 Prague Medical Report / Vol. 123 (2022) No. 4, p. 266–278

Pervitin Intoxication with Two-peak Massive Myoglobinemia, Acute Kidney Injury and Marked Procalcitonin Increase Not Associated with Sepsis

Eva Svobodová[1], Tomáš Drábek[2], Helena Brodská[3]
[1]Department of Anesthesiology and Intensive Care Medicine, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic;
[2]Department of Anesthesiology and Perioperative Medicine, University of Pittsburgh School of Medicine and UPMC, Pittsburgh, United States;
[3]Institute of Medical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University and General University Hospital in Prague, Prague, Czech Republic

Received May 31, 2022; Accepted October 18, 2022.

Key words: Methamphetamine – Procalcitonin – Acute kidney injury – Dialysis – Myoglobin – Rhabdomyolysis

Abstract: Patients intoxicated with methamphetamine-like substances may present with myoglobinuria but rarely require admission. An 18-year-old female was admitted due to intoxication with pervitin, a methamphetamine derivative. She presented with an altered mental status, fever, and increased heart and respiratory rates. Biomarkers showed leukocytosis and markedly increased procalcitonin levels, suggestive of sepsis. However, blood cultures and infectious disease workup were unrevealing. Clinical course was heralded by rhabdomyolysis and myoglobinuria resulting in multi-organ failure including respiratory failure necessitating mechanical ventilation, hemodynamic compromise with need for inotropic support, and an acute renal failure requiring renal replacement therapy. Surprisingly, after a transient improvement, an unexpected second peak of myoglobin was observed on hospital day 5, controlled by intensifying the elimination methods, and administration of dantrolene. Acute kidney injury resolved by hospital day 15, and the patient could be discharged on day 22. While most patients with intoxications are discharged

Mailing Address: Assoc. Prof. Helena Brodská, MD., PhD., Institute of Medical Biochemistry and Laboratory Diagnostics, First Faculty of Medicine, Charles University and General University Hospital in Prague, U nemocnice 499/2, 128 08 Prague 2, Czech Republic; e-mail: brodska@vfn.cz

https://doi.org/10.14712/23362936.2022.25

within 24 hours from emergency departments without being admitted, our case report highlights that the organ injury may evolve beyond the usual observation period, traditional renal-replacement therapies may not be sufficient to mitigate myoglobinemia with resulting acute kidney injury, and that procalcitonin may not be a reliable biomarker of infection in the setting of drug-induced rhabdomyolysis.

Introduction

Pervitin, a methamphetamine parallel, has been synthesized in 1937 and massively marketed to German soldiers during World War II as a psychostimulant to facilitate their alertness and combat capacities for prolonged periods of time, sometimes days (Defalque and Wright, 2011). Scientific explorations striving to characterize the psychomimetic drug effects have been conducted by American psychiatrists in the late 1940s (Levine et al., 1948; Schein and Goolker, 1951). To this date, along with methamphetamine, pervitin ranks among the most popular illicit stimulant drugs, accounting for 30 to 50% of most used drugs in central Europe (Sejda et al., 1998; Seblova et al., 2005).

Intoxication with pervitin is characterized by agitation, restlessness, headaches, mydriasis, tachycardia with arrhythmias, and increased body temperature. Severe intoxications may be complicated by altered levels of consciousness that complicates obtaining a relevant clinical history. The clinical picture of hyperpyrexia in intoxications often resembles that of malignant hyperthermia, including rhabdomyolysis, impaired liver and renal function, disseminated intravascular coagulopathy (DIC) and multi-organ failure. Biomarkers of sepsis are often utilized to differentiate between infectious vs. non-infectious pathologies in patients presenting with fever. Most patients with acute intoxications with methamphetamines are discharged from emergency departments after extended observation period without being admitted. However, a small number of patients presenting with intoxication warrant in-hospital admission and complex care for complex metabolic disturbances.

Case report

Emergency Medical Service crew was dispatched to the railway station to an unconscious patient "found down". At the scene, an 18-year-old female was located. Reportedly, she had injected herself with an extremely high dose (1 g) of pervitin intravenously (IV). No past medical history could be obtained from the patient. She was found delirious, uncooperative, agitated, severely hypoglycemic (1.9 mmol/l), febrile, with mydriatic pupils. She was transported to the Emergency Department of the General University Hospital in Prague, Czech Republic.

