REVIEW ARTICLE

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The Management of Tricyclic Antidepressant Poisoning

The Role of Gut Decontamination, Extracorporeal Procedures and Fab Antibody Fragments

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Contents

Abstract

Although there have been descriptive, uncontrolled clinical reports of removal of tablet debris by gastric lavage, there have been no clinical studies that have demonstrated that this has any impact on outcome in patients with tricyclic antidepressant (TCA) poisoning. There is also the possibility that lavage may increase drug absorption by pushing tablets into the small intestine. Furthermore, gastric lavage in patients with TCA

poisoning may induce hypoxia and a tachycardia potentially increasing the risk of severe complications such as arrhythmias and convulsions. In view of the paucity of evidence that gastric lavage removes a significant amount of drug and the risk of complications associated with the procedure, the routine use of gastric lavage in the management of patients with TCA poisoning is not appropriate.

Volunteer studies have shown generally that activated charcoal is more likely to reduce drug absorption if it is administered within 1 hour of drug ingestion. In the one volunteer study that looked at later administration of activated charcoal, there was a 37% decrease in plasma concentration associated with administration of activated charcoal at 2 hours post-ingestion. There have been no clinical studies that enable an estimate of the effect of activated charcoal administration on outcome in the management of patients with TCA poisoning.

Volunteer studies have shown that multiple-dose activated charcoal increases the elimination of therapeutic doses of amitriptyline and nortriptyline, but not of doxepin or imipramine; however, these studies cannot be directly extrapolated to the management of patients with TCA poisoning. There have been no well designed controlled studies that have assessed the impact of multiple-dose activated charcoal in the management of patients with TCA poisoning. Because of the large volume of distribution of TCAs, it would not be expected that their elimination would be significantly increased by multiple-dose activated charcoal.

Haemoperfusion, haemodialysis and the combination of these procedures do not result in significant removal of TCAs and are not recommended in the management of patients with TCA poisoning.

1. Ipecac Syrup

There is no evidence from clinical studies that the use of syrup of ipecac improves outcome in the management of poisoned patients and it is no longer recommended for any poisoning.[1] Furthermore, significant tricyclic antidepressant (TCA) ingestion is associated with early CNS depression[2] and ipecac-induced emesis is contraindicated in patients with a decreased level of consciousness because of the risk of pulmonary aspiration.[1] In a prospective study of 200 poisoned patients randomised to ipecac and activated charcoal, or activated charcoal alone, four patients who had taken a TCA aspirated after ipecac administration.[3] In summary, ipecac-induced emesis is not recommended in the management of patients with TCA overdose.

2. Gastric Lavage

2.1 Studies

2.1.1 Volunteer Studies

Volunteer studies have shown that the amount of tablet material removed by gastric lavage is unpredictable and decreases with time, varying from 90% recovery of marker substances at 5 minutes post-ingestion[4] to only 30% at 19 minutes.[5]

2.1.2 Clinical Studies

In a study of poisoned patients who underwent gastroscopy after gastric lavage, tablet debris was seen in the stomach in 12 (70.6%) of 17 patients.[6]

There have been no well designed, clinical studies to address the question as to whether gastric lavage has any impact on outcome in patients presenting with TCA poisoning.[7] However, there have been four case series published that describe the use of gastric lavage in TCA poisoning. In the first of these, Comstock et al.[8] describe retrieval of amitriptyline tablets in the lavage fluid of 15 patients with amitriptyline poisoning who underwent gastric lavage between 1 and 4 hours after drug ingestion. They estimated that lavage yielded >10 therapeutic doses in five patients and 2–9 therapeutic doses in a further 3 of the 15 patients.[8] In the second series, Watson et al.[9] describe 13 patients with TCA poisoning. The dose of TCA removed by gastric lavage ranged from 2.4 to 342mg (mean 110 ± 133mg). Of seven patients, where the dose taken was known, the estimated dose recovered was only 8.7% (0.4–22%) of the ingested dose.[9] Bosse et al.[10] conducted a prospective randomised study in 51 patients presenting with TCA overdose. Patients were randomised on an every third day schedule to either: (i) activated charcoal 50g alone; (ii) gastric lavage followed by activated charcoal 50g; or (iii) 25g activated charcoal followed by gastric lavage followed by a further 25g dose of activated charcoal. There were no statistically significant differences in outcome between the three groups, the endpoints studied included length of stay, duration of intensive-care unit admission, duration of sinus tachycardia and number of patients with complications (e.g. seizures, QRS prolongation, hypotension).[10] Gard et al.[11] describe two patients who presented with amitriptyline poisoning and underwent gastric lavage – a total of 5.4% of the ingested dose was recovered by lavage at 2.5 hours after ingestion

in the first patient and 9.6% of the ingested dose recovered by lavage at 3 hours in the second patient.[11]

