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Acute drug poisonings leading to hospitalization

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Keywords: overdose, paracetamol, adverse effects, sedation, medication

Abstract

Knowledge about current trends and epidemiology in poisonings is important to maintain quality in diagnostics, treatment, and prevention. We performed a cross-sectional study of all cases (n=261) admitted with drug poisoning to Aalborg University Hospital during one year in 2017-2018. Median age was 30 [22-49] years, and 58% were female. Fifty % were suicide attempts. In most cases, involved drugs were identified by history taking; blood analysis barely revealed any additional paracetamol and salicylicate poisonings. Drugs prescribed to the patient or available over the counter were involved in nearly two thirds of cases. Weak analgesics dominated by paracetamol (n=91, 35%) was the most frequently involved group of drugs followed by opioids and benzodiazepines. Gender differences were observed with respect to involvement of weak analgesics and central stimulants. A higher prevalence of unidentified involved drugs was observed in 26 cases (10%) in which the length of admission exceeded two days and/or intensive care was needed. No deaths, cardiac arrhythmias, or physical complications occurred. Thus, current handling of the acute poisoning seems effective in most cases. However, a more tailored use of blood analyses including a toxicological screen in selected cases may represent an opportunity for improvement.

Keywords

Toxicity, paracetamol, antidote, psychotropic drugs, epidemiology

Introduction

Acute drug poisonings lead to a significant number of hospitalizations in European countries.[1-3] Involved drugs may vary from time to time and between countries. In a Danish report based on data from the Danish Poison Information Center collected in 2007-2009,[4] a third of all calls concerned pharmaceuticals with paracetamol as the most commonly involved individual drug. Since then, the Danish National Health Agency prohibited over-the-counter sale of paracetamol packages containing more than 10 grams in 2013 to reduce availability of large doses for prevention of intentional poisoning. Furthermore, the illegal drug market in Denmark changes over time with e.g. methadone superseding heroin as the main cause of fatal poisoning in drug users,[5] and new psychoactive substances (NPS) such as fentanyl analogues continuously entering the illegal drug market. [6] In addition, prescription patterns of psychotropic medications, which are often involved in poisonings, [7] may change over time. Altogether, epidemiology of poisonings is ever changing, and updated knowledge about current trends of involved drugs and demographics of patients is important to maintain quality in diagnostics and treatment, as well as to recognize potential areas for prophylactic efforts.

The aim of the present study was to describe involved drugs, demographics, and clinical outcome in patients admitted with acute drug poisoning to a Danish university hospital. Secondly, we wanted to explore the use of blood analysis of paracetamol and salicylic acid for diagnostics, and to characterize cases needing a hospital stay exceeding two days, and/or admittance to the intensive care unit in order to explore potential improvement opportunities with respect to outcome and use of resources.

Methods

Design and identification of patients

We performed a cross-sectional study of all cases hospitalized with a diagnosis of drug poisoning through the Clinical Decision Unit (CDU) at the Acute and Trauma Center, Aalborg University Hospital, during 365 consecutive days in 2017-2018. The Acute and Trauma Center constitutes a gateway to the hospital and comprises the Accidents and Emergency Department (A&E) plus a 36-bed CDU. All patients are initially evaluated at the A&E and those requiring hospitalization come through the CDU from which they can be transferred to other hospital wards including the Intensive Care Unit (ICU). Patients can also stay in the CDU for up to 48 hours before being discharged. Patients were identified by searching the hospital's database using ICD codes covering poisoning with prescription drugs and illegal psychotropic drugs (DT36-DT509, DF110-DF1106, DF120-DF1206, DF130-DF1306, DF140-DF1406, DF150-DF1506, DF160-DF1606 or DF190-DF1906). Patients with a diagnosis of poisonings with ethanol (DT510), carbon monoxide (DT580), and other gases (DT59) were excluded. Children are initially assessed by and admitted to the Pediatric Department at Aalborg University Hospital, which is localized and administered separately from the Acute and Trauma Center. Thus, children were not included in the present study.

