TOXIC REACTIONS AFTER ADMINISTRATION OF PARALDEHYDE

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The sedative drug most widely used in mental hospitals is paraldehyde. Scanty references in the literature to ill effects attest to its high safety margin and its wide range of permissible dosage. However, the danger of decomposition on storage of *B.P.* paraldehyde has been emphasized by pharmacists (Toal, 1937). The present report furnishes clinical evidence of such an occurrence.

Clinical Observations

Six out of nine patients were concerned. To each of them 120 min. of *B.P.* paraldehyde was given during the night as a hypnotic draught. These patients later showed a variety of symptoms, ranging from drowsiness and headache to a comatose condition, which persisted for more than 24 hours. All were chronic mental patients, well accustomed to the drug; neither before this nor since has any one of them shown a similar reaction. Dispensing on this occasion was according to the normal practice at the Bristol Mental Hospital. This is as follows. Paraldehyde, for night use, is dispensed each day in separate bottles containing 120 min. of the drug with mucilage and water to 1 fl. oz. A supply of these draughts is given to the night sister, to be administered according to indications. There are usually a number of spares in excess of estimated requirements. These draughts supplement diurnal sedatives, which may or may not contain paraldehyde. On Saturday a double supply of night draughts is issued for the week-end.

All the toxic reactions were reported on Monday morning and were confined to a group of female patients, every one of whom had received paraldehyde on the previous night. The week-end draughts were therefore suspect. The issue of paraldehyde was stopped pending investigation, but this step was taken too late to allow examination of the draughts as issued on Saturday. Arriving on duty on Monday morning, the dispenser drew the residue of one carboy, about 6 fl. oz., into a glass measure and filled up to 20 oz. from one newly opened; hence the dilution of the residue was 1 part in 3 or 4. (Paraldehyde is supplied in 40-lb. carboys, which cover the requirements of the hospital for about 7 days.) From this new mixture he prepared draughts for use that night. These freshly prepared draughts he packed, as was customary, in dispensing boxes for male and female wards. Together with these latter draughts he included those that were unused from Saturday. It was impossible, thereafter, to separate suspect (Saturday's) from non-suspect (Monday's) draughts. The remainder of the mixture of old stock and fresh paraldehyde, in the 20-oz. measure, was reserved for subsequent analysis.

The following combination of circumstances explains why all the toxic effects occurred only in a small group of female patients and on one night. The week-end draughts were dispensed late on Saturday afternoon, when the carboy of stock paraldehyde was nearly empty. Paraldehyde, believed to be pure, was drawn from the bottom of the container on this, as on previous occasions. The draughts for the male wards were dispensed first. Subsequently the double supply for the female side was made up from the last paraldehyde used that week, drawn from the almost empty carboy; about 6 oz. remained. Paraldehyde is widely employed as a sedative at this hospital, either alone or combined with other drugs. For use during the day it is dispensed in bottles containing 1½ to 3 fl. oz., which, according to indications, will last each patient 3 to 6 days. In the dispensing of these mixtures a large quantity of paraldehyde is used. If these mixtures had not all been dispensed before the carboy was nearly or entirely empty a new

carboy would have been tapped and there would have been no residue to be dispensed in single-dose (night) draughts. It was therefore a rare coincidence that the suspect toxic residue was administered to so many different individuals. That all the reactions occurred after Sunday may be explained by the manner of packing the bottles in the night sister's box. It is reasonable to suppose that bottles made up first from higher levels of paraldehyde, above the "concentrated residue," were placed in one end of the box in rotation and were administered on Saturday and Sunday night in the same order. There is therefore sufficient evidence to attribute all the toxic reactions to administration of paraldehyde from the residue of the carboy.

Emergency draughts on Sunday night were administered to 9 female patients. Seven showed toxic reactions; two senile patients were unaffected. These patients belong to five different wards and, although some had received sedative medicine during the day, the only source of supply common to all was the stock of night draughts. Factors such as diet can be excluded. All patients were in reasonably good health. The symptoms may be briefly summarized as follows:

Case 1.—Aged 52, chronic schizophrenia. Slept after paraldehyde at about 10 p.m. Could not be roused next morning, but about 10 a.m. was drowsy, ataxic, with drunken speech; looked ill and was unable to stand; tendon reflexes almost absent; pupils small, practically inactive; cloud of albumin in urine; pulse weak and thin; blood pressure 100/80 mm. Hg. Remained drowsy all day; could stand next day but did not recover for another 24 hours.

Case 2, aged 57, chronic schizophrenia, and *Case 3*, aged 39, also chronic schizophrenia. Almost identical to Case 1, but no albuminuria. Normal in 48 hours.

Case 4.—Aged 53, chronic mania. Awakened, got up, collapsed before breakfast; returned to bed and was drowsy for about 10 hours; normal thereafter.

