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Case Report Open Access

Neem Extract Poisoning as a Cause of Renal Tubular Acidosis

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Abstract

Context: We report on systemic toxicity caused by ingestion of large quantities of 'neem extract', a traditional medicine widely used throughout the Indian subcontinent and increasingly imported to the developed world. There are case reports of neem extract causing renal impairment and liver damage in a microvesicular pattern but no cases of distal renal tubular acidosis (RTA) have been reported thus far.

Case details: A 51-year old Solomon Islander was transferred to a Sydney Hospital with encephalopathy and a metabolic acidosis. A diagnosis of distal RTA was made requiring four days of continuous veno-venous hemodialysis. He also showed signs of bone marrow suppression, coagulopathy and liver damage, which were successfully managed with supportive care. Further history following the resolution of his encephalopathy revealed ingestion of large quantities of 'neem extract' over the preceding three months.

Discussion: Liver damage is the predominant toxicity reported thus far with 'neem extract' and almost exclusively in children. This is the first report of neem extract causing distal RTA with evidence of mitochondrial toxicity. Physicians should be aware of the increasing use of 'neem extract' as a complimentary medicine and the potential toxicities this may lead to.

Introduction

Neem is the name used to describe a heterogenous group of compounds derived from the tree *Azadirachia indica*, an evergreen of the mahogany family Melaceae and endemic to the Indian subcontinent and other tropical and subtropical areas. It is also known as India Lilac or margosa tree and more colloquially as 'Panacea for all diseases' and 'Village Pharmacy'. Virtually every part of the tree including the leaf, bark, flower, fruit, seed and gum have been processed for use as soil fertilizer, insecticide, dye, wax, fuel, lubricant, soap, spermicide and in traditional medicine [1].

There are reports of Neem extract causing acute tubular necrosis [2] but we are unaware of any reports describing renal tubular acidosis (RTA) associated with Neem. We report a 51-year-old Solomon Islander presenting with RTA, toxic encephalopathy, hepatotoxicity, anemia and coagulopathy after ingesting large quantities of Neem extract. The patient underwent 4 days of continuous veno-venous hemodialysis (CVVDH) before making a full recovery to discharge 15 days later.

Case Report

Mr FA with diet controlled diabetes and hypertension was flown from the Solomon Islands to a Sydney hospital after being admitted to hospital 3 days earlier with confusion thought to be due to 'possible plasmodium falciparum'. Treatment had been commenced with Riamet (arthemeter + lumefantrine).

FA was unable to give a coherent history on arrival in Sydney and was afebrile but clinically dehydrated. His heart rate (HR) was 90 beats per minute, blood pressure 135/66, respiratory rate 26 and oxygen saturation 100% on room air. His 12 lead ECG was unremarkable.

His initial arterial blood gas (ABG) on room air revealed a metabolic acidosis with raised lactate and increased anion gap (Table 1). Interestingly he was hypokalemic in the context of mild renal impairment. His urine was alkaline despite a significant anion gap, suggesting a diagnosis of type 1 (distal) renal tubular acidosis. Urgent blood films and immunochromatography were negative for malaria. His total white cell count was normal but he had lymphopaenia and his CRP was raised at 66.7 mg/L. His chest X-ray and computerized tomography (CT) brain were unremarkable.

Antimalarials were ceased and sodium bicarbonate 8.4%, 100ml (100mequ) administered four hourly. Hartman's solutions' and parenteral potassium was administered. On the second day of his admission he became drowsier and given his decreasing plasma bicarbonate and worsening acidosis he was transferred to intensive care for 4 days of CVVHD.

Normocytic anemia without a reticulocytosis to a nadir of Hb of 81g/L on day 4 of his admission indicated possible bone marrow suppression (Table 2). This coincided with a rise in the prothrombin (21s) and activated partial thromboplastin times (42s) with a relatively low fibrinogen (0.8g/L) and raised D-dimer (1.36mg/L), raising the possibility of DIC.

His liver function tests also became markedly abnormal in a predominantly cholestatic pattern, with his GGT, ALP and bilirubin peaking on day 8-post admission (Table 3).

On day 5, blood ammonia concentration was elevated at 108μmol/L and a 'metabolic screen' to exclude metabolic encephalopathy was performed. Urinary and plasma amino acids and his blood organic acid profile were suggestive of multiple acyl-CoA dehydrogenase deficiency.

