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Adverse cardiac events in ICU patients with presumptive antidepressant overdose

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Summary

Background: Antidepressants account for most poison-related admissions to intensive care units. In selected patients with confirmed cyclic antidepressant intoxication a QRS interval <0.1 s in the ECG limb leads during the first six hours excludes adverse cardiac events. However, the incidence of cardiac events and the value of ECG criteria have never been assessed prospectively on patients with presumed antidepressant overdose.

Aim: To assess ingested drugs, adverse cardiac events, and ECG findings in ICU patients with a presumptive diagnosis of antidepressant overdose.

Methods: 103 consecutive patients with a presumptive diagnosis of antidepressant overdose were enrolled and prospectively followed. Outcome criteria were arrhythmias, mortality, and duration of the ICU stay.

Results: Mixed intoxication was identified in 66 (64%) patients. Tricyclic antidepressants were found in 88 (85%), and serotonin-reuptake inhibitors in 25 (24%) patients. Mean APACHE II score was 9.5 (SD ± 6.0). Arrhythmias affected 15 (15%) and cardiopulmonary resuscitation was performed on 4 (4%) patients. Three patients (3%) died in the ICU. Median duration of the ICU stay was 1 day (12 hours to 6 days). Adverse cardiac events affected patients with normal and prolonged QRS interval at study entry.

Conclusions: Mixed intoxication is present in most ICU patients with suspected antidepressant overdose. There is a considerable risk for adverse cardiac events, even in the presence of normal ECG recordings within the first six hours after hospital admission.

Key words: antidepressant toxicity; arrhythmia; ECG; intoxication; serotonin-reuptake inhibitor; tricyclic antidepressant

Introduction

Up to 50% of the poisoning related ICU admissions are associated with acute antidepressant overdose [1–5]. Acute antidepressant overdose might result in life threatening arrhythmias and seizures [1, 2, 6]. In view of limited health care resources and ICU beds, evaluation of adverse events after acute antidepressant overdose is essential to delineate guidelines for appropriate patient management [5]. Decisions regarding ICU admission of patients with antidepressant intoxication are usually based on clinical judgement and screening tests. Serum level measurements are of no prognostic value for acute cyclic antidepressant overdose [7–9]. Studies on selected patients, which exclusively ingested cyclic antidepressants have shown that ECG criteria, namely a QRS interval <0.1 s within six hours after admission has a high negative predictive value for the occurrence of arrhythmias [3, 7, 10, 11]. However, it is not clear whether risk assessment criteria developed for cyclic antidepressant intoxications also account for patients who ingested several classes of drugs [4, 12].

To clarify this issue we conducted an observational study on all consecutive patients admitted to our ICU with a presumptive diagnosis of antidepressant intoxication.

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Methods

Setting

This observational study was performed on consecutive patients in the medical intensive care unit of the Basel University Hospital, Switzerland.

Patients and interventions

Patients were enrolled on ICU admission, if an experienced attending physician suspected antidepressant intoxication. There were no exclusions. All patients were prospectively evaluated. Monitoring included at least ECG limb leads, non-invasive blood pressure measurement, and pulse oxymetry. Blood chemistry and arterial blood gas analysis were taken at least on admission and were repeated every 12 hours thereafter. The ECG limb leads were assessed for prolongation of QRS defined as a QRS >0.1 s and the corrected QT intervals (QTc) were calculated according to Bazett [13]. Adverse cardiac events were defined as ventricular flutter or fibrillation, any sustained or non-sustained ventricular tachycardia, torsade de pointes, supraventricular tachycardia, and conduction delays. Sinus tachycardia, single premature beats, and 1° AV-block were not considered. The Glasgow Coma Scale (GCS) [14] and the incidences of relevant hypotonia (defined as systolic blood pressure below 90 mm Hg), seizures, and arrhythmias were recorded. The acute physiologic and chronic health evaluation score (APACHE II) was calculated as described by Knaus et al. [15]. Ingested drugs were identified using ambulance charts, patient history, urinalysis and measurement of serum levels.

