Z. Rechtsmedizin 74, 293—299 (1974)

Kasuistik · Casuistry

Legal-Medical and Toxicological Evaluation of 18 Lethal Cases of Poisoning by Phenothiazine Derivatives

Władysław Nasiłowski, Halina Sybirska, and Helena Gajdzińska

Institute of Forensic Medicine Silesian Medical Akademy Katowice (Poland)

Received October 1, 1973

Summary. 18 lethal cases caused by phenothiazine drugs were presented on the base of autopsic, histopathological and analytical examinations of autopsy material.

In toxicological-analytical examinations chromatographic and spectrophotometric methods were used. In 6 cases the combined poisoning with several drugs was found. 16 cases of poisoning were of suicidal character.

The concentrations of drugs and doses of the drugs and the found changes in the liver may show the relatively great toxicity of the neuroleptics of this group.

The authors are of the opinion that the phenothiazine drugs should be under strict control and should be examined on toxicity and metabolism. It would be desirable to introduce diagnostic and organizing instructions for the proper life-saving action in cases of intoxication.

Zusammenfassung. Es wurde über die Sektionsbefunde und die Ergebnisse der histopathologischen Untersuchungen berichtet. In allen Fällen wurde auch eine qualitative und quantitative chemische Analyse von Organen und Körperflüssigkeiten mit Anwendung der Ionen-Austauschpapier-Dünnschichtchromatographie und der Spektrophotometrie vorgenommen.

In 2 Fällen handelte es sich um eine unbewußte Überdosierung, in 16 anderen um Suicide. Form der Arzneimittel: Promazin 4 Fälle, Chloropromazin 3 Fälle, Levopromazin 3 Fälle, einzelne Vergiftungsfälle erfolgten mit Promethazin und Pernazin, andere mit gemischten psychotropen Substanzen.

Die ermittelten Konzentrationen der Phenothiazinderivate in Organen wurden in einer Tabelle zusammengestellt.

Die Ergebnisse, insbesondere die histopathologisch festgestellten degenerativen Prozesse in der Leber und Ecchymosen im Zentralnervensystem wie auch die nicht hohen Dosen der Phenothiazine weisen auf Toxicität dieser Arzneimittel hin. Der Einfluß auf den Organismus und die Toxicität dieser Drogen erfordern weitere Forschungsuntersuchungen. Phenothiazinderivate sollten unter genaue ärztliche Kontrolle gestellt werden.

Key word: Phenothiazine drugs poisoning.

Among psychotropic drugs phenothiazine derivatives, as for example, chloropromazine, promazine, promethazine, levopromazine, thioridazine become more and more available not only for special indications. This may be seen in a rapid consumption of these drugs: in Poland, for instance, 1200000 tablets of promethazine have been used 1965 while this were 1970 already 5080000 tablets. Similarly in 1965 2922000 of levopromazine were consumed while in 1970 the consumption reached 15332000 [1] tablets. Besides the positive therapeutic effects, an increase of severe and lethal intoxications by phenothiazine derivatives is noticed. Furthermore, an rapid increase of intoxications due to other psychotropic drugs is also observed [2—4]. In the Institute of Forensic Medicine in Zabrze 252 lethal cases

of intoxication with drugs were investigated in the years 1959—1972. The psychotropic drugs, excepting intoxications with barbiturate derivatives, caused 103 cases.

In the literature, cases of intoxications by chloropromazine were reported by Randonat and Staak [6], Fatteh [7], Kandibur [8] and Grochowska and Jaegerman [5]. Bonnichsen *et al.* [9] reviewed 66 cases of lethal intoxications with phenothiazine derivatives.

According to literature and our own observations there exist doubts on the toxicity of these drugs, various opinions exist regarding the course of intoxications, clinical and autoptical diagnostics and the possibilities of the diagnosis of intoxications by toxicological analysis of biological material. An additional problem is often the association of other drugs with phenothiazines.