In the emergency department, she was found restless, with mydriatic pupils, minor muscle tremor, chills, fever (axillary temperature 39.2 °C; bladder temperature 41.2 °C). Electrocardiogram revealed stable sinus tachycardia 150/min. She was normotensive and tachypneic > 35 breaths/min. Pulse oximetry showed 95% on room air. No meningeal irritation was observed. The primary and secondary

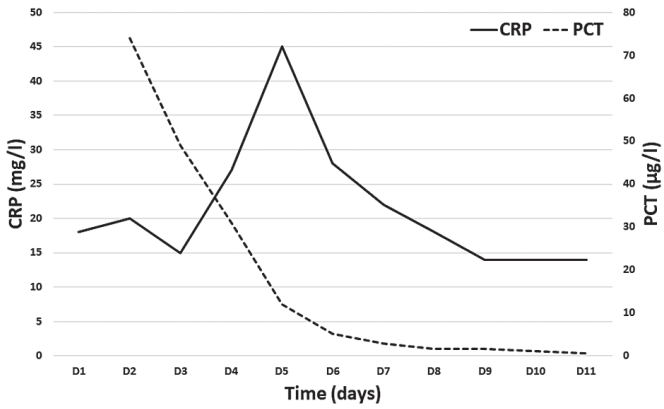

Figure 1 – Dynamics of the biomarkers of sepsis (CRP – C-reactive protein; PCT – procalcitonin).

surveys including focal assessment with sonography in trauma ruled out solid organ injury. Blood and urine samples were obtained, and the patient was admitted to the Intensive Care Unit due to suspected developing septic shock.

Upon admission, her Glasgow Coma Scale score was determined to be 6. She was intubated for airway protection, and mechanical ventilation was commenced. An empiric antibiotic therapy (amoxicillin clavulanate + gentamicin) was started due to fever, high leukocyte count (30.6×10^9/l) and risk of bloodstream infection in an IV drug abuser. Urine toxicology screen was positive for excitatory amines and cannabinoids. Admission laboratory values identified acute kidney injury (AKI), acute liver injury, coagulation abnormalities and rhabdomyolysis with increased myoglobin levels. Biomarkers of sepsis showed markedly increased procalcitonin (PCT) contrasting only a modest increase of C-reactive protein (CRP) (Figure 1). She tested positive for hepatitis C (viral load 3,480 IU/l; normal values < 15 IU/l).

In the next 24 hours, clinical condition of the patient gradually worsened despite ongoing support of her vital functions, ultimately developing multi-organ failure. She required hemodynamic support with norepinephrine at 0.25 µg/kg/min. Acute anuric renal failure developed requiring initiation of continuous renal replacement therapy (CRRT) in the form of continuous veno-venous hemodialysis (CVVHD) using Aquarius Haemodialysis System (Edwards Lifesciences, United Kingdom) with Aquamax HD19 filter (Nikkiso, Belgium).

Laboratory results (summarized in Table 1) were dominated by increased markers of rhabdomyolysis: creatine phosphokinase (CPK, 501 µkat/l), myoglobin (21,266 µg/l) and aspartate aminotransferase (AST, 18.93 µg/l). Increased nitrogenous end products of metabolism (urea 20 mmol/l, creatinine 325 µmol/l) documented AKI. Acute liver injury was documented by increased liver enzymes, specifically alanine aminotransferase (ALT, 13.14 µkat/l) and aspartate aminotransferase (AST, 18.93 µkat/l). Biomarkers of sepsis showed isolated significant increase of PCT (74.31 µg/l) with modest increase of CRP (20.8 mg/l),

and leukocytes (17.7×10^9/l). Coagulation parameters were also altered significantly, suggestive of DIC (INR – international normalized ratio 2.08; aPTT – activated partial thromboplastin time 103 s) with thrombocytopenia (61×10^9/l).

On day 3, PCT level was decreasing, but CRP and leukocytes remained increased (PCT 49.94 μg/l, CRP 15.5 mg/l, leukocytes 15.6×10^9/l). Thus, gentamicin was discontinued, while amoxicillin clavulanate and rifaximin were continued. Spontaneous coagulation disorder and thrombocytopenia persisted, which was treated by pooled platelets and plasma administration. Myoglobin levels decreased to 11,373 μg/l during ongoing CVVHD that was continued for 76 hours (myoglobin clearance 16.9 ml/h). Liver function tests further increased.

On day 4, the patient was extubated as her clinical condition improved. Myoglobin levels increased again to 25,485 μg/l. CRRT method was changed from CVVHD to high-flux continuous veno-venous hemofiltration (CVVH) to facilitate the elimination of myoglobin, and continued for 62 hours. This was confirmed by the evaluation of the dialysate, confirming a successful removal of myoglobin (myoglobin clearance 20.3 ml/h).

On day 5, a second peak of myoglobin (>40,500 μg/l) and CPK (944.64 μkat/l) was observed despite CVVH. At that time-point, dantrolene (100 mg IV) was added to the therapy to further mitigate rhabdomyolysis. On the following days, the myoglobin concentration gradually decreased (Figure 2). The patient remained anuric, requiring continued CRRT.

