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Toxicological Analysis Unveiling the Low Rate of Self-Reporting of Addictive/ Recreative Substances in Acute Severe Drug Overdose Cases

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Abstract

Objective: Toxicological analysis (TA) is advised when assessing the prognosis and the treatment of drug overdose patients. Apart from this use, the value of TA has remained unclear. This study aimed at defining the value of TA regarding the toxicological diagnosis in severe overdose cases that involved addictive or recreational drugs (ARDs) that were used either alone or in combination with medicinal drugs.

Methods: The patients who were enrolled in the study had been admitted to our intensive care unit for the treatment of poisoning. TA was performed using advanced technologies such as mass spectrometry of blood/urine on admission. An occurrence indicated the supposed ingestion of a defined substance. Patients were included in a group depending on the combination of the occurrences of supposed ingested drugs (SID) and the results of the 1) TA: SID+, TA+; 2) SID+, not searched by TA; 3) SID-, TA+.

Results: There were 224 occurrences of 90 substances in 70 patients. ARDs were present in 30 patients (43%). ARD accounted for 24 occurrences in the SID+, TA+ group, 10 occurrences in the SID+, not searched group and 196 occurrences in the SID-, TA+ group. In the SID+, TA+ group, 9 occurrences (69%) of ethanol were confirmed by TA. Ingestion of ethanol was invalidated in 4 occurrences (31%). In the patients who denied ethanol ingestion, TA confirmed the non-ingestion of ethanol using 30 blood measures (81%). Ethanol was involved in 57% of the patients, being the lone substance in only 1 case.

Conclusion: In drug overdose instances that result in organ failure(s) and involve ARDs, self-reporting is of limited value in assessing the patients' exposure to ARD. Multiple consumptions expose patients to unexpected drug interactions.

Keywords: Addiction, overdoses, poisonings, recreational use, toxicological analysis

Introduction

The added value of toxicological analysis (TA) in acute overdose is a pending matter in the scientific debate. While TA is recommended for suspected overdose involving drugs that may benefit from drug monitoring (1, 2), it is recommended in limited conditions, including (2-6): i) a discrepancy between the clinical findings and the expected action of the supposed ingested drugs (SIDs), ii) if the results of TA result in a modification in the medical management (1, 5-7), iii) when the emergency use of invasive methods is considered, including extracorporeal techniques, and iv) to minimise medicolegal consequences in patients with a definite clinical presentation (6).

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If TA is not performed, the lone toxicological reference is drawn from the SID that are either self-reported or based on the patients' history, clinical presentation, or other relevant factors (2, 8).

Despite numerous efforts in the USA, the number of deaths related to drug overdose has been continuously increasing since 1999 (9). An increase in the use of psychotropic drugs and opioid-involved overdose deaths were reported from 2010 to 2015 (10). From 1997 to 2008, drug overdose accounted for about 14% of intensive care unit (ICU) stays in the Ile-de-France area and was associated with an increase in the mortality rate (11). The Netherlands was the lone country where drug-induced fatalities decreased (12). The drugs involved in fatalities have significantly changed over the years, supporting the need to have definitive evidence about potentially lethal substances rather than classes of toxicants.

To address the question of the added value of modern TA in comparison with the clinically suspected overdose by recording the history in patients presenting with organ failure, we performed a retrospective study in an adult population of severe drug overdose cases that had resulted in organ failure and had been admitted to our ICU, focusing on the exposure to addictive and recreative drugs (ARD).

Indeed, to meet pharmacovigilance requirements as defined in the European directives (13) and their application in France (14), in our ICU connected to the SAMU de Paris (15), where we had access to facilities provided by three University Toxicological Laboratories (ToxLab). The second objective was to unveil the presence of ARDs that were not self-reported by the patient on admission.

Methods

We performed a retrospective, monocentric, and observational study on adult patients admitted in the ICU at Necker Hospital from January 2014 to April 2015. The study was approved by the ethical committee of our hospital. The requirement for informed consent was waived as we used the recommendations for TA that were already in practice at our institution.

