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ORIGINAL ARTICLE

Activated Charcoal and Bicarbonate for Aspirin Toxicity: a Retrospective Series

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Abstract

Introduction Aspirin overdose causes acid–base disturbances and organ dysfunction. Management is guided by research reported over 50 years ago when chronic aspirin toxicity was common and accounted for significant morbidity. We investigate our experience of aspirin overdose and the effectiveness of charcoal and bicarbonate administration over 20 years.

Methods This is a retrospective series of acute aspirin overdose from two toxicology units from January 2000 to September 2019. Acute aspirin ingestions > 3000 mg were identified in each unit's database. Excluded were cases of chronic exposure, hospital presentation > 24 hours after ingestion, and cases without a salicylate concentration. Included in our analysis was demographic data, clinical effects, investigations, complications, and treatment.

Results There were 132 presentations in 108 patients (79 females (73%)). The median age was 28 years (range: 13–93 years). The median dose ingested was 7750 mg (IQR: 6000–14,400 mg). There were 44 aspirin-only ingestions. Mild toxicity (nausea, vomiting, tinnitus or hyperventilation) occurred in 22 with a median dose of 160 mg/kg. Moderate toxicity (acid–base disturbance, confusion) occurred in 16 with a median ingested dose of 297 mg/kg. There were no cases of severe toxicity (coma or seizures) due to aspirin alone. The median peak salicylate concentration was 276 mg/L (IQR: 175–400 mg/L, range: 14–814 mg/L). There was a moderate association between dose ingested and peak concentration (Pearson $r = 0.58$; 95% CI 0.45–0.68). Activated charcoal was administered in 36 (27%) cases, which decreased the median peak salicylate concentration (34.2 to 24.8 mg/L/g (difference: 9.4, 95% CI: 1.0–13.1)). Bicarbonate was administered in 34 (26%) presentations, decreasing the median apparent elimination half-life from 13.4 to 9.3 h (difference: 4.2 h, 95% CI: 1.0–6.5 h).

Conclusions Acute aspirin overdose caused only mild to moderate effects in this series. Early administration of activated charcoal decreased absorption and use of bicarbonate enhanced elimination.

Keywords Aspirin · Salicylate · Poisoning · Overdose · Activated charcoal · Bicarbonate

Introduction

Acetylsalicylic acid, first manufactured as aspirin by Bayer over one hundred years ago, is a non-selective inhibitor of cyclo-oxygenase. At therapeutic doses, it confers analgesic, anti-pyretic, anti-platelet and anti-inflammatory benefits. These properties have ensured aspirin is commonplace in many households, allowing it ready accessibility as a means of deliberate self-poisoning. In the past, it was responsible for chronic toxicity, particularly in the elderly taking regular aspirin for arthritis [1], prior to the introduction of newer non-steroidal anti-inflammatory agents. The pathophysiology of aspirin overdose is well described [2]. Aspirin disrupts multiple metabolic processes producing mixed respiratory alkalosis and metabolic acidosis. In severe toxicity, multiorgan dysfunction ensues.

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The research that guides the management of aspirin overdose is largely drawn from the experience of more than 50 years ago [3, 4]. At that time, salicylates ranked second only to barbiturates in overdoses and were the agent involved in approximately one-quarter of unintentional paediatric ingestions [3]. Since then, aspirin poisoning has declined dramatically, particularly in children, with the introduction of safer packaging [5] and the increased awareness of the phenomenon of Reye's syndrome. It is now a relatively uncommon poisoning, and its incidence continues to decline in Australia [6].

Management principles in aspirin poisoning have remained unchanged over the last few decades—good supportive care, early decontamination and enhanced elimination for significant toxicity [2, 7, 8]. However, there is limited evidence to support the effectiveness of commonly used treatments for decontamination or those used to enhance drug elimination. Studies investigating the effectiveness of treatments such as activated charcoal or bicarbonate in aspirin poisoning are largely volunteer studies [9–12] that may not replicate the pharmacokinetics of aspirin in overdose. We aimed to investigate our experience of aspirin overdose over 20 years and evaluate the effectiveness of commonly used therapies, activated charcoal and bicarbonate.