On day 9, the patient remained hemodynamically stable with adequate spontaneous respiration, and re-started oral intake. However, her anuria persisted. She was transferred to the Department of Nephrology for further care, where intermittent hemodialysis treatment (IHD) was provided. The last IHD was performed on day 15, while diuresis gradually resumed. After 22 days of hospitalization, the patient was discharged home.

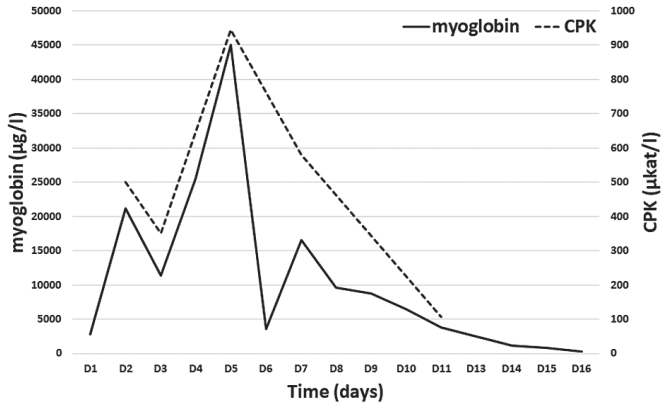

Figure 2 – Dynamics of the biomarkers of rhabdomyolysis (CPK – creatinine phosphokinase).

Table 1 – Biochemical, hematological and coagulation profile

	D1	D2	D3	D4	D5	D6	D7	D8	D9
ABG + electrolytes									
pH	7.36	7.32	7.33	7.33	7.33	7.38	7.43	7.44	7.45
pCO_2 (kPa)	2.610	5.68	4.92	6.32	4.83	5.06	5.37	5.52	5.69
HCO_3^- (mmol/l)	10.90	21.40	18.90	24.50	18.70	22.10	26.20	27.70	28.90
BE (mmol/l)	–12.40	–4.10	–6.00	–1.10	–6.10	–2.10	2.30	3.70	4.80
pO_2 (kPa)	10.70	13.90	19.10	18.50	12.20	12.00	11.20	10.90	12.00
Glucose (mmol/l)	5.40	9.10	6.30	6.20	6.60	6.00	6.30	6.10	5.21
Na^+ (mmol/l)	141.00	139.00	137.00	140.00	137.00	136.00	140.00	139.00	132.00
K^+ (mmol/l)	6.90	4.40	4.50	4.10	4.00	3.90	4.30	4.40	4.50
Cl^- (mmol/l)	110.00	109.00	108.00	102.00	105.00	99.00	98.00	100.00	94.00
Ca^{++} (mmol/l)	0.99	1.01	0.92	0.99	0.99	0.93	0.89	1.10	1.07
Lactate (mmol/l)	2.30	1.70	2.70	1.70	1.50	1.40	1.40	1.60	1.10
Biochemistry									
Urea (mmol/l)	13.00	20.20	9.90	9.20	8.90	13.30	15.80	17.10	24.90
Creatinine (µmol/l)	203.00	325.00	225.00	262.00	225.00	285.00	282.00	275.00	388.00
$Bilirubin_t$ (µmol/l)	65.40	61.10	77.20	67.10	53.70	46.00	26.90	19.50	18.80
$Bilirubin_c$ (µmol/l)	23.90	28.80	32.90	29.80	26.90	20.00	12.80	9.70	7.80
ALT (µkat/l)	6.31	13.14	41.62	52.69	49.76	31.29	21.58	14.03	8.93
AST (µkat/l)	3.27	18.93	45.14	43.66	41.58	31.78	21.16	14.44	10.98
GGT (µkat/l)	0.39	0.38	0.41	0.70	0.77	0.70	0.74	0.64	0.48
ALP (µkat/l)	1.17	1.25	1.51	1.55	1.32	1.15	1.05	0.81	

	D1	D2	D3	D4	D5	D6	D7	D8	D9
Hematology									
WBC ($\times 10^9$/l)	30.60	17.70	15.60	9.00	7.10	7.20	6.30	5.40	5.60
Hematocrit	0.43	0.421	0.36	0.38	0.38	0.34	0.31	0.29	0.22
Platelets ($\times 10^9$/l)	456.00	61.00	34.00	64.00	69.00	94.00	131.00	169.00	167.00
NLR	35.00	9.80	8.70	6.80	7.60	5.70	4.90	3.00	2.00
Coagulation									
INR	1.3	2.3	1.8	1.2	1.0	0.9	0.9	1.1	0.9
aPTT (s)	28	116	32	33	31	29	36	32	38

BE – base excess; ALT – alanine aminotransferase; AST – aspartate aminotransferase; GGT – gamma glutamyltransferase; ALP – alkaline phosphatase; WBC – white blood count; NLR – neutrophil-leukocyte ratio; INR – international normalized ratio; aPTT – activated partial thromboplastin time

She was seen in the outpatient clinic for follow-up after five weeks. She was in a stable clinical condition with normalized glycemia, normal CRP, persisting kidney injury and increased liver function tests with increased hepatitis C viral load (127,000 IU/l).

