

Case report of aspirin overdose: bezoar formation and controversies of multiple-dose activated charcoal in salicylate poisoning

阿司匹靈過量的個案報告：腸胃結石形成及於水楊酸鹽中毒使用多劑量活性炭的爭議

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Bezoar formation is cited to be the cause of delayed absorption of aspirin in overdose of enteric-coated aspirin preparation. However, such phenomenon from oral overdose of regular aspirin preparation has not been clearly demonstrated in human. The use of multiple-dose activated charcoal (MDAC) in salicylate poisoning remains controversial. We report a case of regular-preparation salicylate poisoning with rebound of the serum salicylate level after discontinuation of MDAC administration. Bezoar formation as the underlying cause of the rebound and the effect of MDAC on serum salicylate level are discussed. (*Hong Kong j.emerg.med.* 2010;17:276-280)

過量服用阿司匹靈腸衣製劑而形成腸胃結石，被引述為延慢吸收阿司匹靈的原因。然而，這現象在人類口服過量的阿司匹靈普通製劑中，是沒有清晰的證明。在水楊酸鹽中毒中，使用多劑量活性炭仍然具爭議性。我們報告一個水楊酸鹽普通製劑中毒的個案，在停止施用多劑量活性炭後，血清的水楊酸鹽水平回昇。本文討論形成腸胃結石為血清水楊酸鹽水平回昇的基本原因及多劑量活性炭對血清水楊酸鹽水平的影響。

Keywords: Aspirin, bezoars, overdose, poisoning, salicylates

關鍵詞：阿司匹靈、腸胃結石、過量、中毒、水楊酸鹽

Introduction

Aspirin (acetylsalicylic acid) overdose caused many deaths in the past.^{1,2} Despite the absence of specific antidote for salicylate poisoning, enhanced elimination and prevention of further absorption gained successful outcome in most of the patients with moderate or even severe intoxication.³ Multiple-dose activated charcoal

(MDAC) is widely used in the management of salicylate poisoning but the data to support its use in real poisoned patients is insufficient. The use of MDAC in salicylate poisoning remains controversial among the authorities of clinical toxicology.⁴ We report a case of overdose of regular-preparation aspirin with rebound of blood salicylate level after the discontinuation of MDAC. Our case demonstrates the benefit of MDAC for the disruption of delayed and prolonged systemic absorption of salicylate due to possible bezoar formation, a phenomenon not yet reported in human.

Case

A 33-year-old gentleman, with good past health, presented to the Accident and Emergency Department

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in April 2008 for suicidal attempt with an overdose of aspirin. He had ingested 90 tablets of regular-preparation aspirin (500 mg/tablet) around five hours before arrival. He complained of epigastric discomfort, nausea and tinnitus. He had drunk a can of beer which was around 500 ml but he denied co-ingestion of other medications. The physical examination revealed a normal-size male with an estimated body weight of approximately 70 kg. The Glasgow Coma Scale score was 15/15, blood pressure 159/90 mmHg, pulse rate 106 beats per minute, body temperature 36.8°C and respiratory rate 20 breaths per minute. The electrocardiogram showed sinus rhythm with normal QRS duration and corrected QT interval. The spot blood glucose level was normal. His chest X-ray showed clear lung fields and the abdominal X-ray did not show any radio-opaque foreign bodies or tablets. The initial blood tests revealed elevated salicylate level (3.52 mmol/L, reference range <2.17 mmol/L), normal renal function, international normalised ratio (INR) of 1.1 and no evidence of metabolic acidosis. MDAC was given with the regimen of an initial dose of 50 g and then 25 g every 2 hours for 3 doses. Urinary alkalinisation was also started. An initial bolus of 100 ml of 8.4% sodium bicarbonate solution was given intravenously followed by infusion of a mixture of sodium bicarbonate solution and 5% dextrose water. Potassium, serum and urine pH levels were closely monitored (Table 1). He was subsequently transferred to the Emergency Medicine Ward for further management. The blood salicylate level dropped to 2.60 mmol/L around 6 hours after the initiation of

