HL Tang 鄧漢樂
KH Chu 朱國康
A Cheuk 卓　鷗
WK Tsang 曾偉基
HWH Chan 陳慧嫻
KL Tong 唐國隆

Renal tubular acidosis and severe hypophosphataemia due to toluene inhalation

吸入甲苯造成腎小管性酸中毒和低磷酸鹽血症

A 21-year-old woman developed severe muscle paralysis after sniffing toluene-containing thinner solution for 2 weeks. Her serum chemistries revealed severe hypokalaemia and a normal anion gap hyperchloraemic metabolic acidosis secondary to renal tubular acidosis. Her initial presentation mimicked hypokalaemic periodic paralysis, but toxicology screening of her blood and urine revealed the correct diagnosis of toluene poisoning. Her electrolyte and acid-base status returned to normal 4 days after cessation of toluene sniffing. On another occasion, apart from renal tubular acidosis, the patient also developed severe hypophosphataemia with the phosphate level decreasing to 0.15 mmol/L. Hypophosphataemia with such a low phosphate level after toluene poisoning has been rarely reported in the literature. Toluene inhalation can result in multiple electrolyte and acid-base abnormalities, and should be considered in the diagnosis of any young patient who presents with unexplained hypokalaemia and normal anion gap metabolic acidosis.

本例病者為一名 21 歲女性，在吸入含有甲苯的稀釋液兩星期後，出現嚴重肌肉麻痺。血清化學檢驗顯示，病者出現嚴重低鉀血症，以及由腎小管性酸中毒引起陰離子間隙高氯血症的代謝性酸中毒。初發徵狀酷似低鉀血症導致的周期性麻痺，但血液及尿液毒理學檢查證實為甲苯中毒。病者在中止吸入甲苯稀釋液後四天，電解質水平和酸鹼值回復正常。除了腎小管性酸中毒，病者也出現嚴重的低磷酸鹽血症，磷酸鹽含量低至 0.15 mmol/L。因甲苯中毒造成極低磷酸鹽含量的低磷酸鹽血症病例，在文獻中並不多見。因為吸入甲苯可造成多種電解質和酸鹼值異常，所以在診斷年青病者患上成因不明的低鉀血症和陰離子間隙代謝性酸中毒時，應當考慮是否吸入甲苯所致。

Key words:
Acidosis, renal tubular;
Hypokalemia;
Hypophosphatemia;
Toluene

關鍵詞：
酸中毒，腎小管性；
低鉀血症；
低磷酸鹽血症；
甲苯

Hong Kong Med J 2005;11:50-3

Division of Nephrology, Department of Medicine and Geriatrics, Princess Margaret Hospital, Laichikok, Kowloon, Hong Kong
HL Tang, MRCP, FHKAM (Medicine)
KH Chu, MRCP, FHKAM (Medicine)
A Cheuk, MRCP
WK Tsang, FRCP, FHKAM (Medicine)
HWH Chan, FRCP, FHKAM (Medicine)
KL Tong, FRCP, FHKAM (Medicine)

Correspondence to: Dr HL Tang
(e-mail: pmhrenal@hotmail.com)

Introduction

Toluene is an aromatic hydrocarbon with widespread industrial use as an organic solvent. Habitual inhalation or 'sniffing' of toluene-containing thinner solutions or glues can result in toxicity. Complications following toluene poisoning include electrolyte and acid-base disturbances, gastrointestinal complaints (abdominal pain and haematemesis), and neuropsychiatric disorders (altered mental state, cerebellar abnormalities, and peripheral neuropathy).[1] This report describes a case of distal renal tubular acidosis and severe hypophosphataemia resulting from toluene inhalation.

