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Impact of Severe Yellow Oleander Poisoning on Cardiac Function and Hemodynamics

Arulnithy Kanagasingam[1*], George R Francis[2], Brinda Komagarajah[1], Dushjyanthy Ladchumanan[1] and Ahila Sivapramyan[1]

[1]*Cardiology Unit, Teaching Hospital Batticaloa, 38-Nalliah Road, Batticaloa, Sri Lanka*

[2]*Faculty of Medical Sciences, Eastern University, Trincomalee Hwy, Chenkaladi, Sri Lanka*

[*]**Corresponding author:** Arulnithy Kanagasingam, Cardiology Unit, Teaching Hospital Batticaloa, 38-Nalliah Road, Batticaloa, Sri Lanka, E-mail: karulnithy@yahoo.co.uk

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Abstract

Objective: Severe poisoning with yellow oleander seeds is still a problem in developing world. Toxicity manifest in many ways including shock. We design this study to look into the effect of yellow oleander on cardiac function and hemodynamics.

Methods: Observational study on patients with severe form of Yellow oleander Poisoning admitted to Coronary Care Unit. Basic parameters such as age, sex, number of seeds taken, and delay in seeking medical attention were collected. Status of electrolytes, ECG changes, Ventricular functional assessment with bed side 2D Echo cardiogram and continuous monitoring of pulse and blood pressure measured non-invasively.

Results: Total of 71 patients studied. Mean age is 24.55 years. Female to male ratio was 1.5:1. Vomiting and persisting Nausea were common symptoms (41.9%, 31.4% respectively). Around 39% of patients ingested less than 2 seeds. Mean delay for gastric lavages was 5 hours and 50 minutes. Mean delay in starting activated charcoal was 8 hours and 30 minutes. Almost everyone had abnormal ECGs. 60% of population had hyperkalemia. Half of the study population had Mean Arterial Pressure of less than 60mmHg. And 95.8% of the patients had Diastolic Blood Pressure of less than 60mmHg. Majority of the patients had hyper contractile Left Ventricle with ejection fraction of more than 60% and no one had impaired LV function.

Conclusion: Hypotension in spite of good left ventricular function, mimicking distributary shock probably due to vascular toxicity was a feature in Yellow Oleander Poisoning.

Keywords: Yellow oleander poisoning; Yellow oleander seeds; Morbidity; Mortality; Yellow Oleander; Toxicity; Hypotension; Vascular toxicity; Left ventricular function.

Introduction

Poisoning is one of the major causes for suicidal deaths in developing countries including Sri Lanka. In the Eastern Province of Sri Lanka Yellow Oleander seeds are used as a common means of suicide. Ingestion of Yellow oleander seeds results in poisoning similar to digitalis toxicity [1-3]. Severely affected patients may manifest as Atrioventricular (AV) block with progression to AV dissociation, resistant ventricular fibrillation, shock, and death. Deliberate self-harm with seeds of yellow oleander (*Thevetia peruviana*) results in significant morbidity and mortality each year in South Asia including Sri Lanka [4,5].

Teaching Hospital Batticaloa is the only tertiary referral hospital with a coronary care unit equipped to manage severe poisoning in the eastern part of Sri Lanka. Over a 52 month period extending from November 2011, 1076 patients were admitted with Yellow Oleander Poisoning (YOP) to this hospital [6]. Patients with YOP are initially admitted to general medical wards, and patients with features of severe toxicity are treated at the Coronary Care Unit (CCU). The incidence of YOP is high among young adults in this region and the impact of poisoning may result in death of the victim. Managing these patients is challenging without digoxin-specific antibody fragments (Fab). Fab fragments are highly effective and safe and have transformed the management of cardiac glycoside poisoning [7,8]. In the absence of Fab fragments mortality is as high as 10% in tertiary care centers [9]. Lack of thorough knowledge on YOP in humans and the lack of definite criteria for risk stratification [5] are significant contributors for high mortality. Our study aimed to evaluate further the factors influencing severe toxicity including its effects on cardiac function and hemodynamics. To understand the effects, it is necessary to know the mechanism through which yellow oleander causes poisoning to humans. *Thevetia peruviana* contains a milky sap, consisting of a compound called "Thevetin". Thevetin is used as a heart stimulant but its natural form is extremely poisonous [10]. Thevetin is a cardenolide called Thevetin A and Thevetin B (Cerebroside), others toxins include Peruvoside, Neriifolin, Thevetoxin, and Ruvoside. They produce gastric and cardiotoxic effects [5,11,12]. These digitalis glycosides primarily inhibit the Na^+-K^+ ATPase pump resulting in gastrointestinal, cardiac toxic and autonomic effects. It also increases the vagal tone contributing to bradycardia and atrioventricular nodal block. However, due to the complexity of the components of yellow oleander, there could be many unexpected manifestations that may not mimic simple digitalis toxicity.