Materials and Methods

Study Design and Setting

This is a retrospective review of patients presenting to two clinical toxicology units with deliberate aspirin overdoses. Both units manage all poisoned patients that present to their emergency department from their geographical catchment area. One is located within a tertiary hospital with an emergency department that has approximately 64,000 presentations annually. The other is within a metropolitan hospital, with an emergency department that has approximately 38,000 presentations annually. The toxicology units admit approximately 2000 and 900 patients each year respectively under their own service. These patients are managed in wards throughout the hospital including the short stay unit in the emergency department, the medical ward and the intensive care unit.

Admission data are collected on either a preformatted admission sheet or tablet-based application [6, 13]. The data are entered prospectively into a purpose-built relational database each week by either trained research staff or medical staff. Each week, a clinical toxicologist (a specialist physician with a subspecialisation in clinical toxicology) reviews all admissions and any additional information is obtained directly from the medical record. The toxicology team sees all patients admitted to the service daily and treatment is determined by the attending clinical toxicologist. The use of both databases and patient medical records for research has been granted by the respective local area human research ethics committee.

Selection of Participants

The databases for both units were searched for all aspirin exposures > 3000 mg presenting from January 2000 to September 2019. Exposure to aspirin was determined by patient history as part of the toxicological risk assessment. Chronic exposures (supratherapeutic exposures over multiple days), patients who presented to the hospital more than 24 hours following the ingestion, patients who did not have a salicylate concentration performed and those whose salicylate concentrations were not detected were excluded from the analysis.

Data Collection

We extracted data for all aspirin exposures from both toxicology databases. This included baseline characteristics (age, sex), ingestion details based on patient history (time, dose, intent, co-ingestions), complications (coma (Glasgow Coma Score (GCS) < 9), seizure and hypotension (systolic blood pressure < 90 mmHg)), treatment (charcoal (50 g), intubation, dialysis), disposition, length of stay (LOS) and intensive care unit (ICU) admission.

To obtain further information, the medical records were also reviewed for all patients included in the study. Additional data extracted from the medical records included: patient weight, clinical effects (tinnitus, vomiting, hyperventilation (respiratory rate > 20), confusion, acute kidney injury (defined by KDIGO guidelines [14])), blood gas analysis (respiratory alkalosis (pCO_2 < 30 mmHg), metabolic acidosis (HCO_3 < 20 mmol/L), raised anion gap (anion gap > 16)), salicylate concentration, interventions (activated charcoal or bicarbonate administration) and complications of therapy (hypernatremia (sodium > 150 mmol/L), severe alkalaemia (pH > 7.6) and hypokalaemia (potassium < 3.0 mmol/L)). If the patient weight was not documented, a standardised weight of 60 kg was adopted for women and 70 kg for men.

We designed a data collection sheet prior to data extraction and included parameters from the toxicology database and patient medical records. Three abstractors performed data collection. Double extraction was performed on the first 20/174 (11%) of cases with only a single discrepancy identified, which was corrected for the remainder of the data collection. Missing data was entered into the datasheet as 'not documented'.

Outcomes

The severity of aspirin poisoning was graded in accordance with the classic descriptions [3, 7] asymptomatic; mild (tinnitus, nausea, vomiting or hyperventilation); moderate (acid–base disturbances, confusion) and severe (coma or seizures). To assess the effectiveness of charcoal administration, the peak salicylate concentration (mg/L) per gram of aspirin ingested was compared between those receiving charcoal and those not. The peak salicylate concentration was taken as the highest measured salicylate concentration which was performed during the presentation. To assess the effectiveness of bicarbonate administration, the apparent elimination half-life of salicylate was compared between those administered bicarbonates and those not. Apparent elimination half-life was estimated using non-linear regression assuming a one-compartment disposition model with a mono-exponential decline in salicylate concentrations.