Collection of data

The authors CUA, LPN, and AEO collected data by assessing the relevant part of the patient record. Demographics, comorbidities, concomitant medication, and involved drug(s) were extracted. Symptoms at the time of admission were recorded by checking preformed categories (unconsciousness, agitation, respiratory depression, seizures, dizziness, none, confusion, nausea, vomiting, sedation, urinary retention, palpitations, pain, bleeding, and

other). If the category “other” was checked, the symptoms were described and reviewed after complete collection of data. Based on this, a new category “neurological symptoms”, encompassing visual disturbances, tremor, muscular rigidity, movement disorders, and speech disorders was formed. The first measured value of Glascow coma score (GCS), blood pressure (BP), temperature (Tp), respiratory rate (RR), saturation (SAT), and QTc interval (QTc) on the electrocardiogram (ECG) was recorded. QTc was taken as the value generated by the ECG machine. First measured values of c-reactive protein (CRP), leukocyte count, estimated glomerular filtration rate (eGFR), sodium and potassium values, alanine-aminotransferase (ALAT), coagulation factors II+VII+X (INR), blood glucose, and result of arterial blood gas analysis, according to hospital routines were also extracted. Values of eGFR >90 ml/min/1.73m^2 were given the value 91. Furthermore, we noted any drug analysis performed on blood as well as the result, para clinical diagnostic examinations, treatment modalities, transferral to intensive care unit, length of hospital stay, complications or functional impairment at discharge, and mortality after six months.

Definition of severe poisoning and abnormal clinical values

Severe poisoning was defined as a hospital stay exceeding two calendar days and/or involving admission to intensive care unit (ICU). Length of hospital stay was calculated in days by subtracting the date of admittance from the date of discharge. Abnormal clinical values were defined as follows: Low BP: systolic BP< 100 mmHg, high BP: systolic BP> 180 mmHg, abnormal Tp: Tp<36.4 or Tp>38.0, low SAT: SAT <95%, low RR: RR<12/min, decreased GCS (GCS ↓): GCS<14, and long QTc: QTC>480ms.

Data handling, statistical analysis, and reporting

Study data were entered in REDCap (Vanderbilt, USA) electronic data capture tools hosted at Aalborg University.[8] If the same unique patient was admitted more than once during the study period, it was registered as a new case each time, because the involved drugs and doses could differ between episodes. However, we calculated demographic data for both individual cases and unique patients.

Data were exported for statistical analysis or graphics in STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). Distribution of variables was evaluated by histograms and Q-norm plots. Data with normal distribution were summarized as means ± standard deviations (SDs). Non-parametric data were summarized by medians [25^{th} percentile, 75^{th} percentile]. Differences between groups in parametric and non-parametric data were tested by t-test and Wilcoxon's signed rank test, respectively. Binary outcomes were compared by chi^2-test. Missing data were not imputed. In case of non-complete data, the number of cases included in the analysis is shown by (n=x) in tables.

Blood analyses for identification of poisonings with paracetamol and salicylic acid was assessed as follows: All cases in whom blood analyses were performed were identified and reviewed. Cases in which paracetamol or salicylic acid were revealed by history taking were subtracted. In the remaining cases, concentrations were reviewed according to whether they were above therapeutic interval according to laboratory reference values. The lower limit of detection for paracetamol was 7.94 µM.

The manuscript was prepared following the STROBE checklist for cross-sectional studies.[9]

Ethics

The study was registered at the Danish Data Protection Agency. In accordance with Danish legislation (Act on Research Ethics Review of Health Research Projects § 14 stk. 2 dated 15/09/2017 and the Danish Health Act § 46 stk. 2 dated 02/11/2018), the Danish Patient Safety Authority approved the project, including transmission of the data from the patient records. Data were handled in accordance with the General Data Protection Regulation (GDPR) and the Danish Data Protection Act.

Results

Our search identified 261 admissions due to acute drug poisoning in 227 unique patients. Fifteen cases admitted with a diagnosis of alcohol poisoning, and 13 cases of poisoning with carbon monoxide or other gases during the study period were excluded. Two-hundred-and-two patients were admitted once, 21 patients were admitted twice, and 4 patients more than twice. Table 1 shows the demographics of cases and unique patients, respectively. Median age of all cases was 30 [22-49] years, and 151 (57.9%) were female. The poisoning was a suicide attempt 130 (49.8%) and not a suicide attempt in 110 (42.2%). In 21 cases (8.0%), intentionality was not reported.

