

Report from the Clinical Toxicology Committee of the Society of Toxicological and Forensic Chemistry (GTFCh)

Metamizol Suicide - Lethal Outcome Despite Maximum Therapy

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Abstract

A 70 year old female patient, suffering for years from rheumatoid arthritis and associated chronic pain was referred to the hospital by an emergency physician. Her blood pressure was no longer measurable; a hemiparesis has developed. A preliminary examination was carried out in the emergency department by a neurologist and a cerebral CT was requested. Immediately after examination, the patient suffered from hypodynamic cardiac arrest and had to be cardiopulmonary resuscitated. After stabilisation she was transferred to the Stroke Unit, where tonic-clonic convulsive seizures occurred. Toxicological general-unknown analysis of the patient's serum confirmed a suspected metamizol intoxication. Despite a maximum permissible dose of noradrenaline, she died four days after hospitalisation due to multiple organ failure.

1. Introduction

1.1. Metamizol

Metamizol (novaminsulfone), closely related to phenazone and propyphenazone, is the most powerful analgesic and antipyretic of the pyrazolone derivatives and still on the market. 4-*N*-methyl-aminoantipyrine (MAA) is also effective, but formed through metamizol hydrolysis in the body. Patients with glucose-6-dehydrogenase deficiency should never use metamizol, because a haemolytic crisis could be triggered. In addition, metamizol has a considerable potential for side-effects, of which agranulocytosis is the most significant [1]. Therefore, metamizol is no more licensed in many countries. The side-effects caused by metamizol include disturbances to renal function (very rare), blood pressure decrease up to shock due to rapid intravenous injection, drug-induced rash Lyell's syndrome (very rare), agranulocytosis (of allergic origin) / aplastic anaemia. Basic information regarding the metamizol-induced agranulocytosis is given in Tab. 1. Symptoms of metamizol intoxication are summarized in Tab. 2.

Tab. 1. Basic characteristics of metamizol-induced agranulocytosis.

Pathomechanism	Clinical signs	Treatment	Frequency
Metamizol metabolites bind to granulocytes	Flu-like symptoms (fever, shivering), tonsillitis, thrush, ulcers, sepsis	Antibiotic treatment, symptomatic (intensive) therapy	1 – 6 per 1 million metamizol applications [2].
Antibody development against this complex		Mortality: Europe ~10%, Third World ~100% due to lack of suitable treatment	
Under re-exposure, antigen antibody reaction occurs			

Tab. 2. Dose-dependent symptoms of metamizol intoxication.

Mild intoxication	Severe Intoxication	
	Within a few hours of <6 h	Latency of 24-48 h
Tiredness	Nausea, vomiting, pains in the abdominal region, diarrhoea	Liver damage (jaundice, ALAT increase, clotting)
Mild gastrointestinal symptoms	Central nervous symptoms (restlessness, agitation, vertigo, somnolence, convulsions, coma)	Limitation of renal function (acute kidney failure with acute interstitial nephritis of non-destructive nature).
	Blood pressure decrease → shock, tachycardia	
	Respiratory disturbances, decompensation of the acid-base balance	
	Disturbed serum electrolytes (hypernatraemia, hypocalcaemia), temperature regulation, and water retention	

A metamizol misuse potential is not seen officially, also extensive metamizol abuse is known.

1.2. Case report

The 70 year old female patient has lived for years in sheltered accommodation for the elderly as she suffers from rheumatoid arthritis (treatment with disease-modifying agents for many years: MTX 1 x per week) and a pain syndrome chronified by this (long-term medication: metamizol [Novaminsulfon[®]]). According to information from her relatives, for several days she has taken larger quantities of metamizol due to pains in her left hip, probably caused by a fall 14 days ago, which, however, did not sustain any fractures afterwards, only haematomas over a large area.

According to the emergency physician's record, the patient had been found in her apartment during the day *104.5 hours pre-mortem*, she was apathetic and not co-operative, whereupon the emergency physician was called. Pareses were not observed. In accordance with the overall situation, especially since no blood pressure was measurable, the patient was admitted to hospital.

In the emergency admissions department with volume supply the blood pressure could be stabilised at the lowest level, ECG was normal and showed no indication of an infarction. As during the emergency transport the patient developed hemisymptoms on the left, including turning of the head towards the right, with the working diagnosis of a right hemispheric cerebral infarction the neurological specialist is primarily consulted, whereupon the patient is immediately taken to the CT department in order to investigate a possible fibrinolysis. Here CT, CTA, and CT perfusion were without pathological findings. Immediately after the examination, whilst being transferred from the CT couch onto the bed, the patient suffers hypodynamic cardiac arrest. She was mechanically resuscitated, intubated and ventilated, duration of resuscitation approximately 8 min.

