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To cite this article: Xavier Wittebole & Philippe Hantson (2011) Use of the molecular adsorbent recirculating system (MARS™) for the management of acute poisoning with or without liver failure, *Clinical Toxicology*, 49:9, 782-793, DOI: [10.3109/15563650.2011.624102](https://doi.org/10.3109/15563650.2011.624102)

To link to this article: <http://dx.doi.org/10.3109/15563650.2011.624102>



Published online: 14 Nov 2011.



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REVIEW ARTICLE

Use of the molecular adsorbent recirculating system (MARS™) for the management of acute poisoning with or without liver failure

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Introduction. There is an increasing interest in recent developments in bioartificial and non-bioartificial devices, so called extracorporeal liver assist devices, which are now used widely not only to increase drug elimination, but also to enhance the removal of endogenous substances in acute liver failure. Most of the non-bioartificial techniques are based on the principle of albumin dialysis. The objective is to remove albumin-bound substances that could play a role in the pathophysiology of acute liver failure by dialysing blood against an albumin-containing solution across a high flux permeable membrane. The most widely used device is the Molecular Adsorbent Recirculating System (MARS™). **Methods.** The relevant English and French literature was identified through Medline using the terms, ‘molecular adsorbent recirculating system’, ‘MARS’, ‘acute liver failure’, ‘acute poisoning’, ‘intoxication’. This search identified 139 papers of which 48 reported on a toxic cause for the use of MARS™. Of these 48 papers, 39 specified the substance (eighteen different substances were identified); two papers reported on the same group of patients. **Bioartificial and non-bioartificial systems.** Bioartificial systems based on porcine hepatocytes incorporated in the extracorporeal circuit are no longer in use due to the possibility of porcine retroviral transmission to humans. Historically, experience with such devices was limited to a few cases of paracetamol poisoning. In contrast, an abundant literature exists for the non-bioartificial systems based on albumin dialysis. The MARS™ has been used more widely than other techniques, such as the one using fractionated plasma separation and adsorption (Prometheus™). All the extracorporeal liver assist devices are able to some extent to remove biological substances (ammonia, urea, creatinine, bilirubin, bile acids, amino acids, cytokines, vasoactive agents) but the real impact on the patient’s clinical course has still to be determined. Improvement in cardiovascular or neurological dysfunction has been shown both in acute liver failure and acute-on-chronic liver failure but no impact on mortality has been reported. **Acute poisoning with liver failure.** Randomized controlled trials are very limited in number and patients poisoned by paracetamol or *Amanita phalloides* are usually included for outcome analysis in larger groups of acute liver failure patients. Initial results look promising but should be confirmed. Beyond its effect in liver failure, MARS™ could also enhance the elimination of the drug or toxin responsible for the failure, as is described with paracetamol. **Acute poisoning without liver failure.** Extracorporeal liver assist devices have also been used to promote elimination of drugs that are highly protein bound. Data in various case reports confirm a high elimination of phenytoin, theophylline and diltiazem. However, definite conclusions on the toxicokinetic or clinical efficacy cannot be drawn. **Conclusions.** Despite the lack of large multicentre randomized trials on the use of MARS™ in patients with acute liver failure, the literature shows clinical and biological benefit from this technique. In drug or toxin-induced acute liver failure, such as paracetamol or mushroom poisoning, MARS™ has been used extensively, confirming in a non-randomized fashion, the positive effect observed in the larger population of acute liver failure patients. Furthermore, as MARS™ has been shown in experimental studies to remove protein-bound substances, it is potentially a promising treatment for patients with acute poisoning from drugs that have high protein-binding capacity and are metabolized by the liver, especially, if they develop liver failure concomitantly.

Keywords Extracorporeal liver assist devices; Acute poisoning; Liver failure; MARS; Dialysis

Introduction

There is a recent interest in techniques that allow the removal not only of exogenous but also endogenous substances, particularly in the setting of liver failure. These techniques are

aimed at supporting the failing liver by reducing the severity of some complications like encephalopathy or cardiovascular collapse. As acute liver failure can occur as a consequence of a toxic exposure, it is not surprising that some of these techniques, classified as extracorporeal liver assist devices, have been used.

After defining acute (toxic) liver failure, this review presents the principles of the techniques that are currently available and discusses their effects either on the removal of exogenous or endogenous substances, or on some physiological parameters. The clinical experience will be analysed

Received 6 September 2011; accepted 13 September 2011.

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and a distinction made between acute poisoning alone or acute poisoning complicated by liver failure.

Methods

The relevant English and French literature was identified through Medline using the terms, 'molecular adsorbent recirculating system', 'MARS', 'acute liver failure', 'acute poisoning', 'intoxication'. This search identified 139 papers of which 48 reported on a toxic cause for the use of MARS. Of these 48 papers, 39 specified the substance (18 different substances were identified); two papers reported on the same group of patients. These papers could be classified into two groups: the first described the use of MARS™ in acute poisoning alone; the second the use of MARS™ in acute poisoning complicated by liver failure.

