DISSERTATION ON

A STUDY OF CLINICAL PROFILE OF

OLEANDER SEED POISONING IN ADULTS

Dissertation submitted to

THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY

In partial fulfillment of the regulations
for the award of the degree of

M.D. IN GENERAL MEDICINE

BRANCH – I

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THANJAVUR - 613 004

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CERTIFICATE

This is to certify that this dissertation entitled "A STUDY OF CLINICAL PROFILE OF OLEANDER SEED POISONING IN ADULTS" is the bonafide original work of Dr.SUBHA.G in partial fulfilment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu Dr.M.G.R. Medical University to be held in APRIL - 2015. The period of the study was from January 2014 to August -2014.

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DECLARATION

I, **Dr. SUBHA.G**, solemnly declare that dissertation titled **"**A STUDY OF CLINICAL PROFILE OF OLEANDER SEED POISONING IN ADULTS**"** is a bonafide work done by me at Thanjavur Medical College, Thanjavur, during January-2014 to August-2014, under the guidance and supervision of **Prof. Dr.K.NAGARAJAN, M.D.,** Unit Chief M-II, Thanjavur Medical College, Thanjavur.

This dissertation is submitted to Tamil nadu Dr. M.G.R Medical University towards partial fulfilment of requirement for the award of **M.D. Degree (Branch - I) in General Medicine**.

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submitted by Dr. G. SUBHA of

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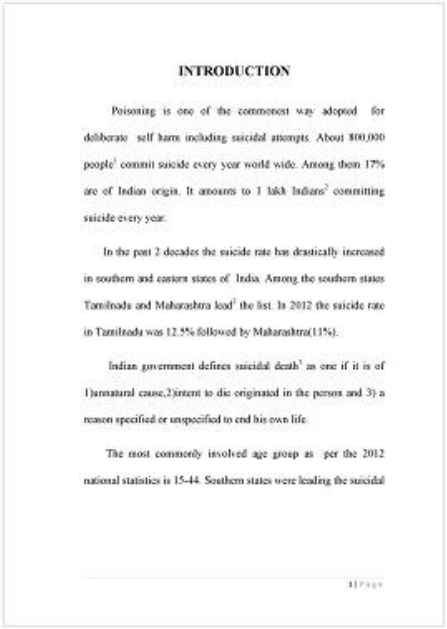

INTRODUCTION

Poisoning is one of the commonest way adopted for deliberate self harm including suicidal attempts. About 800,000 people[1] commit suicide every year world wide. Among them 17% are of Indian origin. It amounts to 1 lakh Indians[2] committing suicide every year.

In the past 2 decades the suicide rate has drastically increased in southern and eastern states of India. Among the southern states Tamilnadu and Maharashtra lead[3] the list. In 2012 the suicide rate in Tamilnadu was 12.5% followed by Maharashtra(11%).

Indian government defines suicidal death[3] as one if it is of 1)unnatural cause,2)intent to die originated in the person and 3) a reason specified or unspecified to end his own life.

The most commonly involved age group as per the 2012 national statistics is 15-44. Southern states were leading the suicidal

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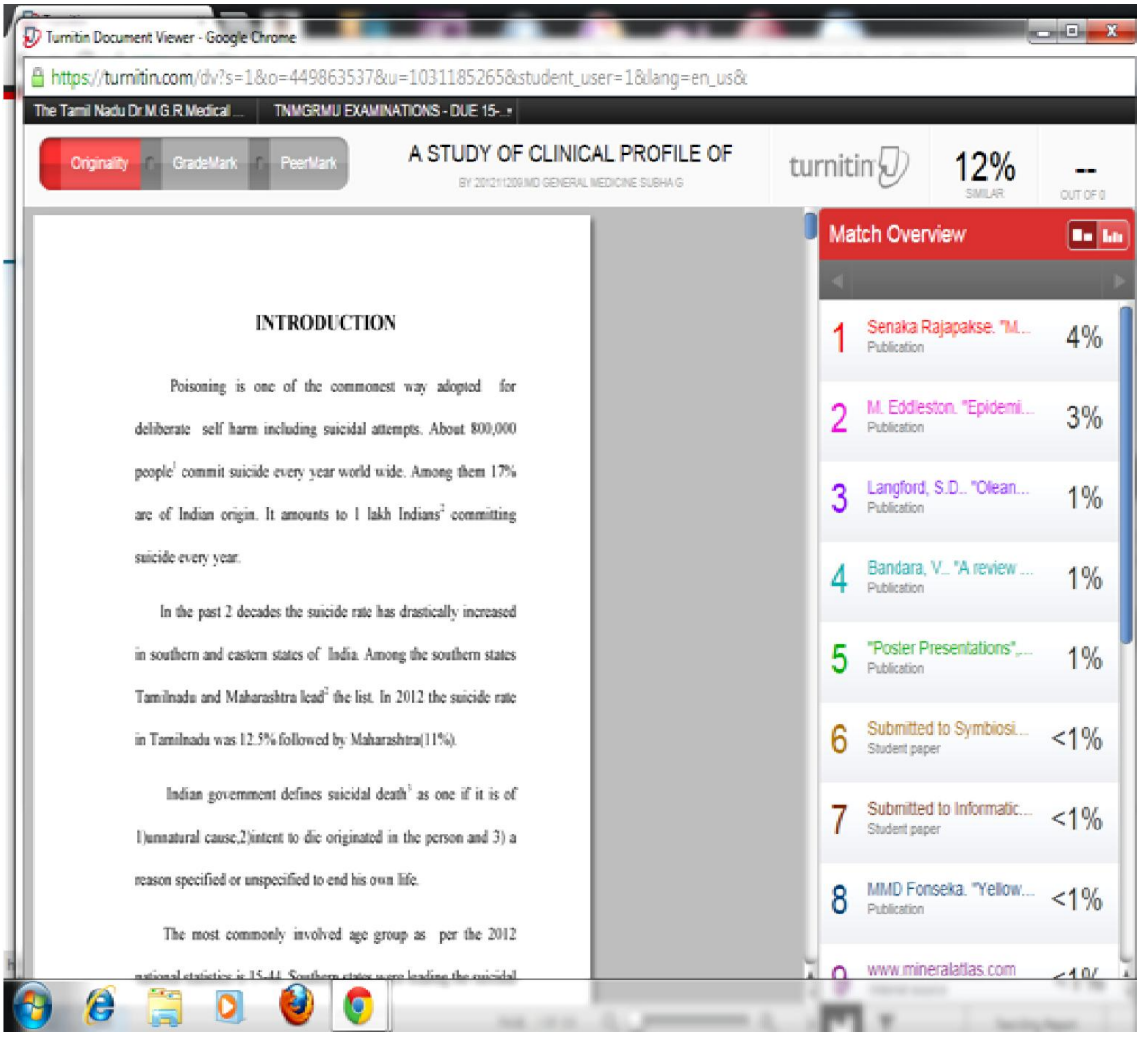
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CONTENTS

ABBREVIATIONS

1. ECG- Electrocardiogram
2. Na^{+} - Sodium
3. K^{+} - Potassium
4. Ca^{2+} - Calcium
5. ATPase- Adenosine triphosphatase
6. AV- Atrioventricular
7. SA- Sinoatrial
8. CNS- Central nervous system
9. LV- Left ventricle
10. ACE- Angiotensin converting enzyme
11. BP –Blood pressure
12. IV- Intravenous
13. GIT- Gastrointestinal
14. SDAC-Single dose activated charcoal
15. MDAC- Multiple dose activated charcoal
16. PAC-premature atrial contractions

A STUDY OF CLINICAL PROFILE OF OLEANDER SEED POISONING IN ADULTS

Deliberate self harm is on the increasing trend and poisoning with yellow oleander seed is common in our region. So our study was directed to assess the clinical profile of yellow oleander seed poisoning in adult patients. This is a prospective study conducted at the Thanjavur Medical college hospital from January 2014 to August 2014. All adult patients with yellow oleander seed poisoning were included. 49 patients with 20 male and 29 female were admitted. The mean number of seeds consumed was 4.65±2.41 . 80 % of patients had gastrointestinal symptoms. Paste form is the most toxic form of ingestion, while chewed was the most common form consumed. ECG changes were noticed in 30 patients with sinus bradycardia being the most common variant. The lethal dose in our study was between 4-8 seeds. Patients who had ECG changes had significantly high potassium levels. There was no in hospital mortality in our study.

Keywords:

Yellow oleander
Pink oleander
Cardiac glycosides
Digoxin
Poisoning
Cardiac dysrhythmias

INTRODUCTION

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Indian government defines suicidal death[3] as one if it is of 1)unnatural cause,2)intent to die originated in the person and 3) a reason specified or unspecified to end his own life.

The most commonly involved age group as per the 2012 national statistics is 15-44. Southern states were leading the suicidal

statistics while northern states like Punjab , Uttar Pradesh had less incidence[2]. Curiously literate population were more indulging in suicides. Cities top the list with Chennai reporting the highest number in 2012 (1283) followed closely by Bengaluru, Delhi[3].

On an average, male suicide rate is twice more than female[3]. But the regional trends may vary.

Reasons cited[2] for suicidal tendency:

Family problems

Illness

Love affairs

Sudden bankruptcy

Failure in examinations

Dowry dispute

Drug abuse

Poverty

Common methods adopted for suicide[2]:

Poisoning (33%)

Hanging (31%)

Self -immolation(9%)

according to 2012 statistics.

Parasuicide[4]:

Para means near or resembling . Parasuicide is an attempted suicide or self harm which does not culminate in death[4]. The term was coined by Norman[4]. It is a serious indicator of future suicide attempts[5]. This practice is more common in adolescents. They should be identified and given proper psychological counselling.

Females do attempt suicides more commonly but males are three times more likely to die out of such attempts[6].

Some studies have found that perfectionism might be the reason behind attempted suicides as those individuals are prone to feelings of failure and hence depression[7].

Now we shall see about the commonest way adopted for suicide, that is poisoning.

Poison:

A poison is defined as a chemical substance capable of causing harm to living organism by chemical reaction or molecular level of action.

A toxin is a substance produced by living organisms for biological function that are harmful to other organisms. Examples are bacterial exo and endotoxins.

A venom is a toxin produced by living organisms that needs to be introduced by sting or bite for exhibiting its action. Examples include snake and scorpion venom.

Classification of poisons:

Broadly classified into gaseous , organic and inorganic poisons.

Gaseous poisons include chemical warfare agents and carbon mono oxide.

Inorganic poisons include corrosives (acids and alkalis) and metallic salts.(lead, mercury)

Organic poisons include plant and animal products. They can be further classified based on the systemic actions they cause.

Local irritants- calotropis

Neurotoxic-

Convulsant-strychnine (nux vomica)

Sedatives-opium and alkaloids

Deliriant- atropica belladonna, dhatura

Cardiotoxic – aconite, oleander, digitalis

So oleander plant whose all parts are poisonous is commonly grown everywhere . The two types of oleander plant are pink oleander and yellow oleander (Thevetia peruviana).

The **yellow oleander** (*Thevetia peruviana*) is a plant grown for its colorfulness. It is grown commonly in tropical countries. The plant contains cardiac glycosides that are poisonous to cardiac muscle and produces a picture similar to digoxin toxicity.

Yellow oleander seed poisoning is common in Thanjavur region. Hence this study is meant to assess the clinical profile of oleander

seed poisoning and its outcome with the management protocol followed in our hospital.

AIMS AND OBJECTIVES

1. To study the clinical profile of yellow oleander seed poisoning in adults.
2. To study the ECG changes in yellow oleander seed poisoning.
3. To study the common type of arrhythmias in yellow oleander poisoning .
4. To correlate the various clinical and biochemical factors with ECG changes.

REVIEW OF LITERATURE

Oleander poisoning – a historical review:

Oleander plant is known since ancient times. It is mentioned in CHARAKA SAMHITA[8]. The name *Thevetia* was given in honour of Mr.Andre Thevit[9]. He has written extensively about this plant. Yellow oleander also has alternative names as follows

- CEREBRA THEVETIA
- THEVETIA NERIFOLIA
- PILA KANER.

All parts of oleander including smoke from burning twigs are toxic. The water in which flower is placed is also toxic. Kernels of seeds are 8 times more toxic than leaves followed by latex. Less toxic parts are flower, bark, root and stem.

It had been used in the past as suicidal, homicidal poison and criminal abortifacient[10]. Arrows poisoned with oleander extract has been used by American tribes for hunting.

It has been used as cattle poison. This lethal plant has been given various names, KARAVIRA and SHATA KUNDU[11,12], describing its lethal nature when misused.

Botany of Yellow Oleander[13]:

The two common species - are *Nerium oleander Linn*

(White or Pink oleander) and Yellow oleander(*Thevetia peruviana Juss).* They belong to the *Apocynaceae* family[13].

Pink oleander is grown in Africa and Europe. *Yellow oleander is grown* in America. Both plants are grown for ornamental purposes in the tropical and subtropical parts of the continents. However, in some countries they are regarded as weeds.

Description of the plant parts:

Pink oleander:

Pink oleander (Fig. 1) is an evergreen shrub. Its leaves are arranged in a linear fashion. They appear to be leathery[12].

The leaves are dark green to yellow green in color. The leaves have vein which is yellow in color running in the center.

Flowers are always arranged in clusters.They bloom at the top of the twigs. The color of the flowers vary from being white, red and pink. The petals are arranged as a whorl. The number of petals is five.

The fruit is arranged as a narrow pod. It has many seeds that seem to be silky haired. The sap formed by the plant is

gummy and clear[12].

Fig 1: Pink oleander plant with flowers.

Fig 2 : Yellow oleander shrub

Yellow oleander[12]:

Yellow oleander is otherwise called as Cerebra thevetia

or Thevetia peruviana. *Cerebra thevetia* is a shrub mostly, and sometimes grows into a big tree. It is diffusely branched. It has dense crown (Fig 2).

Leaves appear to be glossy. They are arranged in a linear manner. They are dark green in color[12].

Flowering occurs in clusters. They are seen at the top of twigs. Different colors of flower are seen. They are yellow,peach,and orange. The flower is tubular. Each flower has five petals.

The yellow flowers are fragrant. The flowers are short lived. They are 5-7 cm in length and 5cm in breadth. Blossoms continue to appear throughout the year.

Fig 3: Picture shows yellow oleander flower.

Yellow oleander flower[12](Fig 3) is a tubular flower and has 5 petals. It is grown in clusters .