Main Points:

- The clinical diagnosis of poisoning is based on self-reporting and toxidrome at presentation.
- Owing to the illegal status of a great number of addictive and recreative substances, accuracy of self-report is far more questionable than with medicinal drug poisonings.
- The present study supports the assumption that toxicological analysis is mandatory for identification of substances when suspecting exposure to addictive or recreative substances.

During the study period, consecutive adult patients were admitted to our intensive care on clinical suspicion of overdose involving ARDs. Patients suffering from an adverse drug reaction before or during their hospitalisation were not included in the study.

Data collection

Data were obtained from the medical records of the patients and included the demographics (gender, age, weight, height), current treatments, medical history and the substances supposedly ingested by the patient. Throughout the text, the basic unit was the occurrence of a substance. An occurrence means the supposed ingestion of a defined substance, either a medicinal or a recreational substance.

All drugs administered during the management of the patient from the pre-hospital setting to the admission to the ICU were not recorded.

Assessment of the clinical severity of the poisoned patients

In order to assess the severity of the poisonings, the patients were classified into at least one of the 7 organ failures: neurological (altered levels of consciousness), cardiovascular (therapeutic intervention required for altered hemodynamic status), respiratory (endotracheal intubation and mechanical ventilation required), metabolic (hypothermia requiring specific therapeutic intervention), renal (assessed by serum creatinine concentration, haematological failure) and hepatic (assessed by liver enzymes and prothrombin time). Global severity was assessed using the SAPS II score calculated at the end of the first 24 hours after admission. A value of 15 and greater is considered the cut-off on the basis of which ICU admission is decided.

Handling of the results of toxicological analysis

For each patient, the toxicological dossier included the chart file record of the patient and the results provided by the different toxicological laboratories.

The blood and urine specimens that were used in the present study were those that had been sampled on admission. In each case, the implementation of TA was performed as follows:

The first batch of biological samples was sent to ToxLab1, the Toxicological Laboratory of our hospital. In case the SID were not present in the list of drugs either detected or quantified by LabTox 1, a batch of biological specimens were sent to ToxLab2, the Toxicological Laboratory on duty at our institution 24 hours a day, 7 days a week. Finally, when the SID were not present in the list of drugs and substances either detected or quantified by LabTox 2, the biological specimens were sent to ToxLab 3, the forensic Toxicological Laboratory of our insti-

tution and the our ICU correspondent for these difficult cases. As the study was retrospective, the ToxLabs were blinded from the aim of the study. The toxicological analyses were ordered at the discretion of the attending physician. Regarding the clinical information sent to each laboratory, there was no attempt to modify the current practice carried out in the ICU at present.

The basic unit in this study was the occurrence of a substance and not a patient. The occurrence was defined clinically by the previous medical history (16). To assess the performance of TA in the adult population, we considered it mandatory to use the results provided in terms of a substance but not in terms of the class of the toxicant. Detection of a class of positive substances without further quantification of a precise substance was not considered as a contributory result, owing to a large amount of cross-reactivity that prevented the further probing into the presence of the substance. In contrast, we cannot deny that the tox-screen of a class might be highly sensitive. Consequently, a negative result of a class detection should be considered as a valuable tool that invalidates the presence of a substance. Therefore, the process of interpretation of the TA was conducted as per previously reported guidelines (1).

For the following substances, the detection by itself was considered specific for substances including cocaine, tetrahydrocannabinol (THC), methadone, 3,4-méthylènedioxy-N-méthylamphétamine (MDMA), ethanol and salicylates.

Ability of TA to detect supposed ingested ARDs as well as non-reported ingested drugs

The comparison of the SID to the results of the TA are classified into the three following groups (17):

a. SID+, TA+: included the occurrence of substances that were declared ingested by the patient or his/her relatives and were also found by TA;
b. SID-, TA+: included the occurrences of substances that were not reported by the patient or his/her relatives but were found by TA;
c. SID+, not searched by TA: included the occurrences of substances that were supposed to be ingested by the patient but were not searched by TA. The lack of search was defined as resulting from either the lack of a request from the attending physician or the lack of search by the ToxLab, without any effort to clarify the condition, which resulted in the lack of an analytical screening.

