

## **Propranolol Hydrochloride and Activated Charcoal as a Treatment of Experimental Oleander Poisoning in Sheep**

**<sup>1</sup>Saeed Ozmaie, <sup>1</sup>Mehdi Sakha, <sup>2</sup>Ahmad Asghari**

<sup>1</sup>*Department of Clinical Science, Science and Research Branch, Islamic Azad University, Tehran, Iran.*

<sup>2</sup>*Department of Surgery, Science and Research Branch, Islamic Azad University, Tehran, Iran.*

Saeed Ozmaie, Mehdi Sakha, Ahmad Asghari: Propranolol Hydrochloride and Activated Charcoal as a Treatment of Experimental Oleander Poisoning in Sheep

### **ABSTRACT**

This study was done to evaluate the effect of propranolol hydrochloride and activated charcoal in the treatment of Nerium oleander intoxication in sheep. Seven male native Iranian sheep (8-12 month) were randomly divided into two groups, 5 treatment and 2 controls. Sheep of both groups were administered the lethal dose of 110 mg/kg body weight of dried oleander leaves. Animal in control group died within 41 to 56 hours after dosing of the plant. Clinical signs of toxicosis were developed within 60 minutes after dosing of the plant, such as distress, teeth grinding, anorexia, colic, vocalization, polyuria, moderate rumen distention, tachypnea and depression.

All sheep in treatment group, one hour after dosing with oleander leaves took activated charcoal (5 gr/kg, single dose) via stomach tube. Immediately after development of ventricular premature arrhythmias, 5mg propranolol hydrochloride was administered intravenously in repeated doses.

Three sheep in treatment group did not show any dysrhythmia and were lived and did not received any drugs. One sheep of treatment group took the propranolol hydrochloride in regime but was died after 80 hours. Propranolol hydrochloride in last sheep of treatment group changed ventricular arrhythmias to sinus rhythm. This sheep was lived after taking the antidysrhythmia drugs. The result suggested that propranolol hydrochloride and activated charcoal can be effective to treatment of acute oleander toxicosis in sheep.

**Key words:** Nerium oleander, cardiac glycosides, propranolol hydrochloride, activated charcoal, sheep.

### **Introduction**

Oleander is an evergreen shrub or small tree from 5 to 25-ft tall containing gummy sticky sap in the dogbane family Apocynaceae. The Apocynaceae (dogbanes) are sources of African arrow poisons (for example Carissa acokanthera, 'bushman's poison' and Strophanthus hispidus) and also contain many of the most beautiful but deadly tropical flowering shrubs such as Plumeria rubra, 'frangipani', Nerium oleander, 'common, pink or white oleander' and Thevetia peruviana, 'yellow oleander' [15]. The main cardiac glycoside of N. oleander is oleandrin with a molecular formula of C<sub>32</sub>H<sub>48</sub>O<sub>9</sub> and a molecular

mass of 576.3 (Fig-1) [3,14].

Its flowers in the spring or summer are white, pink, yellow or red large clusters. All parts of the plant are toxic and Toxicity remains in dried leaves [12]. The basis for physiological action of N. oleander cardenolides is similar to that of classic digitalis glycosides, i.e. inhibition of membrane Na<sup>+</sup>/K<sup>+</sup> ATPase pump, resulting in deficit in conduction of electrical potential, leading to ventricular arrhythmias and eventually loss of myocardial contractility [7]. The cardiac effects of the glycosides are due to direct cardiotoxicity and also to an indirect effect via the vagal nerve [2]. In this study the effect of propranolol hydrochloride and

### **Corresponding Author**

Ahmad Asghari, Department of Surgery, Science and Research Branch, Islamic Azad University, Tehran, Iran.  
E-mail: Ahmad.Asghari@gmail.com

activated charcoal were considered to treatment of cardiac disturbances of oleander (Nerium oleander) intoxication in sheep.

**Material and method**

Seven clinically healthy male native Iranian sheep, 8-12 month, weighting between 25-41.3 kg were used for the study. The animals were purchased from a farm in suburb of Tehran. Fourteen days before the experiments, sheep were carefully examined and dewormed with albendazole (Tolid Daro, Iran).

Leaves from a certain oleander (Nerium oleander) tree with pink flower were collected sufficiently and then cleaned and dried at room temperature. After drying, leaves were finely ground to powder. The powder of oleander leaf was administrated orally to sheep in form of aqueous suspension as a single lethal dose of 110 mg/kg body weight using the stomach tube.