Fruits:

Each fruit is 4-5 cm in diameter. A single fruit has a single nut. (Fig 4 & 5)

Fig 4: Oleander Fruits

 F

ig 5 : Black oleander fruits

The fruit of yellow oleander is fleshy and triangular in shape[13]. Its color varies from green in the beginning to yellow and finally into black.

Nuts[13]:

It is triangular or odd shaped. It has deep groove along edge.

It is light brown in color. Each nut has two seeds. It is hard like a stone.(Fig.6)

Seeds[13]:

It is pale yellow in color and hard like a stone (Fig.6). It has a covering kernel and content of glycosides. 2-5 seeds are present in single nut. Every part of the oleander plant is poisonous to living things and even smoke produced by burning the plant twigs can result in poisoning[13,14]. Similarly intake of liquid from oleander stem and nectar of flower has resulted in toxicity of humans and animals.

Fig 6 : Oleander Nuts and seeds

Lactiferous tissue:

It consists of thin walled greatly elongated much branched ducts containing milky fluid called latex. Lactiferous ducts are of two types. They are latex vessels and latex cells. They have numerous nucleus which

lie embedded in this layer of protoplasm lining the cell which is usually thin and made up of cellulose[13].

Latex

It's a milky juice secreted by the plant. It always contains some waste products and it is often irritating and poisonous. It causes inflammation and even blister when it comes into contact with skin. The secretions of this latex is for defence purposes so that animals avoid such plants[13].

Latex composition:

Latex occurs as an emulsion and consisting of variety of chemical substances . Among the nutritive materials, sugar

starchgrains , proteins and oils are found. The waste products in latex include gum, resin ,tannin ,alkaloids ,rubber etc.

Latex also contains salts, enzymes and poisonous substances.

Function of latex:

The exact function of latex is not clear perhaps in someway it is associated with nutrition , healing of wounds and protection against parasites and animals.

Toxicology :

Biologically active moieties of the oleander plants have been identified as early as 1985 by Hayens et al[15] and further many more researchers have validated that . Biologically active molecules with in the yellow oleander plant have insecticidal and anti-mitotic activity[16,17] . They show inotropic action on cardiac musculature (causing increased force and speed of contraction of cardiac muscle). The component molecules of yellow oleander that cause cardiac effects are called the cardiac glycosides[15,18]. They contribute primarily to the plant's toxicity.

The cardioactive glycosides present in pink oleander[19] are Oleandrin, Folinerin and Digitoxigenin.

The glycoside content of Thevetia peruviana is :

- Thevetin A
- Thevetin B
- Nerifolin
- Thevetoxin
- Ruvoside
- Peruvoside

Cardiac glycosides in oleander, as found out by Langford and boor[10](1996) are shown in Table 1. Karawya et al[19] studied the various parts of the plant , common pink oleander. The researchers[19] found out that the seeds and roots of pink oleander have the maximum quantity of toxins . The leaves of these plants have high amounts of oleandrin. Pink flower producing plants have more cardio active glycosides than white flower producing Nerium oleander.

Various studies[17,20,21] done in the past have found out that the seeds of the yellow oleander plant have maximum quantity of the toxins. The

oleander plants examined by researchers Karawya et al showed that the concentration of the toxins in the various parts differed seasonally. The maximum amount was produced during flowering time.

Table 1: Toxins in oleander[10,19,20]

Nerium oleander	**Thevetia peruviana**
Oleandrin	Thevetin A
Folineriin	Thevetin B
Adynerin	Thevetoxin
Digitoxigenin	Nerifoliin
	Peruvoside
	Ruvoside
Flowers, seeds and roots	Seeds and kernel –most concentrated

The cardiotonic glycosides:

The cardioactive toxic principles seen in various parts of the oleander, belong to a group of naturally occurring drugs called cardiac glycosides[15,18,19,20]. They are naturally obtained steroids that exhibit pharmacological effects on cardiac musculature. The primary therapeutic significance of these molecules lies in their ability to exhibit a good inotropic effect on the heart. Yet the therapeutic

window of these compounds are narrow and hence toxicity results very often.

There are two major types of cardioactive glycosides [22] :

- Bufadienolides
- Cardenolides.

Bufadienolides are steroid compounds produced by glands of toads[23]. Cardenolides are obtained from the plants. The use of cardenolides dates back to ancient times. Nearly two hundred cardenolides have been identified so far. These drugs are still in vogue with the best among them is digitalis[10].

The cardenolides identified till now have a common chemical structure derived from three cardiac glycosides, Digoxin, Oleandrin and Thevetin-A[24]. Oleandrin is the toxin present in pink oleander and Thevetin A found in the yellow oleander (Thevetia peruviana) . Digitoxin is produced by the foxglove plant. Sugar moieties are listed by name only with the number of moieties denoted by subscripts.

Since the oleander cardenolides share the similar structure with the digitalis ,their actions almost mimic the digoxin. They resemble digitalis in the form and function.

Structure of cardiac glycoside:

The plant derived cardiac glycosides are composed structurally of three distinct subunits[24] :

- Steroid ring
- Lactone ring

Sugar moiety-Glycosidic linkage

The steroid part , along with the lactone ring is called as the 'genin' or 'aglycone' portion. Except the carbon 10/13 functional group variations ,the cardenolides share similar genin moieties from compound to compound. An oxygen bridge attaches the carbohydrate moieties to the third carbon of the 'A' ring of the steroid backbone. Naturally occurring cardenolides are usually complex, being composed of the genin with one to four unique monosaccharide units.

The carbohydrate in the cardenolide decides the name for the particular compound (e.g. digitoxose, digitoxin; thevetose, thevetin A;

oleandrose, oleandrin). It is specific for each compound and thus it imparts the variability in the biological activity . The structures of digitoxin, thevetin A and oleandrin are shown in figure (Fig.7) for comparison. The structure-activity relationships for naturally occurring cardenolides are thus influenced by the particular carbohydrate moiety and to a lesser degree, by the various functional groups located at carbon 10 and 13.

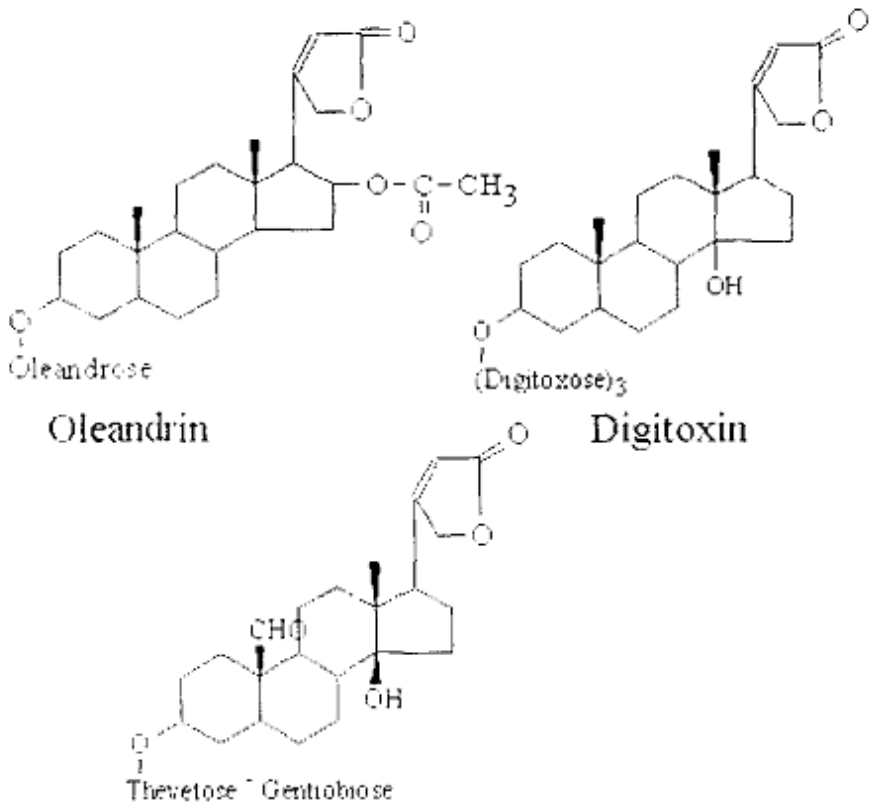

Fig.7 Chemical structure of three cardiac glycosides.

Now lets see few important points about each cardiac glycoside. To begin with it is the prototype cardiac glycoside “DIGOXIN”.

DIGOXIN[25]:

The English botanist and chemist and physician sir William Withering is the first to have made publication on DIGOXIN. It was in the year 1785 he published his observation regarding the use of digoxin in congestive heart failure.

Source:

Digoxin is a glycoside derived from digitalis purpurea (Common name-purple foxglove flower). Since its discovery many researchers have studied its potential use in congestive heart failure. The beneficial mechanisms include:

1. Inhibition of plasma membrane Na^+/K^+ ATPase .
2. Positive inotropic action on failing myocardium
3. Suppression of rapid ventricular response in atrial fibrillation associated with heart failure.
4. By regulating the deleterious effects associated with sympathetic overactivation.

Mechanism of inotropic action[26]:

Normal physiology:

With each cardiac myocyte depolarization, Na^+ and calcium ions enter into intracellular space through L type calcium channels. This calcium in turn releases further calcium from sarcoplasmic reticulum through ryanodine receptor. Calcium interacts with myocardial contractile proteins increasing their contractility. During repolarisation the calcium again is sequesterd by Ca^+ATPase in the sarcoplasmic reticulum and removed from cell by Na^+/Ca^+exchanger[26,27] .

Action of cardiac glycosides:

They bind and inhibit the phosphorylated alpha subunit of sarcolemmal Na^+ / K^+ ATPase and increase the intracellular sodium concentration. This in turn decreases the gradient for calcium exchange and as a result less calcium is removed from cell and more of calcium accumulation in sarcoplasmic reticulum. This results in increased amounts of releasable calcium which enhances cardiac contractility. Elevated extracellular potassium concentrations cause dephosphorylation of alpha subunit of the Na^+/K^+ ATPase[28,29] .

This in turn alters the site of action of digoxin thereby reducing the drug's binding and effect.

Electrophysiologic actions[25]:

At therapeutic concentrations :

It decreases automaticity of atrial and AV nodal tissues.

Increases the maximal diastolic resting membrane potential of atrial and AV nodal tissues.(by increase of vagal tone and inhibition of sympathetic activity) .It prolongs the effective refractory period of AV node and reduces it conduction velocity. These actions contribute to sinus bradycardia, Sinus arrest, Prolongation of AV conduction ,High degree AV block. They also regulate the sympathetic tone. In patients of congestive cardiac failure the sympathetic activity is enhanced due to aberrant baroreflex response to low cardiac output. Reduced blood pressure reduces the baroreflex and thereby baroreflex mediated tonic suppression of CNS sympathetic is reduced.

The sympathetic mediators like plasma norepinephrine and renin and vasopressin is elevated. The cardiac glycosides in turn favourably

influence carotid baroreceptor mechanism. They clinically reduce the CNS sympathetic activity in a not well understood mechanism.

Higher concentrations:

Cardiac glycosides paradoxically increase sympathetic activity at higher concentrations resulting in increased cardiac automaticity and leading to atrial and ventricular arrhythmias. Increased intracellular calcium load and sympathetic tone increases the spontaneous rate of diastolic depolarization and promotes delayed after depolarisations. These in turn leads to malignant ventricular tachy-arrhythmias.

Pharmacokinetics:

Orally given digoxin is observed in proximal small intestine. The time to onset of effect is 30 minutes to 2 hours and the time to peak effect is 2 – 6 hours in case of oral digoxin. The oral bioavailability is 60-80% .When IV digoxin is used 5 to 30 minutes is the time for onset of action and for peak effect 1 to 4 hours. 20 -30% of drug is bound to serum albumin.

It has large volume of distribution due to extensive distribution in heart and kidneys. Skeletal muscle has the largest digoxin storage. The

elimination half life ranges from 26 to 45 hours. Near steady state of drug is achieved 7 days of initiating drug therapy. The main route of excretion is renal clearance(mostly unchanged)which mainly depends on glomerular filtration rate. Some tubular secretion and absorption might be happening. Non renal excretion is 28 to 30%.(mainly biliary). The metabolites include dihydro-digoxin.

Renal clearance time in renal failure patients is 3.5 – 5 days. Digoxin cannot be removed by dialysis. It crosses the placenta and blood brain barrier. The factors influencing the pharmacokinetics and hence toxicity of digoxin are renal function, bioavailability of formulation, volume of distribution, serum albumin concentration, lean body weight, non renal clearance.

In addition drug interactions with that of amiadorone, verapamil and spironolactone influence the circulating digoxin level.

Hypokalemia precipitates digoxin toxicity. Rapid infusion of intravenous calcium in digitalized patients might result in tachyarrhythmias. Measurement of serum digoxin is one way of assessing the need for dose adjustment among many other ways.

Hemodynamic changes caused by digoxin:

1. Increase in cardiac output
2. Increase in left ventricular ejection fraction
3. Decrease in pulmonary capillary wedge pressure, pulmonary artery pressure and systemic vascular resistance.
4. Decrease in end systolic and end diastolic ventricular dimensions.

ECG changes at therapeutic doses:

1. PR interval prolongation
2. ST segment depression.

Clinical use:

Now a days its use is limited to patients with congestive heart failure with LV systolic dysfunction in atrial fibrillation and patients with failure in sinus rhythm remaining symptomatic even after maximum ACE inhibitor and beta blocker use. Therapeutic range -0.8 to 2ng/ml and the toxic range ->2.4 ng/ml.

Clinical features of toxicity include GIT manifestations such as nausea, vomitting ,diarrhea and cardiac arrhythmias and neurological manifestations like xanthopsia .

ECG changes in digoxin toxicity:

Common:

1. Ectopic beats of AV junction or ventricle
2. First degree AV block
3. Accelerated AV nodal rhythm.
4. Sinus bradycardia
5. Sinus exit arrest or block
6. High degree AV block
7. Ventricular arrhythmias.

Treatment of toxicity[30]:

Ectopics or first degree AV block , accelerated junctional rhythm require dosage monitoring . Lidocaine is to be used for digoxin induced ventricular arrhythmias. Electrical cardioversion is to be done with

caution. Effective antidote for life threatening digoxin toxicity is anti digoxin immunotherapy.

Purified Fab fragments from ovine anti-digoxin antisera are available and the effective neutralizing dose needs to be calculated and administered.

Digi Fab dosing[30]:

40 mg of digi Fab binds 0.5 mg of digoxin.

Dose calculation:

Total digoxin ingested / 0.5 mg bound per vial =number of vials to use. It should be given as infusion over 15- 30 minutes after reconstitution with sterile water.

