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Ergometrine and methylergometrine tablets are not stable under simulated tropical conditions

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SUMMARY

Objectives. This study is part of a programme on reduction of postpartum haemorrhage (PPH). Ergometrine and methylergometrine have a favourable effect on both blood loss and maternal morbidity and mortality and oral preparations were regarded as a possible treatment for use in tropical countries. The stability of oral preparations of the two ergometrine compounds under tropical conditions was unknown and was therefore examined in this study.

Study methods. The 'experimental shelf lives' of ergometrine and methylergometrine tablets were examined by exposing the tablets to seven artificially controlled conditions. Samples were analysed by high performance liquid chromatography at nine different sampling times over a period of 1 year to determine the content of ergometrine and methylergometrine.

Results. Under refrigeration (test I), less than 90% of the stated amount of active ingredient was found in the tablets after 14 weeks in the case of ergometrine and 21 weeks in the case of methylergometrine. When stored in the dark at 40°C and 75% relative humidity (test VI), the tablets fall outside accepted specification (=90–110% of state amount of active ingredient) within 3 weeks in the case of ergometrine and 21 weeks in the case of coated methylergometrine tablets. The stability of uncoated ergometrine tablets was far less than that of coated methylergometrine tablets. Instability worsened under extreme humid conditions (test IV and VI), and hot conditions (test V), for both ergometrine

and methylergometrine. From week 31 onwards the coating did not seem to protect the compound anymore, irrespective of the condition of exposure.

Conclusions. Tropical conditions make the tablets unstable with humidity as the main adverse factor. The sugar-coated methylergometrine tablets are more stable under humid/hot conditions than the non-coated ergometrine tablets. Under all simulated conditions both oral ergometrine and methylergometrine tablets are unstable.

INTRODUCTION

Postpartum haemorrhage (PPH) is still one of the most common causes of maternal death, especially in third world countries (1–3). As in these countries emergency referral in case of severe bleeding is difficult to arrange, prevention and management of PPH at all levels of obstetric care is mandatory. For prevention and management of PPH, the routine use of oxytocics in the postpartum period is advocated (4). Drugs have to be stable to be used in tropical climates and the route of administration should be simple when used by untrained people.

The route of choice is by mouth. Among all oxytocic drugs only the scale alkaloids are suitable for oral administration. Therefore, oral ergometrine and methylergometrine with favourable effects on both blood loss and maternal morbidity and mortality were regarded as possible treatments for use in tropical countries.

Manufacturers usually do not investigate the stability of preparations under tropical conditions. They usually perform their tests in temperate climates. In third world countries, it is often practically and/or economically not possible to protect pharmaceutical

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preparations from the harmful effects of high temperatures and high relative humidity during transportation, storage and use. Recent stability studies of both ergometrine and methylergometrine injectable solutions showed high extents of deterioration upon exposure to elevated temperatures and to light (5–7). Moreover, the formulation seems to be more important than whether ergometrine or methylergometrine is used (8).

The aim of this investigation was to examine the stability of ergometrine and methylergometrine tablets to determine whether it was feasible to replace the parenteral route of oxytocics by orally administered drugs. The stability of the compounds have been assessed by using 'experimental shelf life' methodology to demonstrate whether the drugs can be transported and stored without loss of potency.

MATERIAL AND METHODS

Study design

Definitions used in the study are given in Table 1. In the design of this study the recommendations laid down in the *Protocol of the Research of the Stability of Drugs in Aqueous Solutions* by the Dutch Society of Hospital Pharmacists (9) have been used. We simulated seven tropical conditions (Table 2). Taking into account the known vulnerability of ergometrine and methylergometrine on exposure to light, all tablets were tested for light-induced degradation (10).

