Trends in CNS affecting drugs in the calls to the Toxicological Information Center from 1997 to 2012

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ORIGINAL ARTICLE

Abstract

OBJECTIVES: To analyze the number and trends in calls to the Toxicological Information Center (TIC) concerning pharmaceutical poisoning retrospectively during the past 15 years and to compare selected characteristics of the poisonings.
DESIGN: Inquiries arising from drug poisonings in the years 1997–2012 were extracted and evaluated from the Czech database recording the consultations of TIC specialists. In addition, their cause, severity and dose evaluation (data electronically collected after 2005) were compared in the years 2005–2012 using standard statistical methods.
RESULTS: During 15 years total 152,649 calls due to all types of potentially toxic agents were recorded in the TIC database. Central nervous system (CNS) affecting drugs represented 39.8% of calls due to all pharmaceutical poisonings. The proportion of adults was 72.2% and women comprised 64.4% of all patients. Whereas the number of calls caused by poisoning with tricyclic antidepressants (TCAs) and barbiturates decreased (by 366.7% and 340%, respectively), the calls due to selective serotonin reuptake inhibitors (SSRIs) and benzodiazepines overdose increased (by 1347.4% and 359.8%). The dose of CNS affecting drugs in 2005–2012 was considered lethal in 14.6% of the inquiries due to barbiturates and 8.6% due to TCAs, but only in 1.6% calls due to SSRIs and 0.5% of benzodiazepines. The highest percentage of medications errors was found during the treatment with barbiturates (16.4%).
CONCLUSIONS: The current drugs prescription with improved safety profiles brings the beneficial effect of lowering the severity of poisonings and better prognosis of intoxications as observed in the TIC statistics.

Abbreviations:
CNS   - central nervous system
OA   - other antidepressants
SSRIs   - selective serotonin reuptake inhibitors
TCAs   - tricyclic antidepressants
TIC   - Toxicological Information Center

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INTRODUCTION

The Toxicological Information Center (TIC) is the only toxicology unit of its kind situated in the Czech Republic where the population is over 10 million. The TIC provides health care personnel and laypersons with medical information concerning the toxicity of a broad range of substances (drugs, food supplements, chemicals), household products, plants, mushrooms, snake venoms, etc. and recommends the treatment of acute poisonings. Each phone call is registered in a specially designed database so that these calls may be used afterwards for further follow-up.

The aim of this report is to analyze the trends in the calls to the TIC over the past 15 years concerning poisoning due to central nervous system (CNS) affecting drugs in terms of the numbers of drug overdoses and by using characteristics such as prognosis, dose severity and reason for exposure based on the information obtained from the call inquirers.

Antidepressants appear in the top list of substance categories associated with reported fatalities – 103,041 cases in 2010 and 107,528 cases in 2011 were reported in the USA alone (Bronstein *et al.* 2011; Bronstein *et al.* 2012). The studies of relative mortality from overdose of antidepressants have shown that the number of deaths per million prescriptions have been lower for selective serotonin reuptake inhibitors (SSRIs) than for tricyclic antidepressants (TCAs) (Whyte *et al.* 2003). TCAs remain a very common cause of fatal pharmaceutical poisoning as a result of their cardiovascular toxicity manifested by electrocardiography abnormalities, hypotension and dysrhythmias on one side, and CNS toxicity causing coma and convulsions on the other (Bateman *et al.* 2005; Thanacoody & Thomas 2005). However, the situation is more complex as there are wide differences not only between the classes of antidepressants, but within classes, as well (Henry 1997; Hawton *et al.* 2010; Manakova & Hubickova 2011; Horacek *et al.* 2012).

Although it is undeniable that benzodiazepines show a much better safety profile than obsolete barbiturates and some studies even revealed their positive effect in terms of reducing toxicity if co-ingested with TCAs (Eizadi-Mood *et al.* 2012), there is evidence that alprazolam and other benzodiazepines may induce suicidal behavior (Montgomery *et al.* 1989).