Materials and Methods

This was an Observational study performed at Teaching Hospital, Batticaloa. All patients with YOP demonstrating severe toxicity and admitted to the Coronary Care Unit (CCU) during the period commencing from March 2013 up to May 2014 were included in the study.

Data collections

Patients admitted with severe toxicity were identified according to the clinical status of patients. All patients were monitored for clinical features, Data related to the method of ingestion, time taken for gastric decontamination (gastric lavage and activated charcoal) ECG changes, Systolic Blood Pressure (SBP), Diastolic Blood pressure (DBP), Mean Blood Pressure (MAP), heart rate, serum electrolytes, and Left Ventricular (LV) contractility using serial bedside 2D echocardiogram were obtained . At least one 2D echocardiogram was done during the critical phase of the course of illness (Time of 2D Echocardiogram has been guided by low Mean Arterial Pressure) and reported by a Consultant Cardiologist. All data was collected on a pre-defined questionnaire by investigators.

All patients underwent standard management for YOP according to local protocol. All were started and continued on activated charcoal two hourly. Adequate hydration was maintained with intravenous normal saline, patients with persistent bradycardia were treated with Temporary Pace Maker. Hyperkalemia was managed with Insulin dextrose boluses and or infusion.

Data analysis

Data was entered and analysed using the statistical package for social sciences (SPSS) computer software. Data was assessed and analysed by responses to the questions. Results were expressed as a percentage to allow comparisons as well as for statistical reasons.

Ethical consideration

Ethical clearance was obtained from the ethical review committee, Faculty of Medical Sciences, Eastern University, Sri Lanka. Reference number is EUSL/FHCS/ERC/2012/22

Results

We analyzed the data of 71 patients with severe toxicity admitted to the Coronary Care Unit. Patients were young (mean age 24.55 years, range 13 – 64 years) and predominantly female (F/M=1.5:1). Many (42.2%) of the cases were under 19 years (Figure 1).

Commonest symptoms of patients admitted to the CCU were vomiting and persisting Nausea (41.9%, 31.4% respectively), followed by neurological symptoms, severe abdominal pain, and diarrhea. Among the patients, 11 (15.5%) of them had co-morbidities. Five of them had a history of psychiatric illness, while the remaining had Ischemic heart disease and other medical disorders. 27 patients had ingested less than or equal to two seeds (Table 1).

The mean number of seeds taken was 3.53 with a minimum of half seed and a maximum of 16 seeds. Around 13.4% of patients had taken the seed with either alcohol or sweet (7%, 5.6% respectively) others had taken it in either a ground form or as a whole seed. All of the 71 patients were treated for gastric decontamination by Gastric lavage and Activated charcoal either in a peripheral hospital or at Teaching Hospital Batticaloa. The mean time duration taken for gastric lavage to be performed was five hours and fifty minutes with a median value of 4.25 hours. The mean time duration taken for activated charcoal to be administered was 8 hours and 30 minutes and with a median value of 6.5 h.

