

Molecular adsorbent recirculating system (MARS) dialysis for fulminant hepatic failure due to paracetamol overdose in children

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ABSTRACT

Paracetamol is a widely used drug, accidental overdosing being particularly encountered in children. The resulting acute liver failure is a therapeutic challenge. There is little agreement on the optimal therapy in paracetamol overdose. Gastric lavage, activated charcoal ingestion and N-acetylcysteine administration are usually effective just shortly after the poisoning, whereas the usefulness of high-flux haemodialysis and haemoperfusion is controversial. Recently, use of “liver dialysis” (or “albumin dialysis”) showed promising results in the treatment of acute liver failure from various aetiologies. We describe a case of accidental paracetamol overdosing in a 4-year boy, admitted 4 days after the ingestion of 154 mg/Kg body weight of paracetamol for four days. We treated him successfully with two sessions of albumin dialysis (MARS – “Molecular Adsorbent Recirculating System”) for fulminant liver failure and grade III hepatic encephalopathy. After two sessions of MARS dialysis, the patients had a spectacular clinical recovery. The patient was discharged 12 days after admission with normal liver enzymes. Our case suggests that albumin dialysis may be feasible treatment option in acute liver failure due to paracetamol overdose.

Keywords: acute liver failure, liver dialysis, molecular adsorbent regenerating system, paracetamol, poisoning

INTRODUCTION

Paracetamol (acetaminophen) is a widely used drug both in children and adults. In a prospective study of acute liver failure (ALF) including 17 tertiary care centers from the United States, paracetamol overdose in adults accounted for 39% of ALF cases, with a mortality of 28% (1). In children approximately one-third of patients develop end-stage liver failure following paracetamol overdose (2). Most importantly from the perspective of this abysmal outcome, there is little agreement on

the optimal therapy of paracetamol overdose (3). Gastric lavage, ingestion of activated charcoal are only effective in the first few hours after paracetamol ingestion. N-acetylcysteine is efficient usually within the first 24 hours after acute poisoning, but may be efficient also thereafter [4]

The role of daily long-hours high-flux dialysis and/or charcoal haemoperfusion in paracetamol overdose is controversial – despite promising earlier results from our group (5), a recent meta-analysis including controlled studies reached a negative conclusion (6).

There are extremely few data, all in adults, reporting on the paracetamol overdose treatment with the Molecular Adsorbent Recirculating System (MARS) dialysis (an extracorporeal detoxifying treatment also known as “albumin dialysis”) that has emerged in recent years as a powerful tool in treating severe acute liver failure due to several causes, including acute poisoning (7). As far as we know, there is no communication on using MARS dialysis in ALF due to paracetamol overdose *in children*. We present one case of accidentally poisoning with paracetamol, treated successfully by MARS therapy in a paediatric tertiary referral unit. □

CASE REPORT

The patient was a boy at the age of 4 years and six months from a poorly developed rural region of North-Eastern Romania, with scarce primary care conditions. The malnourished child (height = 97 cm, weight = 13 Kg) developed 5 days before admission a febrile state apparently due to an upper respiratory tract infection. His mother, without consulting a physician, medicated him with amoxicillin and paracetamol tablets for adults (2 g/day, for four days, e.g. 154 mg/Kg body weight/day). After 4 days of high-dose paracetamol ingestion, he developed nausea, vomiting, right upper-quadrant pain and his consciousness altered progressively within hours. He was admitted to a county hospital, where severe hepatic cytolysis was determined: AST 3305 IU/L, ALT 1436 IU/L, total bilirubin 1.45 mg/dL, so he was rapidly referred to a tertiary unit, the Saint Mary Paediatric Hospital in Iasi, Romania. At presentation, the patient had grade III hepatic encephalopathy (Glasgow coma score 8), 37.3°C rectal temperature, icteric conjunctivae, bronchial rales at pulmonary auscultation, a blood pressure of 122/77 mmHg, a heart rate of 60 beats/min., hepatomegaly, a diuresis of 300 ml/24 hours. At admission, ALT 3784 IU/L (further rising within 12 hours to 6400 IU/L), AST 4100 IU/L (rising to 6900 IU/L), conjugated

bilirubin 2.4 mg/dL (rising to 7.3 mg/dL), INR=6.5, serum ammonia 160 mg/dL, serum bicarbonate 24 mmol/L, WBC 7100/mL, hemoglobin 10 g/dL. Renal function was normal. He had slightly abnormal amylasuria – 425 U/L (normal < 380 U/L). Urinalysis was normal, with the exception of traces for albumin. Serology for hepatitis A, B, and C was negative. Qualitative determination of paracetamol metabolites in serum was positive.

