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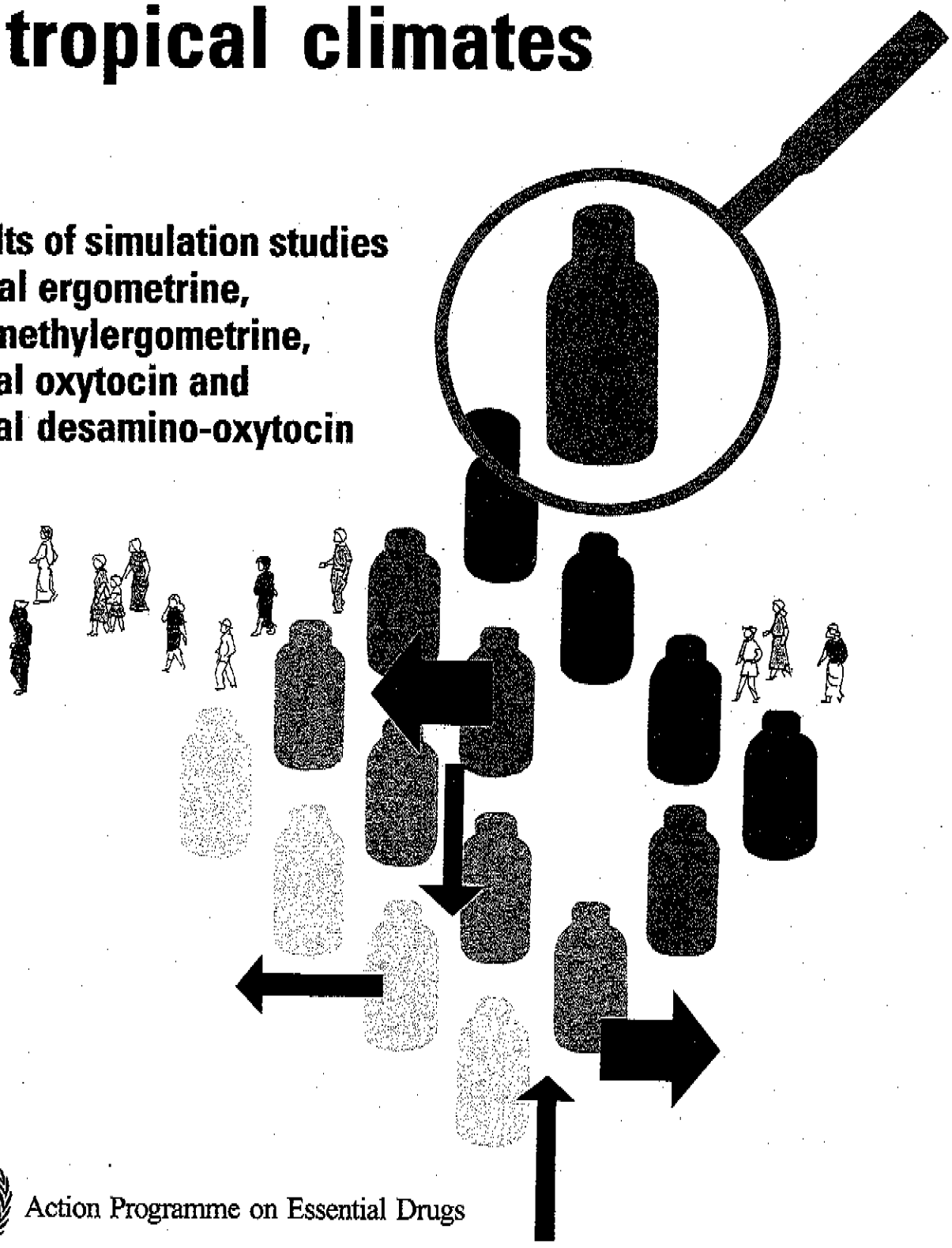

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Stability of oral oxytocics in tropical climates

Results of simulation studies on oral ergometrine, oral methylergometrine, buccal oxytocin and buccal desamino-oxytocin

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ABBREVIATIONS

D	Dark
DOT	Desamino-oxytocin
E	Ergometrine
HPLC	High Pressure Liquid Chromatography
L	Light
ME	Methylergometrine
OT	Oxytocin
PPH	Postpartum Haemorrhage
RH	Relative Humidity
USP	United States Pharmacopeia
WHO	World Health Organization

