Case Report

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Successful treatment of refractory cerebral oedema in ecstasy/cocaine-induced fulminant hepatic failure using a new high-efficacy liver detoxification device (FPSA-Prometheus)

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Erfolgreiche Therapie eines refraktären Hirnödems bei Ecstasy/Kokain-induziertem fulminanten Leberversagen durch effiziente extrakorporale Detoxifikation (FPSA-Prometheus-System)

Zusammenfassung. Das durch MDMA (Ecstasy) ausgelöste fulminante Leberversagen weist – insbesondere bei Auftreten des charakteristischen Hirnödems – eine exzessive Mortalität auf. Die notfallmäßige Lebertransplantation ist die einzige etablierte Behandungsform. Wir berichten über einen jungen Patienten mit kombinierter Ecstasy/Kokain-Intoxikation mit akutem Leberversagen, Rhabdomyolyse, Septuminfarkt und Multiorganversagen. Die Lebertransplantation wurde aufgrund des rezenten intravenösen Drogenkonsums trotz Erfüllung der Transplantationskriterien abgelehnt. Infolge massiver Hyperammoniämie (318 μmol/l) und refraktärer zerebraler Herniation begannen wir eine kontinuierliche extrakorporale Behandlung mit dem FPSA-Prometheus System, welches adsorptive und dialytische Toxinentfernung kombiniert. Nach rascher Normalisierung des Ammoniakwertes kam es innerhalb von 4 Tagen zu Einsetzen von Leberregeneration und vollständiger Rückbildung des Hirnödems. Der Patient konnte das Krankenhaus nach Rehabilitation mit geringgradigen neurologischen Folgeerscheinungen verlassen. Effiziente extrakorporale Detoxifikation kann durch eine rasche Normalisierung von Hyperammoniämie und Hirnödem bei Ecstasy/Kokain-induziertem akutem Leberversagen eine therapeutische Option darstellen.

Schlüsselwörter: Fulminant, Leberversagen, Ammoniak, Hirnödem, Herniation, Ecstasy, Kokain, FPSA, extrakorporale Detoxifikation.

Summary. Ecstasy-induced fulminant hepatic failure is associated with high mortality. If complicated by cerebral oedema, orthotopic liver transplantation is the only established treatment. We report a case of combined ecstasy/cocaine-induced fulminant hepatic failure presenting with severe rhabdomyolysis, myocardial infarction and multiorgan failure. Transplantation was declined by the transplant surgeons because of a history of intravenous drug abuse. As excessive hyperammonaemia (318 μmol/l) and refractory transtentorial herniation developed, treatment with a new liver detoxification device combining high-flux haemodialysis and adsorption (FPSA-Prometheus) was initiated. Within a few hours of treatment, ammonia levels normalised. Cerebral oedema was greatly reduced by day 4 and hepatic function gradually recovered. Following neurologic rehabilitation for ischaemic sequelae of herniation, the patient was discharged from hospital with only minimal deficits. In conclusion, efficient extracorporeal detoxification may be an option for reversal of hyperammonaemia and refractory cerebral oedema in ecstasy/cocaine-induced acute liver failure.

Key words: Fulminant, liver failure, ammonia, cerebral, oedema, herniation, ecstasy, cocaine, FPSA, extracorporeal detoxification.

Introduction

The stimulant drug 3-4 methylenedioxymethamphetamine (MDMA, "Ecstasy") is increasingly recognised as a cause of fulminant hepatic failure (FHF) [1, 2], a life-threatening multisystem disease following severe hepatic injury [3]. Patients with FHF and advanced (grade III–IV) encephalopathy are at risk of cerebral herniation and irreversible neurologic damage unless emergency orthotopic liver transplantation is performed. Recent evidence suggests that cerebral oedema in FHF is caused by acute systemic hyperammonaemia, which gives rise to increased astrocytic glutamine synthesis and subsequent osmotic swelling [4]. Astrocytic swelling acts as a trigger for a disturbance of cerebral autoregulation, thus causing hyperaemia and transcapillary water movement into the brain [5].

