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A clinical study of renal tubular dysfunction in Cleistanthus Collinus (Oduvanthalai) poisoning

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Abstract

Introduction—Self-poisoning through ingestion of Oduvanthalai is common in South India. Mortality may occur due to arrhythmias, renal failure, shock and respiratory distress. The mechanisms of toxicity are unclear. This prospective, clinical study was designed to assess renal tubular dysfunction due to Oduvanthalai poisoning.

Methods—32 consecutive patients admitted with Oduvanthalai poisoning at a tertiary care hospital in South India, from June 2007 to August 2009 (26 months) were evaluated though history, physical examination and laboratory studies. Following an interim analysis, additional studies of renal tubular function were performed on a sub-cohort of 8 patients. These included: 1) urinary pH, daily serum and urine anion gap; 2) 24 hour urine protein and potassium; 3) assessment of urine hexosaminidase and amino acid levels.

Results—Metabolic acidosis (100%) which persisted at discharge (65.6%), hypokalemia (62.5%), and renal failure (15.6%) was apparent in the total cohort. Tests of renal tubular function on the sub-cohort revealed a normal anion gap, hyperchloremic, metabolic acidosis of renal etiology, defective urinary acidification and hypokalemia with kaliuresis, indicative of distal renal tubular acidosis (RTA) in six patients. Urinary hexosaminidase and amino acid levels, markers of proximal tubular dysfunction, were elevated in seven and two patients respectively. .

Conclusions—Distal RTA is an important feature of Oduvanthalai poisoning. Proximal tubular injury and in more severe forms, global tubular dysfunction with diminished glomerular filtration rate (GFR) may occur.

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Keywords

Distal Renal Tubular Acidosis; Cleistanthus Collinus; Hypokalemia; Metabolic Acidosis; Hexosaminidase

Introduction

Deliberate self-poisoning through ingestion of the plant *Cleistanthus Collinus* (Family: *Euphorbiaceae*; local name: Oduvanthalai) is common in rural South India. Hypokalemic metabolic acidosis and cardiotoxicity are described as the cardinal features of Oduvanthalai poisoning. 1-3 Indicators of poor outcomes are consumption of leaf decoctions,1,3,4 hypokalemia on admission and delayed presentation to the hospital (>24 hours).4 The case fatality rate is estimated at 30%.1,3 Mortality is attributed to cardiac arrhythmias,1,4 acute renal failure, shock and respiratory failure.4 All parts of this plant are potentially toxic. The primary toxins in the leaf have been identified as aryl-naphthalene lignin lactones: Collinusin, the glycosides Cleistanthin A and B, and their genin Diphyllin.5,6 However, mechanisms of toxin-mediated injury and the pathogenesis of organ dysfunction in humans are not clearly delineated.

Methods

We conducted a prospective, observational study of 32 consecutive patients admitted with acute Oduvanthalai poisoning at Christian Medical College, Vellore, a tertiary care hospital in South India, over a 26 month period (June 2007 to August 2009). The study protocol was approved by the Institutional Review Board of our hospital. At admission, following informed oral consent, patients were assessed with a detailed history, physical examination and diagnostic studies (an electrocardiogram (ECG), chest X-ray, serum electrolytes and creatinine, urine pH (manual bedside measurement using an Orion Smart Chek pocket pH metre done within 5 minutes of voiding) and arterial blood gas (ABG)). Daily assessments through clinical and biochemical parameters were conducted. All clinical decisions (including potassium replacement, the need for intensive care, trans-venous pacing or dialysis) were at the discretion of the treating team.

Based on an interim analysis conducted after 24 patients were recruited, additional studies of renal tubular function were done in a subsequent sub-cohort of 8 patients. The tests included: daily serum and urine anion gap measurements, assessment for glycosuria, 24 hour urine protein and potassium, measurements of urine hexosaminidase A and B (Affinity Chromatography technique)7 and urine amino acid levels (High Performance Liquid Chromatography).8

Results

19 (59.4%) of the patients were women. The mean age was 27.8 (8.0) years. 20 (62.5%) patients had consumed Oduvanthalai leaves. Gastrointestinal decontamination by gastric lavage had been performed in 27 (84.4%) patients at a primary-care centre prior to admission at our hospital. The median time to presentation to our hospital from consumption was seven hours. The clinical features and laboratory abnormalities at admission are described in Table 1. Two (6.3%) patients were admitted in ICU and 4 patients (12.5%) were mechanically ventilated. The mean duration of hospitalization was 4.8 (1.8) days.

