Int J Legal Med (2009) 123:109–115
DOI 10.1007/s00414-008-0261-3

ORIGINAL ARTICLE

Prevalence of adverse drug combinations in a large post-mortem toxicology database

Terhi Launiainen · Erkki Vuori · Ilkka Ojanperä

Received: 25 January 2008 / Accepted: 27 May 2008 / Published online: 27 June 2008

Abstract The prevalence of important adverse drug combinations was studied among the 37,367 cases included in the Finnish post-mortem toxicology database during 2000–2006. The new SFINX interaction database (Swedish, Finnish, INteraction X-referencing) was utilised to identify adverse drug combinations. Consequently, the 24 drugs chosen for the study generated 96 two-compound combinations possessing potentially severe interactions. The total number of hits for the combinations found in the post-mortem database was 267, which accounts for approximately 0.71% of all cases. The potential role of adverse drug interaction (ADI) in these cases was evaluated from the background information and death certificate. The possible ADI cases comprised 23% of all hits and 0.17% of all cases analysed. In cases with a pharmacodynamic mechanism, the most prominent combinations were medicines causing serotonin syndrome or a β_1-blocker with verapamil or diltiazem. In cases with a pharmacokinetic mechanism, half of the cases involved digoxin in combination with verapamil. In one third of the possible ADI cases, a forensic pathologist had noted the studied compounds as an underlying or contributing cause of death, although the agents' specific role in ADIs was rarely recognised.

Keywords Adverse drug interaction · Post-mortem database · Database research

Electronic supplementary material The online version of this article (doi:10.1007/s00414-008-0261-3) contains supplementary material, which is available to authorized users.

T. Launiainen (✉) · E. Vuori · I. Ojanperä
Department of Forensic Medicine, University of Helsinki,
P.O. Box 40, 00014 Helsinki, Finland
e-mail: terhi.launiainen@helsinki.fi

Introduction

Adverse drug reactions are a significant cause of morbidity and mortality and result in considerable costs to society through hospital admissions. A recent systematic review estimated that 4.9% of admissions are related to adverse drug events, while the odds of being hospitalised are four times higher for the elderly than for younger people [1]. Adverse drug interactions (ADIs) are a major category of adverse drug reactions [2, 3]. Patients commonly use several prescription medicines simultaneously, and especially hospital patients may use five to ten medicines daily. Polypharmacy in the elderly is a well-recognised problem [4]. Besides actual pharmaceuticals, ethyl alcohol is an important congener of central nervous system (CNS) depressants, which is commonly used and abused in all age groups. Apart from accidental interactions, a multitude of medicines and alcohol are often ingested in connection with suicides [5], and the combinations involved in these cases can be rather irrational.

The additive effects of CNS depressants are well known, but more specific ADIs are less familiar within post-mortem toxicology. Drug interactions can be divided into pharmacokinetic interactions, involving changes in the concentrations of the agents, and pharmacodynamic interactions, involving changes in efficacy usually without changes in the concentrations of the agents. Pharmacokinetic mechanisms of interaction include alterations of absorption, protein binding, distribution, metabolism, or elimination. Pharmacodynamic mechanisms take place at the receptor level and include additive or synergistic effects and combined toxicity, but they may also involve antagonistic or opposing interactions. Much data has been published on drug interactions, based on animal studies or in vitro studies, which are often difficult to extrapolate to

clinical practice. To improve the clinical relevance of the fragmented information on drug interactions, electronic databases have been made available for recognising and evaluating the adverse combinations more easily [6].

Based on standardised analytical techniques, many forensic toxicology laboratories are now able to screen for several hundreds of medicines on a routine basis and determine the respective blood concentrations of relevant compounds. Appropriate sampling of femoral venous blood and quality-controlled laboratory performance are necessary in order to assure the validity of qualitative and quantitative results [7]. These comprehensive analytical data serve as a basis of post-mortem databases, which can be utilised beyond routine casework to support interpretation, to identify trends in drug usage and even to advance the safety of pharmaceuticals in society. However, to be generally useful, the database should contain, in addition to the analytical toxicology findings, relevant background information related to the case and, thus, also details about the cause and manner of death, which can e.g. be taken from the final death certificate.

