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Toxicological Data on Phenothiazine Drugs in Autopsy Cases*

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Summary. The concentration and distribution of phenothiazine drugs in the body fluids and tissues of 66 autopsy cases are reported. The cases are presented in three groups: (i) those in which poisoning by a phenothiazine drug was the sole cause of death, (ii) cases with "mixed poisoning" by phenothiazine derivatives and other drugs or ethanol, and (iii) instances of death by physical means where phenothiazine drugs were found but had not directly caused death.

From the data presented it seems that the level of this kind of drugs in the liver can be of value for evaluting the severity of intoxication. The blood values often reflect levels after the maximum concentration has been passed. Kidney contains varying concentrations without significant trends. The drug concentrations in the urine are not directly related to the severity of the poisoning.

A description of the analytical technique used by us is included.

Key-Words: Phenothiazine drugs — Intoxication — Poisoning.

Zusammenfassung. Die Konzentration und Verteilung von Phenothiazinderivaten in Körperflüssigkeiten und Organen von 66 Sektionsfällen werden in 3 Tabellen wiedergegeben (Tabelle 4—6). Sie umfassen 14 Fälle in welchen es sich um reine Phenothiazinvergiftungen handelte, 34 Beispiele von Vergiftungen mit mehreren Agentien und endlich 18 Todesfälle aus körperlicher Ursache, wo aber auch Phenothiazine gefunden wurden.

Die aus unserem Sektionsmaterial erhaltenen Ergebnisse werden mit Angaben aus der Literatur verglichen. Diese beziehen sich einerseits auf Todesfälle, andererseits auf Serumspiegel nach therapeutischen Gaben von Chlorpromazin und Thioridazin.

Für eine Beurteilung tödlicher Vergiftungen mit dieser Gruppe von Arzneimitteln scheint der Giftgehalt der Leber am besten geeignet zu sein. Die zum Zeitpunkt der Sektion beobachteten Serumspiegel sind wahrscheinlich Werte, die einige Zeit nach Überschreiten des Konzentrationsmaximums auftreten. Weder die Nieren noch der Harn enthalten Mengen der Arzneimittel (und deren Metaboliten) die in einem gesetzmäßigen Zusammenhang mit der Schwere der Vergiftung stehen.

Die Arbeit enthält schließlich kurze Angaben über die von uns verwendete analytische Methodik. Auf den Metabolismus der Phenothiazinderivate wird hier nicht näher eingegangen.

Toxicological data on lethal poisonings of humans by phenothiazine drugs are scarce. Since the toxicity of e.g. chlorpromazine in rats, mice and guinea pigs is comparable to that of certain barbiturates [1], one could expect a high incidence of suicides by the phenothiazine type of drugs. These compounds are

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quite commonly used by patients suffering from depressions and similar mental disorders in which suicides are relatively frequent. The widespread use of these drugs also contributes to cases of accidental poisoning, especially in children.

A different type of toxicity is due to the occasionally severe adverse reactions to phenothiazines that can have fatal results even at therapeutic doses or slight overdoses. As we shall see below, phenothiazine derivatives are also found among patients who die from accidents or commit suicide by physical means.

A detailed review on sudden death due to phenothiazines by Leestma and Koenig has recently appeared [2]. It is mainly devoted to deaths occurring during treatment with these drugs. Fiftytwo such fatalities (of which 2 were observed by the authors) are listed. The paper mentions 27 additional cases from the litterature for which details (clinical data, age, doses etc.) were not reported. Three of the incidents cited by Leestma and Koenig were due to single massive doses, with suicidal intent.

Table 1 lists 17 cases of death due to overdoses of chlorpromazine and related drugs which were found in the literature prior to 1968. This list, however, might be imcomplete.