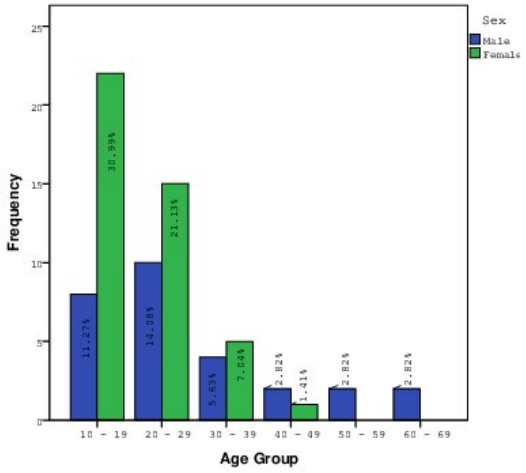

Figure 1: Age of Male and Female patients with severe YOP admitted to the Coronary Care Unit, Teaching Hospital Batticaloa.

No of seeds	n (%)
≤ 2	27 (39.1%)
2-5 seeds	24 (34.8%)
5-10 seeds	14 (20.3%)
≥ 10 seeds	4 (5.8%)

Table 1: Number of yellow oleander seeds ingested by patients admitted to CCU.

ECG Abnormalities	n	%
Normal ECG	1	1.4
Sinus bradycardia	13	18.3
Sinus Tachycardia	1	1.4
Sinus Block	16	22.5
Supra ventricular Tachy arrythmia	1	1.4
1st degree Heart block	10	14.1
2nd degree Heart block	20	28.2
3rd degree Heart block	12	16.9
ST sagging	26	36.6

Table 2: ECG findings of the patients with severe toxicity admitted to CCU Teaching Hospital Batticaloa.

Only one patient had normal ECG findings. ST segment sagging was the commonest ECG abnormality (Table 2). Patients with severe toxicity had either normal K^+ level (40.3%) or Hyperkalemia (59.7%) none of the patients had hypokalemia.

The lowest Mean Arterial Blood Pressure (MAP) was recorded during the stay in the CCU. Out of 71 patients 36 (50.7%) had MAP of less than 60 mmHg (Mean MAP 63.37 mmHg,). The majority of patients recorded a lowest BP between 11-20 hours of intake (Figure 2).

During stay in CCU, lowest Diastolic Blood Pressure (DBP) and corresponding Heart rate were noted (Table 3). Lowest Diastolic Blood Pressure (DBP) was less than 60 mmHg in 68 out of 71 patients (95.8%). Remaining 3 patients also had the lowest DBP at 60mmHg. Lowering of DBP was seen in almost all patients (Figure 3). All except one had a SBP less than 120 mmHg (Figure 4). Mean pulse pressure was 51.65 mmHg with a median value is 50 mmHg. Due to non-availability of resources only 48 out of 71 patients underwent echocardiographic evaluation. 61% demonstrated a Hyper-contractile left ventricle while 38% showed normal LV functions. Impaired LV function was not seen in any patient.

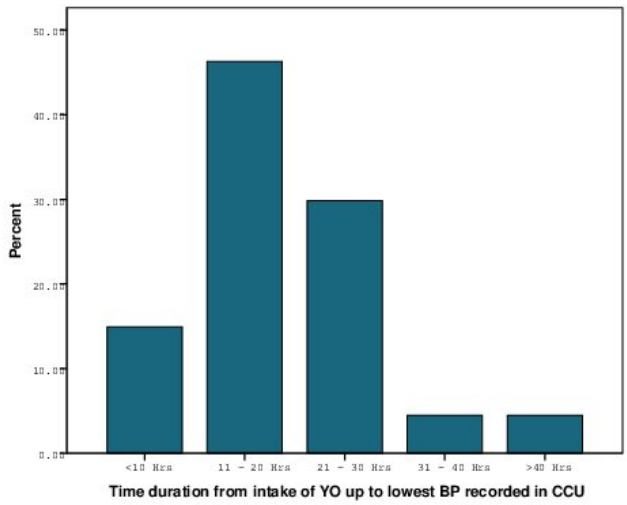

Figure 2: Time taken in Hours after lowest Blood Pressure recorded during the stay in CCU Teaching Hospital Batticaloa.

Heart rate	n (%)
Less than 60 bpm	32 (45.1%)
60-100 bpm	35 (49.3%)
More than 100 bpm	4 (5.6%)

Table 3: Heart rate of patients at the time of lowest BP recorded in CCU.

