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Risk assessment of severe tricyclic antidepressant overdose

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Abstract

Prognostic factors for severe complications in tricyclic antidepressant (TCA) overdose remain unclear. We therefore evaluated the value of clinical characteristics and electrocardiograph (ECG) parameters to predict serious events (seizures, arrhythmia, death) in severe TCA overdose of 100 patients using logistic regression models for risk assessment. The overall fatality rate was 6%, arrhythmia occurred in 21% and 31% of the patients developed seizures. Using an univariable logistic regression model, the maximal QRS interval (OR 1.22; 95% CI 1.06-1.41; $p = .005$), the time lag between ingestion and occurrence of first symptoms of overdose (OR 1.13; 95% CI 0.99-1.29; $p = .072$) and the age (OR 0.73; 95% CI 0.55-0.98; $p = .038$) were determined as the solely predictive parameters. In the multivariable logistic regression model, the QRS interval could not be established as independent predictor, however, the terminal 40-ms frontal plane QRS vector (T40) reached statistical significance regarding prediction of serious events (odds ration [OR] 1.70; 95% confidence interval [CI] 1.02-2.84; $p = .041$), along with age and time lag between ingestion and onset of symptoms of overdose with a sensitivity and specificity of 71% and 70%, respectively. Evaluation of both clinical characteristics and ECG-parameters in the early stage of TCA overdose may help to identify those patients who urgently need further aggressive medical observation and management.

Keywords

TCA overdose, risk assessment, ECG, seizures, arrhythmia, death

Introduction

Although the popularity of tricyclic antidepressants (TCAs) in the treatment of major depression has decreased, TCAs are still frequently implicated drugs resulting in overdose fatalities.[1,2] Seizures and ventricular arrhythmia significantly account for morbidity and mortality associated with serious TCA overdose in the first hours after ingestion.[3,4]

Although many TCA overdose present in a comatose state even with respiratory depression at admission, only few of these patients will develop life-threatening events.[5] Thus, the majority of these poisoned patients can be managed with supportive intensive medical care only. However, there are some conceivable clinical scenarios in which the timely recognition of easily assessable findings indicating a severe course of poisoning would consequentially demand rigorous electrocardiograph (ECG) monitoring or would result in a more specific or aggressive treatment (e.g. sodium bicarbonate).

There is conflicting data if either the blood concentration of TCAs[6] or ECG alterations could serve as reasonable predictors of outcome and many of the studies

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are limited due to their small and heterogeneous study population, merging patients with asymptomatic, mild, moderate and severe intoxications.[3,4,7-12] Additionally, the interpretation of many studies is biased due to the frequently coingested psychotropic drugs (e.g. neuroleptics) doubtlessly influencing ECG parameters according to their inherent cardiotoxicity.[13]

As a consequence, we performed a retrospective analysis of 100 severely intoxicated patients admitted to our toxicological intensive care unit with an intentional single class TCA overdose. The ingested TCAs were amitriptyline (AT), doxepine (DO), Imipramine or Trimipramine (IT) and others (OT). We investigated both clinical and the most frequently reported changes in ECG parameters of TCA-poisoned patients and tested their value to predict serious events (seizures, arrhythmia or death) during inpatient stay.

Methods

Patient selection

A retrospective chart review including all patients admitted to our toxicological department with the diagnosis of intentional TCA overdose from January 1985 until December 2007 was performed. Inclusion criteria for the study were (1) clinically severe TCA overdose defined by either occurrence of seizures, requirement for mandatory ventilation, occurrence of arrhythmia or pronounced deep coma; (2) admission diagnosis of TCA overdose was based on the history and had to be confirmed by qualitative (e.g. HPLC; Remedy®) and/or quantitative analysis of TCA (e.g. FPIA; Abbott AxSym®) and its metabolites in serum or urine, respectively; (3) existence of at least two 12-lead ECGs in the patients' charts; (4) Ethanol and/or benzodiazepines confirmed by HPLC-screening (serum/urine) were the only accepted coingestants, as pure TCA overdoses are scarce and both drugs are believed to have negligible influence on ECG parameters.

A total number of 836 charts were analysed. On the basis of the above-mentioned inclusion criteria, 348 patients were excluded due to coingestants other than ethanol and/or benzodiazepines and another 377 patients were excluded due to clinically mild or only moderate signs of intoxication (absence of deep coma, arrhythmia, ventilatory support or seizures). Eleven patients were omitted as ECGs could not reliably be analysed or had missed some leads. This resulted in a total study population of 100 patients that were finally included. Time of TCA ingestion could be estimated fairly accurate from anamnesis of relatives or retrospectively after patients recovered from overdose.

