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# Oxytocin and desamino-oxytocin 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. Buccal oxytocin and desamino-oxytocin administration with a favourable effect on both blood loss and maternal morbidity and mortality were regarded as possible treatments for use in tropical countries. The stability of buccal oxytocin and desamino-oxytocin under tropical conditions was unknown and therefore tested in this study.

**Study methods.** The 'experimental shelf lives' of buccal oxytocin and desamino-oxytocin were examined by exposing the tablets to seven artificially controlled conditions. Samples were analysed by high performance liquid chromatography to determine the content of oxytocin and desamino-oxytocin at nine different times during the period of 1 year.

**Results.** Oxytocin and desamino-oxytocin are fairly stable under refrigeration. Instability for both drugs was detectable after 20 weeks' storage under humid conditions, independent of temperature. Desamino-oxytocin is more sensitive to light exposure; its concentration declines to 55.6% of the stated amount after 1 year of exposure to light compared to 85% in the case of oxytocin. Oxytocin packaged as supplied by the manufacturer were stable for 21 weeks when exposed to simulated humid (75% relative humidity) conditions. At 40°C and 25% relative humidity there is no difference in stability between tablets in sealed aluminium packs as supplied by the manufacturer and unpackaged tablets.

**Conclusions.** Tropical conditions make oxytocin and desamino-oxytocin tablets unstable, with

humidity as the most adverse factor. The oxytocin tablets were partially protected from the harmful effect of humidity by sealed aluminium package.

## INTRODUCTION

Postpartum haemorrhage (PPH) is still one of the most common causes of maternal death especially in third world countries (1–3). Emergency referral of severe bleeding is difficult to arrange in these countries. Therefore, prevention and management of PPH at all levels of obstetric care is mandatory. For prevention and management of PPH, routine use of oxytocics in the postpartum period is advocated (4). Compared to other oxytocics, oxytocin is the preferred drug for preventing and managing blood loss after childbirth because it is more stable under (simulated) tropical conditions and gives fewer side-effects (3, 5, 6). Oxytocin is usually given intramuscularly but is also available as tablets for buccal and sublingual administration.

To be used in tropical climates, drugs have to be stable and easy to administer when used by untrained people. Moreover, the route of choice is by mouth. Recent stability studies of oxytocin in an injectable form showed marked deterioration upon exposure to elevated temperatures and light (7–9).

The aim of the present investigation was to examine the stability of oxytocin and desamino-oxytocin tablets under simulated tropical conditions to determine whether it is feasible to replace the parenteral oxytocics by sublingual administration. The stability of the compounds have been assessed, using 'experimental shelf life' methodology to demonstrate whether the drugs can be transported and stored without the loss of potency.

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## MATERIAL AND METHODS

### Study design

Definitions used in the study are given in Table 1. In the design of this study, use is made of 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 (10). We simulated seven tropical conditions (Table 2). The following tablets were examined: buccal oxytocin tablets, 200 IU, batch number 00111061, and buccal desamino-oxytocin tablets, 50 IU, batch number 075 MFD 0691. Oxytocin was received in air-tight aluminium packages. These sealed packages are presumed to be light-resistant and humidity-proof. The packages were exposed to tests III, IV and V (Table 2). During storage tests, the tablets were exposed to the intended

conditions, in identical transparent tins. 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 have been investigated. Tablet weight, integrity and colour were assessed prior to assay of drug content.

### Assay method

High performance liquid chromatography (HPLC) was used as the assay method (11–16). In short, the HPLC analysis was as follows. The column was 25 × 4.6 mm ID packed with Spherisorb 5-ODS (particle size, 5 µm; Chrompack, Middelburg, The Netherlands) with a

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. 19)
Batch	The homogeneously produced number of drugs (Ref. 19)
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 18, 20)
Experimental shelf life	The period of time during which under defined experimental conditions a batch fulfils the requirements (Ref. 17)
Pharmaceutical requirements	The level of active ingredient has to be within 90–110% of the stated amount to fulfil the pharmaceutical requirements (Ref. 19)

Table 1. Definitions used in study

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

Table 2. Definitions of simulated tropical conditions

\*Specified within ± 2°C

†Specified within ± 5%.