Although post-mortem database research is still a somewhat rarely exploited area of forensic toxicology, several representative studies have been recently published. Detailed in-house databases were explored to e.g. establish reference concentrations of medicines in the blood [8, 9] and to estimate the magnitude of interactions between various medicines and alcohol [10–13]. Combining national death statistics and medical prescriptions or sales figures allowed the calculation of the fatal toxicity index (FTI) [14–17] for individual medicines or groups of medicines, which is a better indicator of the toxicity of a specific compound than the number of deaths as such.

In this study, we contribute to the post-mortem database research in the area of drug-drug interactions, utilising the new SFINX interaction database (Swedish, Finnish, INteraction X-referencing), which contains updated concise information on more than 7,000 drug interactions. The prevalence of important adverse drug combinations was studied among the 37,367 cases included in the Finnish post-mortem toxicology database during 2000–2006, and the potential role assigned to ADIs in the fatalities was evaluated.

Materials and methods

SFINX database

The SFINX database [18] was accessed through the National Library of Health Sciences in Finland. SFINX classifies ADIs by their clinical significance. The database was introduced in 2006, and it is updated regularly. The present study is based on the database version of 5 October 2007. In SFINX, a query for a medicine generates a list of two-compound ADIs classified by their clinical status from mild (A) to severe (D) and by the level of documentation from sparse (0) to well established (4). The result page lists the brand names of available preparations for both compounds, a summary of the ADIs and recommended measures concerning combined administration. The mechanisms for the ADIs and background information with references are also provided.

Post-mortem database

The Finnish post-mortem database comprised 40,165 cases in the 7-year period of 2000–2006, for which comprehensive screening for drugs was performed in 37,367 cases (93%). The case files in the post-mortem database included a referral from a forensic pathologist, laboratory analysis results and information extracted from the death certificate issued by a forensic pathologist. The referral contained background information, such as a brief description of the circumstances of death, known medications and the main autopsy findings. The analytical data contained analysis results for alcohols, medicines and drugs of abuse and occasionally for other substances, such as volatile substances, ethylene glycol, carbon monoxide and pesticides. Information from the final death certificate included the age and gender of the deceased, the cause of death with contributing factors according to the International Classification of Diseases (ICD 10) and the manner of death (WHO, World Health Organization).

Table 1 shows the 24 primary medicines (compound 1) chosen for the study and the interacting medicines from the SFINX query results (compound 2). The primary medicines were included either based on their frequency as a finding in post-mortem blood (≥40 cases in the year 2006) or their prevalence as the most important finding in fatal poisonings according to the highest ‘concentration-to-therapeutic concentration ratio’ in the post-mortem database [19]. In addition, a few medicines were included because they are generally known to be involved in ADIs.

Data refining

The SFINX database was searched for the selected 24 primary medicines, and among the resulting two-compound combinations, only the severe interactions (D1–D4) were taken into account. The pairs in which compound 2 was not included in the laboratory’s analysis arsenal were excluded. The combinations in which a concentration or an effect was diminished were also excluded. The resulting 96 two-compound combinations were searched against the post-mortem database to reveal cases in which the date of death was between 1 January 2000 and 31 December 2006 and

Table 1 Medicines included in the study and their upper therapeutic concentration[a]

