Modern Intermittent Haemodialysis (IHD) is an Effective Method of Removing Salicylate in Chronic Topical Salicylate Toxicity

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Abstract

Introduction There are limited data on modern intermittent hemodialysis (IHD) efficacy on salicylate elimination from topical poisoning.

Case report A 54-year-old male sought treatment for dyspnea but was then diagnosed with salicylate toxicity from topical application of Dencorub Extra Strength Heat Gel® for 1 week. Each tube contained 100 g with 26 % methylsalicylate (26 g). Laboratory workup was remarkable for an elevated anion gap of 30 and salicylate concentration of 78.7 mg/dL [5.7 mmol/L ($N < 0.4$ mmol/L)]. Treatment with urinary alkalization was followed by hemodialysis for 5 h. Extraction ratios were 0.44 with clearance rates of 78.5 mL/min. Salicylate concentrations fell rapidly following initiation of hemodialysis with no rebound observed.

Discussion Modern high flux IHD is an effective method of removing salicylates in the treatment of chronic topical poisoning.

Keywords Salicylate · Poisoning · Hemodialysis · Topical

Introduction

The use of hemodialysis and its efficacy for salicylate removal in the context of chronic toxicity has not been well described in the literature. We describe a case of chronic topical salicylate toxicity and the efficacy of modern high flux hemodialysis.

Case Report

A 54-year-old male presented with worsening dyspnea over 1 week and was referred to the respiratory team for the management of presumed acute exacerbation of asthma. He had administered Dencorub Extra Strength Heat Gel® in the past week for aches and pains. He applied one tube of 100 g every day for the previous 7 days, each tube containing 26 % methylsalicylate (26 g). Given the patient's weight of 100 kg, this would be 260 mg/kg/day of methylsalicylate or equivalent to 308 mg/kg/day aspirin (assuming equal bioavailability) applied topically. He complained of nausea, vertigo, but no tinnitus. The patient did not have a cough, fever, wheeze, infective symptoms or a past history of asthma. He had a past history of type 2 diabetes mellitus and hypertension. Regular medications included glimepiride, atorvastatin and telmisartan, and there were no other coingestants.

On examination, the patient was afebrile, had a blood pressure of 144/72 mmHg, a respiratory rate of 33 breaths per min, heart rate of 95 beats/min, and an oxygen saturation of 98 % on room air. He was orientated to time, person and place. His chest was clear and he had a soft abdomen. He had significant erythema all over his chest where he had been applying the liniment. He had investigations of an arterial blood gas, pH 7.45 (7.35–7.45), HCO_3^- 10 mmol/L (22–25), pCO_2 14 mmHg (35–45), base excess 14 and lactate 0.9 mmol/L (0.5–1.6) with a raised anion gap of 30. Renal function

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Fig. 1 Salicylate concentrations over time. *IHD* intermittent hemodialysis performed

showed mild renal impairment with a creatinine of 122 micromol/L (90–100). Blood salicylate concentration was 5.7 mmol/L (therapeutic range 0.2–0.7 mmol/L) or 78.7 mg/dL performed by the local laboratory.

He was diagnosed with chronic salicylate toxicity and started on urinary alkalinization. A 100-mmol bolus of IV sodium bicarbonate was given followed by 100 mmol over 4 h to keep a urinary pH > 7.5. Given the elevated salicylate concentration and unchanged clinical state despite urinary alkalinization, he was transferred to a tertiary hospital for intermittent hemodialysis (IHD) and dialyzed for 5 h. High flux hemodialysis was provided using the Fresenius 4008S machine fitted with the FX100 dialyzer (ultrafiltration coefficient 73 mL/h × mmHg and surface area 2.2 m²). Salicylate concentrations were taken from the afferent and efferent limbs of the dialysis machine. Salicylate concentrations fell rapidly following initiation of hemodialysis (Fig. 1) with minimal rebound observed. Half life seemed to decrease dramatically during dialysis to 2 h compared to a pre-dialysis half-life of 12.6 h.