All patients had metabolic acidosis of varying severity at admission (Table 1). Despite therapy, 21 patients (65.6%) had persistent metabolic acidosis (mean venous bicarbonate

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19.3 (2.7) mmol/L) at discharge. The urinary pH was > 6.0 for all patients. Hypokalemia was evident in 20 patients (62.5%): 15 patients had hypokalemia on admission and 5 patients developed hypokalemia subsequently during their hospitalization. 17 of these 20 patients survived, and in these 17 patients, the mean duration of hypokalemia, on therapy, was 3.7(1.5) days. 29 patients (90.6%) were administered potassium replacements (23 intravenous and 6 oral). Nine of these patients were pre-emptively administered potassium supplements. The mean amount of potassium administered throughout hospitalization was 264.0 (273.8) mmol. Five (15.6%) patients had renal failure (three oliguric and two non-oliguric renal failure).

In the sub-cohort of eight patients with detailed studies of renal tubular function (Table 2), the profile of six patients (cases six and seven did not fulfil the definition completely) suggested a normal serum anion gap, hyperchloremic, metabolic acidosis of renal etiology (positive urinary anion gap), defective urinary acidification (urinary ph >6) and hypokalemia with kaliuresis, which is indicative of distal renal tubular acidosis (dRTA). Admission urinary hexosaminidase A and B levels were elevated, which subsequently decreased/ normalized at discharge. Urinary amino acid levels were elevated in 2 patients, which returned to normal by the time of discharge. There was no glycosuria. There was mild proteinuria (mean 24 hour urine protein was 232.5 (276.5) mg).

25 patients (78.1%) received elective trans-venous pacing at admission. None of the patients developed tachyarrhythmias or bradyarrythmias. Four patients (12.5%) died. All four patients had Type 1 respiratory failure (two fulfilled criteria for acute respiratory distress syndrome (ARDS)) warranting mechanical ventilation. Three of these patients had ingested boiled leaf decoctions and presented more than 24 hours after consumption. These patients had crepitations, hypoxemia, refractory hypotension, severe metabolic acidosis, severe hypokalemia and renal failure, and died within 24 hours after presentation.

Discussion

Distal renal tubular acidosis (dRTA) has been defined as a disorder of renal tubular function characterized by hypokalemia, hyperchloremic metabolic acidosis and the inability to lower urine pH below 5.5.9 Based on this definition, we characterized patients to have dRTA if they fulfilled the following criteria: metabolic acidosis (admission venous bicarbonate < 24 mmol/L and arterial base excess < −2 with arterial pH < 7.35 or compensated metabolic acidosis), normal serum anion gap(12±4)10, a positive urinary anion gap and a urine pH > 5.5. Urinary hexosaminidase A and B, urinary amino acids and glycosuria were used as markers of proximal tubular dysfunction. Though the presence of dRTA has been hypothesized previously,11,12 these results demonstrate that it is an important feature in patients with Oduvanthalai poisoning. In the sub-cohort, six patients completely fulfilled the criteria for dRTA. However, defective urinary acidification in the presence of reduced venous bicarbonate was seen in all patients in the entire cohort, which suggests that distal tubular dysfunction of varying severity is consistently present these patients. Persistently low venous bicarbonate at discharge suggests protracted renal tubular dysfunction. Hypokalemia is also an important feature with majority of patients requiring potassium supplementation. Pre-emptive potassium replacement was administered for low normal serum potassium values because of anticipated persistent kaliuresis as the standard practice at our institution.

Hexosaminidase is a lysosomal enzyme located predominantly in the in the proximal tubular epithelial cells. Excretion of amino acids also occurs in the proximal tubule. Hence, estimation of urinary excretion of hexosaminidase and amino acids provides a marker of proximal tubular damage.13 The increased levels of Hexosaminidase A and B at admission

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with subsequent normalization suggests transient proximal renal tubular injury. However, increased aminoaciduria was only evident in two patients and none of the patients had glycosuria. The incomplete and transient nature of proximal tubular dysfunction further suggests that distal tubular injury is probably the predominant abnormality in these patients.

There appears to be a progression of the severity of renal injury: metabolic acidosis in patients with mild tubular injury (documented in 7 patients, 21.9%); more severe forms have metabolic acidosis with hypokalemia (documented in 20 patients, 62.5%); and the most severe forms having tubular dysfunction and decreased GFR resulting in metabolic acidosis, hypokalemia and renal failure (documented in 5 patients, 15.6%). 4 out of 5 patients in the latter severe group died, indicating high fatality and poor prognosis.