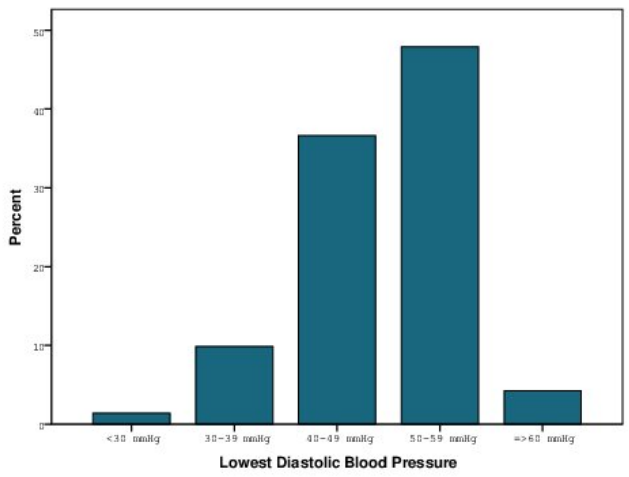

Figure 3: Lowest Diastolic Blood Pressure recorded during severe yellow oleander poisoning.

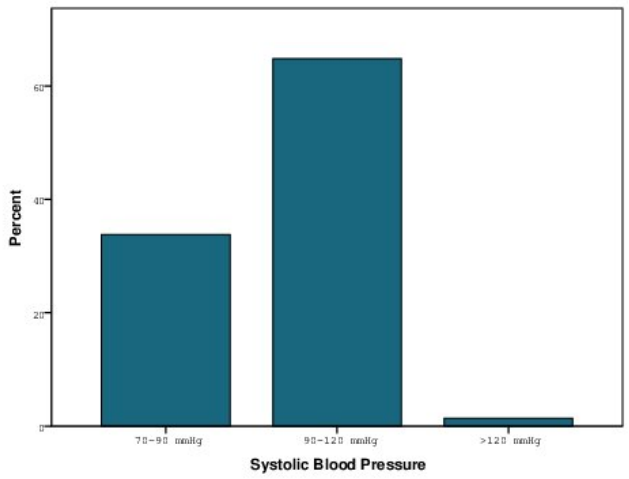

Figure 4: Systolic Blood Pressure recorded during severe yellow oleander poisoning.

Discussion

We studied 71 patients, with severe toxicity by yellow oleander seeds over a 11 month period, admitted to CCU, Teaching Hospital Batticaloa. According to previous literature symptomatic oleander seed poisoning carries a mortality of up to 10% in Sri Lanka [13]. Our institution itself admitted around 1076 patients with the history of acute YOP over 52 months from November 2011 [6]. These figures include patients with severe and non-severe poisoning. Several studies have explained the mechanism of toxicity, clinical features and treatment strategies [5,7-9,11,12,14-16]. Shock, Brady-arrhythmias, tachyarrhythmias, hyperkalemia, severe persistent vomiting, and altered mental state are considered markers of severe toxicity [5,16].

A preponderance of females was noted (60%). And 42% were under the age of 19 years. Vomiting and nausea were the most common clinical finding as previously documented [16]. Only 11% had a history of other medical conditions including mental illness. The majority were previously in good health.

We found a significant number, around 40% of patients with features of severe toxicity had ingested less than or equal to two seeds only. And it has been postulated that these patients become severely toxic as a lesser number of seeds fail to induce vomiting thereby get absorbed into the body [13,17]. Studies have documented poor correlation between the severity and number of seeds ingested [1,2,12,13,16,18]. Indeed some studies have found cardiac involvement more pronounced in patients taking a lesser number of seeds or even leaves [4,18].

It appears that delay in gastric decontamination and delay in starting activated charcoal also play in a major role in causing severe toxicity [9,19]. In our study the mean time taken to do gastric lavage is 5 h and 50 minutes. And the mean time taken to start the initial dose of activated charcoal is 8 hours. This delay is for the toxin to get absorbed cause features of severe toxicity.