Conventional treatment of cerebral herniation employs strategies reducing brain volume and/or cerebral

blood flow, such as intravenous osmotherapeutics, sedatives, moderate hyperventilation, or hypothermia [5, 6]. An additional way to control osmolyte accumulation within the brain would be to reduce hyperammonaemia by efficient clearance using extracorporeal liver-support devices. The fractionated plasma separation and adsorption system (FPSA/Prometheus) is based on a modern hemodialysis system (Fresenius 4008) and has been designed for combined adsorbent and dialytic blood purification [7]. The high-flux dialyser efficiently clears small solutes such as ammonia and uremic toxins (Fig. 1). A new polysulfone hollow-fiber filter with a sieving coefficient of 0.89 for human serum albumin (Albuflow®) facilitates elimination of albumin-bound or high-molecular substances in two adsorbent columns.

Here we report on a patient with ecstasy/cocaine-induced FHF and cerebral herniation who was considered not eligible for transplantation because of a history of illicit drug consumption. Striking normalisation of ammonia levels during FPSA/Prometheus treatment was associated with rapid improvement of cerebral oedema and recovery.

Case report

A 27-year-old male was admitted to the emergency department for suspected drug intoxication. During the previous hours he had allegedly injected ~0.5 g heroin and ~1 g cocaine and had ingested three tablets of MDMA (300 mg) at a clubbing event. His medical history was unremarkable apart from a 4-year history of sporadic injection of drugs and stimulant abuse. On admission, the patient was comatose (Glasgow Coma Scale, 3) and body temperature was 35.5 °C. Blood pressure was 90/45 mmHg, heart rate was 112/min, respirations were 35/min and pulse oximetry on supplemental oxygen read 88%. The remainder of physical examination was unremarkable. Toxicological analysis of a urine specimen yielded opiate and cocaine levels >5000 ng/ml, respectively, MDMA levels >1000 ng/ml and a benzodiazepine level of 70 ng/ml. Clinical and laboratory evaluation revealed evidence of multiorgan dysfunction, rhabdomyolysis, lactic acidosis and profound hypoglycaemia (Table 1). Serum alcohol level was 0.63‰. A hepatitis virus scan was negative. Following administration of intravenous glucose, flumazenil and naloxone, the patient became arousable (GCS 12) but subsequently developed circulatory collapse and oliguric acute renal failure. Electrocardiographic and echocardiographic evaluation suggested a non-penetrating myocardial infarction, which was treated conservatively. On day 2 the patient was transferred to the ICU for supportive treatment including continuous haemofiltration and N-acetylcysteine infusion (50 mg/kg/day). Although progressive liver failure with fulfilment of King's College criteria and a factor V level of 7% predicted a dismal prognosis, transplantation was declined by the transplant surgeons because of the history of illicit drug consumption. Despite continuous haemofiltration, arterial hyperammonaemia (peak level, 318 μmol/l) developed on day 3 and was followed by progression to grade IV encephalopathy. Signs of transtentorial herniation with a fixed dilated right pupil and polyuria did not improve with mannitol, hypertonic saline and moderate hyperventilation. Mechanical ventilation and barbiturate sedation were initiated and desmopressin was administered. A cranial computed tomography (CCT) scan revealed massive cerebral oedema and transtentorial herniation (Fig. 2a).