Medicines	Concentration (mg/l)
Primary compound (compound 1)	
Group 1	
Atenolol	0.6
Bisoprolol	0.1
Fluoxetine	0.5
Metoprolol	0.6
Sertraline	0.25
Warfarin	3.0
Group 2	mg/l
Amitriptyline	0.2
Citalopram	0.4
Dextropropoxyphene	0.75
Digoxin	0.002
Doxepin	0.15
Levomepromazine	0.14
Mirtazapine	0.2
Propranolol	0.25
Tramadol	0.6
Venlafaxine	0.3
Group 3	mg/l
Amiodarone	2.8
Diltiazem	0.3
Fluconazole	19
Fluvoxamine	0.25
Moclobemide	2.5
Selegiline	0.05
Sotalol	4.0
Verapamil	0.35
Interacting compound (compound 2)	
Acebutolol	1.2
Amphetamine	0.6
Betaxolol	0.05
Bupropion	0.1
Carbamazepine	10
Carvedilol	0.3
Celiprolol	0.4
Clomipramine	0.15
Clonidine	0.0015
Dextromethorphan	0.04
Duloxetine	0.05
Esmolol	2.0
Fentanyl	0.002
Glibenclamide	0.36
Glimepiride	0.3
Glipizide	0.49
Labetalol	0.2
MDMA (“Ecstasy”)	
Methylphenidate	0.06
Metronidazole	30
Mianserin	0.13
Midazolam	0.2
Milnacipran	0.2
Nifedipine	0.15
Nortriptyline	0.25
Paroxetine	0.05
Pethidine	0.8
Phenobarbital	25
Phenytoin	20
Pindolol	0.15
Propafenone	1.6
Quinidine	6.0
Sertindole	0.14
Theophylline	20
Timolol	0.05
Tizanidine	0.01
Trazodone	2.5
Triazolam	0.02

Inclusion criteria: Group 1, common post-mortem findings (>40 cases in 2006); Group 2, prevalence in fatal poisonings [19]; Group 3, generally known to be involved in ADIs

[a] The values are mainly from standard compilations of therapeutic concentration data [20–22].

for which femoral blood analysis results were available. Tables S1 and S2 of the Electronic Supplementary Material show the primary medicines together with the adverse combinations and the resulting ADIs.

In data refining, the following generalisations about the toxic drug and alcohol levels were made to remove cases in which an ADI probably did not have a predominant contribution to the death, based on a survey of therapeutic and toxic concentrations [8]. The values in Table 1 for upper therapeutic concentrations are mainly from standard compilations of therapeutic concentration data [20–22]. The exclusion point for predominant alcohol poisonings was set below a published post-mortem median blood alcohol concentration in acute poisonings (3.6 ‰ *w*/*w* [23]) as the fatal blood alcohol concentration is reported to be much lower in combined fatal drug–alcohol poisonings [10–12].

Pharmacodynamic combinations

Among the 169 hits, the following exclusion criteria were applied: (1) any medicine present in blood with a concentration equal to or higher than ten times the upper limit of its established therapeutic level (Table 1), (2) an alcohol concentration in blood equal to or higher than 2.5‰ (*w*/*w*) and/or (3) an obvious external cause of death other than the poisoning stated in the death certificate. For the remaining cases, the background information and death certificates were evaluated to reveal cases with an ADI contributing to the death.

Pharmacokinetic combinations

Among the 98 hits, the following exclusion criteria were applied: (1) concentration of the target compound (i.e. the

agent assumed to be elevated) in blood was lower than five times the upper limit of its established therapeutic level (not applicable to warfarin), (2) a medicine other than the target compound was present in blood with a concentration equal to or higher than ten times the upper limit of its established therapeutic level (Table 1), (3) an alcohol concentration in blood was equal to or higher than 2.5‰ (*w*/*w*), and/or (4) an obvious external cause of death other than the poisoning stated in the death certificate. For the remaining cases, the background information and death certificates were evaluated to reveal cases with an ADI contributing to the death.

Case reports representing a pharmacodynamic and a pharmacokinetic interaction were chosen from the material to illustrate the role of selected ADIs in a medicolegal context.