Acute liver failure

Acute liver failure may be defined as the development of severe acute liver injury leading to impaired hepatic synthetic function and encephalopathy in a previously healthy patient. Bernuau et al.¹ suggested that the term fulminant hepatic failure should be applied to patients in whom encephalopathy develops within two weeks of the onset of jaundice and that sub-fulminant hepatic failure should be applied to those in whom this interval was from two to 12 weeks. This classification includes cases of pre-existing asymptomatic chronic liver disease. Fulminant hepatic failure still carries a high mortality and it is important to determine its etiology because the prognostic implications are different. Acute paracetamol poisoning remains a leading cause of fulminant hepatic failure and *Amanita phalloides* poisoning is a matter of concern. Currently, the cornerstone of treatment for these patients remains orthotopic liver transplantation. Patients who will benefit are usually identified by negative prognostic indicators known as King's College criteria.² However, several factors, including the lack of a suitable graft, invalidate this option for a large proportion of patients. Moreover,

as the liver often maintains regenerative capacity, it is rational to utilize a system that can replace its functions until it recovers or until a graft becomes available. The ideal system would eliminate toxins that accumulate during liver failure and are thought to be responsible for renal failure (hepatorenal syndrome), cardiovascular failure, brain failure and edema due to hepatic encephalopathy, immunodepression and bone marrow depression.³

Techniques and principles

Bioartificial systems

The use of living hepatocytes, maintained within a bioreactor and in contact with blood or plasma, was investigated. The hepatocytes were cultured from either human or porcine origin. Systems utilising pig cells were progressively withdrawn due to fear of possible transmission of a porcine endogenous retrovirus; all pig cells are known to possess endogenous retroviral genomes that may express C-type retrovirus in culture and infect some human cell lines. However, this theoretical risk has not been documented in patients treated with bioartificial liver support.⁴

Non-bioartificial systems

The recent developments of extracorporeal liver assist devices are now mainly based on the principle of albumin dialysis, combining filtration and adsorption. The system about which most has been published is known as MARS™ (Molecular Adsorbent Recirculating System, Gambro AG, Stockholm, Sweden) (Fig. 1). Albumin dialysis involves dialysing blood against an albumin-containing solution separated by a high flux permeable membrane. Protein-bound toxins that accumulate during liver failure are released from the protein by physicochemical interactions with the membrane and cleared from blood by diffusion. Purified albumin molecules pick up the toxins on the dialysate side by specific binding, thereby creating a continuous concentration gradient. The albumin dialysate is cleaned through charcoal and anion exchange

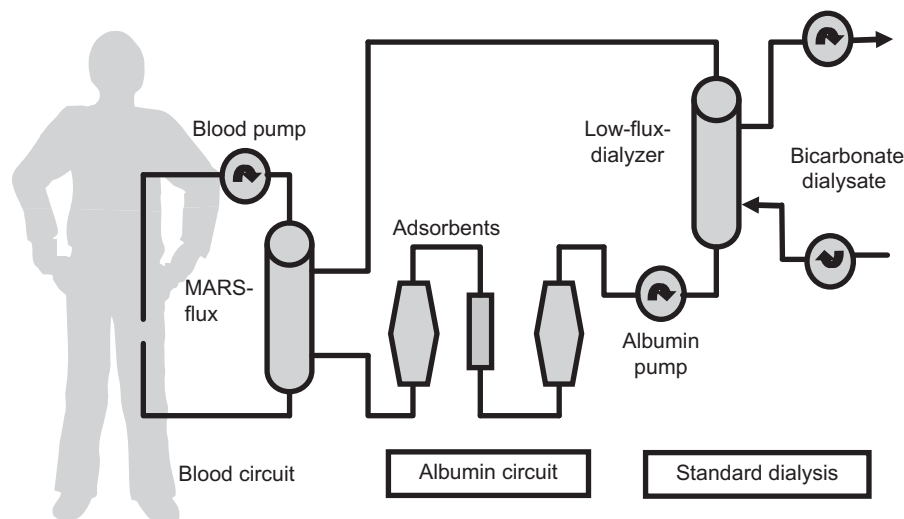


Fig. 1. Schematic representation of the molecular adsorbent recirculating system (MARS™).

columns. Water-soluble substances are removed by conventional hemodialysis or hemodiafiltration using diffusion and/or convection.

Some variants of the MARSTM are also available. Single pass albumin dialysis is basically the same, except that the albumin dialysate is not recycled but discarded and replaced. Another form of albumin dialysis is the PrometheusTM system (Fresenius Medical Care AG, Bad Homburg, Germany) based on a mechanism of fractionated plasma separation and adsorption (FPSA). It uses a filter which allows albumin and other plasma proteins to cross the membrane before they pass through an anion exchanger column and a neutral resin adsorber. The cleaned albumin-protein solution is then returned to the blood before a conventional high-flux hemodialysis filter (Fig. 2).

