SEVERE THEOPHYLLINE POISONING IN CHILDREN

Závažná otrava syntofylínom u detí

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Abstract
Theophylline poisoning in childhood is rare. Apart from accidental poisoning, caused by dosage miscalculation or unintentional ingestion, suicidal poisoning is especially dangerous. The authors present the case of a self-poisoning suicide attempt of a 12-year-old girl who ingested 40 – 50 capsules of sustained release Euphyllin (300 mg tablets) equivalent to approximately 214 mg/kg of theophylline. The clinical presentation of intoxication was extremely severe – seizures, unconsciousness, shock, pulseless ventricular fibrillation, rhabdomyolysis, hypokalaemia, and metabolic acidosis. Plasma concentration of theophylline was 233 mg/l. Symptomatic treatment along with early continuous elimination therapy (continuous renal replacement therapy, CRRT) in duration of 96 hours resulted in a rapid decrease of plasma concentration of theophylline (8.31 mg/l in 36 hours), stabilisation of circulation, resolution of metabolic disorder and the girl´s recovery with no neurological deficit (Tab. 1, Fig. 4, Ref. 13). *Text in PDF www.lekarsky.herba.sk.*
KEY WORDS: theophylline poisoning, CRRT.
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Abstrakt
Otrava syntofylínom v detstve je zriedkavá. Okrem náhodnej otravy spôsobenej nesprávnym výpočtom dávkovania alebo neúmyselným požitím je nebezpečná najmä samovražedná otrava. Autori uvádzajú prípad samovražedného pokusu 12-ročného dievčaťa, ktoré požilo 40 – 50 kapsúl eufylínu s predĺženým uvoľňovaním (300 mg tablety), čo zodpovedá približne 214 mg/kg syntofylínu. Klinický obraz intoxikácie bol extrémne dramatický – záchvaty, bezvedomie, šok, bezpulzová ventrikulárna fibrilácia, rabdomyolýza, hypokáliémia a metabolická acidóza. Plazmatická koncentrácia teofylínu bola 233 mg/l. Symptomatická liečba spolu s včasnou kontinuálnou eliminačnou terapiou (kontinuálna renálna substitučná liečba, CRRT) v trvaní 96 hodín viedla k rýchlemu poklesu plazmatickej koncentrácie teofylínu (8,31 mg/l za 36 hodín), stabilizácii obehu, vymiznutiu metabolickej poruchy a zotavenie dievčaťa bez neurologického deficitu (tab. 1, obr. 4, lit. 13). *Text v PDF www.lekarsky.herba.sk.*
KĽÚČOVÉ SLOVÁ: otrava syntofylínom, CRRT.

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Introduction

Theophylline poisoning in childhood is rare. It is mainly due to the substantial modification of treatment of bronchial obstruction, where theophylline has been almost fully replaced by β_2-agonists (salbutamol, terbutaline). This is primarily due to the higher bronchodilating effect of β_2-agonists especially when administered by inhalation of aerosol (salbutamol) as well as a narrow therapeutic index of theophylline, which could easily be overdosed – therefore, its blood concentration level should be monitored. In real-life setting intoxication of children occurs with errors in treatment dosage and management, as well as random or suicidal ingestion.

Symptoms of intoxication are most likely to occur when plasma concentration of theophylline exceeds 20 mg/l, but may also occur with the concentration of 10 – 15 mg/l. Serum concentration around 50 mg/l is considered lethal. The most common symptoms include disorders of the gastrointestinal tract, central nervous system, and cardiovascular system. Toxic effects are presented in Table 1.

Table 1. Symptoms of theophylline poisoning.

Gastrointestinal disorders	nausea, vomiting, diarrhoea
Circulation	tachycardia, supraventricular and ventricular arrythmia, hypotension
Central Nervous System disorders	CNS irritation – vomiting, hyperventilation, agitation, tremor, seizures
Metabolic disorders	hypokalaemia, hyperglycaemia, hypophosphatemia, hypocalcaemia, metabolic acidosis or respiratory alkalosis
Rare	psychosis, acute pancreatitis, rhabdomyolysis, acute renal failure

There are no antidotes to reverse the theophylline poisoning; therefore, oral decontamination with activa-

ted charcoal is used as well as a quick removal of theophylline by elimination methods in severe cases of poisoning along with the symptomatic therapy to affect the individual symptoms. Oral administration of activated charcoal will decrease the absorption of theophylline from the stomach (decontamination). Repeated oral doses of activated charcoal will increase the elimination of theophylline from the gastrointestinal tract by breaking of the enterohepatic cycle (***gastrointestinal dialysis)***. Numerous studies have demonstrated the good effectiveness of the treatment. When theophylline concentrations exceed the level of 80 mg/l, or the patient develops hypotension, seizures, cardiac rhythm disorder, or the administration of active charcoal is limited by vomiting, elimination ***methods are indicated*** – such as haemoperfusion, haemodialysis, and continuous veno-venous haemodialysis (CVVHD). Using elimination methods to reduce theophylline concentrations proved very effective. The treatment result is mainly based on how quickly the elimination methods were introduced, duration of hypotension and seizures etc. A combination of several unfavourable factors (hypotension, seizures, dysrhythmia, hypokalaemia and other) may lead to various degrees of neurological damage, and severe poisoning may be fatal.