Data Analysis

Continuous variables are reported as medians, interquartile ranges (IQR) and ranges. The difference between groups is compared with the Mann–Whitney *U* test, with 95% confidence intervals calculated. The association between the dose of aspirin ingested in milligram per kilogram and salicylate concentration was determined with Pearson's correlation co-efficient. All analysis was performed in GraphPad Prism 8 for Mac OS (GraphPad Software, San Diego, CA, USA; www.graphpad.com).

Results

There were 174 aspirin poisonings > 3000 mg over the study period. There were 42 exclusions, 22 of these because no salicylate concentration was measured (Fig. 1), leaving 132 presentations in 108 patients that were included in the

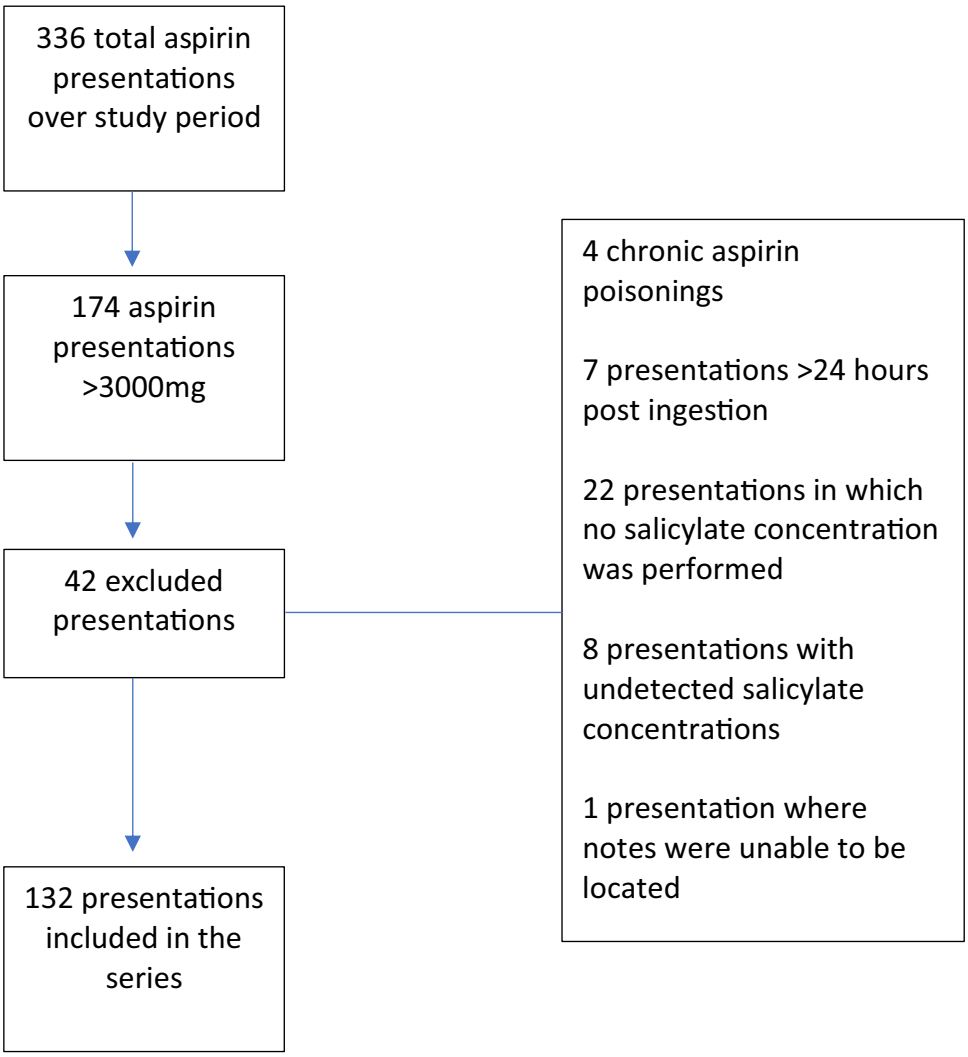

Fig. 1 Recruitment flowchart

study. The median age was 28 years (range: 13–93 years) and there were 79 (73%) females. Aspirin was the only agent ingested in 35 (27%) presentations. The most common co-ingestants were acetaminophen, ethanol, non-steroidal anti-inflammatories and antidepressants (Table 1). The median dose ingested was 7750 mg (IQR: 6000–14,000 mg; range: 3300–86,400 mg) equating to 121 mg/kg (IQR: 80–222 mg/kg; range: 39–1440 mg/kg). Enteric-coated preparations were taken in 20 (15%) presentations; the median dose ingested for enteric-coated preparations was taken was 7000 mg (IQR 5450–9850 mg, range: 4000–18,000 mg) or 89 mg/kg (IQR 76–145 mg/kg, range: 41–225 mg/kg).

Clinical Features

Features of salicylism were common (Table 2) with at least one of either hyperventilation, vomiting or tinnitus occurring in 79 (60%) presentations. Hypotension occurred in 14 (11%), confusion in 12 (9%) and coma in 7 (5%) cases. All cases of coma could be attributed to co-ingested agents, and confusion occurred in only two patients ingesting aspirin alone (ingesting 303 mg/kg and 308 mg/kg respectively). Acute kidney injury occurred in 12/130 (9%) presentations, in which creatinine was performed. In three presentations with acute kidney injury aspirin was the only agent ingested (at doses of 303 mg/kg, 650 mg/kg and 1440 mg/kg). A seizure occurred in a single patient who had co-ingested 2100 mg of venlafaxine.