MARSTM is the system for which the most extensive literature exists. It was demonstrated initially to be effective in decreasing mortality in patients with acute-on-chronic liver failure with type I hepatorenal syndrome⁵ and acute-on-chronic liver failure patients with various precipitating events.⁶ Randomized trials as well as case series have shown that MARSTM can improve various hemodynamic (general⁵ and local including portal pressure⁷), neurological (cerebral blood flow⁸ and encephalopathy) and biochemical parameters.⁹ In a recent comparative study of its use in acute liver failure (including toxic and nontoxic etiologies),¹⁰ a trend towards improved survival with MARSTM was demonstrated in patients who required transplantation for acute liver failure of unknown etiology. Interpretation of the results was difficult in patients with a toxic etiology on account of differing baseline statuses. One prospective randomized multicentre study evaluating the effect of MARSTM in patients with fulminant liver failure was performed in France.¹¹ A trend towards improved survival at 6 months was observed in the MARSTM group as compared to patients treated with conventional treatment. This favourable outcome was even more evident for patients with paracetamol-induced acute

liver failure. Furthermore, the positive effects of MARSTM on hemodynamics,¹² cerebral edema and intracranial pressure control¹³ and other metabolic parameters, have been demonstrated in patients with acute liver failure.

The safety of these extracorporeal liver assist devices has been evaluated through their use in over 3000 patients worldwide. Treatment with either MARSTM or PrometheusTM is usually well tolerated. The only consistent adverse finding is a reduction in platelet count, without any adverse consequences. Theoretically, anticoagulation of the circuit is indicated, but clinical experience has shown that in patients with acute liver failure with decreased coagulation factors, heparin is not always required to prevent clotting of the extracorporeal circuit. Citrate anticoagulation is a possible alternative but requires closer monitoring as citrate metabolism is usually impaired in liver failure patients. One of the major limitations to the general use of extracorporeal liver assist devices (besides the lack of randomized controlled trials) is the additional cost that are estimated at US \$2400 per day.

Removal of biological substances

The removal of several biological substances has been investigated in liver failure of various etiologies. It is not really surprising that ammonia, a water-soluble substance, is well removed. However, the superiority of MARSTM over conventional hemodialysis is not established. Other biological substances that could be theoretically removed by MARSTM include urea, creatinine, bilirubin, bile acids, amino acids and nitric oxide.

Liver failure is consistently associated with an amino acid imbalance characterized by low or normal plasma concentrations of glutamate, branched-chain amino acids (valine, isoleucine and leucine) and tryptophan, whereas the concentrations of most other amino acids (and particularly of some phenolic aromatic amino acids) are elevated significantly.¹⁴

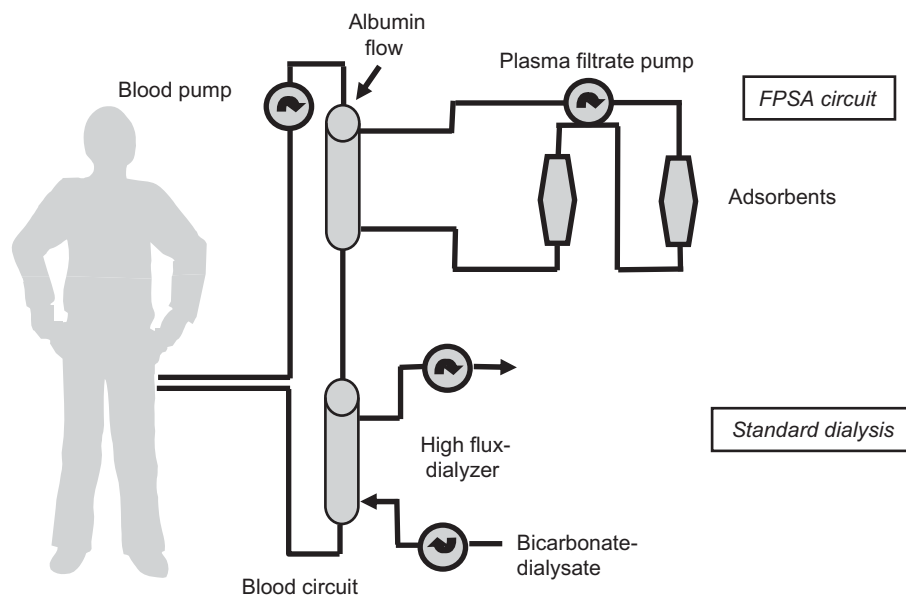


Fig. 2. Schematic representation of the PrometheusTM system or fractionated plasma separation and adsorption (FPSA).

The ratio of the branched-chain to phenolic aromatic amino acids has been suggested by Fischer to correlate with the degree of hepatic encephalopathy (the Fischer Index).¹⁵ The effect of MARSTM on arterial amino acid concentrations has been investigated in patients with acute-on-chronic liver failure^{16–21} and also in some patients presenting with fulminant hepatic failure following paracetamol poisoning.¹⁶ During a single MARSTM treatment (6 h duration), a significant decrease (20%) of the total arterial amino acid concentration was observed, with an increase in the ratio of branched-chain amino acids to the aromatic amino acids which would theoretically be beneficial.¹⁸ The concentration of the amino acids was determined in samples obtained from the jugular venous bulb in order to calculate the cerebral metabolic rate. A single MARSTM treatment had little direct influence upon cerebral ammonia uptake and brain amino acid metabolism.¹⁸

Plasma nitric oxide (NO) is in part responsible for the hemodynamic profile observed in patients with liver failure. It is bound to albumin as a nitrosothiol. Several clinical investigations report on removal of NO by MARSTM,^{22–23} which is one of the possible mechanisms leading to improvement of hemodynamic parameters in those patients undergoing this treatment (see below).