2.2 Contraindications

Gastric lavage is contraindicated in patients with a decreased level of consciousness and an unprotected airway (without endotracheal intubation) and those who have co-ingested hydrocarbons or corrosives.[7]

2.3 Complications

There are a number of potential complications associated with gastric lavage. In a series of 55 patients with self-poisoning who underwent gastric lavage, 11 presented with TCA poisoning; there was a significant fall in arterial oxygen tension (p_aO_2) of 15.7 ± 4.3mm Hg ($p < 0.001$) in these 11 patients after gastric lavage.[12] In another series of 42 poisoned patients who underwent gastric lavage, mean p_aO_2 fell from 95 ± 13 to 80 ± 19mm Hg ($p < 0.001$) and pulse rate rose from 92 ± 19 to 121 ± 23 beats/min ($p < 0.001$) during lavage; these changes were greater in conscious than unconscious patients.[13] These changes could be of clinical significance in patients with TCA poisoning in whom hypoxia and a positive chronotropic response induced by lavage could precipitate convulsions and arrhythmias. Other complications of gastric lavage such as aspiration, mechanical injury to the gut, gut perforation and laryngospasm have also been reported, although these are less common.[7,14-16] Furthermore, studies have suggested that gastric lavage may push gastric contents into the small intestine, potentially increasing the amount of drug available for and the rate of absorption.[17]

3. Activated Charcoal

3.1 Studies

3.1.1 Volunteer Studies

There have been a number of volunteer studies that have looked at the impact of activated charcoal on the absorption of many different drugs. Taken as a whole, these studies show that activated charcoal is most effective when administered within 30 minutes of drug ingestion.[18]

There have been five crossover volunteer studies that have specifically looked at the impact of activated charcoal on the absorption of TCAs. Dawling et al.[19] found that a single 10g dose of activated charcoal at 30, 120 and 240 minutes after a 75mg dose of nortriptyline reduced plasma concentrations by 77%, 37% and 19% ($p < 0.001$) and bioavailability by 74%, 37.5% and 13% ($p < 0.001$), respectively, in six volunteers.[19] In another study involving nortriptyline, peak plasma levels and bioavailability were reduced by 60% (range 30–81%) in six volunteers who were given 5g of activated charcoal 30 minutes after 75mg of nortriptyline.[20] In a further study, Alván[21] gave six volunteers 0.86–1 mg/kg nortriptyline followed by 5g charcoal 30 minutes later and showed a significant decrease in peak nortriptyline concentration associated with activated charcoal administration (31.8 vs 22.1 μg/L, $p < 0.05$).[21] In a study involving amitriptyline (at a dose of 75mg) in six volunteers, activated charcoal (50g) resulted in a 99% reduction in amitriptyline bioavailability (area under the concentration-time curve [AUC_{72h}]) when compared with controls; this study has limited applicability to clinical practice as the activated charcoal was given 5 minutes after the administration of amitriptyline.[22] Scheinin et al.[23] gave eight volunteers 50mg of doxepin showed a significant decrease ($p < 0.01$) in peak doxepin concentration (64.4 ± 5.8 vs 19.1 ± 2.0 nmol/L) and bioavailability (AUC_{48h} 661 ± 75 vs 340 ± 30 nmol/L/hour) associated with 15g of charcoal given 30 minutes after drug administration.[23]

It is not possible to directly extrapolate the results of these studies in volunteers to the management of patients presenting with TCA overdose for a number of reasons. The pharmacokinetics of TCAs at the toxic doses taken in overdose differ considerably to the kinetics in the therapeutic, sub-toxic doses used in the volunteer studies (e.g. differences in gastric emptying and drug dissolution).[24] The volunteer studies were all conducted in fasting volunteers with administration of activated charcoal at fixed time-points; patients who present with TCA overdose have often co-ingested food, alcohol (ethanol) or other drugs that may alter the TCA-activated charcoal interaction.[18]