In the first clinical-chemical laboratory findings, severe decompensated acidosis could be detected with an initial pH of 6.79. Furthermore, there were first indications of acute kidney failure (creatinine in the serum 601 $\mu\text{mol/L}$ [reference range 35-80 $\mu\text{mol/L}$], creatinine in the urine 0.6 mmol/L [reference range 8-27 mmol/L], potassium in the serum 5.98 mmol/L [reference range 3.50-5.10 mmol/L], anuria).

After stabilisation of circulation, she was transferred to the Stroke Unit where she presented tonic-clonic convulsive seizure. Thus, lorazepam 4 mg and valproic acid 1200 mg were given. Then, she was treated with noradrenaline (Arterenol[®]) and infusions buffering with sodium bicarbonate. Due to persistent acidosis, classical haemodialysis (see Fig. 2: “HD”) was performed. Due to suspected previous aspiration, antibiotic treatment with ceftriaxone was carried out. In addition, fitting of a central venous catheter, a dialysis catheter and an arterial blood pressure measurement was carried out.

The toxicological general-unknown analysis in the patient’s serum, only requested 10.5 hours after emergency admission, confirmed *93 hours pre-mortem* the suspicion of metamizol intoxication (initial serum concentration approximately 524 mg/L; potentially toxic concentrations from 20 mg/L). The symptoms correlated with this toxicological finding. Forced diuresis recommended in the literature could not be carried out due to anuria. Therefore, in consultation with the Erfurt Poisons Information Centre – the decision was made to carry out a two-fold haemoperfusion (see Fig. 2: “HP”).

In the course of further progress, in addition to the acute kidney failure, she developed the full picture of multiple organ failure with prognostically crucial liver failure. In addition, high neuron-specific enolase (NSE) values (133.6 µg/L [reference range < 15.0 µg/L], *13 hours pre-mortem*) argued in favour of severe postanoxic brain damage following resuscitation. Two Genius-haemodialyses (see Fig. 2: “GH”) followed. Development of severe rhabdomyolysis occurred with most severe multiple organ failure on the day of death. The patient’s pupils were wide and increasingly reactionless. The rhabdomyolysis increased. Circulation could not be stabilised even with maximum dose of noradrenaline. The lactate acidosis was treatment-resistant. The patient died from multiple organ failure.

2. Materials and Methods

Toxicological analysis was performed using a Prominence-HPLC system (Shimadzu, Kyoto, Japan) consisting of column oven CTO-20AC, photo diode array detector SPD-M20A, auto injector SIL-20AC HT, interface CBM-20A, pump LC-20AD, online degasser DGU-20A3 and software Labsolution 32-bit with UV-spectra library for diode array detectors (2682 UV-spectra). After liquid-liquid extraction [3] at native pH of serum samples the extracts, resolved in eluent liquid, were injected by isocratic elution on separating column LiChroCART 250-4 LiChrospher 100 RP-8 (5 µm) (Merck KGaA, Darmstadt, Germany) with mobile phase acetonitrile/phosphate buffer (pH 2.3) 37/63. UV spectra of active substances and metabolites were recorded using a photo diode array detector SPD-M20A. Compound identification was achieved by comparison of relatively retention time apply to MPPH and by comparison of the spectra with those of the library of Pragst et al. [4]. Concentration of the active substance was estimated from peak areas. These were determined with calibration solutions, prepared by diluting commercial standard solutions with mobile phase buffer after one-point-calibration.

3. Results

3.1. Chromatography

Using HPLC-DAD, metamizol could be identified in serum by library search (Fig. 1). During treatment, metamizol was determined in nine serum sample. The serum levels are depicted in Fig. 2. The time of dialysis and hemoperfusion is indicated in this figure.