The effects of MARSTM on the removal of different cytokines are inconclusive. While some authors observed a decrease in pro-inflammatory cytokines such as TNF- α ,^{24–26} Interleukin-6 and Interleukin-1 β ,^{24,26} others did not.²⁷ In a study conducted in 49 patients with acute liver failure (of whom 26 cases were of toxic origin), Isoniemi et al.²⁵ were unable to demonstrate significant changes in TNF- α , Interleukin-6 and Interleukin-8 concentrations; only Interleukin-10, that possesses anti-inflammatory properties, decreased significantly. Furthermore, the exact influence of cytokine removal on liver regeneration or on the patient's prognosis is still unknown. There is also concern that MARSTM could remove some growth factors essential for liver regeneration.²⁵

Initial *in vitro* experiences with fractionated plasma separation and adsorption showed higher elimination of albumin-bound substances than with MARSTM.²⁸ This was later confirmed in patients with acute-on-chronic liver failure for whom fractionated plasma separation and adsorption cleared bilirubin, urea nitrogen and creatinine better than MARSTM.²⁹ However, it did not alter the concentrations of cytokines, coagulation factors and other plasma proteins.³⁰

Removal of drugs or toxins

Numerous drugs or toxins are good theoretical candidates for MARSTM or other extracorporeal liver assist devices. This applies particularly to substances preferentially bound either to albumin or alpha-1-acid glycoprotein. Diazepam was used as a model in an *in vitro* experiment comparing removal by conventional dialysis and albumin dialysis. While the plasma pool containing diazepam was recirculated, the dialysate was used in a single-pass fashion. All other parameters (flow rates, dialyzer membrane, plasma

and dialysate volumes) were kept constant, and the albumin concentration in the dialysate was changed after 120 min from 0 to 1.6 g/dL. There was no significant change in the plasma diazepam concentration with conventional dialysis. However, albumin dialysis reduced it significantly ($p < 0.05$)³¹ and could be an effective means of removing endogenous 'benzodiazepine-like' substances that are possibly involved in hepatic encephalopathy.

In a study primarily designed to evaluate the effect of MARSTM in a porcine model of acute liver failure, Sen et al.³² studied the elimination of midazolam and fentanyl used to anaesthetize the pigs. Acute liver failure was provoked by an end-to-side porta-caval shunt along with ligation of the hepatic artery. Anaesthesia was induced with pentobarbital and maintained until the liver was devascularized with continuous infusion of pentobarbital, fentanyl and midazolam. Blood samples were collected before and after the MARSTM filter. Samples of albumin dialysate were drawn from various parts of the circuit to determine the specific site of drug elimination. The MARSTM extracted about half of the midazolam. Higher concentrations were found in the dialysate as compared to the outflow of the MARSTM filter, the charcoal column being the main site of extraction from the albumin dialysate. Fentanyl extraction was even higher across the filter, the charcoal column again being the main site of extraction from the albumin dialysate. Since midazolam is strongly bound to albumin, these results were expected. However, the removal of fentanyl, which is bound mainly to alpha-1-acid glycoprotein, demonstrates that albumin dialysis also removes drugs from other plasma proteins. Proposed mechanisms are removal against a concentration gradient (midazolam) and along a concentration gradient (fentanyl).

Influence on physiological parameters

The effect of MARSTM on the physiological variables of patients with acute liver failure has also been studied. Early deaths in acute liver failure are often caused by cerebral edema or refractory cardiovascular collapse possibly triggered by circulating vasoactive substances. While assessing the efficacy of MARSTM on type 1 hepato-renal syndrome, Mitzner et al.⁵ observed an improvement in haemodynamic data. In a more recent group of 83 patients with acute liver failure (including 39 fulminant cases), mean arterial pressure increased and systemic vascular resistance and cardiac index decreased following a single MARSTM session.³³

Lai et al.³⁴ studied eight patients with acute liver failure following paracetamol poisoning. A significant increase in systemic vascular resistances with a concomitant decrease of cardiac index was observed only during the first eight-hour session of MARSTM therapy, and not in the following one. There was no effect on intracranial pressure but the patients had relatively low baseline intracranial pressures and were receiving prophylactic hypertonic saline.