Almost all severe toxic patients had abnormal ECGs but no consistent pattern was noted. Each particular patient had more than one type of ECG change during the stay. ST segment changes with various degrees of heart blocks were documented. Heart blocks and absent p waves correlated with high mortality in previous studies [11].

Hyperkalemia is a known maker of severe toxicity [12,20,21]. Sixty percent of our patients had hyperkalemia. Severe vomiting could be the cause for hypo or normokalemia in patients with severe toxicity [1].

Hemodynamics and cardiac function

Shock is a feature of severe cardiac glycoside poisoning [16]. It was believed that it was cardiogenic [5,13]. It is well known that cardiac glycosides enhance contractility of the heart [22]. Normally in cardiac muscle cells, the initial influx of calcium induces further release of calcium from the sarcoplasmic reticulum, which results in muscle contraction [23]. The sodium-potassium ATPase pump is one of the mechanisms responsible for removing sodium from the cell. Cardiac glycosides reversibly inhibit the sodium-potassium-ATPase pump, causing an increase in intracellular sodium and a decrease in intracellular potassium [24,25]. The increase in intracellular sodium prevents the sodium-calcium antiporter from expelling calcium from the myocyte, which thereby increases intracellular calcium. The net increase in intracellular calcium augments inotropy [26,27]. The magnitude of the inotropic effect of digitalis is proportional to the degree of inhibition of the enzyme [19]. We found that almost all the evaluated patients had hyperdynamic or normal LV contraction in 2D echocardiogram at the time of hemodynamic instability. Thevetin, one of the several components in yellow oleander seed appears to be a potent cardiac stimulant [10]. There is evidence to say that significant structural damage occurs to the heart in lethal cases of YOP. These include, sub-endocardial and perivascular hemorrhage along with focal myocardial edema [28].

When we look at the effects of Digoxin on the vascular tree, it has variable effects on smooth muscles [14,24,29]. In patients with advanced heart failure it causes vasodilatation [30] and in patients without heart failure it causes vasoconstriction. The difference is due to enhanced responsiveness of the baroreceptors in a patient with CHF [31,32]. Early experimental studies confirmed that digitalis increases peripheral resistance in resistant vessels (systemic arterioles) and the capacitance bed (systemic veins) [33]. In high doses, like in poisoning, digoxin increases sympathetic outflow from the CNS [19]. Sympathetic outflow to the vessels causes vasoconstriction and increases vascular resistance. Even though yellow oleander contains digoxin like components, we are not comfortable to assume that it will have the same effect as digoxin, especially with our study findings.

Our patients with severe toxicity demonstrated prominent hypotension. We had only one patient with a SBP>120 mmHg. One third had SBPs of less than 90 mmHg. The impact on diastolic BP was much more prominent. Only 3% had a DBP of>60 mmHg. More than half of the population had a mean arterial pressure of less than 60 mmHg. The mean value of MAP was 63.37 mmHg. The major proportion had the lowest BP recorded between 11 -20 h of intake which appears to correspond to the peak of toxicity. More interestingly the pulse pressure was wider and mean and the median value for pulse pressures were 51.65 mmHg and 50 mmHg respectively. This hemodynamic behavior mimics distributary shock secondary to sepsis [34] or SIRS. During these episodes, the heart rate was maintained>60 beats/min for patients with bradycardia by TPM. The fact that all evaluated patients had hyper-contractile LV with an ejection fraction of more than 60%, virtually excluded a cardiogenic cause for hypotension. It is very clear that the effects of yellow oleander on the vascular tree are much different from the effects of Digoxin [35]. This could be due to yellow oleander containing several components with different physiological effects [5,11,12]. There are enough reasons to believe that there could be direct effects on vascular smooth muscle and/or endothelium in YOP. These effects could be through the ATPase dependent Na-K pump [36] or vasodilatation through ryanodine receptors, which also contribute towards the inotropic effect on the heart [37,38]. Or there could be some other mechanisms not yet known. Whatever the mechanism involved, it is very obvious that hypotension especially diastolic hypotension mimicking distributary shock is a significant feature in YOP at least in patients with severe toxicity. Its role in mortality and morbidity need to be further investigated, however severe hypotension is an additional factor leading towards adverse outcomes in these patients. Therefore the treatment strategy to combat this effect of yellow oleander needs to be carefully considered, in addition to the standard treatment strategies available at present. We were limited by the fact that we couldn't include patients who died on or prior to admission. And invasive hemodynamic monitoring would have been more valuable in this situation.

