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A Report on Autopsy Cases Involving Amitriptyline and Nortriptyline*

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Summary. The concentration and distribution of amitriptyline and nortriptyline in different parts of the body of 55 autopsy cases are reported. The cases are grouped into three categories: i) cases in which poisoning by ami- or nortriptyline seemed to have been the only cause of death, (ii) cases of "mixed poisoning" by these two drugs and other compounds and/or ethanol, and finally (iii) deaths by physical means where ami- or nortriptyline was found but did not play a direct role in the lethal outcome.

The severity of the intoxication by ami- or nortriptyline is best judged by the concentration of the drug (and its metabolites) in the liver, in a similar fashion as for the phenothiazine drugs discussed in an earlier paper.

Key-Words: Tricyclic antidepressive Amines. — Poisoning. — Intoxication. — Amitriptyline. — Nortriptyline.

Zusammenfassung. Die Konzentration und Verteilung von Amitriptylin und Nortriptylin in Körperflüssigkeiten und Organen von 55 Sektionsfällen werden in 3 Tabellen wiedergegeben. Sie umfassen 22 Fälle, in welchen es sich um reine Ami- oder Nortriptylinvergiftungen handelte, 27 Beispiele von Vergiftungen mit mehreren Agentien und 6 Todesfälle aus körperlicher Ursache, bei denen aber auch die oben erwähnten tricyclischen Amine gefunden wurden. Pathologisch-anatomische Befunde von Bedeutung für die Todesursache werden in den Tabellen angeführt.

Für eine Beurteilung tödlicher Vergiftungen mit dieser Gruppe von Arzneimitteln scheint der Giftgehalt der Leber am geeignesten zu sein, ganz entsprechend den von uns früher veröffentlichten Resultaten von Phenothiazinderivat-Vergiftungen. Die Konzentrationen in Blut, Niere und Harn sind nicht ohne weiteres zu einer Beurteilung von Vergiftungen zu gebrauchen.

A report on autopsy cases in which phenothiazine derivatives were found in the liquids and tissues of the bodies has recently been published by our laboratory [1]. The paper also contained an outline of the analytical methods used and a discussion of the phenothiazine drugs' toxicological importance. The present work deals with the role played by amitriptyline and nortriptyline in forensic cases with lethal outcome.

A search of the literature prior to 1969 has yielded only 9 cases of lethal poisoning by amitriptyline but recently a report on 6 additional cases has appeared from Denmark [2]. The most important toxicological data on these 15 incidents are summarized in table 1. At the international conference on poison control centers in New York (June 1969), Bismuth reported 400 clinical cases

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of poisoning by tricyclic antidepressive amines, 38 of which had a lethal outcome, but no chemical data were given.

Among the forensic autopsy cases in Sweden, the findings of amitriptyline and nortriptyline have increased from 4 in 1966, to 15 in 1967, and 23 in 1968 and stayed there in 1969 (20 cases). In Denmark, a similar increase is taking place [2]. In view of this development we thought that a short report on our experiences would be of interest.

Methods of Analysis

Amitriptyline and its desmethyl derivative nortriptyline are chemically only loosely related to the phenothiazine derivatives. They contain neither nitrogen nor sulfur in their ring structure and the central ring is 7-membered.

Amitriptyline and nortriptyline do not give color reactions with iron salts, palladium salts, Folin-Ciocalteus reagent, or vanilline in sulfuric acid such as the phenothiazine derivatives do. Amitriptyline does not either show fluorescence under normal experimental conditions. Oxidation products comparable to the sulfoxides obtained from phenothiazines are not known.

This lack of reactivity limits the scope of routine assays to ultraviolet spectrophotometry, thin-layer chromatography and gas chromatography. The difficulty in detecting these drugs by spectrophotometry can be overcome by the procedure of Wallace and Dahl [3] in which the amine is oxidized to a keto compound with a pronounced absorption peak at 250 mμ.

A number of publications on thin-layer chromatography of the amitriptyline type of compounds have appeared (2,4—10), some of which (2,9) suggest five different solvent systems for development. Specific spray reagents have not been described, however, and the "spots" were either detected in ultraviolet light on fluorescent thin-layer material, or they were made visible with Dragendorff's reagent.

