Yellow Oleander-Thevetia peruviana-Poisoning

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ABSTRACT
Yellow oleander poisoning is one of the commonest poisoning in the eastern terai region of Nepal, and is also common in India and Sri Lanka. Although, most parts of the Yellow oleander plant are poisonous, its seeds are mainly used for suicidal poisoning. Thevetia A and Thevetia B are most common cardenolides found in the fruits of the plant which are structurally similar to digoxin cardenolides. Because of this structural similarity, investigations and treatments developed for digoxin are useful in the management of yellow oleander poisoning. It causes primarily cardiotoxic and gastrointestinal effects. Bradycardia or irregular pulse are most common clinical findings in the patient but various degrees of AV block, sick sinus syndrome and other arrhythmia may occur. Gastrointestinal effects include mainly nausea, vomiting, diarrhoea and abdominal pain. Treatment includes GI decontamination with oral activated charcoal, cardiac monitoring, IV fluids and atropine as 0.6mg IV bolus followed by infusion for some days to maintain pulse rate above 80 beats/min. Digoxin antibodies if available is the first line treatment for reversal of cardiotoxicity. Antiemtics should be used as required. Ventricular fibrillation or asystole is the usual cause of death and may occur suddenly. Mortality varies between 3-10% depending on the resources available for the treatment.

KEY WORDS: Poisoning, Thevetia peruviana, Yellow oleander

INTRODUCTION
The yellow oleander tree (Thevetia peruviana) is a tree from the family Apocynaceae. It has characteristic funnel shaped flowers that are typically yellow (sometimes peach) and green fruits containing one seed.1 It is found commonly through much of the tropics and subtropics including Nepal and India. In parts of Nepal, India and Sri Lanka it has become popular means of self harm. There are now tens of thousands of yellow oleander poisoning cases in South Asia each year and probably thousands of deaths.1-3 Management of patients with severe poisoning may be difficult and costly, placing great stress on the health system due to requirements for expensive treatments and transfers to secondary or tertiary hospitals.

A number of cardenolides have been identified in the bark, leaves, sap, seeds or fruits of the yellow oleander. Thevetina a and Thevetin b (cerebroside) are most common. Drying or heating of plant material does not inactivate the cardenolides. These cardenolides are structurally similar to those derived from Digitalis purpurea, so investigations and treatments developed for digoxin and digitoxin are useful in the management of yellow oleander poisoning.9

MECHANISM OF TOXIC EFFECTS
Gastrointestinal effects are secondary to local effects, although central stimulation may also contribute to this. Cardiotoxicity appears to follow inhibition of Na⁺ -K⁺-ATPase similar to the digitalis glycosides.10-12 Animals studies suggest Thevetia cardenolides bind
with increased potency, but that other mechanisms of toxicity may also be present. An increase in vagal tone may contribute to some of the toxicity noted (e.g., Abdominal colic and bradycardia).

**KINETICS IN OVERDOSE**

Animal studies have demonstrated rapid absorption, with a bioavailability of approximately 50%. In humans, however, the absorption kinetics of *Thevetia* cardenolides appears to be slow and unpredictable. Self poisoning by ingestion of the seed may be associated with ongoing absorption for up to 50 h in some patients. In others, significant absorption may not occur until 6h post-ingestion. The volume of distribution has not been determined in humans. Animal and volunteer studies suggest that *Thevetia* cardenolides distribute and bind to the Na+-K+-ATPase more rapidly than digoxin and digitoxin. *Thevetia* cardenolides appear to be metabolized to active (e.g., Thevetin B is converted to peruvoside; Thevetin A to neriifolin) and inactive products. There is debate regarding the extent to which these cardenolides undergo enterohepatic recycling. Renal clearance appears to be the most important route of clearance.

**CLINICAL EFFECTS**

Acute poisoning with yellow oleander causes primary gastrointestinal and cardiotoxic effects. 

Gastrointestinal effects include nausea, vomiting, abdominal colic and diarrhoea. With severe poisoning, vomiting may be persistent. In cardiac effects, cardiac dysrhythmias such as bradycardia or an irregular pulse are the most common findings on examination. Blood pressure is generally preserved until the patient is pre-arrest. Changes in the ST segment in ECG, and conduction blocks are noted with increasing severity. The time course for progression and resolution of cardiotoxicity is variable. It is not uncommon for the patients to interchange between mild, moderate and severe cardiotoxicity frequently. The mechanism for this is not known, but may relate to the absorption kinetics from the seed. Some patients were asymptomatic for 24h before developing toxicity, while others had mild toxicity for 72h before developing severe toxicity. Up to 40% of patients with severe cardiotoxicity may revert to sinus rhythm after a number of hours without specific treatment, but there is insufficient information to determine which patients will revert and which will require specific treatment.

Cardiac arrest occurs with severe poisoning, usually due to ventricular fibrillation which is often resistant to electrical cardioversion. Ventricular ectopics and tachydysrhythmias are otherwise rare in patients with yellow oleander poisoning without coexistent heart disease. Central nervous system effects include weakness, dizziness, confusion or coma, but these effects are rare. Other effects include hyperkalaemia, renal and hepatic abnormalities. Mortality varies between 3-10% depending on the resources available for the treatment.

**DETERMINATION OF SEVERITY**

The assessment of severity of toxicity is determined by clinical grading of toxicity. Patients with acute poisoning with yellow oleander seeds must be closely monitored for changes in severity of cardiotoxicity. Death generally occurs 6-24hr post-exposure.