In the 44 patients with aspirin-only ingestions, there were six asymptomatic patients, 22 with mild toxicity and 16 with

Table 2 Clinical features of 132 patients presenting with aspirin overdose

Hyperventilation	47 (36%)
Vomiting†	37 (28%)
Tinnitus‡	35 (28%)
Respiratory alkalosis^	33 (28%)
Metabolic acidosis^	32 (26%)
Raised anion gap^	12 (11%)
Hypotension	13 (11%)
Confusion	12 (9%)
Coma	7 (5%)
Acute kidney injury*	12 (9%)
Seizure	1

†Documentation missing in one presentation

‡Documentation missing in seven presentations

^Bloods gas analysis was performed in 116 presentations

*A creatinine was performed in 130 presentations

Table 1 Acute aspirin overdose presentations

Total number of presentations	132
Number of participants	108
Participants with multiple presentations	13
Median number of re-presentations (range)	1 (1–5)
Median age in years (IQR) [range]	28 (19–42) [13–93]
Median time to presentation post-ingestion in hours† (IQR) [range]	3.4 (1.6–6.1) [0.3–22.0]
Median dose of aspirin ingested in mg (IQR) [range]	7750 (6000–14,400) [3300–86,400]
Median dose of aspirin ingested in mg/kg‡ (IQR) [range]	121 (80–222) [39–1440]
Number of presentations with co-ingested agents	88 (67%)
Co-ingestants^	
Acetaminophen	46
Ethanol	35
Non-steroidal anti-inflammatories	21
Antidepressants	21
Opioids	19
Benzodiazepines and Z-drugs	18
Stimulants	10
Antihistamines	8
Antihypertensives	8
Antipsychotics	8
Other drugs	22

†Time of ingestion was not known in 5 presentations

‡Weight was not documented in 5 presentations where an estimated weight (60-kg women, 70-kg men) was used

^Multiple co-ingestions possible in a single presentation

moderate toxicity (Table 3) with median ingested doses of 95 mg/kg, 160 mg/kg and 297 mg/kg respectively. There were no cases of severe toxicity due to aspirin alone.