Evaluation of ECG parameters

ECGs were analysed for rate and rhythm, RR interval, PQ interval, the maximal limb-lead QRS interval, the QT interval and the corrected QT interval (QT_c),[14] the R/S quotient in lead aVR,[3] the mean frontal plane QRS axis and the terminal 40-ms frontal plane QRS vector (T40) in lead I and aVF.[15] The investigators independently measured all intervals and axes manually and ECGs were reviewed and proofread by a blinded cardiologist (CvB). Data regarding ECG as well as clinical information were recorded, including age, sex, time of ingestion, total dose of TCA, coingestants (benzodiazepines and/or ethanol) and time of first symptoms or time of presentation. Furthermore, routine laboratory results, blood gas analysis, toxicological screening results and follow-up information on decontamination measures, complications or other specific treatment were collected until medical discharge.

Statistical analysis

Statistical analyses were performed using SPSS software (version 15.0; SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables were expressed as mean $\pm$ standard deviation and categorical data were reported as counts and percentages. Comparisons of quantitative measurements between independent groups of patients were performed using analysis of variance (ANOVA). Chi-square test was used to compare frequency distribution between patient groups. Spearman correlation coefficient was calculated to quantify bivariate correlation of continuous variables.

To investigate univariable and multiple relationships of patient characteristics and clinical parameters on probability of serious events, binary logistic regression models with variable selection procedures were conducted. In this term, estimates of odds ratios (OR) were reported with 95% confidence intervals (CI). Receiver-operating characteristic (ROC) analyses were performed to evaluate overall performance of the final prediction model by reporting area under the curve (c-index) as well as to determine the most reliable cutoff value in terms of predicting correctly. Sensitivity (Se) and Specificity (Sp) were reported

to assess the accuracy of model-based event prediction. All statistical analyses were performed two-sided at a .05 level of significance.

The ECG parameters, TCA plasma concentrations as well as clinical data and complications were compared between three TCAs (AT, DO, IT) in an exploratory way. The group 'Others' (OT) was not included in the statistical analysis comparing the different TCAs, as the underlying agents were extremely heterogeneous (six different classes of TCAs) and the sample size was rather small in this group ($n = 10$), thus impeding reasonable statistical calculations. A further analysis (all patients) had been performed between patients in whom serious events defined as seizures, arrhythmia or death occurred (SAD+) and in whom they did not (SAD–). Arrhythmia was defined as supraventricular tachycardia (SVT), ventricular tachycardia (VT), ventricular fibrillation (VF), torsades-de pointes tachycardia (TdP), pulseless electrical activity (PEA) or cardiac arrest (CA).

Results

Baseline characteristics of patients

Distribution of the involved TCAs is shown in Table 1. We observed neither clinically relevant nor statistically significant differences between the groups of TCAs ($n = 90$) considered other than the Acute Physiology and Chronic Health Evaluation (APACHE) score on admission and the occurrence of sequelae. Although the APACHE score was significantly lower in the IT group (15 vs. 19; $p = .035$), this group accounted for the highest rate of sequelae. Despite arrhythmia tended to occur earlier in the DO group than in the IT group (2.0 $\pm$ 0.6 hours vs. 14.5 $\pm$ 22 hours), difference was not significant. Including all cases, arrhythmia occurred approximately 7.5 $\pm$ 10 hours after ingestion. Benzodiazepines were coingested in 38% of the SAD+ group vs. 29% in the SAD– group ($p = .363$). Ethanol was coingested in 22% of the SAD+ group (serum concentration 1.4 $\pm$ 1.1 g/L) vs. 31% in the SAD– group (serum concentration 1.9 $\pm$ 1.4 g/L; $p = .335$). For details see Table 2.

ECG parameters during the inpatient course

There was no significant difference between the TCAs tested in terms of the ECG parameters analyzed. Regarding all cases ($n = 100$), approximately 6 ECGs were derived from each case at different times with a mean latency between the estimated ingestion and first recording of 5.6 $\pm$ 5.4 hours. A type-1 Brugada electrocardiographic pattern (BEP) was observed in 11% of the patients, with no significant difference between the TCAs tested (exemplarily shown in Figure 1). The TCA-group OT (although not tested for significance) had comparable ECG parameters apart from the trend to higher QT_c intervals, lower T40 and higher incidence of right bundle branch block (60%) compared to the other classes of TCAs. For details, see Table 3.