Gas chromatography of ami- and nortriptyline meets no special difficulties. Appropriate methods have been described by Street [11], by Wallace and Dahl [3] and others.

Our own analytical method is practically identical with the procedure described for the assay of phenothiazine drugs [1], except for the detection of "spots" on the thin-layer chromatograms. These are visible in ultraviolet light (if fluorescent layers are used) and after spraying with iodoplatinate or Dragendorff's reagent. The position of the absorption maximum at a relatively short wavelength (239 mμ) makes it necessary to use a purification procedure more frequently than in the case of the phenothiazine derivatives. Usually elution of the untreated thin-layer spots will give extracts with a neat ultraviolet spectrum.

When preparing extracts and when purifying solutions of phenothiazines or tricyclic amines it is well to keep in mind that certain ion pairs (notably the hydrochlorides and hydroperchlorates of these drugs) are soluble in many organic solvents, especially chloroform. Thus, in a system hydrochloric acid-chloroform, a considerable portion of the tricyclic amines and phenothiazines will be found in the organic layer after shaking. They will leave the chloroform upon shaking it with sulfuric acid of suitable ionic strength. Some consequences of this behaviour will be discussed in a forthcoming paper [12].

Autopsy Findings

The pathological — anatomical findings were quite non-specific in these cases of lethal intoxications and were usually confined to stasis of the inner organs and (sometimes hemorrhagic) pulmonary edema. Epidermic manifestations, like those observed in poisoning with methaqualone and sometimes with barbiturates, were absent.

In some cases, purulent bronchitis and/or bronchopneumonia were found and regarded as complications of the intoxication. However, it cannot be excluded that in exceptional cases the bronchitis and/or bronchopneumonia existed before the lethal intoxication took place.

In a few instances other pathological conditions of the inner organs were observed, such as considerable myocardial fibrosis, hypertrophy of the heart, or fatty liver.

Table 1. *Cases of fatal intoxications by amitriptyline reported in the literature. The list may not be complete (tr. = trace)*

Year	Authors	Age and sex of victim	Probable dose taken	Concentration found in the autopsy material, expressed in mg per 100 g						Remarks
				Stomach contents	Blood	Liver	Kidney	Urine	Other tissues	
1963	Sunshine and Yaffe [13]	1.2 ys., female	1 g	4.7	0.2	7.6	3.4	—	Spleen 5.6 heart 2.6	Poisoning accident
1964	Kimber [14]	70 ys. female	0.75—1.2 g	—	—	—	—	—	—	Probable suicide Spectrophotometer was used
1964	Im Obersteg and Bäumler [15]	25 ys., male	1.2—2.4 g	—	—	1.5	0.5—1.0	6.8	brain 5.0	Suicide
1964	ibid.	55 ys., female	2.5 + 0.2 g diazepam	—	3—4	—	· ·	1.2	—	Suicide. Diazepam detected in the urine
1965	Forbes *et al.* [16]	26 ys., female	2.0 g	—	tr.	tr.	tr.	50 (!)	—	Suicide
1965	ibid.	47 ys., female	?	—	tr.	tr.	tr.	6	—	Probable suicide
1966	Tipett and Richardson [17]	66 ys., female	?	280	0.6	—	—	2.1	Pooled kidney, liver and spleen 0.4	0.15% ethanol in the blood
1967	Mc Bay [18]	8 ys., ?	1.4 g + 0.1 g perphenazine	24	1.3	3.0	—	1.0	—	Accident
1967	ibid.	33 ys. ?	?	200	1.1	—	—	—	—	25 mg of perfenazine per 100 g of gastr. contents
1969	Munksgaard [2]	23 ys., female	2.5 g	—	1.5	18.8	—	6.9	—	Suicide