A conclusion about the involved drugs was stated in 241 cases (92.3%). In most cases, a single medication or illegal drug was involved, and co-ingestion of ethanol was stated in 85 cases (32.5%) (Figure 1.a). Groups of drugs involved in more than ten cases are shown in Figure 1.b. Weak analgesics were most common (n=105, 40.2%) followed by opioids (n=42, 16.0%) and benzodiazepines (n=40, 15.3%). Paracetamol was by far the most frequently involved individual drug (n=91, 34.8%) (Figure 1.b). Medication prescribed to the patient or/and over-the-counter medication was taken in overdose in 167 cases (63.9%).

Weak analgesics was the most commonly involved group of drugs in all age groups, but the relative frequency among the other involved groups tended to vary. Cardiovascular drugs were almost exclusively involved in cases with age >65 years (Figure 2.a). Weak analgesics were significantly more likely to be involved in female cases, whereas central stimulants and unknown substances were involved in a higher number of male cases (Figure 2.b). Sex differences with respect to weak analgesics and central stimulants were present in all age groups (Figure 2.c and 2.d).

In most cases, the diagnosis of the involved drug(s) was based on information provided by the patient (n=205, 78.5%) or relatives (n=23, 8.8%). Thoracic X-ray, cerebral CT-scan or lumbar puncture for assessment of differential diagnoses were used in a total of 11 cases (4.2%). Medication concentrations were measured in 179 cases (68.6%). Paracetamol was measured in 176 cases (67.4%), salicylic acid in 129 cases (49.4%), and other medications in four (1.5%). Paracetamol was detected in 71 (27.2%) of which history taking had revealed paracetamol poisoning in 68 (26.1%). In less than three of the remaining cases, the concentration was above therapeutic range. Salicylic acid was detected in nine cases (3.4%), and only in concentrations within therapeutic range (below 2 mM).

Antidotes and activated charcoal were the most common treatment modalities used in 131 (50.2%) and 84 (32.2%) cases, respectively. No in-hospitalization deaths occurred, and no cardiac arrhythmias were observed. In three patients, telemetry for cardiac monitoring was undertaken. Less than three patients developed physical sequelae that resulted in increased need for domiciliary care after discharge. After 6 months' follow-up, seven patients with a median age of 52 [43-91] years had died.

Twenty-six cases (10.0%) fulfilled the present study's definition of severe poisoning. Seven (2.7%) were admitted to ICU; four on the same calendar day as they entered the CDU. Hospitalization exceeded two days in 22 (8.4%). The group with severe poisoning differed statistically significantly from the remaining cases by a higher occurrence of unknown involved drugs (Figure 3.a), hallucinations/agitation and neurological symptoms, (Figure 3.b) while there were no differences with respect to clinical findings (Figure 3.c). The group with severe poisoning also had a significantly higher mean CRP, leukocyte count, and lower median sodium levels (Table 2). Furthermore, this group tended to include more men, have a higher age, and a higher ALAT compared to the remaining cases (Table 2). More than 20 different individual drugs were involved in the poisonings in the 26 cases with severe poisoning, and paracetamol was the most frequent drug (n=6).

Discussion

Pattern of involved drugs

One of main findings of our study was that nearly two thirds of poisonings were caused by medication available to the patients by legal means. This suggests that efforts to prescribe the least toxic medication and to restrict access can reduce overall harm related to poisonings. However, weak analgesics mainly driven by young female cases poisoned with paracetamol was still by far the most common finding despite the Danish enforced reduction of pack size of paracetamol available over the counter. Similar restrictions have been implemented in other countries, [10, 11] but still, a recent report from Ireland found that the rate of intentional overdoses with paracetamol increased over time in young females.[11] Thus, the regulation has not eliminated paracetamol as the leading cause of poisoning-related hospitalizations in young females. Even though our data do not reveal if

the severity of the paracetamol poisonings has been reduced after 2013, our data suggest a need for further prophylactic measures to reduce poisonings with weak analgesics, especially in young women.