A murder by hanging after drugging the victim with chlorpromazine was described by Faragó [3]. Toxicological examination gave the following data (mg of chlorpromazine per 100 g of sample): blood 0.1, liver 0.6, kidney 0.3, and urine 2.9 (including metabolites). Curry and Fox [4] observed a lethal poisoning case with chloral hydrate and thioridazine. They found 2 mg of each of these compounds per 100 g of liver. Other reports on "mixed poisonings" are spread through the literature.

Since only a few publications to-date give reliable quantitative chemical data, we considered it worth-while to make a report on a number of autopsy cases which occurred in Sweden and involved poisoning by phenothiazine drugs.

Methods of Analysis

The resonance structure of the phenothiazine nucleus imparts very interesting physicochemical properties to the phenothiazine derivatives and their transformation products. These molecules exhibit typical ultraviolet spectra, give rise to fluorescent products, form complexes with various metals, produce quite stable free radicals on partial oxidation, and can be transformed chemically and biologically into a series of well defined derivatives and metabolites. Also, the typical phenothiazine drugs in the form of their free bases are volatile enough for gas chromatographic investigations. All these properties have been utilized for analytical purposes.

For the detection (screening), separation, and purification of the various phenothiazine derivatives and their metabolites, paper-, thin-layer-, and gas chromatography have been used. Chromatographic procedures can, of course only be used for the above mentioned purposes — and possibly for excluding certain types of compounds. They are of no value for positive identification procedures.

A review on analytical methods for phenothiazinderivatives has been published by Blazek [5].

Extraction

The biological material (10 to 30 g) is made alkaline by adding 50% potassium hydroxide. The volume is estimated, and an equal volume of 50% KOH is added. The mixture is kept at 100° for 5 minutes, cooled under running water and extracted twice with an equal volume of ether.

Table 1. *17 Lethal intoxications (suicides or accidents) by phenothiazine drugs reported in the literature up to 1968. Only cases where large doses of phenothiazine derivatives were thought to have been the principle cause of death are included. Deaths due to allergic reactions, hypersensitivity or complications of other nature (heart conditions, poisoning by other drugs, alcoholism, hypertension etc.) are left out. CPZ = chlorpromazine*

Year of publication	Author(s)	Journal	Age of patient	Probable dose and type of drug	Chemical findings
1957	anonymous	Aust. J. Pharm. **38**, 698[a]	2	9 tablets of CPZ	not reported
1957	L. J. Farber	Amer. J. Psychiat. **114**, 371[b]	30	0.8 g of CPZ	—
1957	R. J. Haggerty	Med. J. Aust. **2**, 903[a]	1	0.75 g of CPZ	not reported
1957	I. S. Wallman	New Engl. J. Med. **256**, 527[a]	5	0.35 g of CPZ	qualitative tests only
1960	M.A. Guerin	J. Méd. Bordeaux **137**, 747[b]	28	1 g thioridazine + unknown dose of metho-trimeprazine	not reported
1961	J. B. Enticknap and B. Gordon	Brit. med. J. II 522[b]	47	ca. 0.3 g of thioridazine	—
1963	N. M. Dilworth, A. E. Dugdale and H. B. Hilton	Lancet I, 137[a]	3	0.8 g of CPZ	qualitative analysis by spectrophotometry
1964	A. Fatteh	J. forens. Med. **11**, 120	67	unknown dose of CPZ	blood: 1.2 Liver: 45.0
1964	Z. Grochowska and K. Jaegermann	Arch. med. sadowej **16**, 53[c]	55	2.5 g of CPZ	urine: 0.5
1965	I. Moraru, I. Quai, C. Nanes, C. C. Cotutiu et S. Voinesco	Acta med. leg. soc. (Liège) **18**, 17	22	2.5 g of CPZ	not reported
1965	same authors	ibid.	36	unknown dose of CPZ	not reported
1965	same authors	ibid.	1	0.25 g of CPZ	not reported
1966	R. I. Kandibur	Sudebouméd. eksp. (Moskva) **9**, 47[d]	2.5 and 3.5 years old. Poisoning by phenothiazine derivatives		
1966	A. J. McBay	Int. Ass. forens. Toxicol. Bull. **3**, No. 2			Blood: 0.2 liver: 12.0 urine: 14.0 (incl. metabolites)