Laboratory Analysis

Blood gas analysis (arterial or venous) was performed in 116 presentations. A respiratory alkalosis was present in 33/116 (28%) presentations, metabolic acidosis in 32 (26%) presentations and a raised anion gap occurred in 12 (11%) cases. The median peak salicylate concentration was 276 mg/L (IQR 175–400 mg/L, range 14–814 mg/L). There was a moderate association between the dose of aspirin ingested and peak salicylate concentration (Pearson $r = 0.58$; 95% CI: 0.45–0.68, Fig. 2). Five patients had salicylate concentrations > 700 mg/L (range: 745–814 mg/L), all four ingested doses of aspirin > 300 mg/kg (range: 333–1440 mg/kg).

Management

Single-dose activated charcoal was administered in 36 (27%) presentations following a median ingested dose of 154 mg/kg (IQR 104–278 mg/kg). In four of these cases, enteric-coated preparations were ingested at doses of 62 mg/kg, 140 mg/kg, 160 mg/kg and 225 mg/kg respectively. The median time of administration was 3.0 h (IQR: 2.0–4.5 h, range: 0.9–12.4 h) post-ingestion in the 31 presentations with a documented time of administration. Patients who received activated charcoal had a 28% lower peak salicylate

Table 3 Clinical severity and treatment of 44 aspirin-only ingestions

	Asymptomatic patients	Mild toxicity	Moderate toxicity
Number of patients	6	22	16
Median aspirin dose mg [IQR] (range)	7100 [6200–7425] (3600–12,000)	9750 [7200–14,400] (3600–21,900)	16,200 [11,425–25,200] (6000–86,400)
Median aspirin dose mg/kg [IQR] (range)	95 [86–123] (72–144)	160 [100–250] (67–337)	297 [198–415] (54–1440)
Median peak salicylate concentration in mg/L [IQR] (range)	258 (47–343)	306 [251–451] (167–593)	511 [399–592] (191–814)
Charcoal administration	1 (17%)	6 (27%)	4 (25%)
Urinary alkalinisation	0	7 (30%)	10 (63%)
Median length of stay in hours [IQR] (range)	12 [7-18] (7–20)	15 [9–21] (2–38)	24 [20–40] (6–64)

Mild toxicity included the presence of nausea, vomiting, tinnitus or hyperventilation

Moderate toxicity included the presence of respiratory alkalosis, metabolic acidosis or confusion. *IQR*, interquartile range