3.1.2 Clinical Studies

There have been no well designed clinical studies that allow an assessment of whether administration of activated charcoal alters outcome in the management of patients presenting with TCA poisoning. There have been three uncontrolled, descriptive case series in which some data on the use of activated charcoal in TCA poisoning have been presented. Hedges et al.[25] describe nine patients with amitriptyline poisoning, who were all treated with gastric lavage within 60 minutes and activated charcoal at between 30 and 250 minutes after presentation to hospital. They found a correlation between earlier administration of activated charcoal after hospital admission and a decrease in amitriptyline peak concentration and half-life.[25] However, no data were given on the timing of activated charcoal administration relative to drug ingestion and the patients received a variable dose of charcoal (from 25 to 75g). Extrapolation of these results to clinical outcome is further limited by the fact that there is a variable correlation between plasma TCA concentrations and clinical features in TCA poison-

ing[26,27] and a wide range of plasma drug concentrations observed both within and between individuals with TCA poisoning.[28]

Hultén et al.[29] randomised 77 patients with confirmed TCA ingestion to gastric lavage alone (control, 43 patients) or gastric lavage and activated charcoal 20g (charcoal group, 34 patients). There was no statistically significant difference in the clinical picture, or TCA peak concentration/half-life between the two groups. However, there was a greater frequency of severe symptoms and signs in the control group at presentation, and no data were given on the timing of activated charcoal administration.[29]

Crome et al.[30] carried out a randomised clinical trial in 48 patients with suspected TCA poisoning, 20 patients were treated with activated charcoal 10g and 28 patients served as the control group. Seventeen patients had ingested a TCA alone, 13 TCA with other agents and 18 no TCA. There was no difference between the two groups in peak, or rate of fall of plasma TCA concentrations. There were insufficient numbers of patients who developed significant clinical effects to allow a comparison between the groups.[30] However, only 10g of activated charcoal was administered, the authors did not investigate the effect of time from ingestion to administration of activated charcoal and did not give data on the numbers of patients who underwent gastric lavage.

3.2 Contraindications

Activated charcoal administration is contraindicated in patients with a decreased level of consciousness and an unprotected airway, without endotracheal intubation.[18]

3.3 Complications

Activated charcoal is generally well tolerated and there have been only a few reports of serious adverse effects.[18] Vomiting has been reported after activated charcoal administration; however, it is difficult to determine whether vomiting was due to activated charcoal, the drugs taken in overdose, or other factors.[18,31,32] Aspiration has been reported after activated charcoal administration;[18,33-38] in a clinical study of TCA overdoses, 2 of 22 patients treated with activated charcoal (9.1%) aspirated.[10] There are two reports in which activated charcoal has been administered directly into the lung by nasogastric tube.[39,40] However, in three series[3,41,42] comprising a total of 559 patients with self-poisoning treated with activated charcoal there were no reports of aspiration. In contrast, in the study by Pond et al.[37] aspiration occurred in 10 (2.3%) of the 429 patients who received gastric emptying (gastric lavage or ipecac) and activated charcoal with sorbitol and 7 (1.7%) of the 407 patients who received activated charcoal with sorbitol alone (these rates are not significantly different).[37] Agents that have been added to charcoal in the past (e.g. povidone, sorbitol) probably increase the risk of pulmonary injury after activated charcoal administration,[18,38] but generally the clinical features seen after aspiration of aqueous activated charcoal do not differ significantly from those seen following the aspiration of gastric contents.[18] There have been no reports of gastrointestinal obstruction, or constipation following the administration of single-dose activated charcoal.

4. Whole Bowel Irrigation

Whole bowel irrigation is a newer method of gut decontamination that involves the administration of polyethylene glycol with the aim of reducing drug absorption by rapidly expelling the intraluminal contents of the gastrointestinal tract.[43] There have been no controlled clinical studies on the use of whole bowel irrigation in poisoning in general, and TCA poisoning in particular; the evidence for whole bowel irrigation is therefore based on volunteer studies and case reports.[43] Based on these limited data, whole bowel irrigation is an option for poisoning with sustained-release or enteric-coated drugs and/or those not adsorbed to activated charcoal.[43] TCAs do not fall into these categories and so we would not recommend the use of whole bowel irrigation as a gut decontamination method in patients with TCA poisoning.