Case report – a 12-year old girl

Family History. Disrupted family circumstances have adversely affected the girl´s development. She was followed by a psychologist; never seen by a psychiatrist.

Current Disease. On 24th May 2022 at approximately 2 p.m. the girl ingested 40 – 50 tablets of Euphylline (300 mg), her mother´s medication. She had no symptoms at home, no fever any or signs of a respiratory tract infection, no vomiting; no ingestion of alcohol or any other drugs were noted.

During the transfer by the urgent medical assistance her blood pressure was 135/90 mm Hg, PP 140/min., blood oxygen saturation level was 98%, GCS 15 points. IV line secured, and 5 mg of Betaloc, a selective β1-blocker, was administered.

Urgent admission department. Second IV line secured. Blood sampling was performed for biochemical parameters, blood count, haemocoagulation and toxicology, including theophylline levels. On admission, the patient was restless, irritant, prone to hypotension, and tachycardia was noted. She was referred to the Department of Paediatric Anaesthesiology and Intensive Care Medicine.

Department of Paediatric Anaesthesiology and Intensive Care. On admission at 17:00 h (3 hrs after drug ingestion) the patient was conscious, well oriented, obesity and scars after automutilation were noted, tachycardia 154/min, hypotension 75/35 mm Hg, good hydration, capillary return within 2 seconds, and periphery warm. Oral administration of activated charcoal was thwarted because of vomiting. A lethal dose of theophylline (>100 mg/kg), estimated based on the ingestion of 40 – 50 capsules of Euphylline (approximately 214 mg/kg) resulted in an immediate preparation for extracorporeal elimination, as there is no antidote for the intoxication.

The patient was clinically deteriorating. After 5.5 hours from the ingestion, she presented with loss of consciousness and seizures (grand mal) with oxygen desaturation (SpO_2 40 %). Endotracheal intubation, artificial lung ventilation (ALV) as well as anticonvulsive treatment was initiated. Within the next few minutes, the patient developed hypotension (xx), sinus tachycardia (200/min), leading from pulseless ventricular tachycardia to fibrillation. Immediate extended cardiopulmonary resuscitation (CPR) called for a repeated defibrillation (3 times) with the recovery of sinus rhythm and clinical improvement after 30 minutes. Cardiopulmonary resuscitation (CPR) was performed during which the elimination process had been initiated by continuous veno-venous hemodiafiltration (CVVHDF), resulting in reduction of the initial theophylline level of 233 mg/l to 44.90 mg/l within 20 hours and to 8.31 mg/l after 36 hours (Fig. 1). Catecholamine support was required during the whole elimination therapy. Due to the risk of adrenal insufficiency, the cortisol level was monitored. The results from the day 3 of hospitalisation suggested temporary central hypocorticism – ACTH 3.3 ng/l (reference values between 7.0 and 63.0), cortisol 83 nmol/l (reference values between 100 and 480), likely caused by hypoperfusion and hypoxia of the central nervous system during CPR. Serum cortisol level resolved within seven days of hospitalisation due to the replacement therapy. Direct toxic cardiac damage was confirmed by an increased level of cardiac enzymes such as NT pro BNP and hs-c Troponin I (Fig. 2). After a decrease of the theophylline concentration, CVVHDF had to be continued due to the early onset of rhabdomyolysis. Nine hours after theophylline ingestion, creatine kinase level was 388 ug/l, and myoglobin level was 3470 ug/l (Fig. 3, 4). The total CVVHDF duration was 95 hours. Myoglobin concentration resolved until Day 7 of hospitalisation. Biochemic results have shown hypokalaemia (2.4 mmol/l lowest concentration), hyperglycaemia (20.9 mmol/l highest concentration), metabolic acidosis (lowest pH 6.77 during CPR) and increased lactate concentration (highest 23 mmol/l during CPR) with a resolution in 48 hours. The girl was transferred to the general paediatric department on Day 8 of hospitalisation.

Discussion

Theophylline poisoning was first described in 1950. In 1956, White and Daeschner have published the treatment results in 4 of their own cases and 16 cases from other authors. Death was declared in 4 children. With regard to frequent use of theophylline in the past, the incidence of poisoning was considered low. Nevertheless, it has also been emphasized that with the first signs of excitation, irritability, vomiting, muscle twitching and paleness the possibility of toxicity must be assumed. Overlooking these symptoms can

Figure 1. Serum teophylline (mg/l).
Obrázok 1. Plazmatická hladina teofylínu (mg/l).