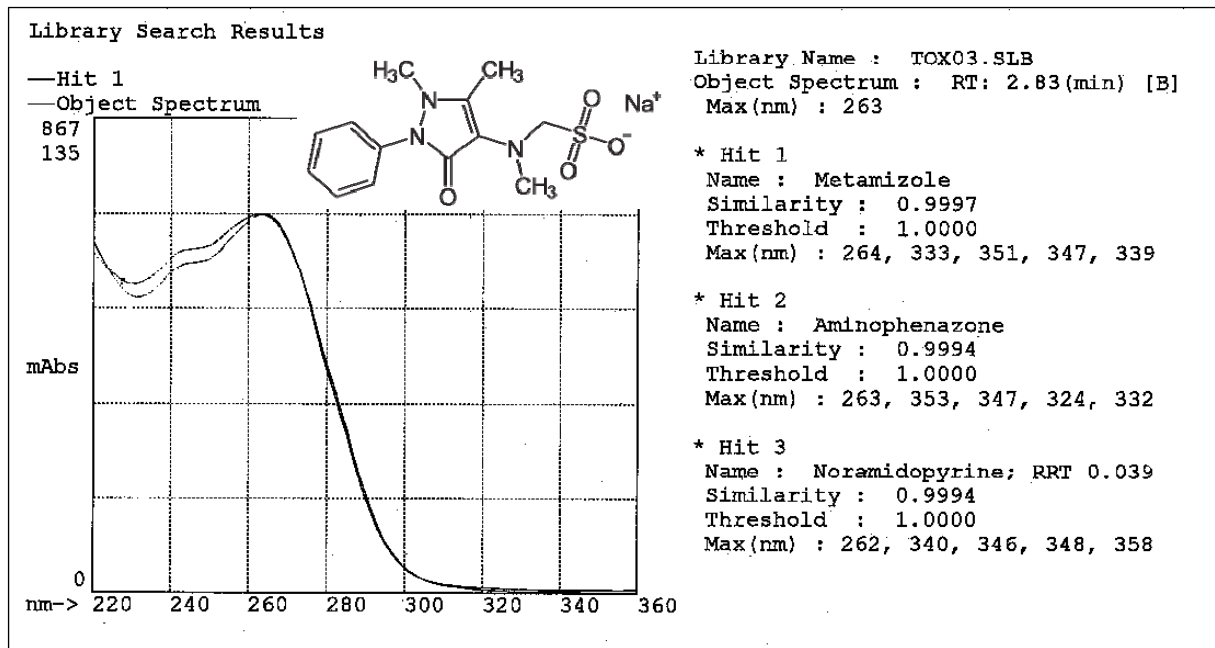


Fig. 1. Library search result indicating metamizol ($C_{13}H_{17}N_3O_4S$; *N*-Methyl-*N*-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)aminomethansulfosäure.

A permanent decrease in the initially highly toxic metamizol concentration was observed ($c_{1\text{metamizol}}$ approximately 524 mg/L with $t_1 = 0 \text{ h} = 93 \text{ h}$ pre-mortem), $c_{9\text{metamizol}}$ approximately 37 mg/L with $t_9 = 55.5 \text{ h} = 38 \text{ h}$ pre-mortem) (potentially toxic concentration from 20 mg/L, serum elimination half-life period 2-4 h) (Fig. 2).

