

Kasuistiken / Casuistics

Death Caused by Orphenadine Poisoning

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Summary. The number of deaths as a consequence of orphenadine poisoning seems to increase, mostly among severely psychotic males. The lethal dose corresponds to the weekly average dose used in the treatment of neuroleptic extrapyramidal side effects. Based on the literature, the serious, rapidly incipient, cardiac, and neurologic symptoms of poisoning are emphasized. The handing out of orphenadine to suicidal persons must be restricted, and even small overdoses (1–2 g) ought to result in the immediate initiation of observation at an intensive care unit.

Key words: Orphenadine poisoning– Poisoning, Orphenadine

Zusammenfassung. Die Zahl der Todesfälle infolge einer Orphenadin-Vergiftung scheint vor allem unter Männern mit schwerem psychotischen Krankheitsbild anzusteigen. Die letale Dosis entspricht der mittleren wöchentlichen Dosis bei der Behandlung neuroleptischer, extrapyramidaler Nebeneffekte. In der Literatur wird besonders auf ernste, sich rasch etablierende cardiale und neurologische Symptome bei einer Vergiftung hingewiesen. Vor der Verordnung von Orphenadin-Präparaten an Suicid-gefährdete Patienten muß eindringlich gewarnt werden. Selbst bei geringer Überdosierung (1–2 g) ist eine kontinuierliche Beobachtung des Patienten auf einer Intensiv-Station angezeigt.

Schlüsselwörter: Orphenadin-Vergiftung – Vergiftung, Orphenadin

Introduction

Orphenadine (Disipal, Lysantin, Norflex) is used predominantly for treatment of extrapyramidal side effects provoked by medication with neuroleptics. Thus, predominantly psychiatric patients are treated with these drugs. Casuistic litera-

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ture, describing several cases of orphenadine intoxication, and death in connection with this, is available [1–7], but only one publication deals systematically with a larger material [8]. In this paper the lethal dose is indicated to be between 2 and 3 g for adults. In the light of the vulnerable character of the patient group the purpose of the present work has been to:

1. Determine the number of deaths from orphenadine poisoning in a well-defined population, and
2. Study whether there has been any change in the number of these deaths over the period in which orphenadine poisoning has been examined medico-legally.
3. Describe the psychopathologic characteristics of the mental disorders, if any, for which the deceased were being treated.

Materials and Methods

The Institute of Forensic Medicine, University of Aarhus (Denmark) serves a well-defined geographical area inhabited by approximately 40% (about 2,093,380 inhabitants) of the Danish population (i.e., the counties of North Jutland, Viborg, Aarhus, Ringkøbing, Vejle, and Ribe). Since December 1, 1968, examination for, among other things, orphenadine has been performed on suspicion at medico-legal autopsies. On going through the medico-legal archives of the period 1.12.1968–31.12.1984 all cases have been selected which meet the following criteria:

1. Detection of the presence of orphenadine at medico-legal autopsies with a medico-chemical examination.
2. orphenadine is the only, or contributory, cause of death.

Hereafter, hospital records have been collected from the local and/or regional psychiatric hospitals. These have been studied with special regard to an overall diagnostic evaluation and determination of a syndrome profile using the "syndrome check list". This has been developed on the basis of The Present State Examination, which is an examination form with a "rating scale" for the examination and assessment of psychopathology [9]. On the basis of the syndrome check list a grouping of described signs and symptoms has been worked out. The co-author of this article has been trained in the use of The Present State Examination at the Medical Research Council, Institute of Psychiatry, London (England).

Results

Orphenadine was demonstrated to be present in the medico-chemical analyses at a total of 22 medico-legal autopsies. Orphenadine was the only (13 cases) or contributory (four cases) cause of death in 17 cases, 12 males with an average age of 27.6 years (16–40) at the time of death and five females with an average age of 36.0 years (17–63). The manner of death was in 13 cases suicide, in four cases suicide?/accident?

Figure 1 shows the material distributed on the year of death. In the first 8-year period, from 1968 to 1976, six deaths were registered, and in the last 8-year period, from 1977 to 1984, 11 deaths have been registered.