As previously outlined, in the present retrospective study (17), we were unable to build a 4th group which would have included substances whose ingestion would be denied by the patient (SID-). Meanwhile, the drug was neither detected nor quantified (TA-). Consequently, we were unable to use the ROC-curve to assess the sensitivity and specificity of TA in terms of ROC-curves for each substance of interest.

Status of the exposure, either confirmed or invalidated by TA

For a substance suspected during a poisoning, the TA was considered positive if the substance was either detected or detected and quantified. Therefore, we classified the SID+ into two subgroups with respect to the limit of detection or quantification:

- SID+ was confirmed by TA when the ratio of the blood concentration of the SID to the LOD/LOQ was at 1 or greater; the patient was classified in the confirmed subgroup.
- SID+ was invalidated when the ratio was lower than 1; the patient was classified in the invalidated subgroup.

Statistical analysis

The 2013 version of Excel software was used for data collection, for exploration, harmonisation and presentation of the database, and for the development of tables. Results are expressed as median (5–95 percentiles) for quantitative parameters or percentage values (95% confidence interval) for qualitative parameters.

Results

Seventy patients were admitted in the ICU during the study period with a diagnosis of poisoning due to drug overdose. A total of 40 (57%) patients were admitted for medicinal drug poisoning, 20 additional patients for drug and ARD co-exposure (29%), and 10 patients for poisoning only involving ARD (14%). There were 52 women and 18 men. The median patient age was 47 years (8–83 years).

The total number of occurrences was 224, which corresponded to 90 medicinal drugs and ARDs. Thirty-six substances had an occurrence greater than 1. The median number of supposed ingested substances by the patients was 3 (1–5 ingested substances).

Table 1 shows the distribution of the patients regarding the occurrence of organ failure during the course of time of poisoning. The most frequent organ failures in the 30 patients were neurological (80%), respiratory (77%) and cardiovascular (33%). The median SAPS II score was 40 [13-69]. Among the 30 patients, 4 patients showed no organ failure. One 38-year-old female presented with cardio-respiratory arrest and required cardiopulmonary resuscitation after having sniffed heroin and ingested alcohol. The patient was discharged two days later without evident neurological sequelae. No patient died from poisoning during the study period. The median duration of stay in ICU was 2 days (0.5–8 days).

Table 1. Repartition of patients regarding organ failure

Organ failure	Neurological	Cardiovascular	Respiratory	Metabolic	Renal	Hepatic	Haematologic
Drug and ARD co-exposure	14 (70%)	8 (40%)	13 (65%)	3 (15%)	1 (5%)	1 (5%)	0
ARDs exposure	10 (100%)	2 (20%)	10 (100%)	2 (20%)	-	-	-

ARD: addictive and recreational drugs

Table 2. Repartition of supposed ingested medicinal drugs and ARD in the three subgroups: SID+, TA+; SID+, not searched; and SID-, TA+

	SID+, TA+	SID+, not searched	SID-, TA+	Total Occurrence
Medicinal drug	50	140	67	257
Addictive/recreational substances	24	10	196	230
Occurrences	74	150	263	
Total	224	263	487	

TA+/-: toxicological analysis positive/negative; SID+/-: supposed ingested drug positive/negative; ARD: addictive and recreational drugs

Table 3. Results of analytical toxicology in terms of detection with and without quantification in response to the supposed ingested ARDs

SID+ involving addictive/ recreative substances	TA+
Cannabis	1
Cocaine	7
Codeine	1
Ethanol	13
GHB	1
MDMA	1
Total (occurrences)	24

MDMA: 3,4-methylenedioxy-N-methylamphetamine; GHB: gamma-hydroxy-butyrate; SID+: supposed ingested drug positive; TA+ : toxicological analysis positive; ARD: addictive and recreational drugs

Table 4. Supposed ingested ARDs that were not searched by TA

SID+ involving addictive/ recreative substances	Not searched
Isopropyl alcohol	1
Heroine	2
Cocaine	1
GHB	2
MDMA	1
Mephedrone	1
Methadone	1
Morphine	1
Total (occurrences)	10

TA: toxicological analysis; SID+: supposed ingested drug positive; ARD: addictive and recreational drugs; MDMA: 3,4-methylenedioxy-N-methylamphetamine; GHB: gamma-hydroxy butyrate