Adverse effects:

Fever, allergic reactions, serum sickness.

Thevetin -A[31]:

It has one methoxyl group and sugar. The sugar content is L.thevetose and two glucose.

Pharmacological actions:

Small doses of thevetin A has stimulating effect on heart while large doses could depress the heart .Many studies reveal small dose of Thevetin increased cardiac output and coronary blood flow. Large doses of thevetin reduces the blood flow.

Effects on cardiovascular system:

When 1-5 cat units of Thevetin-A is given orally it causes fall in heart rate. Maximal effect is seen in 2-3 hours. Thevetin A was found to be absorbed slowly from gastrointestinal tract. Intravenous infusion produces full effect in about 6 minutes and effect wanes in 2-3 hours[31].

In patients of cardiac failure it improves failure by reducing venous pressure and by slowing heart rate. Atrial fibrillation showed improvement with Thevetin[31]. The effect of thevetin on blood pressure is equivocal.

ECG changes:

1. Bradycardia
2. T-wave inversion
3. Prolonged PR interval
4. AV dissociation
5. Ventricular tachycardia
6. Ventricular fibrillation

Thevetin-B

It has one methoxyl group and sugar content is L-thevetose plus two glucose. It has cardiotonic activities. It has very weak digitalis like action. It is one of the weakest of thevetia glycosides. ECG changes are similar to digitalis toxicity.

Nerifolin :

This is the major monoside of Thevetia. It has one methoxyl unit. Moderately potent cardiac glycoside having cardiotonic activities.

Peruvoside:

It has one methoxyl group and L- thevetose molecule. Peruvoside contains an aldehyde group. Peruvoside is more prone to auto-oxidation in liquid form.

Pharmacological actions:

It is effective by oral and intravenous route. It is short acting. It has low serum protein binding. Its effect on serum in therapeutic and toxic doses resembles other cardiac glycosides. It is absorbed from

stomach and excreted by urine, feces and bile. A single dose of peruvoside disappeared in 72-96 hours. There is evidence for entreohepatic circulation. Elimination is faster than digitoxin.

In normal heart after a intravenous dose it produces

1. Increase in ejection velocity in early systole
2. Shortening of pre-ejection period
3. Decrease in heart rate
4. Increase in systolic pressure with diastolic pressure remaining constant.

Effects in congestive heart failure:

1. Increase in cardiac index
2. Decrease in pulmonary arterial pressure.

ECG :

Flattening of T waves.

Indications for the use of peruvoside:

1. Cardiac insuffiency with bradycardia
2. Latent cardiac insuffiency
3. Chronic cor pulmonale

Effects of peruvoside in congestive cardiac failure:

Parameter	Effect
Force of contraction	Powerful inotropic
Heart rate	Decreases
Cardiac output	Increases
Right atrial pressure	Decreased
Left ventricular pressure	Increase in systole and fall in diastole
Systolic BP	Increased
Cardiac minute volume	Increases
Peripheral vascular resistance	Elevated
Coronary blood flow	Augmented
Conductivity	Not affected
Excitability	Not affected

Advantage of peruvoside over oubain:

Its suitable for both oral and IV use. It causes small alterations in ECG. Peruvoside has low toxicity compared to other glycosides.

Ruvoside:

It has one methoxyl group and L-thevetose forms sugar moiety.

Actions:

Absorbtion range is 7 -27% from GIT and eliminated from body in 72-96 hours. It has strong emetic effect. Ruvoside is quick and short acting glycoside with cumulative toxicity.

At low concentration by slowing heart rate it increases force of contraction and at high concentration it stops the heart before any inotropic effort is noted.

Mechanism of toxicity:

Na^+/k^+ ATPase inhibition:

Demiyurek et al[33] and Heard et al[32] have shown that mode of action of cardiac glycosides is by inhibition of the Na^+/k^+

ATPase pump (Fig 7), on the cardiac myocyte cellular membrane. This in turn, produces a intracellular hypernatremia. The high intracellular sodium concentration affects the sodium /calcium exchange channel and intracellular hypercalcemia ensues which leads to increased force of contraction.

The resting membrane potential in the cell membrane is increased due to intracellular hypercalcemia, thus increase in spontaneous depolarization of the cell and hence enhanced automaticity. Lederer WJ[34] in his journal of physiology (1976) has shown that Calcium overload leads to a pulsatile calcium release from the sarcoplasmic reticulum and a fluctuation in resting membrane potential. This fluctuation in resting membrane potential produces some thing called the transient inward current. The transient inward current is the electrophysics behind the arrhythmogenicity of the cardiac glycosides. Two thirds of this transient inward current is caused by an ionic current generated by sodium/calcium exchange while the remaining current is mediated through non specification channels.

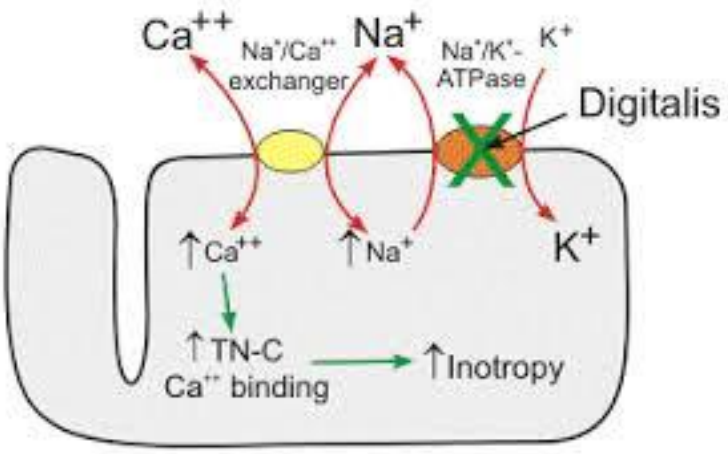

Fig 8 : Mechanism of action of cardiac glycoside

Cardiac glycosides can also produce cardiotoxic effects through release of inflammatory mediators such as histamine, nitric oxide and leukotrienes (Demiyurek et al[33]). When the Na^+/K^+ pump is inhibited it results in hyperkalemia. This has been found out in studies of Haynes et al[15] . Hyperkalemia as an indicator of severeity of acute oleander poisoning has been shown in studies of Bismuth et al[35] .

Autonomic nervous system:

Demiyurek et al[33] have shown that cardiac glycosides cause a profound increase in central sympathomimetic activity on heart which leads to arrhythmias.

Thus use of atropine, or the β-adrenergic agonists, may therefore result in increased tachyarrhythmias .

Role of myocarditis:

Yellow oleander poisoning may produce a picture of toxic myocarditis. It might contribute to some ECG changes.

Role of Electrolyte imbalance:

Electrolyte abnormalities include hyperkalemia, which might contribute to ECG changes.

Anatomic basis of ECG changes:

From various ECG changes we can find out the areas of conducting system involved.

SA node:

It is commonly affected. It manifests as sick sinus syndrome.
Brady type of sick sinus syndrome is most common.
Atrio-venricular node:
Its involvement manifests as

-Junctional rhythm,

-Junctional tachycardia.

Bundle of his:

-Right bundle-occasionally involved

-Left bundle-never involved

-Intraventricular –never involved.

Myocardium:

Myocarditis may occur resulting in non specific ECG changes including ST- T changes.

Mode of poisoning:

- Deliberate Ingestion of plant parts
- Accidental ingestion of plant parts
- Inhalation of smoke produced by burning the oleander dried twigs.
- Ingestion of herbal tea prepared from dried leaves.

Toxic plant parts:

Every part of cardiac glycosides is toxic. Even the smoke produced by burning plant products can induce ECG changes ,when inhaled. But the toxic concentration varies in the plant parts. Highest concentration is seen in the order, as found out by Kyerematen et al[20] .

- Seeds,
- Leaves
- Fruit
- Sap.

Toxic dose:

Ingestion of 8–10 Thevetia peruviana seeds[37] can be fatal to adults. However the toxic dose is variable and it depends on various factors. The toxic manifestations of oleander seed ingestion is determined by variability in toxin concentration of seeds, crushed or non crushed seeds, variability in absorption from the intestine and inter-personal differences in the cardiaovascular response.

Time of symptom onset after ingestion:

It may vary as early as 2 hours to as late as 2 days. The most important factor that determines the rapidity in onset of action is the physical state of the seed ingested. If it's ingested in a well crushed form the symptoms appear rapidly and also more fatal. Eddleston et al[39] noted in two consecutive studies, that significant cardiotoxicity can develop even after 2 days of seed ingestion.

Clinical features[38,39]:

Gastrointestinal symptoms[38,39] :

Oleander seeds can induce abdominal pain, hypersalivation, nausea, vomiting and diarrhea.

Cardio vascular changes (Rhythm disturbances-Fig 9-12)

1. Sinus rhythm
2. Sinus bradycardia
3. Sinus arrest/block (pause >2 s)
4. Mixed AV and sinus block .
5. Nodal bradycardia
6. Atrial fibrillation
7. Atrial flutter with AV block
8. Supraventricular tachycardia
9. First-degree heart block
10. Second-degree heart block
11. Third-degree heart block
12. Ventricular ectopics
13. Nodal tachycardia

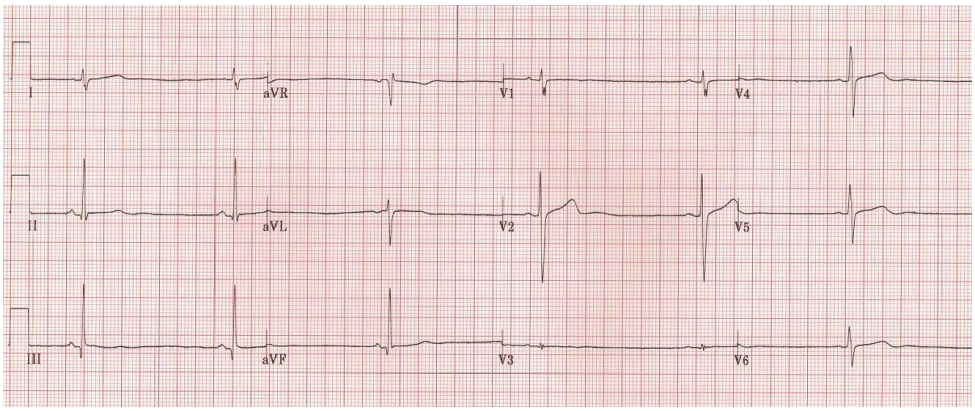

Fig 9: Bradycardia

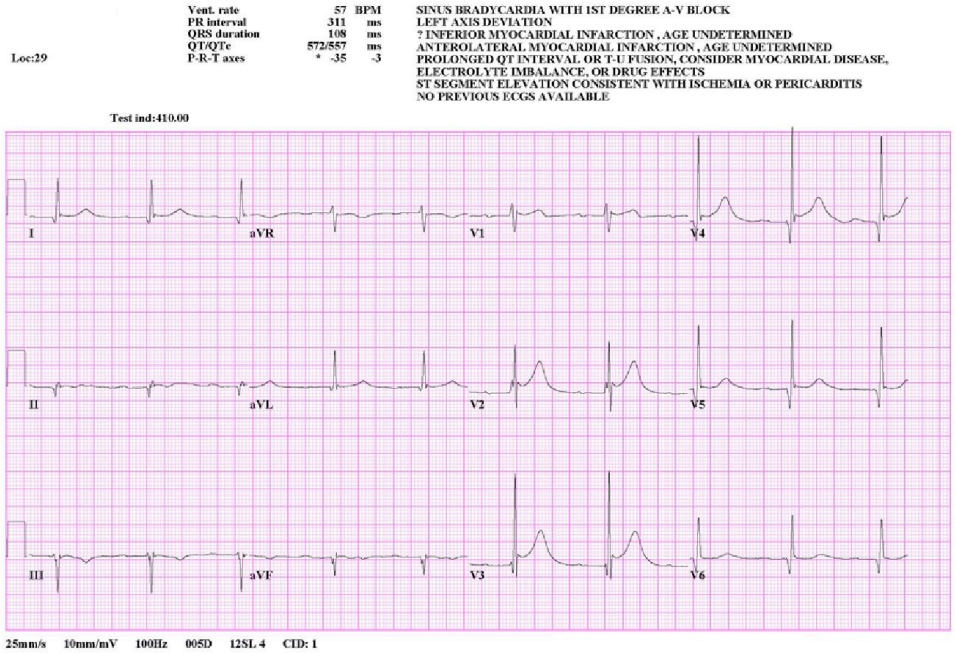

Fig 10: First degree Heart block

13. Ventricular tachycardia

14. Ventricular fibrillation

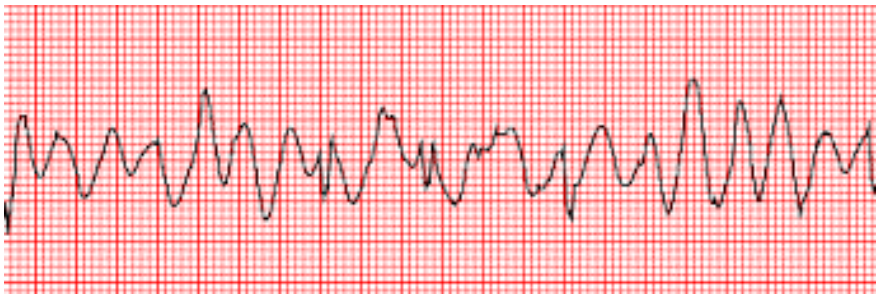

Fig 11: Ventricular fibrillation

Among the cardiac dysrythmias various studies have reported Brady arrhythmias to be more common .In severe poisoning ventricular tachy-arrhythmia and DC resistant Ventricular fibrillation has occurred.

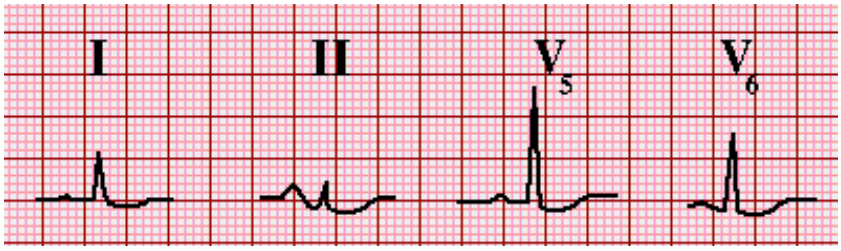

Fig 12: T-wave flatening

Neurological features:

Barceloux et al[38] and Haynes et al[15] observed that oleander poisoning can induce tremor, drowsiness, ataxia, visual disturbances (yellow vision), mydriasis, weakness, convulsions.

