RESEARCH ARTICLE

Does determination of drug level in intoxicated patients offer an advantage in diagnosis, treatment, and reducing complications?

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Abstract

Objective: To investigate the effect of determining the drug type and level on emergency management in patients presenting with intoxication, and to identify the factors behind associated mortality.

Methods: The retrospective, observational, cross-sectional and single-centre study was conducted at a large tertiary care teaching hospital in Istanbul, Turkey, between September and November 2016 using the hospital's toxicology registry. Data was extracted for patients who had presented to the emergency department from January 1, 2011, to February 28, 2013, and were found to have toxic doses of single active ingredients in the plasma. The patients were evaluated in terms of age, gender, demographic characteristics, time from ingestion to presentation, reason for drug ingestion, type of drug ingested, time elapsed before the emergency service was called, treatment given, drug level, hospitalisation and mortality. Data was analysed using SPSS 11.5.

Results: Of the 224 patients, 145(64.8%) were women. The overall mean age was 30.8±15.4 years. Drug ingestion was more common in women aged 18-30 years ($p<0.0001$). Besides, 215(96%) patients had ingested drugs with the intent to commit suicide. The minimum education level of 163(72.8%) patients was high school. The most frequently ingested drug was paracetamol 90(40.2%). Overall mortality was 4(1.8%) and all of them were brought to the emergency department after a delay of more than five hours ($p<0.0001$).

Conclusion: Drug type and quantity were found to be of great importance in taking timely decisions while attending to patients with intoxication in an emergency setting. Delay in presentation was associated with mortality.

Keywords: Intoxication, Plasma toxic doses, Eergency, Drug levels. (JPMA 70: 825; 2020).

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Introduction

Drug toxicity, the principal cause of poisoning, is an important issue in the emergency department (ED). Other causes of poisoning include inhalation of poisonous gases and ingestion of poisonous food.[1]

Drug-related deaths are usually caused by analgesics, antidepressants or sedative-hypnotics.[1,2] Patients who have been poisoned should be promptly evaluated and simultaneously treated. The standard approach should be patient stabilisation with the immediate treatment of the medical emergency.[2]

When a patient intoxicated with a drug is not able to communicate or cannot remember what drug was ingested, or exhibits altered consciousness, it may not be possible to obtain the required information. In such cases, it is necessary to contact any witnesses to gather information about the place and time of intoxication, the amount of drug ingested, the pharmacological characteristics of the drug, and the route of intoxication. If the amount of drug ingested is not determined, it is often assumed that a very high dose has been taken, and the patient is admitted to the hospital for immediate treatment. However, this may result in unnecessary treatment and may incur additional costs. Screening for drugs and dosage are important in ED not only to optimise diagnosis and treatment, but also to reduce complications and medical costs.[3]

The current study was planned to document the demographic characteristics of drug-intoxicated patients

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and to explore whether the determination of plasma drug levels influenced treatment, mortality, and length of hospital stay in such cases.

Patients and Methods

The retrospective, observational, cross-sectional and single-centre study was conducted at a large tertiary care teaching hospital in Istanbul, Turkey, from September to November, 2016, using the hospital's toxicology registry. Data collected was related to patients who consecutively presented to ED between January 1, 2011, and February 28, 2013, and who were found to have toxic drug levels in the plasma. Data related to patients who did not have toxic concentration of drugs in their plasma and those who had taken multiple drugs was excluded.

On arrival, blood was collected from all patients suffering from either diagnosed or suspected drug intoxication, and the plasma levels of paracetamol, carbamazepine, valproic acid, phenytoin, tricyclic antidepressants (TCA), salicylate, and phenobarbital were determined. Data regarding age, gender, demographic characteristics, arrival time, reason for drug ingestion, type of drug ingested, time from ingestion to hospital arrival, treatment, plasma drug level, hospitalisation and mortality was noted and analysed. The patients intoxicated with TCA were evaluated for possible admission to the intensive care unit (ICU) using the Antidepressant Overdose Risk Assessment (ADORA) criteria.[4] For biochemical analyses, serum drug levels were measured using the micro-enzyme immune assay (MEIA) on a Hitachi 902 analyser (Roche Diagnostics, Tokyo, Japan) in the ED laboratory.