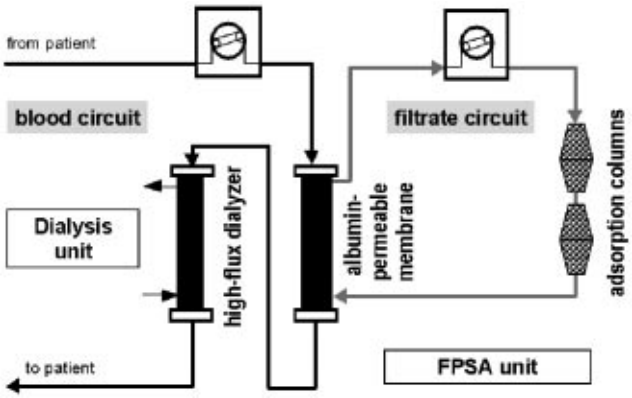

Fig. 1. Schematic representation of Prometheus/FPSA system

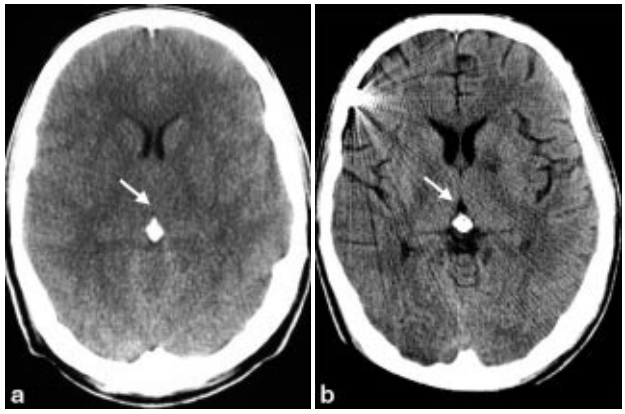

Fig. 2. a Cranial computed tomography scan at level of epiphysis showing sulcal effacement, diffuse white-matter hypodensity, bilateral compression of frontal horns and lacking visibility of third ventricle (arrow) indicating extensive cortical and subcortical cerebral oedema. **b** Cranial computed tomography scan at identical level obtained 4 days after initial examination showing restoration of grey-white differentiation and normal width of sulci and ventricles. Note small hypodensities of left internal capsule and occipital cortex due to ischaemic infarcts and metallic artefact of epidural transducer in the right frontal region

Since the patient was felt to be at immediate risk of irreversible neurological deterioration, treatment with an FPSA prototype (using an activated charcoal column in the FPSA circuit changed 1–2 times daily) was initiated. Blood flow rate was 180–220 ml/min, dialysate flow was 300 ml/min and fluid balance was adjusted according to central venous pressure. Anticoagulation consisted of prostacycline and low-dose heparin. Dialysate sodium was set to 142 mmol/L to avoid any exacerbation of cerebral oedema. The first treatment was performed without technical complications and arterial ammonia levels were normalised within 12 hours (Table 1). After 18 hours without further neurologic deterioration, treatment was discontinued and an epidural intracranial pressure (ICP) monitoring device was inserted. ICP fell from an initial value of 47 mmHg to 27 mmHg within 12 hours of the second treatment period, and cerebral perfusion pressure increased from 43 to >60 mmHg (Fig. 3). Hepatic function gradually recovered and

Table 1. Laboratory and clinical characteristics

Hospital day	1	2	3	4	5	6	7	8	9	Normal values
Extracorporeal support mode	–	–	CVVH	CVVH FPSA	FPSA	FPSA	FPSA	FPSA	CVVH FPSA	
pH	7,02	7,1	7,21	7,35	7,41	7,43	7,49	7,42	7,47	7,35–7,45
Lactate (mmol/l)	20	7,2	6,6	4,4	1,8	2,7	1,8	1,8	1,6	<2,4
Sodium (mmol/l)	142	138	150	147	142	142	139	138	139	135–145
Creatinine (mg/dl)	2,5	3,5	5,0	4,96	3,6	2,5	1,6	1,7	2,1	0,7–1,3
Bilirubin (mg/dl)	1,1	1,6	2,0	4,6	5,2	5,5	6,7	8,5	9,5	<1.05
Aspartate aminotransferase (U/l)	8790	6500	7100	3870	1500	471	220			<18
Alanine aminotransferase (U/l)	5870	8760	6800	3540	2360	1190	846			<20
Lactate dehydrogenase	11030	11800	9900	5190	3190	1040	629			<240
Amylase (U/l)	730	1990	2390	1100	760	379	413			<30
INR	1,6	3,7	3,4	3,2	2,2	1,7	1,5			0,8–1,2
Factor V (%)		7	23	33						65–130
Ammonia (µmol/l)	–	112	170	318	<50	<50	<50	<50	<50	<50
Hepatic encephalopathy (grade)	0	2	2	2–4	4	4	4	4	2	

