ORIGINAL ARTICLE

Paracetamol poisonings in the Czech and Slovak Republic and N-acetylcysteine treatment. Data analysis

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Abstract

OBJECTIVES: Paracetamol overdose belongs to frequent calls to Toxicological Information Centre (TIC) in the Czech Republic and to the National Toxicological Information Centre (NTIC) in Slovakia. The aim of the study was to evaluate outcomes and side effects of paracetamol overdose in both countries.

METHODS: Data concerning paracetamol poisoning extracted from TIC and NTIC databases 2000–2013 and discharge reports were analysed. Numbers and outcomes in patients presenting within 24 hours of a single paracetamol overdose were compared in relation to 3 paracetamol concentration bands (≤100 mg/l, 100–149 mg/l, and ≥150 mg/l).

RESULTS: 5397 inquiries concerning paracetamol were recorded in TIS and NTIC. Data from 196 discharge reports with plasma level were studied. Median age of the patients was 18 (0.2–86) years. Eight/196 (4.1%) patients developed side effects after N-acetylcysteine (NAC) administration. 120 cases fulfilled time criteria of the study and were divided into 3 groups, where 55.7%, 73.1% and 96.9% patients have been treated with NAC. Among these 120 patients, favourable outcome was seen in 100%, 100%, and 92.8%, respectively. One death due to suicidal attempt with plasma level 407 mg/l presenting at 20 hours has been recorded among 120 patients. No patient without NAC treatment died due to acute overdose and plasma concentration ≤150 mg/l at 4 hours.

CONCLUSIONS: These data support the opinion that NAC should not be used in patients with <149 mg/l levels in absence of higher risk factors because of very low risk of hepatotoxicity on one side, and side effects on the other side.

Abbreviations:
ADRs - Adverse drug reactions
ALT - Alanine aminotransferase
AST - Aspartate aminotransferase
CYP2E1 - Cytochrome P450 2E1
i.v. - Intravenous/ly
INR - International normalized ratio
MHRA - Medicines and Healthcare Products Regulatory Agency
NAC - N-acetylcysteine
NAPQI - N-acetyl-p-benzoquinonimine
NTIC - National Toxicological Information Centre (Slovak Republic)
PT - Prothrombin time
TIC - Toxicological Information Centre (Czech Republic)

INTRODUCTION

Overdose of paracetamol (known as acetaminophen in the US and Canada) is very common as more than 137 000 enquiries were made in the US poison centers concerning paracetamol overdose in 2011 (Bronstein *et al.* 2012). Besides other pharmaceuticals such as CNS affecting drugs (Urban *et al.* 2013) paracetamol is also a frequent drug used for suicidal purposes in Central Europe (Zakharov *et al.* 2013a), especially in adolescents (Zakharov *et al.* 2012b, 2013b). Paracetamol can be found in multiple combined analgesic preparations and the strengths vary considerably. It was shown that most deaths originate from the paracetamol part of the combination products in patients using these products intentionally for overdose (Doyon *et al.* 2013).

The major manifestation of paracetamol poisoning is hepato-and nephrotoxicity leading to liver encephalopathy and death (Hinson *et al.* 2010). Main mechanism is the production of intermediate toxic metabolite N-acetyl-p-benzoquinonimine (NAPQI) via minor oxidative pathways (P450 enzymes, mainly CYP2E1) which requires glutathione for further biotransformation to non-toxic metabolites. After glutathione supplies are exhausted, this toxic metabolite binds to sulfhydryl-containing proteins in the liver cell and cause lipid peroxidation disrupting the cell membrane. These events lead to cell death and any organ containing P450 enzymes can develop toxic damage (e.g. liver, kidneys, heart or pancreas). Acute renal failure is a recognized manifestation of paracetamol toxicity, but it is less common and its detecting is more complicated especially within the first 48 hours after ingestion (Waring *et al.* 2009). Finally, paracetamol overdose may result in multiple organ failure with encephalopathy, commonly fatal (Olson *et al.* 2012).