Statistical analysis

MINITAB 13.31. was used for the statistical analysis of the manner of death (Table 2). The expected number of deaths was derived from the proportion of all cases in 2000–2006 and compared with the observed number of suspected pharmacodynamic ADIs using the test for two proportions. For pharmacokinetic ADIs, no statistical analysis was performed due to the low number of cases.

Results

Overview

Tables S1 and S2 of the Electronic Supplementary Material show the 24 medicines chosen for the interaction study based on their prevalence as a finding in the post-mortem toxicology database, their prevalence as a finding in fatal poisonings in the database or their known potential for ADIs according to the literature. The SFINX database search generated 96 two-compound combinations possessing potentially severe interactions. Searching the post-mortem toxicology database for these combinations revealed hits for 52 different combinations of medicines, while for 44 combinations, no hits were found. The total number of hits found was 267, which accounts for approximately 0.71% of all cases. In 26 cases, more than one adverse combination was found. The adverse drug combinations were divided into two groups according to their mechanisms as defined in SFINX. The combinations with pharmacodynamic mechanisms comprised 169 hits (63%; Table S1 of the Electronic Supplementary Material), and the combinations with pharmacokinetic mechanisms comprised 98 hits (37%; Table S2 of the Electronic Supplementary Material). The total number of possible ADIs found was 62, comprising 23% of all hits and 0.17% of all cases analysed.

The typical cases in the present material involved middle-aged persons found dead at home. All hits comprised 137 men and 97 women with an average age of 55.9 (±17.9) years. The possible ADI cases extracted from all hits comprised 30 men and 26 women with an average age of 55.6 (±15.7) years. Death usually occurred without a witness, but in a few cases, the person was found dead in the morning by the spouse or died in spite of the care of paramedics. Evidence for cardiovascular disease was often revealed at the autopsy, and generally, no explicit cause of death could be established.

Forensic pathologists had included adverse combinations of two or more medicines as an underlying or contributing factor of death in 19 (33%) of the 57 death certificates for the 62 possible ADIs shown in Table S1 and S2 of the Electronic Supplementary Material (five cases had two ADIs). In 8 (14% of the total) of the 19 cases, the forensic pathologist had highlighted the same specific two-compound ADI as recognised in this study. Certificates that pointed to only one component of an adverse combination or to completely different medicines or that did not mention medicines at all comprised 67% of all possible ADI cases. The distribution of

Table 2 Distributions of manner of death between possible ADI cases and all cases in the post-mortem database

Manner of death (classification by WHO)	All cases 2000–2006 (%)	All hits (%)	Suspected ADIs	
			Pharmacodynamic findings (%)	Pharmacokinetic findings (%)
Natural (disease)	17,171 (43)	106 (40)	23 (44)	4 (40)
Suicidal	12,725 (32)	93 (35)	12 (23)	3 (30)
Accidental	7,206 (18)	47 (18)	12 (23)	0
Undetermined	2,144 (5)	16 (6)	5 (10)	2 (20)
Medical treatment or procedure	97 (0.2)	4 (1.5)	0	1 (10)
Homicidal	809 (2)	1 (0.4)	0	0
Occupational disease	13 (0.03)	0	0	0
War	0	0	0	0
Total	40,165	267	52	10

manner of death between the possible ADI cases and all cases in the database is shown in Table 2. No statistical difference between all cases and suspected pharmacodynamic ADIs was found (test for two proportions).

Pharmacodynamic combinations

The process described above yielded 52 possible cases, which accounts for 19% of all hits and 31% of the pharmacodynamic hits (Table S1 of the Electronic Supplementary Material). A pharmacodynamic ADI may have contributed to the death of a 63-year-old man with a medical history of hypertension and mental health problems. On the way home, his car drifted off the road at slow speed, and he died at the crash scene. No findings of external trauma could be determined at the autopsy. No alcohol was found in the blood, and there was no information available on his medication. Post-mortem toxicology indicated a slightly elevated concentration of bisoprolol (0.13 mg/l) and a therapeutic concentration of diltiazem (0.1 mg/l) and chlorprothixene (0.2 mg/l) in his blood. A forensic pathologist determined the underlying cause of death as hypertensive heart disease without congestive heart failure and atherosclerosis and malignant prostate cancer as contributing factors.