Data was analysed using SPSS 11.5. Student's t-test was used to explore the significance of differences between mean values, and chi-square (Fisher's exact) test was used to determine those between categorical variables. P<0.05 was considered significant.

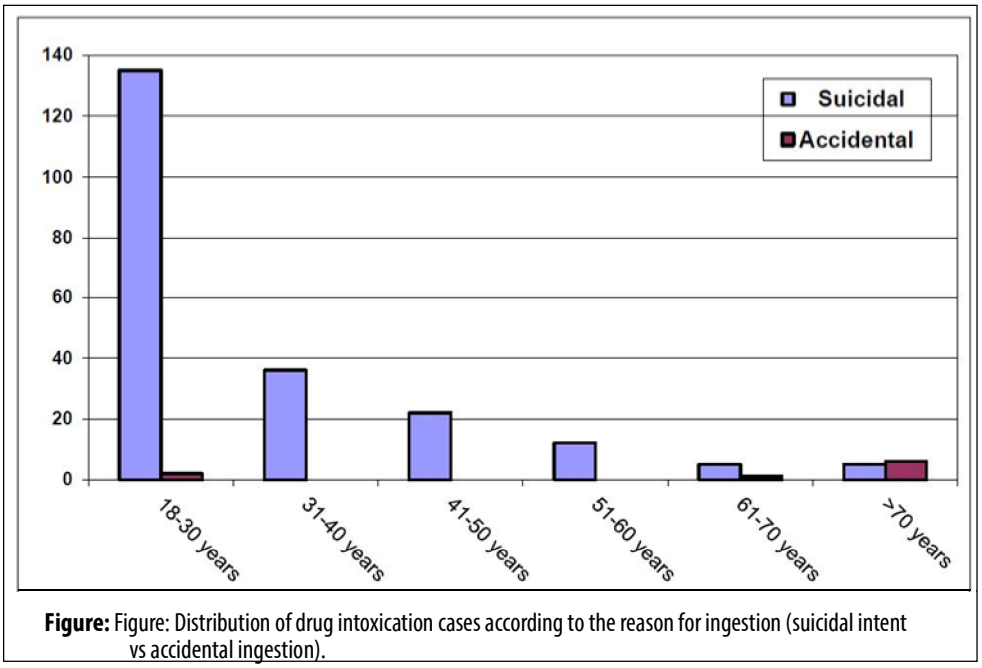

Figure: Figure: Distribution of drug intoxication cases according to the reason for ingestion (suicidal intent vs accidental ingestion).

Results

Of the 502,316 patients presenting to the ED, 8,336(1.7%) either had a history or aroused suspicion of drug intoxication. Of them, 224(2.7%) patients had taken a single drug at a toxic dose and represented the final study sample, with 145(64.8%) of them being women. The overall mean age was 30.8±15.4 years. In terms of education level, 9(4%) patients did not know how to read and write, 52(23.2%) had finished primary school, 86(38.4%) completed secondary school, and 77(34.4%) were university graduates. Also, 215(96%) had ingested the drugs with a suicidal intent, while accidental ingestion was more common in patients aged ≥70 years (Figure). Drug ingestion was more common in women aged 18-30 years (p<0.0001) (Table 1).

Paracetamol was the most commonly ingested drug 90(40.2%), followed by carbamazepine 40(17.9%), valproic acid 40(17.9%), phenytoin 27(12.1%), TCA

Table-1: Case distribution according to age and gender.

Age (years) groups	Male n (%)	Female n (%)	Total n (%)	*p*-value
18 - 30	46 (20.6)	91 (40.6)	137 (61.2)	
31 - 40	13 (5.8)	23 (10.3)	36 (16.1)	
41 - 50	7 (3.1)	15 (6.7)	22 (9.8)	
51 - 60	6 (2.7)	6 (2.7)	12 (5.4)	0.032
61 - 70	5 (2.2)	1 (0.4)	6 (2.6)	
> 70	1 (0.4)	10 (4.5)	11 (4.9)	
Total	78 (34.8)	146 (65.2)	224 (100)	

Table-2: Distribution of ingested drugs according to gender and drug levels.