The following tablets were examined: ergometrine maleate, 0.2 mg tablets, BP88, batch number 91 I 02/590E and containing 147 µg free base, and methylergometrine maleate, 0.125 mg tablets, batch

Table 1. Definitions used in study

Stability	The extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e. its shelf life), the same properties and characteristics it possessed at the time of its manufacture (Ref. 21)
Batch	A homogeneously produced number of drugs
Shelf life	The time during which at least 90% of the declared dose of the active ingredient is still present in the product (t_{90} or time for 10% loss of active ingredient) (Refs 20, 22)
Experimental shelf life	The period of time during which under defined experimental conditions a batch fulfils the requirements (Ref. 10)
Pharmaceutical requirements	The level of active ingredient has to be within 90–110% of the stated amount to fulfil the pharmaceutical requirements (Ref. 21)

Table 2. Definitions of simulated tropical conditions

Test	Storage condition			Notation
	Light exposure	Temperature	Relative humidity	
I	Dark	6–10°C	83–85%: ambient	D6/83
II	Dark	20°C*	75%†	D20/75
III	Dark	30°C*	45%†	D30/45
IV	Dark	30°C*	75%†	D30/75
V	Dark	40°C*	12–28%: ambient	D40/25
VI	Dark	40°C*	75%**	D40/75
VII	Light‡	20–25°C§	20–35%: ambient	L20/30

*Specified within $\pm 2^\circ\text{C}$.

†Specified within $\pm 5\%$.

‡Fluorescent white light, 450–650 nm; 1000 lx.

§Room temperature.

number 2003, 95 µg free base. Tablets were received in closed tins. During the storage tests the tablets were exposed to the intended conditions, in identical transparent tins. Each tin contained four tablets. For each sampling period (weeks 0–52), a different tin was used. One batch from each manufacturer was examined. To achieve acceptable statistical power, four tablets were assayed per storage condition per manufacturer. At weeks 0 and 52, 20 tablets per storage condition per manufacturer were investigated. Tablet weight, integrity and colour were assessed prior to assay of drug content.

Assay method

High performance/pressure liquid chromatography (HPLC) was used in preference to a radio-immunoassay because of its stability-indicating properties despite its lower sensitivity relative to the latter (11–15). The column was 25 cm × 4.6 mm ID packed with Spherisorb 5-ODS (particle size 5 µm; Chrompack, Middelburg, Netherlands) with a guard column (75 mm × 2.1 mm ID) packed with 10 µm pellicular reversed phase (Chrompack, catalogue no. 028653). An injection loop of 100 µl was used. The mobile phase consisted of a mixture of acetonitrile as solvent A and 0.067 M monobasic KH_2PO_4 :0.05% diethylamine H_2O buffer as solvent B. The mixture consisted of 60% of A and 40% of B. All reagents were of analytical grade (Merck, Darmstadt, Germany). The flow rate was 1.2 ml/min. Detection wavelength was 240 nm. The retention time was 6.8 min, the capacity factor was 3.24; the analysis was carried out at room temperature. The detection limit of ergometrine and methylergometrine in water was 0.55 ng, both at a signal to noise ratio of 1:3. The intra-day variation was 1.2% for ergometrine and 2.2% for methylergometrine and the inter-day variation was 1.73% for ergometrine and 5.07% for methylergometrine.

The data were analysed using a general linear model and a logistic regression model for ordinal response variables.

RESULTS

The raw data are published in the World Health Organization/Drug Action Programme Research Series (15). At $T=0$, the initial drug content of 20 tablets of each brand fulfilled the pharmaceutical