Case report

A 21-year-old woman was admitted to Princess Margaret Hospital

Table. Serum and urine chemistries of the patient during her second admission

Site	Laboratory test	Reference range	On admission	12 hours later	4 days later
Blood/serum	Sodium (mmol/L)	135-149	137	135	143
	Potassium (mmol/L)	3.5-4.7	1.4	2.0	4.1
	Urea (mmol/L)	3.3-7.0	0.5	0.2	0.2
	Creatinine (μmol/L)	60-120	67	72	44
	Chloride (mmol/L)	96-106	-	118	104
	Calcium (mmol/L)	2.2-2.6	2.31	1.92	2.29
	Phosphate (mmol/L)	0.8-1.4	-	0.30	0.87
	Magnesium (mmol/L)	0.7-1.1	-	1.09	-
	Albumin (g/L)	35-55	40	33	32
	Glucose (mmol/L)	3.6-6.1	6.4	6.2	-
	Creatine phosphokinase (U/L)	42-245	-	131	-
	Arterial pH	7.35-7.45	7.16	7.30	7.38
	PCO_2 (mm Hg)	35-45	19.2	24.9	44.1
	PO_2 (mm Hg)	83-105	140.8	112.8	84.4
	Bicarbonate (mmol/L)	22-26	6.8	12.3	25.9
	Anion gap (mEq/L) [mmol/L]	5-14	-	4.7	-
Urine	pH	-	-	6.00	-
	Potassium (mmol/L)	-	-	35.2	-

because of a neck injury caused by a fall. She had generalised muscle weakness for 3 days preceding the fall. She did not have a history of vomiting or diarrhoea, and she had denied taking any drugs prior to admission. On physical examination, her overall muscle power grade was only 2/5, and the deep tendon reflexes of all four limbs were diminished. Her sensation was intact and the Babinski sign was absent on both sides. The results of her serum biochemistry were as follows: sodium, 138 mmol/L; potassium, <1.5 mmol/L; urea, 2.0 mmol/L; creatinine, 60 μmol/L; calcium, 2.39 mmol/L; magnesium, 1.05 mmol/L; arterial pH 7.37; PCO_2, 31.4 mm Hg; bicarbonate, 18 mmol/L; and PO_2, 103.3 mm Hg. Tests revealed severe hypokalaemia and she was diagnosed as having hypokalaemic periodic paralysis. Intravenous potassium chloride diluted in isotonic saline was given for potassium replacement. Her potassium concentration recovered to a normal level over 5 days and she regained her full muscle power. Her thyroid function test was shown to be normal and the patient was subsequently discharged home.

One month later, the patient was readmitted because she had generalised limb weakness for 1 day. Physical examination revealed that her upper limb power was grade 3/5 while her lower limb power was only grade 1/5. Results of her serum biochemistry on admission are shown in the Table. Apart from severe hypokalaemia (potassium, 1.4 mmol/L), she also had severe metabolic acidosis (arterial pH 7.16; bicarbonate, 6.8 mmol/L; and PCO_2, 19.2 mm Hg), and her blood glucose level was normal. She was given 230 mmol of replacement potassium chloride (intravenous, 60 mmol; oral, 170 mmol) over 12 hours, and 50 mmol of intravenous sodium bicarbonate over 1 hour. The results from the serum biochemistry, repeated 12 hours later, showed persistent hypokalaemia and metabolic acidosis (potassium, 2.0 mmol/L; chloride, 118 mmol/L; arterial pH 7.30; bicarbonate, 12.3 mmol/L; and PCO_2, 24.9 mm Hg) [Table]. The calculated serum anion gap (Na^+-Cl^--HCO_3^-) was 4.7 mEq/L (mmol/L) and her serum albumin level was low (33 g/L). The urine pH was 6.00, which was inappropriately high despite having metabolic acidosis. She was not volume-depleted or hypotensive. The potassium chloride replacement therapy was subsequently continued. Her serum potassium, chloride, pH, and bicarbonate levels all returned to normal over 4 days (Table).

The blood toxicology screening revealed an excess level of toluene, and the urine toxicology screening showed excess levels of hippuric acid and benzoic acid, which were the metabolites of toluene. On reviewing her history, it was found that she had inhaled more than 10 bottles of 'thinner solution' (used for paint removal) over 2 weeks before she was admitted. She was finally diagnosed as having renal tubular acidosis secondary to toluene poisoning. Unfortunately, the urine sodium and chloride levels had not been recorded during the acute phase of the acid-base disturbance—these values are necessary for the calculation of urine anion gap. The patient was again admitted 3 months later for toluene intoxication. Her serum chemistries revealed hypokalaemia and metabolic acidosis (potassium, 3.4 mmol/L; arterial pH 7.25; PCO_2, 31.4 mm Hg; and bicarbonate, 13.7 mmol/L) and her urine chemistries were also recorded at the same time

(sodium, 5.0 mmol/L; potassium, 17.5 mmol/L; and chloride, 7.5 mmol/L). The calculated urine anion gap ($Na^+ + K^+ - Cl^-$) was +15.0 mEq/L (mmol/L), supporting the diagnosis of renal tubular acidosis.