**Asymptomatic** - no abnormalities on physical or laboratory examination

**Mild** - predominantly gastrointestinal symptoms with flattening or inversion of the T wave and depression of the ST segment

**Moderate** - First degree heart block, sinus bradycardia, sick sinus syndrome (sinus arrest or sinus block)

**Severe** - Second or third degree heart block, ventricular fibrillation, death

There is a poor correlation between the number of seeds ingested and the severity of cardiotoxicity. Death has occurred after ingestion of one or two seeds; in contrast, patients have survived after consuming ten or more seeds without requiring specialized treatments.

**INVESTIGATIONS**

Patients should have serum electrolytes, creatinine and urea tested. Baseline ECG should be done and repeated as indicated clinically. Continuous cardiac monitoring is recommended in all patients with mild, moderate or severe poisoning.

Because of the structural similarities of the cardenolides with digoxin, digoxin assays may be used to measure the concentration of digoxin cross-reacting substances (DXS) in the plasma. Since these assays measure an unknown proportion of these compounds, the correlation with the actual plasma concentration...
of cardenolides is unknown. Although higher plasma concentrations of DXS are associated with increased toxicity, these concentrations do not appear to provide prognostic information, or guide therapy. When two different brands of digoxin assay are used to measure the DXS concentration in patients who have ingested non-digoxin cardenolides, different concentrations are reported. In contrast, similar results are noted with digoxin. This simple test may be useful to confirm the diagnosis of non – digitalis cardenolide poisoning.\(^9,15\)

In Nepal, the detection of poison in the vomitus or gastric contents of the patients with yellow oleander poisoning, or detection of serum level of this poison in such patients is available in the laboratory of Nepal Academy of Science and Technology (NAST), Khumaltar, Lalitpur (phone no. 015526927, 015547268).

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis should include other poisonings or diseases with bradycardia, depending on regional variations.

**TREATMENT**

**Supportive**

Cardiac monitoring should be available, and patients who have ingested yellow oleander seeds should be monitored for 72h if possible. Antiemetics should be administered as required. Hypotension should be treated initially with intravenous fluids.\(^2,11\)

GI Decontamination with oral activated charcoal should be given if the patient presents within 1 hour of ingestion. Since the duration of absorption phase may be prolonged, administration of activated charcoal beyond that time may be appropriate in patients who are cooperative.\(^2,18\) Elimination enhancement with multiple doses of activated charcoal (MDAC) have been proposed as a treatment for yellow oleander poisoning given the potential for enterohepatic recycling of the cardenolides. Two randomized controlled trials have assessed the efficacy of MDAC for acute yellow oleander poisoning, with conflicting results. The true effect of MDAC is unclear since these studies differed in their design (n=401, 50g q6h for 12 doses (de silva 2003); n=1571, 50g q4h for 6 doses (Eddleston 2005). It is therefore not unreasonable to administer MDAC to cooperative patients, although it should not be used in preference to other treatments.\(^19-24\)

Hypokalaemia and hypomagnesaemia should be corrected.

Temporary cardiac pacing has been advocated for treatment of severe cardiotoxicity despite administration of antidotes. Efficacy data regarding this treatment is lacking, and there are theoretical concerns regarding electrical pacing of an irritable myocardium with elevated intracellular calcium.\(^2\)

**ANTIDOTES**

**Atropine**

Atropine (0.6mg bolus) may be useful for reversing bradycardia on the basis of clinical experience, although no studies have assessed the efficacy of this treatment. Atropine bolus is followed by an infusion to maintain the pulse rate above 80 beats/min. Larger doses of atropine 2-3mg are only used for bradycardia less than 40 beats/min accompanied by hypotension. Large doses of atropine may induce anticholinergic delirium and hyperthermia requiring treatments. The effects of atropine on outcomes have not been formally assessed, but clinical experience suggests benefits.\(^2,13,16,19\) The author while working in the hospital of eastern part of Nepal managed several cases of oleander poisoning with supportive measures and atropine with good outcome.

No data is available for which to recommend anti-arrhythmics, and isoprenaline (isoproterenol) infusions are not recommended for treatment of bradycardia given its potential to precipitate ventricular ectopy.\(^2\)

**Digoxin antibodies**

Anti-digoxin Fab antitoxin, if available, is the first line treatment for reversal of cardiotoxicity from cardenolide poisoning. The indications for use will vary between institutions depending on resources available. The randomized controlled trial which established the safety of Fab antitoxin (Eddleston et al 2000) administered Fab using the following criteria: 2nd or 3rd degree AV block, sinus bradycardia<40beats/min, sinus arrest or exit block, atrial tachyarrhythmias, hypotension (SBP<80mmHg) and bradycardia or ventricular tachycardia associated with shock. Since the dose of cardenolide is not known, an empiric intravenous dose of 1200mg of Fab is recommended. It is important to note that some patients may redevelop dysrhythmias after treatment with anti-digoxin Fab antitoxin, which may relate to ongoing absorption or redistribution of the cardenolides to the central circulation. Monitoring for 24-48hr
post-administration of the Fab antitoxin is therefore recommended. 17,18,22,25

LATE COMPLICATION, PROGNOSIS-FOLLOW UP

Long–term sequelae have not been reported.

CONCLUSION

Deliberate self harm with yellow oleander is an important but under-recognised problem in the eastern terai of Nepal. Although, many patients are diagnosed on the basis of history and treated with supportive measures and atropine, better medical managements are urgently required to relieve the burden that this poisoning is imposing on the medical services and to reduce the case fatality.

REFERENCES