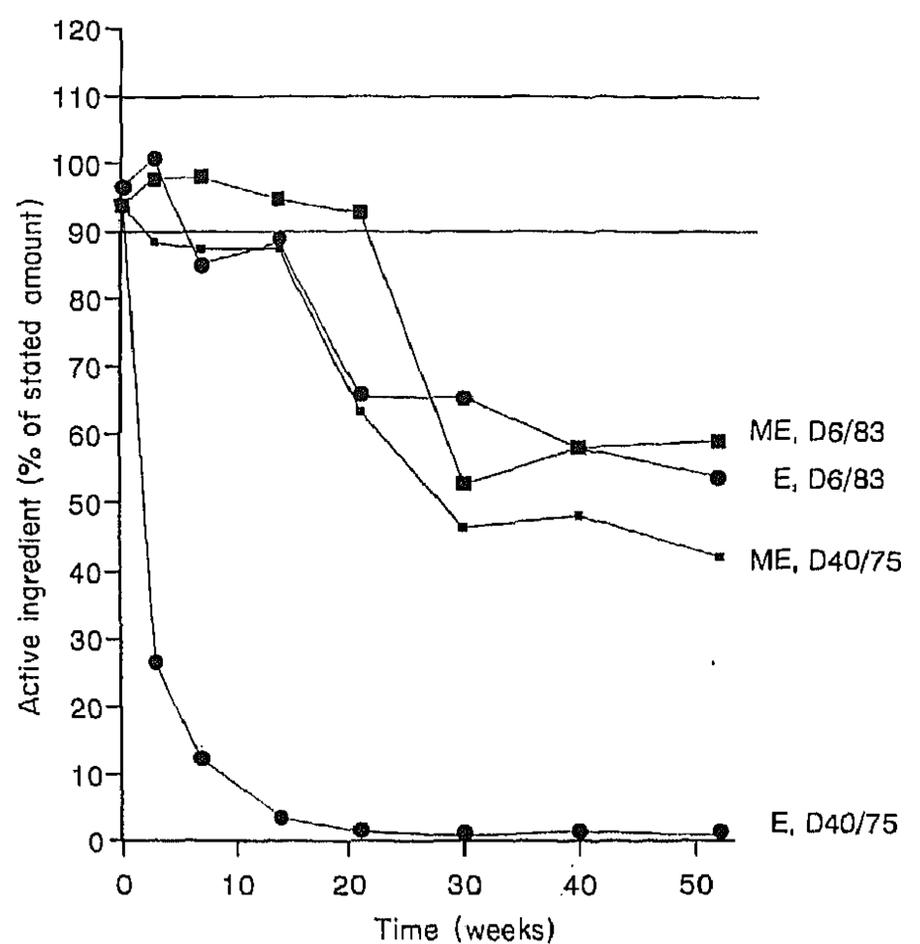


Fig. 1. Stability of oral ergometrine and methylergometrine exposed to least (I) and most (VI) extreme conditions. E, ergometrine; ME, methylergometrine; D6/83, test I: 6°C, 83% relative humidity and darkness; D40/75 test VI: 40°C, 75% relative humidity and darkness.

requirements. The results of test I (least extreme condition) and test VI (most extreme condition) for both ergometrine and methylergometrine tablets are shown in Fig. 1.

Ergometrine

Active ingredient. The level of active ingredient in the product declines when stored under all conditions studied. Under refrigerated storage (D6/83), the least extreme condition, ergometrine remained stable for 3 weeks (content was 100.7% of stated amount; 0.148 ± 0.014 mg/tablet) but at 7 weeks only 85.1% (0.125 ± 0.005 mg/tablet) of the stated amount remained. When stored at 40°C and 75% relative humidity in the darkness (D40/75), the most extreme condition, ergometrine was unstable with only 26.5% (0.039 ± 0.008 mg/tablet) of the stated amount left after 3 weeks, and $\leq 1\%$ (0.001 ± 0.001 mg/tablet) after 52 weeks of exposure (Fig. 1).

The influence of humidity was shown in the combination of test IV (D30/75), very humid, and test V (D40/25), hot and dry. At 30°C and 75% relative humidity in the darkness (D30/75), only 23% (0.034 ± 0.002 mg/tablet) of the stated

amount remained after 21 weeks. At 40°C and 25% relative humidity in the darkness (D40/25), 44.9% (0.066 ± 0.010 mg/tablet) of the stated amount was left after 52 weeks. In these tests humidity had a greater influence on stability than temperature.

