Science and Justice 54 (2014) 61–65

Contents lists available at ScienceDirect

Science and Justice

journal homepage: www.elsevier.com/locate/scijus

Post-mortem evidence of doxylamine in toxicological analyses

Lena Eckes, Michael Tsokos, Sieglinde Herre, René Gapert *, Sven Hartwig

Institute of Legal Medicine and Forensic Sciences, Charité — University Medicine Berlin, Turmstrasse 21, Haus N, 10559 Berlin, Germany

ARTICLE INFO

Article history:
Received 21 June 2013
Received in revised form 24 October 2013
Accepted 28 October 2013

Keywords:
Antihistamines
Intoxication
Suicide
Toxicological examination
Autopsy
Benchmarks

ABSTRACT

Background: Doxylamine (DA) is widely available in pharmacies without prescription and can be used in suicidal intention because of its sedative and anticholinergic properties. Research of literature shows that only a few publications deal with post-mortem evidence of DA and its interpretation during toxicological examination.
Material and methods: In this study, all cases with a positive detection of DA during toxicological analyses with high-performance liquid chromatography in the time period 2000 to 2010 at the Institute of Legal Medicine and Forensic Sciences in Berlin, Germany were retrospectively analysed and interpreted, taking into account police investigations, autopsy results and toxicological analyses.
Results: In total, 22 cases with DA intoxications were discovered (♂ = 16/♀ = 6, age-at-death range 17 to 90 years). Maximum blood concentration was measured at 77.5 μg/mL. Cause of death was due to DA intoxication in eight suicide cases; seven of those were combined intoxications (DA and other substances, particularly diphenhydramine). During the evaluated time period no monointoxications with DA were discovered.
Conclusion: Benchmarks published in past literature are meant as orientation during evaluation of post-mortem DA evidence. These should not be used as absolute values and need to be interpreted individually in each case. Post-mortem redistribution needs to be considered as a main factor in alteration of DA concentration measurement. Furthermore, proof of DA ingestion found in gastric content should only be interpreted quantitatively due to unreliable calculation of the ingested amount. In conclusion, a variety of factors, such as the time period between time of death and the time of the first toxicological analysis, the condition of the body and the findings at autopsy, must also be critically considered.

1. Introduction

Doxylamine (DA), a first-generation H1-antihistamine, is used for the treatment of sleeping disorders as well as nausea and vomiting, especially during pregnancy [1–3]. In the past it was also used to treat allergies, but this was stopped because of its anticholinergic and sedative adverse effects [4,5]. These side effects can be explained by the pharmacodynamic properties of the drug, the ability to cross the blood–brain barrier and the effects on histamine receptors and on muscarinic acetylcholine receptors [6,7].

A dose of 25 mg DA is recommended in the treatment of sleeping disorders [2]. Medication with this substance is considered relatively safe for adults because of its wide therapeutic index [8]. Attention should be paid when treating children: Türk and Ewald [9] reported a lethal intoxication of a one-year-old girl after usage of the recommended dosage for children of liquid Sedaplus with the active DA component. Intoxication with DA has the following clinical symptoms: impaired consciousness and coma, hypotension, cardiac dysrhythmia, dysregulation of body temperature and epileptic seizures as well as anticholinergic symptoms like mydriasis, tachycardia and urinary retention [6,8]. A further complication of DA intoxication can be rhabdomyolysis [10,11]. Children present themselves as rather agitated and are more likely to develop convulsions than adults, who are normally somnolent or comatose [12].

Few studies and case reports exist in forensic literature about DA monointoxication with lethal or non-lethal outcome. Köppel et al. [8] assumed a significant intake of DA in 3.4% of survived poisonings in Berlin around 1987. Furthermore, Bockholdt et al. [13] analysed 6500 autopsies between 1987 and 1997 at the Institute of Forensic Science belonging to the Free University of Berlin and detected 13 lethal intoxications with DA; two of these were monointoxications. The latter cases had DA blood concentrations of 100 μg/mL and 140 μg/mL, respectively, measured by thin-layer chromatography (TLC). The lowest deadly blood concentration in adults was stated in Siek and Dunn [14] with 1.2 μg/mL. However, a survived intoxication with a DA blood concentration of 14.9 μg/mL was reported by Degel et al. [15].