Eleven males and four females were known in the psychiatric hospital system. Table 1 shows that between 12 and 168 months (average = 73) passed for

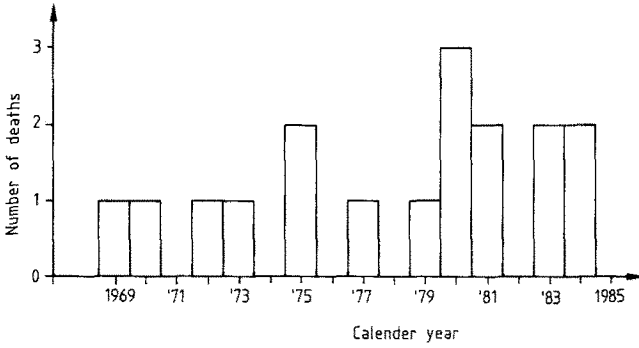


Fig. 1. Number of registered death from orphenadine poisoning examined medico-legally, distributed over the calendar years

Table 1. Time passed from day 1 of hospitalization in psychiatric hospital/ward till death, and time spent in psychiatric hospital/ward

	Males (<i>n</i> = 11)		Females (<i>n</i> = 4)		M + F (<i>n</i> = 15)	
	Average	Min/max	Average	Min/max	Average	Min/max
Number of months passed from day 1 of hospitalization in psychiatric hospital/ward, till death	73	(24/144)	73	(12-168)	73	(12-168)
Number of months spent in psychiatric hospital/ward	24.1	(6-78)	8.4	(1-18)	19.9	(1-78)

these patients from day 1 of hospitalization in psychiatric institutions till the time of death. The total amount of time of hospitalization in a psychiatric institution was 20 months on average which corresponds to 27.1% of the above mentioned interval from day 1 of hospitalization till death.

Ten of 17 had previously expressed suicidal wishes, but only four had expressed thoughts of suicide immediately before the suicide. Six had attempted suicide earlier.

Figure 2 illustrates the per cent frequency of psychiatric syndromes in the 15 persons for whom record material was available from psychiatric ward or hospital. The Arabian numerals on the X-axis refer to the number of the syndrome in the original work by Wing et al. [9]. The Roman numerals refer to a grouping of syndromes previously described by Munk-Jørgensen [10]. Syndromes as well as grouping of syndromes are shown in Appendices A and B. As an example from the Fig. 2 it appears that syndrome no. 1, "Nuclear syndrome", had been present in 60% of the 15 persons in one or more periods of the disease. This syndrome comprises the most severe schizophrenic symptoms: Thought disorders, experience of influence and control, and certain auditory hallucinations. In contrast to this, no specific neurotic syndromes (group V) are seen, whereas non-

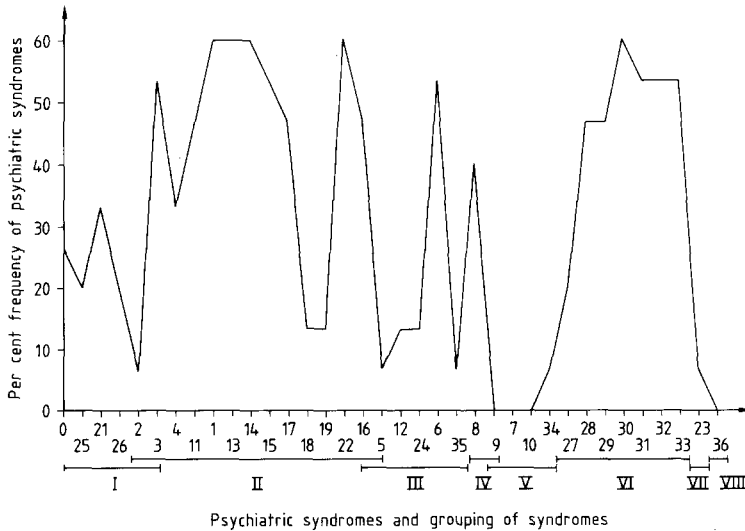


Fig. 2. The per cent frequency of psychiatric syndromes [9] in the patients dead from orphenadine poisoning (syndromes and grouping, see Appendices A and B)

specific syndromes, such as irritability (syndrome no. 31) and tension (syndrome no. 28), which together with several other syndromes are gathered in group VI, have a high per cent frequency in the material.