The crucial investigation is the paracetamol plasma concentrations enabling to timely predict the risk of liver failure, because early after overdose, there are usually no other symptoms than anorexia, nausea, or vomiting. After 24–48 hours, when AST and ALT begin to rise, hepatic necrosis becomes evident. If acute fulminant hepatic failure occurs, coma and death may ensue. Encephalopathy, metabolic acidosis, and a continuing rise in prothrombin time/international normalized ratio (PT/INR) indicate a poor prognosis (Butterworth 2011). Acute renal failure occasionally occurs, with or without concomitant liver failure (Olson *et al.* 2012). However, biochemical markers of liver and kidney damage appear rather late and cannot be used for the decision on the antidotal treatment (Hinson *et al.* 2010; Prescott *et al.* 1979). Hyperammonemia is a major contributing factor to the encephalopathy associated with liver disease. It is now generally accepted that hyperammonemia leads to toxic levels of glutamine in astrocytes. The mechanism by which excessive glutamine is toxic to astrocytes is controversial. Nevertheless, there is strong evidence that glutamine-induced osmotic swelling, especially in acute liver failure, is a contributing factor according to the osmotic gliopathy theory (Brusilow *et al.* 2011).

N-acetylcysteine (NAC), a sulfhydryl donor is considered the antidote of choice for paracetamol poisoning (Prescott *et al.* 1979). The effectiveness of NAC depends on the early treatment. Its benefit is maximal if started within 8–10 hours after ingestion and of diminishing value after 12–16 hours (Isbister & Duffull 2013). Hemodialysis effectively removes paracetamol from the blood but is not generally indicated because the risk of complications is higher and the antidotal therapy is very effective. Dialysis should be considered as early as possible for massive ingestions with very high levels (e.g. above 1000 mg/l) complicated by coma and/or hypotension (Olson 2012). Treatment of hepatic encephalopathy includes a low protein/high carbohydrate diet and lactulose administration. Patients with late admissions and fulminant liver failure may require liver transplant (Wikitox 2014). While vomiting is a more frequent side effect if NAC is orally administered and a longer course of treatment is needed, i.v. administration is preferred, which however may lead to more serious ADRs. Their typical clinical features include nausea, vomiting, abdominal pain, flushing, pruritus, urticaria, angioedema, breathlessness, bronchospasm (Wikitox 2014). Further disadvantage of the conventional i.v. NAC regimen is also the complexity of dosing which results in high risk of medication errors (Thanacoody *et al.* 2013, Zakharov 2012a,b).

The indication for NAC treatment is a toxic level of serum paracetamol according to the Rumack-Matthew nomogram with 150 mg/l paracetamol level at 4 hours after ingestion (Poisindex, Wikitox). In addition, in patients considered to be at high risk, the nomogram uses a high risk treatment line that starts at 100–149 mg/l level at 4 hours after ingestion and runs parallel to the non-high-risk line. These high risk conditions include situations when the overdose is repeated or staggered, the exact timing is unclear, the presentation is delayed, the patient is treated with CYP2E1 inducing drugs (isoniazid), has malnutrition or is a chronic alcohol user (Rumack 2004, Ferner *et al.* 2011). In addition, local and historical practices lead to differences in the guidelines of the countries (Van Pelt & Mostin 2014).

A significant change in the guidelines was introduced in September 2012 when licenced indication for NAC by Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK was changed so that all patients with a plasma paracetamol concentration above 100 mg/l (4 hours post ingestion) nomogram treatment line due to acute paracetamol overdose should be treated, regardless of the presence of high risk factors (MHRA 2012).

Until 2012, TIS and NTIC recommended the treatment according to the Rumack-Matthew nomogram with 150 mg/l paracetamol level at 4 hours after ingestion. In 2012, the new UK guideline has been introduced also in the toxicological database Toxbase, subscribed in Poison Control Centres of several countries in Central Europe.

The objective of this report is to evaluate the management of paracetamol overdose in two Central European countries, Czech Republic and Slovakia in the light of new UK guideline.