Table 1. (Continued)

Year of publication	Authors	Journal	Age of patient	Probable dose and type of drug	Chemical findings
1967	H. Guyot, J. Bachelier-Notter, M. J. Dupret et C. Evreux	Ann. méd. lég. **47**, 250	?	unknown dose of alimemazine	viscera: 2.4
1967	same authors	ibid.	?	unknown dose of CPZ	liver: 0.6 kidney: 0.4

[a] Cit. from Fatteh, A., J. forens. Med. **11**, 120 (1964).
[b] Cit. from Leestma and Koenig [2].
[c] Cit. from Dtsch. Z. ges. gerichtl. Med. **56**, 600 (1965).
[d] Cit. from Dtsch. Z. ges. gerichtl. Med. **60**, 298 (1967).

The combined ether extracts are washed with 0.1 N sodium hydroxide and water (the washings are discarded). The phenothiazine derivatives are now extracted with 0.1 N sulfuric acid. The combined water layers are made alkaline by addition of concentrated ammonia and are extracted with chloroform. The pooled extracts are evaporated to a final volume of 5.0 ml. This solution is kept in the refrigerator and is used for all further qualitative and quantitative analyses.

Spectrophotometry

An aliquot of the extract mentioned above is evaporated to dryness and the residue is dissolved in 3.0 ml of ammoniacal aqueous ethanol. The ultraviolet spectrum is recorded before and after acidification with 0.3 ml of 6 N sulfuric acid. The position of the absorption maxima of the unchanged drugs and of the corresponding sulfoxides are listed in Table 2, where also the extinction coefficients are shown. Quite frequently the phenothiazine derivatives are partially oxidized by metabolic processes and/or as a result of the isolation procedure. In this context, the role of hydroxylated metabolites is not evaluated.

Table 2. *Absorption maxima and extinction coefficients for some phenothiazine derivatives, as well as the colors observed after spraying of thin-layer chromatograms*

Derivative (proprietary name)	Main absorption maxima in ammoniacal ethanol		Color reactions with 3 reagents		
	mμ	$E^{1\%}_{1cm}$ (free base)	A (Folin-Ciocalteus reagent)	B[a] (palladium chloride solution)	C (acid ferric chloride solution)
Promethazine	253	970	pink	reddish-violet	pink
Promazine	253	1,070	reddish-brown	reddish-brown	violet
Chlorpromazine	256	950	reddish-brown	light red	pink
Acepromazine	244	1,040	red	pink	pink
	281	840			
Levomepromazine	252	750	violet	violet	violet
Thioridazine	264	940	blue-green	reddish-brown	blue-green
Perphenazine	257	690	reddish-violet	pink	red
Trifluoperazine	261	380	pink	pink	bright yellow

[a] These colors fade rapidly and must be noted at once.

Thin-layer Chromatography

Aliquots of the chloroform extract containing about 20—60 μg of phenothiazine are spotted on thin-layer plates with a 0.2 mm layer of chloroform-washed fluorescent silica gel. Standards are spotted on the same plate. It must be kept in mind that solutions of most of the phenothiazine derivatives are sensitive to light and oxygen. They must be kept cool and dark, and their ultraviolet spectrum must be taken at regular intervals to insure the absence of disturbing amounts of oxidation products.

The thin-layer plate is first developed with chloroform which removes many impurities to the front, then with methanol: conc. ammonia = 100: 1.5. A great help in discriminating between most phenothiazines are various colour reactions. We employ three spray solutions, and the colours obtained with these reagents are listed in Table 2. It is important to note the colours without delay, since they change with time and fade quite rapidly as a rule.