1969	ibid.	35 ys., female	2.5 g	—	1.8	9.0	—	5.1	—	Suicide?
1969	ibid.	43 ys., female	5 g?	—	0.5	11.8	—	5.9	—	7.2 g of aprobarbital per 100 ml of blood (mixed intoxication) Suicide?
1969	ibid.	48 ys., female	2.5 g?	—	0.5	—	—	13.7	—	Suicide?
1969	ibid.	24 ys., male	2.5 g?	—	1.8	—	—	—	—	0.08% ethanol in the blood. No autopsy performed
1969	ibid.	52 ys., male	1.25 g	—	0.6	9.5	—	—	—	0.06% of ethanol in the blood

Results and Discussion

It is not satisfactory to present analytical data on lethal poisoning cases out of context with anamnetic and pathological-anatomical findings. According to the principles discussed in the paper on phenothiazines [1] we have grouped our material in three main classes:

1) Table 2 shows 22 cases of lethal poisoning very probably due to amitriptyline or nortriptyline alone (usually suicides).

2) Table 3 lists 27 cases of lethal poisonings by a combination of ami- or nortriptyline with other drugs and/or ethanol.

3) Table 4 reports 6 cases where death was due to physical causes or carbon monoxide poisoning, but where minor amounts of ami- or nortriptyline were detected.

Tables 2—4 show the drug concentrations in mg per 100 ml of blood or urine, and mg per 100 g of liver or kidney. The values represent the sum of the parent drugs and their alkaline metabolites with similar ultraviolet spectra.

The drug concentration in the blood was determined in 13 cases (Tables 2 and 3) and found to lie between 0.0 and 1.1 mg of amitriptyline, and between 0.8 and 2.6 mg of nortriptyline per 100 ml of whole blood respectively. The cases from the literature (Table 1) show values ranging from "traces" up to 1.8 mg of amitriptyline per 100 ml of blood. The high level reported in one case by Im Obersteg and Bäumler [15] — 3 to 4 mg per 100 ml — was estimated from the size of "spots" on thin-layer chromatograms and may be in error.

It is very difficult to compare the results of toxicological assays carried out at different laboratories with the help of different methods and techniques, and all such comparisons must be regarded as approximations.

The data for phenothiazine drugs in a comparable set of cases [1] indicate a higher blood level than for amitriptyline. The concentration ranged between 0.1 and 3.5 mg of phenothiazine drug per 100 ml of blood.

Table 2. *Autopsy cases in which an overdose of amitriptyline (A) and/or nortriptyline (N) probably was the only major cause for death. In cases no. A1 to A16, no secondary causes for the lethal outcome were reported by the forensic pathologist. In cases no. A17 to A22, bronchopneumonia, bronchitis, pulmonary tuberculosis, or aspiration of gastric contents were observed as contributing factors. Screening for other drugs and for ethanol was carried out*

Nr.	Sex	Age	Drug	Concentration (mg/100 g)				Other analytical results	Remarks	
				Blood	Liver	Kidney	Urine			
A1	M	48	A	0.7	45	5.9	0.9	Not found: S, B, Met, Mep.	Diabetes mellitus for a few years; Slight myocardial fibrosis	D
A2	F	54	A+N	—	40	—	—	Not found: S, B, Met.	—	D
A3	M	49	A	—	26	—	—	Not found: S, B, Met.	—	AF
A4	F	24	A	0.1	25	—	—	Not found: E, S, B, Met.	—	F
A5	F	22	N	2.6	22	7.8	9.2	—	Slight aspiration of gastric contents	S
A6	F	25	A+N	0.5	17	2.8	1.6	Not found: S, B, Met, Mep.	Found with face buried in pillow	F
A7	M	48	A	—	15	—	—	E: 0.04 bl. Not found: S, B, Met, Mep.	Slight cardiac hypertrophy Slight fatty changes in the liver	AE
A8	F	32	N	—	14	2.1	—	Not found: S, B, Met, Mep.	—	D
A9	F	23	N	—	11	—	6.6	Not found: S, B, Met.	—	ED
A10	M	45	A	—	10	—	—	Not found: E, S, B, Met, Mep.	Slight cardiac hypertrophy	S
A11	M	27	A	—	9.1	—	—	Not found: S, B, Met, Mep.	Slight cardiac hypertrophy	DF
A12	F	69	A	0.1	8	—	—	Not found: E, S, B, Met.	—	D