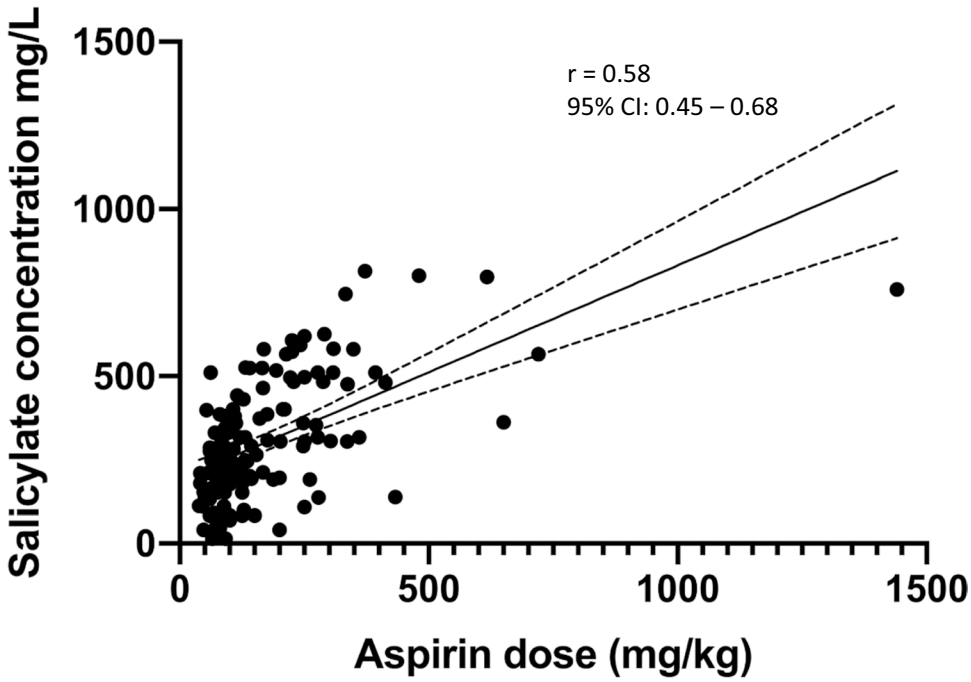

Fig. 2 Association between dose of aspirin ingested and peak salicylate concentration. Dotted line indicates 95% confidence intervals

concentration (mg/L) per gram of aspirin ingested (dose-normalised salicylate concentration) compared to those that did not receive charcoal (24.8 mg/L versus 34.2 mg/L (absolute difference 9.4, 95% CI 1.0–13.1) (Fig. 3)). Multiple doses of activated charcoal were administered in three cases.

Bicarbonate (8.4% sodium bicarbonate) was administered in 34 (26%) presentations following a median ingested dose of 256 mg/kg (IQR 216–337 mg/kg). Documentation regarding the dosing of bicarbonate was available in 30 of these cases. An intravenous bolus was administered in 27/30 cases, with the median bolus of bicarbonate being 100 mmol (range 50–170 mmol). Three patients received only a single bolus of bicarbonate. In those that went on to receive an intravenous infusion, the median dose per hour was 25 mmol/hour (range 13–100 mmol/hour) for a median duration of 11.9 h (range 3.9 to 45.0 h). The median total dose of bicarbonate administered was 262 mmol (50–900 mmol). In cases in which a urinary pH was consistently measured, a urinary pH ≥ 7.5 was achieved in 22/25 (88%) presentations. Patients who received bicarbonate had a shorter apparent salicylate half-life compared to those that did not receive bicarbonate (9.3 h versus 13.4 h (absolute difference: 4.2 h, 95%CI: 1.0–6.5 h) (Fig. 4)). Complications of urinary alkalinisation included hypokalaemia in 10/34 (29%, median potassium 2.8 mmol/L, range 1.6 to 2.9 mmol/L), hypernatremia in one (maximum sodium 152 mmol/L, with 476 mmol total bicarbonate administered over 14 h) and a severe alkalaemia in one (maximum pH 7.62, with 900 mmol total bicarbonate administered over 45 h). There were no cases of dialysis performed to enhance the elimination of aspirin.

Disposition

The majority of patients (100/132 (76%)) was managed solely within the emergency department including their short stay unit. There were 19 (14%) ICU admissions, half of these were for the management of primary aspirin toxicity and the remaining 13 patients being managed on the medical ward. The median length of stay was 19 h (IQR: 12–25 h). There was one death in a 57-year-old man who had ingested 6000 mg of aspirin and had a peak salicylate concentration of 152 mg/L. His death was due to cardiogenic shock secondary to a 7200 mg verapamil co-ingestion.

Discussion

Over the 20-year period in our toxicology units, the majority of aspirin overdoses had only mild features of salicylism—nausea, vomiting, tinnitus and hyperventilation. Activated charcoal administration appeared to be effective in decreasing the peak salicylate concentration, while bicarbonate therapy appeared to enhance clearance, based on decreasing the apparent half-life.