Table 5. ARDs found by TA that were not suspected by the paramedics, rescuers and medically staffed ambulance workers in comatose patients or not self-reported by conscious patients

SID-involving addictive/ recreative substances	Occurrences
6-MAM	1
Buprenorphine	1
Cocaine	35
Codeine	3
Codethyline	1
Ethanol	37
MDMA	34
Methadone	40
Morphine	3
Pholcodine	1
THC	40
Total (occurrences)	196

ARD: addictive and recreational drugs; TA: toxicological analysis; SID: supposed ingested drug; 6-MAM: 6-monoacetylmorphine; THC: tetrahydrocannabinol

The ability of TA to detect supposed reported as well as non-reported medicinal drugs and ARD in the general population is shown in Table 2.

In the SID+, TA+ group, there were 74 occurrences of SID/ARD found by TA.

In the SID+, not searched group there were 150 clinical occurrences.

In the SID-, TA+ group, TA detected 263 occurrences of SID/ARD.

Table 6. Assessment of exposure to the supposed ingested ARDs regarding the results of toxicological analysis at less than, equal to and greater than the limit of detection/quantification in the SID+, TA+ group

SID+ involving addictive/ recreative substances	Invalidated <LOD/Q	Confirmed ≥LOD/Q
Cannabis		1
Cocaine		7
Codeine	1	
Ethanol	4	9
GHB		1
MDMA	1	
Total (occurrences)	6	18

TA: toxicological analysis; SID: supposed ingested drug; ARD: addictive and recreational drugs; GHB: gamma-hydroxy-butyrate; MDMA: 3,4-methylenedioxy-N-methylamphetamine

Table 7. Repartition of supposed ingested ethanol according to the blood ethanol concentration at less than, equal to, or greater than LOQ/D

SID+, including ethanol, TA+	Total
Confirmed	9 (69%)
Invalidated	4 (31%)

TA+: toxicological analysis positive; SID+: supposed ingested drug positive

Table 8. Repartition of ethanol in SID-, TA+ group according to the blood ethanol concentration at less than, equal to, or greater than LOQ/D

SID-, including ethanol, TA+	Total
Evidenced	7 (19%)
Confirmed (non-ingestion)	30 (81%)

TA+: toxicological analysis positive; SID-: supposed ingested drug negative

The TA results in terms of detection with and without quantification in response to the supposed ingested ARDs are as follows:

- Among the 74 occurrences in the SID+, TA+ group, ARD accounted for 24 occurrences (32%) (Table 3).
- Among the 150 occurrences SID+, not searched group, there were 10 clinical occurrences (7%) of ARD (Table 4).
- Among the 263 occurrences in the SID-, TA+ group, TA unveiled 196 occurrences of ARD (Table 5).

Status of the exposure, either confirmed or invalidated by TA

In the SID+, TA+ group, the assessment of the exposure status as confirmed or invalidated is shown in Table 6. Among the 24 occurrences of ARD, 18 occurrences (75%) were above the LOD/LOQ. In 6 occurrences (25%), the exposure to ARD was invalidated (Table 6). In the 196 occurrences of the SID-, TA+ group, the blood and/or urine concentrations were always above the LOD/LOQ.

Table 9. The ARD and medicinal drugs ingested in association with ethanol

Drugs / ARD	Occurrences
Cocaine	4
Zolpidem	4
Alprazolam	3
Risperidone	3
6-MAM*	2
MDMA	2
Venlafaxine	2
Amisulpride	1
Aspirine	1
Bromazepam	1
Chlorpromazine	1
Cyamemazine	1
Diazepam	1
Flunitrazepam	1
Ibuprofen	1
Milnacipran	1
Mirtazapine	1
Oxazepam	1
Oxetorone	1
Zopiclone	1

ARD: addictive and recreational drugs; MDMA: 3,4-methylenedioxy-N-methylamphetamine; 6-MAM: 6-monoacetylmorphine

Assessment of the frequency of occurrences of ethanol in the SID+, TA+ and SID-, TA+ groups

In the SID+, TA+ group, 9 occurrences (69%) of ingested ethanol were confirmed by TA. Ingestion of alcohol was invalidated in 4 occurrences (31%) of supposed ingested ethanol (Table 7).

