changed again to benign ones and normal rhythm as well as the result of the first administration of the drug. This change of cardiac rhythm was also transient. Conversion of the cardiac rhythm following third injection of magnesium sulfate was so short and the animals died following ventricular tachycardia and ventricular fibrillation. Animals of treatment group died within 18 to 34 hours (median 24.5 hours) after receiving of the toxic material (Table 1). Statistical analysis revealed a highly significant difference in survival time between the control and treatment groups ($p < 0.004$).

Discussion

Administration of magnesium sulfate in acute experimental oleander toxicosis in sheep revealed some therapeutic effects, so that the ventricular arrhythmias converted to normal sinus rhythm or benign arrhythmias following intravenous injection of the drug. But this effect was transient and could not save the intoxicated animals. Conversion of ventricular arrhythmias to sinus rhythm was not observed or its duration was very short after third injection of magnesium sulfate. These results agree

Table 1. Survival time in control and treatment group (by magnesium sulfate) of sheep experimentally intoxicated by oleander ($p < 0.004$).

Sheep	Control	Treatment
1	8.5	26.5
2	12	18
3	4.5	25
4	6	24.5
5	10	20
6	-	34
	8.5	24.75

with those of other authors who indicated that in normomagnesemic humans and dogs the protective effects of magnesium against digitalis arrhythmias are transient and inconsistent (Seller, 1977, Adams, 1995). So, alternative treatment for cardiac rhythm conversion should be considered when conversion to sinus rhythm does not occur with magnesium sulfate. Although the effect of magnesium sulfate in conversion of cardiac rhythm was transient, the results showed that using of this substance in treatment of acute oleander toxicosis prolongs survival time of treated animals and in practice this will provide enough time to consider alternative treatments such as supportive ones. The mean survival time of treated sheep was about 3 times of the survival time of the control sheep.

Since the magnesium ion is an essential metallo-coenzyme and activates sodium-potassium dependent membrane ATPase, which is inhibited by cardiac glycosides, it is interesting to speculate presence of magnesium in excess, may to some degree, overcome glycoside blockade of this enzyme (Seller, 1977, Douban, *et al.*, 1996). It has also been shown that magnesium acts as an indirect antagonist of digoxin at the sarcolemma Na^+ , K^+ -ATPase pump and has shown benefit in reducing the incidence of ventricular arrhythmias associated with digoxin toxicity (Kinaly and Buckley, 1995). It is notable that intoxication with cardiac glycosides participated by hypomagnesemia. On the other hand, animal experiments documented a magnesium induced raise of the ventricular fibrillation threshold in the presence of digitalis (Ghani and Smith, 1974).

Oleander intoxication in animals terminated with ventricular fibrillation (Aslani *et al.*, 2004).

The enzyme, Na^+ , K^+ -ATPase is necessary for active transport of potassium into and sodium out of the myocardial cells. Inhibition of that enzyme by cardiac glycosides results in progressive reduction of intracellular potassium which is responsible for many toxic arrhythmogenic activities of the glycosides (Adams, 1995). All antiarrhythmic agents that reduce myocardial loss of potassium suppress the arrhythmias induced by cardiac glycosides. Drugs such as propranolol and reserpin, also are useful in cardiac glycosides arrhythmias and do not affect myocardial potassium kinetics. This suggests that factors in addition to myocardial potassium egress play a role in the development of some cardiac glycosides arrhythmias (Seller, 1977).

On the other hand, administration of the magnesium sulfate reduces serum calcium levels and also antagonizes calcium at cellular binding sites (Hynes *et al.*, 1985). These effects of magnesium may also have a role in conversion of arrhythmias caused by cardiac glycosides. It has been shown calcium-chelating agent such as dipotassium editate is effective in treatment of cardiac glycosides toxicity. Also, it is suggested that reduction of extracellular calcium ion results in a decrease in cellular membrane calcium and consequently enhances the re-entry or influx of potassium ions into myocardial cells (Burton *et al.*, 1965; Adams, 1995).

