A review of two safety factors in the use of paraldehyde

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SUMMARY. Clinical observations and laboratory tests suggest that, contrary to normal practice, paraldehyde can be used with certain plastic syringes and has been safely used when well over six months old. This may make its use as an anticonvulsant in primary care more widely acceptable.

Introduction

PARALDEHYDE is a drug which, while currently unfashionable as a sedative and anticonvulsant, has recently attracted some discussion in this *Journal* (Juel-Jensen, 1977; Maycock, 1977). It is here considered as an anticonvulsant, chiefly in children.

Advantages

The advantages of paraldehyde in general practice (and in any setting where sophisticated help may not be immediately available) are:

1. It is quickly effective intramuscularly. This contrasts with diazepam, which is often regarded as the drug of choice but is given intravenously. As Maycock (1977) observed, in an obese, very young, or convulsing patient, with a poor light and only panic-stricken relatives to help, intramuscular injections are a big advantage.

The use of rectal diazepam has been advocated (*Drug and Therapeutics Bulletin,* 1978) although full trials of the method are awaited. This may well prove useful for parents, provided that they can be made to understand that in the case of a febrile fit diazepam does nothing to remove the cause of the fever, and a medical opinion is still necessary. When medical help is available rectal administration is no easier than intramuscular (as opposed to intravenous) injection.

2. It has wide safety limits; respiratory depression is unlikely to be caused as suddenly as with diazepam or phenobarbitone.

3. It is relatively long acting.

4. It is cheap. Prices vary, but in 1978 in the United Kingdom the cost of a 10 mg injection of diazepam was about one and a half times that of 5 ml of paraldehyde. In Ghana the difference was more marked, a 10 mg injection of diazepam costing four times as much as 10 ml of paraldehyde (5 ml injections being unavailable).

Disadvantages

The disadvantages commonly quoted are:

1. It is painful. This can be ignored in the unconscious patient.

2. It is strong smelling. This is trivial (or even an advantage to hospital staff if in the heat of the moment the general practitioner's letter is lost).

3. It has to be given in glass syringes, as it dissolves plastic.

4. It decomposes after six months to acetic acid and becomes dangerous.

Clinical background

Legon Hospital is a 64-bed general hospital established to cater for the primary health care of the students, staff and staff dependants of the University of Ghana, 15 km from Accra, the capital of Ghana. Other patients are also seen from the nearby villages and towns. Convulsions are common in children, chiefly due to malaria (this is a holoendemic area) as are 'febrile fits', which are frequent in malnourished children, who are liable to get suddenly and seriously ill from any infection. If the patient is brought outside clinic hours the initial treatment is given by nurses, since summoning a doctor takes at least 20 minutes (there are no working telephones). The dose for children often has to be a 'guesstimate' rather than a dose-for-age or dose-for-weight calculation, as the hospital has no scales suitable for toddlers, and village mothers often have no idea of a child's age once he is more than a few months old.

In these circumstances paraldehyde has been found to be safe and effective.

Aim

In my first few months at Legon I noticed that the last

two 'rules' commonly quoted as disadvantages were being ignored with impunity:

1. Plastic syringes were being used to inject the drug. These were Brunswick needles and syringes, manufactured by Sherwood Medical Industries Ltd and sold as a single unit. (They are sold as disposable, but in Ghana they are re-boiled and re-used for as long as possible.) No ill effects on patients or apparatus were seen.

2. Paraldehyde up to 10 years old was being used, again with no clinical ill effects.

At the time the work was done Ghana had a severe shortage of foreign exchange, some effects of which are described by Hanlon (1979), and fresh supplies of drugs were increasingly hard to obtain; I therefore decided to investigate the safety of our remaining stock.

Using paraldehyde with plastic syringes

Introduction

Evans (1961) was the first to refer to paraldehyde dissolving plastic syringes and needle hubs: "Anyone who doubts the efficacy of paraldehyde as a solvent for the plastic hub of a disposable needle should try the experiment of dropping one into a tube containing the drug: the result is the complete disappearance of the plastic hub." Martindale's *Pharmacopoeia* (1977) is more specific, and states that paraldehyde dissolves rubber, polystyrene and styrene-acrylonitrile co-polymer.

Method

Enquiry by letter to Sherwood Medical Industries Ltd brought the reply that British Standard 5081 states that a disposable syringe must be labelled "Not to be used with paraldehyde". Brunswick syringes are, however, made from polypropylene, which is completely compatible with the drug. During a period of 72 hours a quantity of the drug will be absorbed into the rubber tip of the plunger, causing it to swell and making the syringe unusable anyway.

A syringe full of the drug was left for 24 hours.

Result

At the end of 24 hours there was no noticeable change in any part of the syringe.

Discussion

It appears that there is some difference of opinion about whether paraldehyde dissolves rubber. However, since paraldehyde is normally given in an emergency, and the syringe/drug contact time is less than one minute, it is probable that in practice any effect is negligible.

Using paraldehyde more than six months old

Introduction

Paraldehyde on storage may decompose to acetic acid by an oxidation reaction.