In the following lethal intoxications due to phenothiazine drugs examined during the last years in our institute are reported.

Results

In the years 1970—1972 18 lethal cases of poisonings with the drugs of phenothiazine derivatives were registered. Among them 6 cases were caused by phenothiazine combined with other soporific or sedative drugs.

In the above mentioned period 36 cases of intoxications with "TARDYL" (0.125 g glutethimide, 0.125 g amobarbital and 0.0075 g promethazine) were examined. The cited cases, because of their different character, are not included in our paper.

Autoptic examinations were performed and in some of them brain, heart, liver, lungs, and kidneys histologically examined. In all cases a quantitative and

Table 1. Intoxications and kind of drugs

No.	Kind of drugs		Number of cases
1	Promazine (Sparine) 10-(3-Dimethylaminopropyl)-phenothiazin		4
2	Levopromazine (Tisercin) 2-Methoxy-10-(3-dimethylamino-2-methylpropyl)-phenothiazin		3
3	Promethazine (Phenergan) 10-(2-Dimethylaminopropyl)-phenothiazin		1
4	Chlorpromazine (Largactil) 2-Chlor-10-(3-dimethylamino-propyl)-phenothiazin		3
5	Pernazine (Perazine) 10-(3-(4-Methyl-1-piperazinyl)-propyl)-phenothiazin		1
6	Chlorpromazine	Phanodorm	1
7	Levopromazine	Meprobamat	1
8	Promethazine	Bromural	1
9	Levopromazine	Tardyl	1
10	Promazine	Tardyl	1
11	Thioridazine (Melleril) 3-Methylthio-10-(2-(1-methyl-2-piperydyl)-äthyl)-phenothiazin	Tardyl	1
Total			18

qualitative toxicological analysis of autopsy material was carried out. The kind of the drug, the circumstances of the poisoning, suicide or accident, the life-saving actions and clinical treatment, was mostly obtained from the police report.

Table 1 shows the data dealing with the poisonings by phenothiazine drugs.

Autopsy findings did not give usually characteristic results. Mostly hyperaemia and oedema of brain and lungs, dilatation of the heart and the haemostasis in the internal organs were noted. In some cases we observed fatty infiltration of the liver, mucous-suppurative inflammation of the respiratory tracts (bronchi and bronchioli) and focal pneumonia.

In some cases we found pulmonary emphysema, general atherosclerosis, meningeal fibrosis, postinfarctional cicatrices in myocardium, internal hydrocephalus and other atrophic changes. Moreover we observed pleural adhesions and in one case infiltrative-fibrous tuberculosis.

Histopathological investigations were carried out in 9 cases with eosine and hematoxyline staining. Various damages of liver cells in the form of diffuse fatty and vacuolar degenerations were observed, similar lesions were found in the kidneys. In other organs mainly in the brain and in the heart oedema, hyperaemia, and petechial haemorrhages were noted.

Chemical-toxicological investigations were performed with material taken during autopsy: the stomach with its content, the small intestines with its contents, the liver and the kidney and sporadically blood. The material after homogenization was hot deproteinized and extracted according to the method of Borkowski [10]. During the extraction of phenothiazine compounds a pH more than 11 was used. For identification the chromatographic method, both the thin-layer technique on silica gel G and the paper technique was used according to Cochin *et al.* [11], Forrest *et al.* [12], Stolman [13] and Stahl [14]. In the identification procedure, spectrophotometric evaluation in the ultraviolet-light region of eluates from chromatograms was also used. In quantitative determinations besides spectrophotometric and photocolorimetric methods, a ion exchange-paper chromatography on papers obtained from Institute of Chemistry of the University in Poznań, was used [15, 16]. Compact zones of the separated phenothiazine compounds were cut out from the paper-chromatogram and, after clipping with a strip of cation exchange paper, eluated with an appropriate solvent. In this conditions a ion exchange sorption of the phenothiazine compounds occurs on the cation exchange paper, and the area of the visualized zones was found to be proportional to the concentration of the compounds. The applied method made it possible to estimate not only the unchanged drugs, but also their metabolites [17—19]. In cases where two substances of the same group (levopromazine and promethazine in small amounts from Tardyl) were found, they were determined together. The results of quantitative determinations are shown in Table 2.