SUMMARY

Objectives

This study is part of a research programme that aims to reduce postpartum haemorrhage (PPH). The use of oral oxytocics, with their positive effects on blood loss and maternal morbidity and mortality, was regarded as a possible means of reducing PPH in tropical countries. It is known that injectable oxytocin is more stable than injectable ergometrine and methylergometrine, but the stability of oral oxytocics under tropical conditions is unknown, and is the subject of this study. Four oral oxytocics were included: ergometrine tablets (E), methylergometrine coated tablets (ME), buccal oxytocin (OT) and buccal desamino-oxytocin (DOT).

Study methods

The stability of oral oxytocics in tropical climates was examined by exposing the tablets to seven artificially regulated conditions. Temperatures ranged between 6-40°C and relative humidity (RH) between 20-85% in the dark, with ambient temperatures used under exposure to daylight. At nine different times during a period of one year, samples were taken and analysed on the content of active ingredients using High Performance Liquid Chromatography (HPLC).

Results

Ergometrine and methylergometrine

After refrigerated storage of 14 and 21 weeks respectively, E and ME had less than 90% of the stated amount of active ingredient. In the dark at 40°C/75% RH the level fell below 90% within 3 and 21 weeks respectively. Stability of uncoated E-tablets was slightly less than that of the coated ME but for both instability increased with humidity and temperature. From week 31 onwards the coating no longer seemed to protect the stability of ME.

Oxytocin and desamino-oxytocin

Under refrigerated storage OT and DOT were slightly more stable then E and ME. Under humid conditions, the level of active ingredient in both drugs fell below 90% after 20 weeks, independent of temperature. DOT was more sensitive to light than OT (after one year's exposure to light, 60% and 75% of active ingredient respectively remained). For 21 weeks the level of active ingredient in OT remained above 90% at 75% RH at 30 and 40°C. At 40°C/25% RH no difference in stability was noted between the tablets packed in a sealed aluminium package by the manufacturer, and unpacked tablets directly exposed to the defined test condition.

Conclusions

None of the oral oxytocics included in this study were stable under simulated tropical conditions. Oral ergometrine was the least stable under all simulated conditions. It is unlikely that oral oxytocics can be effective in the prevention of PPH in tropical climates.

INTRODUCTION

Background of the project

Postpartum haemorrhage (PPH) is still one of the most common causes of maternal death, especially in third world countries (1,2,3). In these countries emergency referral in cases of severe bleeding is difficult to arrange, so its prevention and management at all levels of obstetric care is vital. For prevention and management of PPH, the use of oxytocics in the postpartum period is advocated (4). Oxytocin is the preferred drug in the prevention and management of blood loss after childbirth (3,5). In tropical climates drugs need to be stable, and when they are used by untrained people the route of administration should be simple. Therefore, the use of oral oxytocic drugs [oral ergometrine (E), methylergometrine (ME), buccal oxytocin (OT) and buccal desamino-oxytocin (DOT)], with a favourable effect on both blood loss and maternal morbidity and mortality, was regarded as a possible solution to these problems in tropical countries.

The stability of preparations under tropical conditions is not normally investigated during manufacturers' stability studies; and if it is, the results are not readily available. In third world countries, it is often practically and/or economically impossible to protect pharmaceutical preparations from the harmful effects of high temperatures and high relative humidity during transportation, storage and use. Protection against the heat is only possible by storing products in cooled storage rooms or refrigerators. More often than not, this is impossible (6,7). Use of humidity-resistant packaging, which could protect the drug until the moment of consumption, is too expensive for general use in developing countries (up to one third of the price of the unpacked drug) (8). Thus, as soon as a sealed container is opened, humidity can penetrate and accelerate physical, chemical, as well as microbiological deterioration and affect the stability of the drug.

Recent reports and stability studies of injectable oxytocics have shown a remarkable degree of instability on exposure to increased temperatures and exposure to light (9-12); injectable E and ME, in particular, are unstable under (simulated) tropical conditions. Moreover, large differences in potency and stability between the various brands and formulations seem to be more important than the differences between ergometrine and methylergometrine. Under tropical conditions, injectable oxytocin is more stable than injectable (methyl)ergometrine (13).