The metabolism of the phenothiazines has been extensively studied, and in the case of chlorpromazine, twenty-odd metabolites have been demonstrated in the body fluids from experimental animals and from man. It was not the purpose of this paper to reexamine the distribution and concentration of these metabolites in different parts of the body. Until recently, very little was known about the distribution of metabolites from phenothiazine drugs in human tissues. In 1968, Forrest *et al* [6] have, however, assayed tissues from 6 patients who had been taking chlorpromazine regularly until their death.

These autors found that, in the liver, the non-phenolic compounds were more abundant than the phenolic metabolites, and that glucuronides could not be found according to the methods used. Among the non-phenolic compounds, the parent drug (Cz), desmethyl-Cz, and disdesmethyl-Cz were predominating, whereas only traces of the corresponding sulfoxides were found.

In the method used by us, only Cz and its demethylated derivatives are isolated and assayed, since the first extraction is carried out at very elevated pH. The hydroxylated metabolites are not extractable at that pH. In the 6 patients mentioned above, this group of metabolites accounted for: traces 14, 16, 32, 40 and 60% respectively of the total drug content of the liver.

It stands to reason that, in an acute fatal intoxication, metabolism has not proceeded to the same extent as in chronically dosed individuals. In order to test this assumption, we have assayed a number of liver samples from such poisoning cases for both non-phenolic and phenolic metabolites.

Liver tissue from four recent autopsy cases were extracted with ethanol. The extracts were evaporated, hydrolyzed with aqueous potassium hydroxide, and extracted at very high pH as described under "methods". The pH of the aqueous layer was then adjusted to 8.7—9.3 by the addition of hydrochlorid acid and the extraction repeated with diethylether, following the technique used by Forrest *et al* [6]. This latter extract contained hydroxylated metabolites.

Both extracts (pH 13 and pH 9.0) were analyzed by spectrophotometry and thin-layer chromatography as described above. With the help of the R_F-values, and size of the spots obtained, a rough estimate of the relative abundance of the parent drug, the non-phenolic and the phenolic metabolites was made. The result appears in Table 3.

These data indicate that the major part of the drugs and their metabolites are extracted and assayed in the procedure used in this work and outlined under "methods".

The yield of the method is, in general, satisfactory. When 1—4 mg of phenothiazines or tricyclic antidepressive amines were added to 30 g of liver tissue, about 70—100% of the added drugs were recovered. In the case of thioridazine, however, recoveries were low but constant (about 50—60%). The reasons for this loss are, at present, not known to us.

Results and Discussion

Toxicological data are traditionally presented in the form of [1] animal experiments, [2] detailed reports on individual clinical poisonings, or [3] purely chemical investigations of scattered post mortem cases. The information available

Table 3. *Rough estimates of the relative abundance of parent drug and metabolites found in the liver tissue of four autopsy cases (these four cases do not appear in Tables 3—5). The total concentration (in mg per 100 g of liver) was determined by spectrophotometry, the relative abundance was estimated on the basis of number and size of "spots" appearing on thin layer chromatograms*

Parent drug	Chlor-promazine	Chlor-promazine	Pro-methazine	Pro-methazine
Approximate amount of parent drug plus metabolites per 100 g of liver	12 mg	30 mg	4.0 mg	1.3 mg
Relative share of parent drug	~35%	~47%	~95%	~98%
Relative share of nonphenolic metabolites	~62%	~45%	< 1%	< 1%
Relative share of phenolic metabolites	~ 3%	~ 8%	~ 5%	~ 2%

The data reported in Tables 4 - 6 represent the sum of parent drug and non-phenolic metabolites with similar ultraviolet spectra.

from such publications is rarely sufficent for evaluating toxic, let alone lethal doses of a given type of drug for the human organism, since such doses are by no means sharply defined but depend on a large number of factors.

