Patterns of toxicity and factors influencing severity in acute adult trimipramine poisoning

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Trimipramine poisoning is a relatively frequent occurrence.
- Although differences between tricyclic antidepressants in receptor affinity and adverse effects profile are documented, previous overdose studies mostly summarize all tricyclics or they only compare the fatality rate of different antidepressants including trimipramine.
- The factors influencing the severity of trimipramine poisoning have not been previously investigated.

WHAT THIS STUDY ADDS

- We have demonstrated that trimipramine poisoning mainly occurs as a consequence of suicide attempts in young female patients and that moderate poisoning can already occur after ingestion of doses in the high therapeutic range.
- We were able to identify a clear dose–effect relationship, a minimal dose for moderate and severe toxicity and the dose bearing a 50% risk of developing moderate or severe symptoms.
- Our study suggests that patients with trimipramine poisoning might benefit from an early gastrointestinal decontamination.

AIMS

To analyze the clinical features of trimipramine poisoning, identify a minimal toxic dose, and the dose bearing a 50% risk of developing a moderate, severe or fatal outcome.

METHODS

All acute adult trimipramine monointoxications reported by physicians to the Swiss Toxicological Information Centre between January 1992 and December 2009 were identified.

RESULTS

Two hundred and thirty cases (26 confirmed and 204 probable) were analyzed, the mean age was 35.7 years and 74% were females. One hundred and thirty-seven patients showed mild, 54 moderate and 21 severe symptoms. Three cases were fatal due to refractory cardiovascular collapse. Ninety-three per cent of the events were attempted or completed suicides. The most common symptoms were central nervous system depression (79.2%), tachycardia (19.1%) and QT_c prolongation (13.9%). The severity of poisoning depended significantly on the ingested dose ($P < 0.001$). The minimal dose for moderate symptoms was 250 mg (median dose 1.2 g) and 850 mg for severe symptoms (median dose 2.7 g). The dose for a 50% risk of developing a moderate, severe or fatal outcome was 5.11 g. In 38 patients early gastrointestinal decontamination was performed. Overall, these patients ingested higher trimipramine doses than the late- or not-decontaminated patients ($P = 0.113$). The median doses were also higher in the decontaminated group within each severity category except in the fatal cases.

CONCLUSIONS

We demonstrated that moderate trimipramine poisoning can already occur after ingestion of doses in the high therapeutic range. Poisoned patients have to be monitored for central nervous system depression, dysrhythmias and QT_c prolongation. Early decontamination might be beneficial.

Introduction

Trimipramine is a tricyclic antidepressant (TCA) mainly used in the treatment of major depression, as well as for insomnia and pain relief in chronic pain syndromes [1–3]. It has been on the market since 1962 in Switzerland, where it is available as 25, 75 and 100 mg tablets, as well as a liquid formulation with a 4% (40 mg ml⁻¹) concentration of trimipramine, and since 1979 in the United States.

Trimipramine has a well-defined adverse effects profile, which is quite similar to other TCAs. Compared with amitriptyline, trimipramine is more sedative and anxiolytic whereas it has less anticholinergic side effects [1, 4, 5]. In contrast to other TCAs, trimipramine blocks the presynaptic dopamine receptors, which may contribute to its antidepressant activity [2]. Furthermore, it has only a very weak inhibitory activity on norepinephrine and serotonin re-uptake, as well as a lack of down regulation of β_1 -adrenoceptors, showing less cardiovascular side effects [1, 2, 6]. This lack of re-uptake inhibition is also probably responsible for the absence of hyperpyrexia in combined treatment with monoamine oxidase inhibitors [2, 6]. Trimipramine does not suppress REM sleep in humans [1].

Trimipramine is a relatively frequently overdosed antidepressant. In a study investigating suicides with psychotropic drugs in Switzerland in 1994, antidepressants were involved in 20.3% of all cases and trimipramine ranked third in this group [7]. A similar result can be found in a recent German study, where trimipramine was the second most frequently ingested antidepressant in cases of suicides with this class of drugs, and was clearly over-represented in relation to its prescription frequency [8].