Occurrence of serious events (SAD+)

We recorded the occurrence of fatalities in 6%, seizures in 31% and arrhythmia in 21% of our study population. Distribution of arrhythmia were as follows: CA ($n = 4$), PEA ($n = 1$), VT (11 cases), VF (n = 2), TdP (n=1) and SVT ($n = 2$). In performing univariable logistic regression analysis ($n = 100$), there was a significant trend of the younger aged in the occurrence of SAD+ ($p = .038$). We could not detect any significant predictive value for SAD+ of the parameters gender, ingested amount of TCA, Δt and the TCA concentration in serum on admission. Evaluation of the ECG parameters offered the maximum QRS interval as the only significant parameter to distinguish between patients who developed serious events and those who did not ($p = .005$). For details see Table 2 and Figure 2, respectively.

In the multivariable logistic regression model, the only significant values to predict SAD+ were T40, age and Δt. Age was the only significant parameter to predict SAD+, both in the univariable and the multivariable logistic regression model. In the latter, every increase of age was associated with a lower risk for the occurrence of SAD+. For details, see Figure 3. The multivariable logistic regression model had been adjusted to the different TCAs with no single class of TCA found to have a higher risk for SAD+ than another. In the ROC analysis, overall predictive performance of the final multivariable logistic regression model reached 0.729 (c-index). Considering an optimal cut-off value of predicted probability of 41.7%, a sensitivity of 70.7% and a specificity of 70.4% could be achieved.

Discussion

In patients with intentional TCA overdose, risk assessment using TCA-plasma concentrations is generally believed to be unreliable.[6,9,16] The ECG,

Table 1. Baseline characteristics and therapeutic measures

	All patients ($n = 100$)	Amitriptyline ($n = 48$)	Doxepine ($n = 22$)	Imipramine/ Trimipramine (n = 20)[a]	Others ($n = 10$)[b]	p Value[c]
Age	43 ± 14	44 ± 15	43 ± 14	42 ± 14	42 ± 11	.982
Men	35 (35%)	15 (31%)	9 (41%)	8 (40%)	3 (30%)	.658
Mean amount of TCA ingested (mg)[d]	3406 ± 2031	3438 ± 2196	2728 ± 1500	3653 ± 1804	4183 ± 2492	.332
Δt (h)[e]	3.5 ± 3.7	3.3 ± 2.5	3.7 ± 5.6	3.7 ± 4.0	3.6 ± 3.2	.896
APACHE II score at admission	18 ± 6	19 ± 7	19 ± 5	15 ± 5	19 ± 6	.035[f]
Glasgow coma score at admission	4.9 ± 2.7	4.7 ± 2.6	4.5 ± 2.0	6.2 ± 3.1	4.7 ± 3.4	.052
Mean pulse (bpm) at admission	109 ± 25	113 ± 26	113 ± 22	102 ± 15	99 ± 35	.155
Mean arterial pressure (mmHg)	81 ± 23	79 ± 21	77 ± 29	87 ± 19	88 ± 19	.202
Seizures	31 (31%)	14 (29%)	7 (32%)	7 (35%)	3 (30%)	.891
Arrhythmia	21 (21%)	8 (17%)	5 (23%)	3 (15%)	5 (50%)	.238
Anticholinergic syndrome	29 (29%)	17 (35%)	3 (14%)	6 (30%)	3 (30%)	.174
Required intubation	88 (88%)	44 (92%)	20 (91%)	15 (75%)	9 (90%)	.217
Days ventilated	5.5 ± 7.9	5.7 ± 8.8	5.9 ± 8.2	5.0 ± 7.5	4.9 ± 3.2	.945
Days in ICU	7.1 ± 9.9	7.2 ± 8.6	7.8 ± 9.2	7.5 ± 15.2	6.6 ± 3.7	.976
Needed defibrillation	6 (6%)	2 (4%)	2 (9%)	–	2 (20%)	.357
Gastric lavage[g]	33 (33%)	16 (33%)	9 (41%)	4 (20%)	4 (40%)	.340
Activated charcoal	80 (80%)	40 (83%)	18 (82%)	13 (65%)	9 (90%)	.223
Antiarrhythmic therapy[h]	5 (5%)	2 (4%)	1 (45%)	–	2 (20%)	.640
Fatalities	6 (6%)	2 (4%)	1 (4%)	2 (10%)	1 (10%)	.615
Restitutio	91 (91%)	45 (94%)	21 (96%)	16 (80%)	9 (90%)	.137
Sequelae[i]	3 (3%)	1 (2%)	0 (0%)	2 (10%)	0 (0%)	.028[f]

APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; TCA, tricyclic antidepressants; bpm, beats per minute.