We believe that more information can be obtained by assembling relatively large numbers of lethal intoxications by a rather uniform group of drugs. For such a study it seems essential to combine anamnetic, pathological and toxicological data, as well as pertinent results of police investigations if useful conclusions are to be drawn. Obviously, this method has great limitations, since all the essential facts about a death can never be known and since biological systems always show considerable individual variations. The data in this paper should therefore be perused with the necessary caution.

For lack of better knowledge, the over-all toxicity of the various phenothiazine drugs encountered in this study (chlorpromazine, promethazine, thioridazine, levomepromazine, perphenazine, trifluoperazine, and dixyrazine) have been assumed to be comparable. This is, of course, a simplification, and in reality differences are bound to exist between them.

Our material is grouped into three categories and presented in Tables 4—6. The first group comprises examples of probable suicides where poisoning by phenothiazine drugs appeared to have been the only cause of death (Table 4, 13 cases). Wherever possible, screening analyses were performed for excluding the presence of significant amounts of other drugs than phenothiazines. Such screening procedures have their obvious limitations and cannot guarantee the absence of less common toxic agents such as heavy metals, pesticides, inorganic anions etc. However, in none of the cases reported here was there reason to believe that such agents had been used.

A second group of cases concerns deaths which were due to the combined effect of phenothiazines and other drugs. Frequently hypnotics of various kinds are prescribed to mental patients together with phenothiazines. Overdoses of these hypnotics, taken by intent or by accident, are then the main cause of death.

Table 4. *Suicide cases, where death with all probability was due to phenothiazine derivatives alone. No somatic cause for death was found*

Case nr.	Sex	Age	Drug	Concentration in mg of free base per 100 g of sample. In the urine mainly sulfoxides were found.				Ethanol (per cent)
				blood	liver	kidney	urine	(blood)
1/65	m	23	chlorpromazine	0.3	20.0	—	10.0	—
1/66	m	53	dixyrazine	1.0	13.0	7.4	2.8	—
2/66	m	34	thioridazine	0.1	11.0	1.8	2.8	—
3/66	f	28	chlorpromazine	3.5	211.0	74.0	75.0	—
1/67	m	73	chlorpromazine	1.4	5.4	0.4	trace	—
2/67	m	41	chlorpromazine	—	14.0	—	8.5	—
3/67	m	27	chlorpromazine	—	9.3[a]	32.0	23.0	—
4/67	f	27	chlorpromazine	—	18.0	—	—	—
5/67	m	30	chlorpromazine	—	6.1	3.3	—	—
6/67	m	38	levopromazine	0.8	16.0	—	—	—
1/68	m	21	promethazine	—	5.0	2.6	—	—
2/68	m	21	promethazine	0.8	18.0	9.2	5.0	—
3/68	f	30	chlorpromazine	—	9.0	—	—	0.08

[a] The yield as low in this case.

In such cases the dose of phenothiazine drugs was low, or else death occurred before these drugs had taken full effect. Thirty-four incidents of lethal combined drug intoxication are presented in Table 5.

Since many patients receiving phenothiazines are mentally depressed and have a tendency towards suicide, one can expect that in suicides by physical means (drowning, hanging, shooting, jumping from high places etc.) minor amounts of these drugs are present in the tissues. Also, the drowsiness produced by most phenothiazines (notably in persons who had not used them previously) can increase the proneness to accidents in the patient, e.g. when driving a motor car, swimming etc. We have collected 18 cases of this type in Table 6. The presence of phenothiazines was here more or less coincidental.

It was not possible to draw sharp boundaries between these three groups of lethal intoxications or accidents, and in some cases the classification is uncertain. Nevertheless, we believe that such a grouping is significant and can contribute to a better understanding of drug toxicity in autopsy cases.

In most cases cited, very little is known about the individuals habituation to the drug taken, but we know that habituation can lead to a considerable decrease in toxicity. On the other hand, hypersensitivity, especially noted for chlorpromazine, can produce dramatic responses to even small doses of this class of drugs. In cases where phenothiazines had only been detected "on the side" the role of hypersensitivity is impossible to assess.