ammonia levels remained < 50 µmol/l. Symptoms of cerebral herniation abated during the following days of continuous FPSA treatment. Since the level of sedation prevented a detailed neurological assessment and ICP measurements became increasingly erratic, a CCT scan was repeated four days after initial examination. Cerebral oedema was greatly reduced compared with baseline, but several small ischemic lesions were identified (Fig. 2b). FPSA treatment was continued for two further days. Since no recurrence of cerebral oedema was seen on an additional CCT scan and hepatic function had improved further, the patient was switched to haemofiltration for renal support. Encephalopathy gradually resolved and the patient responded to verbal commands by day 9. Following self-extubation on day 10, tracheal haemorrhage required reintubation. The patient was finally extubated on day 13 and transferred to a neurologic rehabilitation unit to treat sequelae of herniation including dysphagia, dysarthria, motor weakness and gait disturbances. By week 3, hepatic and renal function had recovered completely. Six weeks after admission, the patient was discharged to resume an independent life.

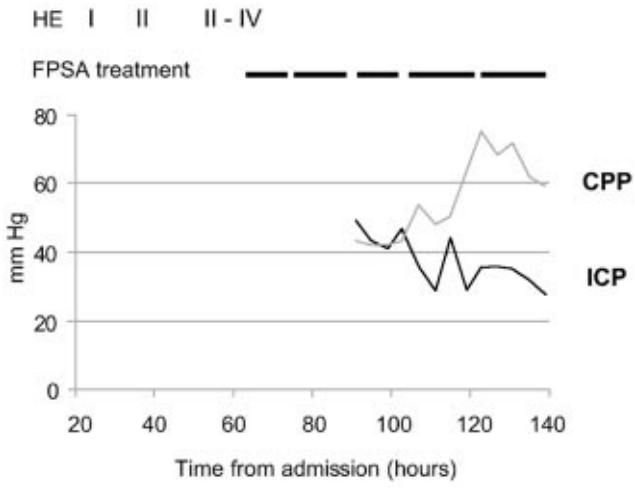

Fig. 3. Evolution of hepatic encephalopathy (HE) and effects of FPSA treatment on intracranial pressure (ICP) and cerebral perfusion pressure (CPP). Owing to transducer malfunction, only the first 54 hours are represented

Discussion

This report demonstrates that life-threatening refractory cerebral oedema and multiorgan failure can be successfully managed by dedicated intensive care and efficient extracorporeal detoxification. Although an array of therapeutic interventions was applied, only extracorporeal liver support normalised ammonia levels and led to a gradual resolution of cerebral oedema. Thus, efficient detoxification might be a useful approach for preventing cerebral herniation and sustaining vital functions in patients with FHF and contraindications for transplantation or when a donor organ is not available.

Based on the "toxin hypothesis" of hepatic encephalopathy [8, 9], treatment of FHF has adopted various strategies of extracorporeal detoxification including plasma exchange, high-flux haemodialysis, and haemoperfusion [10]. There is still no evidence to substantiate the postulated lack of hepatocyte-derived neuroprotective factors, where a certain amount of liver synthesis would be required to prevent encephalopathy ("critical mass hypothesis") [11]. In line, hepatic coma can be ameliorated by plasma exchange [12] but not plasma infusion, which provides most of the factors synthesised by normal liver. There is abundant evidence to suggest a key role of ammonia and intracellular glutamine in the pathogenesis of cerebral oedema [4, 13]. Ammonia infusion can cause cerebral oedema even in the absence of hepatic necrosis [14]. Accordingly, coma and herniation were preceded by a massive rise in arterial ammonia levels in our patient. The typical delay of 12–24 hours between emergence of hyperammonaemia and cerebral herniation [15] is mainly

due to the slow increase in astrocytic glutamine concentrations. Modulating factors such as temperature, osmoregulatory compensation, hyponatraemia, infection [16] or acid-base status [17] apparently contribute to individual variation in ammonia toxicity [18].