His clinical state improved with his tachypnea resolving and salicylate concentrations falling to within therapeutic range. Salicylate concentrations were monitored and extraction ratios and clearances calculated (Table 1). The blood flow rate during

dialysis was 350 mL/min and dialysate rate 500 mL/min with initial clearance of 78.5 mL/min. The second clearance rate of 64.5 mL/min of salicylate during dialysis was lower. Salicylate concentrations fell to therapeutic levels over another 24 h post-cessation of dialysis. He recovered, education was given on the appropriate use of salicylate medication, and he was discharged on day 3 post-hospital presentation.

Discussion

Clinical toxicity of salicylate poisoning may be apparent following either acute or chronic exposure. Salicylates uncouple oxidative phosphorylation, increasing cellular metabolism, and directly stimulate the respiratory centre. They also inhibit the citric acid cycle altering amino acid and lipid metabolism [1]. Symptoms of acute salicylate toxicity include nausea, vomiting, tinnitus, vertigo, tachypnea, pulmonary edema, delirium, cerebral edema and coma. Chronic salicylate toxicity may present more insidiously with confusion, hallucinations, and delirium and may go unrecognized, especially in the elderly. Laboratory findings may include a respiratory alkalosis,

Table 1 Extraction ratio, clearance and expected efficacy of intermittent hemodialysis of salicylate

Time PI (h)	Dialysis mode	HCT	BFR (mL/min)	DR (mL/min)	Pa (mmol/L)	Pv (mmol/L)	ER	K (mL/min)
28	IHD	0.49	350	500	3.9	2.2	0.44	78.5
32	IHD		350	500	1.9	1.2	0.36	64.3

PI time post last use salicylate, *HCT* hematocrit, *BFR* blood flow rate, *DR* dialysate rate, *Pa* plasma salicylate concentration from arterial (afferent) limb, *Pv* plasma salicylate concentration from venous (efferent) limb, *ER* extraction ratio, *K* instantaneous clearance, *IHD* intermittent hemodialysis

high anion gap metabolic acidosis, hyperkalemia and coagulation abnormalities.

Since our patient applied methylsalicylate topically for a week, this case likely represented chronic toxicity and steady-state plasma concentrations. Salicylate absorption after 30 min of contact time is thought to be 2 % [2]. However, 12–20 % of a topical dose of methyl salicylate may be absorbed after 10 h [3]. The stratum corneum layer of the skin acts not only as a barrier but also a potential reservoir in the transcellular lipid portion. Ongoing absorption from a dermal reservoir may have contributed to the longer half life of 50 h observed after hemodialysis. In addition, the calculated equivalence to oral aspirin applied daily was large compared to therapeutic use of aspirin, e.g. 80 mg/kg/day in rheumatoid arthritis [4]. Salicylate toxicity from topical application/gels is uncommon, but a recognized risk and our case has one of the highest recorded salicylate concentrations from topical application [5].

Treatment of salicylate toxicity includes maintenance of euolemia, gastrointestinal decontamination with activated charcoal, urinary alkalinization with sodium bicarbonate, and hemodialysis. Salicylic acid is a weak acid (pKa 3.0) and is ionized in an alkaline environment. In addition to enhancing salicylate renal elimination, sodium bicarbonate administration will raise blood pH and thereby reduce salicylate entry into the brain.

Salicylates have a low molecular weight (138 Da) and volume of distribution (0.2 L/kg) but are highly protein bound at therapeutic concentrations (90 %) [6]. In overdose, the extent of protein binding decreases considerably, making it an ideal poison for extracorporeal removal with IHD [7, 8]. Indications for dialysis include altered mental status, new hypoxemia, a salicylate concentration >7.2 mmol/L (100 mg/dL) in cases of acute poisoning, or lower concentration in cases of chronic poisoning, or with renal impairment [9]. Even though these criteria were not met, given the patient's ongoing symptomatology despite alkalinization, we elected to proceed to dialysis. Dialysis may help decrease length of stay in hospital, especially if urinary alkalinization is not proving effective, and help correct acid-base status, but does have its risks (e.g. catheter placement, infection, and fluid shifts).