Discussion

The main toxicity seen with methamphetamines including pervitin is acute behavioral disturbance, which is usually managed adequately with sedation. The most common complications are rhabdomyolysis (30%) and acute kidney injury (15%). Less than 15% of patients seen in emergency departments are admitted, usually to behavioral units (Isoardi et al., 2019). However, severe intoxications may present under complex picture of altered mental status prohibiting obtaining relevant medical history, with a combination of chronic and acute medical problems. The propensity of intoxicated patients to develop rhabdomyolysis has been recognized (Penn et al., 1972). Initial care is often based on physical assessment of vital signs, supported by panels of laboratory assessments to facilitate diagnostic process and initiate treatment.

Multiple biomarkers are utilized to diagnose infection in patients presenting with fever. The most commonly used biomarkers in patients with suspected sepsis are CRP and PCT, both with excellent diagnostic capacities including high sensitivity and specificity to differentiate between bacterial infection vs. systemic inflammatory response syndrome (Hu et al., 2017).

Our case is interesting in two distinct aspects: first, initially high CRP and PCT levels with fever suggested bacterial infection. Second, myoglobin profile had a second, higher peak occurring late on day 5 of in-hospital stay, despite ongoing CRRT.

Increased PCT without evidence of infection

Fever, tachycardia, high white blood count along with high initial CRP level and PCT level (on day 2) were originally suggestive of bacterial infection, as suspected in an IV drug abuser presenting with fever. Hence, antibiotic therapy was initiated accordingly. However, if infection was found to be the underlying pathology, a different course of PCT values had been expected in the following days. PCT peaks in 24 hours, CRP peaks with a slight delay in 48 hours. PCT usually shows an upward tendency in the first days. CRP values would mirror high PCT levels (with slight delay) in patients with preserved protein synthesis capacities.

Once the admission blood cultures and swabs returned negative, antibiotic therapy was de-escalated on day 3. Due to persistently high, albeit decreasing, PCT and CRP levels, we continued amoxicillin clavulanate for 6 days on an empirical basis. After repeated negative findings on microbiological examination of swabs and blood cultures, we excluded concurrent infection and started to consider a non-infectious origin of the increased PCT level. Our hypothesis of a non-infectious origin of the

high PCT levels was supported by the persistently low CRP values during the early in-hospital stay. The high leukocyte count and neutrophil-lymphocyte ratio (NLR) in the first three days of hospitalization could be interpreted as a nonspecific marker of inflammation. NLR is more likely to be a marker of severity of the condition. However, we cannot exclude with certainty an infectious etiology of the condition (only less than 50% of sepsis cases show an infectious agent) although this seems less likely.

In massive rhabdomyolysis, a marked increase in PCT levels associated with sympathomimetic drug intoxication has been described in several case-reports (Lovas et al., 2014). PCT is produced by injured tissues and macrophages. Its secretion is activated by damage associated molecular patterns (DAMPs), mainly alarmins, which are endogenous mediators produced by processes such as ischemia, trauma or necrosis, in the case of hyperpyrexia triggered by heat shock proteins (HSPs). Kodama et al. (2021) described a similar increase of PCT in a 20-year-old female following sympathomimetic drug overdose after ingestion of ephedrine, ephedrine derivative, yohimbine and caffeine in an apparent suicide attempt. No bacterial infection was identified (Kodama et al., 2021). Zuberi et al. (2019) describe a massive PCT increase after intoxication of a psychostimulant kratom, associated with hypotension and transient AKI. The patient required hemodynamic support with vasopressors. AKI was managed with IV fluid therapy without the need for dialysis (Zuberi et al., 2019).

Two-peak myoglobinemia

Our patient also presented with high levels of myoglobin suggestive of rhabdomyolysis, characterized by spillage of the contents of myocytes into plasma. Large amounts of potassium, myoglobin, creatine, phosphate and CPK are released into the circulation. Rhabdomyolysis is a common cause of AKI. The mechanisms of renal failure in rhabdomyolysis probably include intrarenal vasoconstriction, direct toxic and ischemic tubular injury, and tubular obstruction (Bosch et al., 2009).