The universal occurrence and persistence of metabolic acidosis and the correlation of metabolic abnormalities to clinical outcome, suggests that renal injury is a significant component of the Cleistanthus Collinus toxicity profile. Toxin mediated inhibition of the vacuolar H^+ATPase activity in the renal brush border membrane appears to be the underlying mechanism of injury.14 In animal models it was hypothesized that these toxins caused a depletion/inhibition of thiol/thiol dependent enzymes with subsequent loss of ATPase activity.15 The distal tubular cell appears to be the most susceptible, though proximal tubular injury and in more severe forms global tubular dysfunction with diminished glomerular filtration rate (GFR) may occur. The etiology of oliguric renal failure is probably multifactorial including renal hypoperfusion secondary to shock.

Cardiotoxicity has thus far been considered an important feature of Oduvanthalai poisoning. 1-4 We have not documented any arrhythmias in our study. While trans-venous pacing is being routinely offered to the patients, the benefit of this intervention is not clear as mortality in all four of our patients occurred despite elective pacing. It may not be warranted unless there is evidence of bradyarrythmias or QT prolongation.

The limitations of the study are that the complete panel of tests for renal tubular function was only conducted for the sub-cohort of eight patients. However, the occurrence of varying degrees of metabolic acidosis and hypokalemia in majority of the 32 patients would suggest that tubular abnormalities are an underlying feature of the entire cohort. The sub-cohort of patients that were analyzed appears to have milder toxicity with relatively lesser degrees of tubular dysfunction and consequent metabolic acidosis and hypokalemia. Another drawback of the study was that further tests to delineate proximal tubular function and follow up venous bicarbonate after discharge to document tubular recovery were not done.

These results have implications for the development of treatment strategies. Serum potassium underestimates total potassium deficit in the background of metabolic acidosis, and hence early replacement of potassium with frequent monitoring is essential. Focus should be placed on aggressive correction of metabolic acidosis with fluid resuscitation and bicarbonate supplements.

Conclusion

Oduvanthalai related toxin mediated renal tubular injury appears to be an important manifestation, most often resulting in dRTA. The resultant hypokalemic metabolic acidosis is integral to the clinical presentation. There is also evidence of proximal tubular dysfunction. Global tubular dysfunction and decreased GFR occur in more severe cases.

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Table1

Clinical presentation and laboratory profile at Admission (32 patients)

	Number of patients (%)
Clinical Symptoms and Signs	
Vomiting	26 (81.2%)
Subjective weakness	11 (34.3%)
Dyspnea	9 (28.1%)
Headache	8 (25%)
Giddiness	8 (25%)
Tachycardia (Pulse rate > 100/min)	11 (34.3%)
Abdominal tenderness	6 (18.7%)
Tachypnea (Respiratory Rate > 24/min)	5 (15.6%)
Hypoxia (SpO_2 < 90)	4 (12.4%)
Crepitations (Respiratory)	3 (9.3%)
Hypotension (Systolic BP < 90 mm)	3 (9.3%)
Laboratory Profile	
Serum Bicarbonate	
Mild acidosis (21-23mmol/L)	7 (21.8%)
Moderate acidosis (17-20mmol/L)	14 (43.7%)
Severe acidosis (<16mmol/L)	11 (34.3%)
Serum Potassium *	
Normal potassium (3.5-5mmol/L)	17 (53.1%)
Mild hypokalemia (2.8-3.4mmol/L)	10 (31.2%)
Moderate hypokalemia(2.4-2.7mmol/L)	2 (6.3%)
Severe hypokalemia(<2.3mmol/L)	3 (9.4%)
Mean Serum Sodium (135-145mmol/L)	138 (122-146)
Mean Serum Creatinine (0.7-1.4 mg %)	1.2 (0.7-5.4)
Renal failure (serum creatinine > 1.4 mg %) **	3(9.3%)
ECG abnormalities	
Sinus tachycardia (>100/min)	11(34.3%)
Sinus bradycardia (<60/min)	1(3.1%)
ST depression (>1mm)	3(9.3%)

* 15 patients had hypokalemia on admission while 5 patients developed hypokalemia subsequently during their hospital stay