the MDAC therapy. There was rebound of the blood salicylate level up to 4.74 mmol/L around 5 hours after the last dose of MDAC. Repeated doses of activated charcoal (25 g every 2 hours) were given and the blood salicylate level dropped progressively without further rebound (Figure 1). The patient had deranged clotting profile with the INR increased up to 1.6 at around 26 hours post-ingestion and the INR then gradually improved. There was no clinical evidence of bleeding. The patient had stable vital signs all along during his stay in hospital and was discharged on day 2 after psychiatric assessment.

Discussion

Despite the belief that aspirin overdose is associated with the formation of 'pharmaco-bezoar', direct evidence of this phenomenon for the regular preparation in human is lacking. The clinical features of pharmaco-bezoar include space occupying effect in the gastrointestinal (GI) tract (i.e. nausea, vomiting or intestinal obstruction) and, more importantly, delayed absorption of the pharmacological agents in the bezoars.⁵ Formation of pharmaco-bezoars from chronic use of enteric-coated aspirin were frequently reported in literatures.⁶⁻⁹ On literature review, most of the reported cases of acute aspirin overdose with delayed absorption were associated with modified preparations, especially enteric-coated forms.¹⁰⁻¹³ Delayed manifestation of salicylate toxicity up to 35 hours without early symptoms of toxicity has been reported

Table 1. Time course of laboratory findings

	Time after presentation (hour)										
	0	2	4	6	8	12	16	22	28	34	40
Serum pH	7.41	7.44	7.56/7.53	7.41	7.57 [†]	7.4	7.43	7.5	7.48	7.4	7.42
pCO ₂ (kPa)*	5.5	4.8	4.4/4.5	4.7	4.3	5.22	3.97	3.97	5.19	5.86	5.38
HCO ₃ (mmol/L)	26	24.5	29.5/28.4	27.9	29.3	23.5	19.2	22.8	28.2	26.8	25.4
BE (mmol/L)	1.2	0.7	7.4/5.7	5	7.5	-1.2	-3.8	0.8	4.5	1.6	0.8
K (mmol/L)	3.8	3.7	3.7	3.3	2.8	3.8	3.6	4.6	2.9	4.1	3.7
Urine alkalinisation	–	#1	#2	#3	#4						

*Venous blood was taken for blood gas analysis; [†]Arterial blood gas; #1: 100 ml 8.4% NaHCO₃ IV full rate; #2: IV infusion of mixture of 50 ml 8.4% NaHCO₃ in 500 ml 5% Dextrose solution at a rate of 137.5 ml/h; #3: IV infusion of mixture of 50 ml 8.4% NaHCO₃ in 500 ml 5% Dextrose solution at a rate of 91.7 ml/h; #4: IV infusion of mixture of 50 ml 8.4% NaHCO₃ in 500 ml 5% Dextrose solution at a rate of 137.5 ml/h