MATERIALS AND METHODS

Data concerning CNS affecting drugs have been extracted from the database of the TIC for the years 1997 through 2012, i.e. dataset of electronic forms filled in by the toxicologists during each phone call of a healthcare specialist or a lay person. Recorded information includes the patient's and the medical facility's identification data, time of exposure, patient's age, gender, toxic agent, route of exposure, dose, symptoms,

severity, reason of exposure and, finally, the treatment recommended or elimination method to be used. The total number of inquiries and their trends during these years have been studied and compared among the groups of CNS affecting pharmaceuticals. After 2005, more detailed characteristics of the cases (such as reason of poisoning/evaluation/ and prognosis) were introduced in the database of the TIC specialists. Therefore, these additional parameters were compared in the years 2005–2012.

A readily identifiable subset of calls concerning poisonings due to CNS affecting drugs was selected. From the initial dataset, only those intoxications that were caused by a single toxic agent (i.e. monopoisonings) were involved in our study. If the patients were exposed to multiple drugs, these reports were excluded.

Severity of the symptoms was classified according to the Poisoning Severity Score (Persson *et al.* 1998). In addition, the severity and frequency of poisonings with TCAs was assessed and compared to SSRIs and other antidepressants (OA) including noradrenergic and specific serotonergic antidepressants, serotonin antagonists reuptake inhibitors, selective serotonin reuptake enhancers, serotonin and noradrenalin reuptake inhibitors and benzodiazepines based on the evaluations of TIC specialists.