In earlier studies, different methods for DA detection and quantification have been used, e.g. thin-layer chromatography, gas chromatography using flame ionization, nitrogen phosphorus detection or in combination with mass spectrometry and high-performance liquid chromatography (HPLC) [8,16,17]. Nowadays, HPLC with photodiode array detection or gas chromatography with mass spectrometry is used for quantification for DA since it seems to bring the most reliable

* Corresponding author at: Human Anatomy, UCD School of Medicine & Medical Science, Health Sciences Centre, University College Dublin, Belfield, Dublin 4, Ireland.
E-mail addresses: lena-friederike.eckes@charite.de (L. Eckes), michael.tsokos@charite.de (M. Tsokos), sieglinde.herre@charite.de (S. Herre), rene.gapert@ucd.ie (R. Gapert), sven.hartwig@charite.de (S. Hartwig).

1355-0306/$ – see front matter © 2014 Forensic Science Society. Published by Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.scijus.2013.10.005

results for concentration [15,17,18]. It has a limit of detection of 5 ng/mL and 10 ng/mL [16,19].

The amount of intake considered lethal ranges between 25 mg/kg and 250 mg/kg for adults, which is much higher than therapeutic doses [13]. Concentration benchmarks can be found, e.g. in the work of Schulz et al. [20]: therapeutic blood concentrations range between 0.05 μg/mL and 0.2 μg/mL, concentrations between 1 μg/mL and 2 μg/mL are considered toxic and those higher than 5 μg/mL comatose or lethal. Levine et al. [21] suggested interpreting concentrations of up to 0.8 μg/mL as therapeutic concentrations when measured post-mortem.

The aim of this study was to analyse the frequency of postmortal evidence of lethal intoxication with DA in Berlin, Germany. The cases were evaluated for relevance of DA in the cause of death by comparing toxicological measurements and forensic circumstances. Benchmarks for toxic and lethal concentrations given by literature were re-evaluated during this work.

2. Methods

In the following study the results of toxicological analyses carried out at the Institute of Legal Medicine and Forensic Sciences (ILMFS) in Berlin from the beginning of 2000 to the end of 2010 were scrutinized for evidence of DA. All cases that proved positive for the substance in either blood, gastric content, liver tissue or all of these combined were included. The samples were analysed by high-performance liquid chromatography with photodiode array detector (HPLC-DAD) for systematic toxicological analysis. DA was identified by using library data (UV spectra, relative retention time) and quantified by external calibration (method according to Pragst [18]). Whenever possible, blood from the femoral vein was obtained; otherwise, cardiac blood was used for measurement. During the examined period of 11 years, 8131 autopsies were performed at the ILMFS and approximately 5000 of these were toxicologically analysed. In 22 of these cases, DA was detected.

All cases in which DA was found were systematized and divided into groups depending on whether the involved person died by suicide and, in cases of intoxication, whether these included DA concentrations that were possibly responsible for cause of death. Concentration benchmarks provided by Schulz et al. [20] were used for orientation during evaluation of the blood concentration levels measured by the toxicology department. Additionally, further information was collected for each case: age, sex, circumstances of death as noted in the police reports and important facts from the autopsy report such as macroscopic signs of intoxication. The total amount of DA remaining in the stomach was calculated by using the concentration in gastric content and the absolute volume of liquids in the stomach. The empty packages and blister packs found close to the body were used for assessment of the ingested number of pills and the DA amount they contained. This was related to the total body weight of the deceased.