Aspirin overdose has declined in Australia in recent years [6]. While it remains an important cause of morbidity and

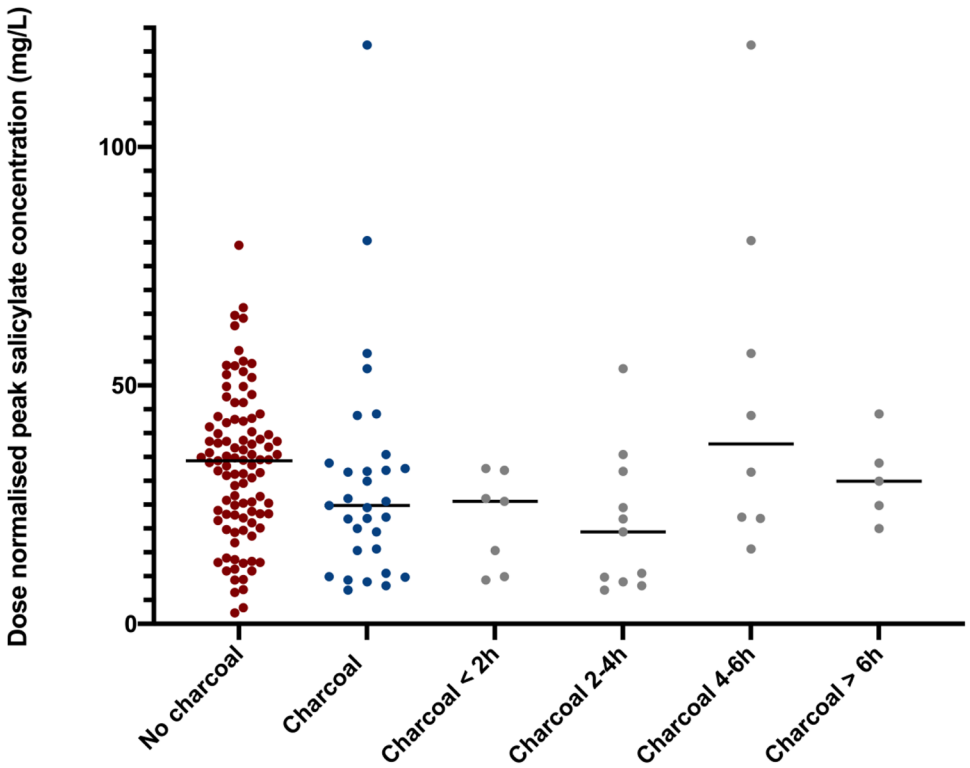

Fig. 3 Dose normalised peak salicylate concentration in mg/L in patients who received and did not receive activated charcoal

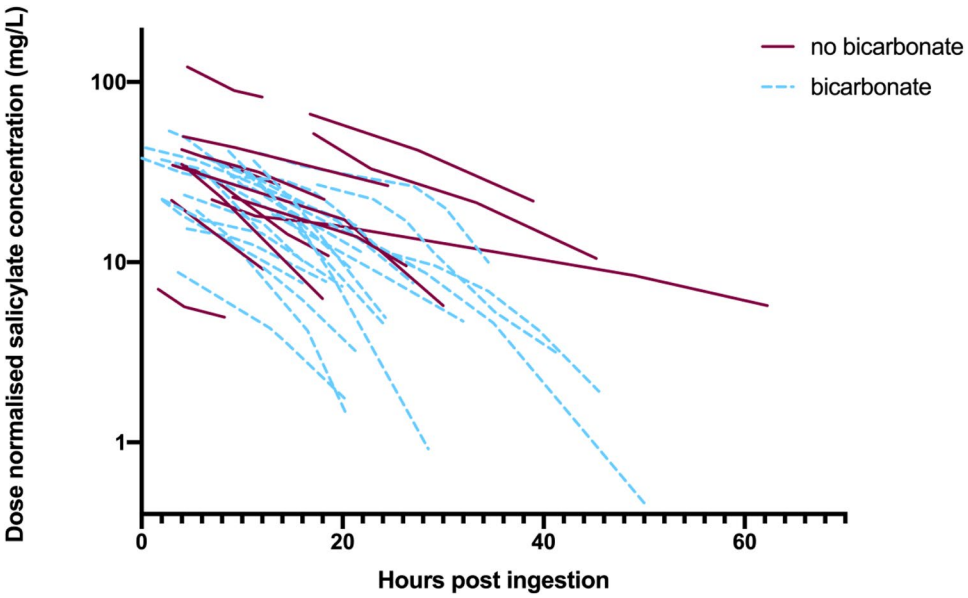

Fig. 4 Dose normalised salicylate concentrations (mg/L) over time in patients who received and did not receive bicarbonate therapy