Case 5.—Aged 75, senile dementia. Draught at about 1 a.m.: very confused, drowsy, looked ill; coated tongue, tendon reflexes almost absent, pupils fixed, no reaction to light; could scarcely be roused all day; mumbled in incoherent fashion; slept off and on for the next 24 hours. Recovered slowly in the course of the next 48 hours.

Case 6.—Aged 55, mild depression. Draught at midnight; at 10 a.m. still asleep; roused an hour later; conversed with difficulty in a drunken voice; complained of severe headache and nausea. She slept most of the time for the next 24 hours, and was not free from subjective symptoms for a further 24 hours.

Case 7.—Aged 54, chronic neurosis. Had been in the habit of demanding and receiving two draughts each night almost continuously for years, in addition to any sedative medicine prescribed by day. Her regular nightly requirements were therefore not less than 240 min. of paraldehyde. She was an exceptionally well built woman, with a highly developed tolerance for sedatives of all sorts. She received one draught at 10 p.m., woke up at midnight, was restless, and asked for another. It was administered at 1 a.m. She slept and could not be roused for about 10 hours. She then spoke in a slurred, drunken voice, and complained of violent headache, giddiness, and nausea. For the next 24 hours she remained very much the same, and was not free from symptoms for a further 24 hours.

All these patients were treated similarly with copious fluids, glucose, vitamin B complex, strong coffee, and nikethamide (coramine) 4-hourly for the first 24 hours. Although there was no fatality, great anxiety was felt about Case 1 and to a less extent Cases 2, 3, and 5. The clinical picture was that of intoxication with a drug which exercised a severe depressant effect on higher cortical function and which evidently was slowly eliminated from the body. Patient No. 7, who was well acquainted with the effects of alcohol, described the after-effects as resembling an extreme "hangover," but more prolonged and much worse than anything she had ever experienced. There were no residual mental reactions and no signs of permanent damage to any part of the central nervous system.

Toxicity Tests

These were conducted as follows: The minimal lethal doses of (a) the suspect paraldehyde and (b) a fresh sample of paraldehyde, which complied with the requirements of the *British Pharmacopoeia*, were determined. Suitable doses of 5% solutions (in physiological saline) of the two preparations were injected subcutaneously into mice. The results are recorded in the accompanying Table.

Table showing Results of Toxicity Tests

Dose in ml. of a 5% Solution per 100 g. Mouse (Subcutaneous Injections)	Proportion of Mice Killed	
	Suspect Paraldehyde	Control Paraldehyde
3.00	3 out of 5	0 out of 5
3.15	2 " " 5	0 " " 5
3.30	4 " " 5	1 " " 5
3.45	2 " " 5	0 " " 5
3.60	4 " " 5	4 " " 5
3.75	4 " " 5	1 " " 5
3.90	3 " " 5	3 " " 5
4.05	3 " " 5	4 " " 5
4.35	5 " " 5	5 " " 5

Mice injected with equal amounts of the suspect and of the control solution were tested on the same day. The test animals were all of the same batch of mice, and had been fed on a standard diet for several weeks before use. LD50 was determined by Kärber's method (Burn, 1937). The following figures were obtained: LD50 for the suspect material = 3.69 ml./100 g. mouse; LD50 for the control paraldehyde = 3.99 ml./100 g. mouse (both figures in terms of a 5% solution). In other words, a somewhat smaller average dose of the suspect material was needed to kill 50% of the mice tested. It will be remembered that the suspect sample was a 1 to 3 or perhaps 1 to 4 dilution of the clinically toxic material with fresh innocuous paraldehyde. Therefore only a small difference between the LD50 of the suspect and the control was to be expected. It would be reasonable to assume that had the suspect material not been diluted the difference would have been more pronounced; the abnormal clinical symptoms and signs can therefore be fairly attributed to a contaminating toxic substance in the suspect paraldehyde and not, for example, to errors of dispensing. This conclusion was supported by the results of tests for chemical purity prescribed by the B.P. 1932. These tests, which Mr. E. Lloyd, of the Bristol Royal Infirmary, was kind enough to perform, gave the following results:

Boiling-point, acetaldehyde, peroxidized compounds, acidity were all within limits. Melting-point, 10.5° C. (B.P. melting-point is not less than 11° C.). Distillate from boiling-point determination discoloured.

Mr. Lloyd added the following remarks:

"Impurities which may be removed by washing are within limits. The slightly low melting-point indicates the presence of some other impurity."

