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Instability of (methyl)ergometrine in tropical climates: an overview

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Abstract

Parenteral ergometrine is widely used for the prevention and treatment of excessive uterine bleeding following birth. Unfortunately, in tropical climates it is often found to contain very little active ingredient: only 32 of 100 field samples from Bangladesh, Gambia, Malawi, Yemen and Zimbabwe contained 90–110% of the amount of active ingredient stated on the label, and 34 contained less than 60%. In this paper the results of nine studies, of which eight were initiated and coordinated by WHO, are reviewed to formulate answers to the following questions: (1) what is the extent of the problem of low potency of ergometrine in tropical climates; (2) is the problem due to instability or low initial quality, or both; (3) which practical measures can assure the quality of injectable ergometrine; and (4) are there any alternative drugs which are more stable? Injectable ergometrine is very unstable under tropical conditions and particularly if stored unrefrigerated and exposed to light, when it may loose up to 20% of its potency per month. However, there are differences between brands. Practical measures to assure the quality of injectable ergometrine therefore include a careful supplier selection and refrigerated storage. Ergometrine injection should always be protected from light until given to the patient. Loss of active ingredient can easily be detected by regular visual checks of the colour of the solution. Any discoloration implies that the solution contains less than 90% of the stated amount of active ingredient, and should not be used. Methylergometrine is no more stable than ergometrine. Parenteral oxytocin is more stable than both ergometrine and methylergometrine injection. Oral and buccal dosage forms are less stable than injections. In view of the better stability in tropical climates, similar cost, fewer side effects and comparative efficacy, parenteral oxytocin, rather than parenteral ergometrine, is the drug of choice in the prevention and treatment of postpartum haemorrhage.

Keywords: Ergometrine; Drug quality; Drug stability; Developing countries; Tropical climates

1. Introduction

Parenteral ergometrine is widely used for the prevention and treatment of excessive uterine bleeding following birth. It is classified as an essential drug in the WHO Model List of Essential Drugs, it is widely available and cheap. In view of the potentially fatal complications of excessive uterine bleeding, especially in developing countries where blood transfusions are difficult and dangerous, it has been considered a vital drug that should always be available, and of good quality.

In the late 1980s anecdotal reports emerged of occasional ineffectiveness of injectable ergometrine in tropical climates. The first documented evidence, published by WHO in the Lancet in 1988 [1], was quite alarming: of 24 samples of injectable ergometrine taken from 20 rural health facilities in Bangladesh, Yemen and Zimbabwe, only nine (37%) conformed to United States Pharmacopoeia and British Pharmacopoeia guidelines with a level of active ingredient between 90 and 110% of the stated amount; seven (29%) contained less than 20% active substance. These early findings were soon confirmed by a longitudinal study of the stability of five essential drugs, including ergometrine, during transport between Sweden and rural Sudan [2].

The WHO Action Programme on Essential Drugs and the WHO Safe Motherhood Research Programme then initiated and coordinated a research effort which involved the main non-profit suppliers of essential drugs, UNICEF in Copenhagen and the International Dispensary Association (IDA) in Amsterdam; national

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Table 1
Level of active ingredient of injectable ergometrine in rural health facilities in tropical climates

	No. of samples	Active ingredient[a]		
		90–110%	60–89%	<60%
Bangladesh, Yemen, Zimbabwe [1]	24	9 (37%)	8 (33%)	7 (29%)
Gambia, Malawi [3]	9	1 (11%)	5 (55%)	3 (33%)
Total	100	32 (32%)	34 (34%)	34 (34%)

[a] As percentage of stated amount.

essential drugs programmes in Gambia, Malawi, Nigeria, Sudan, Uganda and Zimbabwe; and seven drug quality control laboratories in Denmark, the Netherlands, Sweden and Zimbabwe. The main research questions concerning the low potency of ergometrine were: (1) What is the extent of the problem in the field? (2) Is the problem caused by instability or low initial quality of the products? (3) Which practical measures could ensure the quality of oxytocics, including injectable ergometrine, at the level of the end-user? (4) Are there alternative drugs which are more stable?

The results of a series of inter-related research studies have already been published in the medical literature and the full data are available as WHO reports. In this paper the findings of the various studies are considered together and used to formulate answers to the research questions.