All patients with suspected antidepressant intoxication were treated according to the following in-house guidelines: 1. Patients with GCS ≤8 and/or unable to protect their airways were intubated. 2. Hypotension was treated with saline and norepinephrine, if refractory [16]. 3. For treatment of seizures intravenous lorazepam was used [17]. 4. Infusion of sodium bicarbonate, titrated to a urine pH >7.5 [18] was administered to all patients with seizures, arrhythmias or prolonged QRS intervals >0.1 s. 5. Charcoal was repeatedly administered for 12 hours to all patients [19]. 6. Potassium levels were adjusted to 4–5 mmol/l. 7. Patients were hydrated with 25–30 ml/kg/24 hours of normal saline.

Symptom free patients were dismissed from the ICU after at least 12 hours of uneventful monitoring following the last adverse event. All patients who survived were contacted six months after ICU discharge.

Statistics

Data analysis was on an intention-to-treat basis. Dichotomous data were analysed by Fisher's exact test. A p value <0.05 was considered significant.

Study ethics

Prospective data collection on the ICU patients was approved by the local ethical committee of the Basel University Hospital and was in accordance with the guidelines of the declaration of Helsinki.

Results

Over a period of two years 103 consecutive patients with a presumptive diagnosis of antidepressant overdose were included. No patients were excluded from analysis. Table 1 reviews the baseline characteristics of the study population. Of note, no patients were admitted later then six hours after drug ingestion. Sodium bicarbonate was given to fifty-eight (56%) patients, including all cases with prolonged QRS length at baseline.

Adverse cardiac events

A total of nineteen adverse cardiac events were recorded in fifteen patients (table 2). Three patients showed several types of arrhythmias. Adverse cardiac events were observed among patients with prolonged and normal QRS interval at study entry. QTc prolongations were observed in eleven of these fifteen patients. Cardiopulmonary resuscitation had to be performed on four patients during ICU stay, in two due to ventricular fibrillation, in one due to torsade de pointes and in one due to pulseless electric activity.

Mean potassium blood level was 3.4 mmol/l at study entry. Nevertheless, we did not find a correlation between these potassium levels and the numbers of adverse cardiac events in our analysis. In terms of co-morbidities, we identified three patients with coronary heart disease, one patient with COPD, two patients with diabetes mellitus, and two patients with a convulsive disorder (table 3).

Table 1

Patient's baseline characteristics.

Age (years)		39	(range 14–80)
Sex	male	26	(25%)
	female	77	(75%)
ECG	QRS >0.1 s	19	(18%)
	QTc >0.44 s	66	(64%)
Resuscitated[1] patients		8	(8%)
GCS[2] on admittance		11	(± 4.0)
APACHE II[3] scores		9.5	(± 6.0)
Potassium (mmol/l)		3.4	(± 0.4)
Sodium (mmol/l)		139	(± 4.0)

[1] refers to the number of patients who were intubated out of hospital
[2] Glasgow Coma Scale (GCS)
[3] APACHE II denotes acute physiologic and chronic health evaluation II [15].

Fatal outcome, duration of ICU stay and follow-up

Three patients died, and two deaths were attributed to cardiac arrhythmias that occurred during ICU stay (table 3). Necropsy was performed in these two patients and showed no evidence of cardiovascular disease. One patient, who had been resuscitated out of the hospital died from anoxic brain injury during follow-up. The median duration of the ICU stay was one day ranging from twelve hours to six days. All discharged patients were contacted after six months. There were no

Table 2

Adverse cardiac events in 15 of 103 patients with presumed antidepressant intoxication[1].

	Conduction delay[2]	Torsade de pointes	Ventricular fibrillation	Ventricular tachycardia	Supraventricular tachycardia	total events	patients[3]
Number of events	6	4	3	4	2	19	15
QRS <0.1	3	3	1	4	2	13	10
QRS >0.1	3	1	2	0	0	6	5
QTc <0.44	2	1	0	0	1	4	4
QTc >0.44	4	3	3	4	1	15	11

[1] Three patients had more than one adverse cardiac event

[2] Complete right bundle branch block in 4 patients and 2° AV- block in 2 patients

[3] Arrhythmias occurred in 10 of 84 patients with QRS <0.1s vs. 5 of 19 patients with QRS >0.1s (p = 0.1457), and in 11 of 66 patients with QTc >0.44s vs. 4 of 37 with QTc <0.44s (p = 0.564), respectively.