MATERIALS AND METHODS

Retrospective review of all cases of paracetamol intoxications reported to Czech TIC and Slovak NTIC from 2000 to 2013 was carried out. The data were extracted from TIC and NTIC electronic database and discharge reports from the hospital.

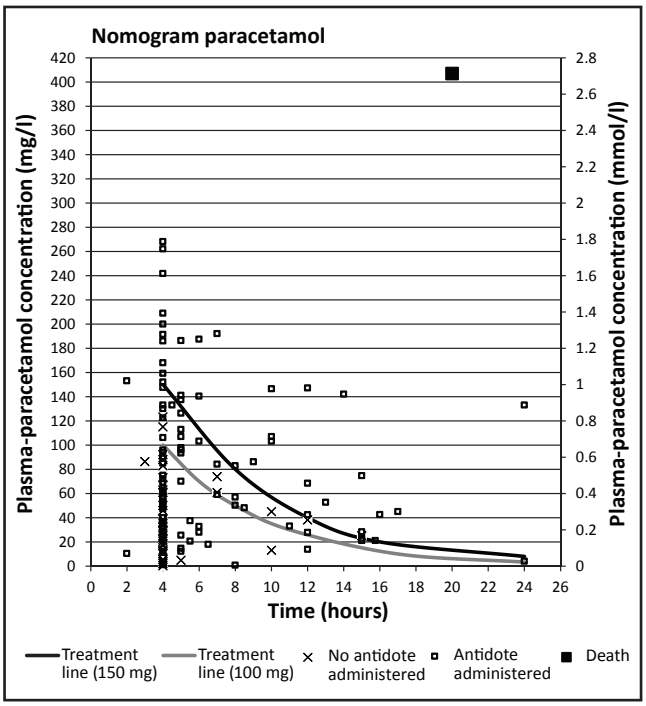

Fig. 1. Rumack-Matthew nomogram indicating all subjects with paracetamol overdose with known time of acute ingestion and paracetamol plasma levels reported to TIC and NTIC within the period 2000-2013. Paracetamol concentration is shown on the y axes (as both mmol/l (right hand axis) and mg/l (left hand axis) and the time from overdose on the x axis.

Besides other information recorded to the database, following variables were extracted: co-ingested medication/alcohol, time interval from intoxication to the blood collection, paracetamol levels, antidote administration, values of AST/ALT and INR, hospital stay duration and the outcome at the discharge. In parallel, the clinical features of ADRs were investigated. Finally, data for patients presenting within 24 hour of an acute timed single paracetamol overdose were plotted into the nomogram. Antidote use and the outcome in relation to 3 paracetamol concentration bands (≤100 mg/l, 100–149 mg/l, and ≥150 mg/l) were analysed.

RESULTS

Over 5000 inquiries concerning paracetamol were recorded in TIS and NTIC. Discharge reports of paracetamol overdose with plasma paracetamol measured have been collected in 196 patients (113 in the Czech Republic and 83 in the Slovak Republic). Median age of the subjects was 18 (0.2 to 86) years, females prevailed (60.2%). The most frequent reason of intoxication was a suicidal attempt (72.5%) followed by unintentional overdose (13.8%), medication error by layman (10.2%), medication error by health care professional (0.5%) and unknown reason (3%) in the remaining cases. Median time from ingestion to plasma collection was 4.5 (2–72) hours. By the time of discharge from the hospital, 193 patients recovered. Among them 79.5% recovered fully and 18.9% still had one or more laboratory signs of the poisoning, most commonly AST and/or ALT exceeding the upper reference range, or prolonged INR. Elevation of AST and/or ALT due to hepatic injury following paracetamol overdose was observed in 30.3% patients and the rise of INR occurred in 36.3% cases. Among 30.1% patients who co-ingested other drugs, full recovery occurred in 88.1% cases. Co-ingestion of ethanol was less frequent (19.4%), and full recovery was the lowest (in 84.2% subjects only).