2. Extent of the problem

On several occasions field samples of injectable ergometrine were taken from government medical stores, district hospitals and rural clinics in Bangladesh, Gambia, Malawi, Yemen and Zimbabwe [1,3,4]. The results from these studies indicate that the potency of injectable ergometrine at the level of the end user is a real problem (Table 1). Only 32% of 100 non-expired samples did comply with the USP/BP standards of 90–110% active ingredient, and 34% contained less than 60% of the stated amount. This low quality was found in all five countries and related to products of eight different manufacturers, which shows that the problem is both serious and widespread.

3. Instability or low initial quality?

A low level of active ingredient at the level of the end user may be caused by instability of the product, low initial quality, or a combination of these factors. To distinguish between the two effects, several longitudinal studies were done.

In four different longitudinal field studies batches of ergometrine were followed and tested throughout the distribution chain (Table 2). All these studies showed a steady decrease in the level of active ingredient: 5.8% loss of active ingredient after two months international transport from the UNICEF warehouse in Copenhagen to Lagos and Entebbe [5,6], 10% loss after one month in Sudan [2], 17% loss after 5 months inland transport in Zimbabwe [4], more than 18.6% after 16 months in Sudan [7,8] and 47% after 24 months in Sudan [2]. The final assay values of 82% after 2 months, 69% after 5 months and about 50% after 16–24 months are in line with the results of the field samples discussed above.

Lack of initial quality may also be a factor. In the Zimbabwe study [4] 26 samples of three brands of injectable ergometrine were taken when the drugs were delivered to Government Medical Stores; of these, 17 (65%) contained less than 90% active ingredient. All had been manufactured less than 7 months before. In one of the Sudan studies [7,8] the reference sample contained only 62% of active ingredient, which was probably at least partly due to low initial quality.

The WHO/UNICEF longitudinal study on the stability of essential drugs during international transport [5,6] included a system of 3-hourly temperature monitoring within the drug containers for the full duration of the 2-month voyages from Copenhagen to Lagos and Entebbe. The results indicated that, even within the containers, the drugs were exposed to extreme temperatures ranging from −3.5°C in November in Aarhus harbour to 42.2°C in Mombasa in January. These data were used to set the conditions for simulation studies on the stability of injectable and oral oxytocics.

A longitudinal simulation study on the stability of four brands of injectable ergometrine under various tropical conditions [9,10] confirmed the picture of a gradual loss of active ingredient over time, the decline being faster at higher temperatures. In addition, ergometrine was very unstable under the influence of light with a mean loss of 21% in 1 month (range 14–61%) and over 90% in 1 year. Short (2–4 weeks) exposure to temperatures of 40–50°C in the dark, which often occurs during transport in tropical countries, had no serious effect on the drugs. There were considerable differences between different brands of the drug.

Table 2
Longitudinal field studies on the stability of injectable ergometrine in tropical climates

	Brands	Tests	Mean loss of active ingredient[a]	Mean final assay[b]
Denmark to Nigeria/Uganda [5,6]	1	8	5.8% in 2 m	82%
Sweden to rural Sudan [2]	1	12	10% in 1 m, 47% in 24 m	53%
Inland transport Zimbabwe [4]	3	50	17.1% in 5 m	69%
Netherlands to rural Sudan [7,8]	1	4	>18.4% in 16 m	51%

[a] Percentage of initial amount of active ingredient, over number of months.
[b] Percentage of stated amount.

It can therefore be concluded that injectable ergometrine is very unstable in tropical climates, and especially when stored unrefrigerated. The effect is worse when the drugs are exposed to higher temperatures and particularly if exposed to light. In some cases inferior initial quality is also a factor.

4. Practical measures to ensure the quality of injectable ergometrine

The simulation [9,10] and the Zimbabwe [4] studies have clearly demonstrated that considerable differences may exist between products of different manufacturers. This implies that careful supplier selection and frequent quality control measures are necessary.

Although most manufacturers indicate that injectable ergometrine should be kept under refrigeration, this is rarely done in practice. In addition, phials of ergometrine are often kept ready for use in open trays in the dispensary or labour ward. This combination of high temperature and exposure to light leads to a rapid loss of active ingredient (probably at a rate of about 20% per month). It is therefore obvious that injectable ergometrine should be kept under refrigeration as much as possible. This applies to the manufacturer, the wholesaler, the central warehouse and the health facilities. It should be considered to include the drug in the cold chain for refrigerated transport. Ergometrine should not be included in drug ration kits.