Hutchison (1930) described sloughing of the rectal mucosa after the local use of oxidized paraldehyde. The reaction is

$$CH_3CHO + O \rightarrow CH_3COOH$$

and as no water is formed glacial acetic acid is the end product. This acts as an autocatalyst, and up to 75 per cent of the paraldehyde may decompose. As Hutchison pointed out, free availability of air in the container is a critical factor. Decomposed paraldehyde is also dangerous by the intramuscular route.

The effects of storage were investigated chemically by Toal (1937, 1939) who assessed the decomposition of samples during a period of two months and found that a very sensitive index was the acidity of the sample as tested by the *British Pharmacopoeia* (now *European Pharmacopoeia)* (1973) method—5 ml of paraldehyde mixed with 50 ml of freshly boiled and cooled water should require for neutralization not more than 1·5 ml N/10 NaOH, phenolphthalein being used as the indicator. He found that:

1. Storage in the dark made little difference to the rate of decomposition.

2. The use of amber coloured bottles rather than plain glass bottles offered some protection.

3. The greatest rate of decomposition was in those bottles that were only partly filled. Corked or stoppered bottles were used, of a large size (for example 4 oz of paraldehyde in a 16 oz bottle was found to decompose rapidly). Thus the availability of oxygen was again said to be a critical factor.

4. The only sample found not to deteriorate was a commercial sample that remained stable over six months even in a partly filled container. This was believed to contain a preservative, although it was never identified. The *British Pharmacopoeia* has since 1948 recommended the addition of a preservative (*British Medical Journal,* 1956).

There is unfortunately no 'bed-side' method for testing the acidity of paraldehyde, as in order to assess the amount of acetic acid present it is necessary to ionize it by dissolving it in large amounts of distilled water. Martindale's *Pharmacopoeia* recommends that the drug should not be used if it has a brownish colour or a sharp, penetrating smell of acetic acid; however, the use of smell as an indicator in this situation was tested by Agranat and Trubshaw (1955) and found not to be reliable.

Method

The paraldehyde available at Legon was manufactured by Inter Alia, London, England. The date of manufacture stamped on the vials was October 1968, November 1968, or December 1969 (three different batches). It had been stored in cardboard boxes which

appeared to be light-proof, and kept in a store-room until required and then on the ward. Neither place was air-conditioned; the temperature of the store was about 20°C and that of the ward about 25°C. The vials were made of clear glass and contained 5 ml of paraldehyde with 1·5 ml of space above it (that is, a 6·5 ml vial). The *British Pharmacopoeia* recommends storage in a small, well-filled and well-closed container, in complete darkness and in a cool place.

The West Midlands Drug Information Service kindly attempted to trace Inter Alia but found that it had sold out between 1969 and 1972 to Overseas Pharmaceuticals Ltd of London, who were themselves untraceable. It was thus not possible to discover what, if any, preservative had been added, nor whether the dead space in the vials was filled with air or another gas.

Samples of the November 1968 batch were analysed using the method for assessment of acidity described above. In view of the severe shortage of the drug it was not felt to be ethical to use more of it for testing. The other tests described in the *European Pharmacopoeia* (1969), for acetaldehyde and peroxidized compounds, were not performed.

Children admitted to hospital after a convulsion were observed for possible injection abscesses or skin sloughing. It was not possible to arrange regular outpatient follow-up, but since university employees use the hospital for free primary care their children were generally seen at a later date with some other episode of illness.

Results

Five vials analysed on 27 October 1978 required 0.4, 0.5, 0.4, 0.5 and 0.5 ml of N/10 NaOH to neutrality. A further five analysed on 6 December 1978 (when the drug was 10 years old) required 0.5, 0.5, 0.45, 0.5 and 0.45 ml of N/10 NaOH to neutrality. All 10 were thus well within the limit of 1.5 ml quoted in the *European Pharmacopoeia.*

Clinical observations

No injection abscesses or skin sloughing (such as might be expected from intramuscular acetic acid) were seen in children who had been admitted to hospital following a convulsion. There were no unexplained deaths, and in particular no deaths or neurological sequelae among the children shown to have malaria (who were all cured with chloroquine and thus formed a group in which the primary disease process was quickly eliminated, so that side-effects would have been easily observed). No systemic or local toxic effects from the use of the drug were observed in children seen after being discharged.

Conclusions

Despite the restrictions generally applied, certain disposable plastic syringes (those made from polypropylene) can be used for paraldehyde; this obviates the need for boiling and packing glass syringes and all-metal needles to carry in the general practitioner's bag when the use of the drug is contemplated.

It is normally recommended that paraldehyde over six months old should be discarded. Ten-year-old paraldehyde is in constant use in one tropical hospital, with no clinical ill effects. Chemical analysis of a small sample has shown that, judging by a standard test used by Toal in the 1930s and found to be reliably sensitive, it does not decompose. This accords with his observation that the use of well filled containers slows down the rate of oxidization, and may also reflect the use of an efficient preservative. This could well repay more extensive investigation.

Two of the so-called disadvantages of using paraldehyde as an anticonvulsant are therefore possibly invalid and this may make its use in primary care more widely acceptable.

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