A13	F	61	A+N	—	7.1	—	—	Not found: E, S, B, Met, Mep.	Slight myocardial fibrosis	—
A14	M	26	A	—	7	—	—	Not found: E.	Considerable autolysis	F
A15	M	34	N	—	5	—	—	Not found: S, B, Met.	Chilling to death cannot be excluded	D
A16	M	59	A	—	2.6	—	—	D: 0.1 u. 0.02 bl. Not found: E, S, B, Met, Mep.	No satisfactory explanation for death	D
A17	M	47	A+N	—	11	—	3.3	Not found: S, B, Met, Mep.	Bronchopneumonia	S
A18	F	22	N	—	8.6	—	—	Not found: S, B, Met, D.	Bronchopneumonia Survived in hospital for $2^1/_2$ days	D
A19	M	30	A	0	3.9	4.2	2.7	Not found: D.	Considerable aspiration of gastric contents Pulmonary tuberculosis	D
A20	M	23	N	—	3.2	—	—	Not found: S, B, Met, D.	Considerable aspiration of gastric contents	T
A21	F	21	N	—	2.0	1.5	—	Not found: S, B, Met, Mep.	Bronchopneumonia lower nephron nephrosis Survived in hospital for 4 days	DT
A22	F	20	N	0	0.8	0.7	2.5	Not found: S, B, Met.	Bronchitis No microscopic examination of lungs performed	—

Abbreviations used: 1. *Drug:* A amitriptyline and N nortriptyline. — 2. *Concentrations:* O drug concentration below the limit of reliable detection, — no analysis performed (usually for lack of sample). — 3. *Other analytical results:* B barbiturates, D benzodiazepinderivatives, E ethanol, Mep meprobamate and related compounds, Met Methaqualone, and S salicylates. Also: bl blood, li liver, and ur urine. All concentrations are expressed as mg of drug per 100 ml or 100 g of sample, except for ethanol, the concentration of which is given in parts per hundred (per cent). — 4. *Last column*: A history of alcoholism established, D patient treated for depressions or similar psychiatric conditions, E previous suicidal attempt(s) known, F fare-well letter or equivalent message found, S other evidence supporting probable suicide found.

Table 3. *Autopsy cases in which death was apparently due to poisoning by both amitriptyline (A) or nortriptyline (N) and other drugs, or in which blood alcohol levels exceeded 0.1%. No. B1 to B19 are cases with minor or no secondary causes for death, whereas such causes were observed in cases no. B20 to B26. The same abbreviations and units as in table 2 are used*

Nr.	Sex	Age	Drug	Concentration (mg/100 g)				Other analytical results	Remarks	
				Blood	Liver	Kidney	Urine			
B1	F	59	A	—	22	—	—	Met: 1.7 bl, 4.2 li. Not found: S, B, Met, Mep.	—	F
B2	M	58	N	0.8	14	9.4	12	D: 0.4 ur, 0 bl.		T
B3	M	36	A	—	14	—	—	E; 0.27 bl. Not found: S, B, Met, Mep.	Slight fatty changes in liver	D
B4	M	54	A	—	12	—	—	Phenobarbital: 7 li. Mep: 5 li.	—	DF
B5	F	48	A	—	11	—	—	D: 1.0 ur, 0 bl. Not found: S, B, Met, Mep.	—	DT
B6	F	18	A	1.1	8.7	5.3	5.4	Chlordiazepoxide: 2.5 bl.	—	F
B7	M	24	A	—	8	—	—	S: 3.3 li. Not found: B, Met, Mep.	Slight aspiration of gastric contents	DT
B8	M	57	A	—	7.8	—	—	E: 0.13 bl. Not found: S, B, Met, Mep.	—	DF
B9	M	32	A	—	7.3	—	—	E: 0.07 bl. Not found: S, B, Met, Mep, D.	—	—
B10	M	28	A	—	7	—	—	E: 0.1 bl. Not found: S, B, Met, Mep.	—	T
B11	F	22	A	—	6.7	—	1.1	Chloralhydrate: 0.7 bl. Not found: S, B, Met, D.	—	—
B12	M	33	A	—	6.4	—	—	E: 0.11 bl. Not found: S, B, Met, Mep.	—	A
B13	F	42	A	—	5	—	—	E: 0.14 bl. Not found: S, B, Met.	Slight aspiration of gastric contents	—
B14	M	28	A	—	4.4	—	—	E: 0.16 bl. Chlordiazepoxide: 0.2 ur. Not found: S, B, Met, Mep.	—	D