Almost nothing is known about the stability of ergometrine, methylergometrine or oxytocin tablets under tropical conditions. Recommendations for storage of ergometrine and methylergometrine tablets all advise the use of well-sealed containers for ergometrine tablets and tight, light resistant containers for methylergometrine tablets. General storage temperature recommendations indicate storage at a temperature not exceeding 8°C (6,9,14) and not exceeding 25°C for oxytocin (15). We assumed that the stability of tablets would be better than the stability of ampoules. The absence of stability data on tablets in both temperate and tropical climates meant that a stability study of oxytocic tablets under (simulated) tropical conditions was needed.

The aim of the investigation was to examine the stability of ergometrine, methyl-ergometrine, oxytocin and desamino-oxytocin tablets, in order to determine whether it would be feasible to replace the parenteral route of oxytocics by these drugs. The stability of the compounds was assessed by an experimental shelf-life methodology.

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The Ergot Task Group consists of A.N.J.A de Groot, Investigator; P.W.J. van Dongen, Gynaecologist; J. van Roosmalen, Gynaecologist; T.B. Vree, Chemist; and Y.A. Hekster, Clinical Pharmacist. The chemical analyses were carried out at the Laboratory of Clinical Pharmacy in Nijmegen by Mrs M. van den Biggelaar-Martea and Mrs A.M. Baars, Technicians, whose active and enthusiastic collaboration is very much appreciated. Statistical advice was given by G.F. Borm, Statistician at the Medical Statistics Department of the University of Nijmegen.

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MATERIALS AND METHODS

Definitions used in the study

Table I: Definitions used in the study

Stability: The ability of a drug to retain its properties within specified limits throughout its shelf-life. The following aspects of stability are to be considered: chemical, physical, microbiological and biopharmaceutical.

Shelf-life: The period of time during which a drug product is expected, if stored correctly, to remain within specifications as determined by stability studies on a number of batches of the product. The shelf-life is used to establish the expiry date of each batch.

Source: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Geneva: 1990; Tech Rep Series 790:30

Simulated tropical conditions

The design of this study followed the recommendations laid down in the "Protocol for research on the stability of drugs in aqueous solutions" by the Dutch Society of Hospital Pharmacists (19). Tropical conditions were simulated (Table II). Taking into account the known vulnerability of ergometrine and methylergometrine to exposure to light, all tablets were tested for light specific degradation (18).

Table II: Definitions of simulated tropical conditions

	Storage condition			Notation of conditions in text and figures
		Temperature	Relative humidity	
I	dark (D)	6-10°C	ambient: 83-85%	D6/83
II	dark (D)	20°C	75%	D20/75
III	dark (D)	30°C	45%	D30/45
IV	dark (D)	30°C	75%	D30/75
V	dark (D)	40°C	ambient: 12-28%	D40/25
VI	dark (D)	40°C	75%	D40/75
VII	light (L)	20-25°C; room temperature	ambient: 20-35%	L20/30

Materials

Tablets to be tested

The following products were examined:

- Ergometrine maleate 0.2 mg tablets BP88; 147mg free base;
- Methylergometrine maleate 0.125 mg coated tablets; 95mg free base;
- Buccal oxytocin tablets 200 IU;
- Buccal desamino-oxytocin tablets 50 IU.

Packaging of the drugs

Tablets were received in closed tins, the manufacturing dates were as recent as possible and the differences in production dates between the different brands as small as possible. Tablets were exposed to the test conditions in identical open containers covered by cottonwool. There were four tablets in each container, and a different container was used for each sampling period (week 0-52).

Oxytocin was received in air-tight, aluminium packages. These sealed packages were presumed to be light-resistant and unaffected by relative humidity. In these cases the temperature was the only parameter tested.

Number of batches and tablets examined

One batch per manufacturer was examined. To achieve acceptable statistical power, four tablets per storage condition per manufacturer were investigated. At week 0 and 52, 20 tablets per storage condition per manufacturer were tested.

Quality characteristics

Before analysing the tablets, weight, physical appearance and colour were determined.