Statistical methods

The basic statistical characteristics were calculated using simple statistical tests and modules from MS Excel 2010 software (Microsoft, Czech Republic). For the calculation of confidence intervals, Student's t-test was used.

RESULTS

Within the period of fifteen years, a total of 152,649 calls due to all types of potentially toxic agents were recorded in the TIC database.

Drugs affecting the CNS represented the biggest group (39.8%) of calls due to all pharmaceutical poisonings followed by drugs affecting the respiratory system (13.7%), drugs affecting the alimentary tract and metabolism (13.1%) and drugs affecting the musculoskeletal system (10%). A total of 7,680 inquiries related to CNS affecting drugs (monopoisonings) were used for further evaluation. Ingestion was the most frequent route of exposure. The proportion of adults was 72.2% and women prevailed in the calls (64.4%).

The reasons of exposure are presented in Figure 1. As can be seen, suicidal attempts were the main reason of overdose with CNS affecting drugs. There were no significant differences within the groups of drugs regarding the reason of exposure, except medication errors. Among the groups of CNS affecting drugs studied, barbiturates exhibited the highest percentage of medication errors caused by both professionals (9.1%) and lay persons (7.3%) compared to all other drugs. Both
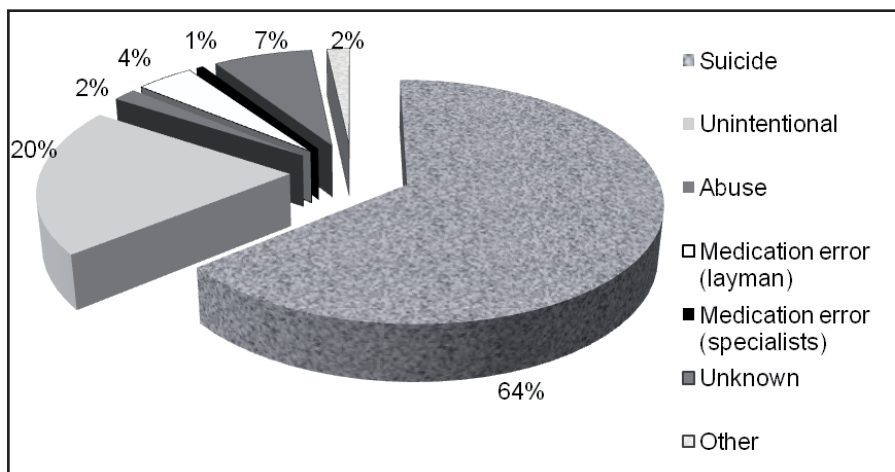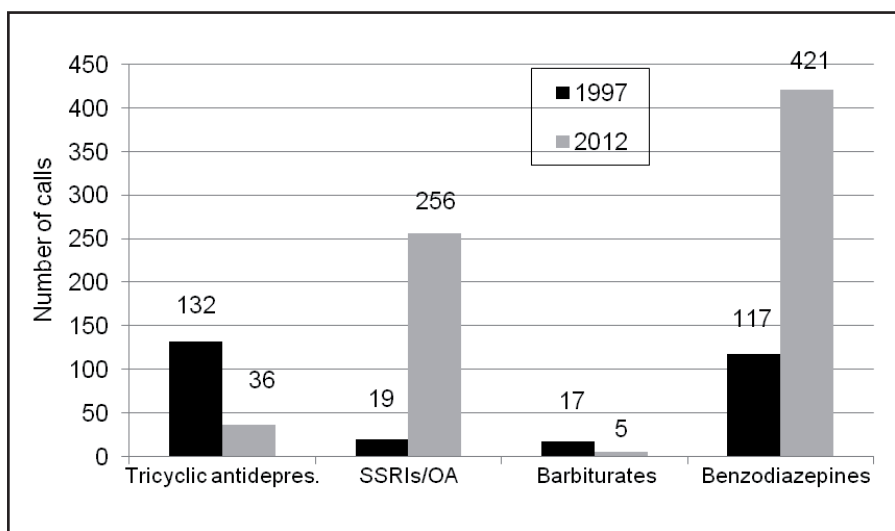
in the medication errors of healthcare personnel with barbiturates ($p \leq 0.05$), and in the medication error by layman a significantly higher frequency compared with the medication errors with other psychoactive pharmaceuticals was seen ($p \leq 0.05$).