Opioids and benzodiazepines including benzodiazepine-like medications were the second and third most common groups of involved drugs, respectively. This agrees well with the toxicity and addictive potential of these drugs in combination with a considerable co-existence of illicit drug misuse and psychiatric disease disposing to self-harm in Denmark as described by Reuss et al. [7] Poisoning due to central stimulants primarily occurred in young male cases, and cocaine was most frequently involved. Cocaine is of increasing concern in Denmark, where it is found in an increasing number of drug seizures and fatal poisonings in drug addicts.[5] Furthermore, increasing abuse of cocaine is a concern in USA and other European countries, [12, 13] indicating that information to young people about the dangers of cocaine is crucial. Our data point towards young men as a primary target for prophylactic efforts to reduce use and acute poisonings with cocaine and other central stimulants.

In the present study, antidepressants were involved in less than 8% of cases, and tricyclic antidepressants (TCAs) known to cause a relatively high risk of cardiac toxicity in overdose [14] were not encountered. Thus, increased use of selective serotonin reuptake inhibitors (SSRIs) instead of TCAs may have decreased the occurrence of severe poisonings caused by antidepressants. Although we do not know the incidence of fatal TCA poisonings occurring outside the hospital, a report based on legal autopsies in psychiatric patients in Denmark in 2013-2015 [7] found that SSRIs were detected considerably more frequently than TCAs in cases dying from poisoning. This supports that TCAs' role in poisonings is

decreasing. Interestingly, quetiapine was the fourth most frequent single drug in our study in contrast to the study from 2011 [4] in which chlorprothixene was the most frequently involved antipsychotic. This may also reflect an altered prescription pattern; quetiapine is one of the most used antipsychotics in Denmark [15], and may, additionally, have abuse potential. [16]

Diagnosis and treatment

The poisoning resolved within 1-2 days in more than 90% of cases with supportive treatment, use of antidote, and/or activated charcoal. Thus, the current way to diagnose and treat poisoned patients seems adequate in most cases with respect to the acute situation. Diagnosis was predominantly made by history taking and use of other diagnostic tools was limited. Measurements of paracetamol and salicylic acid barely identified any patients intoxicated with these drugs that were not identified by history taking. Thus, use of these analyses could be reduced to cases poisoned by an unknown agent in addition to cases where the patient claims to be poisoned with paracetamol or salicylic acid. In the latter, a quantitative analysis may have prognostic value. In 7%, the involved drug(s) remained unknown, and this was associated with a more severe poisoning. Thus, a toxicological screening analogous to the one we perform in legal autopsy cases [17] might be useful to guide treatment in patients with severe poisoning caused by an unknown substance. Furthermore, a toxicological screening could be a key to expose emerging NPS that may pose a particular risk to drug users due to unknown potency and toxicity.[18] However, to meet the needs in the acute situation, the toxicological analysis we use in forensic case work [17] should be modified in order to enable faster reporting of the results.

Patients with severe poisonings

One tenth of cases required a longer observation period or intensive care, and these differed from the rest by a higher rate of unknown involved drugs, agitation/hallucinations, neurological symptoms, higher CRP and leukocyte counts, and lower sodium levels. These characteristics could assist early identification of patients at risk of a more severe clinical course. However, more research is needed to identify how these factors could be included in e.g. predictive tools. An increased CRP and leukocyte count may reflect acute phase response in relation to the poisoning. The tendency towards a higher level of ALAT could be related to ingestion of higher paracetamol dose as the duration of N-acetyl cysteine depends on paracetamol concentration and hepatic enzyme levels. [19] A recent study [20] found that age >55 years, a GCS <6, and respiratory insufficiency were the most prominent factors associated with need for intensive care. Our data also pointed towards increased age as a risk factor for a longer hospitalization or stay at intensive care unit. However, less than five patients had GCS <6, and a low SAT according to the definition in the present study occurred with the same rate in patients with and without severe poisoning. The finding that agitation and/or hallucinations was associated with severe poisonings was not expected. It may be related to risky behaviour in male drug users taking central stimulants or unknown drugs, which results in a more complicated clinical course.