In instances where death probably resulted from secondary causes, such as aspiration of stomach contents or pneumonia, it is hardly feasible to reconstruct the outcome had these complications been absent. The possibility must further be kept in mind that a metabolite may more toxic than the parent drug. In

Table 5. *34 cases of suicide where death resulted from the intake of phenothiazines in combination with other drugs and/or alcohol*

Case nr.	Sex	Age years	Drug	Concentrations found. For drugs (some metabolites included) in mg per 100 g of sample. For ethanol per cent			
				blood	liver	kidney	urine [a]
1/63	f	60	chlorpromazine	—	5.0	—	—
			phenobarbital	4.2	4.3	—	—
2/63	f	57	promethazine	.	—	20.0	—
			ethanol	0.14	—	—	—
1/64	m	54	promethazine	—	2.7	2.0	0.5
			amytal	2.0	—	—	—
2/64	f	37	thioridazine	1.9	—	—	—
			secobarbital	2.5	—	—	—
3/64	m	51	promethazine	—	7.2	—	—
			phenobarbital	1.4	—	—	—
4/64	f	78	chlorpromazine	0.6	—	—	33.0
			amytal	1.4	—	—	—
5/64	m	35	chlorpromazine	1.3	—	—	—
			meprobamate (free)	7.0	—	—	—
6/64	f	38	chlorpromazine	—	6.5	10.0	—
			(acetyl) salicylic acid	12.0	—	—	—
7/64	f	50	promethazine	0.2	2.4	—	3.2
			phenobarbital	0.8	0.6	—	—
			meprobamate (free)	—	4.3	—	43.0
1/65	f	63	promethazine	2.3	9.3	—	—
			ethanol	—	—	0.21	—
2/65	m	41	promethazine	—	0.4	—	3.8
			(acetyl) salicylic acid	12.0	2.8	—	—
1/67	m	16	promethazine	—	0.2	—	5.8
			ethanol	0.09	0.05	—	0.16
2/67	m	40	chlorpromazine	—	1.2	—	—
			secobarbital	0.9	1.5	—	—
3/67	m	47	thioridazine	—	1.2	—	—
			ethanol	0.05	—	—	0.10
4/67	f	23	dixyrazine		—	2.6	3.6
			ethanol	positive (no quantitative data)			
5/67	f	53	levomepromazine	—	4.7	—	0.2
			hexobarbital	trace	0.7	—	—
			ethanol	0.27	—	—	0.37
6/67	m	69	promethazine	—	7.5	—	—
			meprobamate (unconjugated)	0.7	1.5	—	—
			ethanol	0.27	—	—	0.30

[a] Mainly sulfoxide metabolites.

Table 5. (Continued)