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	10/09/011 (venous)	12/09/11 (arterial)	15/09/11 (arterial)	Units
pH	7.25	7.41	7.44	
pO2	34	85	95	mmHg
pCO2	26	26	27	mmHg
HCO3	11	16	18	mmol/L
Lactate	2.8	4.7	2.6	mmol/L

Table 1: Blood gas results, all on Fi02 of 0.29.

	10/09/11	14/09/11	21/09/11	Range	Units
Hb	156	83	108	130-180	Units
Plt	185	45	217	150-400	g/L
Neutrophils	7.8	3.8	6.6	2.0-7.5	10x9/L
Lymphocytes	0.5	0.5	1.1	1.5-4.0	10x9/L

Table 2: Blood indices.

	10/09/11	18/09/11	21/09/11	Range	Units
Sodium	131	136	135	137-146	mmol/L
Potassium	2.9	3.7	4.3	3.5-5.0	mmol/L
Chloride	101	100	96	95-110	mmol/L
Bicarbonate	9	20	30	24-31	mmol/L
Creatinine	110	90	97	60-12	umol/L
Urea	14	6.5	6.8	3.0-8.5	mmol/L
Albumin	36	41	40	36-52	g/L
Bilirubin	14	48	24	0-18	umol/L
ALT	49	229	248	0-30	U/L
AST	21	164	125	0-30	U/L
ALP	53	407	312	30-100	U/L
GGT	28	1330	836	0-35	U/L

Table 3: Plasma electrolytes, creatinine, urea and liver function tests.

On the fifth day of admission his confusion had almost completely resolved and a more thorough history revealed consumption of large quantities of Neem extract imported from India (200ml three times per day) over the preceding 3 months in order to treat his diabetes. It was unclear which part of the *A indica* tree this extract was from.

His urine and serum levels of lead, cadmium, mercury and copper were tested and unremarkable.

On day 5 he was transferred back to the ward and from day 8 to day 20 his biochemical and haematological parameters improved. He returned to the Solomon Islands on day 21 post admission fully recovered.

Discussion

It is highly likely that Mr FA was poisoned with Neem extract causing distal RTA, hepatitis with metabolic encephalopathy and disturbances in hematopoiesis and coagulation. Riamet is not known to be associated with renal toxicity [3].

In traditional medicine, extracts of *A indica* from the seed, to make 'margosa' or 'neem' oil and from the leaf, have been used to treat a myriad of diseases from leprosy to helminthic infections. The potential medicinal properties have been reviewed by van der Nat et al in their ethnopharmacognostical survey [1]. The main active compounds in Neem oil are limonoids, including azadirachtin and particular attention has been directed to the antimalarial activity of compounds such as gedunin and nimbolide [4, 5]. Animal and human studies of orally administered *A indica* seed and leaf extracts have shown hypoglycemic effects in non-diabetic and type 2 diabetic patients similar to sulphonylurea drugs, although there is controversy regarding the mechanism of action [6,7]

There are numerous human case reports as well as animal studies of Neem extract revealing toxic effects including toxic encephalopathy and status epilepticus [8,9], Reye's like syndrome of microvesicular fatty liver [10,11] and metabolic acidosis [12]. Almost all of these case reports are from children receiving Neem oil and the case fatality rate was high. *In vitro* experiments have demonstrated a possible mechanism for Neem oil toxicity namely uncoupling of mitochondrial oxidative phosphorylation. These extracts have also been found to decrease intra-mitochondrial levels of acetyl CoA in rat liver mitochondria, which may explain the metabolic screen results in this patient [13].

Contamination of Neem extracts with either solvents used during extraction or aflatoxins [10] may cause acute toxicity. Also, contamination with heavy metals such as lead and cadmium [14] is also widely reported in Ayurvedic medicines and renal dysfunction may result. There is only limited systematic toxicology data, almost exclusively from animal studies, regarding the safety of neem derived products [15].

A indica is very similar in appearance and often grows in proximity to the Chinaberry tree (Melia azedarach), all parts of which are extremely poisonous to mammals and so there is also a risk of toxicity through mistaken identity [16].

Proximal RTA has been reported to occur with the intake of Chinese herbs [17,18], often containing aristolochic acid. Distal RTA is a documented complication of amphotericin B, lithium carbonate and toluene exposure [19] but to our knowledge this is the first documented case of distal RTA caused by a traditional herbal medicine .

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