Discussion

It is clear from the circumstances under which the present cases of "paraldehyde poisoning" occurred that the toxic effects were due to decomposition products (or contaminating constituents) of the paraldehyde preparation. In a series of 7 hospitalized patients no physical disability obscured the clinical picture. The multiplicity of cases and the system of dispensing rendered a dispensing error unlikely. The same dose of paraldehyde drawn from less- or non-deteriorated samples had previously been administered to these patients on many occasions. The response to the standard dose of paraldehyde was therefore known, and the abnormal symptoms described cannot be attributed to idiosyncrasy. The patients have since received the same dose of a paraldehyde preparation which complied with pharmacopoeial requirements without exhibiting any abnormal reaction. Toxicity tests on mice, when compared with the effect of a "normal" preparation of paraldehyde, showed a smaller mean lethal dose (LD50) of the suspect sample.

Toal, who investigated 7 commercial samples of paraldehyde in 1937, found that only one satisfied pharmacopoeial requirements. Formation of peroxidized compounds and an increase of acidity were the main changes which had taken place. One case of "paraldehyde poisoning" traced to excessive formation of acid compounds in the deteriorated sample has been recorded (Hutchison, 1930). An additional change noted by Toal was the increase in the specific gravity of the deteriorated samples. This was not associated with the development of acid or peroxidized compounds, but, in his opinion, was due to decomposition and polymerization combined. Our sample did not contain excessive amounts of acid or peroxidized compounds. Its toxicity, as manifested clinically and in a toxicity test on

mice, will therefore have to be ascribed to chemically undefined products of deterioration, possibly to polymerization products of acetaldehyde other than paraldehyde. It is remarkable that toxic effects of paraldehyde in therapeutic doses have not been noted more often, if decomposition of paraldehyde occurs as frequently as Toal's findings suggest; and, to our knowledge, no series comparable to ours appears in the literature. However, several reasons for this may be advanced: (1) in isolated cases it may have been difficult to exclude the possibility that an overdose had been administered by accident; (2) when used as a basal anaesthetic a toxic effect of paraldehyde may have been masked by the subsequent use of a volatile anaesthetic or may have been attributed to the latter; (3) if the deteriorated sample appeared to furnish the pharmacological picture of an enhanced action of pure paraldehyde the toxic effect may have passed unnoticed, especially if the drug had been given to a single case for the first time. A more intense and prolonged effect of paraldehyde may have been attributed to idiosyncrasy (Brown, 1935; Kotz, Roth, and Ryon, 1938).

The clinical picture presented no specific features. Severe cases showed ataxic drunken speech and corresponding gait. There were no significant reflex or ocular abnormalities, but all patients complained of intense headache, a feeling of nausea, and prolonged drowsiness. They compared the subjective symptoms to those of the after-effects of a severe intoxication with alcohol. (It is of interest that the U.S.P. XI requires that paraldehyde should comply with purity tests for impurities derived from fusel oil and amyl alcohol.) The effect, though largely due to a cortical disturbance, was evidently unlike the response to overdosage of pure paraldehyde. The long duration of the "hangover" and the slow recovery were remarkable, especially in one of the patients (No. 7), who, as a drug addict, showed herself, both before and since the event, to be highly resistant to hypnotic drugs.

The present report cannot detract from the value of paraldehyde as a clinically satisfactory and, normally, very safe hypnotic. It may, however, be regarded as a toxicological supplement to the observation (Toal, 1937, and others) that the drug, though stable when stored according to the prescriptions of the B.P. 1932, will deteriorate "under the practical conditions of everyday use." It reinforces the plea for an official sanction for the addition of a suitable preservative to the pharmacopoeial preparation of paraldehyde. Its storage in use should be carefully supervised and the residue of any that has been in hand some time should be regarded with suspicion. In mental hospitals only enough emergency draughts for one session should be kept and, for purposes of check-up, the date of issue should be stamped on the label. In general hospitals, where paraldehyde is used as a basal anaesthetic, a large quantity should not be stored, and only fresh supplies should be administered.

Summary

Severe and alarming toxic reactions after the administration by mouth of 120-min. doses of paraldehyde were observed in a series of 7 out of 9 mental patients.

A toxicity test on mice showed that the suspect sample had a higher toxicity than that of a standard preparation.

The suspect sample did not conform entirely to B.P. requirements.

The toxic reaction was due not to acid or peroxidized substances but to some unknown product(s) of decomposition.

The clinical picture was similar to a severe intoxication with ethyl alcohol, but the "hangover" was more prolonged.

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S. Zelman (*Amer. J. med. Sci.*, 1944, **207**, 461) determined the blood diastase in a series of 89 cases of mumps on admission to hospital and on discharge: 73% were above normal on admission and 9% on discharge; 3% were subnormal on admission and 20% on discharge. Of this series 15% showed evidence of pancreatitis some time during the course of the illness. In the pancreatitis cases there was an especially high percentage of increased diastase values on admission.