Symptoms of trimipramine poisoning include depression of the central nervous system (CNS) ranging from somnolence to coma, as well as agitation, confusion, disorientation, hallucinations and seizures (which can also occur within the therapeutic dose range). Cardiac manifestations include alterations in heart rate and blood pressure, widening of the QRS complex and other conduction abnormalities, QT_c prolongation and asystole. Respiratory depression may be observed in severe poisonings.

Supportive care with protection of the airways and monitoring of the cardiovascular system are the cornerstones of treatment for patients with trimipramine overdose. Gastrointestinal decontamination with activated charcoal should be considered for patients presenting within a few hours of a large overdose [9].

Although differences between TCAs in their receptor affinity and the adverse effects profile are documented, previous TCA overdose studies mostly summarize all tricyclics [10, 11] or they only compare the fatality rate (deaths per million National Health Service prescriptions or number of suicide deaths corrected by defined daily doses per 1000 inhabitants per day) of different antidepressants including trimipramine [8, 10, 12]. The few publications that address specifically overdoses with trimipramine are

predominantly case reports [13, 14]. Studies focusing exclusively on trimipramine poisonings, their clinical features and the factors influencing the severity of poisoning, are lacking to our knowledge in the medical literature.

We report a retrospective study of consecutive trimipramine overdoses over an 18 year period to investigate the influence of age, gender and weight on the severity of poisoning, and to evaluate the effect of decontamination measures. We also aimed at identifying a minimal toxic dose and the dose bearing a 50% risk of developing moderate or severe symptoms.

The goal of this study was to delineate factors that may contribute to the timely identification of moderate and severe trimipramine poisoning cases, with a view to improving management of patients with acute intoxication and avoiding unnecessary treatments.

Methods

Data acquisition and study design

The Swiss Toxicological Information Centre (STIC) provides 24 h 7 days a week nationwide free medical advice in cases of poisoning to health professionals and the general public. The referral population is about 7.8 million people. Demographic and detailed clinical information on exposure cases, such as age, gender and weight of the patient, circumstances of poisoning, ingested doses of all substances involved, symptoms and causality, are recorded in a systematic and standardized manner by a physician trained in clinical toxicology and blinded to any study hypotheses at the time of the initial phone call. These data are prospectively entered into an in-house structured electronic database [15]. For reports by health care professionals, the STIC collects additional specific clinical data, including complementary information on type and, if applicable, concentration of the substances ingested (drug screening, plasma drug concentration, blood alcohol concentration), current history and circumstances of substance intake, observed symptoms and signs including heart rate and blood pressure, Glasgow Coma Scale (GCS) score, an electrocardiogram, therapeutic interventions and any decontamination measures performed, latency to decontamination, observed clinical course and eventual medical complications, using a standardized report form which is sent to the treating physician. Hospital physicians are also asked to provide a discharge letter and any laboratory results, as well as the results of other examinations. This follow-up information is then matched with the data taken during the initial call and entered into the database to complement the case files. At this stage evaluation of severity and causality is performed. Each case is then reviewed by a senior clinical toxicologist to ensure completeness and correctness of entered data before finalizing recording into the database. Additionally, all cases included in the study have been reviewed in detail by the

first author. The very rare discrepancies have been resolved by consensus in an expert panel including a clinical toxicologist, a senior clinical toxicologist, a clinical pharmacologist and a general internist.

The present study was designed as a retrospective review of cases of acute trimipramine overdose in adults, which were reported by physicians to the STIC between January 1992 and December 2009.

Inclusion criteria

The following criteria had to be met for reported cases to be included in the study:

- Acute single substance poisoning with trimipramine
- Patient age ≥ 16 years
- Availability of written feedback from the treating physician with sufficient data about symptoms and evolution
- Ingested trimipramine dose of 100 mg (= highest approved initial therapeutic dose) or higher
- Ingested trimipramine dose quantifiable within a limit of $\pm 10\%$ (if dose range was reported)
- Confirmed or likely causal relationship between exposure and clinical effect. Causality assessment was based on a clear temporal relationship between drug ingestion and symptoms, absence of other drugs or diseases that could explain the symptoms, and the presence of symptoms that are described for the drug in question or are plausible from a pharmacodynamic point of view. Since these criteria could not be used for asymptomatic patients, these cases were judged according to the ingested dose reported by the patient or another person close to the patient. Analytical detection of the substance in a body fluid defined a case as confirmed [16].