[a] Equally contributed to Imipramine ($n = 10$) and Trimipramine ($n = 10$).

[b] Opipramol ($n = 3$), Maprotiline ($n = 1$), Clomipramine ($n = 2$), Dibenzepine ($n = 1$), Mianserine ($n = 1$) and unspecified ($n = 1$).

[c] Statistical differences were calculated using analysis of variance (quantitative data) or Chi-Square test (categorical data). Statistical differences were calculated only for the groups Amitriptyline, Doxepine and Imipramine/Trimipramine as the group "Others" was largely inhomogeneous and represented by a small sample size only.

[d] The amount ingested was assessed based on anamnesis from relatives or the patient after convalescence or empty blisters.

[e] The time lag between ingestion and first symptoms (Δt) was assessed based on emergency physicians, relatives or retrospectively through anamnesis.

[f] Statistical significant values ($p < .05$).

[g] Mean volume for lavage was 20 ± 5 L (all patients).

[h] Antiarrhythmic therapy ($n = 5$) consisted of magnesiumsulfate ($n = 1$), amiodarone ($n = 2$), ajmaline ($n = 1$) and physostigmine salicylate ($n = 1$).

[i] Three patients stayed impaired with critical illness Polyneuropathy ($n = 1$), parkinsonoid ($n = 1$) or ulnar paralysis ($n = 1$).

however, is a readily available tool with the commonly discussed feasibility to predict severe clinical events during the first critical hours following massive TCA overdose.[7,11,17] TCA-induced cardiotoxicity is the most important factor contributing to patient mortality[18] and is expressed as a prolongation of QRS intervals and right axis deviation of the T40 vector.[19]

Interestingly, our study failed to demonstrate a significant predictive value of the most commonly reported ECG parameters despite the maximal QRS interval and the T40 vector, which correlated in the unadjusted univariable analysis with a significantly increased risk for occurrence of SAD+. However, in the multivariable analysis, T40 remains the only significant ECG parameter as well as the baseline parameters age and Δt. Since there was some correlation between the maximal QRS interval and T40 (Spearman rho: .37, $p < .001$) both parameters competed in the multivariable analysis and the maximal QRS interval became significant (OR 1.18; 95% CI 1.013-1.377; $p = .033$) by excluding T40 with a weak specificity of this model (61%). According to the literature, we observed no influence on the effect

Table 2. Clinical characteristics and ECG parameters of patients developing serious events (SAD+) and those who did not (SAD–)[a]

Characteristics	Seizure, arrhythmia or death ($n = 45$)	No seizure, arrhythmia or Death ($n = 55$)
Age (year)	40 ± 15	46 ± 13
Men	15 (33%)	20 (36%)
Benzodiazepines coingested[b]	17 (38%)	16 (29%)
Ethanol coingested[c]	10 (22%)	17 (31%)
Ethanol quantitative in serum (g/L)[d]	1.4 ± 1.1	2.2 ± 1.5
TCA ingested (mg)	3674 ± 1986	3097 ± 2094
TCA concentration in serum at admission (μg/L)[e]	1330 ± 1107	1757 ± 2896
Δt (h)	4.3 ± 5.2	2.9 ± 1.7
QRS on admission (msec)	135 ± 38	124 ± 24
QRS at maximum (msec)	147 ± 41	127 ± 22
T40 on admission (°)	178 ± 102	149 ± 88
PQ on admission (msec)	177 ± 40	176 ± 30
QTc on admission (msec)	509 ± 83	503 ± 53
R wave on admission in lead aVR (mm)	2.5 ± 2.0	2.0 ± 1.5
S wave on admission in lead aVR (mm)	5.5 ± 3.4	5.9 ± 3.4
R/S quotient on admission	0.73 ± 0.8	0.46 ± 0.44

ECG, electrocardiograph; TCA, tricyclic antidepressants; SAD, seizures, arrhythmia or death.

[a] Statistical differences were calculated using analysis of variance (quantitative data) or Chi-Square test (categorical data). Most other levels of significance of the effective parameters to differentiate between SAD+ and SAD– are shown in Figure 1.

[b] $p = .363$.

[c] $p = .334$.

[d] $p = .324$.

[e] TCA concentration in serum was determined with a TDx assay (Abbott Laboratory, Abbott Park, IL, USA) based on a fluorescence polarization immuno-assay (Abbott Laboratories). Consider that this assay is calibrated to amitriptyline only, thus comparison of concentrations between different classes of TCAs is not reasonable, offhand.