They can also cause irritation of the mucus membranes, resulting in buccal erythema, numbness, dysesthesias and a burning sensation in mouth.

Rare manifestations:

Samal et al[40] in his study observed jaundice and renal failure after Thevetia peruviana poisoning . He subsequently reported an additional four patients with jaundice and renal failure after Thevetia peruviana poisoning (Samal, 1990[40]). However, jaundice and renal failure have not otherwise been associated with Thevetia peruviana poisoning. Pahwa and Chatterjee[41] (1990) reported inflammatory and degenerative changes in liver and kidney in an in vivo study of yellow oleander poisoning in Rat animal model study.

Diagnosis[42]:

1. Detailed history to be recorded.

2. Part of plant taken ,time of intake and amount ingested

3. Time of appearance of symptoms after ingestion. However, this is only possible in patients who present before onset of significant cardiac symptoms[42].

Patients who present to the hospital with established cardiac manifestations should be given appropriate treatment for the arrhythmias before the plant is identified. Dwivedi et al[43] have quoted that in a geographical area where oleander is present, a history of poisoning

(especially with known plant or plant product ingestion) and ECG abnormalities similar to digoxin toxicity ,it should be considered oleander poisoning unless proved other-wise.

Toxicological analysis[42]:

1. Fluorescence polarization immunoassay (FPIA)[44]
2. Digoxin immunoassay (Digoxin 111)[45] considered to be the most sensitive and rapid for detecting oleander poisoning.
3. Liquid chromatography[46] -electrospray tandem mass spectrometry (LC-MS/MS) is a new direct method.

   It can be used in sensitive medicolegal cases.

Management [42,47,48]:

We shall review the management under the following topics:

1. Initial assessment and supportive management
2. Decontamination
3. Management of arrhythmias
4. Specific antidote

Initial assessment and Supportive care:

Airway , breathing and circulation of the patient should be assessed as early as possible. This initial management is similar to other poisoning cases. If there is dehydration it should be corrected with IV fluids. The consciousness of the patient should be taken note of , as well

his ability to protect his airways. The patient's vitals should be monitored periodically. Immediately after taking care of the basics an ECG is recorded and continuous cardiac monitoring should be initiated. In the ECG especially cardiac rhythm disturbances should be looked for .

Duration of monitoring:

Some individuals of oleander seed poisoning with continuous sinus rhythm may suddenly develop cardiac arrest. The mechanism probably could be the use of anticholinergic atropine excessively which can precipitate sudden tachyarrhythmias.

So , for the safe discharge of a patient consider factors such as:

1. Absence of symptoms
2. Normal ECG 24 hours after oleander seed ingestion
3. Stable vital signs.

In any patient of oleander seed poisoning minimum of 24 hours of cardiac monitoring is recommended. Severe poisoning is indicated by presence of

1. Brady arrhythmias
2. Shock
3. Hyperkalemia

4. Persistent vomiting
5. Prolonged abdominal pain

Supportive care:

Fluid management:

Fluids form the first line of management in any poisoning.

The patients of yellow oleander poisoning may be dehydrated due to vomiting most commonly and sometimes diarrhea.

They may develop hypotension if dehydration is very severe.

Very vigorous rehydration should be started immediately.

So far studies have not been conducted to decide the type of IV fluid to be used . Yet normal saline is preferred to be the best.

Sometimes if vomiting is very severe the use of antiemetic like metachlopromide or ondansetron are warranted.

Electrolytes monitoring:

Serum Potassium:

Hypokalemia can potentiate digitalis toxicity. Similarly hypokalemia can precipitate toxicity in yellow oleander Poisoning. So serum potassium levels should be checked regularly at an interval of 6 hours. Any hypokalemia should be corrected with IV potassium.

Hyperkalemia:

Yellow oleander poisoning results in hyperkalemia similar to other cardioactive glycosides. It is a ominous sign and leads to poor outcome. Hyperkalemia has to be corrected.

Trials have not proven that correction of hyperkalemia prevents arrhythmias or death. Insulin-dextrose infusion is used to correct the hyperkalemia. Still its role in glycoside poisoning like yellow oleander is not studied. Insulin dextrose has been found to be cardioprotective in animal models of digoxin toxicity. Apart from lowering the serum potassium level by means of transcellular shift , the insulin dextrose infusion also modifies the accessibility of sodium/potassium(Na^+ /K^+) ATPase channels by digoxin. This action might reduce the toxicity of cardiac glycoside. Potassium binding resin should be avoided as the total body potassium is not increased . It might worsen the hypokalemia if present. If renal failure or metabolic acidosis supervenes hyper kalemia can be corrected with sodium bicarbonate, otherwise it is unlikely to be used.

Serum Magnesium:

Cardiac glycoside poisoning is an arrhythmogenic state and hence all electrolyte disturbances has to be taken seriously. No data is available in

the literature regarding serum magnesium levels and severity of oleander poisoning. Both hypermagnesemia and hypomagnesemia can occur. Hypomagnesemia can coexist with hypokalemia and its correction is important as it may precipitate significant arrhythmias. Further magnesium correction will improve the potassium levels in the body.

Serum Calcium:

Oleander poisoning leads to a state of intracellular hypercalcemia and so there may be a transient intravascular i;e extracellular hypocalcemia. Usage of IV calcium to correct thus hypocalcemic state can precipitate dangerous arrhythmias.

Gastric decontamination:

Gastric lavage and induced vomiting[48]:

Gastric lavage has been used since time of Hippocrates for poisoning. Though there is no evidence in favour of gastric lavage in literature ,it is continued to be used in clinical practice..

Activated charcoal[49]:

Cardiac glycosides gets absorbed from small intestine , metabolized in liver and re-secreted in to the intestine . That again gets absorbed .Thus there is a enterohepatic and enterovascular cycle ,that continues till all the

drug gets eliminated . Logic says that interruption of this cycle may reduce toxicity. Hence activated charcoal is being used to break this cycle. Activated charcoal diminishes glycoside toxicity by two mechanisms.

1) It prevents absorption of glycosides into systemic circulation after ingestion.

2) It interrupts the entero hepatic and enterovascular cycles and hence increases the elimination.

In experimental studies with animals activated charcoal has been shown to bind cardiac glycosides, thus favouring enhanced excretion of the glycoside. Multi dose activated charcoal has been found out to enhance the elimination of cardiac glycoside. Patients with yellow oleander poisoning who were treated with single dose or multidose activated charcoal in a study trial were shown to have a less total hospitalization time ,due to reduced half life of the drug. There was no significant difference between single or multiple doses of activated charcoal usage. This may be explained by two mechanisms.

1) activated charcoal acts even long after consumption of cardiac glycoside by interfering with the notorious enterohepatic and enterovascular cycling.

2) atropine given concomitantly in these patients delays the gastrointestinal transit time and SDAC had more time to adsorb the glycoside.

It's a double edged sword and at times delayed gastrointestinal transit time might backfire as more time is available for glycoside absorption and hence increased toxicity. So many studies have been conducted to study whether SDAC or MDAC is effective. It is difficult to have a final say whether SDAC or MDAC is efficacious. In clincal practice single dose activated charcoal is being used widely[49,50]. More studies are needed to establish the superiority of MDAC if any.

Management of Rhythm disturbances[51]:

Bradyarrthymias[51] are the most commonly encountered rhythm disturbance in oleander poisoning. They are the most important primary cause of death in yellow oleander poisoning. They are commonly treated with

1) Atropine,

2) Isoprenaline

3) Temporary pacemaker insertion .

Ideally all symptomatic bradyarrhythmias should receive a temporary pacemaker. However in rural areas with out tertiary care facilities , pacing may not be available and hence pharmacotherapy is considered. Beta-adrenergic agonists or anticholinergics are used commonly in this setups. The benefit of treating asymptomatic bradyarrhythmias with these drugs is not proven.

This may be a double edged sword. Increasing the heart rate results in elevated intracellular calcium concentrations. Elevated intracellular calcium precipitates abnormal electrical activity, like early and delayed after depolarizations.

The aberrant electrical activity can precipitate ventricular fibrillation.

Glycoside increases intracellular Ca^{2+} concentration. Beta-adrenergic stimulation increases peak systolic intracellular Ca^{2+} concentrations . Isoprenaline is one of the common beta-agonist used to treat the bradycardia in oleander poisoning.

Theoritically speaking isoprenaline can itself precipitate tachyarrhythmias. Despite the regular use of isoprenaline in clinical practice to treat brady arrhythmias its safety and efficacy is not known.

Few words about isoprenaline:

Isoprenaline is a strong beta 1 and beta 2 adrenergic agonist. It has a half life of 3-7 hours. It is metabolised by liver and lungs and excreted in the urine 50-80%

Dose: can be given as bolus dose or continuous infusion.

Bolus dose:

Initially if IV bolus is used it is given at the dose of 0.02-0.06mg followed by 0.01-0.02mg .

Infusion dose :

5 microgram per minute followed by doses of 2-20microgrm minute based on patients response.

Common adverse effects encountered are tachycardia, hypertension, dysrhythmia, confusion, tremor, headache, angina and syncope.

Another drug used commonly to increase the heart rate is atropine. It improves atrioventricular nodal conduction. The effects of

atropine are short-lived .So repeated doses or infusion of atropine may be required. The beneficial role of atropine in reducing mortality or decreasing the need of temporary pace maker insertion is not proven in scientific trials.

Atropine is anticholinergic and hence it also reduces gastrointestinal motility causing a state of ileus. This can increase the time available for absorption of cardiac glycosides . So atropine may also paradoxically increase the toxicity of oleander glycosides. Hence atropine has to be with held when features of atropine toxicity like restlessness, confusion, blurred vision, tachycardia, hypertension occur .

Large doses of atropine can increase the myocardial workload, due to increase in heart rate. This may result in a further rise in intracellular calcium concentrations (as in the case of isoprenaline) and precipitate dangerous tachyarrhythmias, including ventricular fibrillation .

But these effects are least likely if low doses of atropine alone are used. Careful dosing and small increments of atropine may prevent tachyarrhythmias. In patients of yellow oleander poisoning the incidence rate of atropine toxicity causing tachyarrhythmia is not known. The target

heart rate when using atropine should be between 60 and 90 beats per minute.

Few words about atropine perse:

Atropine is a muscarinic receptor antagonist. It has a half life of about 2- 3 hours.

It is metabolized in the liver and excreted in the urine.

For sinus bradycardia the dose is 0.5 to 1 mg or 0.04 mg /kg every 5 minutes not to exceed 3 mg.

Commonly observed adverse effects include palpitations , dry mouth, dry skin , difficulty in micturition , restlessness and confusion.

Cardiac pacing[51]

Temporary pacemaker insertion is the common method of treatment if the heart rate of the patient is below 40/min with any form of sick sinus syndrome or heart block .

Though there are no randomized control trials, in setting of oleander poisoning ,temporary pacing should be offered to all patients with heart rate < 40/min.

Temporary cardiac pacing should be continued till the rhythm returns to normal . However pacing is not available every-where and adequate training is important in pacemaker insertion ,as following complications can occur

1. Local trauma,
2. Pneumothorax,
3. Bleeding, and
4. cardiac perforation-very rare

The much feared complication associated with pacemaker insertion is the development of tachyarrhytmias due to stimulation of irritable myocardium directly by the pacing wire.

Tachyarrhythmias[52,53]:

The most dreaded rhythm disturbance in yellow oleander poisoning is tachyarrhythmias . They are resistant to usual treatment methods. Research studies are not available regarding the use of antiarrhythmic agents in oleander poisoning . Whatever scientific data available is from digitalis poisoning. Lidocaine is the preferred agent in the treatment of ventricular arrhythmias.

Lidocaine 100 mg is administered intravenously(50 mg if circulation is impaired), followed by 4 mg/min for 30 min, 2 mg/min for 2 h, then 1

mg/min). Other antiarrhythmic agents like Amiodarone, quinidine, and calcium-channel blockers are contraindicated as they may increase digitalis concentrations. The use of beta-blockers may worsen heart block.

Ventricular tachycardia seen in oleander poisoning is often resistant to treatment with electrical cardioversion. Electrical cardioversion is to be avoided as it can also result in ventricular fibrillation or asystole. It possibly has a role in resistant ventricular tachycardia cases using lower energy.

Atrial fibrillation associated with digitalis toxicity shows a slow ventricular response . It requires no specific management.

Role of intravenous magnesium:

Normally magnesium is required for Na^+/K^+ pump functioning. Hence it opposes the action of digoxin. So intravenous magnesium can be considered in case of cardiac glycoside poisoning even in the presence of hypermagnesemia or normomagnesemia. More studies are required to prove its efficacy.

The specific antidote:

Digoxin specific antibody fragments:

In management of any poisoning the use of specific antidote plays a crucial role. Digoxin specific antibody fragments[54,55] are the specific antidote in oleander poisoning. . Various studies have confirmed it to be effectively reverting dangerous arrhythmias and hyperkalemia.

It is likely that a reduction in cardiac arrhythmias will result in a reduced mortality. A single observational clinical study done in Srilanka has shown reduced mortality with the use of this specific antidote.

The effective dose of digoxin specific antibody fragment , is 1,200 mg intravenously, irrespective of age, sex, or body weight.

The use of smaller doses over longer period has not been proven to be effective than usual dose in trials. The dose needed in yellow oleander poisoning is significantly higher than that in digoxin poisoning.

Digoxin specific antibody fragment is very expensive. A single dose (1,200 mg) of digoxin-specific antibody fragments is dissolved in 100 ml of normal saline and given by intravenous infusion over 20 min. The ideal dosing regimen is yet to be formulated through various studies and trials.. Side effect is uncommon, and a test dose is not needed.

One should be alert and watchful for the development of anaphylactic reactions. Yet prophylactic use of antihistamine or steroid is not needed. In the event of anaphylactic reactions, the infusion has to be stopped immediately and the standard management protocol for anaphylaxis has to be followed.

In some non-responsive patients, a second or rarely a third dose of digoxin-Specific antibody might be needed.

Other measures:

Hemodialysis or hemoperfusion have not been found to be effective in cardiac glycoside poisoning because of the large volume of distribution. Yet studies have not been done studying their role in yellow oleander poisoning.

Role of oleander as medicine:

Charakas, a pioneer in Ayurvedic medicine and Sushrutha an ancient surgeon have made references about this plant in their treatises. According to the literature, oleander has been used as medicinal plant to treat various diseases in Indian system of medicine.

Role in Ayurveda :

To treat Dropsy

Rheumatism

Skin infections

Anal fissure and hemorrhoids

Ureteric stone

Malaria

Role in Unani:

To treat skin lesions of

Leprosy

Syphilis.