Case nr.	Sex	Age years	Drug	Concentrations found. For drugs (some metabolites included) in mg per 100 g of sample. For ethanol per cent			
				blood	liver	kidney	urine[a]
7/67	m	44	promethazine	—	4.8	—	1.4
			ethanol	0.05	—	—	0.26
8/67	m	47	levomepromazine	traces	4.8	0.3	—
			ethanol	0.21	—	0.27	—
9/67	m	23	levomepromazine	—	1.6	—	0.4
			vinbarbital and aprobarbital	3.6	—	—	—
10/67	m	56	chlorpromazine	1.6	0.7	—	—
			etchlorvynol	0.20	—	—	—
			ethanol	0.31	—	—	—
11/67	m	24	thioridazine	—	0.4	—	—
			phenobarbital	—	4.0	—	—
			meprobamate (free)	—	2.0	—	—
1/68	f	27	levomepromazine	—	2.8	—	—
			amytal	0.7	1.0	—	—
2/68	f	40	chlorpromazine meprobamate	—	3.2	—	—
			(unconjugated)	—	12.0	—	—
3/68	m	25	promethazine	—	3.0	—	0.4
			ethanol	0.16	—	—	0.28
4/68	f	26	perphenazine	—	4.5	—	—
			orphenadrine	—	6.0	—	—
5/68	m	57	levomepromazine	—	6.8	—	—
			ethanol	0.14	—	—	0.26
6/68	m	40	levopromazine	—	1.8	—	—
			vinbarbital and aprobarbital	0.5	—	—	—
			ethanol	—	—	—	0.09
7/68	f	32	thioridazine and levopromazine	—	ca. 5	—	—
			phenobarbital	—	2.0	—	—
8/68	f	49	promethazine	—	3.3	—	—
			unconjugated meprobamate	11.0	9.5	—	—
			(acetyl) salicylic acid	6.5	5.2	—	—
9/68	m	30	levopromazine	—	12.0	—	—
			amytal	—	12.0	—	—
			ethanol	0.06	—	—	—
10/68	f	30	levomepromazine	—	30.0	—	—
			vinbarbital and aprobarbital	—	6.8	5.1	—
11/68	f	30	levopromazine	—	4.3	—	—
			metaqualone	—	2.5	—	—
12/68	f	68	promethazine	—	1.7	—	—
			amytal	—	7.2	—	—

[a] Mainly sulfoxide metabolites.

Table 6. *18 Cases (mainly suicides but also some accidents) where death occurred from physical causes, but where phenothiazines were nonetheless found in the tissues*

Case nr	Sex	Age years	Probable manner of death	Cause of death	Drug (ethanol)	Concentrations found. For drugs (some metabolites included) mg/100 g of sample. For ethanol per cent			
						blood	liver	kidney	urine[a]
1/65	f	53	suicide	scull fracture	chlorpromazine	—	1.7	—	—
					ethanol	0.12	—	—	0.08
1/67	m	25	accident	aspiration	levomepromazine	—	1.8	—	6.6
					meprobamate	0.8	—	—	—
2/67	m	58	natural death	coma diabeticum	thioridazine	—	0.6	—	0.6
3/67	f	26	suicide	drowned in the bathtub	chlorpromazine	—	6.4	—	trace
4/67	m	41	accident	collum fracture	thioridazine	—	0.5	—	—
5/67	f	52	suicide	drowned in the bathtub	promethazine	0.1	1.2	—	—
6/67	m	36	natural death	heart failure	thioridazine	0.2	3.6	1.1	0.2
7/67	m	27	suicide ?	drug abuse 5 days after operation for stomach ulcer	promethazine	0.04	1.3	0.7	stomach cont. 1.0
8/67	m	60	accident	aspiration	chlorpromazine	—	0.7	—	—
					ethanol	0.12	—	—	0.22
9/67	m	68	natural death	heart failure	thioridazine	—	0.3	—	—
10/67	f	44	natural death	heart failure	thioridazine	—	0.5	—	—
11/67	f	68	suicide	drowned in the bathtub	thioridazine	—	0.3	—	—
1/68	f	27	accident	aspiration	trifluoperazine	—	1.7	—	—
					ethanol	0.20	—	—	0.29
2/68	f	30	suicide	strangled herself	promethazine	—	0.9	—	—
3/68	f	30	natural death	epileptic attack	levomepromazine	—	0.4	—	—
4/68	f	30	suicide	drowned in a lake	thioridazine	—	7.0	—	—
5/68	m	60	suicide	aspiration of porridge of tablets	levomepromazine	—	1.0	—	—
					amytal	—	2.1	—	—
					ethanol	0.17	—	—	0.27
6/68	f	45	accident	aspiration	promethazine	—	2.5	—	—
					metaqualone	—	1.1	—	—
					amytal	—	0.4	—	—

[a] Mainly sulfoxide metabolites.

such a case, at least two "levels" of drug concentrations in this tissues could be encountered: a higher one, shortly after the drugs resorption and distribution in the organism, and a lower one in all those cases where metabolism had its course, producing the more toxic compound responsible for the lethal outcome. Attempts to separate individual metabolites and to determine their concentrations in various parts of the organism have been published [7] but to do this routinely would constitute an enormous task.