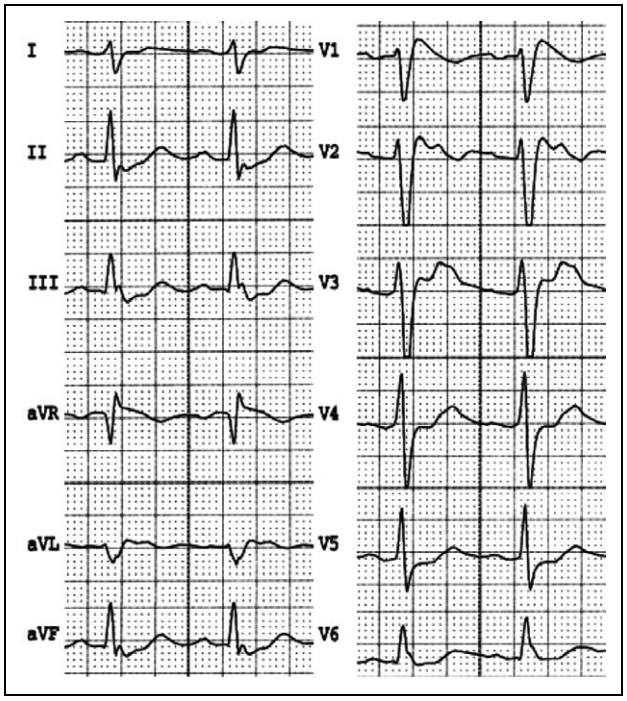

Figure 1. Exemplary demonstration of a type-1 Brugada electrocardiographic pattern (BEP) in the course of tricyclic antidepressants (TCA) poisoning with a right bundle branch block, QTc elevation, downsloping ST-segment elevation in leads V1-V3 and T-negativity. See also the R wave being ≥3 mm in aVR.

parameters after adjusting for the different classes of TCAs.[20]

A QRS interval >100 msec is frequently reported to predict seizures and arrhythmia.[10] This has been widely disputed by others, although it appears evident that a QRS < 100 msec has a good negative predictive value as these patients rarely have arrhythmia or seizures.[21] In a meta-analysis, the pooled sensitivity (Se) and specificity (Sp) of the QRS complex to predict seizures, arrhythmia or death was in a comparable range. In this context, our findings are in line with recent data showing that QRS duration alone is not a good positive predictor of TCA-induced adverse effects.[11,17]

Extreme rightward deviation of the QRS axis in TCA overdoses – expressed as T40 being between 130° and 270° – was reported to be a more sensitive indicator of general toxicity compared to the QRS interval alone,[8,22] an observation congruent with our results.

In a retrospective analysis of TCA overdoses, patients had significantly greater QT_c intervals than controls.[8] Although we observed clearly prolonged QT_c intervals (525 ± 61 msec) on admission (mostly attributed to QRS prolongation),[23] QT_c was not predictive for SAD+ (OR 1.13; 95% CI 0.62-2.07; $p = .698$).

Other frequently cited ECG parameters with more or less poor prognostic value for SAD+ are the occurrence of BEP,[24] a decreased RR variation[25] and a R wave of ≥3 mm in aVR.[3] However, none of these parameters have been shown to be significantly predictive for severe events, neither in our study nor in a meta-analysis.[17]