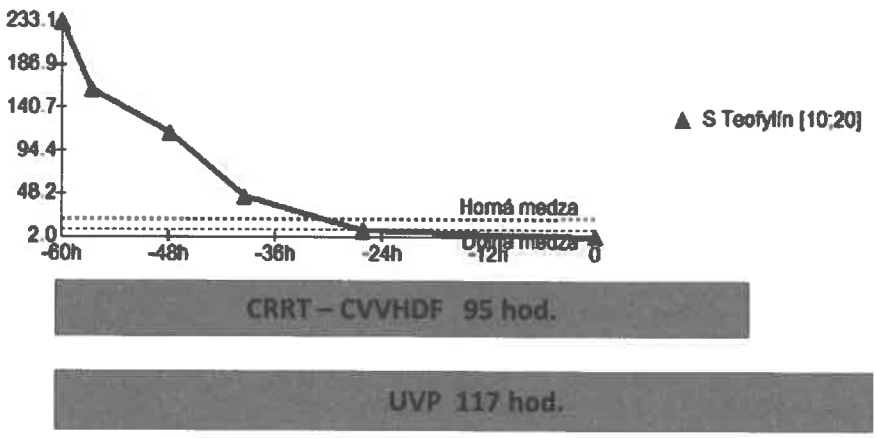


Figure 2. Cardiac enzymes (NT pro BNO, hs-c Troponin I (ng/l)).
Obrázok 2. NT pro BNO, hs-c Troponin I (ng/l).

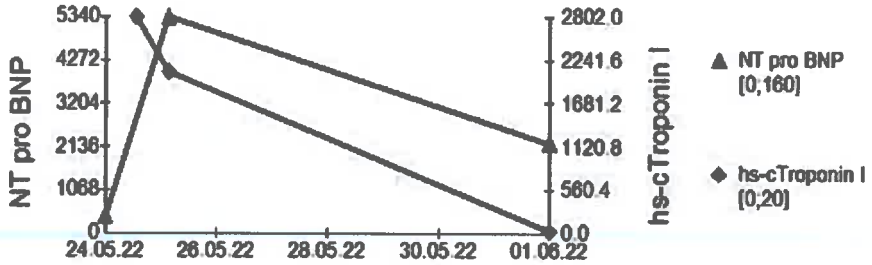


Figure 3. Creatin kinase (µg/l).
Obrázok 3. Kreatinkináza (µg/l).

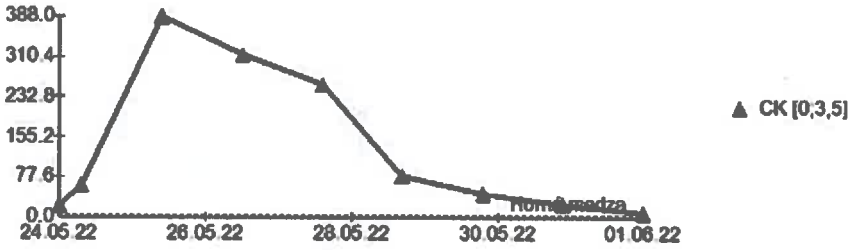
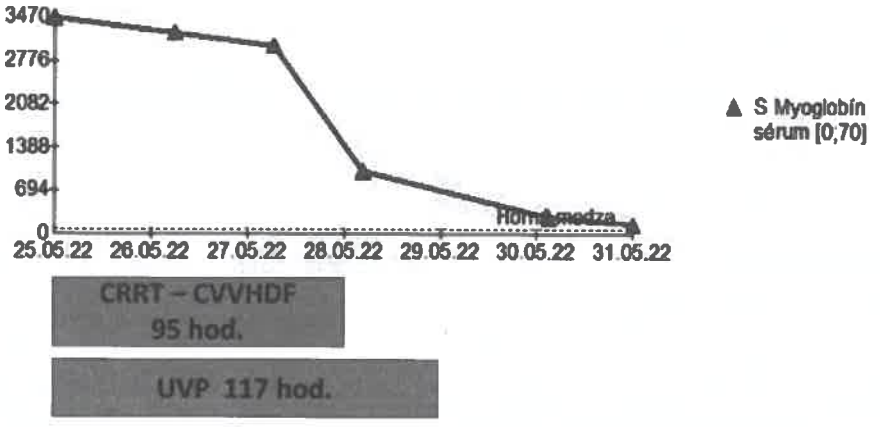


Figure 4. Plasma concentrations of myoglobin (µg/l).
Obrázok 4. Plazmatická koncentrácia myoglobínu (µg/l).



lead to the development of severe intoxication or death (1).