All available paracetamol plasma levels in patients with known time of acute poisoning were then plotted in Rumack-Matthew nomogram (see Figure 1). Sixty-one/120 (50.8%) subjects have been classified in the <100 mg/l band group, 26/120 (21.7%) in the 100–149 mg/l band group, and 33/120 (27.5%) in the ≥150 mg/l band group. In these groups, 34/61 (55.7%), 19/26 (73.1%) and 32/33 (96.9%) patients, respectively, have been treated with NAC. Eight patients developed ADRs after NAC administration such as dyspnoea (5×), rash (4×), vertigo (2×), vomiting (2×), face flushing (1×), cough (1×), pruritus (1×) and bronchial mucus hyperproduction (1×). The median length of hospitalization of patients treated with NAC was 3 (1–27) days.

Fatal outcome due to paracetamol overdose with hepatorenal failure with encephalopathy was recorded in 3/196 patients. Only one woman could be plotted into the nomogram as she had plasma paracetamol

measurement within 24 hours of the acute single paracetamol overdose. This 33 y-o psychotic patient committed a suicide with 50 g of paracetamol. She was admitted to the hospital 20 hours later, her paracetamol plasma level was 407 mg/l, i.e. the highest (see Figure 1). NAC treatment was started, in spite of it she developed liver failure, pulmonary oedema and massive brain oedema and died three days later. Further two patients died but their data could not be included in the nomogram. There was a 37-y-o man who had ingested an unknown amount of paracetamol in a suicidal attempt at least 24 hours earlier. He was found at home in coma, he developed severe metabolic acidosis, rhabdomyolysis, liver and renal failure and died three days later. Last patient, 35-y-o man had been treating himself with 8 g paracetamol daily for toothache for 7 days. He was admitted to the hospital with icterus, hepatorenal failure, and severe metabolic acidosis. His paracetamol plasma level on admission was 3 mg/l, NAC was not administered. He was on the list for liver transplant but he developed multiorgan failure and died within two days.

DISCUSSION

The outcome of the subjects, hospitalized for paracetamol overdose in the Czech and Slovak Republic and consulted with the Poison Controls Centres of the two countries was very favourable. It concerns all paracetamol concentration bands, as the recovery and survival was in the range from 92.8% to 100%. Even in the subjects, who still had AST and/or ALT exceeding the upper normal range at the time of discharge, prognosis is expected to be favourable due to centrizonal character of liver damage with a high potential to regenerate. The outcome of the patients is known to be good in case they survive 4–5 days after ingestion, rarely also in patients with hepatic encephalopathy (Brusilow *et al*. 2011).

It was shown, however, that in spite of the recommendation of TIS and NTIC of the NAC treatment according to the Rumack-Matthew nomogram, treatment has been used very frequently. In the paracetamol plasma band 100–149 mg/l, it was less frequent comparing to the UK after the limit change (73.1% vs. 94%), respectively (Bateman 2014c). Rather surprisingly, NAC use in our patients in ≤100 mg/l paracetamol plasma band was even 7 fold higher (55.7% vs. 8%) comparing to the UK. It shows that the new standard, introduced also into the toxicological database Toxbase and used in both Czech Republic and Slovakia, has not been the key factor for this conservative approach. The patients were being treated presumably because they were considered at high risk for a health condition or there was some uncertainty about the timing of the overdose in these subjects. Other possible explanations may be a technical problem and NAC treatment initiation before the results of paracetamol levels measurements become available.

The minimum duration of the infusion of regimen is 21 hour period (Prescott *et al.* 1977) which is then prolonged in subjects with elevated liver enzymes. Median hospitalization of the patients from this study treated with NAC was 3.0 (from 1 to 27) days. Very probably, not all Czech and Slovak patients received the full treatment regimen, but this information could not be found in the most of the discharge reports. In small hospitals the plasma paracetamol level was not available within a short time interval (especially in the night) to be used for the decision. Therefore, NAC treatment was initiated, and then withheld several hours later in case the paracetamol level was proven to be low.