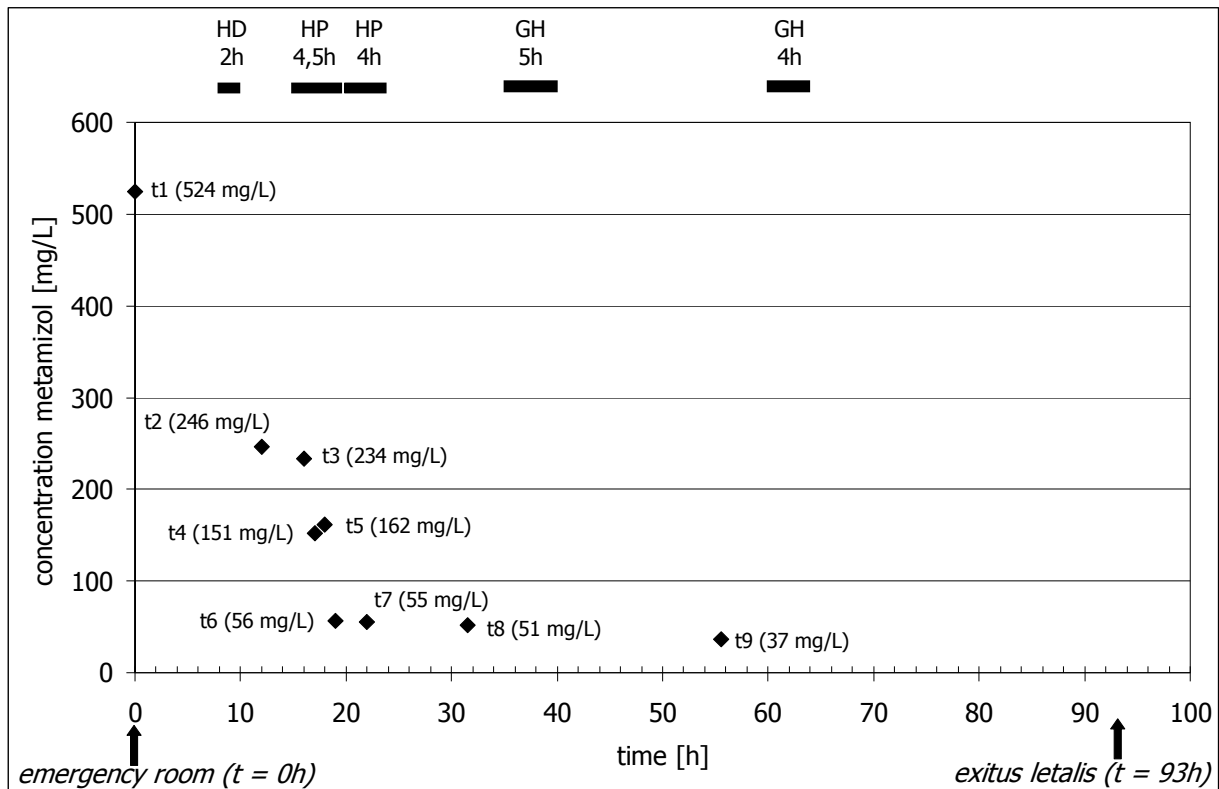


Fig. 2. Serum metamizol concentration profile (therapeutic up to 10 mg/L, potentially toxic from 20 mg/L [5], serum elimination half-life period 2 - 4 h [6]); HD = classical haemodialysis, HP = haemoperfusion, GH = Genius-haemodialyses.

Due to initial oliguric acute kidney failure, it was not possible to influence this and reduction of the massively increased metamizol level by forced diuresis, which otherwise would have been the appropriate method of pyrazolone elimination [7], was not possible. Therefore classical haemodialysis (HD) was carried out short-term. As a result of this the metamizol level could be reduced from approximately 524 mg/L (t_1) to approximately 246 mg/L (t_2).

A further clear reduction of the metamizol level from approximately 234 mg/L (t_3) to approximately 55 mg/L (t_7) was achieved by haemoperfusion (HP) on two occasions, which thus represents a more effect therapeutical measure for the effective reduction of a toxicologically relevant metamizol level [8]. Both four hour and five hour Genius-hamodialyses (GH) subsequently carried out – due to the continued and then anuric kidney failure - did not influence the metamizol level significantly (reduction from approximately 51 mg/L (t_8) to only 37 mg/L (t_9)).

3.2. Pathogenesis

The progress of the patient's illness can be illustrated as follows (see Fig. 3).