Study limitations

The retrospective design has immanent limitations and precludes focused interview and structured observations. Furthermore, the identification of cases relies on the diagnoses given by the attending physicians. We cannot rule out that some cases could be missed due to misclassification. On the other hand, we assessed the relevant part of the records of all

included patients meaning that our material does not contain patients misclassified with a poisoning diagnosis. We identified relatively few elderly poisoned patients, which may be prone to e.g. digoxin or metformin poisonings due to decreased renal function, or poisonings due to drug-drug interactions caused by polypharmacy. In contrast to evident overdose, there might be a risk that other diagnoses could be given to this type of poisonings. On the other hand, the design may reduce selection bias considerably as all identified cases are included. We excluded 15 cases with a primary diagnosis of poisonings with ethanol in order to focus on poisonings with medications and illegal drugs. Although we cannot exclude that medications or drugs contributed to the admission in these cases, we do not suspect that it would significantly affect the conclusions. Additionally, it is possible that a few patients could be transferred directly to the ICU at our hospital after being initially treated at another hospital and therefore not be identified in our search. Finally, the fact that one unique patient could account for more than one case may bias the results. However, one unique patient represented the vast majority of cases.

With respect to the involved drugs, we have no objective findings to verify the information given by patients except for paracetamol poisonings where intake of the drug could be confirmed. In most cases, the attending physician touched upon the question of suicide attempt suggesting a fair quality of these results. However, cultural differences in the patient-physician relationship may influence the willingness of patients to tell about their intake, which may affect the external validity of our finding regarding analysis of paracetamol and salicylic acid levels as well as intentionality.

In the present study, we limited evaluation of outcome to complications regarding physical health in the acute situation. However, psychiatric evaluation and follow-

up of patients with intentional poisonings or accidental poisonings due to illegal drugs is a very important aspect of poisoning treatment. The fact that 25 unique patients were admitted due to poisoning more than once during the study period, and seven with a median age of 52 years died within six months' follow-up underlines that acute poisoning is a risk factor for serious future events.

Conclusions

Weak analgesics dominated by paracetamol, opioids and benzodiazepines were the most frequently involved drugs in the present study. Gender differences suggests that differentiated prophylactic efforts to reduce poisonings with weak analgesics in women, and central stimulants in men may be warranted. The recovery of most cases within 1-2 days suggests that current diagnostics and acute treatment is adequate in most cases. We suggest that developing a broad and fast toxicological blood analysis might help to guide treatment in cases severely poisoned by an unknown substance.

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Conflict of Interest Statement

None declared.

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Table 1. Demographics

		All cases	**Unique patients**
Number		261	227
Age	Years	30 [22-49]	31 [22-51]
Female sex	n (%)	151 (57.9)	126 (55.5)
Height (N=117)	cm ± SD	171 ± 10.2 (n=117)	170.9 ± 10.2 (n=100)
BMI	Kg/m^2	25.6 ± 6.1 (n=102)	26.0 ± 6 (n=87)
Any co-morbidity	n (%)	204 (78.5)	172 (75.8)
Psychiatric disease	n (%)	156 (59.8)	128 (56.4)
Depression	n (%)	*35 (13.4)*	*30 (13.2)*
Chronic alcoholism	n (%)	*35 (13.4)*	*32 (14.1)*
Personality disorder	n (%)	*32 (12.3)*	*24 (10.6)*
Drug addiction	n (%)	62 (23.8)	55 (24.2)
Cardiovascular disease	n (%)	34 (13.0)	33 (14.5)
Endocrine disease	n (%)	26 (9.9)	24 (10.6)
Respiratory disease	n (%)	27 (10.3)	24 (10.6)
Gastrointestinal disease	n (%)	23 (8.8)	20 (8.8)
Total number of prescribed medications		3 [1-6]	3 [0-7]

Table 1. Demographic characteristics of all cases and unique patients.