Neurologic improvement following extracorporeal liver support has been traditionally explained as resulting from the removal of metabolites such as methanethiol, dimethyl sulfide, phenols, benzodiazepine ligands and protein-bound toxins [19, 20]. Unfortunately, few studies have addressed the role of ammonia removal. Ammonia can be dialysed at a rate dependent on blood and dialysate flow and dialyser surface [21]. Out of 40 FHF patients treated with high-flux haemodialysis, total recovery of consciousness occurred in 17 patients and partial recovery in seven, resulting in an overall figure of 61,5% [22]. Recovery of consciousness was not related to liver regeneration as assessed by levels of factor V or hepatocyte volume fraction. Similar findings have been reported in FHF patients with grade IV encephalopathy treated with high-flux haemodialysis [23]. Interestingly, patients dying from cerebral oedema had less parenchymal damage than those dying from hepatic failure, which clearly refutes the "critical mass hypothesis" [24]. A recent case report confirmed improvement of cerebral oedema following high-flow-rate haemodiafiltration in hepatitis B virus-induced FHF, despite progressive liver failure necessitating transplantation [25].

In our patient, reduction of astrocytic glutamine concentration and improvement of cerebral oedema was apparently related to reversal of hyperammonaemia [4]. Removal of inflammatory cytokines and inhibitory factors could have further ameliorated cerebral hyperaemia, prevented further breakdown of the blood-brain-barrier and supported regeneration [26]. Hypothermia, which reduced intracranial pressure in patients with paracetamol-induced FHF [6] and lowered arterial ammonia levels [27], played no appreciable role as body temperature was kept between 36 and 37 °C during treatment. Moreover, all the patients treated by hypothermia died without recovery [6]. Thus, extracorporeal removal of ammonia seems to provide the greatest benefit, while additional effects of adsorption of large-molecular and protein-bound toxins by the FPSA system are likely.

From a pathophysiologic viewpoint, it seems somewhat ironic that development of extracorporeal detoxification including charcoal haemoperfusion, plasma separation and "bioartificial" support devices has moved from ammonia-lowering dialytic strategies towards methods aiming to remove bilirubin or ill-defined high-molecular toxins, where biocompatibility problems apparently offset potential clinical benefits [10]. Given their inability to resemble normal hepatic structure or functional organisation *in vitro*, extracorporeal hepatocytes ("biologic liver support") do not necessarily enhance toxin clearance. The role of potential hepatocyte-derived neuroprotective factors is still highly speculative and not substantiated by experimental data. To further complicate the issue, biologic liver-assist devices are usually combined with detoxification, making separate evaluation impossible. Clearly a large randomised study in FHF patients who are not candidates for liver transplantation would allow the cerebral and hepatic effects of extracorporeal liver support to be addressed, but this remains an elusive goal.

To the authors' knowledge, only one case of combined ecstasy-cocaine hepatotoxicity and rhabdomyolysis has been reported so far [28]. Characteristics of combined intoxication are difficult to differentiate from those of ecstasy-induced FHF: cocaine, which has been reported as a rare cause of FHF [29], causes oxidative hepatic damage (potentially enhanced by alcohol) [30] and induces vasoconstriction, which apparently contributes to myocardial damage [31]. Rhabdomyolysis, acute renal failure and cerebral ischaemia have been described in both cocaine and ecstasy intoxication [32]. Hyperthermia, a characteristic feature of severe intoxication, was absent in our patient.

We cannot rule out that our patient would have improved without extracorporeal liver support. However, fulfilment of both King's College and Clichy criteria indicates excessive spontaneous mortality. Patients reported to have similar degrees of ecstasy-induced liver damage and cerebral oedema ultimately died or succumbed to irreversible neurological damage if transplantation was not performed [32]. Previous studies have suggested that the presence of radiographic cerebral oedema in children with FHF indicated such a poor prognosis that termination of care seemed to be a reasonable option [33]. In contrast, we believe that our experience of successful "bridging to regeneration" using combined high-flux dialysis and adsorption should encourage clinicians to apply efficient detoxification strategies in patients with FHF and severe encephalopathy for whom liver transplantation is not an option.

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