Specific antidotal treatment for digitalis intoxication is administration of Fab fragments from specific antibodies directed against digoxin and it has now been utilized to bind oleander-derived glycosides in both humans and canines (Langford and Boor, 1996). It has been shown that antidigoxin Fab fragments were highly effective in treating oleander-induced arrhythmias and electrolyte disturbances in humans. Fab fragment infusion may also cause adverse events as anaphylactoid reaction in some cases (Eddleston and Persson, 2003). In spite of efficacy of Fab fragments in treatment of oleander toxicosis, the cost and availability has limited its utilization (Eddleston *et al.*, 2003; Smith *et al.*, 2003).

Antiarrhythmic drugs such as lidocain



hydrochloride, phenytoin and propranolol have also been used for managing cardiac glycosides-induced tachyarrhythmias in equid and canine cases (Szabuniewicz *et al.*, 1971; Palambo *et al.*, 1975; Wunberd *et al.*, 1999; Smith *et al.*, 2003). However, efficacy and dosage regimens as well as residual of these drugs in ruminants are unknown and need to be investigated.

Magnesium sulfate can be used in treatment protocols of oleander toxicosis in animals as a complementary therapeutic agent to convert life threatening cardiac arrhythmias and increases survival time of affected animals. Further investigation is required, however, to determine accurate dosage regimens of magnesium sulfate in treating of arrhythmias in animals intoxicated with oleander or other sources of cardiac glycosides and to examine its use in combination with other antiarrhythmic agents.

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مطالعات اثرات درمانی سولفات منیزیم در درمان مسمومیت تجربی با خرزهره (*Nerium oleander*) در گوسفند

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در این مطالعه یازده راس گوسفند نژاد بومی به دو گروه کنترل ۵ راس و درمانی ۶ راس، تقسیم شدند. برگ خشک شده خرزهره به مقدار 110 mg/kg وزن بدن به گوسفندان هر دو گروه تجویز گردید. ریتم قلب دام‌های هر دو گروه به وسیله الکتروکاردیوگرافی هر ۱۰ تا ۱۵ دقیقه ثبت شد. به گوسفندان گروه درمانی با ظهور آریتمی‌های بطنی سولفات منیزیم با دز 100 mg/kg وزن بدون به صورت داخل وریدی و به آرامی تزریق گردید. با کنترل الکتروکاردیوگرام این دام‌ها بعد از ظهور مجدد آریتمی‌های بطنی تزریق سولفات منیزیم با همان دز تکرار گردید. نشانه‌های مسمومیت در دام‌های هر دو گروه در عرض ۳۰ تا ۴۰ دقیقه بعد از دریافت خرزهره ظاهر گردید. الکتروکاردیوگرافی گوسفندان گروه کنترل آریتمی‌های متنوع و در نهایت بدخیم را نشان داد. این دام‌ها ۴/۵ تا ۱۲ ساعت بعد از دریافت خرزهره تلف شدند (با میانه ۸/۵ ساعت). تزریق سولفات منیزیم به گوسفندان گروه درمانی آریتمی‌های بطنی را بر طرف نمود و به آریتمی‌های خوش خیم و یا ریتم سینوسی تبدیل کرد. با این حال این اثر گذرا بود و ۳ تا ۳/۵ ساعت بیشتر دوام نداشت. دومین تزریق سولفات منیزیم اثر مشابهی داشت ولی در تزریق سوم اثرات درمانی قابل توجهی مشاهده نشد. دام‌های گروه درمانی نیز در عرض ۱۸ تا ۳۴ ساعت بعد از دریافت خرزهره تلف شدند (با میانه ۲۴/۵ ساعت). زمان مرگ دام‌های دو گروه اختلاف شديداً معنی داری ($p < 0.004$) را نشان داد. تجویز سولفات منیزیم در موارد مسمومیت با خرزهره به تنهایی برای درمان کافی نمی‌باشد ولی در کنار سایر اقدامات درمانی برای تعدیل آریتمی‌های بطنی می‌تواند مفید باشد.

واژه‌های کلیدی: خرزهره، گوسفند، گلیکوزیدهای قلبی، سولفات منیزیم، آریتمی‌ها، گیاه سمی.