For the analysis of the effect of gastrointestinal decontamination procedures, we considered cases in which activated charcoal was administered and/or gastric lavage was performed. Early decontamination was defined as a gastrointestinal decontamination measure initiated within 1 h of ingestion of the trimipramine overdose.

Data classification

According to the Poisoning Severity Score (PSS) developed by the European Association of Poison Centres and Clinical Toxicologists, the International Programme on Chemical Safety and the European Commission [17], the severity of symptoms of individual patients were classified as 'minor' if only minor symptoms were present, as 'moderate' if at least one moderate symptom was recorded, as 'severe' if at least one severe symptom was observed or as fatal. The classification of symptoms according to their severity is shown in Table 1 with details in the footnote.

Statistical evaluation

Statistical analysis was performed with SPSS 18.0 (SPSS Inc. Chicago, IL, USA). The relationship between dose and sever-

ity was examined using multivariate ordinal logistic regression analysis with a polytomous universal model (PLUM). Decontamination, age, gender and weight were modelled as predictor variables. A Kruskal–Wallis test was conducted to evaluate differences between the five degrees of severity (asymptomatic, minor, moderate, severe and fatal) with respect to changes in dose. Follow-up tests were used to evaluate pairwise differences among the five groups by using the Bonferroni approach. Concerning decontamination, an analysis of covariance (ANCOVA) with a between-subjects factor (decontamination early vs. late or none) and a covariate (logarithm of dose) was used. In addition Kendall's rank correlation coefficients were calculated for analysis of dose–effect relationship. The dose for a 50% risk of developing a moderate severe or fatal outcome was calculated with the statistical software package R (R Development Core Team, 2011, R Foundation for Statistical Computing, Vienna, Austria) and the doBy package (Søren Højsgaard *et al.*, 2011, R package version 4.3.1).

Results

A search of our database identified 1976 cases related to trimipramine ingestion during the study period. The exclusion process is reported in Figure 1. A total of 230 cases fulfilling all inclusion criteria were available for analysis.

The demographic characteristics of the patients were as follows: 170 females (74%), 56 males (24.3%) and four cases (1.7%) for which gender was not specified. The age of the patients ranged from 16 to 77 years, with a mean of 35.7 years.

The causal relationship between trimipramine overdose and clinical effect was rated probable in 204 cases and confirmed (analytical detection in blood (9) or positive urinary toxicological screening for TCA (17)) in 26 patients. Fifteen of the 204 probable cases involved asymptomatic patients and were judged according to the reported ingested dose. Almost all exposures were due to suicide attempts or completed suicides (214 cases, 93%). The other 16 cases included 15 accidental ingestions (either erroneous intake because of confusion of medication or inadvertent ingestion, or ingestion of a higher dose than prescribed) and one patient (a chronic alcohol abuser) who ingested a bottle of liquid trimipramine in abuse to obtain a psychoactive effect.

The most common symptoms and signs involved the CNS and the cardiovascular system. Somnolence was by far the most frequently reported symptom (60.9% of the cases), followed by tachycardia (19.1% of the patients). Other frequent symptoms and signs were coma (18.3%), QT_c prolongation (13.9%), agitation (12.2%), dysarthria (10.9%), hypotension (8.7%), confusion/disorientation/delirium (7.4%), gastrointestinal symptoms (7%), widening of the QRS complex (6.5%) and convulsions (6%). Three patients (1.3%) developed asystole. Respiratory

Table 1

Clinical effects (n, %)