The clinical signs were examined carefully and electrocardiograms were recorded using a base-apex lead (BTL-England). ECG and clinical signs were recorded with 15-min intervals after oleander administration. In treatment group, one hours after administration of oleander leaves, activated charcoal (Merck co.) Administrated via stomach tube. Immediately after producing of ventricular arrhythmias, propranolol hydrochloride was slowly administrated intravenously with dose of 5mg/head and repeated every 15 minutes in cases of maintaining of ventricular tachycardia up to disappearing of ventricular arrhythmias.

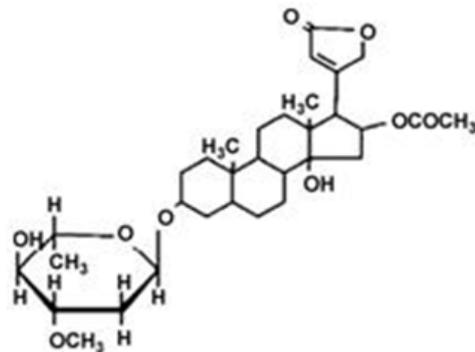
**Result and discussion**

*Clinical and ECG findings:*

Sheep in control group (n=2) developed clinical signs of oleander toxicosis within 60 minutes after dosing of the plant. Clinical signs such as abdominal pain, manifested by restlessness, teeth grinding or groaning also dyspnoea, depression, ruminal atony with moderate to severe tympany, bloat, diahrrea and dehydration were evident. Additional signs including drooling of saliva, tenesmus, dribbling of urine and muscular tremor (table 1).

Both sheep in control group showed ventricular dysrrhythmia in late stage and died few minutes after occurring ventricular fibrillation. These sheep died within 41 to 56 hours (median 48.5 hours) after receiving the toxic dose.

Sheep in treatment groups (n=5) showed clinical signs of oleander toxicosis within 50-60 minutes after dosing of the plant. Clinical signs such as restlessness, grinding of the teeth, anorexia, constipation, frequent urination and ruminal atony were the most common signs for intoxicated sheep. Body temperature remained within normal limits during the experiment. All sheep in treatment group were administrated by activated charcoal (5 gr/kg, single dose) One hour after dosing with oleander leaves, via stomach tube. In 3 sheep of treatment group there was no cardiac arrhythmia and so they had no treatment by propranolol hydrochloride. In two rests, cardiac dysrrhythmia were evident and treatment was done by propranolol hydrochloride (5 gr/head) IV injection.



**Fig. 1:** Chemical structure of oleandrin

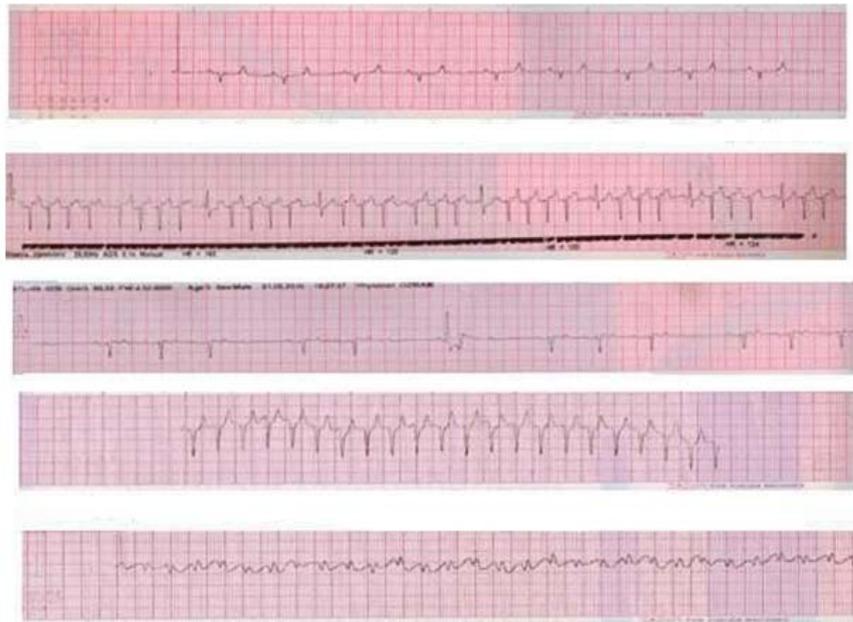
**Table 1:** Clinical signs in control and treatment groups