Conclusion

Managing patients with YOP is still challenging in Sri Lanka in the absence of a definite antidote. This necessitates improvement to understand, detect and treat pathophysiological changes in these patients. In addition to previously known factors associated with mortality, vascular toxicity and shock mimicking distributary in nature also play a major role. Vascular toxicity is a probably a feature overlooked so far. Therapy targeting vascular toxicity would help to reduce mortality and morbidity in patients with severe toxicity caused by yellow oleander.

References

1. Sreeharan N, Putharasingam S, Ranjadayalan K, Satkurunathan K, Ganeshamoorthy J (1985) Yellow oleander poisoning-clinical manifestations and prognostic criteria. Jaffna Med J 20: 100-101.
2. Saravanapavananthan N, Ganeshamoorthy J (1988) Yellow oleander poisoning-a study of 170 cases. Forensic Sci Int 36: 247-250.
3. Fisch C, Surawicz B (1969) Digitalis. Grune and Stratton, New York.
4. Pirasath S, Arulnithy K (2013) Yellow oleander poisoning in eastern province: an analysis of admission and outcome. Ind J Med Sci 67: 178-183.
5. Rajapakse S (2009) Management of yellow oleander poisoning. Clin Toxicol (Phila) 47: 206-212.
6. Madhura J, Arulnithy K, Mathiventhan U, Mathiventhan T (2016) Yellow Oleander (Thevetia peruviana) Seed Poisoning (YOSP) in the Batticaloa District, Sri Lanka: Is related with Fruiting Season? Int J Res Stud Biosci 4: 8-13.
7. Kelly RA, Smith TW (1992) Recognition and management of digitalis toxicity. Am J Cardiol 69: 108-118.
8. Antman EM, Wenger TL, Butler VP Jr, Haber E, Smith TW (1990) Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. Circulation 81: 1744-1752.
9. De Silva HA, Fonseka MMD, Pathmeswaran A, Alahakone DGS, Ratnatilake GA, et al. (2003) Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial. Lancet 361: 1935-1938.
10. Kishan S, Krishnakumar A, Vimlesh M, Mubeen, Alok S (2012) A review on: Thevetia peruvina. Int Res J Pharm 4: 74-77.
11. Roberts DM, Southcott E, Potter JM, Buckley NA (2006) Pharmacokinetics of digoxin cross-reacting substances in patients with acute yellow oleander (Thevetia peruviana) poisoning, including the effect of activated charcoal. Ther Drug Monit 28: 784-792.
12. Bandara V, Weinsteina SA, Whitea J, Eddleston B (2010) A review of the natural history, toxinology, diagnosis and clinical management of Nerium oleander (common oleander) and Thevetia peruviana (yellow oleander) poisoning. Toxicon 56: 273-281.
13. Eddleston M, Ariaratnam CA, Meyer WP, Perera G, Kularatne AM, et al. (1999) Epidemic of self-poisoning with seeds of the yellow oleander tree (Thevetia peruviana) in northern Sri Lanka. Trop Med Int Health 4: 266-273.
14. Smith TW (1988) Digitalis. Mechanisms of action and clinical use. N Engl J Med 318: 358-365.
15. Eddleston M, Rajapakse S, Rajakanthan, Jayalath S, Sjöström L, et al. (2000) Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: a randomised controlled trial. Lancet 355: 967-972.
16. Gopalakrishnan SK, Kandasamy S, Isaac B, Jayasankar C, Chandru C (2017) Oleander toxicity-the clinical spectrum and mortality predictors: an observational study. Internet Journal of Medical Update 12: 1.
17. Eddleston M, Ariaratnam CA, Sjöström L, Jayalath S, Rajakanthan K, et al. (2000) Acute yellow oleander (Thevetia peruviana) poisoning: cardiac arrhythmias, electrolyte disturbances and serum cardiac glycoside concentrations on presentation to hospital. Heart 83: 301-306.