It has been used as an abortifacient too.

MATERIALS AND METHODS

Study design:

This study is a single centre non randomized prospective study meant to study the clinical profile of yellow oleander seed poisoning.

Study period:

Consecutive patients of yellow oleander seed poisoning admitted in Thanjavur medical college hospital during the period of 8 months between January 2014 to August 2014 were taken up for the study.

Inclusion criteria:

All adult patients of yellow oleander seed poisoning aged above 18.

Exclusion criteria:

1)Pediatric patients

2) Patients who had coexisting cardiac illness

3) Patients who were taking cardiotoxic drugs

4) Patients who had ingested plant parts other than seed.

5) Patients who were known cases of dyselectrolytemias

Study centre

This study was carried out in Department of Medicine, Thanjavur medical college hospital, Thanjavur, Tamilnadu.

All cases were admitted and examined in detail in the wards and clinical data was recorded in the proforma annexed herein. All cases were followed till discharge or death.

Clinical details:

Personal particulars like age , sex and socio-demographic details were obtained. Clinical details regarding the poisoning such as color of the seed , number of seed , form of consumption, taken in empty stomach or with food were enquired and recorded. Time interval between poisoning and hospitalization and details of first aid were obtained . Clinical symptoms experienced by the patients were recorded.

Clinical examination:

Examination was done in a detailed manner and vital signs were recorded and system examination was carried out.

ECG Monitoring :

ECG was taken in all cases after admission. Routine conventional limb leads ,chest leads and long strips were recorded. Continuous cardiac monitoring was done in the first 24 hour period and thereafter in some needful patients. After that ECG was recorded twice for the second day and thereafter once daily until discharge.

Lab investigations:

1. Random blood sugar
2. Blood urea
3. Serum creatinine
4. Serum potassium
5. Serum sodium
6. Urine routine

These investigations were carried out in all patients.

Echocardiogram : It was carried out in all patients who were included in the study.

Treatment :

All patients were admitted and initially treated with gastric lavage with normal saline. They were treated with IV fluids and steroid . If sinus bradycardia was there orciprenaline was started and given until the bradycardia resolved. If there was severe bradycardia with heart rate <40 the patients were kept in ICU and treated with small doses of atropine. Pacing facilities as well as digoxin specific antibodies are not available in our hospital.

STATISTICAL ANALYSIS

The patients data were collected prospectively and entered in the proforma (Annexure). The data was digitalised in Microsoft excel software . Statistical analysis was done using SPSS 20 software.

The categorical variables have been described as proportions and percentages. The continuous variables have been expressed as Mean and Standard deviation, as well as range.

The effect of various factors on presence of ECG changes and no ECG changes was analysed by unpaired 't'test (difference between means) for continuous data. Chi-square test and Fischer's exact test (difference between proportions) have been used to compare the categorical data. P-value <0.05 was considered significant in the study.

OBSERVATION AND RESULTS

49 patients of yellow oleander seed poisoning were enrolled in the study period from January 2014 to August 2014.

Age Incidence :

Out of the total 49 patients the number of patients below age

20 were 7(15%) and between 20 and 40 were 38 (77.6%) and age above 40 were 4 (8.2%). The mean age was 27.89± 9.06. In our study incidence of poisoning is more in the age group between 20 and 40.

Table 2 : Age Incidence

Age group (years)	Number of patients	Percentage
<20	7	14.2%
20-40	38	77.6%
>40	4	8.2%

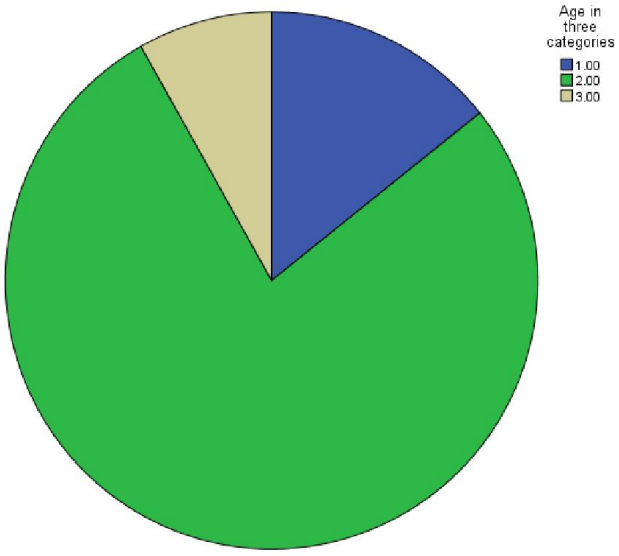

Fig 13 : Age incidence Pie Chart

Sex Incidence :

Out of the total 49 cases 20 were males and 29 were females . The male female ratio was 1:1.6. Percentage of males in this study was 40.8%. In men the common age group was 20 -40 years and the number of cases in this age group was 17 (85%). Number of cases in the age group below 20 years was 1 (5%) and above 40 was 2(10%). Incidence appears to be more in the females 29 (59.2%). In females the common age group was between 20-40. The number of patients were 21(72.41%). The number of female patients in the age group below 20 was 6(20.6%). The number of female patients in the age group above 40 was 2(6.8%).

Table 3: Sex incidence

Age group in years	Male n(%)	Female n(%)
<20	1(14.3%)	6(85.7%)
20-40	17(44.7%)	21(55.3%)
>40	2(50%)	2(50%)

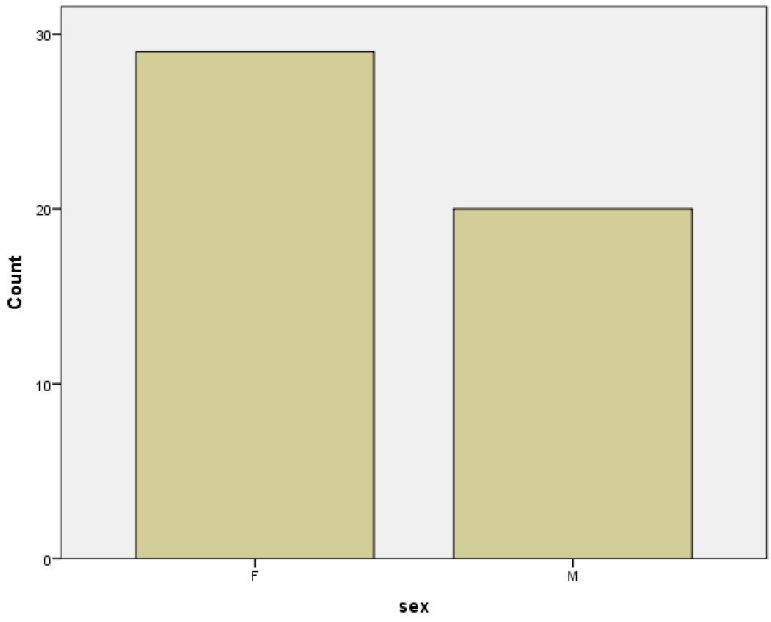

Fig 14 : Sex distribution

Number of seeds consumed:

The mean number of seeds consumed was 4.65±2.41. The range being from 1-10. Minimum of 1 seed was consumed by 2 patients and the maximum of 10 seeds were consumed by 1 patient. 10 patients had consumed 2 seeds (20.4%).

Table 4: Number of seeds consumed

No of seeds consumed	No of patients	Percentage
1	2	4.1%
2	10	20.4%
3	8	16.3%
4	5	10.2%
5	6	12.2%
6	7	14.3%
7	3	6.1%
8	4	8.2%
9	3	6.1%
10	1	2%

Forms of consumption :

The seeds were taken most commonly in the chewed form. Number of patients in chewed form were 22(44.9%).

Table 5: Forms of seed consumption:

Form of consumption	Number of patients	Percentage
Chewed	22	44.9%
Paste	21	42.9%
Grounded	6	12.2%

Paste form is considered to be dangerous as glycoside bioavailability is increased.

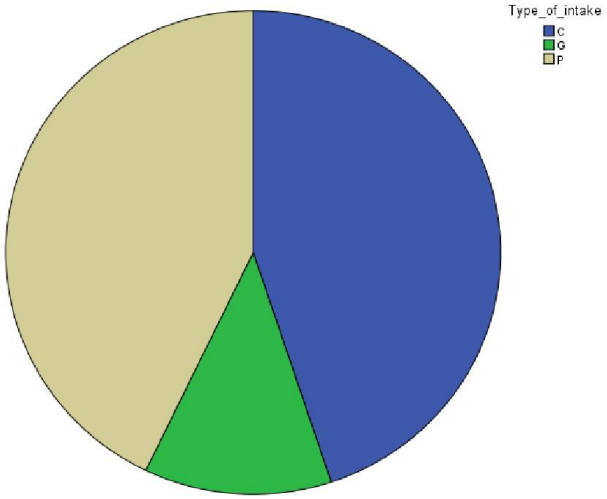

Fig 15 : Form of seed Pie chart

Time interval between consumption of poison and admission:

The number of patients admitted within 6 hours of poisoning were 29 (59.2%). The number of patients admitted between 6 -12 hours of poisoning were 20(40.8%).

Table 6: Time interval between consumption and admission

Time interval between poisoning and admission	Number of patients	Percentage
Less than 6 hours	29	59.2%
6-12 hours	20	40.8%
Total patients	49	

Gastrointestinal symptoms:

Out of the 49 patients 37 patients had GIT symptoms ,12 patients had no GIT symptoms .

Table 7: Gastrointestinal symptoms

GI symptom	Number of patients	Percentage
Vomiting	30	61.2%
Diarrhoea	1	2%
Vomiting and Diarrhoea	6	12.2%
No symptoms	12	24.5%

Cardiac symptoms:

Out of the 49 patients enrolled in the study only 7 patients had cardiac symptoms . All the 7 patients developed palpitations.

Table 8: Cardiac Symptoms

No cardiac symptoms	**42**	**85.7%**
Palpitations	7	14.3%

Mean pulse rate at admission:

Out of 49 cases 30 patients had pulse rate in the range of 60-90.Only 19 patients had pulse rate in the range of 40-60 (38.72%). None of the patients in our study had pulse rate less than 40 at admission. The mean pulse rate at admission was 69±14.

Table 9: Pulse rate at admission

Pulse rate range	**Number of patients**	**percentage**
<40	0	0
40-60	19	38.72%
60-90	30	61.2%

Incidence and Type of ECG changes:

Out of 49 cases , 30 patients (61.2%) showed ECG changes. 19 patients had normal ECG. Various types of ECG changes are shown in table 9. Sinus bradycardia is the most common type of ECG change. The other types of ECG changes are also shown in the table.

Table 10: Types of ECG change

Types of ECG change	ECG change present (n)	ECG change absent (n)	Total patients
Sinus bradycardia	24	25	49
I-deg.AV block	9	40	
Premature atrial contraction	5	44	
Tall T waves	3	46	
T wave inversion	4	45	
ST depression	2	47	
Junctional rhytm	1	48	

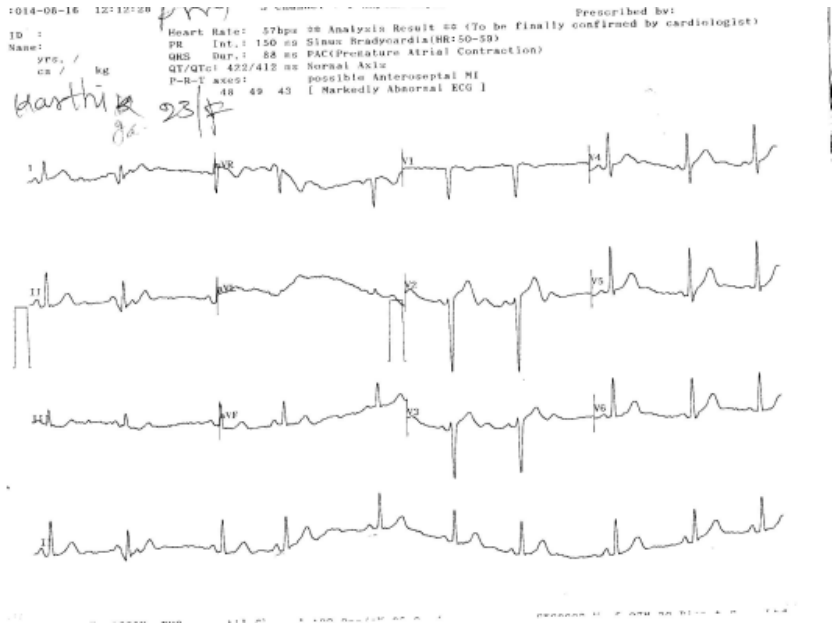

Fig 16: ECG showing , Bradycardia and PAC

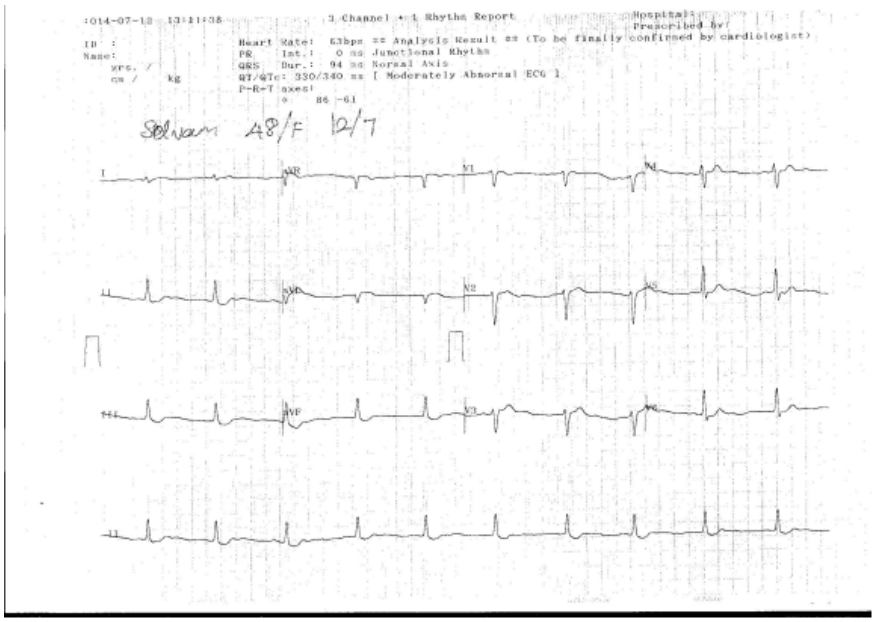

Fig 17: ECG shows sinus brady cardia

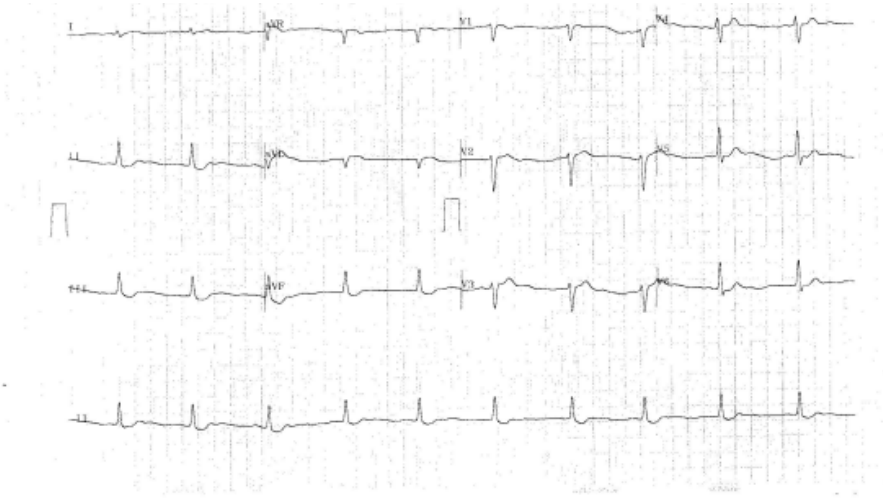

Fig 18: ECG shows junctional rhythm with no p waves visible.