The evaluation of the circumstances and course of intoxication revealed that among 18 persons who died due to intoxication by phenothiazine drugs 11 were women and 7 men. The mean age was 32, in the range from 22—55.

Excepting 2 persons, all of them had already been treated in psychiatric and neurologic clinics with the following diagnosis: psychoneurosis, depression syndroms, alcoholism and schizophrenia. The majority of them had already tried to commit suicide. In these 16 cases the motive of suicide was rather obvious. One

Table 2. Results of quantitative examinations

No. case	Kind of drugs	The total concentration (mg/100 g) parent drugs and its metabolites			
		stomach with contents	small intestine with contents	liver	kidney
1.	Chloropromazine	—	—	3.00	5.44
2.		16.00	0.81	0.45	1.50
3.		14.00	6.70	2.30	1.00
4.[a]		trace	trace	trace	trace
5.	Promazine	113.50	210.00	23.00	6.98
6.		163.20	13.50	5.00	2.30
7.		285.00	—	4.80	5.30
8.[b]	Promazine and Promethazine	18.80	4.70	0.80	0.60
9.	Levopromazine	190.00	114.00	3.10	3.60
10.		35.00	18.20	3.00	1.40
11.		3.00	—	—	—
12.[c]		22.40	4.10	1.10	0.80
13.[d]	Levopromazine and Promethazine	79.80	—	12.00	—
14.	Promethazine	—	21.30	26.70	—
15.[e]		2.10	—	0.60	—
16.	Pernazine	64.70	100.50	6.65	4.53
17.[f]	Thioridazine and Promethazine	0.60	3.70	1.70	—

[a] Intake in combination with Phanodorm.
[b] Intake in combination with Tardyl.
[c] Intake in combination with Meprobamate.
[d] Intake in combination with Tardyl.
[e] Intake in combination with Bromural.
[f] Intake in combination with Tardyl.

case might be caused by an overdose of promazine and the other one was unexplained. The obtained information concerning the doses used and the course of intoxication were not precise in the majority of the cases. In 1 case 30 tablets of promazine (3 g) were thought to be the cause of death after 3—4 hrs. The death followed vomiting and coma. An other case was caused by 100 promazine tablets (5 g) and the death occurred during symptoms of deep coma during 10 hrs. In the last case the patient had taken 100 ml of chloropromazine drops (4 g). In 9 cases the period of time between the ingestion of the drugs and death was known: 4—11 hrs in 5 cases, in 1 case 20 hrs, 2 days in 2 cases, 5 days in 1 case. In cases of early death first symptom was vomiting gradually increasing followed by coma, first slight, then turning to deep, unconsciousness and decortification syndrom. In the other cases the symptoms developed more slowly. There was jaundice observed, the lungs were swollen, inflamation of the respiratory tract and lungs occurred. In 8 cases blood alcohol was determined. In 2 cases blood alcohol was present concentration (1.78 and 1.08‰). The first case was an intoxication with chloropromazine, the second with thioridazine. The concentration of the drugs in both cases was low: 14.1 mg% in the stomach and 2.3 mg% of chloropromazine in the

liver. Thioridazine was found only in very small amounts in the stomach, liver and blood. Low concentrations of the drugs with a rapid course of intoxication may suggest a synergism of alcohol and of a small dose of the drug.