Pharmacokinetic combinations

The process described above yielded ten possible cases, which accounts for 3.8% of all hits and 10% of the pharmacokinetic hits (Table S2 of the Electronic Supplementary Material). A possible pharmacokinetic ADI is presented in the case of an obese schizophrenic 54-year-old woman living in a nursing home and found dead on a sofa in the morning. The day before, she had been taken to hospital because of agitation and insomnia but returned to the nursing home the same day. Autopsy revealed coronary artery disease. Post-mortem toxicology indicated a therapeutic concentration of fluoxetine (0.3 mg/l) and a markedly elevated concentration of dextromethorphan (0.5 mg/l) in her blood. Levomepromazine (0.2 mg/l), clozapine (0.9 mg/l) and lorazepam (0.01 mg/l) were also detected, all within or close to the therapeutic range. No alcohol was found in the blood. A forensic pathologist classified the death as natural (disease), and coronary artery disease was defined as the underlying cause of death. Cardiac insufficiency and fibrosis, in addition to obesity and the combined effect of the medicines, were marked as factors contributing to the death.

Discussion

During the study period, the frequency of medicolegal autopsies in Finland was high, covering more than 20% of all deaths, and toxicological samples were collected in more than 50% of the cases, corresponding to approximately 6,000 cases a year [19]. The Finnish post-mortem database is thus representative for studying ADIs in a medicolegal context. Moreover, contrary to most clinical studies, the results in the present study were based on the actual measured concentrations of pharmaceuticals in blood. Clinical studies tend to evaluate the incidence of ADIs based on overlapping prescriptions [24–26] or on co-reporting in a database of suspected ADI reports [18], indicating a relatively low ADI incidence (<2%). In a study conducted in Finnish hospital wards, potentially serious ADIs occurred in 1.4% of the prescriptions, and potentially toxic combinations occurred in 1.0% [27].

The 0.71% prevalence of serious two-compound combinations found here is consistent with the clinical studies, even though the spectrum of medicines is somewhat different. The lack of a routine screening method excluded some important ADIs from this study, such as those of antibiotics (e.g. rifampicin and erythromycin) and the combinations of warfarin and nonsteroidal anti-inflammatory analgesics (non-steroidal anti-inflammatory drugs). Additive or synergistic pharmacodynamic interactions between medicines having similar pharmacological effect, such as with two CNS depressants, were not included, and in general, these types of combinations are not flagged in the SFINX database. Although many additive interactions are trivial, some combinations have special importance in fatal poisonings, such as intravenous buprenorphine combined with benzodiazepines [28]. According to the recommendations given in SFINX, class D (severe) combinations should be completely avoided in therapy, or the potential adverse effect should be prevented by other means, e.g. by taking the concentration change into account when adjusting the dose. Despite the known severe consequences of some combinations of medicines, in most cases, it is very difficult to predict how many patients will ultimately experience an adverse outcome [29]. Under medical supervision, it may sometimes be necessary and justified to treat a patient with a combination of medicines with potential ADIs, but in the present study, it was not possible to judge the victim's intentions or awareness of the risks.