Findings of a recent study confirm that ADRs, particularly vomiting and anaphylactoid reactions are associated commonly with the standard UK regimen for NAC administration (Bateman *et al.* 2014b). In addition, extending the time of the initial NAC infusion from 15 min to 1 hour based on the new recommendation of MHRA turned out to have no special benefit on ADR profile and it only extends later symptoms (Bateman *et al.* 2014b). It is also important to note that anaphylactic reactions are more common in patients with low paracetamol plasma levels and that some groups, e.g. asthmatics are more likely to develop ADRs (Pakravan *et al.* 2008, Schmidt & Dalhoff 2001). Therefore as more patients with low paracetamol concentrations are treated, anaphylactic reactions are likely to become a bigger problem (Bateman *et al.* 2014a). Hepatic failure was reported in a patient after receiving 8 doses of paracetamol orally at intervals of at least 4 hours over a 48 hour period, i.e 109 mg/kg/24 hours (Elamin & Thanacoody 2013, Brown & Thanacoody 2013) which is in agreement with our data as medication error led to a fatal outcome in our 3rd patient.

Most European countries including Germany did not adopt new UK criteria and yet the number of fatal cases of paracetamol overdose is comparable to other countries (Stürer *et al.* 2008). Similarly, Australian Wikitox and U.S. Poisindex keep the 150 mg/l threshold for paracetamol treatment (Wikitox 2014, Poisindex 2014) to avoid higher incidence of ADRs after antidote administration and increased treatment costs associated with longer hospitalization.

Bateman *et al.* compared the numbers of admissions and NAC treatment in three UK hospitals before and after the change of the threshold for NAC (Bateman *et al.* 2014c). It was shown that in the group of patients with paracetamol plasma levels in the band 100–149 mg/l, hospital admissions increased by 64.1% and number of NAC treatment by 126.7%. The detailed MHRA review identified merely one death in the UK for patients in this concentration band who had not initially been treated with NAC over the last 20 years and they suppose that additional 110,000 episodes would have required NAC treatment to prevent only one single death (MHRA 2012). In addition, it has been estimated that the cost of saving this single life has been

approximately 28 million USD. Therefore, treatment with subjects under 100 mg/l is not medically justified and should be avoided, as it is a group without the risk of hepatotoxicity and higher risk of ADRs (Bateman *et al.* 2014c).

The limitation of this study is that Poison Control Centres data do not cover all paracetamol poisonings in the country. More experienced physicians and those from bigger teams do not need to consult the treatment. Consequently, more inquiries may have come from the smaller hospitals with limited availability of the laboratory analysis. This may have also increased the percentage of NAC treatments in the two lower bands (≤100 mg/l, 100–149 mg/l), due to the necessity to start the NAC therapy within 8 hours after overdose.

CONCLUSIONS

Our findings based on the data from the Czech and Slovak Republic in the years 2000–2013 document a favourable outcome of paracetamol poisonings in subjects in all paracetamol plasma concentrations bands on one side. According to the discharge reports, only 3/196 patients have died. On the other side, this study shows a very conservative approach to the management of paracetamol overdose in the Czech Republic and Slovakia. Obviously, this approach has not been initiated by the new UK guideline, the reason is probably a technical problem and the necessity to make decision about NAC treatment initiation before the results of paracetamol levels measurements became available.

Even NAC treatment at the levels under 150 mg/l in the absence of individual risk factors has been repeatedly criticized in the UK and there are sufficient data proving it leads to futile hospitalizations and high financial expenses that are not medically justified. Because paracetamol poisoning is very common in Central Europe, higher availability of laboratory settings to measure paracetamol in plasma is needed to decline the frequency of treatment in subjects in whom it is not indicated.

In conclusion, to our opinion, NAC treatment in the 100–149 mg/l nomogram range should be limited to the subjects who fulfil criteria of high risk category, uncertainty of timing of the overdose, including those with staggered paracetamol intake. Others should be treated only in case of ≥150 mg/l plasma level according to the Rumack-Matthew nomogram. There are sufficient literature data from the UK and other countries to support this guideline. This approach may prevent not only futile expenses and hospital workload, but also ADRs.

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