The psychiatric main diagnosis given last was schizophrenia in ten cases. The remaining five cases had in connection with the last hospital stay been diagnosed as borderline psychotic condition, personality disorder, cannabis psychosis, affective disorder, and reactive paranoid condition. Two men had never been in contact with the psychiatric hospital system, and there was no evidence of any mental disorder in these two. On the basis of all information available, the authors have given the diagnosis schizophrenia in all 15 cases, where psychiatric hospital records were available at all.

Case Reports

Case Report 1

Single man. Since puberty very sensitive with lack of self-confidence. At the age of 19, these character traits were aggravated. Depressive symptoms developed increasingly. Shyness, general anxiety, and ideas of reference after suicide attempt. First admitted to psychiatric hospital at the age of 20. Treated with antidepressants and ECT with doubtful effect. During hospitalization poor contact with other patients, asponaneous, passive, and without initiative. During the following about 10 years he showed progressive signs of thought disorders: Thought block, thought insertion, a feeling of other people being able to read his thoughts. He had experiences of influence and derealization with a feeling of personality dissolution. In addition, productive psychotic symptoms in the form of reproachful auditory hallucinations and experiences of reference. His behavior was characterized by loss of energy, isolation, self-neglect, and poor concentration. During his 12 hospitalization periods he spent a total of 40 months in psychiatric wards which corresponds to 27% of the period from day 1 of admission till his

suicide. This happened after a period of about 4 weeks, during which there had been a relief in the symptomatology. The suicide was unpredictable. Overall diagnosis: Schizophrenia.

Case Report 2

Single woman. First admitted to psychiatric institution at the age of 25. Previous to hospitalization she had isolated herself with her family during about 18 months, without taking any interest in education or work. By the time of admission severe depersonalization and derealization. Auditorily hallucinated and violent behavior in a state of severe regression. The subsequent stages of illness were characterized by poor concentration, social unease. Was, at a later stage of the disease, given alternative, unauthorized treatment. Admitted to psychiatric hospital twice. The time of stay in hospital constituted about 8% of the almost 2 years passing from the first contact to the psychiatric hospital system till the time of suicide. Overall diagnosis: Schizophrenia.

Discussion

The number of deaths from orphenadine poisoning has increased, and suicides are strongly represented. There is reason to believe that the frequency of autopsy is high. There does not seem to be any systematic change in the frequency of autopsies in this field. On April 1, 1977, a new law of medico-legal inquests, Certification of Deaths etc., was introduced, whose most essential amendment, concerning report of a death to the police, is: "... the physician who is called in on the occasion of a death shall report to the police, ... if death may be a result of a mistake, negligence, or an accident in connection with treatment or prevention of disease; ...". This amendment has, in the opinion of the authors of the present work, no influence on the result of this study. We therefore assume that the true incidence of orphenadine deaths is close to the number registered.

The syndrome profile of mental illness shown in Fig. 2 illustrates the heavy and comprehensive psychiatric symptomatology ranging from a massive presence of non-specific symptoms to a marked presence of severe schizophrenic symptoms. Thus, no specific syndromes may be said to characterize this clientele, but the heaviness in symptomatology must be said to be striking.

The overall diagnostic evaluation based on all information available shows that it may be assumed with great certainty that the 15 patients, for whom psychiatric hospital records were available, have suffered from schizophrenia in a moderate to severe degree. This is emphasized by the extensive utilization of psychiatric beds. Twenty-seven per cent of the time from day 1 of admission to psychiatric institution till death was spent in psychiatric hospital or ward. This finding may be compared to the study in which Munk-Jørgensen [11] found that the utilization by schizophrenics of psychiatric beds in the psychiatric hospital system was 20% and 16% of a 10-year period from day 1 of admission for males and females, respectively.

The suicides in the present study are characterized by the same unpredictability which characterizes suicides of schizophrenics in general. They may happen at any stage of the disease and lack any relation at all to events such as admission or discharge [12].