No. Of animal	diarrhea	ruminal atony	colic	distress	polyuria	taypnea
1©	+	+	+	+	++	+
2©	+	+	+	+	+	+
3	+	+	+	++	++	+
4	+	+	+	-	+	+
5	++	-	-	-	-	-
6	-	-	-	-	-	-
7	+	+	+	-	-	-

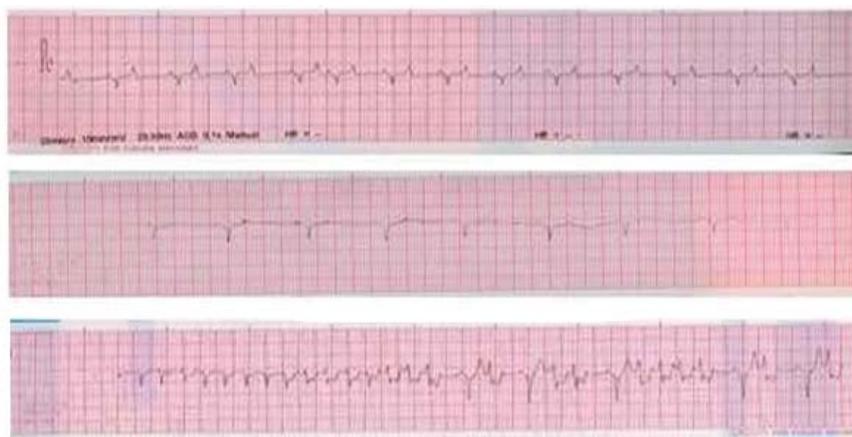
© Controlgroup

One sheep of two was died after 81 hours even after 6 doses of propranolol hydrochloride with 15 minutes interval. Ventricular tachycardia has changed to sinus tachycardia and AV block during the treatment but it finally changed to ventricular tachycardia and ventricular fibrillation and death. The serial ECG changes in this case from dosing up to death are shown in figure 2.

Another sheep that took the propranolol hydrochloride regime was lived after showing ventricular tachycardia. This case took 16 doses of propranolol hydrochloride during 3 days after induction of toxicity and showed multiple dysrhythmias. The serial ECG changes in this case are shown in figure 3.



**Fig. 2:** a Normal sinus rhythm in a sheep before oleander administration.  
 b. Sinus tachycardia and ventricular premature complex 17 hrs after receiving of the oleander  
 c. Second-degree atrioventricular block and ventricular premature complex 30 minutes after receiving of propranolol hydrochloride  
 d. Ventricular tachycardia 78 hours after receiving of the oleander  
 e. Ventricular fibrillation after 81 hours.



**Fig. 3:** a. Normal sinus rhythm in a sheep before oleander administration.  
 b. Sinus bradycardia 6 hours after receiving of the oleander.  
 c. Multifocal ventricular premature beats and sinus tachycardia 13 hours after receiving of the oleander.

### Discussion

Oleander contains two potent cardiac glycosides or cardenolides, oleandrin and nerine, which are present in all parts of plant [6,10].

Cardiac glycoside are the most important toxic compounds of the oleander. The more known cardiac glycosides of the plant are oleandrin, folinerin and digitoxigenin. The toxicity of oleander cardiac glycosides is related to their ability in inhibition plasmalemmal sodium, potassium adenosine triphosphatase ( $\text{Na}^+$ ,  $\text{K}^+$ -ATPase), leading to sodium accumulation in excitable cells such as nervous tissue and myocardium [9,10]. The cardiac effects of the glycosides are due to direct cardiotoxicity and also to an indirect effect via the vagal nerve [1]. In this study the main clinical signs observed were related to cardiac and gastrointestinal systems. The malignant and lethal effects of oleander were cardiac arrhythmias especially ventricular arrhythmias which finally led to ventricular fibrillation and death possibly due to more absorption of oleander toxins.

In this study bradycardia was the first arrhythmia noted 30 min after administration of oleander to sheep with development of toxicosis and several forms of tachyarrhythmia were found. Ventricular tachycardia were evident in two sheep. In one sheep, ventricular tachycardia goes to ventricular fibrillation and lead to death.

Diuretic effects of oleander toxicity are linked to direct effects of glycosides on renal tubules because sodium reabsorption in kidneys is an ATPase-dependent transport process. Whereas positive inotropic effect of glycosides, especially in early stages of poisoning, results in elevation of renal blood flow and increased glomerular filtration and diuresis [2].

