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Toxicology of Some Autopsy Cases Involving Tricyclic Antidepressant Drugs

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Summary. The widespread prescription of antidepressant and tranquilizing drugs has resulted, perhaps inevitably in an increasing incidence of these drugs in specimens from Coroner's autopsy cases. Particularly prominent are the tricyclic compounds imipramine and amitriptyline.

Examples of toxicological investigations involving these and some other structurally related drugs, nortriptyline, dothiepin and dibenzepin form the basis of this paper.

Zusammenfassung. Die großzügige Verschreibung der Antidepressiva sowie der Tranquilizer haben zur Vermehrung der Todesfälle geführt. Dabei treten besonders Vergiftungen durch Imipramin und Amitriptyline hervor.

In der Arbeit werden Vergiftungen von Imipramin, Nortriptylin, Dothiepin und Dibenzepin beschrieben und die Ergebnisse der chemischen Analysen dargestellt.

Key words: Intoxication, imipramine and amitriptyline — Imipramine — Amitriptyline

All of the data obtained relate to autopsy cases from a part of London. In every case the pathologist was dependent on the toxicological data for providing a cause of death either because of an absence of natural disease or insufficient evidence of natural disease to satisfactorily account for death.

Publications involving the examination of autopsy materials for some tricyclic antidepressant drugs have appeared [1—3]. The data for the distribution of a drug obtained by analysis of various organs collected at autopsy facilitates a proper assessment of the cause of death by the pathologist.

Experimental

Quantitative analytical data may be obtained by the application of various physicochemical methods to suitable extracts of biological samples. Where it is desirable to assay both the unchanged drug and its metabolite or metabolites, gas chromatographic methods are usually the most appropriate.

In general the drug was recovered by extraction of the fluid specimen or tissue homogenate, adjusted to a pH value of 10, with a large excess of chloroform. Solvent extracts were evaporated and an internal standard, codeine or benzhexol, was added before gas chromatography of the concentrate on a 6′ 3.8% W 98 on Diatoport S column at 190—220°C; precise experimental conditions were adjusted according to the substance present. Thin-layer chromatography of extracts on silica gel provided further characterisation of the drug; two solvent systems were used (1) ethyl acetate: methanol: ammonia (85:10:5) and (2) methanol: ammonia (100:1.5). Dragendorff's reagent and accidified iodoplatinate spray were used to locate the substances.

Table 1. Concentrations of imipramine

	Case 1 female of 20 years		Case 2 female of 20 years	
	imipramine	desipramine	imipramine	desipramine
Blood (μg/ml)	0.9	Nil	0.2	0.5
Liver blood (μg/ml)	2.0	16.8	0.9	17.0
Bile (μg/ml)	47.0	0.1	484[b]	1460[b]
			746[c]	2700[c]
Urine (μg/ml)	—	—		60.8
Stomach contents (mg)	130	Nil	1.04	6.90
Estimated Dose (mg)	3300			

[a] milligram per 100 ml. — [b] free. — [c] Bound. — + Present but not measureable.

This routine method of drug extraction was applied for each of the drugs considered, except in the case of dibenzepin when the method of Brochon *et al.* [4] was used. For amitriptyline and nortriptyline the chloroform extract was washed once with 10 ml distilled water prior to evaporation of the solvent with codeine added as an internal standard. For imipramine and desipramine the solvent was extracted with 0.5 N sulphuric acid, the pH adjusted 10 10 and re-extracted with chloroform; codeine was then added as internal standard.

For dothiepin, the chloroform extract was washed with 5 ml 0.1 N caustic soda and back extracted through 5 ml N hydrochloric acid prior to the addition of benzhexol as internal standard.

Case Results and Discussion

Imipramine is the most frequently occurring member of the tricyclic group in autopsy cases and the detailed analytical findings from the examination of 5 cases of imipramine overdosage are shown in Table 1.

The first case was that of a 20-year-old girl (case 1) who allegedly swallowed 150 tablets each containing 25 mg of imipramine hydrochloride. Although treated in hospital there was still 147 mg of imipramine hydrochloride remaining in the stomach contents at autopsy. While the liver blood contained a considerable concentration of the desmonomethyl metabolite remarkable little metabolite was detected in the bile.