Discussion

In the influence exerted of phenothiazine drugs on CNS, the increase of excitability threshold of brain stem cells upon nervous and neurohormonal impulses — giving effects of emotional composure and decrease of anziety tension — are emphasized. This can be compared to cortical — subcortical pharmacological lobotomy. It is accompanied by general activity of more toxic character in the form of inhibition of some conditional reflexes, and by analgesic, anti-shock, adrenolytic, hypothermic and hypotensive activities.

Large doses of phenothiazine may cause Parkinson's syndrom [13, 20]. It has been found that phenothiazines produce a decrease of cellular exidation in neurones, it can be linked with an inhibition of ATP transformation and flawoprotein oxidation on mitochondrial level. It can be presumed that phenothiazine drugs showing multidirectional inhibiting effects upon nervous system can be toxic when overdosed. General complications such as damages of liver parenchyma (jaundice) and marrow function (agranulocytosis), allergy, parkinsonism and depressive — impregnatory syndrom are noted. In longlasting treatment a broad range of toxicity and some cumulation effects can be demonstrated. In the presented quantitative determinations we observed in the initial part of the digestive tract (small intestines and stomach), relatively high concentrations of unabsorbed drugs, also in cases with longer surviving time. The data may suggest that the doses exceeded the therapeutic levels and that the process of absorption was slow. But the drug levels in parenchymatous organs do not allow such interpretation. The values may be an effect not only of a single overdose but also of the mentioned phenomenon of cumulation of the drugs used during the previous psychiatric treatment. Slow phenothiazine elimination (10—14 days with a dose of 50 mg) promotes increasing of their level in parenchymatous organs [11]. This is confirmed by investigations of Forrest *et al.* [12] on the phenothiazine drugs level in parenchymatous organs of autopsy material of psychiatric clinic patients. These patients had been treated with high doses of the drugs for some months before death.

The concentrations of phenothiazine compounds shown by Forrest *et al.* are similar to the majority of our cases.

The presented material in confrontation with the hitherto existing points of view allows to draw some conclusions. First of all intoxication as the only cause of

Table 3. Forrest *et al.* investigations

Organ	Abundance of chloropromazine and metabolites (mg%)				
	case I	case II	case III	case IV	case V
Liver	55.0	44.2	14.0	3.8	13.0
Kidney	12.6	4.6	17.3	16.2	13.1
Lungs	43.0	138.0	52.0	0.13	1.1

death was doubtful in our cases. Complications such as respiratory — vascular insufficiency, damage of the liver, pneumonia can also be considered as cause of death. The more so, because the concentrations of drugs detected in the organs were sometimes low. This may be an evidence for a more complex course of poisoning, i.e. lowering of toxicity threshold on phenothiazine with simultaneous changes in organs. Perhaps the changes may be related to a prolonged treatment with phenothiazine and a cumulation of these drugs. Also the histopathological examinations carried out for the cases with long surviving time confirmed the relatively high toxicity of the drugs of this group (fatty and parenchymatous degenerations of the liver and kidneys).

In 2 cases low doses of drugs (2—4 g) were found. This fact should be a warning when phenothiazines are administered and it raises doubts if the drugs can be held as fully safe. The clinical course of intoxication was mostly gradually preceeded by vomiting and increasing drowsiness until the loss of consciousness. If the patient died suddenly the concentrations of nonresorbed drugs in the stomach and intestines were very high (in 2 cases some residue of tablets were found in the stomach). This confirms the well known treatment of rapid gastric lavage in cases of intoxications with drugs [21]. The clinical observations proved to be insufficient. As a rule we observed diagnostic errors especially in the first phase of intoxication, which is the most important period for treatment and therefore it was already too late for help and gastric lavage. Our material is too small to discuss the problem of alcohol and phenothiazine synergism, 1 case only seem to support the idea of an obvious synergism.

The cases of combined poisoning with some drugs (6 cases in our material) caused clinical and toxicological difficulties in diagnosis.