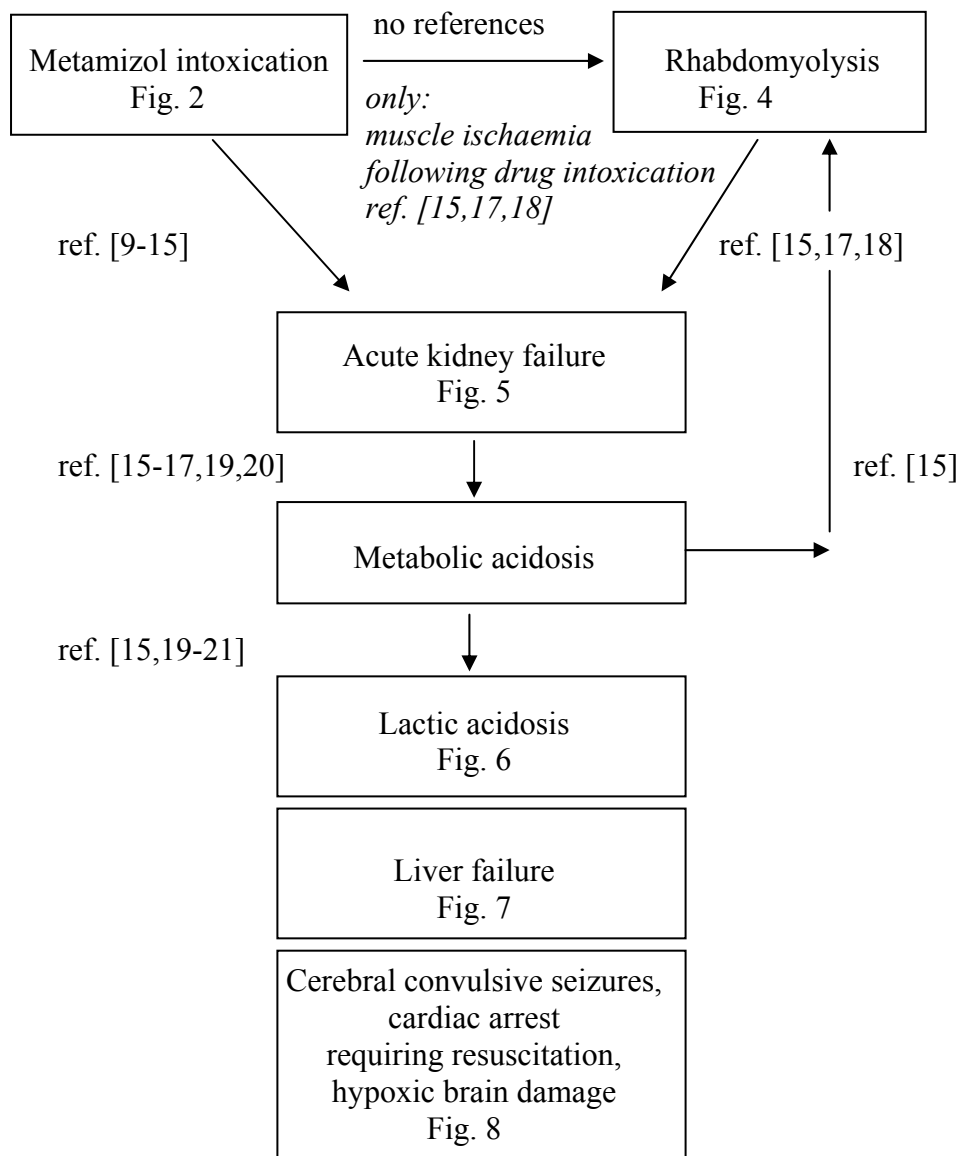


Fig. 3. Possible pathogenesis in the patient.

The clinical-chemical analyses presented below are summarised organ-related/function-related and – insofar as measurements were available – represent at six points in time t_a to t_f with following values: $t_a = 0 \text{ h} = 93 \text{ h pre-mortem} = t_1$ (see Fig. 2), emergency room; $t_b = 8 \text{ h} = 85 \text{ h pre-mortem}$; $t_c = 20 \text{ h} = 73 \text{ h pre-mortem}$; $t_d = 32 \text{ h} = 61 \text{ h pre-mortem}$; $t_e = 56 \text{ h} = 37 \text{ h pre-mortem}$; $t_f = 80 \text{ h} = 13 \text{ h pre-mortem}$.

Rhabdomyolysis (Fig. 4)

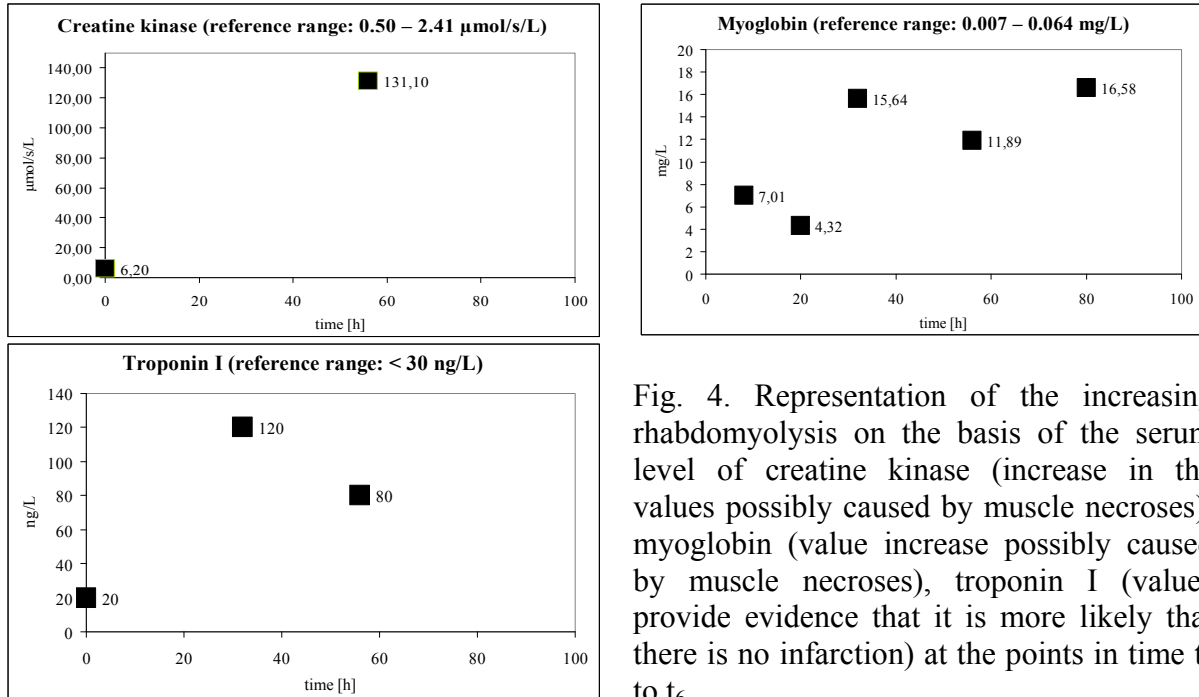


Fig. 4. Representation of the increasing rhabdomyolysis on the basis of the serum level of creatine kinase (increase in the values possibly caused by muscle necroses), myoglobin (value increase possibly caused by muscle necroses), troponin I (values provide evidence that it is more likely that there is no infarction) at the points in time t_1 to t_6 .