Previous experiments using a non-inflammatory model of acute liver failure induced by hepatic devascularization in pigs had shown that MARSTM attenuated, but did not normalize, increased intracranial pressure. Attenuation was not associated

with any significant change in either cerebral blood flow or arterial ammonia levels.³⁵ This positive effect has been observed in patients suffering from acute-on-chronic liver failure³⁶ and in fulminant failure including some secondary to toxins.^{37,38}

Equally important, improvement in hepatic encephalopathy has been observed in a large number of studies including some assessing the efficacy of MARSTM in toxin-induced acute liver failure. This may be related to improvement in cerebral arterial flow^{39,40} as well as removal of endogenous substances.

Acute poisoning with liver failure

Paracetamol

An extracorporeal liver assist device using cells derived from a human hepatoblastoma cell line was assessed initially in paracetamol-induced acute liver failure in dogs.⁴¹ Two of the three treated animals recovered sufficient liver function after 42 to 48 h of treatment that they could be disconnected from the device. Regenerative nodules in the third animal demonstrated that even in the presence of severe liver injury the device was capable of supporting total liver function. These encouraging results led to the use of extracorporeal liver assist devices in 24 patients with acute liver failure⁴² including 17 caused by paracetamol poisoning. The time to reach an International Normalized Ratio (INR) below 2 was shortened and the grade of encephalopathy lowered. However, no effect on mortality was demonstrated.

The Hepatassist® system that uses porcine hepatocytes was tested in a randomized controlled trial, but did not affect overall mortality.⁴³ Subgroup analyses, however, suggested a potential benefit in patients with a well-defined etiology, such as paracetamol poisoning.

MARSTM has been used extensively to treat paracetamol-induced liver failure^{12,38,44–58} and has shown positive effects on clinical indices including encephalopathy, biochemical indices, hemodynamic parameters, liver recovery, intracranial pressure control and outcome. However, prospective randomized trials on the specific role of MARSTM in paracetamol-induced acute liver failure do not exist; these patients are generally included in larger groups of varying etiologies, and the conclusions described above are usually drawn from larger groups of acute liver failure patients. One paper reports on possible enhanced paracetamol clearance with MARSTM, the drug half-life decreasing from 3.4 h without albumin dialysis down to 1.2 h after initiation of the procedure.⁵⁷

One of the largest studies of MARSTM in the treatment of acute liver failure comes from Helsinki,^{52,55} 113 patients were treated between 2001 and 2007. They were compared with a historical group of 46 patients treated without MARSTM between 1995 and 2001. A toxic etiology was responsible in 63 of 113 patients; 32 were secondary to paracetamol poisoning. Comparison of paracetamol cases in the MARSTM group (n = 32) and the control group (n = 6) should be cautious, as patient characteristics were different at baseline. MARSTM-treated patients had significantly lower mean Model for End-stage Liver Disease (MELD) scores compared

with the controls. Also MARSTM was started before the development of encephalopathy in 15 out of 32 patients while all patients in the control group were encephalopathic. Six-month survival was 84% in the MARSTM group and 67% in the control group (not statistically different). The liver recovered in 81% of the MARSTM patients and 33% of the controls (p = 0.031). One patient in the MARSTM group received liver transplantation, compared with two in the control group; all three survived. Factors predictive of survival were tested separately using stepwise binary logistic regression analysis with the causative drug or poison regarded as an independent prognostic factor. The unwanted or negative endpoint was defined as death within 6 months or liver transplantation. In the paracetamol subgroup, the only significant predictor of survival was the grade of hepatic encephalopathy at the beginning of treatment.

Experience with other extracorporeal liver assist devices in paracetamol poisoning is more limited. Toxin-induced acute liver failure was also reported to benefit from fractionated plasma separation and adsorption.⁵⁹ This study included three patients with paracetamol poisoning and four patients with mushroom intoxication. Finally, in a paracetamol-poisoned patient who met the King's College criteria for liver transplantation, but had psychosocial contraindications, five runs of single pass albumin dialysis were helpful while awaiting spontaneous liver recovery.⁶⁰ However, in the most recent case-control study of six patients with paracetamol-induced acute liver failure, single pass albumin dialysis was not associated with differences in clinical outcome.⁶¹

Amanita phalloides

Mushrooms within the families Amanitaceae, Agaricaceae and Cortinariaceae contain various toxins. While phalotoxins and virotoxins most probably do not exert acute toxicity after ingestion, amatoxins are highly toxic and as little as 0.1 mg/kg body weight may be lethal in adults,⁶² children being even more sensitive. The mortality rate for children with *Amanita phalloides* poisoning complicated with fulminant hepatic failure approaches 80% when liver transplantation is not possible. Amatoxin interacts with RNA polymerase II, leading to a decreased cell mRNA content and to cell death due to lack of protein synthesis.⁶³ Another potential mechanism of toxicity could be apoptosis related to a synergistic effect with endogenous cytokines such as tumour necrosis factor.⁶⁴ Gastrointestinal epithelial cells, hepatocytes and proximal tubular cells transport amatoxins and are therefore subject to toxic injury, explaining the classical course of intoxication after ingestion. Following a latent period of 8–24 h, the patient develops acute gastrointestinal symptoms including watery diarrhea, abdominal pain and vomiting; 36–48 h after ingestion, liver enzyme activities gradually increase. The kidney may be damaged directly but also indirectly as a consequence of severe dehydration and the hepatorenal syndrome. Due to rapid absorption and distribution to body compartments, amatoxins are rarely detected in plasma after 36–48 h.⁶⁵

The rapid time course of absorption and excretion of amatoxins explains why hemoperfusion and/or hemodialysis to remove them are of limited value even if applied within the first 24 h after poisoning.^{66,67} MARS™ and other extracorporeal liver assist devices do not remove amatoxins but support failing liver function by continuously removing protein-bound endogenous toxins, thereby allowing the liver to recover spontaneously or, more often, to 'bridge' the patient until a graft becomes available.