Table 2. Characteristics of cases without and with severe poisoning

		Not severe		**Severe**		P value
Number of cases	n (%)	235 (100)		26 (100)		-
Age	Years	30.0 [22-48]		41 [25-64]		0.07
Female sex	n (%)	140 (57.7)		11 (42.3)		0.09
Any co-morbidity	n (%)	181 (77.4)		23 (88.4)		0.2
Psychiatric co-morbidity	n (%)	138 (58.7)		18 (69.2)		0.3
Chronic alcoholism	n (%)	30 (12.7)		5 (19.2)		0.35
Drug addiction	n (%)	55 (23.4)		7 (26.9)		0.7
Number of involved drugs	n	1 [1-2]		1[1-2]		0.8
Co-ingestion of alcohol	n (%)	77 (32.8)		8 (30.8)		0.8
Suicide attempt	n (%)	117 (49.8)		13 (50.0)		1
CRP	mg/l	2 [0.7-5.7]	(n=209)	4.6 [1-15]	(n=23)	0.047
Leukocytes	10^9/l	8.2 [6.8-10.2]	(n=220)	10.3 [8.6-11.8]	(n=25)	0.001
eGFR	ml/min	91 [91-91]	(n=212)	91 [91-91]	(n=26)	0.3
Sodium	mmol/l	141 [140-143]	(n=225)	140 [139-141]	(n=25)	0.03
Potassium	mmol/l	3.8 [3.6-4.1]	(n=225)	3.9 [3.6-4.3]	(n=25)	0.8
ALAT	U/l	18 [13-31]	(n=223)	27 [16-42]	(n=25)	0.054
INR		1.1 [0.9-1.1]	(n=221)	1.1 [1-1.1]	(n=24)	0.6
Glucose	mmol/l	5.7 [5.2-6.5]	(n=201)	6.2 [5.4-8.0]	(n=21)	0.1
pCO_2	kPa	5.2 [4.7-5.75]	(n=56)	5.1 [4.3-6.4]	(n=11)	0.8

Table 2. Characteristics and laboratory values in patients without and with severe poisoning.

Definitions: Not severe: Cases with hospital stays ≤2 days and not admitted to intensive care unit. Severe: Cases with hospital stays >2 days and/or admitted to intensive care unit.

Abbreviations: CRP: C-reactive protein, eGFR: estimated glomerular filtration rate/1.73 m^3, ALAT: alanin-amino-transferase, INR: coagulation factors II+VII + X