An unexpected finding of the simulation study was that the colour of ergometrine is a very reliable indicator of its quality [11]. Any visible discoloration of the injectable solution, when compared with distilled water in identical glass tubes against a well-lit white background, indicates that the solution contains less than 90% active ingredient, and should not be used. This test has a sensitivity of 100% and a specificity of 86%; this implies that no defective samples are missed, but that approximately 14% of the rejections are unjustified. The test can easily be used to check every batch upon arrival in central medical stores. In addition, district or hospital pharmacists can check their stock from time to time, especially those more than 1 year after manufacture. In case of doubt, or when large quantities are involved, the level of active ingredient should be measured in a drug control laboratory.

5. Are there alternative drugs which are more stable?

5.1. Injectable methylergometrine

It has been suggested that methylergometrine is more stable than ergometrine, and could be used as an alternative in tropical climates [12]. This hypothesis was specifically tested in the first simulation study [9,10] and no differences in stability were found (Table 3). First, the mean level of active ingredient of four brands of each of the two drugs did not differ significantly, both after 1 year storage at 4–8 and 30°C in the dark and at room temperature in the light. Secondly, no difference was found between ergometrine and methylergometrine produced by the same manufacturer. Thirdly, no difference in stability was found between a specially and uniformly produced pair of injectable ergometrine and methylergometrine. It can therefore be concluded that methylergometrine as an active substance is not more stable than ergometrine, and that any difference between ergometrine and methylergometrine, as observed in some studies, is caused by the same factors that cause the differences between brands of the same drug.

5.2. Injectable oxytocin

Parenteral oxytocin in the active management of the third stage of labour is almost as effective in the prevention of postpartum haemorrhage as the combination of oxytocin and ergometrine, particularly if 10 IU is used [13]. However, the combination of oxytocin and ergometrine is associated with far more frequent side effects of nausea and vomiting and raised blood pressure [14–16]. There are though only very few field data on the stability of oxytocin in tropical climates. Of five unexpired samples taken from different district hospitals in Zimbabwe, one sample contained 107% of the stated amount, and the other four samples contained 112–142% [10]. Some of this overfill may have been intentional.

Table 3
Results of simulation studies on the stability of oxytocics under tropical conditions

Storage	Brands	Batches	Mean active ingredient[a] after 12 months storage		
			Dark 4–8°C	Dark 30°C	Light 21–25°C
Injectable oxytocics [9,10]					
Ergometrine	4	8	95 (80–100)	69 (56–83)	9 (2–15)
Methylergometrine	4	8	96 (92–100)	82 (69–94)	9 (0–22)
Oxytocin	3	6	101 (99–102)	86 (83–90)	93 (91–95)
Oral oxytocics [17–19][b]					
Ergometrine	1	1	54	9	44
Methylergometrine	1	1	59	50	57
Oxytocin	1	1	83	33	85
Desamino-oxytocin	1	1	51	36	56

[a] Percentage of initial amount (95% confidence limits).
[b] Tablets removed from their container, kept at approximately 75% (4–8 and 30°C) or 30% (21–25°C) relative humidity.

Three brands of injectable oxytocin were included in the first longitudinal simulation study (Table 3). Like ergometrine and methylergometrine, oxytocin showed a gradual loss of active ingredient over time, the decline being faster at higher temperatures. However, the effect was much less than with the other two drugs and not aggravated by light. It can therefore be concluded that, under tropical conditions of temperature and light, oxytocin is more stable than either ergometrine or methylergometrine.

5.3. Oral oxytocics

A separate simulation study was carried out to measure the stability of oral oxytocics (oral ergometrine, oral methylergometrine and buccal oxytocin) [17–19]. Although somewhat limited in the number of different brands studied, the outcome was very clear: as soon as tablets were taken from their container or sealed package, they deteriorated within a matter of weeks. The effect increases with temperature and especially with higher relative humidity. We may conclude that, in general, oral dosage forms are even less stable than injectables.

6. Conclusion

Injectable ergometrine is very unstable under tropical conditions and particularly when stored unrefrigerated and under the influence of light. However, there are considerable differences between brands, and in some cases low initial quality is also a factor. Practical measures to assure the quality of injectable ergometrine include careful supplier selection and refrigerated storage. Ergometrine injection should always be protected from light until given to the patient. Loss of active ingredient can easily be detected by regular visual checks of the colour of the solution. With regard to possible alternatives, methylergometrine as an active substance is not more stable than ergometrine, although some individual products are. Parenteral oxytocin is more stable than either ergometrine or methylergometrine injection. Oral dosage forms are even less stable than injections. The better stability and equal cost may be added to clinical arguments that parenteral oxytocin is the drug of choice in the prevention and treatment of postpartum haemorrhage.

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