5. Multiple-Dose Activated Charcoal

Multiple-dose activated charcoal involves the administration of repeated doses (more than two) of activated charcoal in an attempt to decrease the absorption and/or increase elimination of drugs taken in overdose.[44] TCAs have a large volume of distribution[45] and enterohepatic recirculation accounts for only 15% of their elimination[11] and so from a kinetic perspective multiple-dose activated charcoal is unlikely to have a significant effect in the management of TCA poisoning.

5.1 Studies

5.1.1 Volunteer Studies

There have been four crossover volunteer studies that have looked at the impact of multiple-dose activated charcoal on the kinetics of TCAs. Crome et al.[20] gave four 5g doses of activated charcoal 30, 120, 240 and 360 minutes after a 75mg oral dose of nortriptyline and compared this with a single dose of 5g of activated charcoal 30 minutes after 75mg nortriptyline in six volunteers. There was a significantly greater decrease in both peak nortriptyline concentration (58% [range 30–81%] vs 72% [62–78%], $p < 0.01$) and availability (AUC_{72h} 55% [32–67%] vs 70% [58–67%], $p < 0.01$) when the multiple and single dose charcoal administration were compared.[20] In another study, four

volunteers were given imipramine 12.5mg/70kg intravenously over 1 hour followed by either water or 180g activated charcoal over 24h (20g at 0, 2, 4, 6, 9, 12, 20, 24 hours), there was no significant difference ($p > 0.05$) in imipramine half-life (9.0 ± 0.8 vs 10.9 ± 1.6 hours) or clearance (992.2 ± 138.3 vs 930.3 ± 101.9 mL/min/70kg) in controls compared with the activated charcoal group.[46] In a further study, eight volunteers were given doxepin 50mg orally and followed by activated charcoal 15g 3 hours later and then 10g activated charcoal at 6, 9, 12, 24 hours. When multiple-dose was compared with controls, there was no significant difference in half-life (16.2 ± 2.3 vs 17.9 ± 4.3 hours) or clearance (1.23 ± 0.31 vs 0.93 ± 0.03 L/h/kg) of doxepin.[23] In the final study, oral amitriptyline 75mg was given to six volunteers, followed by 50g activated charcoal 6 hours later and then 12.5g at 12, 18, 24, 30, 36, 42, 48, 54 hours. Multiple-dose activated charcoal was associated with a significant shortening of the elimination half-life (27.4 ± 4.8 to 21.1 ± 3.3 hours, $p < 0.05$), decrease in urinary excretion (0.70 ± 0.18 to 0.41 ± 0.11 μmol, $p < 0.05$) and decrease in the AUC_{72h} (3.51 ± 0.50 to 2.43 ± 0.20 μmol/L/hour, $p < 0.05$) of amitriptyline.[22]

In summary, the four volunteer studies looking at the impact of multiple-dose activated charcoal on TCA kinetics have had conflicting findings, two showing that multi-dose charcoal decreased bioavailability and half-life (of amitriptyline and nortriptyline an active metabolite of amitriptyline),[20,22] with the other two showing no effect of multi-dose charcoal (of doxepin and imipramine).[23,46] However, as discussed above, a number of kinetic and practical factors make it impossible to directly extrapolate the results of these studies in volunteers to the management of patients presenting with TCA overdose.

5.1.2 Clinical Studies

There have been two small descriptive, uncontrolled clinical series describing patients with TCA overdose who have been treated with multiple-dose activated charcoal. The first of these reports described three patients with severe amitriptyline poisoning (all of the patients also underwent gastric lavage).[47] The first patient received two doses of activated charcoal (50g at 2 hours followed by 25g at 10 hours post ingestion), the second patient received three doses (50g at 2 hours, 25g at 6 hours and 25g at 23 hours post-ingestion) and the third patient received four doses (40g at 1 hour, 20g at 4 hours, 20g at 9 hours and 20g at 21 hours). The reported half-life of amitriptyline was in each patient was 4.9, 9.6 and 4.9 hours, respectively, and although this is lower than in historical controls,[48,49] the data in this report were uncontrolled and, therefore, cannot be used to support the authors conclusion that multiple-dose activated charcoal decreased amitriptyline half-life.[47]