The distribution of the drugs between blood, liver, kidney and urine varies considerably from case to case. In general, the blood levels observed by us were rather low, less than 2 mg per 100 ml of whole blood. The only data from the literature are two values from autopsy cases: 0.2 and 1.2 mg of chlorpromazine per 100 ml of blood (cf. Table 1). It is quite possible that the drug level in the blood has passed its maximal value when death occurred.

A few data have recently become available on the concentration of phenothiazines in the plasma of patients or volunteers who had taken therapeutic doses of these drugs. Plasma concentrations of chlorpromazine varied widely from individual to individual. Iwasa *et al.* [8] found maximum concentrations of 0.2 mg chlorpromazine (and certain metabolites) per 100 ml after doses of 600—700 mg. Curry and Marshall [7] measured the parent drug and each of three metabolites arriving at a total of 0.015 mg of drugs per 100 ml of plasma (after doses of 200 mg) and up to 0.058 mg after a 500 mg dose.

Mellinger *et al.* [9] have reported steady-state blood levels of thioridazine after 3—4 days medication. After 200 mg of thioridazine per day, about 0.15 mg of the drug was found per 100 ml of plasma, and after 600 mg per day, levels of between 0.2 and 0.5 mg per 100 ml were measured.

It must be kept in mind, when comparing these results with autopsy data, that concentrations in the whole blood are somewhat lower than those in the plasma.

The kidney always contained more phenothiazine derivatives than the blood, and less than the liver. No doubt, in both organs, a number of metabolites are assayed at the same time as the parent drug as long as these are alkaline and have similar spectra (cf. Methods of Analysis).

The highest drug concentration was found in the liver, as expected. The question arises as to how large the phenothiazine depot in the liver can be under conditions of prolonged therapy. Unfortunately, very little is known in this respect, since toxicological liver data on patients with a contolled dosage of phenothiazines are rare — except when the very drug was responsible for death. The majority of the data of Table 6 (persons who died from physical causes) indicate that this type of drugs are not stored to a large extent in the liver during normal therapy (cf. even ref. [6]).

The concentration of the phenothiazine drugs found by us in the liver varies within wide limits. In order to evaluate its significance, a simple statistical reduction of the data is needed. If, for a set of values, the smallest 25% and the largest 25% are eliminated one arrives at a medium range which we have earlier defined as the "Q-value" [10]. If the data of Tables 3—5 are treated in this way one obtains the following drug concentration ranges per 100 g of wet liver:

1) Pure phenothiazine poisoning (Table 4)	range	5 - 211 mg
	Q-value	8.4 — 18 mg
2) Mixed poisoning cases (Table 5)	range	0.05 — 12 mg
	Q-value	1.8 — 5 mg
3) Cases with incidental findings of phenothiazine	range	0.3 — 7 mg
	Q-value	0.5 — 1.8 mg

It seems that the drug concentration in the liver can be of considerable help in evaluating the role of phenothiazine poisoning in autopsy cases. It is imperative, however, in all doubtful cases, to screen the material for ethanol and for other drugs, and — before all — to evaluate the pathological findings and anamnetic data before attempting to pronounce phenothiazine poisoning as the main cause of death.

The drug levels in the urine are subject to great variations and can rarely be of help in judging the severity of phenothiazine intoxications. In cases of clinical poisoning incidents the urine is a useful material for screening tests and for qualitative analyses. Also, in connection with investigating drivers who have taken large doses of phenothiazines, urine assays should only be used for qualitative demonstrations of the presence of a given drug. The effect of the drug on driving ability cannot be measured in this way [11, 12].

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