	Minor	Moderate	Severe
CNS			
Somnolence	140 (60.9%)		
Coma ¹		20 (8.7%)	22 (9.6%)
Agitation		25 (10.9%)	3 (1.3%)
Dysarthria	25 (10.9%)		
Confusion/disorientation/delirium		17 (7.4%)	
Seizures ²		10 (4.3%)	4 (1.7%)
Other symptoms of the nervous system ³	14 (6.1%)		
Dizziness	9 (3.9%)		
Gait disturbance, ataxia	7 (3%)		
Changes in muscular tonus	5 (2.2%)		
Hallucinations		3 (1.3%)	
Tremor	3 (1.3%)		
Extrapyramidal symptoms	3 (1.3%)		
Aggressiveness		2 (0.9%)	
Cardiovascular system			
Tachycardia ⁴	41 (17.8%)	3 (1.3%)	
QT _c prolongation ⁵	10 (4.3%)	22 (9.6%)	
Hypotension ⁶	14 (6.1%)	3 (1.3%)	3 (1.3%)
Widening of QRS complex ⁷	3 (1.3%)	12 (5.2%)	
AV block ⁸		6 (2.6%)	1 (0.4%)
Bradycardia ⁹	4 (1.7%)	2 (0.9%)	
Hypertension ¹⁰	6 (2.6%)		
Conduction abnormalities	6 (2.6%)		
Right bundle branch block ¹¹	3 (1.3%)	2 (0.9%)	
Arrhythmia ¹²		3 (1.3%)	1 (0.4%)
Asystole			3 (1.3%)
Respiratory system			
Respiratory insufficiency			6 (2.6%)
Aspiration pneumonia		4 (1.7%)	
Apnoea			2 (0.9%)
Various			
Gastrointestinal symptoms ¹³	13 (5.7%)	3 (1.3%)	
Dry mouth	12 (5.2%)		
Severe erosive gastritis			1 (0.4%)
Ocular symptoms ¹⁴	8 (3.5%)		
Miosis	6 (2.6%)		
Mydriasis	4 (1.7%)		
Diaphoresis	1 (0.4%)		
Urinary retention	1 (0.4%)		
Diabetes insipidus	1 (0.4%)		

¹moderate: GCS 8–9; severe GCS ≤ 7; ²moderate: simple; severe: multiple seizures; ³hypo- or hyperreflexia, paraesthesia and others not specified; ⁴minor: 100–139 beats min⁻¹; moderate: 140–179 beats min⁻¹; ⁵minor: QT_c >390 ms ♂, >440 ms ♀; moderate: QT_c >430 ms ♂, >485 ms ♀; ⁶minor: 80–100 mmHg; moderate: 55–79 mmHg; severe: <55 mmHg; ⁷minor: borderline value; moderate: <160 ms; severe: >160 ms; ⁸moderate: AV block I and II; severe: AV block III; ⁹minor: 51–59 beats min⁻¹; moderate: 40–50 beats min⁻¹; severe: <40 beats min⁻¹; ¹⁰minor: 150–189 mmHg; severe: >190 mmHg; ¹¹minor: partial; moderate: complete; ¹²moderate: ventricular extrasystoles, atrial fibrillation; severe: ventricular tachycardia, ventricular fibrillation; ¹³minor: nausea, vomiting, diarrhoea, epigastric pain, hypersalivation; moderate: repeated vomiting; ¹⁴diplopia, nystagmus, strabismus, feeble light reaction.

symptoms/signs were observed in moderate and severe poisonings and required intubation in 4.7% of the cases (in 2.6% because of respiratory insufficiency, in 1.7% due to aspiration pneumonia and in one case (0.4%) because of a laryngospasm that developed during activated charcoal administration). Two patients (0.9%) showed apnoeas. The reported symptoms and signs and their severity classification are shown in Table 1.

The outcome was fatal in three patients (1.3%), and 21 (9.1%) showed severe overall toxicity according to the poi-

soning severity score (Table 2). Fifty-four patients (23.5%) had moderate symptoms, 137 (59.6%) minor symptoms and 15 (6.5%) remained asymptomatic.

The ingested trimipramine doses ranged from 0.1 to 30 g (1.37 mg to 461 mg kg⁻¹ body weight), the mean ingested dose was 1.73 g (27.6 mg kg⁻¹ body weight) and the median dose 1 g (14.28 mg kg⁻¹ body weight).

Laboratory confirmation with quantitative trimipramine determination was available for six patients (one