In the SID-, TA+ group, 7 occurrences (19%) of ethanol were evidenced by the TA, especially in the patients who denied ethanol ingestion. TA confirmed the non-ingestion of ethanol in 30 occurrences (81%) of this group (Table 8).

Over 30 patients having ingested ARD alone or in combination with medicinal drugs, 17 (57%) patients also ingested ethanol. Ethanol was ingested alone in only 1 occurrence. Table 9 shows the ARD and medicinal drugs ingested in association with ethanol.

Discussion

The present study dealt with a series of 70 consecutive patients admitted in our hospital's ICU on suspicion of acute

drug overdose. The mean age of the study population (47 years) was similar to the mean age of poisoned patients who had been previously admitted to an ICU in Paris (11). The present study showed that ARDs were involved in 43% of the whole population of drug overdoses, 20 patients for drug and ARD co-exposure (29%), and 10 patients for overdoses involving only ARD (14%). The clinical severity of the study patients was assessed by a SAPS II score of 40 (13–69 score) which compared favourably with the mean value previously reported in Paris (11). Among the 30 ARD patients and in comparison with the population of poisoned patients in Paris, there was an overrepresentation of patients presenting with neurological, respiratory and cardiovascular failure (11).

In the patients where the occurrence of ARD and medicinal drugs was suspected on account of their history, 24 ARD and 50 medicinal drugs were confirmed by TA. In contrast, in the patients in whom history did not suggest exposure to ARD, the TA unveiled exposure to 67 medicinal drugs that could be compared to 196 ARDs. The 196 occurrences included 40 exposures to THC. However, cannabis was not shown to cause organ failure by itself. Therefore, only 156 occurrences out of 196 may have played some role in the onset of organ failure. The results of the present study support the hypothesis that any study dealing with drug overdose that might involve ARD requires modern TA to confirm or invalidate the exposure to masked ARD, which might play an active and significant role in the onset of organ failure. The hallmark of the population in the SID-, TA+ group was the poly-consumption of ARD in the form of complex mixtures. The evidence of poly-consumption of ARDs associated with admission to ICU raises the question about any possible drug interactions of either pharmacodynamic or pharmacokinetic origin. Positive interactions were already shown between ethanol and GHB as well as diazepam and methadone. The results of modern TA are a valuable tool in clarifying the frequent associations of ARDs, including ethanol, that should be checked for drug-drug interactions.

We fully agree with the limitation of TA in the daily management of overdose cases admitted in ER. We can even add other arguments that may further limit the use of TA. Indeed, the potential interest of TA is further hampered by the delay in obtaining the results (1, 2, 6) and the significant additional cost (1, 6, 18). Furthermore, the overall morbidity and mortality in overdosed patients who are properly decontaminated and supported is low (1, 19, 20). The complexity in the interpretation of the results of toxicological analyses should be outlined so that the practice of TA receives regular updates of knowledge (21). Furthermore, the physician's ability to interpret the results accurately was shown to be poor (22) and heterogeneous interpretation was outlined, even in large teaching hospitals (23). According to the results, modern TA should be performed only in specialised centres for the treatment of poisoned patients (24).

We might question whether improvement in technologies may obviate these limitations. Unfortunately, even studies using more sophisticated technologies failed to show any improvement in the added value regarding the management of poisoned patients (6, 18, 25-31). Nowadays, in spite of progress in modern TA, there is presently no evidence supporting the assumption that TA improves the management of poisoned patients (17). However, the consistency of the negative results regarding the usefulness of TA in drug overdoses should be considered in the light of limitations of the previous studies as well as the underestimated expectations that TA may carry.

The limitations regarding the recommendations for TA in overdosed patients result from the fact that these recommendations were made for and limited to the emergency departments (2, 6, 32). Consequently, the severity of the poisonings was rather low, resulting in short durations of observational time of the patients, which were reduced to 4.8 hours (8) from 7.2 hours (6). This short duration of observation agrees with the global low severity of the poisoned patients seen in the ED. These short durations of observation and medical interventions contrast with the median duration of stay in ICU, which was 2 days (0.5–8 days) in the present study. Consistently, in Mahoney et al. (6) study, only 14% (23/164) of the poisoned patients seen in the emergency department were admitted to ICU, while 16% of the patients studied in Kellerman et al. (8) study were eventually intubated. In contrast, 87% of our patients presented at least one organ failure. We are not aware of any study performed in other ICUs. In France, recommendations were made about TA to be ordered in patients of acute poisonings involving medicinal drugs and addictive and recreative substances who had been admitted to an ICU. However, in the absence of specific studies, the recommendations were based only on experts' opinions. The conclusions did not differ from those that had been made for emergency department (33) and did not account for the onset of organ failure in overdosed patients admitted to ICU.