At least 48 cases of *Amanita phalloides*-related liver failure treated with MARS™ have been described in case reports or in case series,^{51,68–81} including 16 patients treated in Gdansk; the clinical course of these 16 patients are summarized in Table 1. For the vast majority of patients, MARS™ was successful in improving symptoms and biological parameters, and its use allowed patients to recover from their impaired liver function (23 of 35 patients) or to undergo liver transplant (5 of 35 patients) in better condition.

In the recent Helsinki study,^{52,55} 10 out of 63 patients with acute liver failure of toxic etiology were poisoned with *Amanita phalloides* (n = 9) or herbal products (n = 1). If the patient had ingested a lethal amount of amatoxin, MARS™ therapy was usually initiated even in the absence of encephalopathy. All the nine mushroom-poisoned patients enrolled in the MARS™ group survived, though the number that recovered spontaneously or went on to liver transplantation is not known. The factors predicting six-month survival were the grade of hepatic encephalopathy and coagulation factor concentrations.

Unfortunately, none of these studies was controlled or randomized. All the patients were treated late after mushroom ingestion and already displayed severe liver failure. Therefore, the beneficial effect of MARS™ was more likely related to an effect on liver function rather than toxin elimination. No toxicokinetic data were presented. An additional problem in the assessment is that the severity of liver failure was rarely well defined. While the clinical grade of encephalopathy is generally provided, other parameters of liver function such as INR, factor V level, lactate concentrations are usually missing. There is also great heterogeneity in respect of the number and duration of treatments. For all these reasons, definite conclusions cannot be made.

Cocaine

MARS therapy is not described; however, treatment with fractionated plasma separation and adsorption was initiated in a 27-year-old man who developed liver failure following combined cocaine/MDMA use.⁸² The patient fulfilled the King's College criteria for liver transplantation and massive cerebral edema was detected on brain CT. When transplantation was declined by the surgeons because of the history of illicit drug consumptions, six sessions of fractionated plasma separation and adsorption treatment were performed over six days. This resulted in marked neurological improvement, a decrease of arterial ammonia and a reduction of brain edema. The patient was discharged completely recovered.

Amfetamines

Sein Anand et al.⁸³ reported amfetamine and MDMA poisoning in a 17-year-old man complicated by disseminated intravascular coagulation, acute renal failure, acute respiratory failure and acute liver failure. As he was considered ineligible for liver transplantation due to putative drug addiction, MARS™ was used for a total of 5 sessions over 10 days. The patient recovered.

Other substances

MARS™ has also been used in acute liver failure due to other drugs and toxins such as antibiotics,⁵⁰ tuberculostatics,^{50,84} diet pills,⁵⁰ Chinese traditional medicines,^{10,50,85,86} disulfiram,^{10,12} nimesulid,^{12,87,88} methylene bis(thiocyanate),⁸⁹ halotane⁴⁵ and allopurinol⁹⁰ with some improvement of encephalopathy and reduction of bilirubin and ammonia concentrations. In the Helsinki study,⁴⁴ the six-month survival in the non-paracetamol poisoned patients, was 74% in the MARS™ group (n = 31) and 100% in the control group (n = 6). Here also, the mean Model for End-stage Liver Disease score was lower at baseline in the MARS™ group; additionally, 36% of the MARS™ group patients were non-encephalopathic at baseline.

Acute poisoning without liver failure

Phenytoin

Phenytoin is one of the most commonly prescribed anti-epileptic drugs. Due to its narrow therapeutic index, toxicity may result from intentional overdose, drug interactions, dosage adjustment or alterations in physiology. In the most severe cases, neurological dysfunction (leading to coma and seizures) and cardio-circulatory disorders (arrhythmias and hypotension) are features. Risk factors for toxicity are well-known.⁹¹ Phenytoin is extensively bound to albumin (up to 90%), and is therefore not a suitable candidate for conventional hemodialysis.⁹²

MARS™ was used in a 45-year-old man who presented with severe phenytoin poisoning (alteration of consciousness, severe arrhythmias requiring cardiac pacing, increased liver enzyme activities which indicated liver toxicity rather than liver failure and deteriorating renal function).⁹³ Total and free serum phenytoin concentrations were very high (respectively 79 µmol/L or 19.93 mg/L and 17.6 µmol/L or 4.44 mg/L with a plasma albumin concentration of 27 g/L). Despite eight days of hemofiltration resulting only in a mild decrease in the serum phenytoin concentration to 40 µmol/L or 10.09 mg/L, the patient continued to deteriorate and a single 11.5 h MARS™ treatment was commenced. The total and free serum concentrations fell rapidly from 32 µmol/L (8.07 mg/L) to 11 µmol/L (2.775 mg/L) and from 9.8 µmol/L (2.47 mg/L) down to 2 µmol/L (0.5 mg/L), respectively, and there was substantial clinical improvement. Phenytoin was found in the albumin dialysate, indicating its effective removal from the patient, the charcoal column being the main site of its removal from albumin.