** 3 patients had renal failure at admission while 2 patients developed renal failure subsequently

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Table 2

Laboratory Profile of sub-cohort of eight patients

	Case 1	**Case 2***	**Case 3**	**Case 4**	**Case 5***	**Case 6***	**Case 7***	**Case 8**	**Mean (SD)**
Serum Sodium (admission) (135-145 mmol/L)	135	133	143	137	140	139	133	138	137 (3.5)
Serum Potassium (admission) (3.5-5.0 mmol/L)	3.5	2.8	2.8	4.4	3.5	3.7	2.4	4.0	3.4 (0.7)
Serum Chloride (admission) (95-105 mmol/L)	110	100	109	102	109	105	98	101	104.3 (4.7)
Serum Bicarbonate (admission) (24-28 mmol/L)	19	17	20	15	17	21	23	20	19.1 (2.8)
Serum Bicarbonate (discharge)	26	18	25	16	18	17	22	20	20.3 (3.7)
Serum Creatinine (admission) (2.7-1.4 mg/dL)	1.1	1.3	1.3	1.1	1.0	0.7	0.8	1	1.0 (0.2)
Arterial pH (admission) (7.35-7.45)	7.33	7.26	7.41	7.29	7.33	7.42	7.52	7.37	7.37 (0.08)
Base Excess (admission) (±2)	−7.5	−9.2	−4.1	−10.1	−11.7	0.8	6.4	−4.5	−5.0 (6.1)
ABG $PaCO_2$ (admission) (35-45mmHg)	33	40	31	32	29	39	36	36	34.5(3.9)
ABG PaO_2# (admission) (>90mmHg)	163	89	63	92	78	93	66	91	91.8(31)
Serum Anion Gap (admission) (12±4)	6	16	14	20	14	13	11	17	13.9 (4.2)
Urine pH (admission) (>6)	7	7	7	7.5	7	6.8	7.7	6.6	7.1 (0.4)
Urine Anion Gap (admission)	-	20	30	32.5	80.9	6.9	30.2	−2.6	28.3 (26.7)
24 hour urine protein (<150 mg)	64	144	644	78	-	-	-	-	232.5 (276.5)

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	Case 1	**Case 2***	**Case 3**	**Case 4**	**Case 5***	**Case 6***	**Case 7***	**Case 8**	**Mean (SD)**
24 hour Urine Potassium (mmol)	24	65	32	55	124	-	-	-	60.0 (39.5)
Admission Urine Hexosaminidase A (<100U/mg creatinine)	42.64	478.5	42.5	2028.5	3680	454.5	170	312.2	948.9 (1264.8)
Admission Urine Hexosaminidase B (<100U/mg Creatinine)	44.25	1042.8	2595	1471.4	14960	545.4	350	418.6	2678.4 (5028.4)
Discharge Urine Hexosaminidase A (<100U/mg Creatinine)	180	-	243.5	300	-	172.2	-	-	223.9 (59.9)
Discharge Urine Hexosaminidase B (<100U/mg Creatinine)	108	-	207.6	262.5	-	183.3	-	-	190.4 (64.1)
Urine Amino acid levels (admission)##	Normal	Increased	In creased	Normal	Normal	Normal	Normal	Normal	
Urine Amino acid levels (discharge)	Normal	-	Normal	Normal	-	Normal	-	-	

The amino acid profile at admission was abnormal in patients 2 and 3.

Patient 2 - the profile revealed an elevated glutamate - 594μmoles/ gm creatinine; glycine – 5250 μmoles/ gm creatinine and alanine – 845 μmoles/ gm creatinine.

Patient 3 - the profile revealed an elevated glutamate – 414 μmoles/ gm creatinine and glycine – 3596 μmoles/ gm creatinine.

Reference normal levels for these three urinary amino acids are16

- Glutamate - 0-80 μmoles/ gm creatinine; Glycine – 0-2953 μmoles/ gm creatinine; Alanine – 68-534 μmoles/ gm creatinine

Patient 2 was discharged on specific request and hence was unable to complete the tests.

The investigations could not be completed for patient 5 as the patient died.

The 24 urinary collections could not be completed for patients 6, 7 and 8 as they were discharged within 24 hours of admission.

#Patient 1 was administered oxygen by mask at 4 liters/minute. All the other patients were on room air at the time of testing.

##The amino acid profile included estimation of urine levels of Taurine, Aspartate, Glutamine, Threonine, Asparagine, Serine, Glutamate, Proline, Glycine, Alanine, Valine, Methionine, Isoleucine, Leucine, Tyrosine, Phenyl-alanine, Histidine, Ornithine, Lysine, Tryptophan, Arginine, β-Amino isobutryic acid.

*Urine anion gap was not calculated for patient 1 as patient presented at night and the research officer was not available at the time.