To monitor the course of rhabdomyolysis, we chose the level of myoglobin, along with CPK and AST. Myoglobin is a 17.8 kDa protein found in striated and cardiac muscle. Increased myoglobin concentrations in plasma are detected as early as 2 hours after the injection; maximum values are reached after 4–12 hours and then, in case of intact renal function, rapidly decrease. Myoglobin has an advantage over CPK as it is less dependent on the total lean body mass. AST is primarily a liver enzyme but is also found in muscle, increasing after muscle damage after 4 hours, reaching maximum after 16–48 hours. CPK is present in myocardium, skeletal muscle, and brain. The plasma concentration of total CPK increases approximately 3–6 hours after muscle or myocardial injury.

The increase in liver function tests is generally accepted as a biomarker of liver injury. We acknowledge that skeletal muscle injury can also induce an isolated increase of ALT and/or AST (Pettersson et al., 2008; Khatri et al., 2021). However,

this was not probably the case in our patient, as increased levels of ALT and AST were also accompanied by increased levels of bilirubin and ALP. MDMA ("ecstasy" – methylenedioxymethamphetamine) use per se is well known cause of liver injury (e.g. Andreu et al., 1998) which was probably the leading cause of increased liver function tests in our patient.

Initial myoglobin levels were significantly increased despite initial fluid-resuscitation therapy. Markers of AKI increased, and the patient became anuric. This prompted us to initiate CRRT. Creatinine, urea and myoglobin levels initially decreased, as expected. Surprisingly, myoglobin levels started to increase again, peaking on day 5 at two-fold higher level than the original peak observed on day 1. This was observed despite the ongoing, intensified regimen of CRRT using hemofiltration (Amyot et al., 1999; Zhang et al., 2012). We did not use CVVHD with a high cutoff dialyzer (Weidhase et al., 2020) or hemoadsorption (Dilken et al., 2020; Scharf et al., 2021; Moresco et al., 2022) which was reported to effectively eliminate myoglobin as this method was not available to us at that time. We acknowledge that conventional CVVHD does not effectively remove myoglobin (Zeng et al., 2014). However, biochemical assessment of the dialysate supported an effective elimination of myoglobin with our technique. At that time, we have decided to add to the complex therapy dantrolene based on its previously reported beneficial effects on both rhabdomyolysis and neuroleptic malignant syndrome caused by traditional anticholinergics or illicit drugs with similar properties (Russell et al., 2012; Musselman and Saely, 2013). Dantrolene, a ryanodine receptor type 1 (RYR-1) antagonist, was used to induce skeletal muscle relaxation through a dose-dependent inhibition of sarcoplasmic calcium release, primarily at skeletal-muscle RYR-1 receptors, directly inhibiting excitation-contraction coupling. The safety of dantrolene use for MDMA-induced hyperpyrexia has been documented before (Grunau et al., 2010). This approach appeared to be beneficial as the myoglobin levels started to downtrend.

The CRRT could be discontinued over next few days. The patient was transitioned to IHD and discharged. A resulting chronic renal injury persisted.

Methamphetamine abuse is known to cause both acute and chronic kidney injury. Myoglobinemia and AKI are frequent complications of acute intoxications. However, most cases are mild and do not necessitate treatment. Richards et al. (1999) reports that less than 10% of patients with methamphetamine intoxication develop acute renal failure, and only 3% required dialysis. This is in concert with a recent report by Isoardi et al. (2020) who reports that rhabdomyolysis is present in 30% of patients, while only 13% had AKI. All episodes of AKI resolved with supportive care, including IV rehydration. Concurrent rhabdomyolysis occurred in 23 (56%) patients with AKI (Isoardi et al., 2019, 2020). The progression of rhabdomyolysis into AKI worsens the prognosis of the patient (Rogliano et al., 2020). The expected duration of CRRT after illicit drug use does not seem to be longer than in patients with rhabdomyolysis from other causes, with only 5% of

patients requiring RRT at 3 months (Lim et al., 2020). Chronic methamphetamine use can result in end-stage renal disease even without a sentinel event of rhabdomyolysis (Foley et al., 1984; Baradhi et al., 2019).

Multiple case reports highlighted the possibility of AKI following methamphetamine intoxication (Scandling and Spital, 1982), requiring a combination of CRRT and IHD up to three weeks (Terada et al., 1988). Novel amphetamine compounds may be associated with even higher risk for rhabdomyolysis and AKI, e.g. synthetic cathinones (O'Connor et al., 2015). A delayed presentation five days after methamphetamine use resulting in simultaneous acute liver injury and AKI has also been reported. The patient was managed with five IHD sessions (Gurel, 2016).