Table 3. ECG parameters during the inpatient course

	All patients ($n = 100$)	Amitriptyline ($n = 48$)	Doxepine ($n = 22$)	Imipramine/ Trimipramine ($n = 20$)[a]	Others ($n = 10$)[b]	p Value[c]
Δt p.i. and occurrence of arrhythmia (h)	7.5 ± 10	7.8 ± 10.4	2.0 ± 0.6	14.5 ± 22	8.3 ± 4.8	.098
Number of ECGs analyzed	5.6 ± 5.2	5.3 ± 4.7	4.5 ± 6.4	5.8 ± 4.5	9.4 ± 4.6	.072
Δt p.i. and first ECG (h)	5.6 ± 5.4	5.6 ± 4.3	6.4 ± 7.8	5.1 ± 5.8	4.8 ± 3.2	.285
ECG maximal pathological p.i. (h)[d]	7.2 ± 7.4	7.2 ± 6.5	7.0 ± 7.7	7.7 ± 10.3	6.1 ± 3.8	.492
PQ interval (msec) at admission	176 ± 35	180 ± 37	165 ± 30	180 ± 22	177 ± 53	.199
QRS interval at admission (msec)	130 ± 32	134 ± 35	126 ± 32	120 ± 24	133 ± 23	.263
QRS interval at maximum (msec)	136 ± 34	139 ± 37	131 ± 27	131 ± 26	135 ± 21	.855
QRS interval at maximum p.i. (h)	7.1 ± 7.4	7.2 ± 6.5	6.9 ± 7.8	7.7 ± 10.1	5.8 ± 3.8	.949
QTc interval at admission (msec)	505 ± 67	500 ± 70	523 ± 74	493 ± 37	519 ± 90	.572
QTc interval at maximum (msec)	525 ± 61	519 ± 51	523 ± 72	522 ± 57	572 ± 36	.980
QTc interval at maximum p.i. (h)	7.5 ± 7.4	7.5 ± 6.5	7.2 ± 7.7	7.7 ± 10.3	7.5 ± 4.1	.180
T40 at admission (°)	161 ± 95	149 ± 92	183 ± 90	185 ± 101	121 ± 101	.213
T40 at maximum (°)	166 ± 93	150 ± 93	185 ± 84	191 ± 96	144 ± 99	.176
R wave in lead aVR (mm) at admission	2.4 ± 1.6	2.2 ± 1.3	2.7 ± 1.9	2.8 ± 1.5	1.9 ± 2.1	.964
S wave in lead aVR (mm) at admission	5.9 ± 5.3	5.0 ± 3.1	4.2 ± 2.2	4.7 ± 2.0	8.6 ± 3.2	.534
R/S ratio in lead aVR at admission	0.47 ± 0.82	0.51 ± 0.89	0.38 ± 0.51	0.38 ± 0.59	0.42 ± 0.82	.810
Right bundle branch block	44 (44%)	26 (54%)	7 (32%)	9 (45%)	6 (60%)	.236
Left bundle branch block	16 (16%)	7 (15%)	4 (18%)	1 (5%)	2 (20%)	.306
Brugada-pattern	11 (11%)	5 (10%)	2 (9%)	2 (10%)	2 (20%)	.985

p.i., post ingestion; QTc, corrected QT interval.
[a] Equally contributed to Imipramine ($n = 10$) and Trimipramine ($n = 10$).
[b] Opipramol ($n = 3$), Maprotiline ($n = 1$), Clomipraminee ($n = 2$), Dibenzepine ($n = 1$), Mianserine ($n = 1$) and unspecified ($n = 1$).
[c] Statistical differences were calculated using analysis of variance (quantitative data) or Chi-square test (categorical data). Statistical differences were calculated only for the groups Amitriptyline, Doxepine and Imipramine/Trimipramine, as the group "Others" was largely inhomogeneous and represented only a small sample size
[d] The maximal pathological ECG was defined as the maximum of T40, QRS interval, QT_c or R/S ratio in aVR, respectively

Previous studies had suggested a combination of both clinical and ECG findings to identify patients at risk after TCA overdose.[5,26,27] The use of the "Antidepressant Overdose Risk Assessment" (ADORA) criteria[26] in our study population is hampered by the fact that serious events partially accounting for the ADORA classification were the inclusion criteria for our study.

The only clinical parameters with significant predictive value in our study were both age (young age was correlated with SAD+) and Δt (the higher Δt, the more probability for severe events). Age was affected through the higher incidence of seizures in the younger age group, which was statistically significant (mean age difference: 11.7 ± 2.9, $p < .001$, data not shown). In a recent study, age has also been reported to be lower in the group experiencing seizures and arrhythmia (26 ± 12) than in the group without serious events (31 ± 16), which was attributed to the higher TCA serum concentrations in the younger group (difference not significant). As it was the case in our study, Δt was reported to be longer in the SAD+ group compared to the SAD– group (3.2 ± 3.8 hours vs. 2.6 ± 2.6 hours).[3]

It could be hypothesized that SAD+ may have been underestimated and not recorded in our study if they had occurred in the preclinical stage of toxicity. Additionally, delayed absorption of TCAs from the intestines may have occurred due to a more pronounced anticholinergic activity in the SAD+ group. Thus, the onset of toxicity may be later in the more severe group, resulting in a higher Δt value.[28]

Although the accuracy of the ECG is likely time-dependent,[28] ECG abnormalities, if they occur, universally develop within 6 hours after ingestion.[29] Large-scale retrospective studies have shown that TCA overdoses manifest evidence of severe toxicity within the first few hours after ingestion.[16] We could not observe relevant discrepancies of QRS, QT_c and T40 between admission and the next few hours later. The maximal pathological values were similar to those recorded at admission, which is in accordance