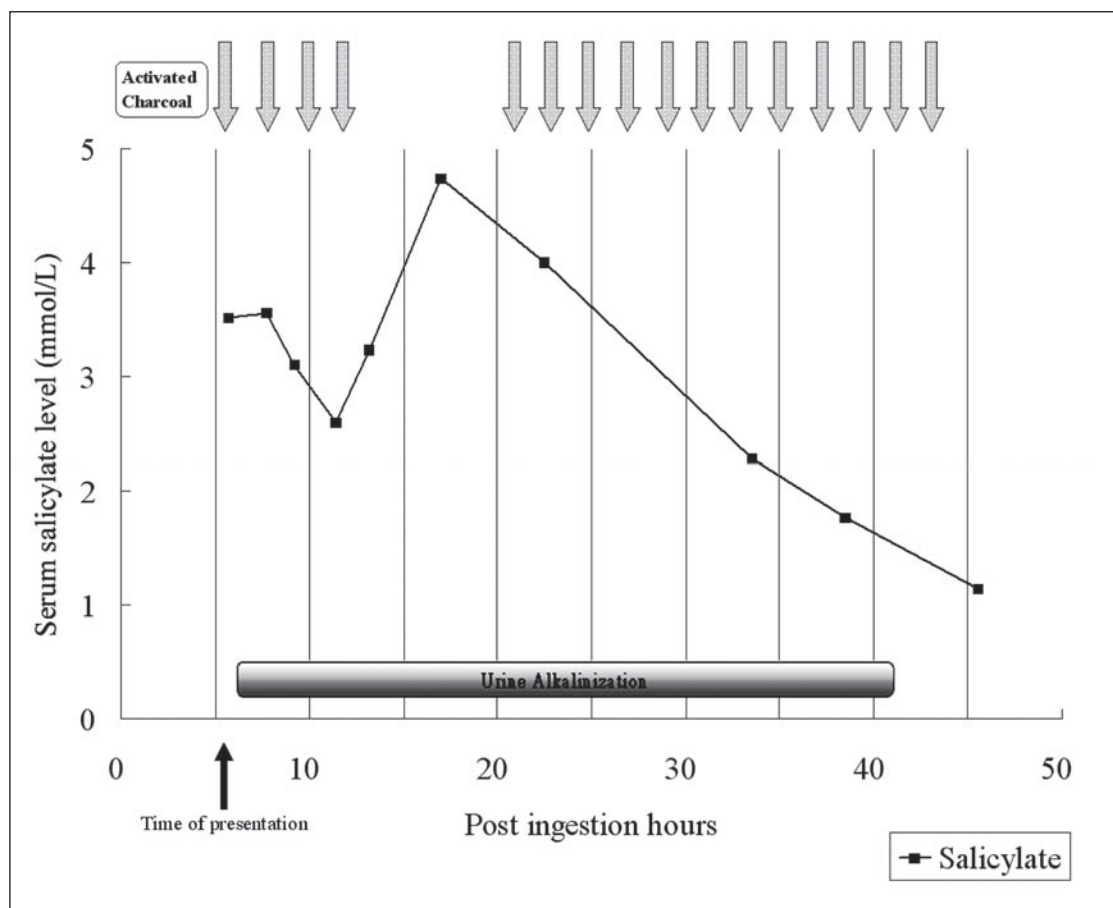


Figure 1. Time course of serum salicylate level.

in a patient with extended-release aspirin overdose.¹⁴ However, there is no documented case report to support the formation of bezoar or delay absorption from regular-preparation aspirin. Salhanick et al reported a case of aspirin bezoar formation at the distal oesophagus documented by upper endoscopy but the nature of the aspirin preparation was not mentioned.¹⁵ Animal study showed delayed and multiple erratic peaks of serum acetylsalicylate level after ingesting a large dose (500 mg/kg) of aspirin (normal preparation) in pigs. The result indicated the formation of bezoar or concentration after ingesting a large dose of regular-preparation aspirin in animal.¹⁶ Our case illustrates a rebound of blood salicylate level which supports the postulation of bezoar formation from massive oral overdose of regular-preparation aspirin tablets in the acutely poisoned patient. The only risk factor for bezoar formation in our case was the large ingested dose.

The management of acute aspirin overdose involves supportive therapy, prevention of further absorption, assessment of the severity of poisoning and enhanced elimination including urine alkalinisation and hemodialysis.¹⁷ Concerning gastrointestinal decontamination, activated charcoal (AC) was shown to be highly effective to adsorb aspirin in an in-vitro study.¹⁸ Human volunteer studies have also shown significant reduction of aspirin absorption by AC even if it is administered within 3 hours after aspirin ingestion, provided there is still presence of the drug in the GI tract.¹⁹ Administration of AC effectively reduces the absorption of aspirin in both regular and modified release forms.³