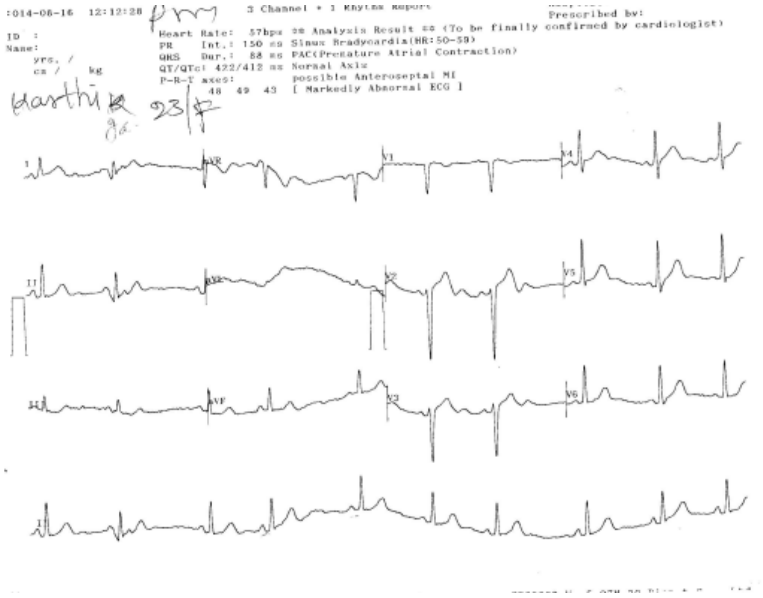

Fig 19: PAC

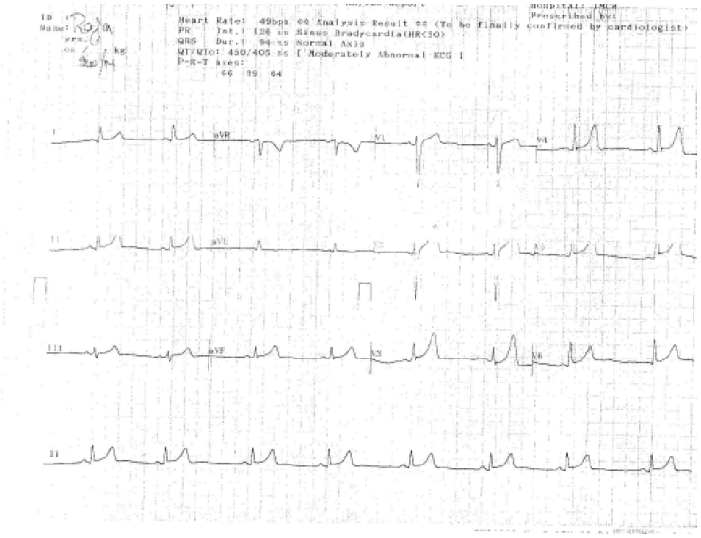

Fig 20 : Sinus bradycardiaT.his ECG shows sinus brady cardia with Heart rate -49/minute.

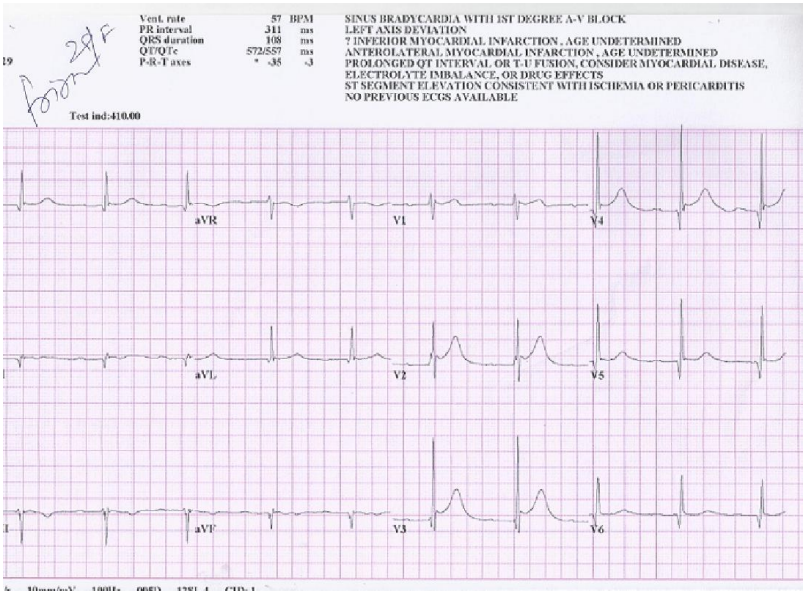

Fig 21: Bradycardia, 1st degree Heart block

Correlation between age and ECG changes:

Out of 7 patients in the less than 20 age group 5 patients had ECG changes (71.4%). Out of 38 patients in the age group between 20-40 , 22 patients had ECG changes (57.8%). Out of 4 patients in the age group above 40 ,three patients had ECG changes(75%). In our study patients < 20 years and > 40 years had more ECG changes.

Table 11 : ECG changes among age groups

Age group (n) years	Number of patients with ECG changes	Percentage
<20 (7)	5	71.4%
20-40 (38)	22	57.8%
>40 (4)	3	75%

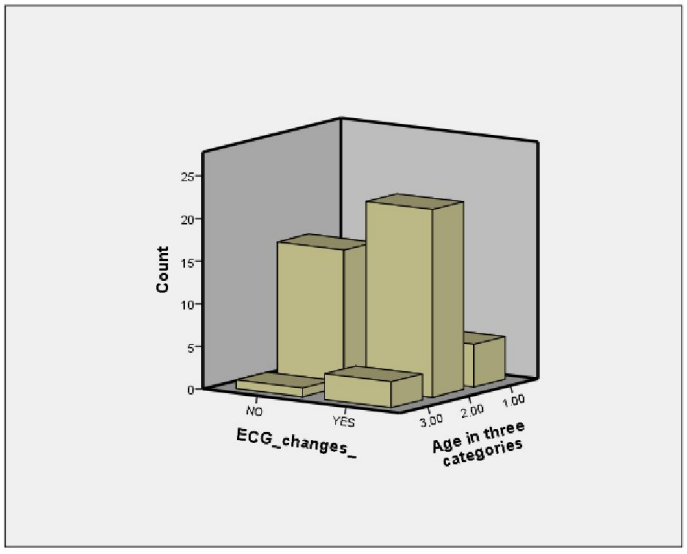

Fig 22: ECG changes among different age groups

Correlation of type of intake with ECG changes:

Maximum number of ECG changes was seen when seeds were taken in paste form. 90% of the patients who had taken the seeds in paste form

developed ECG changes. 83% of the patients who took the seeds in grounded form developed ECG changes. When the seeds were taken as such or chewed and eaten only 27% developed ECG changes.

Table 12: ECG changes-Relation to form of seed taken

Type of intake (n-Patients)	Patients with out ECG changes	Patients with ECG changes	p-value
Chewed (22)	16	6 (27.27%)	0.01
Ground (6)	1	5 (83.33%)	
Paste (21)	2	19 (90.47%)	

P<0.05 –significant

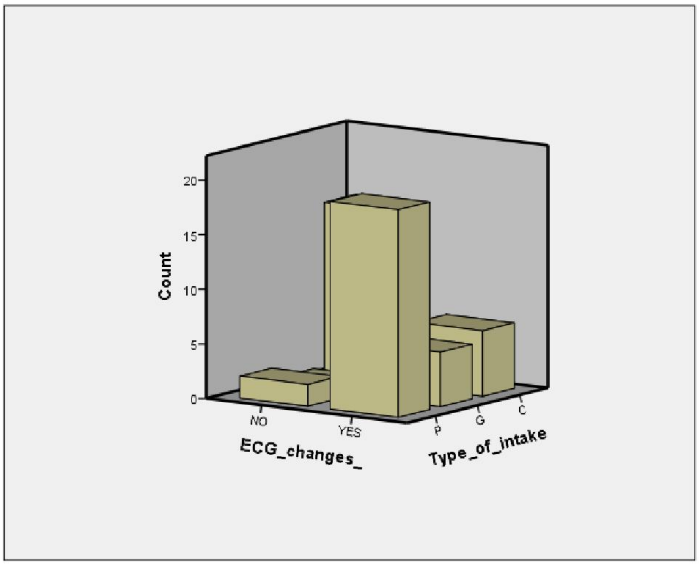

Fig 23: ECG changes and type of consumption

ECG changes and Time of Hospitalisation after poisoning :

The patients who presented earlier to the hospital had less incidence of ECG changes than those presented later to the hospital after poisoning .This is proved by the fact that ,the mean duration of admission to hospital after poisoning was 2.9 hrs in those with out ECG changes ,compared to 6hrs in those with ECG changes .

Table 13: Time after poisoning and ECG change

ECG change	Mean Duration of admission after poisoning(hrs)	P-value
Present	6.03±2.25	0.001
Absent	2.94±1.43	

P<0.05 –significant

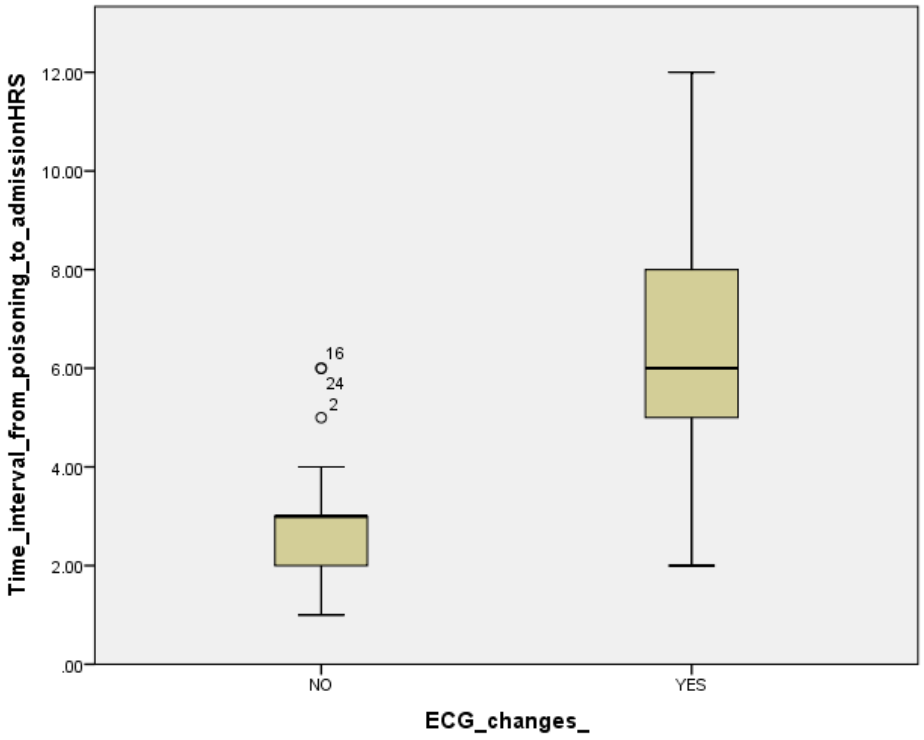

Fig 24 : ECG changes and Time interval from poisoning

Correlation between ECG changes and number of seeds taken:

In our study patients who had ECG changes had taken significantly more number of seeds than those who did not have ECG change. The mean number of seeds in group with ECG change was 5.86 versus 2.73 in those with out ECG change .

Table 14: Number of seeds and ECG change

ECG change	Mean number of seeds(n)	p-value
Present	5.86±2.20	0.001
Absent	2.73±1.19	

P< 0.05-significant

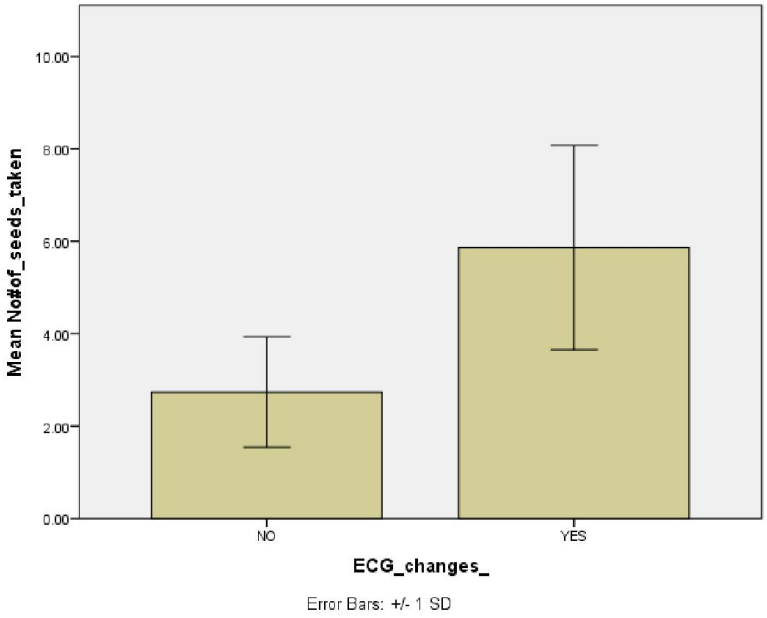

Fig 25: ECG changes and No. of seeds ingested

Correlation between ECG changes and S.K^{+}

In our study the mean serum potassium levels was 5.01±0.58 meq/l (3.5-6.0) . The mean serum potassium was higher in those with ECG changes than in those without.