B15	M	35	A	—	4.4	—	—	E: 0.04 bl. Amytal: 0.2 bl. Not found: S, Met, Mep.	Slight fatty changes in the liver	A
B16	M	22	A	0.1	3.5	2.0		S: 1.3 bl. Not found: B, Met, Mep.	—	D
B17	M	23	A+N	—	3.2			E: 0.25 bl. Not found: S, B, Met, Mep, D.	—	D
B18	F	15	A	—	2.5			Met: 0.6 bl, 2.6 li. Not found: S, B, Mep, D.	—	F
B19	M	47	A	—	2			Mep: 1.4 li. S: 1.4 li. Not found: E, B, Met.	—	D
B20	F	22	A	0.3	19	—	0.4	E: 0.12 bl. Not found: S, B, Met, Mep, D.	Considerable aspiration of gastric contents	DT
B21	F	66	N	0.3	6.4	—	—	Aprobarbital: 0.1 bl. Not found: S, Met, Mep.	Bronchopneumonia	—
B22	M	34	A	—	4.5	—	—	Chlordiazepoxide: 0.5 ur., 0.1 bl. S: 0.11 ur. Not found: S, B, Met, Mep.	Bronchopneumonia Diabetes mellitus	D
B23	M	45	A	—	1	—	—	Trimipramine: 2.0 li. Primidone: 0.2 li. Not found: E, S, B, Met, Mep.	Purulent bronchitis Epilepsy	AD
B24	F	26	N	—	0.5	—	—	Amobarbital: 0.4 li. Not found: S, Met, Mep, E.	Probable suffocation (face burried in pillow) Diabetes mellitus	D
B25	M	55	A	0.2	4.1	—	4.5	Chlordiazepoxide: 0.7 ur. Not found: S, B, Met, Mep.	Considerable coronary arteriosclerosis	AF
B26	M	48	A	—	3	—	—	Brallobarbital+ Secobarbital: 6.2 li. Not found: E, S, Met.	Considerable fatty changes in the liver Fatty changes in the myocardium Cardiac hypertrophy	AD
B27	M	54	A	—	0.9	—	—	E: 0.14 bl. Not found: S, B, Met, Mep.	Considerable fatty changes in the liver Cardiac hypertrophy	AD

Table 4. *In six cases presented here, death was not due to the tricyclic amines found in the tissues and body fluids, but was caused by physical means or by poisoning by carbon monoxide. Abbreviation used for carboxyhemoglobin HbCO, followed by a number expressing the relative CO-saturation of the blood. The other symbols and units are the same as for Table 2*

Nr.	Sex	Age	Drug	Concentration (mg/100 g)				Other analytical results	Remarks	
				Blood	Liver	Kidney	Urine			
C1	M	46	A	0.3	4.7		7.6	Not found: E, S, B, Met, Mep.	Probable strangulation	A
C2	F	48	A		4.4			Not found: S, B, Met, Mep.	Drowning	DS
C3	F	29	A		2			HbCO: 75 Aprobarbital: 1.4 bl.	Intoxication by carbon monoxide	DS
C4	F	60	A		1.2			Not found: S, B, Met, Mep.	Drowning	D
C5	M	30	N				3.9	HbCO: 55 Not found: S, B, Met, Mep, P, D.	Intoxication by carbon monoxide	DF
C6	M	18	A		0.6		1.0	Not found: E, S, B, Met.	Probable chilling to death	—

It seems highly questionable if the concentration of this type of drugs in the blood of autopsy cases gives significant information about the severity of the intoxication, quite apart from the analytical difficulties often encountered at such relatively low drug levels as long as conventional methods are employed.