18. Osterloh J, Herold S, Pond S (1982) Oleander interference in the digoxin radioimmunoassay in a fatal ingestion. JAMA 247: 1596-1597.
19. Ganpisetti R, Chandluri P, Lakshmi BVS, Swami PA (2016) Cardiac Glycosides Uses In Heart. World J Pharmaceut Med Res 2: 291-299.
20. Bismuth C, Gaultier M, Conso F, Efthymiou ML (1973) Hyperkalemia in acute digitalis poisoning: prognostic significance and therapeutic implications. Clin Toxicol 6: 153-162.
21. Roberts DM, Gallapatthy G, Dunuwille A, Chan BS (2016) Pharmacological treatment of cardiac glycoside poisoning. Br J Clin Pharmacol 81: 488-495.
22. Ahmed A, Waagstein F, Pitt B, White M, Zannad F, et al. (2009) Effectiveness of digoxin in reducing one-year mortality in chronic heart failure in the Digitalis Investigation Group trial. Am J Cardiol 103: 82-87.
23. Matthews CG (1998) Cellular Physiology of Nerve and Muscle (3rd edn) Blackwell Science, Malden.
24. Rocco TP, Fang JC (2006) Pharmacotherapy of congestive heart failure. In: Brunton LL, Lazo JS, Parker KL (eds) Goodman & Gilman's The Pharmocological Basis of Therapeutics. McGraw-Hill, New York, pp: 869.
25. Eichhorn EJ, Gheorghiade M (2002) Digoxin. Prog Cardiovasc Dis 44: 251-266.
26. Li-Saw-Hee FL, Lip GY (1998) Digoxin revisited. QJM 91: 259-264.
27. Demiryürek AT, Demiryürek S (2005) Cardiotoxicity of digitalis glycosides: roles of autonomic pathways, autacoids and ion channels. Auton Autacoid Pharmacol 25: 35-52.
28. Barceloux DG (2008) Medical Toxicology of Natural Substances. A John Wiley & Sons Publication. 854-855.
29. Newton GE, Tong JH, Schofield AM, Baines AD, Floras JS, et al. (1996) Digoxin reduces cardiac sympathetic activity in severe congestive heart failure. J Am Coll Cardiol 28: 155-161.
30. Ribner HS, Plucinski DA, Hsieh AM, Bresnahan D, Molteni A, et al. (1985) Acute effects of digoxin on total systemic vascular resistance in congestive heart failure due to dilated cardiomyopathy: a hemodynamic-hormonal study. Am J Cardiol 56: 896-904.
31. Tisdale JE, Gheorghiade M (1992) Acute hemodynamic effects of digoxin alone or in combination with other vasoactive agents in patients with congestive heart failure. Am J Cardiol 69: 34-47.
32. Hauptman PJ, Kelly RA (1999) Digitalis. Circulation 99: 1265-1270.
33. Mason DT (1981) Effects of Cardiac Glycosides on Vascular System. Cardiac Glycosides 56: 497-515.
34. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, et al. (2013) Surviving Sepsis Campaign. International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Crit Care Med 41: 580-637.
35. Dvela M, Rosen H, Feldmann T, Nesher M, Lichtstein D (2007) Diverse biological responses to different cardiotonic steroids. Pathophysiology 14: 159-166.
36. Eisner DA, Smith TW (1991) The Na-K pump and its effectors in cardiac muscle. In: Fozzard HA, Haber E, Katz AM, Morgan HE (eds) The Heart and Cardiovascular System. Raven Press, New York, pp: 863.
37. Sagawa T, Sagawa K, Kelly JE, Tsushima RG, Wasserstrom JA, et al. (2002) Activation of cardiac ryanodine receptors by cardiac glycosides. Am J Physiol Heart Circ Physiol 282: H1118-H1126.
38. Guerrero-Hernández A, Gómez-Viquez L, Guerrero-Serna G, Rueda A (2002) Ryanodine receptors in smooth muscle. Front Biosci 7: d1676-d1688.