Figure 1

Exclusion process for case selection

Table 2

Severe cases with ingested doses and symptoms/signs

Dose (g)	Dose (mg kg ⁻¹)	Most important symptoms/signs
0.85	*	Severe coma, seizures
1.25	19.23	GCS 6–7, important agitation
1.25	17.85	GCS 3, bradycardia
1.7	*	GCS 3, tachycardia
1.9	*	GCS 3, QRS widening
2	25	Severe agitation
2	22.22	Convulsive status epilepticus, respiratory insufficiency, ventricular tachycardia, hypotension, aspiration pneumonia
2.063	25.15	Seizures, tachycardia, hypotension
2.1	*	GCS 6, tachycardia, QT _c prolongation, QRS widening
2.25	37.5	GCS 6, hyperreflexia, myoclonia, tachycardia
2.5	41.667	GCS 7, respiratory insufficiency, supraventricular tachycardia
2.5	*	GCS 5, tachycardia
3	42.85	GCS 4, seizures, tachycardia, AV block I, QT _c prolongation
4	*	GCS 6, delirium, hypersalivation
4	66.66	Severe coma, seizures, AV block III, severe bradycardia, hypotension
5	83.33	GCS 3–4, tachycardia, AV block I
5	100	GCS 6–7, seizures, QT _c prolongation
5	83.33	GCS 3, seizures, QT _c prolongation
10	125	GCS 3, respiratory insufficiency, QT _c prolongation
10	*	GCS 3, seizures, hypotension, QRS widening
15	*	GCS 3, hypotension, QRS widening, QT _c prolongation, aspiration pneumonia

*Body weight not available.

minor, three moderate and two severe cases, described in Table 3).

Analysis and modelling for a dose–effect relationship by means of logistic regression (PLUM) did not show a significant dependency on age, gender or weight for the

Table 3

Cases with known plasma trimipramine concentrations

Age (years)/ Gender	Dose (mg kg ⁻¹ BW)	Decontamination and time to treatment	Plasma concentration (therapeutic: 0.5–1.2 µmol l ⁻¹)	Time from ingestion to blood drawing	Symptoms	Severity
23 F	150 mg 2.5 mg kg ⁻¹ BW	No decontamination	0.3 µmol l ⁻¹ (sub-therapeutic)	8 h	Somnolence, uneventful recovery	Minor
32 F	750 mg 12 mg kg ⁻¹ BW	Gastric lavage and charcoal 2 h post ingestion, sodium bicarbonate	1.44 µmol l ⁻¹ and 0.23 µmol l ⁻¹	Approx. 3 h and approx. 17 h	Single tonic-clonic seizure, disorientated, agitated, then somnolent. ECG: tachycardia, QRS 0.12 ms, right bundle branch block, prolonged QT _c	Moderate
46 M	1875 mg ? mg kg ⁻¹ BW	None	6.78 µmol l ⁻¹	Unknown	Comatose, suspected postictal state	Moderate
33 F	2200 mg 41.5 mg kg ⁻¹ BW	5 h post ingestion charcoal through nasogastric tube	3.21 µmol l ⁻¹	Approx. 5 h	Single generalized seizure (preexisting epileptic seizures), GCS 8–9, sinus tachycardia 123 beats min ⁻¹	Moderate
36 F	2250 mg 37 mg kg ⁻¹ BW	Intubation, gastric lavage, charcoal	4.54 µmol l ⁻¹	Approx. 3 h	Deep coma, hyperreflexia and muscular spasms	Severe
37 F	4000 mg ? mg kg ⁻¹ BW		3.8 µmol l ⁻¹	Approx. 3 h	Deep coma for 12 h, hypersalivation, ataxia and delirium	Severe

BW, body weight; QT_c, corrected QT interval.

Table 4

Doses for asymptomatic/mild, moderate and severe/fatal cases

Severity	Number of cases	Minimum dose and range (g)	Minimum dose and range (mg kg ⁻¹ body weight)	Median dose (g) (mg kg ⁻¹ body weight)	Mean dose (g)	SD
A/M*	152	0.1–30	1.4–461.5§	0.9 (12)	1.3	2.6
M†	54	0.25–10	7.7–57.1¶	1.2 (20)	1.5	1.4
S/F‡	24	0.85–25	17.9–277.7**	2.7 (55)	5.3	5.6

*asymptomatic/mild; †moderate; ‡severe/fatal; §information available for 91 cases; ¶information available for 28 cases; **information available for 16 cases.

