

Correspondence

Clinical toxicology: 'bones' of contention

We refer to the two recent articles on diagnosis and management of poisoning published in the Journal.^{1,2} It is an enormous task to review all the literature regarding the diagnosis and management of deliberate self poisoning, made all the more difficult by the considerable biases and conflicts within that literature. The European association of poison control centres and clinical toxicologists and American association of clinical toxicology have attempted this in the critical areas of decontamination³⁻⁸ and the American heart association has published a systematic review on the acute cardiac resuscitation of the poisoned patient.⁹ These remain the current consensus views of these bodies (and their members); unfortunately some of the recommendations in the two articles in the Journal are not supported by these reviews. The authors of this letter, who provide primary and tertiary toxicology consultative services through a number of Australian poison information centres and toxicology treatment centres, also have problems with several aspects of these two articles. Whilst some of these disagreements could be perceived as being 'academic', we believe that some of the recommendations presented in the articles in the Journal have the potential to cause harm. In the interests of patient care we have provided brief notes on some of the areas of these articles that concern us.

Gastrointestinal decontamination

Gastrointestinal decontamination is no longer performed routinely, and should only be performed after an individual risk assessment of the poisoned patient.³⁻⁸ The indications for lavage, activated charcoal and whole bowel irrigation in the two articles are contrary to the consensus statements produced by the American and European toxicology societies.³⁻⁸ There is no evidence to support the indications for lavage detailed in table 4, and these recommendations fall outside current clinical toxicology practice. There is no evidence to suggest that sorbitol added to activated charcoal increases efficacy⁵ nor is there any role for desferrioxamine in lavaging a patient with iron overdose.

Forced alkaline diuresis for aspirin overdose

Forced alkaline diuresis is contraindicated in the management of aspirin overdose.¹⁰ This recommendation could potentially worsen the condition of a significantly poisoned patient. Prescott *et al*, demonstrated that it was the alkalinisation of the urine that increased

the renal excretion of aspirin and that forcing a diuresis was unnecessary and potentially dangerous as it may precipitate cerebral and/or pulmonary oedema.¹⁰

Tricyclic antidepressant (TCA) poisoning

The major cardiotoxic effect of TCA poisoning is Na⁺ channel blockade. The ECG changes seen with a TCA overdose predict the risk of an adverse event. A QRS width of > 0.16 s indicates a high risk of developing ventricular dysrhythmias.¹¹ As this QRS widening is a manifestation of the Na⁺ channel blockade it is illogical to use another Na⁺ channel blocking drug (e.g. phenytoin), which may worsen the sodium channel blockade to control seizures. Bolus injection of sodium bicarbonate is the treatment of choice for both dysrhythmias and seizures,⁹ and is superior to hyperventilation. Physostigmine is no longer used in acute TCA overdose, as there is no evidence that it is effective and its use has produced fatal dysrhythmias¹² and seizures.²⁰

Lithium toxicity

Significant acute lithium overdose presents with gastrointestinal symptoms. If renal function is normal even large overdoses rarely require haemodialysis. Adequate crystalloid fluid resuscitation to maintain a good urine output will manage most acute lithium overdoses without further intervention. It is the clinical condition of the patient, not the lithium level that will dictate the need for haemodialysis.

Sympathomimetic drugs

The delirious and agitated amphetamine intoxicated patient is almost always successfully managed with appropriate doses of benzodiazepines. Beta-blockers are contraindicated because of resultant unopposed alpha adrenoceptor mediated vasoconstriction.⁹ Severe hypertension refractory to benzodiazepines may be treated with an alpha-blocker such as phentolamine or a direct smooth muscle relaxant agent but these are seldom required in the well-sedated patient.⁹

Calcium channel blocker (CCB) overdose

The CCBs that are potentially lethal are those available in sustained release preparations with predominantly cardiac effects (e.g. verapamil and diltiazem).¹³ A large (> 10 tablets) overdose seen early would be an indication for whole bowel irrigation and preparation for early intubation and ICU admission.¹⁴ The doses of calcium chloride recommended in the article are too low.⁹

Toxic alcohols

As intravenous ethanol is sometimes not available, it is important that oral (via nasogastric tube) ethanol be considered for blocking alcohol dehydrogenase. Ethanol prevents further production of toxic metabolites and should be administered early whilst haemodialysis is being prepared. Haemodialysis is indicated whenever there is evidence of an osmolar and anion gap metabolic acidosis. As most toxic alcohol assays are "sent out" and the results unavailable in a timely manner, a decision to treat must be made on clinical grounds. Fomepizole also blocks alcohol dehydrogenase but is not available in Australia.

Toxicological problems are common in clinical practice. Between 100 - 400 patients per 100 000 population present to emergency departments per year with deliberate self poisoning.¹⁷ Up to 30% will require intensive care. The care of these patients is usually undertaken by emergency physicians, general physicians and intensivists. For some patients, specific toxicological expertise is required for safe and effective care while for many others such expertise can make management much more efficient.^{18,19} Several Australian cities have hospital based toxicology treatment services and there is a 24 hour a day, 7 day a week consultant toxicologist available through the poisons information centres (131126) to assist in the management of the poisoned patient.