The influence of light was shown in test II (D20/75) and test VII (L20/30). At 3 weeks of exposure the influence of light was stronger than that of humidity with only 61.2% (0.090 ± 0.010 mg/tablet) of the stated amount left (test VII), whereas in test II 70.7% (0.104 ± 0.008 mg/tablet) of the stated amount was still left. However, over a period of a year the influence of light was weaker than that of humidity, showing only 15.6% at 52 weeks in test II (D20/75) and 44.2% in test VII (L20/30).

Methylergometrine

The drug was unstable under all conditions studied. Under refrigerated storage (D6/83), the least extreme condition, methylergometrine was stable for 21 weeks (92.6% of stated amount; 0.088 ± 0.003 mg/tablet) but after 30 weeks it no longer fulfilled the pharmaceutical requirements (52.6%; 0.050 ± 0.002 mg/tablet). At 40°C and 75% relative humidity in the dark (D40/75), the most extreme condition, the methylergometrine product was unstable, with 63.2% (0.060 ± 0.003 mg/tablet) of the stated amount left after 21 weeks, and $\leq 50\%$ (0.040 ± 0.002 mg/tablet) after 52 weeks (Fig. 1).

Hardly any difference was seen between the results of test IV (D30/75) and test V (D40/25), with, respectively, 49.5% (0.047 ± 0.003 mg/tablet) and 51.6% (0.049 ± 0.002 mg/tablet) of drug left after 52 weeks of exposure.

Under all conditions, the uncoated ergometrine tablets were far less stable than the coated methylergometrine ones. Instability rises with humidity (D30/75 or D40/75) and temperature (D40/25), for both ergometrine and methylergometrine. In the least extreme condition the coating did not seem to protect the compounds anymore from week 31 onwards (Fig. 1).

No differences in weight larger than 0.1 mg were noticed. Discolouration occurred in the tablets especially when stored under humid conditions. Growth of mould was observed on some tablets stored in humid conditions (tests II, IV and VI).

DISCUSSION

Tablets

Drug stability is dependent on many product-related factors (16,17), i.e. the active ingredient, the excipients, the dosage form, the manufacturing process and the nature of the packaging. Methylergometrine tablets were included in our investigation because of the claims that methylergometrine shows less hypertensive side effects and less influence on postpartum prolactin levels than ergometrine (18,19). When supplied by Unicef, methylergometrine tablets are as cheap as ergometrine. The choice of manufacturer was dependent on the availability of their products. Although ergometrine and methylergometrine are supposedly being produced on 'market demand', in practice they are produced only once a year. Only one batch was available from each manufacturer. As only one brand of ergometrine and methylergometrine are generally distributed, comparison between brands as recommended by Hogerzeil *et al.* (8) was not possible in this study.

Sampling points in time

Long-term stability studies under 'temperate climate' conditions normally last 5 years (10). The tablets in this study have been subjected to conditions that are more extreme. A shorter period of investigation has been accepted, as deterioration of tablet quality will appear sooner. The stability test was performed for a period of 1 year only as in actual practice in tropical countries tablets should not be stored after opening of the box for longer periods. Loss of potency by water absorption was expected to occur early (20). Therefore, the sampling was done more frequently during the early stages and eight samplings were done over the first 21 weeks (9).

Under the least harmful storage conditions (D6/83) ergometrine and methylergometrine were not stable for more than 7 and 21 weeks, respectively. The results are alarming, indicating that careful storage of those products is critical when used under tropical conditions. Refrigerated storage may be necessary. Protecting the tablets from humidity by coating or special packaging may help, as humidity seems to be more harmful than temperature. Light is not as damaging on tablets as on ampoules of the drugs (21). Methylergometrine is substantially more stable than ergometrine even under test VI (D40/75).

CONCLUSIONS AND RECOMMENDATIONS

Both ergometrine and methylergometrine tablets are not stable under simulated tropical conditions. These tablets are the only oxytocic drugs given by mouth and therefore easy to administer when used by untrained people. However, because of their strong instability under the conditions studied, those preparations are not suitable for use as prophylactic agents of PPH. Moreover, pharmacokinetic data suggest that their absorption is also unreliable (23).

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