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

§Room temperature.

guard column (75 × 2.1 mm ID) packed with 10- $\mu$ m pellicular reversed phase (Chrompack, catalogue no. 028653). An injection loop of 100  $\mu$ l was used. The mobile phase consisted of a mixture of acetonitrile in H<sub>2</sub>O (1:1) as solvent A and 0.1 M monobasic KH<sub>2</sub>PO<sub>4</sub> buffer as solvent B; the mixture consisted of 55% of A and 45% of B. All reagents were of analytical grade (Merck, Darmstadt, Germany). The flow rate was 1.2 ml/min. Detection wavelength was 225 nm. The retention time was 6.7 min, the capacity factor was 1.84 and the analysis was carried out at room temperature. The detection limit of oxytocin and desamino-oxytocin in water was 0.50 ng both at a signal to noise ratio of 1:3. The inter-day variation was 1.95% for oxytocin and 3.19% for desamino-oxytocin and the intra-day variation was 1.06% for oxytocin and 1.96% for desamino-oxytocin.

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

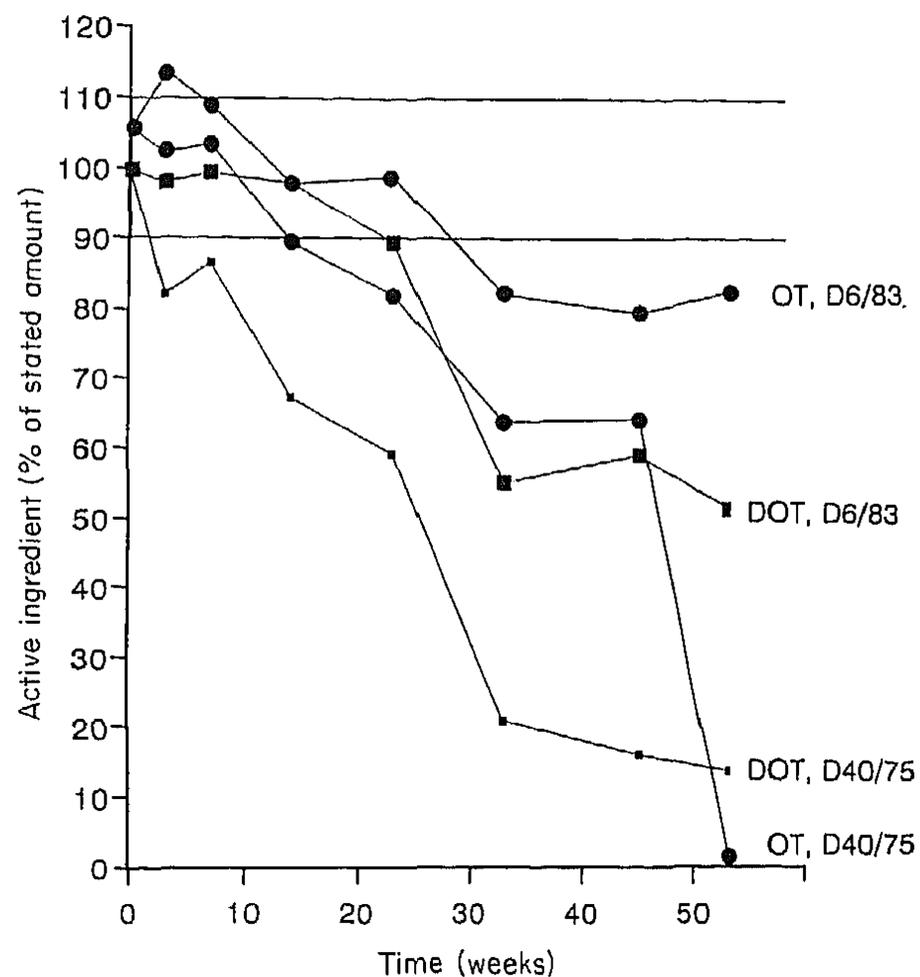
## RESULTS

The raw data of the simulation study are published in World Health Organization/Drug Action Programme Report (16). At  $t=0$ , the initial drug content of 20 tablets of each brand fulfilled the pharmaceutical requirements. The results of test I (least extreme condition) and test VI (most extreme condition) for both oxytocin and desamino-oxytocin tablets are shown in Fig. 1.