Drugs	Male n (%)	Female n (%)	Total n (%)	Mean level (μg/mL)	Toxic level (μg/mL)	*p*-value
Paracetamol	24 (26.7)	66 (73.3)	90 (100)	168.1	> 150	< 0.0001
Carbamazepine	13 (32.5)	27 (67.5)	40 (100)	18.2	> 15	=0.027
Valproic acid	20 (50.0)	20 (50.0)	40 (100)	164.9	> 150	>0.05
Phenytoin	12 (44.4)	15 (55.6)	27 (100)	36.8	> 20	> 0.05
TCA	3 (21.4)	11 (88.6)	14 (100)	924.1	> 500	> 0.05
Salicylate	5 (50.0)	5 (50.0)	10 (100)	475.2	> 300	> 0.05
Phenobarbital	1 (33.4)	2 (66.6)	3 (100)	42.7	> 40	> 0.05
Total	78	146	224			

TCA: Tricyclic antidepressants

Table-3: Cases admitted to ICU according to ADORA criteria.

Cases	Age (year)	TCA level (ng/ml)	QRS > 0.10 sec	Mental status (GCS<14)	Respiratory depression (rr<8/min)	SBP < 90 mmHg
1	21	2480.00	-	12	-	80
2	21	530.00	-	-	-	70
3	23	670.00	0.16 sec	-	-	90
4	32	537	0.14 sec	-	-	80
5	37	1864.00	-	11	6/min	70
6	17	836.00	-	13	-	80
7	48	700.00	0.14 sec	-	-	90
8	42	656.00	13	-	-	80
9	51	600.00	0.16 sec	-	-	-
10	21	1640	-	13	7/min	70
11	19	1476.00	-	13	-	80

ICU: Intensive Care Unit., ADORA: Antidepressant Overdose Risk Assessment, TCA: Tricyclic Antidepressant, GCS: Glasgow Coma Scale, rr: respiration rate, SBP: Systolic Blood Pressure.

Table-4: Distribution of hospitalized cases according to the type of ingested drug.

Drug	ICU n (%)	Internal Medicine n (%)	Total n (%)	*p*-value
Paracetamol	1 (1.1)	89 (98.9)	90 (100)	< 0.0001
Carbamazepine	5 (12.5)	35 (87.5)	40 (100)	< 0.0001
Valproic acid	4 (10.0)	36 (90.0)	40 (100)	< 0.0001
Phenytoin	1 (3.7)	26 (96.3)	27 (100)	< 0.0001
TCA	11 (71.4)	3 (28.6)	14 (100)	< 0.0001
Salicylate	3 (30.0)	7 (70.0)	10 (100)	< 0.044
Phenobarbital	-	3 (100)	3(100)	>0.05
Total	24 (10.2)	200 (89.8)	224 (100)	

TCA: Tricyclic Antidepressants, ICU: Intensive Care Unit.

14(6.2%), salicylate 10(4.4%) and phenobarbital 3(1.3%). The female patients tended to ingest paracetamol and carbamazapine at a significantly higher rate than the males (Table 2).

Of all the patients, 111(49.6%) presented to ED within two hours of drug ingestion. Overall, 160(71.4%) patients underwent gastric lavage, and 165(73.6%) were given activated carbon. All paracetamol-intoxicated patients received intravenous (IV) N-acetyl cysteine. Sodium bicarbonate was given to 7(70%) cases of salicylate intoxication and 3(21.4%) cases of TCA intoxication. On applying ADORA criteria, there were no cases of either arrhythmias or seizures, and 11(78.6%) of the TCA-intoxicated patients were admitted to the ICU (Table 3). All patients who had taken toxic levels of drugs were hospitalised; 200(89.2%) to the Internal Medicine ward, and 24(10.8%) to the ICU (Table 4). The mean hospitalization time was 2.3±1.0 days for the former and 2.6±0.7 days for the latter. The overall mortality was 4(1.8%), and all of them had arrived at the ED more than 5h after drug ingestion ($p<0.0001$) and had high levels of intoxication. Of the 4 patients, 3(75%) were females and 1(25%) was male. The mean age of the four patients was 57.3(±19.4) years, and they all died in the ICU.