severity of the intoxication. The severity of the intoxication was significantly related to the ingested trimipramine dose ($P < 0.001$; Table 4). The dose for a 50% risk of developing a moderate, severe or fatal poisoning was 5.11 g (95% confidence interval 2.0, 8.2) or 98 mg kg⁻¹ (95% confidence interval 18, 178), respectively. The differences between the ingested doses among asymptomatic patients vs. those showing minor toxicity, as well as among those showing minor vs. moderate toxicity, were not statistically significant, even though we observed a tendency towards higher doses among more severe cases. There was a significant difference ($P < 0.01$) between doses ingested by patients showing moderate symptoms vs. those developing severe toxicity. The same applies for dose differences observed between patients showing severe toxicity vs. those with a fatal outcome. The minimal dose for moderate symptoms was 250 mg (median dose 1.2 g) or 7.7 mg kg⁻¹ (median dose 20 mg kg⁻¹), respectively, and 850 mg (median dose 2.7 g) or 17.9 mg kg⁻¹ (median dose 55 mg kg⁻¹), respectively, for severe symptoms.

In three cases (1.3%) the outcome was fatal due to refractory cardiovascular collapse after ingestion of 8.4 g, 10 g and 25 g of trimipramine, respectively. In the first case, a 38-year-old woman was found comatose approximately 18 h after ingestion of 8.4 g (129 mg kg⁻¹ body weight) of trimipramine. The patient subsequently developed asystole, but transiently recovered after 1 h of cardiopulmonary resuscitation. She expired approximately 2 days later due to irreversible hypoxic brain damage. The ingestion of trimipramine was confirmed by a markedly increased plasma concentration (precise result unavailable). Another patient, a 45-year-old male, was found comatose approximately 30 min after ingestion of 10 g (143 mg kg⁻¹ body weight) of trimipramine. He initially showed no cardiovascular complications. Activated charcoal was administered on admission to the hospital. The patient developed a sinus bradycardia 2.5 h later, followed by refractory hypotension and finally cardiac arrest. Resuscitation efforts with sodium bicarbonate, an external pacemaker and catecholamines were unsuccessful. The third fatal case involved a 37-year-old female patient who ingested 25 g (278 mg kg⁻¹ body weight) of trimipramine. After the ingestion she vomited once and was found deeply comatose (Glasgow Coma Scale score of 3) approximately 2–6 h

later. A late gastrointestinal decontamination with activated charcoal was attempted. The patient was haemodynamically unstable with a blood pressure of 45/20 mmHg. Despite aggressive treatment with intravenous fluids, catecholamines, sodium bicarbonate, magnesium and glucagon, the patient developed pulseless electrical activity and cardiocirculatory arrest. The plasma trimipramine concentration was found to be markedly elevated (precise result unavailable).

In 38 patients (16.5%) with trimipramine overdose, early gastrointestinal decontamination (within 1 h of ingestion) was performed. In 84 patients (36.6%) decontamination was accomplished later than 1 h after ingestion and in 108 cases (47%) no decontamination was performed. Most patients received only activated charcoal and in a few cases an initial gastric lavage was followed by administration of activated charcoal. No patient received gastric lavage as the sole procedure. The two procedures were therefore analyzed together. The distribution of the severity categories among the different decontamination groups is shown in Table 5. As a measure of the strength of dependence between the ingested dose and the corresponding effect observed in late and not decontaminated patients we used the Kendall's rank correlation test and obtained a significant result (Kendall's tau beta = 0.38, $P < 0.001$). This dose–effect relationship was also significant for the group of early decontaminated patients (Kendall's tau beta = 0.46, $P < 0.001$). An analysis of covariance (ANCOVA) with the between subjects factor 'decontamination early vs. late or none' and the covariate 'logarithm of dose' revealed no significance ($P = 0.113$). Nevertheless, a tendency towards higher median ingested doses was observed for the early decontaminated group overall as well as in every severity category, except the fatal (Table 6).

Discussion

This study investigated the factors influencing the severity of trimipramine poisoning in adults. We found a significant correlation between ingested trimipramine dose and severity of poisoning. On the contrary, no correlation was found between age, gender or body weight and poisoning severity. The decision to prioritize absolute doses rather

Table 5Number of cases in every decontamination group: early (≤ 1 h), late and none with their respective severity

Decontamination	Severity					Total
	No symptoms	Minor	Moderate	Severe	Fatal	
Early	2	27	4	4	1	38
	5.3%	71.1%	10.5%	10.5%	2.6%	100.0%
Late	0	44	25	13	2	84
	0%	52.4%	29.8%	15.5%	2.4%	100.0%
None	13	66	25	4	0	108
	12.0%	61.1%	23.1%	3.7%	0%	100.0%
Total	15	137	54	21	3	230
	6.5%	59.6%	23.5%	9.1%	1.3%	100.0%

