Salicylate-induced Fanconi-like syndrome

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Abstract

Salicylate intoxication is a very common problem in everyday clinical practice. We describe a new case of salicylate-induced reversible Fanconi's syndrome in a 28-year-old Cypriot male who ingested 50 g of acetylsalicylic acid with suicidal intent. To our knowledge, this is the second case ever described. It is suggested that clinicians should be aware of this salicylate intoxication-induced complication.

Key words: salicylate, Fanconi syndrome, aspirin.

Introduction

Fanconi's syndrome is characterized by a generalized transport defect in the proximal tubules that leads to inappropriate losses of glucose, amino acids, bicarbonates, uric acid, phosphate, potassium, and other organic compounds. Numerous substances have been implicated in the pathogenesis of this syndrome [reviewed in ref 1]. However, so far there are limited data concerning the role of salicylate intoxication as a cause of proximal tubular dysfunction in humans.

Case report

A 28-year-old patient was admitted to our internal medicine clinic due to drug poisoning. Six hours before his admission he ingested 50 g of acetylsalicylic acid with suicidal intent. His parents brought him to the emergency department of our hospital due to abdominal discomfort and the patient confessed the ingestion of the drug. The patient had a medical history of mild depression and was receiving paroxetine 20 mg daily for the last year. No other medical history was noted. Clinical examination revealed moderate hyperpnoea and mild abdominal tenderness. Gastric lavage followed by the administration of activated charcoal via the nasogastric tube was performed in the emergency department and then the patient was admitted to our clinic. After written informed consent was obtained, blood and urine samples were collected and normal saline and omeprazole were administered intravenously. Blood gases showed the presence of a mixed acid-base disorder consisting of respiratory alkalosis and metabolic acidosis (pH: 7.47, PCO_2: 21 mmHg, HCO_3^-: 15.1 mmol/l). Serum uric acid levels were remarkably low (2.7 mg/dl), whereas the other measured parameters were within normal values (Table I). Serum acetylsalicylic acid level was 631 mg/dl. Interestingly, urine analysis revealed profound albuminuria and glucosuria (in the face of normal serum glucose

Table I. Patient's serum and urine parameters on admission

Parameter	Serum level	Urine level	Fractional excretion [%]
Glu [mg/dl]	79	968	–
Urea [mg/dl]	28	1695	69.5
Creat [mg/dl]	1.01	88	–
UA [mg/dl]	2.7	46.47	19.75
Na [mmol/l]	145	58.88	0.5
K [mmol/l]	3.72	103.81	32
Ca [mg/dl]	8.5	0.43	0.05
PO4 (mg/dl)	3.2	88.09	31.6
Mg [mg/dl]	2.02	1.31	0.7
Cl [mmol/l	100	90.42	1.03
Prot [mg/dl]	7	33.99	–

Glu – glucose, Creat – creatinine, UA – uric acid, Na – sodium, K – potassium, Ca – calcium, Cl – chloride, PO_4 – phosphate, Mg – magnesium, Prot – proteins

concentrations) as well as the presence of some granular casts. The subsequent analysis of a spot urine sample revealed a pattern consistent with a generalized proximal tubular dysfunction (Table I).

On the second day of hospitalization the patient developed acute renal failure with serum creatinine levels rising to 1.87 mg/dl. However, the determination of serum and urine metabolites on subsequent days showed that the salicylate-induced proximal tubular dysfunction was rapidly reversible. Indeed, the electrolyte fractional excretion values showed a trend towards normalization while serum creatinine levels were 1.25 mg/dl on the fourth day of hospitalization. The patient was discharged and a follow-up determination of serum and urine metabolites fifteen days later revealed the complete correction of the proximal tubular dysfunction.

Discussion

High doses of acetylsalicylic acid (aspirin) have been used since ancient times due to its anti-inflammatory properties [2]. The evolution of non-steroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drugs (DMARDs) led to a reduction in the use of aspirin in the treatment of rheumatic diseases; however, this compound is currently used in low doses in the prevention of thrombotic events in individuals with established cardiovascular disease [3]. The precise dose of salicylates that results in clinically significant toxicity remains indeterminate. Temple stated that doses of 150-300 mg/kg would be expected to produce mild to moderate toxic reactions, 300-500 mg/kg would produce serious reactions, and doses in excess of 500 mg/kg would be potentially lethal [4]. However, these thresholds vary considerably in the literature since evidence regarding dose, toxicity, and time of onset is primarily limited to case reports and case series [5]. The signs and symptoms of salicylate intoxication are related to local irritation of the gastrointestinal tract, direct stimulation of the central nervous system respiratory centre, stimulation of the metabolic rate, disturbance of carbohydrate and lipid metabolism, and interference with haemostasis [5]. In infants salicylate poisoning may resemble diabetic ketoacidosis [6]. On the other hand, the effects of acute salicylate poisoning on renal physiology remain ill-defined. Although short-term administration of therapeutic doses of aspirin in healthy subjects has no obvious effects on renal function [7], ingestion of aspirin in toxic doses has been reported to induce reversible generalized proximal tubular dysfunction [8] and in more severe cases acute polyuric renal failure (possibly consistent with acute tubular necrosis [9]). On the other hand, the short-term administration of therapeutic doses of aspirin in patients with compromised renal function (such as those with cirrhosis, congestive heart failure or chronic renal insufficiency) may lead to the development of acute oliguric renal failure [10-12]. In these cases the inhibitory effect of aspirin on the production of renal vasodilatory prostaglandins may represent the most important cause of the acute renal failure. The underlying pathophysiological mechanism of salicylate-induced proximal tubular dysfunction is not well characterized. However, it has been proposed that the covalent binding of salicylate or its metabolites (some studies indicate 2,5-dihydroxybenzoic acid as the more nephrotoxic metabolite of salicylate [13]) to the mitochondria of the proximal tubular cells may alter the function of these organelles, thus interfering with the provision of energy [14]. The decreased content of adenosine triphosphate (ATP) in the renal cortex (but not medulla) of dogs treated with high doses of salicylates is consistent with this hypothesis [15]. The decreased provision of energy in proximal tubular cells may lead to the dysfunction of active transporters or, in more severe cases, in cellular death.

In conclusion, this report publishes the second case of Fanconi's syndrome following salicylate intoxication in humans. Once more the salicylate-induced Fanconi syndrome was rapidly reversible. We suggest that clinicians should be aware of this rare renal complication of salicylate intoxication.

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