The most prominent ADI in the pharmacodynamic group (Table S1 of the Electronic Supplementary Material) is serotonin toxicity [30], which accounts for 58% of the possible ADIs in the group. Serotonin toxicity is a result of over-stimulation of 5-HT_{1A} receptors by serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), tricyclic antidepressants (TCAs) and monoamine oxidase (MAO) inhibitors. The syndrome may develop in a few hours, involving agitation, increase in body temperature, muscle rigidity, multi-organ failure and death [31, 32]. A single serotonergic agent rarely causes severe toxicity,

but most of the life-threatening or fatal outcomes by serotonin toxicity are due to ADIs [33]. In this study, fluoxetine, moclobemide and tramadol were the three most prevalent individual medicines associated with the risk of the serotonin syndrome, contributing to 13, 11 and 9 possible ADI cases, respectively. Fluoxetine, a widely used SSRI, has a relatively low FTI compared to the other newer antidepressants [13]. Moclobemide is a MAO-A inhibitor that is reported to be well tolerated when taken alone [34]. The commonly used analgesic tramadol is a partial μ-opioid receptor agonist that also inhibits the re-uptake of noradrenalin and 5-HT [35].

Another group that stands out in Table S1 of the Electronic Supplementary Material is the combination of a β_1-blocker and either of the calcium antagonists, verapamil or diltiazem, comprising 22 potential ADI cases. It is not uncommon for patients with ischaemic heart disease and hypertension to be deliberately treated with this kind of combination as both compounds exert a negative chronotropic effect and lower the blood pressure. This combination can, however, lead to bradyarrhythmia and other cardiovascular adverse drug reactions, such as atrioventricular block, even with therapeutic doses [36]. We hypothesise that in the above-described fatality of a 63-year-old man, this ADI may have played a role in the fatality.

In the pharmacokinetic group (Table S2 of the Electronic Supplementary Material), an elevated concentration of the target compound is shown in 10% of cases. Approximately half of all cases involved the cardiac glycoside, digoxin, in combination with the calcium antagonist, verapamil. Verapamil increases the digoxin concentration by inhibition of P-glycoprotein mediated excretion [37]. Digoxin is known to undergo post-mortem re-distribution leading to difficulty in interpretation of post-mortem digoxin concentrations [38]; however, in this study, results exclusively from peripheral blood samples were included. Only one case was identified in which the digoxin concentration was high enough to meet the set criteria of a potential ADI and to reach a suggested level of life-threatening toxicity [39].

In the cases involving warfarin, the potential enhancing effect of CYP2C9 enzyme inhibitors was evaluated by autopsy findings of bleeding given in the death certificate, not based on the warfarin concentration, as the optimal therapeutic range of the medicine is narrow and highly patient specific. Spontaneous bleeding and haematoma were reported in the death certificates of only 2 of the 14 cases. CYP2D6 inhibitors may have increased the concentration of dextromethorphan in three cases. In the above-described case of a schizophrenic woman, we believe that her death could be more directly attributed to an ADI, as fluoxetine inhibits the metabolism of dextromethorphan. The elevated dextromethorphan concentration may also be explained by genetic polymorphism of CYP2D6, as it has been estimated that approximately 7–10% of the European population are poor metabolisers [40].

The present study is the first to systematically survey the prevalence of ADIs in a comprehensive post-mortem database. The distribution of manner of death between possible ADI cases and all cases in the database suggests a higher percentage of pharmacodynamic ADI cases in accidental and undetermined categories and a lower percentage in suicides (Table 2). However, this difference was not statistically significant. Obviously, ADIs can become important for interpreting death cases with only moderate concentrations of medicines and little or no pathological findings.

Assessing the role of two-compound ADIs as a cause of death is even more difficult than assessing the role of individual compounds, which is more directly related to their concentrations in blood. The 0.71% prevalence of severe adverse drug combinations and 0.17% prevalence of possible ADIs found in this study are probably underestimates, but the figures are in any event of the same order of magnitude as those obtained in clinical studies. The study setting did not permit us to judge whether the combinations of medicines were prescribed or if a concomitant administration decision was made by the patient. In one third of the possible ADI cases, a forensic pathologist had noted the studied compounds as an underlying or contributing cause of death, although the agents' specific role in ADIs was rarely recognised. For example, serotonin toxicity was stated as a cause of death in only two death certificates, both involving citalopram and moclobemide. Although ADIs are not a serious pitfall in cause of death investigations, they do deserve more attention. Polypharmacy poses a common challenge, calling for concerted action by forensic pathologists and toxicologists. Continually updated databases, such as SFINX, are also of great assistance in detecting and keeping up with the growing amount of information on pharmaceuticals.