The intoxication symptoms, i.e., cardiac arrhythmia and neurologic symptoms, such as unconsciousness and convulsions [8], can develop rapidly, within about 1 h [5]. Therefore, it is very important that the suspicion of orphenadine poisoning will be followed by immediate admission to an intensive care unit.

It is important to be careful as to how great quantities of orphenadine are handed over to patients in this vulnerable group, especially if there is any suspicion of suicidal impulses. When orphenadine for 1 week – at a dose of 100 mg × 3 per day – is given, the lethal dose has already been exceeded.

Appendix A

Grouping of Syndromes

I – Behavior and speech	V – Neurotic
II – Psychotic	VI – Non-specific neurotic
III – Affective	VII – Derealization
IV – Anxiety	VIII – Organic

Appendix B

The numbers and the Names of the Syndromes [9]

1 Nuclear syndrome	19 Olfactory hallucinations
2 Catatonic syndrome	20 Overactivity
3 Incoherent speech	21 Slowness
4 Residual syndrome	22 Non-specific psychosis
5 Depressive delusions and hallucinations	23 Depersonalization
6 Simple depression	24 Special features of depression
7 Obsessional syndrome	25 Agitation
8 General anxiety	26 Self-neglect
9 Situational anxiety	27 Ideas of reference
10 Hysteria	28 Tension
11 Affective flattening	29 Lack of energy
12 Hypomania	30 Worrying, etc.
13 Auditory hallucinations	31 Irritability
14 Delusions of persecution	32 Social unease
15 Delusions of reference	33 Loss of interest and concentration
16 Grandiose and religious delusions	34 Hypochondriasis
17 Sexual and fantastic delusions	35 Other symptoms of depression
18 Visual hallucinations	36 Organic impairment

References

1. Malizia E, Sarcinelli L, Pascarella M, Ambrosini M, Smeriglio M, Russo A (1980) Cardio-toxicity from orphenadine intoxications in humans. *Arch Toxicol [Suppl]* 4:425–427
2. Bozza-Marrubini M, Frigerio A, Ghezzi R, Parelli L, Restelli L, Selenati A (1977) Two cases of severe orphenadine poisoning with atypical features. *Acta Pharmacol Toxicol (Copenh)* [Suppl 2] 41:137–152
3. Sangster B, van Heijst ANP, Zimmerman ANE (1977) Treatment of orphenadine overdose (cont.). *N Engl J Med* 296:1006–1008

4. De Mercurio D, Chiarotti M, Giusti GV (1979) Lethal orphenadine intoxication: Report of a case. *Z Rechtsmed (Berl)* 82:349-353
5. Munk-Jørgensen P, Kold ÅV (1981) Orphenadine poisoning. *Ugeskr Læger* 143:753
6. Sangster B, Van Heijst AN, Zimmerman AN, De Vries HW (1977) Intoxication by orphenadine HCL: Mechanism and therapy. *Acta Pharmacol Toxicol (Copenh) [Suppl 2]* 41:129-136
7. Robinson AE, Holder AT, McDowall RD, Powell R, Sattar H (1977) Forensic toxicology of some orphenadine-related deaths. *Forensic Sci Int* 9:53-62
8. Sangster B, Van Heijst ANP, Zimmerman ANE (1978) Orphenadine intoxication (Disipal). *Ned T Geneesk* 122:988-991
9. Wing JK, Cooper JE, Sartorius N (1974) Measurement and classification of psychiatric symptoms. An instruction manual for the PSE and catego program. Cambridge University Press, Cambridge London New York, pp 36-58
10. Munk-Jørgensen P (1986) General practitioners selection of patients for treatment in community psychiatric service. *Psychol Med* (in press)
11. Munk-Jørgensen P (1986) Schizophrenia in Denmark. Incidence and utilization of psychiatric institutions. *Acta Psychiatr Scand* (in press)
12. Barner-Rasmussen P (1986) Suicide in psychiatric patients in Denmark, 1971-1981. Hospital utilization and risk groups. *Acta Psychiatr Scand* (in press)

Received April 22, 1986