The formulae we used to calculate the extraction ratio and clearance are:

$$\text{Extraction ratio} = \frac{P_a - P_v}{P_a}$$

$$\text{Plasma flow rate} = \text{blood flow rate} \times (1 - \text{haematocrit})$$

$$K = \text{extraction ratio} \times \text{plasma flow rate}$$

where P_a is the plasma salicylate concentration from arterial limb (afferent), P_v is the salicylate concentration from venous limb (efferent), and K is the instantaneous clearance.

Extraction ratios for salicylate decades ago in older hemodialysis machines have been quoted as 0.2 to 0.7 [10].

Previous cases of topical salicylate toxicity where dialysis has been used have not looked at clearance [11, 12]. In our case, clearance of salicylate was higher during the initiation of HD compared to later in dialysis treatment, likely due to the greater presence of free salicylate at higher concentrations and higher protein binding at lower concentrations. Hemodiafiltration and sustained low-efficiency dialysis (SLED) has been used to dialyze salicylates previously [13, 14]. Decrease in salicylate half-life during dialysis is universal but comparison between these papers and ours are difficult due to the lack of extraction ratios and clearance rates. As a result, the reporting of overdose cases treated by extracorporeal therapies should be standardized as suggested by Lavergne [15].

Conclusion

Large topical salicylate use can cause systemic toxicity. This case suggests that modern HD machines are an effective method of removing salicylates in the treatment of chronic topical poisoning.

Compliance with Ethical Standards

Conflict of Interest The authors declare they have no competing interests.

References

1. Temple AR. Pathophysiology of aspirin overdosage toxicity, with implications for management. *Pediatr (Suppl)*. 1978;62:873–6.
2. Lotte C, Wester RC, Rougier A, Maibach HI. Racial differences in the vivo percutaneous absorption of some organic compounds: a comparison between Black, Caucasian and Asian subjects. *Arch Dermatol Res*. 1993;284:456–9.
3. Robert MS, Favretto WA, Meyer A, Reckmann M, Wongseelashote T. Topical bioavailability of methylsalicylate. *Aust NZ J Med*. 1982;12:303–5.
4. Aspirin Dosage. www.drugs.com/aspirin.html Last accessed 7th August 2015
5. Brubacher JR, Hoffman RS. Salicylism from topical salicylates: review of the literature. *Clin Toxicol*. 1996;34(4):431–6.
6. Fertel BS, Nelson LS, Goldfarb DS. The underutilization of hemodialysis in patients with salicylate poisoning. *Kidney Int*. 2009;75:1349–53.
7. Jorgensen HE, Wieth JO. Dialyzable poisons: hemodialysis in the treatment of acute poisoning. *Lancet*. 1963;1(7272):81–4.
8. Doolan PD, Walsh WP. Acetylsalicylic acid intoxication. A proposed method of treatment. *JAMA*. 1951;146:105.
9. Juurlink DN, Gosselin S, Kielstein JT, Ghannoum M, Lavergne V, Nolin TD, et al. Extracorporeal treatment for salicylate poisoning: systematic review and recommendations From the EXTRIP workgroup. *Ann Emerg Med*. 2015;66(2):165–81.

10. Winchester JF, Gelfand MC, Helliwell M, Vale JA, Goulding R, Schreiner GE. Extracorporeal treatment of salicylate or acetaminophen poisoning- is there a role? *Arch Intern Med*. 1981;141:370–4.
11. Chin RL, Olson K, Dempsey D. Salicylate toxicity from ingestion and continued dermal absorption. *Cal J Emerg Med*. 2007;8(1):23–5.
12. Raschke R, Arnold-Capell PA, Richeson R, Curry SC. Refractory hypoglycemia secondary to topical salicylate intoxication. *Arch Intern Med*. 1991;151(3):591–3.
13. Wrathall G, Sinclair R, Moore A, Pogson D. Three case reports of the use of hemodiafiltration in the treatment of salicylate overdose. *Hum Exp Toxicol*. 2001;20:491–5.
14. Lund B, Steifert SA, Mayersohn M. Efficacy of sustained low-efficiency dialysis in the treatment of salicylate toxicity. *Nephrol Dial Transplant*. 2005;20(7):1483–4.
15. Lavergne V, Ouellet G, Bouchard J, et al. Guidelines for reporting case studies on extracorporeal treatments in poisoning: methodology. *Semin Dial*. 2014;27:407–14.