Along with standard NAC i.v. treatment, MARS dialysis has been instituted (8 hours/session) on the first day after admission (MARS 1) – see Figure 1. The second treatment session (MARS 2) followed 24 hours later. The technical parameters used were: Q-albumin = 150 mL/min, Q-blood = 100-150 mL/min, Q-dialysate 2000 mL/h; P_{AA} was between 100 and 225 mmHg (max. 400) and P_{AE} between 130 and 400 mmHg (max. 500). The treatment with the MARS system of the patient described here has been approved by the local ethical committee and is in accordance with the Helsinki declaration of 1975.

The evolution of hepatic transaminases, serum ammonia and total bilirubin during the first week after admittance is shown in Figure 1. At the end of MARS 1, ALT dropped from 6400 to 5020 IU/L, AST from 6900 to 5720 IU/L, total bilirubin (almost all conjugated) from 7.3 to 3.8 mg/dL. The kinetics of relevant biochemical parameters during MARS therapy is shown in Table 1. Immediately after MARS 1, consciousness level improved significantly, mental status being near-to-normal 24 hours after the second MARS therapy session. The patient was discharged 12 days after admittance fully recovered, with an ALT level of 33 IU/L. □

DISCUSSION

Liver toxicity due to paracetamol in paediatric patients may occur at a minimal, single dose of 120 to 150 mg/kg of body weight. However, even lower doses may be toxic (4). An association between paracetamol overdose and

Time	1 st MARS session	Change from baseline (%)	2 nd MARS session	Change from baseline (%)
Baseline	7.3	100	4.18	100
+ 3 hours	5.83	20.14	3.02	27.76
End of session (+ 8 hours)	3.8	47.95	2.1	49.77

TABLE 1. Kinetics of bilirubin (mg/dL) during the two MARS therapy sessions

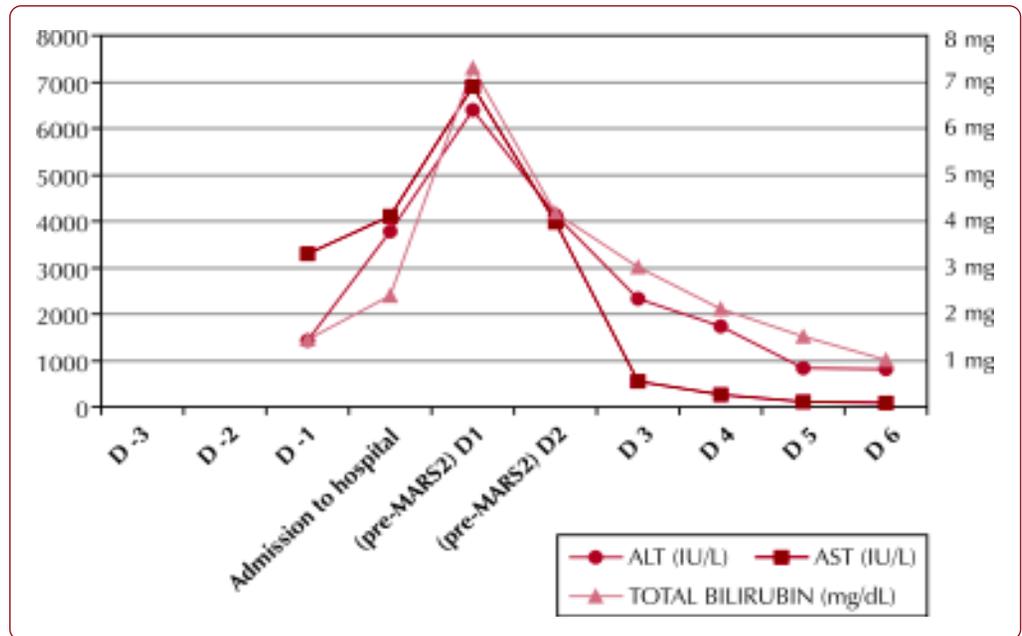


FIGURE 1. Evolution of transaminases and bilirubin during hospitalization, with two sessions of molecular adsorbent regenerating system (MARS) dialysis in the case of a 4 year old child accidentally poisoned with paracetamol.

social deprivation has been described (8). Enhanced paracetamol toxicity has been described in association with malnutrition, inherited differences in hepatic enzyme activity, ethanol ingestion, drug interactions, or concomitant medical disorders (4). Severe coagulopathy (INR>7), severe acidosis and encephalopathy at presentation – similar to our cases – are associated with an 80-90% mortality. Risk of death remains high even with hepatic transplantation: >50% (9). In the presented case, malnutrition seemed to be an important favoring cause for hepatic paracetamol toxicity in both cases.