Medication errors by professionals and patients (lay persons) using SSRIs occurred in 0.3% and 4.5%, respectively; in benzodiazepines 4.3% and 0.5%, respectively, and only 2.2% of recorded TCA cases were caused by treatment errors (lay persons and health professionals). However, most adverse drug reactions were found due to TCAs ($p \leq 0.05$).

In the past 15 years a substantial decrease in the number of calls due to poisoning with TCAs and barbiturates was recorded. On the other hand the number of calls due to SSRIs and OA overdose increased from 1997 through 2012 as shown in Figure 2. Trends in the number of calls due to four most common types of benzodiazepines are presented in Figure 3.

Differences between the severity evaluations of the poisonings with CNS affecting drugs can be seen in Figure 4. The severity did not differ significantly among the groups excepting the benzodiazepines where the largest proportion of exposures ($p \leq 0.05$) was classified as non-toxic/minor toxic (Figure 4). The symptom severity due to different classes of CNS affecting drugs is shown in Figure 5. The prognosis of poisonings caused by benzodiazepines was rather severe/severe in only 0.7% of calls and 2.5% in SSRIs, in contrast to 15.8% in TCAs and 9.1% in barbiturates.

DISCUSSION

Sedatives, hypnotics, and antipsychotics are not only in the top six drug groups human are exposed to, as shown by TIC reports from the US, they are in the top two groups of drugs with the highest rate of exposure increase over the last 12 years (up to eight-fold for most of them, comparing to the numbers at the beginning of this time interval) (Bronstein *et al.* 2012). In this study, CNS affecting drugs were associated with the largest number of fatalities, as they represent the most common group of pharmaceuticals used to commit suicide, which was confirmed in the Czech popula-
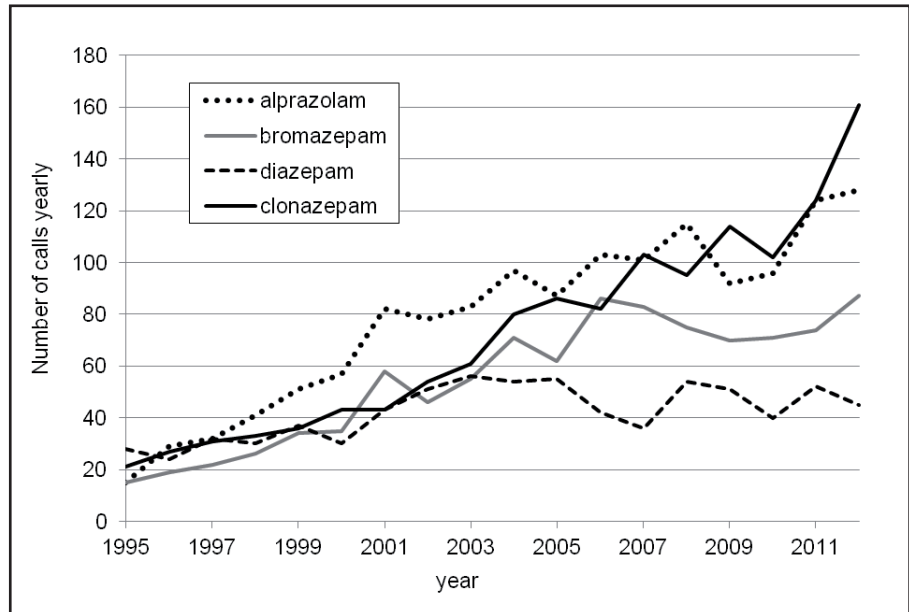
Fig. 3. Number of calls yearly due to four most common benzodiazepines from 1997 to 2012.
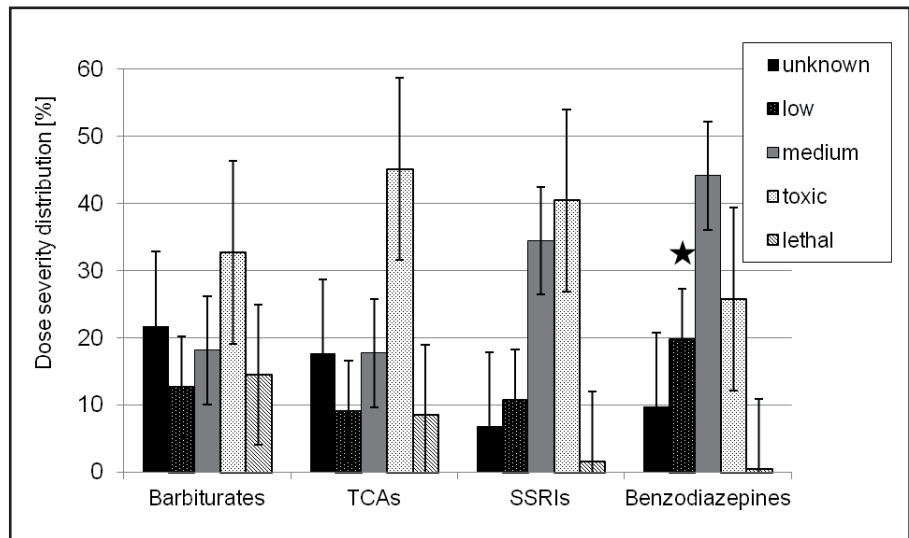

Fig. 4. Dose severity evaluation in different types of central neural system affecting drugs (%). The severity did not differ significantly among the groups excepting the benzodiazepines where the largest proportion of exposures ($p \leq 0.05$) was classified as non-toxic/minor toxic (denoted by ★). Note: TCAs (tricyclic antidepressants), SSRIs (selective serotonin reuptake inhibitors), OA (other antidepressants). The error bars correspond to the confidence intervals on significance level 0.05.