In the second report, three of eight patients with dothiepin overdose were treated with multiple-dose activated charcoal (50g at 8 and 20 hours after ingestion in the first, 50g at 4, 8, 12 and 16 hours after ingestion in the second and 50g at 0, 4, 8 and 12 hours after admission in the third). Sufficient data were available to calculate dothiepin half-life (mean ± SD) in the three charcoal-treated patients (12.1 ± 1.3 hours) and in four of the non-charcoal treated patients (21.7 ± 7.1 hours), these were not statistically different ($p = 0.07$). However, these data should be interpreted with caution because the half-lives were calculated on only 3–4 samples on each patient over a mean time period 2.8 times (range 0.8–3.6) the calculated half-life.[50]

5.2 Complications

The complications of multiple-dose charcoal are similar to those for single-dose activated charcoal administration, but it is generally well tolerated other than transient constipation.[44] The other rare complication of multiple-dose activated charcoal administration is bowel obstruction,[44] two of the reported cases involved multiple-dose activated charcoal administration for amitriptyline poisoning.[51,52]

6. Extracorporeal Procedures

TCAs have a large volume of distribution (10–20 L/kg)[45] and are highly protein bound (75–95%).[53,54] For these kinetic reasons they would not be expected to be removed to a significant degree by extracorporeal techniques.

6.1 Peritoneal Dialysis

Peritoneal dialysis is, in general, an inefficient method of drug removal in the management of poisoning.[55,56] This is particularly the case in TCA poisoning, because the technique relies on blood flow rate to the peritoneum, which is likely to be reduced in hypotensive patients with severe TCA poisoning. This has been confirmed in two published cases of amitriptyline poisoning treated with peritoneal dialysis in which there was an insignificant amount of amitriptyline removed in the peritoneal fluid.[57,58]

6.2 Haemoperfusion, Haemodialysis and Combination Haemodialysis-Haemoperfusion

6.2.1 Resin Haemoperfusion

There have been five reports of the use of resin haemoperfusion in patients with TCA poisoning. Heath et al.[59] described four patients who were treated with 0.5–4 hours of resin haemoperfusion with a successful clinical outcome; data on amitriptyline clearance (135 and 190 mL/min) and extraction ratio (0.65 and

0.93) was reported in two of these cases.[59] These clearances show effective removal of drug from the blood compartment, but because TCAs have a large volume of distribution a more important measure is the total amount of drug removed by haemoperfusion, these data were not available in this series. Pentel et al.[60] reported a patient with imipramine poisoning treated with resin haemoperfusion. Despite imipramine clearance of 130–180 mL/min by the haemoperfusion column, only 0.91% of the ingested dose was removed by the procedure – this would not be expected to result in significant clinical benefits.[60] Trafford et al.[61] describe two patients treated with resin haemoperfusion. In the first of these cases, a patient with clomipramine poisoning, no data were given on clearance or drug removal by the technique. In the second case, a patient with amitriptyline poisoning, clearance rates of 240 and 280 mL/min were reported for amitriptyline and nortriptyline, respectively.[61] However, when the data were re-examined by Crome et al.,[62] these clearance values represent removal of only 16.8mg of amitriptyline and 14.5mg of nortriptyline, which would not be expected to have a significant impact.[62] Ryan et al.[63] reported the use of resin haemoperfusion in a 3-year-old boy with imipramine poisoning and showed no improvement in clinical features and no change in serum imipramine/desipramine concentrations during haemoperfusion.[63] Heath et al.[64] reported a series of eight patients with severe TCA poisoning. Although they reported a high extraction ratio (0.91–0.98) and clinical improvement during haemoperfusion, the total amount of drug removed by HPF was, at most, 3.1% of the estimated ingested dose and so this clinical improvement was not due to drug removal by haemoperfusion.[64]