Figure 1. Involved drugs

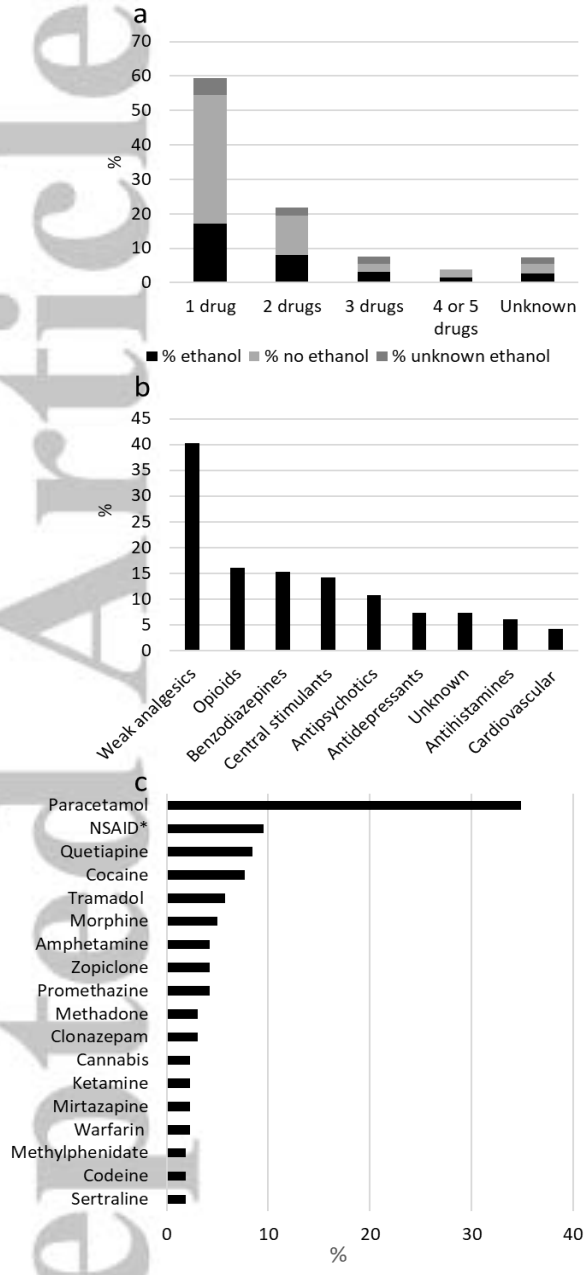

Figure 1. a: Bars show the proportion of cases in which 1, 2, 3, 4 or 5, or an unknown number of medications or drugs were involved. Subdivisions of bars show the proportion of cases in which alcohol was co-ingested. Ethanol is not included in the count of drugs (1, 2, 3, 4 or 5). **b** and **c**: bars show the proportion of all cases in which the respective drug classes (**b**) and individual drugs (**c**) were involved in the poisoning. Substances involved in ≥ 5 cases are shown. *Individual NSAIDs were not registered. Abbreviations: drugs: medications or illegal drugs, ethanol: ethanol co-ingestion.