### Oxytocin

**Active ingredient.** The level of active ingredient in the product declines gradually when stored under all conditions studied. The stated amount was 200 IU/tablet. Under refrigerated storage (D6/83), the least extreme condition, oxytocin remains stable for more than 23 weeks. At 40°C and 75% relative humidity in the dark (D40/75), the most extreme condition, oxytocin was less stable, with only 89.4% (178.8 ± 2.90 IU/tablet) of the stated amount left after 14 weeks (Fig. 1).

Test IV (D30/75), very humid, and test V (D40/25), hot and dry, demonstrate the influence of humidity. At 30°C and 75% relative humidity in the darkness (D30/75), the product retained only 41.2% (82.34 IU/tablet) of the stated amount of the active ingredient



**Fig. 1.** Stability of oral oxytocin and desamino-oxytocin exposed to least (I) and most (VI) extreme conditions. DOT, desamino-oxytocin; OT, oxytocin; D6/83, test I: 6°C, 83% RH and darkness; D40/75, test VI: 40°C, 75% RH and darkness.

after 33 weeks. Exposed to 40°C and 25% relative humidity in the dark (D40/25), 82.8% (165.6 ± 3.5–0 IU/tablet) of the stated amount of active ingredient remained after 53 weeks. In these tests humidity had a greater influence on stability than temperature. Tablets packed as supplied by the manufacturer fulfilled pharmaceutical requirements for 23 weeks at 75% relative humidity, and 80.7% remained after 33 weeks of exposure.

The influence of light was shown in test II (D20/75) and test VII (L20/30). After 23 weeks of exposure in test II, only 17.5% (35.0 U/tablet) of the stated amount remained, whereas with full exposure to light (test VII), even after 53 weeks' exposure, 85% (170.0 U/tablet) of the stated amount remained.

### Desamino-oxytocin

The drug was unstable under all conditions studied. Under refrigeration (D6/83), the least extreme condition, desamino-oxytocin remained stable for more than 14 weeks. At 40°C and 75% relative humidity in the dark (D40/75), the most extreme condition, the desamino-oxytocin is less stable, with only 67.2% (33.6 ± 3.38 IU/tablet) of the stated amount of the active ingredient left after 14 weeks (Fig. 1).

Test IV (D30/75), humid, and test V (D40/25), hot and dry, showed that the influence of humidity on stability was more marked than that of temperature. At 30°C and 75% relative humidity in the dark (D30/75), the product has only 37.2% ( $18.6 \pm 1.35$  IU/tablet) of the stated amount of the active ingredient left after 33 weeks. At 40°C and 25% relative humidity in the dark (D40/25), 60.9% ( $30.5 \pm 1.58$  IU/tablet) of the stated amount of active ingredient was left after 53 weeks.

Under all conditions (except test III) oxytocin is more stable than desamino-oxytocin.

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

## DISCUSSION

Buccal oxytocin and desamino-oxytocin tablets have been withdrawn from the market as greater control in induction and augmentation of labour is achieved by intravenous or intramuscular administrations of oxytocin. However, those tablets have never been used as prophylactic agents in the prevention of PPH. The stability of those tablets was unknown and hence the reason for undertaking the present study. We have been able to examine just one brand of desamino-oxytocin, batch 075 MFD 0691, and one brand of oxytocin, batch number: 001061.

### *Sampling points in time*

Long-term stability studies under 'temperate climate' conditions normally last 5 years (17). The tablets in this study have been subjected to conditions that are more extreme to speed up the degradation process. The stability test was performed for a period of 1 year only, because in actual practice in tropical countries, tablets are not stored for longer periods. Loss of potency by water absorption was expected to occur especially in the early stages (18). Therefore, the sampling was done more frequently in the early stages and eight samples were made in the first 21 weeks (10).

Both oxytocin and desamino-oxytocin brands failed the pharmaceutical requirements for stability within  $\pm 23$  weeks. When packed as supplied by the

manufacturer, stability is improved, but even then, after 33 weeks of exposure in test IV (D30/75), only 80.7% of the active ingredient remained. This is too short a shelf life in tropical countries, considering the fact that the time needed for transportation is already several weeks. Humidity is the most adverse factor compared with both temperature and light.