Table 6

Symptom severity and median ingested dose in early vs. late or not decontaminated patients

Severity	Early (≤ 1 h) decontamination		Late (> 1 h) or no decontamination	
	Number of cases	Median dose (g)	Number of cases	Median dose (g)
No symptoms	2	0.61	13	0.50
Minor	27	1.20	110	0.89
Moderate	4	1.65	50	1.10
Severe	4	2.75	17	2.25
Fatal	1	10.00	2	16.70

than doses corrected for weight (mg kg^{-1} of body weight) for the statistical analyses was due to the fact that information on weight and height is often inaccurate (estimated) or lacking in the critical care setting where poisoned patients are managed. In this study, information on weight was available for 135 patients.

Most patients included had a probable exposure (204) and in 26 cases the ingestion was analytically confirmed. However, serum trimipramine concentrations to corroborate the reported doses were available in only six patients. Therefore, we cannot exclude a possible inaccuracy of dose information in some cases, especially the suicidal ones, but tried to minimize this through our selection process. Moreover, major inaccuracies in the doses used in our analyses are not expected since there is increasing evidence from pharmacokinetic studies that the reported drug amounts in acute overdose are quite reliable for research purposes and allow a good estimate of the true ingested dose [18–20].

The over-representation of the female gender and the relatively low mean age of our patients may be explained by the fact that 93% of included cases were suicide attempts or completed suicides, as it is known that young women have the highest rates of suicide attempts among all age-by-gender groups. Accordingly, in the United States, poisoning was the most common method of suicide for women in 2004 [21, 22]. In contrast, the few patients who ingested trimipramine accidentally because of erroneous intake due

to confusion of medication or inadvertent ingestion, or ingestion of a higher dose than prescribed, were generally elderly institutionalized patients. The two main causes of trimipramine overdose in this study, i.e. suicide attempt and accidental ingestion, also explain the wide dose range observed in our cases. Ingested doses were considerably higher among patients attempting suicide compared with the patients ingesting trimipramine accidentally. Even within the group of patients overdosing on trimipramine in suicide attempts we observed remarkable differences in ingested doses. This phenomenon is probably due to those patients whose suicide attempt reflects a help-seeking behaviour, as they usually ingest lower doses than those who clearly want to die.

The identification of a minimal dose for moderate and severe symptoms (250 mg and 850 mg, respectively) and the dose bearing a 50% risk of developing a moderate, severe or fatal poisoning (5.11 g), may help clinicians in the evaluation process of acutely poisoned patients, allowing the timely identification of patients requiring hospital admission and advanced care. However, due to the limited number of cases included in this study, caution should be exercised in interpreting and generalizing these results. The detection of the minimal trimipramine dose of 250 mg or 7.7 mg kg^{-1} , respectively, for developing moderate symptoms deserves some attention because this dose is very close to the high therapeutic dose range. In patients at risk for deliberate self-harm, prescribers should therefore

be aware that toxic doses can be obtained with relatively few tablets, so that the implementation of strategies to limit and control access to this drug seems reasonable. Compared with a previous pre-hospital management consensus guideline [9] in which triage of trimipramine overdoses to medical care was recommended at a dose greater than 2.5 mg kg^{-1} , our finding of the minimal dose of 7.7 mg kg^{-1} for developing moderate symptoms seems to suggest a more favourable safety profile of the substance. However, caution is required when comparing these values, because the two reported thresholds are not identical, but their clinical relevance is reasonably similar. In any case, due to the absence of definitive evidence and to the partially discordant findings, we suggest that the final decision regarding patient disposition, should take into account the whole clinical picture and not only be based on ingested dose.

The symptoms of trimipramine poisoning described in this study are compatible with those reported in the literature [23, 24], with a clear predominance of CNS, with CNS depression as a cardinal symptom, and cardiovascular symptoms. Respiratory symptoms were mainly observed in severe cases. The reported frequency of seizures should be interpreted with caution. This may be an underestimate, since the possibility of some outcome misclassification cannot be ruled out due to the difficulty for the clinician in establishing the diagnosis of seizures in some cases. Moreover, particularly in the pre hospital setting, it is plausible that not all cases of seizures have been identified and recorded in the case history, as some episodes may be mild and missed by lay persons. However, it is likely that severe episodes, which are most relevant to the analysis, have not been missed.