The second case was that of a 20-year-old girl (case 2) found dead. Both imipramine and desipramine were detected in all specimens but neither the quantity of drugs ingested nor the timing was known and no prescribing history was available. The analysis indicated that all desipramine concentrations exceeded those of imipramine and because of the desipramine content of the stomach both imipramine and the desipramine may have been ingested. In these 2 cases the liver blood and bile levels of the drug are significant while much lower peripheral blood levels were recorded.

The third case concerned a 54-year-old female found unconscious possibly some 2—3 days after taking an overdose. She survived a further 48 hrs in hospital during which time she was treated by peritoneal dialysis, 1 l volumes being changed every hour.

The data obtained from the analysis of autopsy fluids (Table 1) and tissue specimens, Table 2 show the prominence of the desmonomethyl metabolite.

and desipramine in autopsy specimens

Case 3 female of 54 years		Case 4 female of 72 years			Case 5 male of 28 years
imipramine	desipramine	imipramine	desipramine	alcohol[a]	imipramine
1.0	0.4	0.5	Nil	326	1.0
0.4	8.2				—
Nil	12.5				+
—	—	+	0.4	254	5.2
0.92	Nil	1090			11.9

Imipramine was not detected in the bile or kidney specimens, and despite the clinical management of this case, imipramine persisted at a level of 0.10 mg/100 ml in the heart blood. Liver blood contained a modest concentration of parent drug but a far greater concentration of metabolite, in keeping with the levels found in the 2 previous cases. The bile specimen contained the metabolite only.

Case 4 was found at the bottom of a flight of stairs in her home. A tablet container and a whisky bottle, both empty, were at the top of the stairs. About

Table 2. Organ distribution of imipramine female of 54 years (case 3)

Tissues	μg base/g	
	imipramine	desipramine
Liver	1.7	19.2
Right lung	0.7	75.8
Left lung	0.7	56.6
Right kidney	Nil	5.4
Left kidney	Nil	4.5
Heart	0.5	4.5

Table 3. Eight cases involving amitriptyline

Case	μg base/ml				mg base
	blood	liver blood	bile	urine	stomach contents
1 Female of 26 years	2.9	—	2.0	3.4	0.18
2 Male of 64 years	1.7	—	32.5	11.0	3.9
3 Female of 50 years	5.2	—		10.4	20.0[a]
4 Female of 72 years	3.1	9.7	39.7	4.8	127
5 Female of 60 years	2.8	4.2	600	11.9	0.45
6 Male of 62 years	0.16	—		0.1	151
7 Male of 41 years	1.9	0.6		7.2	7.3
8 Female of 55 years	0.35	2.76		—	11.7

[a] An intermediate-acting barbiturate was present in the extract of stomach contents only at a level of 0.48 mg/100 ml, calculated as amylobarbitone.

sixty 25 mg imipramine hydrochloride tablets were missing. She had been treated for depression.

Case 5 was that of a student who took his own life; an empty imipramine tablet container was found but the drug had not been prescribed for the deceased.

Analytical data obtained for 8 *amitriptyline* cases is presented in Table 3. The peripheral blood concentrations are similar to those reported by other workers for amitriptyline overdose cases [1, 2]. There were no useful case histories for cases 1, 3, 4, 7 and 8. The 64-year-old male, case 2, a chronic bronchitic who had been treated for nervous depression, was found in a confused state and admitted to hospital where he died 11 hrs later. It was subsequently discovered that amitriptyline tablets were missing at his home. Case 5, the 60-year-old female was receiving amitriptyline therapy for depression and was found dead with an empty tablet container beside her. Amitriptyline had also been prescribed for case 6, who was found dead in a tin shed in a sleeping posture with tablets scattered on the floor.

Table 4 presents data for 2 *nortriptyline* cases. The nortriptyline levels in the autopsy specimens from the 38-year-old female correlated well with cases reported by Bonnichsen *et al.* [2]. The second nortriptyline case also involved chlorpromazine, which confuses assessment of the data.