Table 1. Recent experience collected in Poland (Gdansk), with MARS™ in *Amanita phalloides* poisoning (produced by courtesy of Dr Jacek S. Anand; adapted from⁶²⁻⁶⁵). As expected, most patients were admitted after a significant delay after mushroom ingestion, but MARS treatment was started within 30 h in all the cases.

Patient	Age (yrs)	Gender (F-female, M-male)	Delay between mushroom ingestion and clinical signs/ MARS (hours)	Encephalopathy (E) (Y/N- Grade) at the time of MARS	INR and PT (sec) before MARS	ASAT/ALAT before MARS (IU/l)	Bilirubin before MARS (mg%)	Serum creatinine before MARS (mg%)	King's College criteria (or other) at the time of MARS	Liver transplantation (LTx) (Y/N, Refusal or contra-indicated)	Immediate outcome (A-live/ D-death)	Adverse events due to MARS (Y/N)	Benefit of MARS on hemodynamics	Benefit of MARS on CNS (E grade)
1	46	F	20/30	3	INR – no clotting PT – no clotting	3710/3300	3, 87	0, 9	2, 5	Y (dead after transplantation because of cerebral hemorrhage)	A (D after LTx)	N	+	1 (before LTx)
2	66	F	18/26	2	INR – 4,88 PT – 22	4950/4361	N/A	2, 4	2, 5	N	A	N	+	0
3	68	F	20/30	3	INR – 3,23 PT – 32,24	279/1238	11, 39	0, 9	2	R (because of age)	D	N	+	1
4	20	M	19/26	2	INR – 3,7 PT – 28,38	2140/3263	2, 2	0, 84	2, 5	N	A	N	+	0
5	54	F	19/30	2/3	INR – 3,42 PT – 30,7	9000/5760	1, 6	0, 81	2	N	A	N	+	0
6	49	F	18/24	3	INR – no clotting PT – no clotting	4055/7168	8, 8	2, 76	2, 5	Dead on the waiting list	D	N	+	1
7	67	F	22/31	3	INR – 2,43 PT – 43,9	2436/5025	N/A	0, 9	2	N	A	N	+	0
8	54	M	14/26	2	INR – 2,42 PT – 44,22	9101/5210	N/A	0, 7	2	N	A	N	+	0
9	34	M	18/25	2/3	INR – 1,95 PT – 31	2731/2020	5, 52	0, 81		N	A	N	+	0
10	50	M	21/25	2	INR – 2,15 PT – 49,58	1731/3430	2, 83	1, 1	2	N	A	N	+	0
11	46	F	19/28	2	INR – 2,33 PT – 41,0	9499/3642	2, 06	0, 7	2	N	A	N	+	0
12	69	F	20/26	2/3	INR – 3,15 PT – 33,96	4226/6147	N/A	1, 06	2	N	A	N	+	0
13	45	M	16/24	2/3	INR – no clotting PT – no clotting	6461/5438	3, 97	0, 9	2, 5	N	A	N	+	0

Charcoal hemoperfusion without albumin dialysis has also been shown to be effective.⁹⁴

Lamotrigine

Lamotrigine is an anti-epileptic medication proposed as a single or an 'add-on' therapy for some forms of seizures. Plasma protein binding is 55%.⁹⁵ Hepatic toxicity is uncommon but some cases of acute liver failure have been described in adults and children, one of whom was treated with MARSTM.⁹⁶ Initial therapy for this 30-year-old epileptic woman admitted with lamotrigine-related acute liver failure included the discontinuation of lamotrigine and the administration of corticosteroids, diuretics and vitamin K supplementation. Because of her worsening condition, she was placed on the emergency transplantation list and underwent two MARSTM sessions, for a total of nine hours. This led to improvement in her general condition, laboratory findings and her EEG returned to normal. Since the patient presented with liver failure on admission, the positive effect observed with MARSTM was more likely related to liver function improvement rather than to lamotrigine elimination. Definite conclusions cannot be drawn because toxicokinetic data are not available.