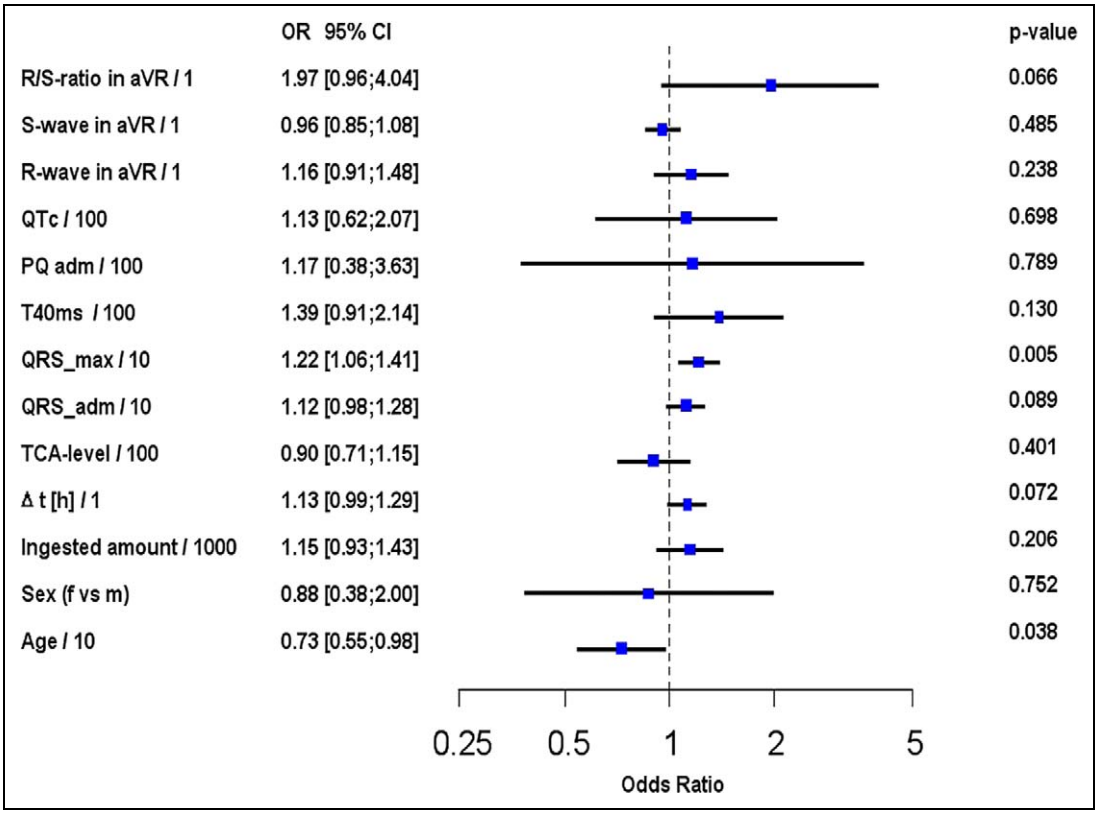

Figure 2. Odds ratio (OR) estimates of relevant clinical study variables for the occurrence of serious events (seizure, arrhythmia or death) in tricyclic antidepressants (TCA) overdose patients determined by univariable logistic regression. Units given after slash define the OR corresponding to an increase of the given value (e.g. QTc/100: increase of the QRS of 100 msec).

with data in the literature where the maximum QRS interval and T40 occurred at presentation in the majority of patients.[28]

Our study includes a fairly large number of patients with relevant toxicity, the use of standardized and commonly in the emergency department assessable parameters and a representative distribution of TCA-classes involved.[17] The combination of clinical and ECG parameters to predict the risk of severe events as a result of our multivariable analysis has the advantage that – despite the determination of T40 that offers some interobserver variability[30] – age and Δt in most of the cases are easy to determine if the time of ingestion was known. Thus, our model for risk assessment is thought to be applicable for the most scenarios of TCA overdose.

However, our study has several limitations. It was a retrospective, unblinded observation study with arbitrary time intervals between the ECGs derived. Thus, it may therefore not necessarily reflect the culmination of pathological findings during the course of poisoning. The study's generalizability may be limited to a selection bias towards more seriously poisoned patients. Ingestion of benzodiazepines may or may not have affected the occurrence of seizures and – ambiguously – arrhythmia. Additionally, coingestion of benzodiazepines and ethanol may have biased the severity of overdose due to their impact on requirement for mandatory ventilation or occurrence of deep coma, which were both including criteria in our study. However, it is unlikely that this fact could have affected the primary intention of our study, as both substances were distributed fairly equally in the SAD+ and the SAD– group. Administration of sodium bicarbonate may have affected ECG parameters, arrhythmia and indirectly death,[31,32] however, these measures were equally allocated to the SAD+ and SAD– group. Additionally, the ECG parameters were derived mostly from ECG on admission before any specific treatment was initiated.