Renal function (Fig. 5)

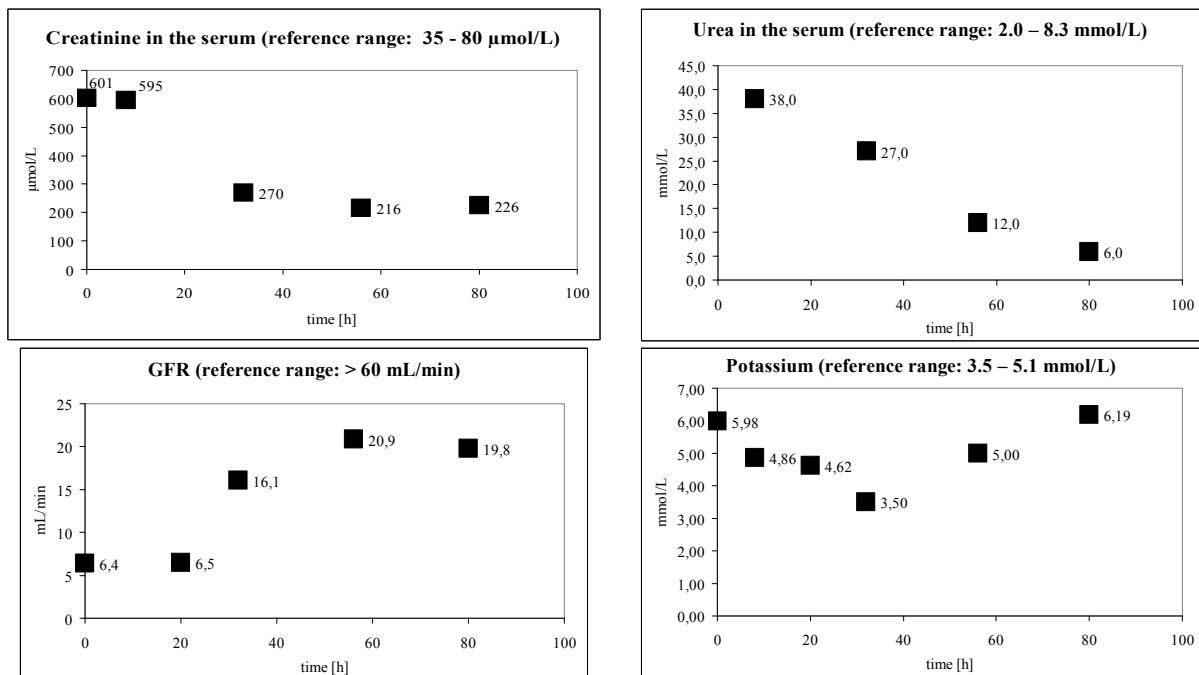


Fig. 5. Representation of the limitation of renal function and value optimisation due to dialysis on the basis of the serum level of creatinine (increased values possibly caused by muscle necroses and renal insufficiency), urea, glomerular filtration rate GFR and potassium (value fluctuations possible due to haemolysis, rhabdomyolysis) at the points in time t_1 to t_6 .

Lactic acidosis (Fig. 6)

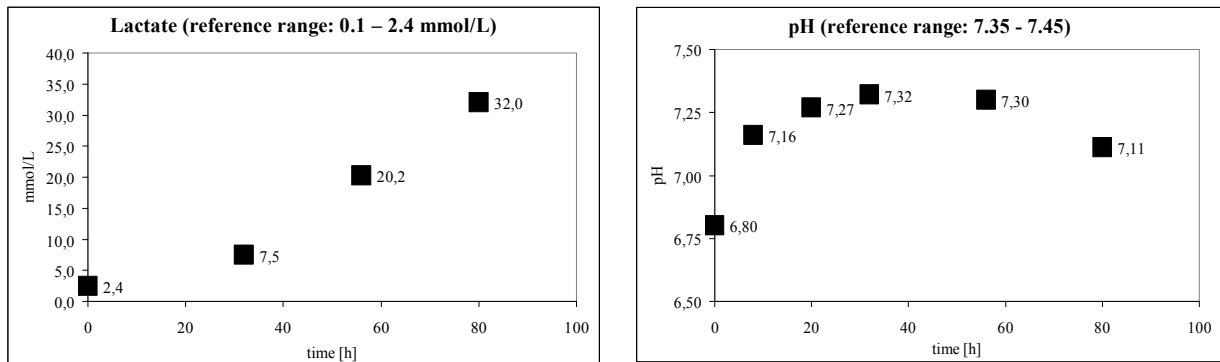


Fig. 6. Representation of the lactic acidosis as the expression of the anaerobic metabolism on the basis of the lactate-plasma level at the points in time t_1 to t_6 .