Theophylline

Symptoms of acute theophylline poisoning include agitation, convulsions, gastro-intestinal disorders, cardiac arrhythmias, acidosis and hypokalemia. Since about 50–60% of theophylline is protein bound, hemodialysis is only moderately effective at removing the drug in acute intoxications. Indeed, the clearance is about 50% of the dose delivered to the dialyser.⁹⁷ Therefore, albumin dialysis could be of potential use in patients with severe poisoning. Early *in vitro* studies with MARSTM demonstrated its ability to clear theophylline.⁹⁸

This was further evaluated in a 45-year-old patient who presented with rapidly rising serum concentrations above 100 mg/L after a deliberate overdose of 9 g of modified release aminophylline.⁹⁹ When cardiovascular instability developed without liver failure, an eight-hour MARS treatment was started resulting in a rapid decrease in the plasma theophylline concentration and improvement in the patient's blood pressure. The efficacy of the treatment was likely related to the presence of the charcoal filter. Charcoal hemoperfusion, without the MARSTM circuit, has been found more effective than hemodialysis for the management of severe theophylline poisoning.¹⁰⁰ Unfortunately, though it is less expensive than MARSTM, it also has limited availability.

Calcium channel blockers

Calcium channel blockers are a heterogeneous class of compounds mainly used to treat arterial hypertension, angina and supraventricular arrhythmias. They prevent the opening of voltage-gated calcium channels, thus reducing the entry of calcium into the cell. Their effects depend on whether they act mainly on cardiac channel (verapamil, diltiazem)

14	79	M	14/25	2/3	INR - 5 PT - 29,7	9928/7789	3,3	1,6	2,5	R (because of age)	D	N	+	1
15	73	F	16/20	2/3	INR - 2,08 PT - 51,38	718/869	1,5	1,63	2	R (because of age)	D	N	+	1/2
16	39	M	14/22	3	INR - 4,54 PT - 23,84	3544/10242	3,1	0,9	5	Y	A	N	+	0/1 (before LTx)

King's College criteria: The type and number of criteria at the time of MARS treatment are presented for each patient according to the following list:

1. INR greater than 6.5; or,
2. Patient age of less than 11 or greater than 40 years;
3. Serum creatinine of greater than 300 µmol/L;
4. Time from onset of jaundice to the development of coma of greater than seven days;
5. INR greater than 3.5; or,
6. Drug toxicity, regardless of whether it was the cause of the acute liver failure.

or vascular channels (amlodipine, nifedipine). Traditionally, the management of calcium channel blocker poisoning has included calcium salts, glucagon, adrenergic drugs and high-dose insulin with supplemental dextrose and potassium.¹⁰¹ Since a high proportion of circulating calcium channel blocker is bound to proteins (for instance, diltiazem is about 80% bound to albumin and alpha-1-glycoprotein acid at therapeutic concentrations),¹⁰² elimination techniques such as albumin dialysis could be of value.

Pichon et al.¹⁰³ reported on a 55-year-old depressed woman who was admitted after the intentional ingestion of 28 tablets of 300 mg sustained-release diltiazem. Despite standard medical treatment, she developed refractory shock with lactic acidosis and acute renal failure requiring high doses of vasopressors. There was no sign of liver failure. As a high proportion of diltiazem is bound to protein, MARSTM therapy was commenced 14 h after ingestion. Although during the single 6 h treatment lactate concentrations normalized, plasma diltiazem concentrations decreased significantly, and rapid tapering of vasopressor doses was possible, the contribution of MARS in increasing diltiazem elimination is uncertain.

Heavy metals

Because of their rapid binding to erythrocytes and proteins, acute intoxication with chrome- and copper-containing substances are deposited in various solid organs with multiple organ failure as a consequence. A 3.5-year-old girl developed acute liver and kidney failure after accidental ingestion of a fluid containing both copper and chromium.¹⁰⁴ Despite the efficacy of MARSTM on some biological parameters during the 35-hour treatment period, the patient died because of the lack of an appropriate donor. In this case, MARSTM therapy was started very late after the onset of intoxication, by which time the patient already displayed signs of severe liver insufficiency. Furthermore, as the albumin dialysate is not 'cleaned' (the charcoal column and the anion exchanger column do not remove copper or chromium), alternative management such as continuous hemodialfiltration¹⁰⁵ must be considered if organ failure is present.

Conclusions

There is a considerable enthusiasm for the use of techniques to support the failing liver, and toxic substances are well represented among the etiologies of acute liver failure. While it appears that MARSTM, the most widely used technique, may improve some biological and physiological parameters, decreased mortality in acute liver failure from all origins has not been clearly demonstrated. Extracorporeal liver assist devices should be used preferably in centres experienced in the intensive care management of patients with acute liver failure and with a program of liver transplantation. In most centres, these devices are used in patients who meet the criteria commonly accepted for urgent liver transplantation to provide support until a graft becomes available or until spontaneous recovery of the native liver occurs.

The benefit of using these devices to increase drug or chemical elimination in acutely poisoned patients without liver failure is uncertain. Very few toxicokinetic data are available, and no comparison with other elimination techniques has been undertaken. However, the use of MARSTM in patients with liver failure to increase the elimination of protein-bound substances normally metabolized by the liver is promising.

Acknowledgements

We would like to thank Dr Jacek S. Anand from Pomorskie Centrum Toksykologii (Gdańsk, Poland) for his extremely helpful contribution to the presentation of the pertinent data concerning *Amanita phalloides* poisoning.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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