The volume of distribution of salicylate is small.²⁰ Thus, it has been believed that enhanced elimination by MDAC would also be beneficial for salicylate poisoning. The hypothesis for the use of MDAC in

acute poisoning situation is based on the "gut dialysis" theory.²¹ Repeated administration of AC lowers the concentration of free drugs in the GI tract. This process favours the diffusion of drugs in the bloodstream back into the GI tract. However, only selected drugs have been shown to go through this recirculation pathway in the body. It has been shown that MDAC enhanced the elimination of already absorbed phenobarbital²² and theophylline.²³ Currently, there is no strong evidence to support the use of MDAC for the management of acute salicylate poisoning. MDAC was shown to have no effect on the clearance of salicylate after intravenous administration of aspirin in pig.²⁴

Hillman et al reported five cases of acute oral salicylate poisoning treated with repeated doses of AC and found significant shortening of the half-life of salicylate among all the five patients. However, a definite benefit for MDAC in salicylate poisoning was still not clearly demonstrated as no comparable control groups of patients were recruited in their study.²⁵ The use of MDAC in salicylate poisoning was well investigated in volunteer studies but most of the studies did not demonstrate an increased salicylate clearance with MDAC therapy. Barone et al performed a volunteer study to compare the effect of AC in different regimens (i.e. one-dose, two-dose and three-dose) on the absorption of orally administered aspirin by using urine salicylate recovery as the outcome measure and found a significant decrease in urinary excretion of salicylate in the group treated with the three-dose regimen of AC. Their result showed an enhanced non-renal (i.e. GI tract) excretion of salicylate.²⁶ In another volunteer study, it was found that no significant difference in the blood salicylate level when AC was given in post-absorption phase (i.e. 4 hours after oral aspirin administration).²⁷ By using both serum and urine salicylate concentrations as the outcome measure, Kirshenbaum et al found positive result to support that MDAC enhanced the excretion of salicylate from the body by a non-renal route but the amount was not significant. Thus, the efficacy of MDAC in real overdose situations was questionable.²⁸ Both MDAC and whole-bowel irrigation were also shown to be ineffective to increase clearance of absorbed salicylate in a volunteer study performed by Mayer et al.²⁹ The

major drawback of volunteer studies is that the toxic or even fatal doses of aspirin can never be studied. Thus, it may be difficult to apply the results into real overdose situations.

Although there is insufficient evidence to support the use of MDAC in salicylate poisoning as a method for enhanced elimination by the process of 'gut dialysis', MDAC has a special role in preventing absorption in aspirin overdose particularly when there is massive ingestion with a risk of bezoar formation. Firstly, the bezoar formed by aspirin tablets retains in the GI tract for a prolonged period of time and undergoes further dissolution resulting in the presence of a significant amount of soluble salicylate in the GI tract. Repeated doses of AC provide more binding sites and prevent further systemic absorption of the salicylate. Moreover, breakdown of the bezoar due to the mechanical action of the gut may lead to a sudden surge of aspirin absorption. By recoating the surfaces of the bezoar fragments with AC, ongoing absorption can be reduced. Lastly, there is a process of 'desorption' of the aspirin from AC with evidence supported from volunteer studies. Neuvonen et al conducted a volunteer study for the effect of AC on the absorption of aspirin and found a 'desorption phenomenon' of the adsorbed aspirin from the AC with the evidence of a considerably greater excretion of salicylate in urine during the second to fourth days following the ingestion of aspirin with AC.³⁰ The desorption phenomenon was confirmed by a further volunteer study.³¹ MDAC is therefore protective for the tendency of continuous desorption of aspirin from the AC especially in overdose situations.

Conclusion

Aspirin overdose may lead to bezoar formation in the gut. A delayed and erratic absorption of aspirin in a regular preparation was clearly demonstrated in our case. Although there is insufficient clinical data to support the recommendation on the use of MDAC for enhancing elimination in salicylate poisoning, MDAC should be considered as a means of GI decontamination in massive aspirin overdose.

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