In the toxicological analysis of the biological material the application of ion-exchange paper for drugs determination was of great value. It has been stated, that phenothiazines show a high affinity to phenol-sulphonic cation exchanger, mechanically attached to cellulose fibres of the paper. Under special conditions ion-exchange sorption of phenothiazine compounds occurs on the cationic paper.

References

1. Nasiłowski, W.: Psychophysical condition of people involved in read traffic accidents and accident rate. Probl. Kryminal. **89**, 94 (1971)
2. Jakliński, A.: Significance of psychotropic drugs in toxicology. Probl. Kryminal. 88, 711 (1970)
3. Markiewicz, J.: Drugs as poisons. Probl. Kryminal. 88, 703 (1970)
4. Szuchovszky, G., Kenyeres, I., Harsanyi, L.: Analyse von 2956 Vergiftungs-Selbstmordfällen. Dtsch. Z. ges. gerichtl. Med. **66**, 19 (1969)
5. Grochowska, Z., Jaegermann, K.: Fatal poisoning with chlorpromazine. Arch. Med. Sąd. Psych. Sąd. Krym. **16**, 53 (1964)
6. Randonat, H. W., Staak, M.: Zur biochemischen und forensisch-medizinischen Problematik einer tödlichen Megaphenvergiftung beim Kleinkind. Z. Rechtsmedizin **67**, 125 (1970)
7. Fatteh, A.: Death from chlorpromazine poisoning. J. forens. Med. **11**, 120 (1964)
8. Kandibur, R. J.: Aminazine poisoning. Soudeb. med. eksp. (Mosk.) **9**, 47 (1966)
9. Bonnichsen, R., Geertinger, P., Maehly, A. C.: Toxicological data on phenothiazine drugs in autopsy cases. Z. Rechtsmedizin **67**, 158 (1970)

10. Borkowski, T.: The method of isolating organic poisons from biological material. Arch. Med. Sąd. i Krymin. **18**, 95 (1968)
11. Cochin, J., Daly, J. W.: The use of thin-layer chromatography for the analysis of drugs. Identification and isolation of phenothiazine, tranquilizers and of antihistaminics in body fluids and tissues. J. Pharmacol. exp. Ther. **139**, 160 (1963)
12. Forrest, I. S., Bolt, A. G., Serra, M. T.: Distribution of chlorpromazine metabolites in selected organs of psychiatric patients chronically dosed to the death. Biochem. Pharm. **17**, 2061 (1968)
13. Stolman, A.: Progress in chemical toxicology. New York-London: Academic Press 1965
14. Stahl, E.: Dünnschichtchromatographie. Berlin-Heidelberg-New York: Springer 1967
15. Lewandowski, A., Witkowski, H.: Polski Patent No. 38801 — 1955
16. Lewandowski, A.: Ionenaustauscherpapier als einfaches Mittel zur quantitativen Bestimmung von Alkaloiden. Acta Med. leg. soc. (Liège) **16**, 117 (1963)
17. Lewandowski, A., Sybirska, H.: Determination of mickrogram amounts of izonicotinic acid and its hydrazide by means of ion-exchange paper. Chem. Anal. **13**, 319 (1968)
18. Sybirska, H., Gajdzińska, H.: Bestimmung der Bestandteile eines Kombinationspräparates aus Glutethimid, Amobarbital und Promethazin im Sektionsmaterial einiger Selbstmordfälle. Arch. Toxicol. **27**, 226 (1971)
19. Sybirska, H., Gajdzińska, H.: Application of action exchange paper in chemical toxicology. Arch. Med. Sąd. i Krymin. XXI, Suppl. **1**, 183 (1971)
20. Danysz, A.: Farmakologia. PZWL 1968
21. Szajewski, J. M.: Zasady leczenia ostrych zatruć. Biuletyn Informacyjny "Cefarm", Polfa **9—10**, 321 (1972)

Dr. Wł. Nasiłowski
Institute of Forensic Medicine
PL-41-800 Zabrze
3-go Maja 13, Poland