References

1. Beijer HJM, de Blaey CJ (2002) Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci 24:46–54
2. Mozayani A, Raymon LP (eds) (2003) Handbook of drug interactions. A clinical and forensic guide. Humana, Totowa, NJ
3. Baxter K (ed) (2005) Stockley's drug interactions, 7th edn. Pharmaceutical Press, London, UK
4. Lampela P, Hartikainen S, Sulkava R, Huupponen R (2007) Adverse drug effects in elderly people—a disparity between clinical examination and adverse effects self-reported by the patient. Eur J Clin Pharmacol 63:509–515
5. Öhberg A, Vuori E, Ojanperä I, Lönnqvist J (1996) Alcohol and drugs in suicides. Br J Psychiatry 169:75–80
6. Indermitte J, Erba L, Beutler M, Bruppacher R, Haefeli WE, Hersberger KE (2007) Management of potential drug interactions in community pharmacies: a questionnaire-based survey in Switzerland. Eur J Clin Pharmacol 63:297–305

7. Drummer OH (2007) Requirements for bioanalytical procedures in postmortem toxicology. Anal Bioanal Chem 388:1495–1503
8. Druid H, Holmgren P (1997) A compilation of fatal and control concentrations of drugs in post-mortem femoral blood. J Forensic Sci 42:79–87
9. Reis M, Aamo T, Ahlner J, Druid H (2007) Reference concentrations of antidepressants. A compilation of postmortem and therapeutic levels. J Anal Toxicol 31:254–264
10. Koski A, Ojanperä I, Vuori E (2002) Alcohol and benzodiazepines in fatal poisonings. Alcohol Clin Exp Res 26:956–959
11. Koski A, Ojanperä I, Vuori E (2003) Interaction of alcohol and drugs in fatal poisonings. Hum Exp Toxicol 22:281–287
12. Koski A, Vuori E, Ojanperä I (2005) Relation of postmortem blood alcohol and drug concentrations in fatal poisonings involving amitriptyline, propoxyphene and promazine. Hum Exp Toxicol 24:389–396
13. Koski A, Vuori E, Ojanperä I (2005) Newer antidepressants: evaluation of fatal toxicity index and interaction with alcohol based on Finnish postmortem data. Int J Legal Med 119:344–348
14. Vuori E, Ruohonen A, Penttilä A, Klaukka T, Lahti T (1989) Fatal poisonings with antidepressants in Finland 1985–1987. Acta Psychiatr Scand Suppl 354:55–60
15. Buckley NA, McManus PR (2002) Fatal toxicity of serotonergic and other antidepressant drugs: analysis of United Kingdom mortality data. BMJ 325:1332–1333
16. Cheeta S, Schifano F, Oyefeso A, Webb L, Ghodse AH (2004) Antidepressant-related deaths and antidepressant prescriptions in England and Wales, 1998–2000. Br J Psychiatry 184:41–47
17. Hoiseth G, Bramness JG, Christophersen AS, Morland J (2007) Carisoprodol intoxications: a retrospective study of forensic autopsy material from 1992–2003. Int J Legal Med 121:403–409
18. Strandell J, Bate A, Lindquist M, Edwards IR, The Swedish, Finnish, INteraction X-referencing Drug–Drug Interaction Database (the SFINX group) (2008) Drug–drug interactions—a preventable patient safety issue? Br J Clin Pharmacol 65:144–146
19. Vuori E, Ojanperä I, Nokua J, Ojansivu RL (2006) Oikeuskemiallisesti todetut myrkytyskuolemat Suomessa vuosina 2002–2004. Suomen lääkärilehti (Finnish Medical Journal) 61:2339–2344 (in Finnish, English summary: fatal poisonings in Finland 2002–2004)