Figure 2. Involved drug classes according to age and sex

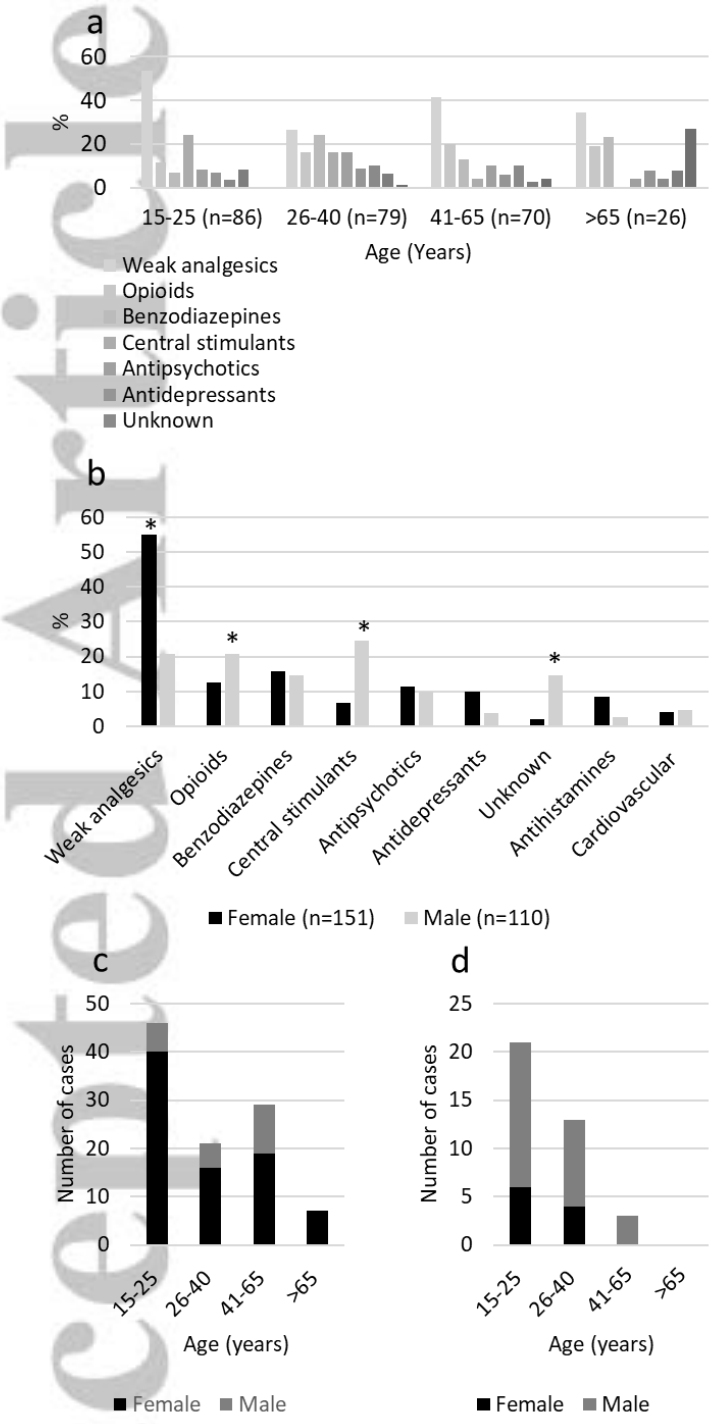

Figure 2. a and **b** show the percentage of cases in each age and sex group, respectively, in which the separate drug classes were involved. **c** and **d** show the absolute number of cases according to sex and age in which weak analgesics and central stimulants were involved, respectively. Results involving less than three individuals are not shown *: p-value of chi^2 test (female vs male) <0.05.

Figure 3. Involved groups of drugs, symptoms, and clinical findings in patients with severe poisoning

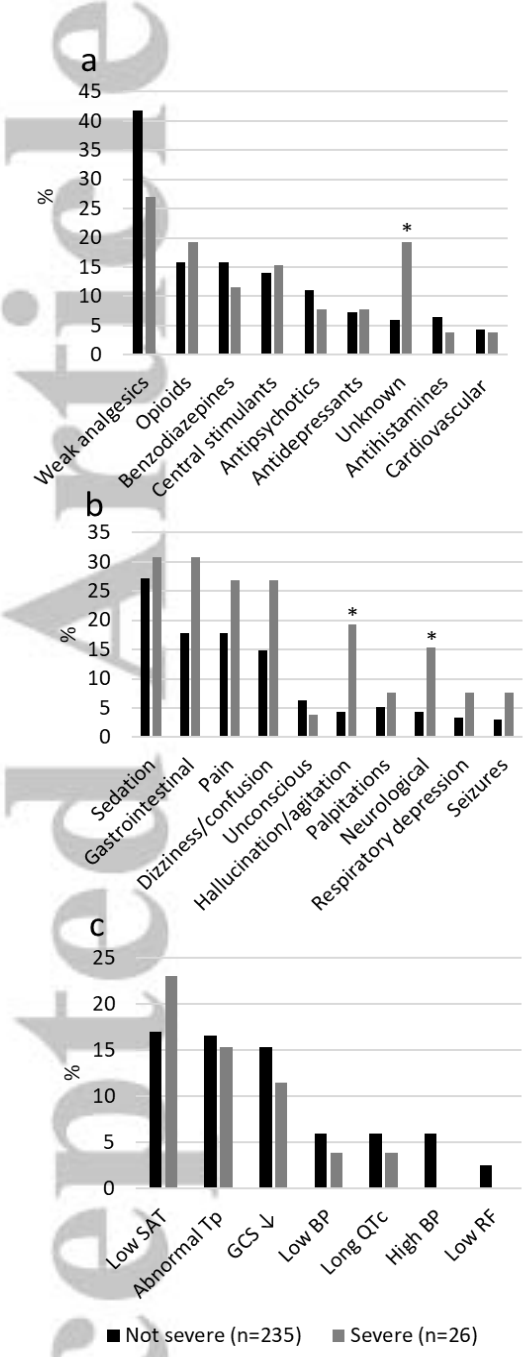

Figure 3. Involved groups of drugs (a.), symptoms (b.), and clinical observations (c.) in cases without (Not severe) and with a stay exceeding two calendar days and/or admission to intensive care unit (Severe), respectively. More than one medication or illegal drug, symptom or clinical finding could apply per case. *: p-value of chi^2 test (not severe vs severe)<0.05. Abbreviations: SAT: oxygen saturation, Tp: temperature, GCS: Glascow coma score, BP: blood pressure, QTc: corrected QT-interval, RF: respiratory frequency.