Three *dothiepin* overdosage cases are presented in Table 5; dothiepin being the sulphur containing analogue of amitriptyline. The first case, a 25-year-old female, showed peripheral blood and bile levels similar to those obtained for amitriptyline overdosage; but there is no published information for comparison. The second case was that of a 32-year-old female; both fluid and tissue specimens being available for analysis. The drug levels found in the peripheral blood greatly exceeded that expected at the peak plasma concentration following therapeutic dosage but the relationship between plasma and whole blood concentrations does not appear to have been documented. The small quantity of drug remaining in the stomach contents may be attributed to the success of the emergency treatment on her admission to hospital: she was thought to have taken 20 to 50 mg capsules of dothiepin (25 mg) and she died 2½ hrs after ingestion.

The results for a single case of *dibenzepin* overdose involving a 21-year-old female are present in Table 6. She had received psychiatric treatment from the age of 15 years and had had an abortion 3 months prior to her death. She was then

Table 4. Cases involving nortriptyline

	Male of 26 years μg base/ml		Female of 38 years μg/ml
	nortriptyline	chlorpromazine	nortriptyline
Ante-mortem blood	1.4	0.9	
Gastric wash (50 ml)	39.8	13.1	
Post-mortem blood	1.0	4.3	2.6
Liver blood	2.5	0.7	5.4
Bile	6.1	4.8	28.5
Urine	3.4	0.2	
Stomach contents	1.35 mg	1.8 mg	9.38 mg total

Table 5. Autopsy cases involving dothiepin only

	Female of 25 years (μg base/ml)	Female of 32 years (μg/ml)	Female of 19 years (μg/ml)
Peripheral blood	1.4	2.4	2.5
Bile	268	161.4	
Urine		3.8	4.5
Stomach contents	19.8 mg total	3.2 total[a] μg/g	1.8 g total μg/g
Liver		14.2	2.0
Right kidney		3.1	
Left kidney		3.7	

[a] Stomach washout applied.

Table 6. Fatal dibenzepin poisoning in a female of 21 years. Concentrations in autopsy specimens

	μg base/ml
Peripheral blood	4.2
Liver blood	8.4
Bile	63.2
Urine	73.3
Stomach content	33.7 mg (total)
	μg base/g
Liver	34.0
Right lung	157.6
Left lung	118.0
Spleen	18.4
Right kidney	31.6
Left kidney	31.2
Brain	9.1

treated for servere depression with dibenzepin and nitrazepam. She was found dead in bed; an empty tablet container was found beside her body. The peripheral blood level is indicative of dibenzepin overdosage and as with other tricyclic antidepressants a high concentration of the unchanged drug appeared in the lungs. The concentration of drug in the liver agreed well with levels recorded in the literature.

General Discussion

Interpretation of the analytical data obtained from analysis of post-mortem specimens is not always easy since published clinical data relating to therapeutic dosage may be quoted for plasma or serum rather than for whole blood. The figures may apply to either peak levels or to a steady state condition.

Published data [5] has shown that on long term oral therapy patients receiving a 50 mg daily dosage of imipramine reach a mean peak plasma level of 0.06 μg/ml while on 150 mg daily dosage of imipramine a peak plasma level of 0.11 μg/ml was recorded. A group of volunteers who were orally dosed on 50 mg imipramine

attained a peak plasma level of 0.03—0.05 μg/ml in 2—4 hrs after dosage; no metabolite was observed in this group. Thus we have levels for therapeutic dosage ranging from 0.03—0.11 μg imipramine/ml plasma. Blood levels from the autopsy cases (Table 1) exceeded this range but the blood/plasma ratio is not known.

Similarly with amitriptyline, Braithwaite and Widdop [8] reported a range of 0.02—03 μg amitriptyline/ml for "steady state" plasma levels during therapeutic dosage. Again the whole blood/plasma ratio is known but the blood level at autopsy (Table 3) usually exceeded this range.

Recent work with methadone showed that not only is the peak plasma drug concentration after dosage much higher than the peak whole blood levels, but the two peaks are separated by a time interval, and it may be prudent to consider whether the pattern is common with other drugs [6].

Interpretation of toxicological data should perhaps take account of the kinetics of drug absorption and elimination both in therapeutic dosage and overdosage with all the attendant implications of pKa values and perhaps more important, drug-protein interation [7]. It appears worthwhile to pursue this aspect of the tricyclic antidepressant drugs in view of their widespread clinical use.

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