Liver function (Fig. 7)

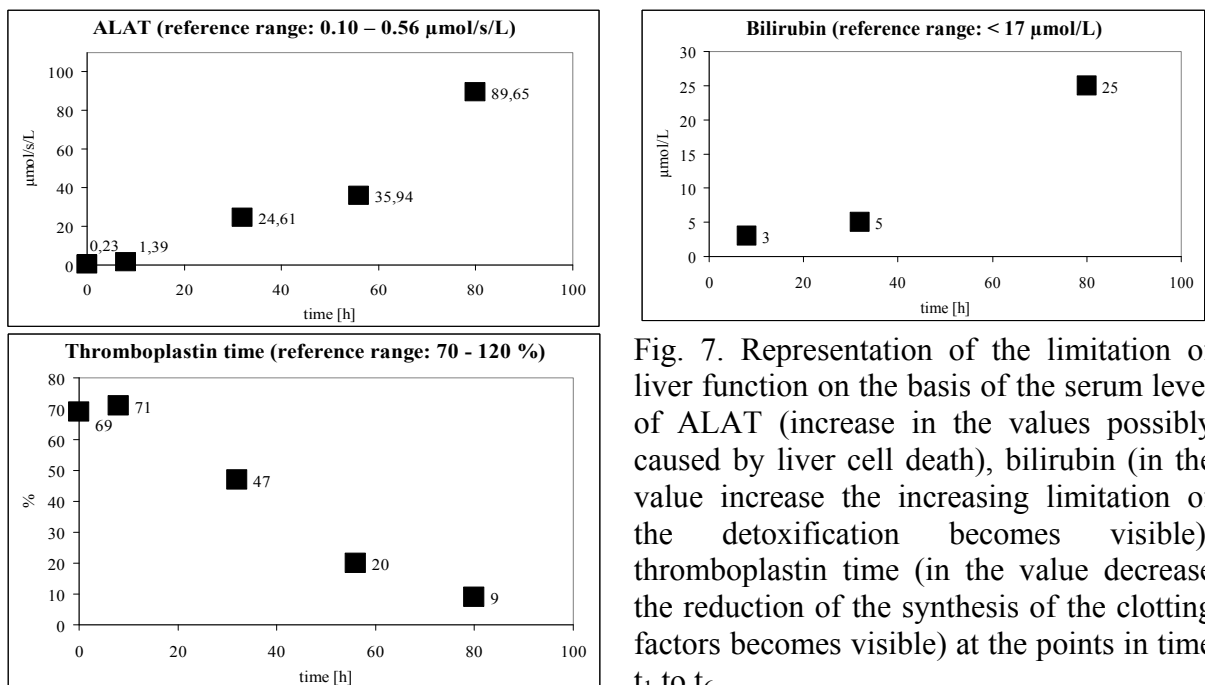


Fig. 7. Representation of the limitation of liver function on the basis of the serum level of ALAT (increase in the values possibly caused by liver cell death), bilirubin (in the value increase the increasing limitation of the detoxification becomes visible), thromboplastin time (in the value decrease the reduction of the synthesis of the clotting factors becomes visible) at the points in time t_1 to t_6 .

Neuron specific enolase NSE (Fig. 8)

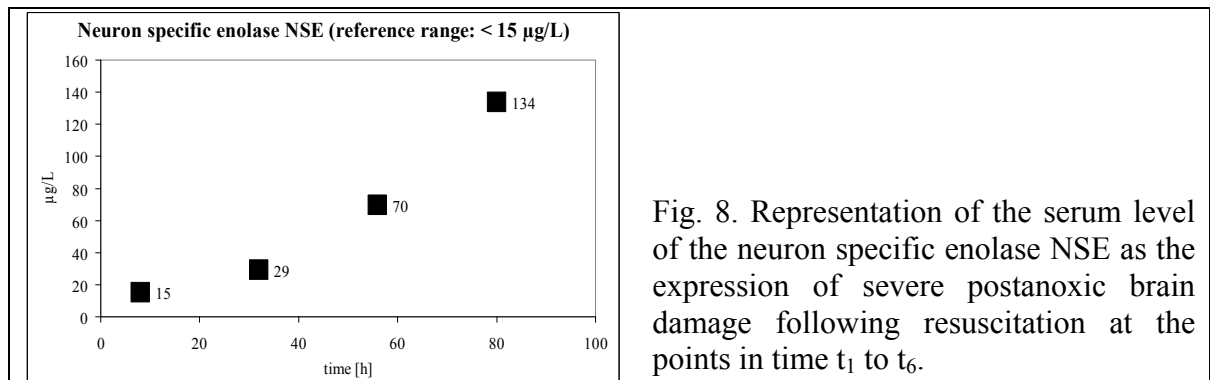


Fig. 8. Representation of the serum level of the neuron specific enolase NSE as the expression of severe postanoxic brain damage following resuscitation at the points in time t_1 to t_6 .

3.3. Case assessment

According to the history, a few days prior to inpatient admission the patient had taken a high dose of metamizol due to an increasing pain syndrome with known rheumatoid arthritis. This correlates with the extremely high metamizol level ($c_{\text{Metamizol}}$ approximately 524 mg/L) which was present on admission.