20. Schulz M, Schmoldt A (2003) Therapeutic and toxic blood concentrations of more than 800 drugs and other xenobiotics. Pharmazie 58:447–474
21. Jack DB (ed) (1992) Handbook of clinical pharmacokinetic data. Macmillan, London, UK
22. The International Association of Forensic Toxicologists (TIAFT) (2008) Therapeutic and toxic drug concentrations. Available at: http://www.tiaft.org/tmembers/ttvidx.html
23. Jones AW, Holmgren P (2003) Comparison of blood–ethanol concentration in deaths attributed to acute alcohol poisoning and chronic alcoholism. J Forensic Sci 48:874–879
24. Chen YF, Avery AJ, Neil KE, Johnson C, Dewey ME, Stockley IH (2005) Incidence and possible causes of prescribing potentially hazardous/contraindicated drug combinations in general practice. Drug Saf 28:67–80
25. Peng CC, Glassman PA, Marks IR, Fowler C, Castiglione B, Good CB (2003) Retrospective drug utilization review: incidence of clinically relevant potential drug–drug interactions in a large ambulatory population. J Manag Care Pharm 9:513–522
26. Åstrand B, Åstrand E, Antonov K, Petersson G (2006) Detection of potential drug interactions—a model for a national pharmacy register. Eur J Clin Pharmacol 62:749–756
27. Gronroos PE, Irjala KM, Huupponen RK, Scheinin H, Forsstrom J, Forsstrom JJ (1997) A medication database—a tool for detecting drug interactions in hospital. Eur J Clin Pharmacol 53:13–17
28. Reynaud M, Petit G, Potard D, Courty P (1998) Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addiction 93:1385–1392
29. Levy RH, Thummel KE, Trager WF, Hansten PD, Eichelbaum M (eds) (2000) Metabolic drug interactions. Lippincott Williams & Wilkins, Philadelphia, PA
30. Sternbach H (1991) The serotonin syndrome. Am J Psychiatry 148:705–713
31. Neuvonen PJ, Pohjola-Sintonen S, Tacke U, Vuori E (1993) Five fatal cases of serotonin syndrome after moclobemide–citalopram or moclobemide–clomipramine overdoses. Lancet 342:1419
32. Vuori E, Henry JA, Ojanperä I, Nieminen R, Savolainen T, Wahlsten P, Jäntti M (2003) Death following ingestion of MDMA (ecstasy) and moclobemide. Addiction 98:365–368
33. Isbister GK, Buckley NA, Whyte IM (2007) Serotonin toxicity: a practical approach to diagnosis and treatment. Med J Aust 17 (187):361–365
34. Iwersen S, Schmoldt A (1996) Three suicide attempts with moclobemide. J Toxicol Clin Toxicol 34:223–225
35. Grond S, Sablotzki A (2004) Clinical pharmacology of tramadol. Clin Pharmacokinet 43:879–923
36. Edoute Y, Nagachandran P, Svirski B, Ben-Ami H (2000) Cardiovascular adverse drug reaction associated with combined beta-adrenergic and calcium entry-blocking agents. J Cardiovasc Pharmacol 35:556–559
37. Verschraagen M, Koks CH, Schellens JH, Beijnen JH (1999) P-glycoprotein system as a determinant of drug interactions: the case of digoxin–verapamil. Pharmacol Res 40:301–306
38. Yarema MC, Becker CE (2005) Key concepts in postmortem drug redistribution. Clin Toxicol 43:235–241
39. Bauman JL, Didomenico RJ, Galanter WL (2006) Mechanisms, manifestations, and management of digoxin toxicity in the modern era. Am J Cardiovasc Drugs 6:77–86
40. Cascorbi I (2003) Pharmcogenetics of cytochrome P4502D6: genetic background and clinical implication. Eur J Clin Invest 33 (Suppl 2):17–22