All fatal cases were due to cardiovascular failure despite aggressive resuscitation procedures. Management in the intensive care unit is therefore mandatory for patients at risk for severe outcome.

We identified a tendency towards a benefit of gastrointestinal decontamination in the first hour after ingestion of the trimipramine overdose. These patients had rapid access to medical care facilities where treatment was promptly initiated. We are aware that this may be difficult in settings with limited resources and this may limit generalizability of our findings. Patients with late gastrointestinal decontamination and those not decontaminated were analyzed together assuming no benefit for late gastrointestinal decontamination on outcome after maximum plasma concentration has been reached [25]. Patients treated with activated charcoal within the first hour showed fewer and milder symptoms compared with those with no or late decontamination, after ingestion of comparable doses. Even if our results did not reach statistical significance, possibly because of the limited number of cases included in our study, the identified tendency towards a benefit for early gastrointestinal decontamination may be considered an important finding, since in the literature

only a few studies have shown a significant benefit for gastrointestinal decontamination, and these were mainly pharmacokinetic studies demonstrating a decrease of the relative absorbed fraction of the substance and an increase in clearance [18, 20]. Until further studies investigating the effects of decontamination procedures on the clinical course of trimipramine poisoning are available, we recommend the administration of activated charcoal, in the absence of contraindications, within 1 h of poisoning if severe symptoms are expected [25], considering its potential benefits and the low complication rate of this procedure observed in our study. Actually, we only observed two cases of vomiting with a clear relationship to charcoal administration and a case of laryngospasm during activated charcoal administration requiring intubation. Nevertheless we only recommend activated charcoal in intubated patients or in patients without disturbances of consciousness or signs/symptoms of ileus.

In summary our data show that trimipramine behaves like other tricyclic antidepressants in an overdose setting. This observation suggests that the main therapeutic mode of action is not relevant for intoxication, but that anticholinergic and antihistaminergic properties are.

Study limitations

The interpretation of our findings is limited by the retrospective nature of the study design. This implies that detailed information that may be relevant might not have been recorded at the time of the initial call, since data collection occurred separately from any study hypotheses. In addition, data from poison control centres are subject to reporting bias, as we do not know the percentage of cases reported to our centre [26]. A further limitation is that a high proportion of included patients were young adults and this may limit the generalizability of our findings. Furthermore, our strict inclusion/exclusion criteria, in particular the decision to only include monointoxications and cases with well-defined ingested doses led to small case numbers. However, we are convinced that these restrictions were necessary to be able to interpret the findings properly, in particular because we were not able to obtain trimipramine plasma concentrations in most cases to confirm the ingested amount. Moreover, a possible inaccuracy of dose information in some cases cannot be excluded, and should be considered when interpreting the results. Finally, as infants and children younger than 16 years were excluded, our results may not necessarily be extrapolated to this population.

Conclusion

The results of the present study indicate that trimipramine poisoning mainly occurs as a consequence of suicide attempts in young female patients. Moreover, it was shown that moderate trimipramine intoxication can already

occur after ingestion of doses in the high therapeutic range, indicating that dosing errors may be particularly dangerous. The minimal dose for moderate symptoms was 250 mg (median dose 1.2 g) or 7.7 mg kg⁻¹ (median dose 20 mg kg⁻¹), respectively, and 850 mg (median dose 2.7 g) or 17.9 mg kg⁻¹ (median dose 55 mg kg⁻¹), respectively, for severe symptoms.

The identification of minimal doses for moderate and severe toxicity, and of the dose bearing a 50% risk of developing moderate, severe or fatal poisonings, may help clinicians managing acutely poisoned patients. The symptoms of trimipramine poisoning predominantly involved the central nervous and the cardiovascular systems, whereas respiratory symptoms were observed only in severe cases. Fatalities were due to refractory cardiovascular collapse. A possible beneficial effect of early gastrointestinal decontamination with activated charcoal was identified, but this result should be interpreted with caution, considering the limited number of patients included in this study.

Competing Interests

The authors declare that they have no conflicts of interest.

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