Table 15: Serum potassium and ECG changes

ECG change	Mean serum potassium (meq/l)	p-value
Present	5.26±0.58	
Absent	4.61±0.26	0.001

p<0.05-significant

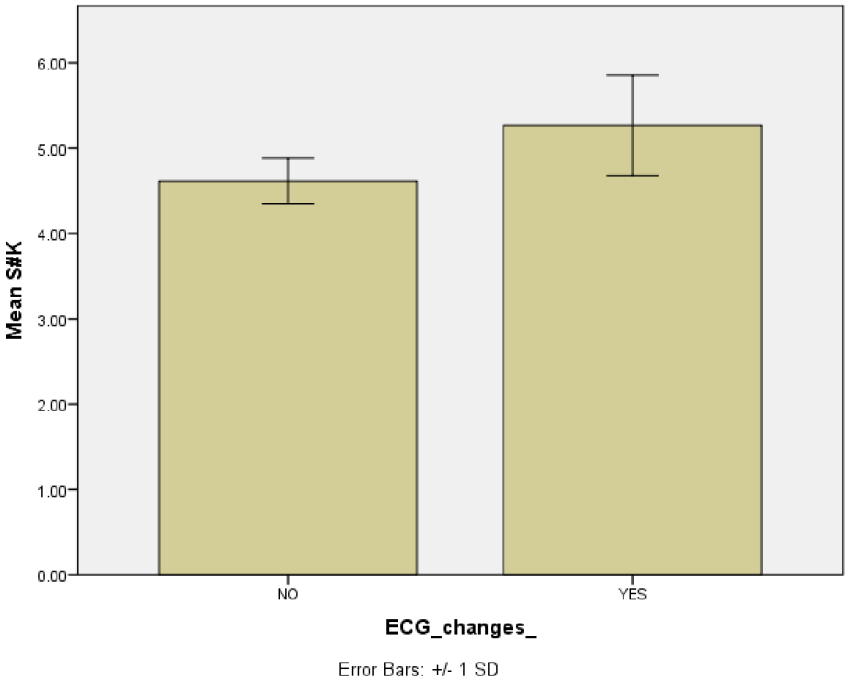

Fig 26: ECG changes and Serum Potassium

Total hospitalization days and ICU stay.

In our study the mean hospitalization stay was 4.10±1.48 days (range 2-8 days). The mean stay was more in those with ECG changes than in those with out ECG changes . 7 patients were admitted to the ICU .

Table 16: ECG change and total hospitalization

ECG change	Total hospitalization(days)	p-value
Present	4.73±1.54	0.001
Absent	3.10±0.43	

P< 0.05 –significant

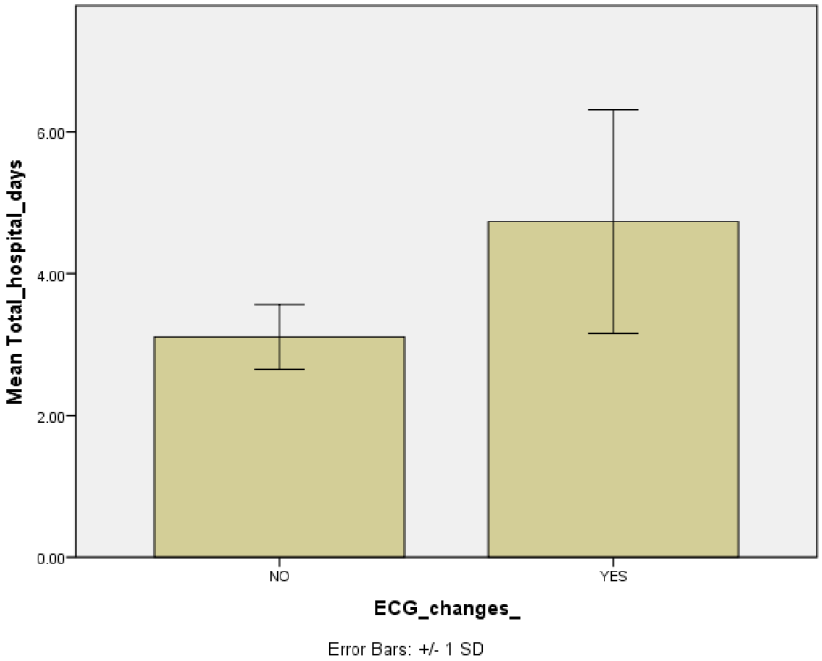

Fig 27: ECG changes and Hospital days

Correlation between ECG changes and Serum creatinine

The mean serum creatinine in patients with ECG changes was 0.88±0.08 mg% versus 0.87±0.07mg% in those with out ECG changes. There was no significant difference between these two groups.(p-0.965)

Table 17: ECG change and Serum creatinine

ECG change	Mean serum creatinine (mg%)	p-value
Present	0.88±008	0.965
Absent	0.87±0.07	

p< 0.05 –significant

Correlation between Gastrointestinal symptoms and form of seeds taken

The gastrointestinal symptoms are directly proportional to the oleander toxin local action . Oleander taken in paste form produces more GI symptoms than other forms .

Table 18: GI symptoms and form of seed ingested.

Form of seed taken	GI symptom present n(%)	GI symptom absent n(%)
Paste	20(95.2%)	1(4.8%)
Chewed	12(54.5%)	10(45.5%)
Grounded	5(83.3%)	1(16.7%)

DISCUSSION

Yellow oleander is a commonly found plant in our geographical area. Poisoning is epidemic in our region and most commonly found in middle age group (20-40 yrs-77.6%),as depicted in the results. This causes increased morbidity on the productive work force of the predominantly agricultural community of our district. The findings in our study echoes and is consistent with few other studies published from our country and from other countries of the sub-continent. Fonseka et al [48] from Srilanka have published their series in 2002 ,with the mean age of 24.8 years and a female preponderance. The results of our study was also similar ,with mean age of 27.9±9.06 years and female preponderance (F: M=1.6:1).

As elaborated in review of literature ,all parts of oleander plant are poisonous . Even smoke from burning the twigs[56] can cause inhalational toxicity and produce ECG changes. In our study we included patients with seed ingestion alone .Oleander seeds are one of the most toxic parts of the plant. One of the most debated topic of oleander poisoning is the lethal dose of the seeds and the how the seeds were ingested –the physical form it is taken and its relation to the severity of symptoms. Regarding the

lethal dose of the oleander seeds ,we found that those who had significant ECG changes had significantly (Table-14 ,p-0.001) higher number of seeds ingested than those who did not have ECG change. Our results thus show that the lethal dose of oleander seeds may be between 4-8. This is consistent with studies by Sreeharan et al[57] (1985) and Saravanapavananthan et al [21] (1988). To the contrary Eddleston et al [51,54,55,64] could not find any simple relationship between the number of seeds ingested and toxic manifestations. The possible explanation for such a factor is that in Eddleston et al's study there is no mention of physical form of the seed ingested is being shown. Mostly the seeds might have been ingested as a whole rather than taken in a paste or grounded form. In our study the majority of intake is in the paste form ,the most lethal type of intake. This is validated by our results that ECG changes were found in 90% of patients who took oleander in a paste form, compared to 80% in grounded form and 27% in chewed form (p-0.01).

Yellow oleander is predominantly cardio-toxic. It can produce gastrointestinal and neurologic manifestations. There are no detailed studies on these effects as they don't cause major morbidity. In our study we found that there was no neurologic effects but 75% of patients had

gastrointestinal effects , with vomitting as major symptom. Vomiting is due to drug induced gastritis. We also found that in patients whom there was gastrointestinal symptoms, there was significant cardiac symptoms. The possible explanation is from the fact that , patient who took the oleander paste-most toxic form had both gastrointestinal and cardiac symptoms.

Cardiac toxicity is the hall mark of oleander seed poisoning. Cardiac glycosides inhibit Na^+/K^+ ATPase pump which results in increased intracellular Na^+ and Ca^+ . The intracellular hypercalcemia leads to spontaneous depolarisations and hence increased arrhythmogenicity. The rhythm disturbances varies from simple bradycardia to complex bradyarrhythmias . The incidence of various bradyarrhythmias in our study (Table 10) is similar to other studies . Results of our study correlate with the figures of most recent evidence available in literature. Zamani et al[58] in 2010 published the incidence of various cardiac rhythm disturbances in yellow oleander poisoning .There was 40% incidence of bradyarrhytmias .This is similar to our study in which we found out 50% incidence of bradycardia and 25% incidence of heart block. We did not find any case of ventricular fibrillation or ectopics

. But in literature the incidence of ventricular ectopics reported is quite high. Even in Zamani et al's study there is 82% incidence of ventricular ectopics and 10% incidence of ventricular tachycardia.

The relationship between cardiac toxicity and the serum biomarkers such as potassium and creatinine are studied in our study . Our results showed that there was no significant difference between patients with or with out ECG changes in respect to serum creatinine . The mean serum creatinine in both groups was around 0.8mg% and the p-value 0f 0.935 in students 't' test. This is comparable to studies by Zamani et al and Lokesh et al. In both of the above studies there was no difference between normal and abnormal ECG groups in respect to the mean serum creatinine levels.

In Lokesh et al' s[59] study the mean serum potassium in abnormal ECG group was 5.3meq/l vs 3.5meq/l in normal ECG group with a p-value of 0.01. These results are comparable to our statistics in which the mean serum potassium was 5.26 meq/l in abnormal ECG group in comparison to 4.6meq/l in normal ECG group. The p-value was 0.001 and significant. These findings emphasize the fact that blockage of Na^+/K^+ ATPase pump leads to the hyperkalemia , and in conjunction with

the intracellular hypercalcemia it precipitates the arrhythmias. Zamani et al in their publication published similar results in 2010 that patients with ECG changes had significantly higher potassium levels than those with normal ECG.

Oleander toxicity is time bound and the toxicity increase with more time elapsing after ingestion .This is possibly explained by the fact that , more the time seeds in the stomach,more absorption of the toxin and more serious the cardiac effect. The patients who reached hospital early had less morbidity and mortality in various studies . In our study also, earlier the admission ,lesser the morbidity .This is proved by the fact that the mean duration from poisoning to hospital admission was 6.0±2.0 hrs in patients with cardiotoxicity ,compared to 2.9±1.4 hrs in those with out cardiotoxicity (Table-16 , p-0.001).

Morbidity in oleander glycoside toxicity is due to the cardiac effects. Hence those with electrocardiographic changes needed some form of intervention .We used mostly pharmacologic intervention . Drugs used by us are atropine and orciprenaline .We did not use digoxin antibodies and our hospital didn't have facility for cardiac pacing. None of our patients however needed pacing and there was no hospital mortality.

The total hospital stay was significantly higher in patients who had cardiac morbidity .The mean stay was 4.7±1.5 days in patients with abnormal electrocardiograph vs 3.1±0.45 days in patients with normal electrocardiograph. This is akin to several studies from other parts of the subcontinent.

Although the yellow oleander tree is common throughout

the tropical and subtropical countries , the use of oleander seeds for suicidal attempts is common only in southern India and parts of Sri Lanka. In Malaysia, Indonesia and Thailand though the oleander palnt is common ,it is not a popular modality for suicidal use.

Even in our country there are scant reports from north India when compared to south India. There are only occasional reports from central and northern India (Modi 1988[60]; Saraswat et al. 1992[61]; Ahlawat etal [62]). Accidental poisonings have been reported from across the world, for example the Solomon Islands, Brazil and Australia (Pearn [63] 1989). However, intentional poisonings in these regions are very uncommon (Pearn 1989).

Oleander poisoning as a epidemic is seen in South India and Sri Lanka. Control of this epidemic must involve both lowering the high incidence of deliberate self-harm and improving the medical management of these patients

(Eddleston et al. 1998[64]). Sociological and psychiatric research should help elucidate the cause of the epidemic. However, in the immediate future, better medical treatments are urgently required both to relieve the burden that oleander poisoning is imposing on the medical services and to reduce the case fatality (Eddleston 1997).

Polyclonal antidigoxin antibodies (Antman et al. 1990; Kelly & Smith 1992) neutralize the cardiotoxic effects of common oleander leaves in dogs (Clark et al. 1991). These antibodies have also been used in clinical practice to treat poisoning due to ingestion of oleander leaves (Shumaik et al. 1988; Safadi et al. 1995) and bufadienolides (Centers for Disease Control & Prevention 1995; Brubacher et al. 1996[65]). The response has been mixed and there has been no clinical trial to test their efficacy – all reports so far have been of single cases. It is essential that a clinical trial of these antibodies is carried out to determine their efficacy. The current cost of treating oleander poisoning will then need to be

evaluated against the cost of the antibodies. If such therapy is judged to be economical and enters clinical practice, it will be important to determine whether the availability of an antidote for oleander poisoning influences its use for acts of deliberate self-harm.

SUMMARY AND CONCLUSIONS

1. Yellow oleander poisoning is common type of suicidal poisoning in Thanjavur district.

2. In our study there was a female preponderance and poisoning was more common in age group of 20-40 years.

3. Chewed form is the most common type of intake followed by paste form.

4. The paste form is the most toxic ,with 90% of patients exhibiting gastrointestinal and cardiac manifestations.

5. 75% of patients had Gastrointestinal symptoms in our study.

6. No patient had neurological manifestations in our study.

7. 14% of patients had palpitations and 61.2% of patients had ECG abnormalities

8. The most common electrocardiographic abnormality is Bradycardia (50%) .First degree AV block was seen in 25% of patients.