mortality, severe poisoning is uncommon [15, 16]. Possible explanations include the shift in its main indication to an anti-platelet agent rather than an anti-inflammatory and the rise of well-tolerated analgesics like acetaminophen and ibuprofen. The relatively low acuity of toxicity in our Australian series is similar to the experience in other developed nations. In the USA in 2019, there were 17,158 calls to the poison centres regarding exposures involving aspirin, of which there were 261 cases with major effects and 19 fatalities [15]. These figures were lower than the same annual figures from two decades earlier in 1999 when there were 21,738 aspirin-related exposures with 329 having major effects and 55 deaths [16].

Our findings support traditional principles [7] of early charcoal decontamination and urinary alkalinisation to mitigate aspirin toxicity. The use of activated charcoal and bicarbonate may have contributed to the low rates of severe poisoning in our series. Both were used more frequently in patients with larger ingested doses and may have prevented severe toxicity particularly in those patients who ingested > 500 mg/kg, in which life-threatening toxicity can occur [7]. Activated charcoal decreased the peak concentration of salicylate, with the majority (75%) of patients receiving charcoal within 4.5 hours following overdose. While some guidelines [17] recommend charcoal within 6 hours, the benefit in our series appeared to be when charcoal was given within 4 hours post-ingestion. This effectiveness is consistent with two small volunteer studies that demonstrated activated charcoal was effective in decreasing the peak salicylate concentration following administration of 1000 mg and 2925 mg of aspirin respectively [10, 11]. Further pharmacokinetic analysis is required to determine whether charcoal only decreases absorption or whether it also increases clearance. In the latter case, it will be important to investigate the interaction between charcoal and bicarbonate on changing clearance.

Patients receiving bicarbonate therapy had a shorter estimated salicylate half-life. This was demonstrated previously in a small case series [18], in which there was a significant decrease in the mean plasma half-life (over 4–16 hours) from 29.4 hours in the control group to 9.0 hours in the group receiving 225 mmol bicarbonate over 3–4 hours.

This study has several limitations that should be acknowledged, the most important being there were few cases of severe toxicity in this two decade series, thus preventing adequate assessment of the impact of treatment on severe poisoning. Furthermore, the study was limited by its retrospective design and potential inaccuracies in the toxicological risk assessment. Similarly, the retrospective design limited the accuracy of pharmacokinetic analysis with the peak concentration estimated to be the highest available measured concentration. While true peak concentration may have been underestimated in some cases, this would have been similar for those with and without charcoal administration. Furthermore, the pharmacokinetic analysis assumed a simple one-compartment dispositional model and did not consider population variability or the interaction between charcoal use and bicarbonate therapy. A population pharmacokinetic analysis, including uncertainty in dose [19], would provide a better estimate of the effects of charcoal and bicarbonate on drug exposure.

In summary, acute aspirin overdose was only mild to moderate in severity in our series and resulted in no clinical effects or mild salicylism in two-thirds of patients. Activated charcoal and bicarbonate appeared to limit aspirin absorption and improve salicylate clearance.

Author Contribution K.I. and G.I. conceived the study. K.I., C.H. and K.H. completed the data collection. K.I. and G.I. analyzed the data. K.I. drafted the manuscript, and all authors contributed substantially to its revision. K.I. takes responsibility for the paper as a whole.

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Declarations

Conflict of Interest The authors declare no competing interests.

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