In summary, although these articles have attempted to provide an overview of the field of clinical toxicology, we believe there are a considerable number of recommendations presented that are not in keeping with current toxicological advice or practice and have the potential to negatively impact on patient care.

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In reply

In a two part presentation of clinical toxicology it is likely that there can be additions to a reference list that will be beneficial, and those added by Little *et al*,¹⁻⁶ are useful in this regard. Moreover, I would acknowledge that the toxicology treatment services mentioned by Little *et al*, are genuinely helpful in the management of the poisoned patient. Unfortunately, the remainder of their letter has many troubling aspects. Apart from numerous errors of fact, they have misread my articles and have misquoted their own references.

For clarity I will answer their points chronologically, stating where they are wrong and quote exactly what has, and has not, been said.

Gastrointestinal decontamination

Little *et al*, state that "The indications for lavage, activated charcoal and whole body irrigation in the two articles are contrary to the consensus statements produced by the American and European toxicological societies." This is untrue.

I will quote the statements of these bodies verbatim.

- 1) *gastric lavage*. The American and European toxicological societies state:¹ "gastric lavage should not be considered unless a patient has ingested a life-threatening amount of poison", a statement that is concordant with my own statement of "gastric lavage is becoming more and more selective, as controlled trials have not shown benefit from lavage in all patients".⁷ The procedure I describe is performed only when "the patient's airway is protected (i.e. has effective glottic reflexes or has an endotracheal tube in place)". The indications used in table 4 are included for life threatening poisonings and the contraindications are carefully detailed.⁷ The main difference is that they recommend the procedure if

the poison has been ingested within 60 minutes of ingestion.¹

- 2) *activated charcoal*. The American and European toxicological societies state:² "The administration of activated charcoal may be considered if a patient has ingested a potentially toxic amount of a poison (which is known to be adsorbed to charcoal)", a recommendation also proposed in my articles.^{7,8} The main difference is that they recommend the administration of activated charcoal if the poison has been ingested within 60 minutes of ingestion.² A later statement by the American and European toxicological societies concerning multi-dose activated charcoal states "multiple-dose activated charcoal should be considered only if a patient has ingested a life-threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline".⁵ These agents are included in table 5 of my first article.⁷ Other agents are also included in their reference with acknowledgement that there is insufficient data to "support or exclude" the use of this therapy.⁵

The statement by Little *et al*, that "There is no evidence to suggest sorbitol added to activated charcoal increases efficacy" appears to ignore my statement of "co-administration of sorbitol (100 g sorbitol per 50 g charcoal) or mannitol as a cathartic is common practice, although it reduces the capacity of drug absorption by charcoal".⁷

As controlled trials of desferrioxamine in severe iron toxicity in humans have not been performed, the statement by Little *et al*, that there is "no role for desferrioxamine" is misleading. They obscure the difference between "no clinical studies to demonstrate beneficial effect have been performed" for "clinical studies to demonstrate no beneficial effect have been performed". Severe iron toxicity is lethal, early gastric decontamination has been useful⁹ and as such oral desferrioxamine currently has merit.

- 3) *whole bowel irrigation (WBI)*. The American and European toxicological societies state:⁴ "(WBI) may be considered for potentially toxic substances of sustained-release or enteric coated drugs", an almost exact replica of my statement of "catharsis (or whole bowel irrigation) should only be considered when potentially toxic sustained release or enteric-coated drugs have been ingested".⁷

Forced alkaline diuresis for aspirin overdose

Concerning the management of salicylate overdose Little *et al*, state that "forcing a diuresis was unnecessary and potentially dangerous as it may precipitate cerebral and/or pulmonary oedema". There is little

difference between this and my statement of “excretion of salicylate is at best only moderately promoted by keeping the urine pH greater than 7.5 (an effect which is not enhanced by the use of diuretics), and pulmonary oedema, cerebral oedema, hypokalaemia and hyponatraemia may develop following the large volumes of fluid and sodium bicarbonate required”.⁷

Tricyclic antidepressant (TCA) poisoning

Little *et al*, state that the cardiotoxic effects of TCA poisoning is due to “Na⁺ channel blockade”, that “bolus injection of sodium bicarbonate is the treatment of choice for both dysrhythmias and seizures”, that it is “illogical to use another Na⁺ channel blocking drug (e.g. phenytoin)”, that “sodium bicarbonate is superior to hyperventilation” and that “physostigmine is no longer used in acute TCA overdose”.

To argue that it is illogical to use “another Na⁺ channel blocking agent” is as valid as to say that “It is illogical to use phenytoin (a Na⁺ blocking agent) to control seizures, as seizures can be caused by Na⁺ blocking agents (e.g. quinidine)”. Phenytoin poisoning does not cause seizures or cardiovascular collapse.^{10,11} TCA poisonings do. They are not the same agents.