Our observation of two-peak myoglobin levels is unique but has some support in the literature. Zarlasht et al. (2017) report similarly shaped two-peak profile of CPK levels in a patient with rhabdomyolysis refractory to IV fluid therapy. The breakpoint was achieved after administration of high-dose corticosteroids (Zarlasht et al., 2017).

Slightly increased CRP levels followed the two-peak pattern of myoglobin values. Thus, we consider the pattern of CRP response to be more reflective to non-infectious insult rather than bacterial infection (Figure 1).

PCT increase is probably not due to rhabdomyolysis itself but is the result of the global response to a trigger that causes rhabdomyolysis. In our patient, PCT has been declining steeply since the first measurement and did not mirror the two-peak profile of myoglobin. The exact mechanism remains unknown. We could speculate that the PCT peak was caused by rhabdomyolysis. The second peak in a two-peak release of myoglobin or CPK did not represent further tissues breakdown but rather a washout from a covert depot. This hypothesis would also be supported by the observation that AST dynamics were also characterized by a single peak. Alternatively, the second instance of rhabdomyolysis on day 5 did not trigger such a strong systemic response, which was reflected by an isolated CRP increase without PCT increase.

It remains undetermined why myoglobin peaked again during CRRT. Myoglobin levels were monitored in the dialysate. As plasma myoglobin levels increased, dialysate myoglobin levels also increased and accounted for approximately 10% of plasma levels. One of the reasons could be the administration of neuroleptics (melperone, haloperidol) for sedation due to restlessness since day 3. Neuroleptics can induce neuroleptic malignant syndrome in this setting. It is possible that the patient was more sensitive to this adverse effect after the muscle damage had already taken place. However, in this scenario, a concurrent increase of AST would be expected. Psychostimulant intoxication, neuroleptic malignant syndrome and serotonin syndrome were reported to be clinically overlapping (Demirkiran et al., 1996). Dantrolene has been used successfully in the treatment of both methamphetamine toxicity and neuroleptic malignant syndrome (Dixit et al., 2013). Indeed, we have seen a decrease in myoglobin levels shortly after administration of dantrolene.

Dantrolene is a cornerstone of the treatment of malignant hyperthermia, usually associated with the use of triggering anesthetics or depolarizing muscle relaxants in susceptible persons. However, its use outside this scenario has been documented previously (Krause et al., 2004). Intoxications with psychostimulants is also characterized by extremely high temperatures with muscle breakdown. Dantrolene has been used with beneficial effects in intoxications with MDMA presenting with fever (Kunitz et al., 2003; Hall and Henry, 2006; Moon and Cros, 2007).

Conclusion

Intoxicated patients may present with severe impairment of consciousness and multi-organ failure. Detailed history is often unobtainable. Physical examination, laboratory and microbiological investigations support the decision-making process and help to guide therapy. Intoxication with psychostimulants may be accompanied by rhabdomyolysis with myoglobinemia, potentially resulting in AKI. Dialysis therapy may be needed for several days. A serial monitoring of myoglobin levels seems warranted given the reported delayed myoglobinemia despite ongoing CRRT. A possible complementary role of neuroleptics used for sedation in these cases could not be ruled out. An array of biomarkers of sepsis should be assessed simultaneously in the diagnostic process as isolated PCT increase without increase in other biomarkers may not be indicative of sepsis.

In summary, our case report highlights two important aspects of care for patients with acute psychostimulant intoxications. First, myoglobin levels may have a delayed, higher peak several days after the intoxication, further aggravating AKI. However, an alternative cause of the second myoglobin increase triggered by administration of neuroleptics could not be ruled out. Second, PCT levels may not be specific for a bacterial infection in this setting. Clinicians caring for these patients should be cognizant of these complex considerations.

References

Amyot, S. L., Leblanc, M., Thibeault, Y., Geadah, D., Cardinal, J. (1999) Myoglobin clearance and removal during continuous venovenous hemofiltration. *Intensive Care Med*. **25(10)**, 1169–1172.

Andreu, V., Mas, A., Bruguera, M., Salmeron, J. M., Moreno, V., Nogue, S., Rodes, J. (1998) Ecstasy: A common cause of severe acute hepatotoxicity. *J. Hepatol*. **29(3)**, 394–397.

Baradhi, K. M., Pathireddy, S., Bose, S., Aeddula, N. R. (2019) Methamphetamine (N-methylamphetamine)-induced renal disease: Underevaluated cause of end-stage renal disease (ESRD). *BMJ Case Rep*. **12(9)**, e230288.

Bosch, X., Poch, E., Grau, J. M. (2009) Rhabdomyolysis and acute kidney injury. *N. Engl. J. Med*. **361(1)**, 62–72.