The results of the present study are in agreement with Ellenhorn's report (5) in the late nineties that a few potentially important unsuspected drugs might be found in most poisoned patients and in some cases while testing for toxins, where it may provide additional or better guidance (1). Indeed, an unexpected finding was that in a limited population of 30 overdose cases involving ARDs either alone or in combination with medicinal drugs, TA found 196 occurrences of ARD consumption. The very small number of clinical occurrences that did not benefit from TA agrees with the low self-reporting use or abuse of ARD in severely overdosed patients. One major problem when dealing with ARD is the difficulty

in determining the ranges of concentrations associated with expected and toxic effects. The range of concentrations are known for only a limited number of ARD. However, it should be noted that in these cases, the clinical presentation of the patients fit well with the detected substances. To support this assumption, we paid particular attention as to whether the detection/quantification considered positive were above the threshold for quantification. In the SID+, TA+ group, the exposure to ARD was confirmed by TA in 75% (18/24) of occurrences. Noteworthy, for ethanol, in 81% of the patients in whom ingestion was suspected, the TA confirmed ingestion. Conversely, patients denying ethanol ingestion were confirmed in 81% of cases with blood ethanol concentration below the level of quantification. Unfortunately, TA was not ordered in 10 cases in whom the ingestion of ARD was suspected. Nonetheless, these findings suggest a high rate of under-self-reporting, which contrasts with a high rate of detection/quantification of ARD in unselected severe overdose cases occurring in a large urban area. In the case of alcohol ingestion resulting in organ failure, this study highlighted that ethanol was involved alone in only one case, while in the other patients, ethanol masked multiple exposures to medicinal drugs and ARD.

The present study suffers from limitations. This study is a retrospective study and was performed in a single centre. However, the demographic characteristics did not exhibit significant differences from the present population in comparison with the previous population of acute poisonings admitted in an ICU in Paris, who were from a dwelling with about 13,000,000 inhabitants (11, 34). Finally, this study did not aim at making a correlation between drugs and ARDs unveiled by TA and the number and magnitude of organ failures. Further studies are needed to clarify this major issue. The unveiling of ARDs may have been facilitated by the fact there is a limited list of substances established at the level of Ministry of Health, including selected ARDs that might be checked for toxicological screening using modern TA. The major concern results from the endless increase in the number of medicinal drugs resulting in misuse and abuse, as well as increasing the number of non-medicinal ARDs. Finally, the added value of modern TA in overdoses admitted in ICU remains specifically determined.

Conclusion

In overdoses involving ARD and requiring admission to ICU due to organ failure, self-reporting is of limited value in accurately assessing the patients' exposure to ARD. TA unveiled the exposure to a number of ARDs frequently used during poly-consumption. The use of TA with modern technology is important for the following reasons: to update the list of substances that may result in ICU admission, to give support for the types of drugs that should be taught to students and the ones that should be looked for by TA, the toxicity of the drugs that should be investigated in depth both alone and in selected combination as ARD-ARD interactions, and those ARDs that should be a concern for health authorities.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Comité de Protection des Personnes, Paris-Ile de France 2 (Number ID-RCB: 2016-A01278-43 on 2017-06-03).

Informed Consent: Due to the retrospective design of the study, informed consent was not taken.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – F.B.; Design – K.A.A., F.B.; Supervision – F.B.; Data Collection and/or Processing – K.A.A., Jh.R.; Analysis and/or Interpretation – C.L.B., R.J.; Literature Search – F.B., K.A.A.; Writing Manuscript – K.A.A.; Critical Review – K.A.A., F.B., A.L.L.L., L.L., Jh.R., R.J.

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