Finally, there are many other mostly unknown confounding factors contributing to whether a patient develops toxicity or not (e.g. acute or acute on chronic overdose; metabolism status; underlying risk for prolonged QT; genetic factors for QT prolongation, etc.).

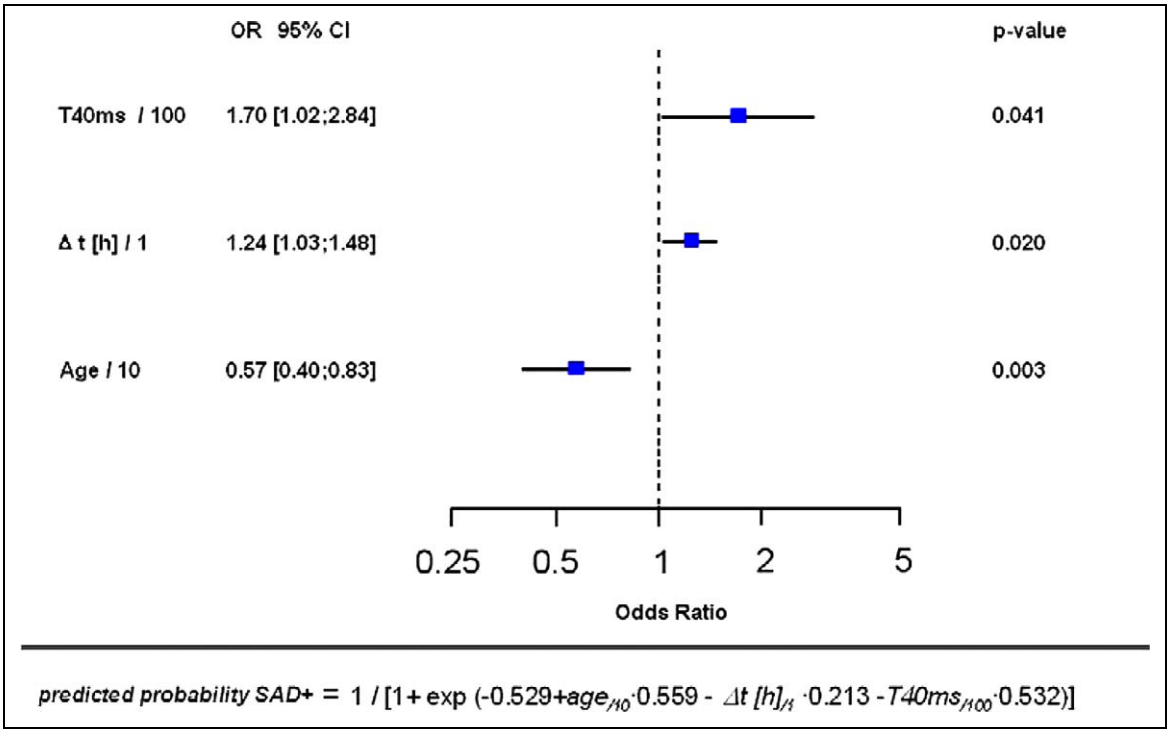

Figure 3. Odds ratio (OR) estimates of relevant clinical study variables for the occurrence of serious events (seizure, arrhythmia death) in TCA overdose patients determined by multivariable logistic regression. Units given after slash define the OR corresponding to an increase of the given value (e.g. T40ms/100: increase of the T40 of 100°).

Conclusion

According to recent studies investigating the predictive value of ECG parameters for SAD+ in TCA overdose, we demonstrated the T40 and – in part – the QRS interval to be applicable. Our final multivariable logistic regression model – including the assessable parameters T40, age and Δt provides acceptable sensitivity and specificity and has demonstrated to be applicable in the very early stage of TCA overdose in most cases. However, one must yet consider that neither the ECG nor any other single clinical parameter can unequivocally rule in or rule out impeding toxicity. In recognizing these limitations, clinicians are strongly encouraged to evaluate the patient's condition as well as the ECG repeatedly to identify those patients who urgently need thorough monitoring or further aggressive medical management.

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