Little *et al*, fail to understand that the sodium channel is a complex structure that has differing characteristics at differing sites which can be blocked in the active or inactive states with a recovery that has fast, medium and slow time constants, depending on the agent used.¹²⁻¹⁴ The various standard cardiac drugs of lignocaine, propranolol, amiodarone and verapamil are often used in combination and all have Na⁺ blocking actions on the myocyte Na⁺ channel.^{12,15,16}

The statement that “bolus injection of sodium bicarbonate is the treatment of choice for both dysrhythmias and seizures” and “sodium bicarbonate is superior to hyperventilation” is not supported by the reference they use. Their reference states “Sodium bicarbonate is the drug of choice for the treatment of ventricular dysrhythmias and/or hypotension due to TCA poisoning” and “rapid systemic alkalosis may be achieved with hyperventilation”,⁶ no mention is made of bicarbonate for seizures or clinical trials with evidence of superiority of hyperventilation compared with sodium bicarbonate for TCA poisoning.

The facts are:

- 1) bicarbonate does not readily cross the blood brain barrier (BBB) and therefore cannot have an immediate effect on an epileptogenic focus. Carbon dioxide rapidly crosses the BBB and has an immediate effect on neural tissue,
- 2) bicarbonate will only have an effect on the extracellular pH if the patient maintains adequate ventilation, as 100 mmol of NaHCO₃ will produce

2.53 L of carbon dioxide when it buffers 100 mmol of H⁺ at STP.¹⁷ In the presence of a reduced capacity to excrete carbon dioxide, sodium bicarbonate increases the arterial PCO₂ and worsens respiratory (and therefore intracellular) acidosis, and,

- 3) I stated: “hyperventilation and sodium bicarbonate (to keep the pH > 7.45) are generally accepted as the first line treatment for ventricular tachycardia, torsade de pointes or ventricular fibrillation”.⁷

The idea that sodium bicarbonate should be administered before securing the airway and hyperventilating the TCA poisoned patient who presents with seizures or cardiac arrest (which often follows seizures) does concern me as it has a great potential for causing harm. Their statement concerning physostigmine is in effect no different to mine.

Lithium toxicity

Neurological features (not gastrointestinal features) dominate the clinical presentation of lithium poisoning¹⁸ and they can be life threatening. The statement by Little *et al*, that “Adequate crystalloid fluid resuscitation to maintain a good urine output will manage most acute lithium overdoses without further intervention” ignores the fact that intravenous fluids have not been shown to be of any value in increasing the excretion of the lithium ion and have only been reported to cause life threatening complications of hypernatraemia and pulmonary oedema.¹⁹

To state that it is the “clinical condition of the patient, not the lithium level that will dictate the need for haemodialysis” is also troubling. To treat lithium toxicity by ignoring lithium levels and without using haemodialysis (or continuous haemodiafiltration which is commonly used in the ICU) when high levels of lithium are recorded, early renal insufficiency exists and before neuronal toxicity occurs is therapeutic nihilism and potentially dangerous.

Sympathomimetic drugs

Little *et al*, state “that beta-blockers are contraindicated because of resultant unopposed alpha adrenoceptor mediated vasoconstriction”, and use a reference that discusses acute coronary syndromes (ACS) in patients with cocaine toxicity. Their reference highlighted the adverse effect of non-selective beta-blockers (e.g. propranolol) in these patients and suggested nitrates and benzodiazepines with the addition of pentolamine (in resistant cases) for cocaine induced ACS.⁶

However, to suggest that beta-blockade is contraindicated in sympathomimetic drug toxicity is not correct. This uses the logic that beta-blockers should not be used in the operative management of phaeochromo-

cytomas where the combined use of alpha- and beta-blockade is standard management.²⁰ While the use of non-selective beta-blockers only in the management of cocaine toxicity (or phaeochromocytomas)²¹ is potentially hazardous, this effect does not extend to the combined use of alpha- and beta-blockers in clinical sympathomimetic toxicities, particularly when malignant tachycardias develop with the unopposed stimulation of beta-adrenergic receptors during alpha-receptor blockade.

Calcium channel blocker (CCB) overdose

Little *et al*, state that the doses of calcium chloride recommended in the article are too low, yet once again use a reference that does not support this statement. The reference they use states that “calcium salts may be beneficial in cases of mild to moderate CCB poisoning”, which is consistent with my recommendation, and that “The safety and efficacy of high-dose calcium therapy have not been clearly established”.⁶

Toxic alcohols

Little *et al*, state nothing new under this heading, although I would inform them that fomepizole is available in Australia under the special access scheme category A. I would also add that intravenous ethyl alcohol should always be readily available, as the inconsistent absorption of enteral ethanol and the ability for vomiting and inhalation in a patient with alcohol toxicity make the recommendation of nasogastric ethyl alcohol potentially hazardous.

There is no doubt that the majority of poisoned patients may be managed by careful observation and without specific intervention, and that the risk/benefit ratio of the various procedures and antidotes improves only when dealing with the critically ill (or potentially critically ill) poisoned patient. Little *et al* may have misinterpreted the various therapeutic options mentioned in my text as that which would be indicated in all cases. In this regard I would like them to return to the conclusion in my abstract which states: “In the critically ill overdosed patient, while activated charcoal, continuous renal replacement therapy and specific antidotes may be of benefit in selected cases, maintenance of the patient’s airway, ventilation and circulation still remain the most important aspects of management”.⁷

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