There is no specific treatment for the poisoning, but procedures that are intended to reduce absorption or improve elimination of the toxin present in digestive tract, such as oral administration of activated charcoal, can be efficient in the early stages [8]. Drugs like atropine, lidocaine, propranolol, phenytoin, metoclopramide, and epinephrine are all examples of such compounds and are given in response to specific cardiovascular symptoms (10). Tachycardia can be treated by application of the adrenergic blocking drugs such as propranolol. In this study propranolol hydrochloride was administered in two sheep that showed tachyarrhythmia. In one sheep after 6 doses the cardiac rhythm not returns to sinus rhythm although some temporary sinus rhythm and sinus tachycardia were recorded. In another sheep the propranolol hydrochloride was effective and after 16 doses the cardiac rhythm was returned to sinus rhythm. So it is concluded that propranolol hydrochloride can be use in cases of oleander poisoning and may be need to administrate numerous

doses.

### Acknowledgments

The authors wish to acknowledge the council Research of Islamic Azad University, Science and Research Branch for the financial assistance.

### References

1. Adam, S.E.I., M.A. Al-Yahaya, A.H. Al-Farhan, 2001. Acute toxicity of various oral doses of dried Nerium oleander leaves in sheep. *Am J Chin Med.*, 29: 525-32.
2. Adams, H.R. Digitalis and vasodilator drugs. 1995. In: Adam HR. *Veterinary Pharmacology and therapeutics*, 7th ed, Iowa State University Press, Ames, pp: 455-463.
3. Adam, S.E.I., M.A. Al-Yahaya, A.H. Al-Farhan, 2001. Response of Najdi sheep to oral administration of Citrillus colocynthis fruits, Nerium oleander leaves or their mixture. *Small Rum Res.*, 40: 239-244.
4. Aslani, M.R., A.R. Movassaghi, H. Janati-Pirouz, M. Karazma, 2007. Experimental oleander (Nerium oleander) poisoning in goats: a clinical and pathological study. *Iran J Vet Res.*, 8(1): 58-63.
5. Aslani, M.R., A.R. Movassaghi, M. Mohri, A. Abbasia, M. Zarehpou, 2004. Clinical and pathological aspects of experimental oleander (Nerium oleander) toxicosis in sheep. *Vet Res Commun.*, 28: 609-616.
6. Begum, S., B.S. Siddiqui, R. Sultana, A. Zia, A. Suria, 1999. Bio-active cardenolides from the leaves of Nerium oleander. *Phytochemistry*, (50): 435-438.
7. Cheeke, P.R., 1998. *Natural Toxicants in Feeds, Forages, and Poisonous Plants*, second ed, Interstate, Danville, pp: 479.
8. Eddleston, M., E. Juszczak, N.A. Buckley, L. Senarathna, F. Mohamed, 2008. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet*, (371): 579-87.
9. Galey, F.D., 2009. Disorders Caused by Toxicants. In: *Large Animal Internal Medicine*, 4<sup>th</sup> ed. (Smith, B.P. ed.), Mosby Elsevier, St. Louis, pp: 1697.
10. Langford, S.D., P.G. Boor, 1996. Oleander toxicity: an examination of human and animal Toxic exposures. *Toxicology*, (109): 1-13.
11. Radostits, O.M., C.C. Gay, K.W. Hinchcliff, P.D. Constable, 2007. *Veterinary Medicine*, 10<sup>th</sup> ed, Saunders Company, London. pp: 1862-1863.
12. Ramesh, C.G., 2007. *Veterinary Toxicology: Basic and clinical principles*. 1<sup>st</sup> ed, Elsevier Company, USA, pp: 201.

13. Soto-Blanco, B., J.D. Fontenele-Neto, D.M. Silva, Reis PFCC. 2006. Acute cattle intoxication from *Nerium oleander* pods. *Trop Anim Health Pro*, (38): 451--454.
14. Wasfi, I.B., O. Zorob, N.A. Al katheeri, A.M. Al Awadhi, 2008. A fatal case of oleandrin poisoning. *Forensic Science International*, (179): 31-36.
15. Watt, M.V., M.G. Breyer-Brandwijk, 1962. *The medicinal and poisonous plants of southern and eastern Africa*, 2<sup>nd</sup> ed. Edinburgh, E&S Livingstone, pp: 107-9.