A literature search was performed using PubMed and MEDPILOT to locate existing articles concerning intoxication or overdoses with DA using the keywords ‘doxylamine’, ‘intoxication’, ‘overdose’, ‘fatality’ and ‘suicide’. The procedure was last repeated using various word combinations in English and in German on 18th May, 2013.

3. Results

A total of 22 (♂ = 16/♀ = 6) cases of DA intoxications detected in blood or other specimens were discovered in autopsies performed between 2000 and 2010 at the ILMFS in Berlin, Germany. The average age was 51 years (range 17 to 90 years; median 57 years). Nineteen persons committed suicide; nine left a suicide note.

All cases are listed in Table 1, which indicates their DA blood concentrations. In one case, DA was measured at 0 μg/mL. Furthermore, it was not possible to draw blood from the body in two other cases because of severely advanced decomposition. It was not possible to identify the quantity of DA in yet another three cases and only the qualitative presence of the substance could be determined. Table 1 also provides information about concentrations in gastric content and liver tissue as well as a calculated total amount of DA in gastric liquid measured during autopsy. The time between death and the collection of samples is also provided. The highest concentration of DA measured in femoral blood was 77.5 μg/mL.

Table 1
Concentration of DA in blood, liver tissue and gastric content.

Case ID	Concentration in blood (μg/mL)	Concentration in gastric content (μg/mL)	Absolute amount in stomach (mg)	Concentration in liver tissue (μg/g)	Days between death and sample collection
1	0	14.0	0.14	n/a	11
2	0.3	1.0	n/a	0	2
3	0.4	0	0	4.9	7
4	0.6	9.2	2.3	5.1	6
5	0.7	[a]	n/a	8.4	11
6	1.7	70.0	4.2	n/a	7
7	2.2[b]	16.0	1.3	38.3	6
8	5.0	137.0	75.35	17.4	5
9	9.6[b]	n/a	n/a	40.6	19
10	13.9	42.7	17.1	231.0	n/a
11	14.2[b]	793.0	39.65	n/a	11
12	16.3[b]	25.5	1.28	n/a	4
13	18.8[b]	39.0	3.12	n/a	4
14	23.1[b]	633.0	37.98	n/a	3
15	31.0	70.0	n/a	88	3
16	34.2[b]	96.2	1.92	n/a	3
17	77.5	930.0	n/a	500.0	3
18	[a]	560.0	224	47.0	16
19	[a]	n/a	n/a	n/a	4
20	[a]	n/a	n/a	n/a	3
21	n/a[c]	106	5.3	n/a	3
22	n/a[c]	70.8	2.1	130	73

DA doxylamine
DPH diphenhydramine
n/a not available

[a] Positive; no quantification possible.
[b] Measurement in cardiac blood.
[c] No blood available because of advanced body decomposition.

Seven cases were determined to be suicidal DA intoxication in combination with other substances. In 15 of the cases, DA had no relevant impact on the cause of death as there were obvious other causes such as polytrauma or strangulation. An overview can be found in Table 2. Groups A and B in Table 2 demonstrate the suicidal intoxication found in this study. Group B contained a case (Case 3) in which the person had written down that he would kill himself with acetyldigoxin. The toxicological examination was able to demonstrate intoxication with this substance and also discovered DA; however, this was not considered relevant for the cause of death. More important to this study were the Group A cases (suicidal intoxications with DA relevant in the cause of death).

Table 3 provides a summary of all suicidal intoxications as well as blood concentrations of ingested substances other than DA. Macroscopic signs of intoxication in each case are listed along with information about packages or blister packs of tablets found close to the body. The ingested amount was calculated in total as well as in relation to the body weight.

4. Discussion

The study presented in this paper demonstrated the frequency and interpretation of post-mortem evidence of DA. DA is an over-the-counter drug and therefore easily available in pharmacies; it can be assumed that it is a substance often used in suicide. In none of the 19 suicide cases that proved positive for DA in blood or other specimens was DA the only substance used to commit suicide; in 11 cases the suicide was not even carried out through intoxication, but by other means