## CONCLUSIONS AND RECOMMENDATIONS

Oxytocin and desamino-oxytocin tablets have too short a shelf life for use in tropical countries. Neither of the preparations available are suitable for use as prophylactic agents in the prevention of PPH.

Currently available buccal oxytocin and desamino-oxytocin tablets are no alternatives to the parenteral products for PPH prevention. The formulation of a stable non-injectable alternative to oxytocin injection is advocated.

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## REFERENCES

1. Van Roosmalen J. (1988) *Maternal Health Care in the Southwestern Highlands of Tanzania*. Thesis, University of Leiden, The Netherlands.
2. Royston E, Armstrong S. (1989) *Preventing Maternal Deaths*. World Health Organization, Geneva.
3. Van Dongen PWJ, van Roosmalen J, de Boer CN, van Rooy J. (1991) Oxytocics for the prevention of postpartum haemorrhages, a review. *Pharmaceutisch Weekblad* [Scientific edition], **13**, 238–243.
4. Prendiville WJ, Harding JE, Elbourne DR, Chalmers I. (1988) The effects of routine oxytocic administration in the management of the third stage of labour: an overview of the evidence from controlled trials. *British Journal of Obstetrics & Gynaecology*, **95**, 3–16.

5. McDonald SJ, Prendiville WJ, Blair E. (1993) Randomised controlled trial of oxytocin alone versus oxytocin and ergometrine in active management of third stage of labour. *British Medical Journal*, **307**, 1167–1171.
6. Hogerzeil HV, Walker GJA, de Goeje MJ. (1994) Oxytocin more stable in tropical climates. *British Medical Journal*, **308**, 59.
7. Walker GJA, Hogerzeil HV, Lindgren U. (1988) Potency of ergometrine in tropical countries. *Lancet*, **ii**, 393.
8. Hogerzeil HV, de Goeje MJ, Abu-Reid IO. (1991) Stability of essential drugs in Sudan. *Lancet*, **338**, 754–755.
9. Hogerzeil HV, Battersby A, Srdanovic V, Stjernstrom NE. (1992) Stability of essential drugs during shipment to the tropics. *British Medical Journal*, **304**, 210–212.
10. Anonymous. (1992) *Protocol of the Research of the Stability of Drugs in Aqueous Solutions*. Dutch Society of Hospital Pharmacists, The Hague, **125**, 953.
11. Anonymous. (1980) Oxytocin tablets. In: *British Pharmacopoeia*. Vol. 2, p. 799, London.
12. Anonymous. (1987) Oxytocin solutio iniectionis: examination by liquid chromatography. In: *Dutch Pharmacopoeia*. 9th edn, pp. 519.1–519.7, The Hague.
13. Rao PS, Weinstein GS, Wilson DW, *et al.* (1991) Isocratic performance liquid chromatography–photodiode-array detection method for determination of lysine- and arginine-vasopressins and oxytocin in biological samples. *Journal of Chromatography*, **536**, 137–142.
14. Maxl F, Siehr W. (1989) The use of high performance liquid chromatography in the quality control of oxytocin, vasopressin and synthetic analogues. *Journal of Pharmaceutical Biomedical Analysis*, **7**, 211–216.
15. Amico JA, Ulbrecht JS, Robinson AG. (1987) Clearance studies of oxytocin in humans using radioimmunoassay measurements of the hormone in plasma and urine. *Journal of Clinical Endocrinology and Metabolism*, **64**, 340–345.
16. De Groot ANJA, Vree TB, Hogerzeil HV. (1994) *Stability of Oral Oxytocics in Tropical Climates*. WHO/DAP Research Series no. 12, Geneva.
17. Hartmann V, Krummen K, Schnabel G, Bethke H. (1982) Techniques of stability testing and shelf-life predictions. *Pharmazeutische Industrie*, **44**, 71–79.
18. Bos CE. (1990) *Tropical Tablets: The Development of Tablet Formulations for Use in Tropical Countries*. Thesis, University of Groningen, The Netherlands.
19. USP ID (1994) Section VI. In: *Approved Drug Products and Legal Requirements*. Vol. 3, 4th edn, pp. 1–29.
20. York P. (1977) The shelf life of some antibiotic preparations stored under tropical conditions. *Pharmazie*, **32**, 101–105.