Defalque, R. J., Wright, A. J. (2011) Methamphetamine for Hitler's Germany: 1937 to 1945. *Bull. Anesth. Hist*. **29(2)**, 21–24, 32.

Demirkiran, M., Jankovic, J., Dean, J. M. (1996) Ecstasy intoxication: An overlap between serotonin syndrome and neuroleptic malignant syndrome. *Clin. Neuropharmacol*. **19(2)**, 157–164.

Dilken, O., Ince, C., van der Hoven, B., Thijsse, S., Ormskerk, P., de Geus, H. R. H. (2020) Successful

reduction of creatine kinase and myoglobin levels in severe rhabdomyolysis using extracorporeal blood purification (CytoSorb®). *Blood Purif*. **49(6)**, 743–747.

Dixit, D., Shrestha, P., Adelman, M. (2013) Neuroleptic malignant syndrome associated with haloperidol use in critical care setting: Should haloperidol still be considered the drug of choice for the management of delirium in the critical care setting? *BMJ Case Rep*. **2013**, bcr2013010133.

Foley, R. J., Kapatkin, K., Verani, R., Weinman, E. J. (1984) Amphetamine-induced acute renal failure. *South. Med. J*. **77(2)**, 258–260.

Grunau, B. E., Wiens, M. O., Brubacher, J. R. (2010) Dantrolene in the treatment of MDMA-related hyperpyrexia: a systematic review. *CJEM* **12(5)**, 435–442.

Gurel, A. (2016) Multisystem toxicity after methamphetamine use. *Clin. Case Rep*. **4(3)**, 226–227.

Hall, A. P., Henry, J. A. (2006) Acute toxic effects of "Ecstasy" (MDMA) and related compounds: Overview of pathophysiology and clinical management. *Br. J. Anaesth*. **96(6)**, 678–685.

Hu, L., Shi, Q., Shi, M., Liu, R., Wang, C. (2017) Diagnostic value of PCT and CRP for detecting serious bacterial infections in patients with fever of unknown origin: A systematic review and meta-analysis. *Appl. Immunohistochem. Mol. Morphol*. **25(8)**, e61–e69.

Isoardi, K. Z., Ayles, S. F., Harris, K., Finch, C. J., Page, C. B. (2019) Methamphetamine presentations to an emergency department: Management and complications. *Emerg. Med. Australas*. **31(4)**, 593–599.

Isoardi, K. Z., Mudge, D. W., Harris, K., Dimeski, G., Buckley, N. A. (2020) Methamphetamine intoxication and acute kidney injury: A prospective observational case series. *Nephrology (Carlton)* **25(10)**, 758–764.

Khatri, P., Neupane, A., Sapkota, S. R., Bashyal, B., Sharma, D., Chhetri, A., Chirag, K. C., Banjade, A., Sapkota, P., Bhandari, S. (2021) Strenuous exercise-induced tremendously elevated transaminases levels in a healthy adult: A diagnostic dilemma. *Case Reports Hepatol*. **2021**, 6653266.

Kodama, S., Kashiura, M., Moriya, T. (2021) Procalcitonin elevation induced by sympathomimetic drug overdose. *Acute Med. Surg*. **8(1)**, e687.

Krause, T., Gerbershagen, M. U., Fiege, M., Weisshorn, R., Wappler, F. (2004) Dantrolene – A review of its pharmacology, therapeutic use and new developments. *Anaesthesia* **59(4)**, 364–373.

Kunitz, O., Ince, A., Kuhlen, R., Rossaint, R. (2003) Hyperpyrexia and rhabdomyolysis after ecstasy (MDMA) intoxication. *Anaesthesist* **52(6)**, 511–515. (in German)

Levine, J., Rinkel, M., Greenblatt, M. (1948) Psychological and physiological effects of intravenous pervitin. *Am. J. Psychiatry* **105(6)**, 429–434.

Lim, A. K. H., Azraai, M., Pham, J. H., Looi, W. F., Bennett, C. (2020) The association between illicit drug use and the duration of renal replacement therapy in patients with acute kidney injury from severe rhabdomyolysis. *Front. Med. (Lausanne)* **7**, 588114.

Lovas, A., Agoston, Z., Kesmarky, K., Hankovszky, P., Molnar, Z. (2014) Extreme procalcitonin elevation without proven bacterial infection related to amphetamine abuse. *Case Rep. Crit. Care* **2014**, 179313.

Moon, J., Cros, J. (2007) Role of dantrolene in the management of the acute toxic effects of Ecstasy (MDMA). *Br. J. Anaesth*. **99(1)**, 146.

Moresco, E., Rugg, C., Strohle, M., Thoma, M. (2022) Rapid reduction of substantially increased myoglobin and creatine kinase levels using a hemoadsorption device (CytoSorb®) – A case report. *Clin. Case Rep*. **10(1)**, e05272.