Discussion

Drug-associated poisoning is an increasing public health problem that can usually be readily addressed with proper management and appropriate medical treatment. The rates of visits to emergency services vary by region, age, gender, and social and economic factors.[5] In Turkey, poisoning accounts for 0.4-1.7% of all emergency service referrals,[6] which is consistent with the rate obtained from the current study (1.7%).

Previous studies have found that females and younger patients are more likely to be intoxicated with drugs.[7] In the present study, 64.8% of all patients were female and most had attempted suicide. This could be attributed to Turkish society's repressive attitude towards women, which may be a cause of young females attempting suicide in the mistaken belief that this can 'solve' their problems.

Gastric irrigation performed within one hour after drug ingestion results in the elimination of 42-90% of the ingested material.[8] In the present study, 38 patients arrived at the ED within one hour of drug ingestion and were recorded as having undergone gastric irrigation.

Paracetamol has been reported to be the principal drug used in intoxication cases);[9] however, anticonvulsants carbamazepine and valproic acid have also been found to be commonly taken.[10] We determined that paracetamol was the drug most commonly taken, with

carbamazepine and valproic acid being the most common anticonvulsants ingested. Paracetamol is readily accessible, inexpensive, and can be bought over the counter without a prescription. We believe that antiepileptic drug poisoning is not uncommon because such drugs are taken regularly by the epileptics, and in Turkey, prescriptions cover three-month supplies. Additionally, epileptic patients sometimes experience personality changes that may trigger a tendency towards suicide.[11]

Intoxication with certain drugs requires specific treatments, including N-acetyl cysteine that is used to treat paracetamol intoxication, and bicarbonate for TCA and salicylate intoxication.[12] In our study, all paracetamol-intoxicated patients were given N-acetyl cysteine. Bicarbonate was given to 77.8% of salicylate-intoxicated and 25% of TCA-intoxicated patients. N-acetyl cysteine benefits paracetamol-intoxicated patients by exerting an antioxidant effect and increasing glutathione levels.[13]

In TCA intoxication, the associated systemic acidosis results in the release of protein-bound TCA, thereby increasing the toxic effects of the drug. Sodium bicarbonate is given to increase the serum potential of hydrogen (pH), which, in turn, elevates the level of protein-bound drug, reducing the toxic effects. In patients with salicylate intoxication, bicarbonate is applied to correct acidosis and increase salicylate excretion in alkaline urine.[14]

Although several TCA-intoxicated patients were admitted to the ICU, their rate of admission did not significantly differ from the admission rate of those intoxicated with other drugs. All TCA-intoxicated patients admitted to the ICU had serum drug levels >650 µg/mL, and thus met one of the ADORA criteria.[15]

In the present study, nine of the 11 patients admitted to the ICU had plasma drug levels >650 µg/mL. In TCA-intoxicated patients, a plasma drug level >650 µg/mL is often used as a cut-off point, but decisions must be based on the patient's clinical status even if the plasma level is below this threshold.

Reported hospital admission rates for treatment of drug intoxication range from 26% to 72%.[16,17] In the present study, only 224(2.7%) of 8,336 drug-intoxicated patients presenting to the ED required hospitalisation, and the remaining patients were discharged after treatment. In contrast to earlier studies, we evaluated patients with any measurable level of a toxic drug in their plasma; thus, our hospital admission rates were much lower than those reported in literature.[16,17] This is why we emphasise that measurement of plasma drug levels reduce hospitalisation rates and medical costs.

The mortality rates of drug-intoxicated patients visiting ED have been reported 0.03-0.05%.[2,18] Early arrival at the ED and immediate initiation of treatment greatly reduce both mortality and morbidity.[19] In the present study, the mortality rate was 1.8%, which was higher than reported in literature.[20] We attribute this to the fact that we only evaluated patients with toxic levels of drugs in their plasma.

The current study has several limitations. First, it was retrospective in nature. Second, the total number of patients was low, and the study period was only 14 months. Lastly, we did not conduct a long-term follow-up. These issues should be considered in future studies to further clarify the effects of drug screening and dosage on cases of drug intoxication.

Conclusion

Drug type and dosage were found to be of great importance in taking timely decisions while attending to patients with intoxication in an emergency setting. Delay in presentation was associated with mortality.

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