Subsequently, in 1957 Hyman collected 33 children with theophylline intoxication, 10 of which had died. The children were between 6 months and 6 years of age, with average age of 27 months. 82 % of children were under 3 years of age. The most constant and earliest symptom was restlessness, almost always followed by vomiting. Immediate treatment discontinuation was recommended otherwise irreversible damage or death most probably occurred (2). The few case reports came from the period of limited supportive therapy before the

use of activated charcoal in decontamination and its repeated administration to discontinue the enterohepatic circulation of theophylline (gastrointestinal dialysis).

The first successful cases of elimination of theophylline originate from the 1970s and 1980s in which haemoperfusion with coated activated charcoal was used (3, 4, 5). It has been confirmed that haemoperfusion may shorten the duration of clinical symptoms, decrease morbidity and mortality, and is relatively safe. In the same period studies had been accumulating that confirmed the decontamination effect of oral administration of activated charcoal in repeated doses using the mechanism of disruption of enterohepatic circulation of theophylline (6, 7). The indication for haemoperfusion with coated activated charcoal was formulated based on the clinical symptoms and theophylline plasma concentrations – >100 mg/l in an acute intoxication and > 60 mg/l in a chronic intoxication.

In the beginning of the 1990s Stegeman and Jordans summarised the existing knowledge on theophylline intoxication in their own case report. Hemoperfusion was considered the therapy of choice at theophylline plasma concentration > 80 mg/l even in the absence of the symptoms of severe toxicity (8). The first successful hemoperfusion in the treatment of theophylline intoxication in Slovakia was performed by professor Mydlík et al. (9). Later studies of larger patient groups have reported haemodialysis as an alternative modality of hemoperfusion, although its effectiveness was lower by 40 % at the same elimination time. However, there was no evident difference in survival results, while haemoperfusion was accompanied by more frequent fatal complications (10).

The development of dialysis therapy has substantially improved the treatment choices of severe theophylline intoxications because the elimination methods have become part of the intensive care medicine. The available continuous elimination therapy (CRRT) ensures a 24-hr control of internal environment (body fluids) while eliminating all dialysable endogenous and exogenous toxins. Their main disadvantage is a gradual and relatively slow resolution of body fluids composition; therefore, they are not considered ideal modalities in intoxications with dialysable poor protein-bound molecules. The recommendation issued by the expert group for extracorporeal therapy of theophylline intoxication has specified the criteria for elimination therapy: plasma concentration > 100 mg/l, seizures, life-threatening dysrhythmias or shock, increase in concentration, and clinical deterioration despite optimal therapy. Intermittent dialysis is the preferred elimination method, and elimination is discontinued at theophylline concentration < 15 mg/l (11). In this case, the continuous elimination method was indicated because of its immediate availability and because haemodialysis is a high-risk procedure in the presence of acute cardiac shock. The rate of decline of theophylline concentration was comparable with the case reports from Turkey and the US (12, 13). Indication of the appropriate elimination method in children should always be adjusted to the distribution volume of the toxin, patient´s clinical status and the availability of the elimination method.

Remarkable treatment results in this case report include:

- Survival of intoxication with theophylline plasma concentration of 233 mg/l after ingesting the lethal dose (approx. 214 mg/kg), that extends far beyond the concentrations in children and adults previously published in literature.
- Early elimination by CVVHDF 4 hrs after the ingestion of Euphylline during CPR has quickly and effectively decreased plasma concentrations of theophylline to 8.31 mg/l after 36 hours.
- Development of transitory central hypocorticism as a possible consequence of CNS perfusion disorders during the resuscitation phase of the therapy, which resolved after replacement therapy with hydrocortisone.
- Cardiotoxicity of theophylline resulted both in dysrhythmias and direct damage of myocardial cells documented by an increase in cardiac enzymes.
- Recovery with no neurologic deficit.

Conclusion

Early comprehensive therapy of the symptoms of theophylline intoxication associated with gastrointestinal, central nervous system, circulation and metabolic disorders (hyperglycaemia, metabolic acidosis) together with early initial elimination may lead to the recovery even in cases of fatal intoxications. Early start of the elimination therapy plays a significant role and results in a rapid decrease of theophylline concentrations with a resolution of metabolic disorders. The continuous veno-venous haemodiafiltration (CVVHDF) we opted for was successful despite a slower decrease of theophylline concentration when compared to haemodialysis, which remains a recommended method of elimination in theophylline poisoning. However, the availability of CRRT in intensive care units enables an immediate elimination that is fundamental to successful therapy.*

*Compliance with Ethics Requirements: The authors declare no conflict of interest regarding this article. The authors declare, that all the procedures and experiments of this research respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008 (5), as well as the national law.

Conflict of interest: The authors declare no conflict of interest.

Informed consent: Informed consent was obtained from all individual participans included in the study.

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