The acute kidney failure to be ascertained on admission, as a consequence of which metamizol-induced interstitial nephritis is to be seen, which became evident approximately 24 hours after metamizol intoxication [9], was initially oliguric, then anuric. The following played an important part:

- 1.) the prostaglandins, whose synthesis is inhibited by non-steroidal anti-inflammatories and the consequently reduced glomerular capillary permeability could no longer be compensated by intrarenal, prostaglandin-mediated vasodilatation [15] and
- 2.) high serum myoglobin, which is excreted from a concentration of approximately 2 mg/L in the urine and thus causes a tubular obstruction through pigment cylinders as well as a direct tubule toxicity due to released iron ions [17]. In addition, myoglobin weakens the vasodilating effect of nitrous oxide [15].

Due to the haemodialyses and haemoperfusions, the urinary retention values (creatinine [decrease from 601 $\mu\text{mol/L}$ to 226 $\mu\text{mol/L}$, reference range 35-80 $\mu\text{mol/L}$], GFR [increase from 6.4 mL/min to 19.8 mL/min, reference range > 60 mL/min], urea [decrease from 38.0 mmol/L to 6.0 mmol/L, reference range 2.0-8.3 mmol/L]) were to be influenced positively; however, the patient remained anuric.

The decompensated metabolic acidosis, which was still to be ascertained at the time of admission, is to be viewed in connection with the acute kidney failure. The same proved to be treatment-resistant. As intracellular structures are destroyed and/or limited in function and enzyme systems (e.g. those of the respiratory chain) are still also blocked by acidosis, an impairment of multiple organ systems results with for example conversion to anaerobic metabolism combined with lactate development/lactic acidosis (initially lactate level almost normal at 2.4 mmol/L, then increasing pathologically to 32.0 mmol/L, reference range 0.1-2.4 mmol/L), as well as liver failure (correlating with the increase in the transaminases [increase from 0.23 $\mu\text{mol/s/L}$ to 89.65 $\mu\text{mol/s/L}$, reference range 0.10-0.56 $\mu\text{mol/s/L}$] and the bilirubin [increase from 3 $\mu\text{mol/L}$ to 25 $\mu\text{mol/L}$, reference range < 17 $\mu\text{mol/L}$] as well as the decrease in the thromboplastin time [decrease from 69% to 9%, reference range 70-120 %] and the high ammonia level ($c_{\text{ammonia}} = 111.2 \mu\text{mol/L}$ [reference range 16.0-53 $\mu\text{mol/L}$] with $t = 83 \text{ h} = 10 \text{ h pre-mortem}$).

The causes of the markedly and ultimately persistently massively increased myoglobin level (increase to $c_{\text{myoglobin}} = 16.58 \text{ mg/L}$, reference range 0.007-0.064 mg/L), which was also evident at the time of admission ($c_{\text{myoglobin}} = 7.01 \text{ mg/L}$, reference range 0.007-0.064 mg/L), in the form of rhabdomyolysis remain unclear. With assessment of current literature research a connection with the metamizol intoxication is not to be established. Only JÖRRES et al. [17] and VISWESWARAN et al. [18] describe that trigger situations for rhabdomyolysis can be, amongst others, drug-induced immobilisations, caused by for example cocaine, heroin, phencyclidine, fluvastatin, enflurane, succinylcholine, propofol. As a relevant traumatic origin is not identifiable in the patient's history, the decompensated metabolic acidosis with the resulting disturbances of intracellular processes within the musculature is possibly to be considered with regard to cause. Chronic acidosis causes at least muscular decay and reduces the albumin level [15]. Massive rhabdomyolysis can lead to acute kidney failure (see above).

The generalised convulsive seizures observed on the day of admission and the cardiac arrest requiring resuscitation are to be viewed as most probably the consequence of the uraemia and

the metabolic acidosis in the context of the acute kidney failure. In the case of the aforementioned patient it was from these uraemia complications that hypoxic brain damage resulted, which correlated with an increase in the NSE level (increase from 15 µg/L to 134 µg/L, reference range < 15 µg/L).

4. Discussion

Metamizol intoxications are clinically accompanied by e.g. clouding of consciousness. Patient's somnolence causing hospitalisation can be explained by the highly-toxic concentrations of active metamizol metabolites. Forced diuresis is recommended for such cases, but could not be performed because of existing anuria and acute kidney failure; the final decision was to carry out haemoperfusion twice (haemoperfusion charcoal, cellulose coated). Severe rhabdomyolysis has developed, Further haemodialyses and large doses of noradrenaline were administered but could not prevent the present lethal outcome.

5. Conclusions

The misuse potential for metamizol, which is not accepted officially, is to be reassessed, as the aforementioned case study shows. Due to extensive abuse of metamizol over many years with a tendency to dosage increase, an accumulation of the active ingredient occurred. The lethal outcome was not to be prevented despite maximum therapy.

6. References

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