Fig. 5. Symptoms in different types of central neural system affecting drugs (%). Note: TCAs (tricyclic antidepressants), SSRIs (selective serotonin reuptake inhibitors), OA (other antidepressants). The error bars correspond to the confidence intervals on significance level 0.05.
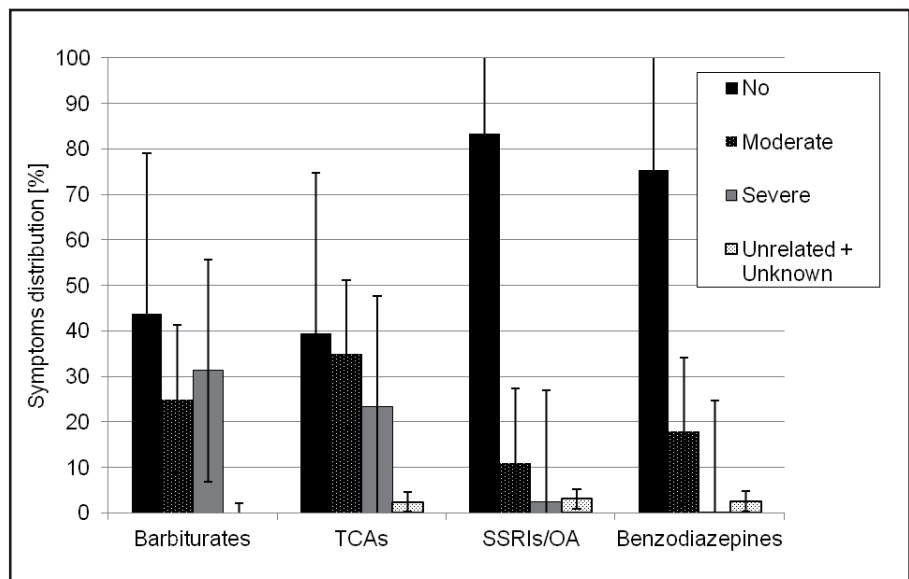
tion of adolescents, who committed suicide, where the proportion of CNS affecting pharmaceuticals reached 39.0%, the dose was evaluated as toxic in 73.0% and severely toxic in 3.0% of the subjects (Zakharov *et al.* 2013a; Zakharov *et al.* 2013b). Not only psychically ill adults, but also young subjects, including children, are involved. The latter usually do not use such medication but find these drugs easily accessible in the home medicine cabinet.

In addition, CNS affecting drugs accounted for 25.1% of all calls concerning medication errors and thereby became the most common drug class of unintentional overdose by the patients, parents of the children and even health care specialists (Zakharov *et al.* 2012a; Zakharov *et al.* 2012b). Our study confirms a decrease in the TCAs and barbiturates exposures and therefore a positive trend in the spectrum of pharmaceuticals, dose severity and prognosis of the poisonings thanks to a professional trend to prescribe safer drugs with fewer side effects.

There have been numerous studies documenting a very low incidence of barbiturate poisoning compared to all other CNS affecting drugs (Nowers & Irish 1988; McGrath 1989). Nevertheless, current medical literature (Lynton 2007) still pays close attention to barbiturates as if this class of drugs represents a major issue in current toxicology.

Poison control data are attractive as it serves as a valuable surveillance system reflecting current trends in drug use and poisonings, as seen in the example of the US studies published for almost three decades (Bronstein *et al.* 2011). The use of TIC specialist to document calls presents an opportunity to specify details of drug poisoning within the data. However, the utility of the data has been questioned due to several limitations. First and foremost, physicians consult the TIC on a voluntary basis and the actual number of intoxications is therefore higher. Thus, beyond the absolute data, long-term trends provide additional useful data. As can be seen from the US document, not only the proportions of pharmaceutical poisonings differ, but also trends in the treatment, charcoal or antidotes or extra corporal elimination methods of treatment may be evaluated. The availability of an antidote, such as flumazenil for benzodiazepines may surely improve the prognosis of poisoned patients.

CONCLUSION

This first report showing trends in poisonings due to CNS affecting drugs in Czech Republic in such a long period demonstrates that in the course of the past 15 years, the number and proportion of CNS affecting drugs reported in the calls to the TIC have substantially changed. The reduction in the number of calls due to barbiturate and TCAs poisonings reflects the use of pharmaceuticals with improved safety profiles and lower toxicity. Although some of the above men-

tioned older drugs are still being prescribed for their original indication and for a variety of other disorders (e.g. TCAs antidepressants are also used for neuropathic pain, migraine, obsessive-compulsive disorder etc. (Brush & Aaron 2007), our findings concerning drug poisoning cases confirm the current trend in the preferential prescription of drugs with improved safety profile to those routinely prescribed in the past. In addition, we have shown that the TIC is able to effectively identify trends in poisoning in emergency departments and may serve as a useful part of any pharmaceutical surveillance system. However, additional tools to evaluate poisonings should be used for drug monitoring to provide a more complex toxicovigilance system.

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