Table 3

Co-morbidities, adverse events, interventions and outcome of the 103 patients with presumed antidepressant intoxication.

Co-morbidities	
Coronary heart disease	3 (3%)
COPD	1 (1%)
Convulsive disorder	2 (2%)
Other non-psychiatric diseases	3 (3%)
Adverse events	
Arrhythmias[1]	15 (15%)
Minimal GCS[2]	9 (range 3–5)
Seizures	13 (13%)
Hypotension[3]	16 (16%)
Interventions	
Intubation	29 (28%)
Vasoactive drugs	7 (7%)
Resuscitation in the ICU	4 (4%)
Outcome	
ICU stay (days)	1 (range 1–6)
Death in ICU	3 (3%)

[1] number of patients with arrhythmias, as defined in the methods section

[2] GCS denotes Glasgow Coma Scale

[3] systolic blood pressure below 90 mm Hg

deaths during follow-up. However, twelve of the patients were readmitted to a hospital because of other drug intoxications.

Ingested drugs

Ingested drugs were identified using ambulance charts, history, urine screening and blood analysis. Cyclic and atypical antidepressants were identified in 88 (85%) (table 4A), and serotonin-reuptake inhibitors in 25 (24%) (table 4B) patients. Mixed drug intoxication was present in most of the patients.

Cyclic and atypical antidepressants were identified in thirteen patients, and serotonin-reuptake inhibitors in three of the fifteen patients with arrhythmias. Monointoxication with serotonin-reuptake inhibitors was present in two patients with arrhythmias. Two of the deaths, including the case with anoxic brain injury were associated with trimipramin monointoxication, whereas a combination of venlafaxine, maprotilin and fluoxetine was identified in the third patient who died.

Discussion

Our study revealed relevant morbidity and mortality in terms of adverse cardiac events for patients with presumed antidepressant overdose. So far, ICU monitoring of vigilant patients with antidepressant intoxication was not recommended if the QRS length was normal within the first six hours after admission [3, 20–22]. This policy is based on studies showing a high negative predictive value for adverse cardiac events in patients with cyclic antidepressant overdose presenting with QRS intervals <0.1 s within six hours after admission [12]. However, this idea is questioned by our study showing that patients with presumptive antidepressant intoxication and a normal QRS length on admission are also at risk for adverse cardiac events such as ventricular fibrillation, ventricular tachycardia, or torsade de pointes. Even a normal QTc interval did not exclude serious arrhythmias in our setting. Despite the fact that our study was too small to reveal significant differences in the risk of adverse cardiac events between patients with normal and prolonged QRS intervals, our findings justify close monitoring of all patients with presumed antidepressant intoxication for at least twelve hours.

Potassium blood levels are well known to play an important role inducing cardiac arrhythmias. Despite the low potassium levels at study entry, our analysis did not reveal a significant correlation between serum potassium levels and the occurrence of adverse cardiac events. This might be due to the fact that electrolyte levels were closely monitored and immediately and aggressively corrected in our setting.

There were no deaths after ICU discharge in our study population despite the presence of a still prolonged QRS interval and/or QTc interval at discharge. Because ECG monitoring ended at discharge we cannot exclude the occurrence of late potentially life-threatening arrhythmias. However, this risk appears to be quite low as suggested by retrospective studies [20, 23–25]. Most reported cases of "late adverse events" occurred after transfer of previously – i.e. <12 hours after the last

Table 4

Drugs identified in 103 patients with presumed antidepressant intoxication.

A) Cyclic antidepressants	**88 (85%)**
Trimipramine	44
Amitryptiline	13
Venlafaxine	10
Maprotilin	5
Clomipramin	5
Others	11
B) Serotonin-reuptake inhibitors (SSRI)	**25 (24%)**
Paroxetine	8
Sertaline	6
Citalopram	6
Fluoxetine	5
C) Type of intoxication	
Monointoxication with antidepressants	
Tricyclic antidepressant	31 (30%)
Serotonin-reuptake inhibitor (SSRI)	6 (6%)
Intoxication with cyclic antidepressants and SSRI	
Tricyclic antidepressant and SSRI	5 (5%)
Tricyclic antidepressant and SSRI and other	5 (5%)
Intoxications with antidepressants and other drugs	
Antidepressants / benzodiazepines	36 (35%)
Antidepressants / neuroleptics	10 (10%)
Antidepressants / neuroleptics / benzodiazepines	10 (10%)
Other substances	
Ethanol	13 (13%)
Opiates	4 (4%)
Amphetamine	1 (1%)
Cocaine	1 (1%)

event – symptomatic patients to unmonitored wards [20, 21].