9. No patient had second degree or third degree heart block.

10. There was no case of ventricular fibrillation or tachycardia noted in our study.

11. The mean number of seeds ingested was significantly higher in the patients with ECG manifestations.

12. The lethal dose of oleander seed in our study was between 4-8.

13. The serum potassium was significantly higher in patients with ECG changes.

14. Patients who developed cardiac manifestations had significantly longer hospital stay and ICU stay.

15. Patients who presented to the hospital early had less incidence of toxic manifestations.

16. First aid given at home doesn't bear any correlation to the toxic cardiac manifestations.

17. There was no mortality in our study. All patients had normal ECG at discharge.

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PROFORMA

NAME

AGE

SEX

ADDRESS

IP NO

OCCUPATION

EDUCATION

DATE OF ADMISSION

DATE OF DISCHARGE / DATE OF DEATH

DETAILS OF POISONING:

DATE AND TIME OF POISON

NO OF SEEDS

COLOUR

FORM- PASTE /GROUNDED/ CHEWED

TAKEN - EMPTY STOMACH/ WITH FOOD /ALCOHOL

FIRST AID GIVEN AT HOME-YES/NO

TREATED OUTSIDE HOSPITAL-YES/NO

TIME INTERVAL BETWEEN ADMISSION AND CONSUMPTION

SYMPTOMS

GIT- VOMITTING/ DIARRHOEA/ TINGLING SENSATION IN MOUTH

CARDIAC- PALPITATIONS/ SYNCOPE/ DYSPNOEA

CNS-HEADACHE / SEIZURES

VITALS AT ADMISSION-

BP-

PR-

RR-

CVS-

RS-

INVESTIGATIONS

RBS

RFT-

Serum Potassium

ECG Changes

At admission

Day 1

Day 2

Day 3

ECHO-

TOTAL HOSPITALIZATION DAYS-

ICU STAY –

OUTCOME-

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR. G.SUBHA,** post graduate in department of General medicine, Thanjavur medical college & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of participant

Name	IP No	Age	sex	D O A	D O D	Time interval from poisoning to admission(HRS)
TAMILSELVAM	25087	27	M	24/5/14	30/5/2014	8
SHANTHI	1493270	27	F	28/1/14	30/1/14	5
MALLIKA	1488805	45	F	1/2/2014	5/4/2014	2
SINTHAMANI	37523	18	F	25/7/14	29/7/14	8
SUDHA	36364	23	F	20/7/14	25/7/14	6
LAKSHMI	26743	34	F	31/5/14	2/6/2014	8
ANANDHI	26659	25	F	31/5/14	2/6/2014	7
KOKILA	17461	28	F	11/4/2014	14/4/14	3
DURGADEVI	12936	14	F	16/3/14	18/3/14	1
LAKSHMI	12690	38	F	14/3/14	17/3/14	6
PRIYA	1488670	29	F	2/3/2014	7/3/2014	6
SENTHILJOTHI	31604	22	F	25/6/14	27/6/14	3
PAPPU	22076	30	F	7/5/2014	9/5/2014	2
MYTHILI	148995	28	F	6/3/2014	10/3/2014	4
YASODA	1480847	15	F	4/8/2014	9/8/2014	5
JAYASEELA	1473175	21	F	5/8/2014	7/8/2014	6
RAJATHI	1470823	45	F	22/2/14	28/2/14	5
SASIKALA	1467153	21	F	31/7/14	2/8/2014	2
NADIYA	1458725	29	F	12/5/2014	15/5/14	7
MALINI	20829	16	F	30/4/14	2/5/2014	2
AMARAVATHI	10613	30	F	2/6/2014	4/6/2014	3
KAMALA	8737	24	F	19/2/14	23/2/14	8
JOTHI	6871	18	F	12/2/2014	15/2/14	7
MALLIKA	6251	28	F	5/2/2014	7/2/2014	6
KARTHIGA	41096	21	F	14/8/14	18/8/14	6
RAMESH	37480	30	M	25/7/14	28/7/14	5
KARTHIK	30761	26	M	20/6/14	22/6/14	4
SELVAM	34651	40	M	12/7/2014	20/7/14	12
MURALI	28312	18	M	8/6/2014	10/6/2014	2
RAJA	23666	28	M	16/5/14	22/5/14	6
SATHYAMOORTHI	20214	21	M	27/4/14	2/5/2014	8
PALANISAMY	12998	48	M	17/3/14	18/3/14	2
MOHAN	27851	40	M	3/4/2014	5/4/2014	1

SUGANYA	40247	40	F	10/8/2014	14/8/14	3
RENUGA	48605	25	F	12/8/2014	14/8/14	2
ANANDARAJ	28807	22	M	11/6/2014	15/6/14	6
RAMACHANDRAN	18090	30	M	15/4/14	17/4/14	3
PARVATHY	10847	27	F	3/3/2014	5/3/2014	2
SASIKALA	28776	38	F	6/6/2014	11/6/2014	5
JOHNKARTHIK	34039	25	M	8/7/2014	11/7/2014	5
MURALI	28312	22	M	8/6/2014	10/6/2014	5
KUMAR	28775	56	M	10/6/2014	15/6/14	6
RANJIT	15090	21	M	29/3/14	4/4/2014	10
SANGEETHA	68521	16	F	9/5/2014	11/5/2014	3
PRABHU	19155	27	M	21/4/14	23/4/14	2
MILTON	34946	21	M	13/7/14	15/7/14	5
GOPALAKRISHNAN	38510	30	M	31/7/14	2/8/2014	3
NEELAKANDAN	36787	35	M	21/7/14	26/7/14	8
MURUGAN	17858	25	M	14/6/14	16/4/14	3

Form of plant taken	No.of seeds taken	Type of intake	Associated intake	First Aid	GIT symptoms
SEEDS	9	G	F	Y	V
SEEDS	2	C	E	Y	V
SEEDS	1	C	E	N	NO
SEEDS	7	P	F	Y	V
SEEDS	5	P	F	N	V
SEEDS	5	P	E	N	V,D
SEEDS	3	C	F	N	V
SEEDS	3	C	E	Y	V,D
SEEDS	2	C	E	N	V,D
SEEDS	5	G	F	Y	V
SEEDS	8	P	F	Y	V,D
SEEDS	3	C	F	Y	NO
SEEDS	2	C	E	N	V
SEEDS	4	C	E	Y	V
SEEDS	6	P	E	Y	V
SEEDS	3	P	F	Y	V
SEEDS	5	P	F	N	V
SEEDS	2	C	E	N	V
SEEDS	4	P	E	N	V
SEEDS	2	C	F	Y	V
SEEDS	4	G	F	Y	V
SEEDS	9	P	F	N	V,D
SEEDS	6	P	F	N	V
SEEDS	2	C	E	Y	NO
SEEDS	6	P	E	N	D
SEEDS	7	P	E	N	V
SEEDS	3	C	F	Y	NO
SEEDS	8	P	A	N	V
SEEDS	1	C	E	Y	V
SEEDS	6	P	F	N	V
SEEDS	9	P	A	N	V,D
SEEDS	3	C	E	Y	NO
SEEDS	2	C	E	N	NO

SEEDS	3	G	F	N	NO
SEEDS	2	C	F	Y	NO
SEEDS	8	P	F	N	V
SEEDS	2	C	E	Y	V
SEEDS	3	C	E	Y	V
SEEDS	6	G	E	Y	V
SEEDS	4	P	E	N	V
SEEDS	7	G	E	Y	V
SEEDS	5	C	A	Y	V
SEEDS	10	P	A	N	V
SEEDS	2	C	E	Y	NO
SEEDS	6	C	A	N	NO
SEEDS	8	P	A	N	NO
SEEDS	4	C	A	N	NO
SEEDS	6	P	A	N	V
SEEDS	5	P	A	N	V

cardiac symptoms	CNS symptoms	Pulse rate	ECG changes	Type of ECG Change	SB
PALPITATIONS	NO	50	YES	SB,1DAVB,PAC	YES
NO	NO	80	NO		NO
NO	NO	90	NO		NO
NO	NO	80	YES	SB	YES
NO	NO	70	YES	SB,1DAVB	YES
NO	NO	78	YES	SB,PAC	YES
NO	NO	56	YES	SB	YES
NO	NO	80	NO		NO
NO	NO	70	NO		NO
NO	NO	70	YES	SB	YES
NO	NO	50	YES	SB,1DAVB,PAC	YES
NO	NO	88	NO		NO
NO	NO	88	NO		NO
NO	NO	60	YES	SB,1DAVB	YES
NO	NO	59	YES	SB	YES
NO	NO	85	NO		NO
NO	NO	58	YES	SB,1DAVB	YES
NO	NO	87	NO		NO
NO	NO	65	YES	STD	NO
NO	NO	87	YES	TI	NO
NO	NO	50	YES	SB	YES
PALPITATIONS	NO	49	YES	SB,1DAVB,TI	YES
NO	NO	56	YES	SB,STD	YES
NO	NO	80	NO		NO
NO	NO	50	YES	SB,PAC	YES
PALPITATIONS	NO	56	YES	SB	YES
NO	NO	80	NO		NO
PALPITATIONS	NO	42	YES	SB,JR	YES
NO	NO	76	YES	TI	NO
NO	NO	60	YES	SB,PAC,TALL T	YES
PALPITATIONS	NO	42	YES	SB,1DAVB	YES
NO	NO	80	YES	STD	NO
NO	NO	78	NO		NO

NO	NO	80	NO		NO
NO	NO	89	NO		NO
PALPITATIONS	NO	48	YES	SB,1DAVB	YES
NO	NO	78	NO		NO
NO	NO	79	NO		NO
NO	NO	60	YES	SB	YES
PALPITATIONS	NO	60	YES	SB,1DAVB	YES
NO	NO	80	YES	SB	YES
NO	NO	67	YES	TALL T	NO
NO	NO	50	YES	SB,TALL T	YES
NO	NO	78	NO		NO
NO	NO	87	NO		NO
NO	NO	56	YES	SB	YES
NO	NO	78	NO		NO
NO	NO	65	YES	TI	NO
NO	NO	78	NO		NO

1DAVB	PAC	TI	STD
YES	YES	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
YES	NO	NO	NO
NO	YES	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
YES	YES	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
YES	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
YES	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	YES
NO	NO	YES	NO
NO	NO	NO	NO
YES	NO	YES	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	YES	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	YES	NO
NO	YES	NO	NO
YES	NO	NO	NO
NO	NO	NO	YES
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NO	NO	NO	NO
NO	NO	NO	NO
YES	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
YES	NO	NO	NO
NO	NO	NO	NO
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NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	NO	NO
NO	NO	YES	NO
NO	NO	NO	NO

TALL T	JR	ECG I	ECG II	ECG III	ECG IV
NO	NO	1DAVB,SB,PAC	SB,1DAVB	SB,1DAVB	SB
NO	NO	N	N	N	N
NO	NO	N	N	N	N
NO	NO	N	SB	SB	SB
NO	NO	N	1DAVB	SB	SB
NO	NO	N	SB	SB	PAC
NO	NO	SB	SB	SB	N
NO	NO	N	N	N	N
NO	NO	N	N	N	N
NO	NO	N	SB	SB	N
NO	NO	SB,1DAVB	SB,1DAVB	SB	PAC
NO	NO	N	N	N	N
NO	NO	N	N	N	N
NO	NO	SB	SB	SB,1DAVB	1DAVB
NO	NO	SB	SB	SB	N
NO	NO	N	N	N	N
NO	NO	SB	SB	SB,1DAVB	N
NO	NO	N	N	N	N
NO	NO	N	N	STD	TI
NO	NO	N	N	N	TI
NO	NO	SB	SB	SB	N
NO	NO	SB,1DAVB	SB,1DAVB	SB	TI
NO	NO	SB	SB	SB	STD
NO	NO	N	N	N	N
NO	NO	SB,PAC	SB	N	N
NO	NO	SB	SB	SB	N
NO	NO	N	N	N	N
NO	YES	SB	SB	SB	JR
NO	NO	N	N	N	TI
YES	NO	SB	SB ,TALL T	SB, TALL T	SB
NO	NO	SB,1DAVB	SB,1DAVB	SB	SB
NO	NO	N	N	N	STD
NO	NO	N	N	N	N

NO	NO	N	N	N	N
NO	NO	N	N	N	N
NO	NO	SB ,1DAVB	SB,1DAVB	SB	SB
NO	NO	N	N	N	N
NO	NO	N	N	N	N
NO	NO	N	SB	SB	SB
NO	NO	SB,1DAVB	SB,1DAVB	SB	SB
NO	NO	SB	SB,T I	T I	N
YES	NO	TALL T	TALL T	N	N
YES	NO	SB,TALL T	SB,TALL T	SB	SB
NO	NO	N	N	N	N
NO	NO	N	N	N	N
NO	NO	SB	SB	N	N
NO	NO	N	N	N	N
NO	NO	TI	SB	N	N
NO	NO	N	N	N	N

ECG V	ECG VI	SR.C	S.K+	RBS	ECHO	ICU stay	Total hospital days
N	N	0.9	5.6	80	N	NO	6
N	N	0.8	5	70	N	NO	3
N	N	0.9	4.5	89	N	NO	3
N	N	1	5	90	N	NO	5
SB	N	0.9	5.7	75	N	NO	6
N	N	0.8	5.5	67	N	NO	3
N	N	0.9	5	78	N	NO	3
N	N	0.8	4.7	87	N	NO	3
N	N	0.8	4.4	76	N	NO	3
N	N	0.9	4.9	88	N	NO	4
SB	N	0.8	5.7	90	N	YES	6
N	N	0.9	4	98	N	NO	3
N	N	0.9	4.6	78	N	NO	3
N	N	1	5.5	67	N	NO	5
N	N	0.8	4.9	76	N	NO	6
N	N	0.8	5	74	N	NO	3
SB	N	0.9	5.6	75	N	NO	7
N	N	0.8	4.3	78	N	NO	3
N	N	0.9	5	96	N	NO	3
N	N	0.8	4.8	72	N	NO	3
N	N	0.8	5	83	N	NO	3
N	N	0.9	5.7	78	N	YES	5
N	N	0.8	5	87	N	NO	5
N	N	0.8	4.6	87	N	NO	3
N	N	0.9	5.5	97	N	NO	5
N	N	0.9	5.8	95	N	NO	4
N	N	1	4.8	76	N	NO	3
N	N	1	5.7	78	N	YES	8
N	N	0.8	4.4	98	N	NO	3
PAC	N	0.9	6	74	N	YES	7
N	N	0.7	5.9	78	N	YES	7
N	N	1	4.7	65	N	NO	2
N	N	0.8	4.8	78	N	NO	3

N	N	0.9	4.8	89	N	NO	5
N	N	1	4.8	74	N	NO	3
N	N	1.1	6	76	N	YES	5
N	N	0.9	5	86	N	NO	3
N	N	1	4.6	76	N	NO	3
N	N	0.8	3.5	67	N	NO	4
SB	N	0.9	6	68	N	NO	4
N	N	0.8	4.5	87	N	NO	3
N	N	0.9	4.6	87	N	NO	5
SB	N	0.9	5.8	89	N	YES	7
N	N	1	4.3	90	N	NO	3
N	N	0.9	4.5	98	N	NO	3
N	N	0.8	5	89	N	NO	3
N	N	0.9	4.5	67	N	NO	3
N	N	0.9	5.7	84	N	NO	5
N	N	0.8	4.5	84	N	NO	3

Outcome
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