Musselman, M. E., Saely, S. (2013) Diagnosis and treatment of drug-induced hyperthermia. *Am. J. Health Syst. Pharm*. **70(1)**, 34–42.

O'Connor, A. D., Padilla-Jones, A., Gerkin, R. D., Levine, M. (2015) Prevalence of rhabdomyolysis in sympathomimetic toxicity: A comparison of stimulants. *J. Med. Toxicol*. **11(2)**, 195–200.

Penn, A. S., Rowland, L. P., Fraser, D. W. (1972) Drugs, coma, and myoglobinuria. *Arch. Neurol*. **26(4)**, 336–343.

Pettersson, J., Hindorf, U., Persson, P., Bengtsson, T., Malmqvist, U., Werkstrom, V., Ekelund, M. (2008) Muscular exercise can cause highly pathological liver function tests in healthy men. *Br. J. Clin. Pharmacol*. **65(2)**, 253–259.

Richards, J. R., Johnson, E. B., Stark, R. W., Derlet, R. W. (1999) Methamphetamine abuse and rhabdomyolysis in the ED: a 5-year study. *Am. J. Emerg. Med*. **17(7)**, 681–685.

Rogliano, P. F., Voicu, S., Labat, L., Deye, N., Malissin, I., Laplanche, J. L., Vodovar, D., Megarbane, B. (2020) Acute poisoning with rhabdomyolysis in the intensive care unit: Risk factors for acute kidney injury and renal replacement therapy requirement. *Toxics* **8(4)**, 79.

Russell, T., Riazi, S., Kraeva, N., Steel, A. C., Hawryluck, L. A. (2012) Ecstacy-induced delayed rhabdomyolysis and neuroleptic malignant syndrome in a patient with a novel variant in the ryanodine receptor type 1 gene. *Anaesthesia* **67(9)**, 1021–1024.

Scandling, J., Spital, A. (1982) Amphetamine-associated myoglobinuric renal failure. *South. Med. J*. **75(2)**, 237–240.

Scharf, C., Liebchen, U., Paal, M., Irlbeck, M., Zoller, M., Schroeder, I. (2021) Blood purification with a cytokine adsorber for the elimination of myoglobin in critically ill patients with severe rhabdomyolysis. *Crit. Care* **25(1)**, 41.

Schein, J., Goolker, P. (1951) A preliminary report on the use of d-desoxyephedrine hydrochloride in the study of psychopathology and psychotherapy. *Am. J. Psychiatry* **107(11)**, 850–855.

Seblova, J., Polanecky, V., Sejda, J., Studnickova, B. (2005) Trends in substance abuse by teenagers in the Czech Republic. *J. Emerg. Med*. **28(1)**, 95–100.

Sejda, J., Studnickova, B., Polanecky, V. (1998) Trends in the incidence of problematic drug addicts in the Czech Republic, 1995–1996. *Cent. Eur. J. Public Health* **6(1)**, 18–24.

Terada, Y., Shinohara, S., Matui, N., Ida, T. (1988) Amphetamine-induced myoglobinuric acute renal failure. *Jpn. J. Med*. **27(3)**, 305–308.

Weidhase, L., de Fallois, J., Haussig, E., Kaiser, T., Mende, M., Petros, S. (2020) Myoglobin clearance with continuous veno-venous hemodialysis using high cutoff dialyzer versus continuous veno-venous hemodiafiltration using high-flux dialyzer: A prospective randomized controlled trial. *Crit. Care* **24(1)**, 644.

Zarlasht, F., Salehi, M., Sattar, A., Abu-Hishmeh, M., Khan, M. (2017) Short-term high-dose steroid therapy in a case of rhabdomyolysis refractory to intravenous fluids. *Am. J. Case Rep*. **18**, 1110–1113.

Zeng, X., Zhang, L., Wu, T., Fu, P. (2014) Continuous renal replacement therapy (CRRT) for rhabdomyolysis. *Cochrane Database Syst. Rev*. **6**, CD008566.

Zhang, L., Kang, Y., Fu, P., Cao, Y., Shi, Y., Liu, F., Hu, Z., Su, B., Tang, W., Qin, W. (2012) Myoglobin clearance by continuous venous-venous haemofiltration in rhabdomyolysis with acute kidney injury: a case series. *Injury* **43(5)**, 619–623.

Zuberi, M., Guru, P. K., Bansal, V., Diaz-Gomez, J., Grieninger, B., Alejos, D. (2019) Undifferentiated shock and extreme elevation of procalcitonin related to kratom use. *Indian J. Crit. Care Med*. **23(5)**, 239–241.