Early treatment with gastric lavage, NAC p.o. or i.v., the antidote for paracetamol, and ingestion of activated charcoal is beneficial. NAC remains effective even after 24 hours or more of ingestion (10). However, when liver failure occurs, these measures become ineffective. Indeed, in one study, the most important predictor of serious liver injury was time between overdose and arrival to the hospital (11). In patients with grade III-IV hepatic encephalopathy, admitted within 42 hours after overdose, our group showed that daily long-hours high-flux dialysis and/or charcoal haemoperfusion reduces mortality significantly compared with those treated by the same methods after 42 hours – 11 % vs. 45% (5).

However, a very recent Cochrane review analyzing nine randomized controlled trials (all small and of low methodological quality) identifies no evidence of a beneficial role for haemoperfusion in the treatment of paracetamol-induced ALF. Liver transplantation in this analysis seems to be beneficial, but refinement of selection criteria for transplant is still needed (6). Furthermore, in numerous situations, liver transplantation is not possible and/or not feasible. In our described cases, orthotopic liver transplantation was not a realistic option, for several reasons. Nevertheless, the presence of severe acidosis, INR>7, and encephalopathy on presentation – such in our case, results in 80-90% mortality without transplantation and >50% mortality even with hepatic transplantation (9).

Molecular adsorbent recirculating system (MARS) dialysis, an extracorporeal detoxifying treatment, may improve radically the outcome of patients with severe liver failure due to several conditions, including acute alcoholism, viral hepatitis, various poisonings (drugs, mushrooms etc), liver graft dysfunction, acute on chronic hepatopathy (5). The principles of MARS therapy are described in detail elsewhere (12). Basically, the system uses an albumin-rich, closed-loop circuit, with two areas of depuration. In one area, the toxin-free “albumin dialysate” is in contact with patient’s blood

through a polysulphone membrane. Albumin-bound substances are transferred from patient's serum albumin to the unoccupied ligand binding sites of the system's albumin. In a second area, the "albumin dialysate" is in contact with a standard bicarbonate dialysate through a high-flux membrane, which permits the elimination of the water-soluble substances. The albumin toxin-charged solution is continuously regenerated by de-ligandization obtained by passage on charcoal and ion-exchange columns. Blood purification of liver toxins through MARS therapy allows time for hepatic regeneration.

There are extremely scarce data on using MARS dialysis in severe liver failure due to paracetamol intoxication. One case report (13) describes recovering of an adult patient with hepatic coma, increased intracranial pressure and severe coagulopathy after 3 days of MARS therapy. McIntyre and colleagues (14) also described recently a 30-year old schizophrenic patient who ingested 40 g of paracetamol and presented 36-48 hours later to the physician with grade II encephalopathy, other signs of severe liver dysfunction, and renal failure. He received 5 consecutive 8-h treatments with MARS. Consciousness returned to normal after two sessions, there was a marked and rapid

improvement of biochemical indices. The same was true with MARS therapy in our case – see Figure 1. Finally, a recent work by Koivusalo and colleagues (15) describes successful early MARS (and NAC) treatment in five patients with paracetamol overdose, of whom four survived without liver transplantation.

In our case, presenting with numerous negative prognostic markers, the implementation of the MARS dialysis permitted the successful recovery of the patient. The use of albumin dialysis controlled for the effect of albumin-bound toxins and allowed time for the hepatic regeneration, interrupting the vicious circle of further hepatic damage. Due to our experience in this case (and similar cases with acute liver poisoning due to mushroom intoxication), very late initiation of MARS treatment is associated with unfavorable outcome (16).

An important issue is also the significant reduction in costs elicited by a reduced stay in the ICU. We believe that MARS may be useful for all acute poisoning with paracetamol. However, a randomized trial (MARS versus N-acetylcysteine) is urgently needed to confirm this proposal and to establish clinical and laboratory markers / scores for treatment initiation.

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There is no conflict of interest in our article.

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