Sjöqvist [19] observed 10 patients who got a daily dose of 3×50 mg of nortriptyline. After about 2 weeks, the plasma concentration reached a fairly constant level, but this level varied from about 0.03 mg to 0.12 mg, and reached in 3 patients about 0.15, 0.22 and 0.3 mg respectively per 100 ml of serum. The corresponding values for whole blood would be expected to be about 30% smaller. Genetic factors, as well as interaction with other drugs were thought to be responsible for these variations [19].

The determination of the concentration of the drugs in the liver has more practical value than that in the blood. One must, of course, be aware of possible accumulation of both the parent compounds and their metabolites in patients who had been taking these drugs for some time (cf. ref. [1]). No values for amitriptyline concentrations in the liver of such patients were found in the literature .However, the cases of Table 4, in which death had resulted from other causes than amitriptyline poisoning, might be indicative of such an accumulation: the highest values lie somewhat over 4 mg of drug per 100 g of liver.

By contrast, all bona fide intoxications by the amitriptyline type of drugs lie over 5 mg of amine per 100 g of liver, with only one exception (case A 16).

A definite correlation between the analytical data on the one hand and the circumstances of death as well as the morphological findings at autopsy on the other hand would be of great value and considerable interest.

It has usually not been possible to establish the time interval between the intake of the drug and death with any degree of certainty. The police reports gave very few clues, and even the autopsy findings (condition of the digestive tract and the like) could only rarely clarify this question.

If the cases of poisoning by ami- or nortriptyline alone are considered (Table 2) one finds lower values (0.8—11 mg per 100 g of liver) in cases (A 17, A 18, and A 22) with purulent bronchitis and/or bronchopneumonia than in cases (A 1—A 16) without such complications (2.6—45 mg, with an average of 16—17 mg of drugs per 100 g of liver). The lower set of values may be explained by the assumption that the survival time was considerably longer in cases with complications, and that metabolism and excretion of the drugs had therefore continued for a longer period of time. The pharmacokinetics of ami- and nortriptyline show great individual variations (Sjöqvist [19]).

In two other instances of intoxication by amitriptyline or nortriptyline alone (cases A 19 and A 20), massive aspiration of stomach contents was observed. This was presumably due to vomiting at an early stage of the poisoning process, and death occurred before the absorption and distribution of the drug were completed. The relatively low drug concentrations (3.2 and 3.9 mg respectively per 100 g of liver) observed in these instances indicate that this assumption could be essentially correct.

In some cases the period of time between drug intake and death could be limited to a few hours (A 2 and A 5). In these instances the concentrations were relatively high (40 and 22 mg of drugs per 100 g of liver). In case A 18, however, 100 g of liver still contained 8.6 mg of drugs after $2^1/_2$ days of hospital treatment.

In the instances of "mixed poisonings" (Table 3), 100 g of liver was found to contain from 7 to 22 mg of amines, where complications were found to be absent. Cases with secondary causes for death showed lower levels (0.5—6.4 mg per 100 g), with one exception (case B 20).

In many of these "mixed poisoning" cases, the concentration of ami- or nortriptyline was surprizingly high. It is possible that the combination of several drugs taken in large doses leads to a relatively rapid death, so that the metabolism and excretion of the amines had not lowered their concentration in the liver to any greater extent.

In cases where pathological conditions of the organs were observed, such as myocardial fibrosis, hypertrophy of the heart or fatty liver it was not possible to decide for certain if these conditions had played a significant role for the lethal outcome of the poisoning cases, since other drugs were present and complicated the picture.

Only ten values for the kidney are available. The drug concentrations found in the kidney were always higher than in the blood and lower than in the liver. The number of cases is too small to warrant a detailed discussion of their significance.

The diagnostic value of urine analyses in poisoning cases with this type of drug is obviously limited to qualitative data as discussed for the phenothiazine

drugs [1]. Diuresis, the pH of the urine, and individual variations in metabolism (by habituation and by heredetary factors) are, no doubt, factors responsible for the great variations in the concentrations observed.

It seems fairly safe to state that the level of ami- and nortriptyline in the liver gives the best and least erratic lead in evaluating the role played by these drugs in lethal intoxication cases.

In connection with this study, no effort was made to isolate and assay drug metabolites, as had been done by Munksgaard [2].

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