So far, only few studies have prospectively assessed cardiac events in patients with antidepressant ingestion [7, 22]. All these studies excluded patients who ingested agents other than non-cyclic antidepressants, or in whom the cyclic drug was not predominant. In contrast, our analysis involved consecutive patients with a presumptive diagnosis of antidepressant intoxication. Our data therefore represent the commonest situations where the culprit agents are not yet identified, but clinical evaluation strongly suggests antidepressant overdose. This is a very important point because in practise detailed toxicological evaluations are usually not available for urgent decision making in most emergency departments.

The mortality rate of 2–3% in our study was in the range predicted by the APACHE II scores [15]. Two of the patients died of cardiac arrhythmias, despite close monitoring and the immediate availability of trained ICU staff. This may be due to several reasons. Most notably, mixed drug intoxication was present in most patients. Given the potential interactions and synergistic actions between various antidepressants [26] or other drugs like neuroleptics [27], the ingestion of several agents may promote cardiac events and contribute to their treatment resistance. In addition, it is well known that the usual management of arrhythmias is inappropriate in antidepressant toxicity. Antiarrhythmics are contraindicated or ineffective [3]. Data on the salutary effects of sodium bicarbonate infusions are based on retrospective data [18, 28] and animal models evaluating their effect on QRS width and blood pressure. Their value in the treatment of acute symptomatic arrhythmias remains speculative. Cardiovascular co-morbidity might also be an explanation of such a high mortality rate in the context of the large age range, but patients' co-morbidities did not have an impact on the outcome of the study.

Twenty-five of our patients ingested serotonin-reuptake inhibitors. Serotonin-reuptake inhibitors appear to be less harmful [29–31], although serious side effects cannot be excluded, particularly in the presence of cardiovascular co-morbidity [32–34] or after ingestion of very high doses. Hence, we also observed adverse cardiac events in these patients.

Of note, our study mainly included patients who were transferred to an ICU because an experienced attending physician considered them being at high risk. Risk assessment took not only ECG criteria but also the presence of seizures or – importantly – altered mental status into account [12]. Our study population is therefore selected, and we do not know how many patients were treated in an ambulatory setting because they were considered being at low risk. Furthermore, patient enrolment depended on a presumptive mainly clinical diagnosis and we cannot exclude that some patients were missed because initial assessment did not suggest antidepressant intoxication. Further and larger prospective studies on patients with presumptive antidepressant overdose are therefore clearly warranted.

In conclusion, mixed intoxication is present in most ICU patients with suspected antidepressant overdose, and there is a considerable risk for adverse cardiac events, even in the presence of normal ECG recordings within the first six hours after admission.

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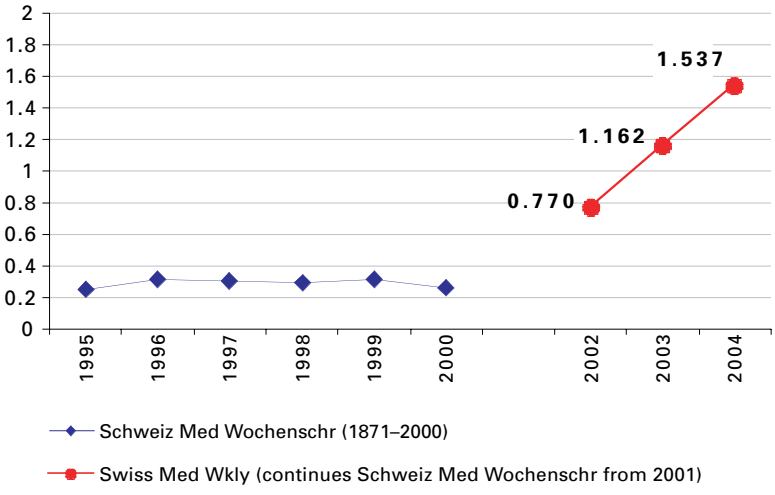

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