6.2.2 Charcoal Haemoperfusion

Diaz-Buxo et al.[65] reported clearance data in one of three patients with amitriptyline poisoning who improved clinically during treatment with charcoal haemoperfusion, the reported clearance was 100–112 mL/min but from the data given in the paper only 0.1% (4.4mg) of the ingested dose was removed by haemoperfusion.[65] Iversen et al.[66] reported a case of nortriptyline poisoning in which 3 hours of charcoal haemoperfusion resulted in no clinical improvement and only 1% (1mg) of the ingested drug was removed by the procedure.[66] Comstock et al.[67] reported the use of charcoal haemoperfusion in an adult with amitriptyline poisoning, the procedure resulted in the removal of just 0.75% (5.5mg) of the ingested dose.[67] Engstrom et al.[68] reported no effect of charcoal haemoperfusion on plasma doxepin concentrations or doxepin clearance in an adult with doxepin poisoning.[68] Similar findings were reported in two series of patients with self-poisoning treated with charcoal haemoperfusion. In these series, 4 of 48 cases in the first and 3 of 60 cases in the second were patients with severe TCA poisoning. There was no significant drug removal[69] or clinical improvement in any of these seven patients.[69,70] A more recent report[71] described clinical improvement in a child during treatment with charcoal haemoperfusion. However, the procedure was only associated with a 31% decrease in serum amitriptyline concentrations and no data were presented on total amount of drug removed by haemoperfusion.

6.2.3 Haemodialysis

Two studies have shown insignificant removal of TCAs (nortriptyline and doxepin, at therapeutic concentrations) in patients undergoing haemodialysis for renal replacement therapy.[72,73] Bailey et al.[74] reported the use of haemodialysis in a patient with imipramine and amitriptyline poisoning, although there was clinical improvement associated with the procedure there was no change in the rate of fall of plasma TCA concentrations and no imipramine was detected in the dialysate.[74] Harthorne et al.[75] reported minimal removal (0.56% of the ingested dose) of imipramine in a patient treated with haemodialysis for 5.5 hours for imipramine poisoning.

6.2.4 Combined Haemodialysis-Haemoperfusion

There have been three case reports describing the use of combination haemodialysis-haemoperfusion in TCA poisoning. De Broe et al.[76] described the use of combined haemodialysis/charcoal haemoperfusion in a patient with amitriptyline poisoning, there was no significant removal of amitriptyline by the procedure.[76] In the second case report, Durakovic et al.[77] described a patient with a mixed imipramine, doxepin and amitriptyline ingestion who was treated with combination haemodialysis/resin haemoperfusion; the patient improved clinically during the procedure and plasma TCA concentrations fell, but no data were available on clearance or drug removal by the extracorporeal device.[77] The third case report was a patient with doxepin poisoning who was treated with 5 hours combination resin haemoperfusion-haemodialyis and whilst there was a fall in the plasma doxepin levels and clinical improvement during the procedure, no data were available on clearance or drug removal by the extracorporeal device.[78]

6.2.5 Haemofiltration

There are no reports of the use of haemofiltration in patients with TCA poisoning. However, due to their high protein binding, large volume of distribution it would not be expected that haemofiltration would be of use in the management of TCA poisoning.[79]

7. Tricyclic Antidepressant Fab Antibody Fragments

TCA specific antibody fragments (TCA-Fab) have been developed and their effectiveness at reversing cardiovascular toxicity has been demonstrated in animal models of desipramine toxicity.[80,81] However, in one animal study, although TCA-Fab use was initially effective in reducing desipramine toxicity, there was a subsequent increase in cardiovascular toxicity at 2–3 hours after TCA-Fab administration.[82] There has been one human case report describing the use of TCA-Fab in a patient with amitriptyline poisoning. There was an improvement in QRS and QT intervals after administration of a total of 14g of intravenous TCA-Fab over a 4-hour period; however, the patient was also treated with 88 mmol sodium bicarbonate immediately prior to the administration of TCA-Fab.[83] TCA-Fab should only be considered a research tool; they are not widely available and there are insufficient data on their safety and efficacy.

8. Conclusions

Gastric lavage, ipecac-induced emesis and whole bowel irrigation are not recommended in the routine management of patients with TCA poisoning. There are no data from clinical studies that can be used to assess the impact of activated charcoal administration on outcome in patients with TCA poisoning. However, based on volunteer studies, we would recommend administration of activated charcoal within 1 and possibly 2 hours of ingestion in all patients presenting with significant TCA poisoning. Due to the large volume of distribution and high protein binding of TCA, multiple-dose activated charcoal and extracorporeal procedures such as haemodialysis and haemoperfusion do not result in significant removal of TCAs and are not recommended in the management of patients with TCA poisoning. TCA-Fab should only be considered a research tool; they are not widely available and there are insufficient data on their safety and efficacy.

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