After discharged home, the patient continued to practise her solvent-sniffing habit, and was repeatedly admitted for similar electrolyte and acid-base disturbances. Eleven months after her first presentation, she was readmitted because of muscle paralysis and generalised tonic-clonic convulsion, which she did not previously display. She had 9 episodes of generalised tonic-clonic convulsion during her admission. Examination revealed hypokalaemia and a normal anion gap metabolic acidosis, but the patient also had a very low phosphate level of 0.21 mmol/L. Her serum calcium, magnesium, sodium, and blood glucose levels were all normal. Moreover, computed tomographic scan of the brain revealed no abnormality. Her convulsions subsided over 1 day and her phosphate level subsequently returned to normal after cessation of toluene sniffing. Furthermore, in a later admission, her phosphate level even fell down to 0.15 mmol/L. Despite the severe hypophosphataemia during these two admissions, she did not display any rhabdomyolysis or elevated creatine phosphokinase level.

Discussion

Renal tubular acidosis as a consequence of toluene sniffing was first reported by Taher et al[2] in 1974. Subsequently, similar cases of toluene-induced renal tubular acidosis have been reported.[1,3-9] We described here a case of the habitual sniffing of toluene-containing thinner solution by a 21-year-old female. The patient initially presented with hypokalaemic periodic paralysis, but the diagnosis during a later relapse revealed renal tubular acidosis (likely type 1, distal) with severe hypokalaemia causing muscle paralysis. The diagnosis of distal renal tubular acidosis was indicated by the normal anion gap hyperchloraemic metabolic acidosis, hypokalaemia, and an inappropriately high urine pH of greater than 5.5. Other causes of these acid-base disturbances, such as diarrhoea and volume depletion, were excluded. The positive urine anion gap in the presence of acidaemia indicates impaired ammoniagenesis and ammonium excretion, which further supported the diagnosis of renal tubular acidosis.

In our patient, both the metabolic acidosis and hypokalaemia recovered in 4 to 5 days after the end of the toluene exposure. Another cause of metabolic acidosis in patients exposed to toluene is the over-production of hippuric acid metabolite.[3] Toluene is oxidised to benzoic acid which is then conjugated with glycine to form hippuric acid. Excess hippuric acid can also give rise to a normal anion gap metabolic acidosis due to the rapid urinary excretion of the unmeasured anion, hippurate. In this case, the urine pH was greater than 5.5 in the presence of metabolic acidosis, suggesting a failure of urine acidification by the kidney tubules. This high urine pH indicated that the metabolic acidosis was unlikely to be induced by the over-production of hippuric acid. The exact mechanism of distal renal tubular acidosis caused by toluene is unknown. It has been suggested that decreased proton conductance through the active transport pathway is a mechanism by which toluene causes defect in distal acidification.[4]

The patient also developed severe hypophosphataemia, with the phosphate level decreasing to a very low concentration on one occasion (0.15 mmol/L). Despite this severely depressed phosphate level, there was no clinical evidence of rhabdomyolysis and this level normalised after she stopped the inhalation of toluene. The development of hypophosphataemia after toluene sniffing has been rarely reported in the literature.[1,5] In one of these reports, the phosphate level was lower in those patients presenting with muscle weakness (mean, 0.48 mmol/L) than in either those having gastro-intestinal complaints or neuropsychiatric symptoms.[1] From our data, it is unknown whether hypophosphataemia is due to renal phosphate wasting or other mechanisms, for example, internal phosphate re-distribution. Our patient developed convulsion during one of her admissions; however, it is not known whether her convulsive attacks could have been secondary to severe hypophosphataemia or due to the direct toxic effect of toluene on the central nervous system.

The presentation of toluene-induced distal renal tubular acidosis can mimic that of hypokalaemic periodic paralysis. The clinical picture of hypokalaemic periodic paralysis after chronic toluene exposure has been previously reported by Bennet and Forman.[10] In this case, our patient was misdiagnosed as having hypokalaemic periodic paralysis during the first admission; however, the correct diagnosis was disclosed by the blood and urine toxicology screening during her second admission. Therefore, toluene poisoning should be considered in the diagnosis of young patients presenting with unexplained hypokalaemic paralysis and a normal anion gap metabolic acidosis. Toxicology screening should be an important test to establish this diagnosis.

The mechanisms by which toluene causes renal tubular acidosis and hypophosphataemia remain to be elucidated. Further case studies on the toxic renal effects of this aromatic hydrocarbon are necessary.

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