Sampling intervals

A homogenous and sufficiently frequent sampling was undertaken during the year, to detect a trend in stability decrease. Loss of potency by water absorption had been expected to occur, especially in the beginning (8). Therefore, sampling was done more frequently at the beginning of the experiment. Eight different points in time were tested (19). These were: after 0, 3, 7, 14, 21, 31, 41 and 52 weeks exposure to specific storage.

Conditions of storage

Conditions of storage are summarized in Table II.

Assay method

Level of active ingredient was measured by High Performance/Pressure Liquid Chromatography (HPLC). This method can differentiate between the active principle and its degradation products. The Radio Immuno Assay, another assay method, is

unable to make this distinction. However, this latter method is more sensitive than the HPLC assay (15,21-27).

HPLC-conditions: ergometrine and methylergometrine

Column:	Spherisorb 5 ODS (250*4.6 mm) chrompack (Bergen op Zoom, Netherlands)
Mobile phase:	A = acetonitrile B = 0.067 M KH_2SO_4 : 0.05% diethylamine H_20 A = 60%; B = 40%; (1:1)
Wavelength:	UV: 240 nm
Flow:	1.2 ml/min
Injection volume:	100 ml
Retention time:	6.8 min
Reference solutions:	Freshly made before each new set of runs, with increasing concentrations from solution I to IV
Apparatus:	SP8800 ternary HPLC pump, a Spectra Physics UV detector 757 and an SP 4290 integrator (Spectra Physics)
Calibration curves	Ergometrine: r = 0.9999 Methylergometrine: r = 0.9999

Table III: Inter-day and intra-day coefficients of variation of (methyl)ergometrine in water

Compound		*Coefficient of variation (n =4/6) (%)*	
	Concentration of free base (mg/tablet)	Inter-day (n=4)	Intra-day (n=6)
Ergometrine	147	1.2	1.73
Methyl-ergometrine	95	2.2	5.07

HPLC-conditions: oxytocin and desamino-oxytocin

Column:	Spherisorb 5.0 ODS(250*4.6mm) chromopack
Mobile phase:	A: acetonitrile/H_2O 1:1 B: 0.1 M monobasicKH_2PO_4 buffer A = 55% ; B = 45%
Wavelength:	UV: 225 nm
Flow:	1.2 ml/min
Injection volume:	100 ml
Retention time:	6.7 min
Reference solutions:	Freshly made before each new set of runs, with increasing concentrations from solution I to IV.
Apparatus:	SP8800 ternary HPLC pump, a UV detector 757 and an SP 4290 integrator (Spectra Physics).
Calibration curves:	Oxytocin: r = 0.9999 Desamino-oxytocin: r = 0.9999

Table IV: Inter-day and intra-day coefficients of variation of desamino-oxytocin in water

Compound		*Coefficient of variation (n =4/6) (%)*	
	Concentration (IU/tablet)	Inter-day (n=4)	Intra-day (n=6)
Oxytocin	200	1.90	2.06
Desamino-oxytocin	50	3.19	1.96

Statistics

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

RESULTS

The results of the simulation study are given in Annexes 1-6. For each preparation the mean analytical results per condition are reported, with the standard deviation, coefficients of variation and the number examined.

At t=0, the initial amount of 20 tablets of each brand contained between 90-110% of the stated amount of the active ingredient and thus met BP requirements. The level of active ingredient, expressed as a percentage of the stated amount, is shown over time for each preparation and for all conditions (Annex 5). The main findings are illustrated in Annex 6, showing the level of active ingredient over time in the least (test I) and most harmful conditions (test VI) and after exposure to light. Results of the simulation studies of E and ME are given in Figures 1 to 3 and the results of OT and DOT in Figures 4-8.

Ergometrine (E)

The level of active ingredient in the product decreased over time under all conditions. Under refrigerated storage (D6/83) the level of active ingredient remained above 90% for 3 weeks. After that it no longer met pharmaceutical requirements. At D40/75 ergometrine was very unstable, with only 26.5% of the active ingredient left after 3 weeks, and 1% after 52 weeks of exposure (Figure 1).

The influence of humidity on stability is stronger than the influence of temperature (Figure 2). After 21 weeks at 30°C in darkness and 75%RH (D30/75), the product had only 24% of the stated amount of the active ingredient. Exposed to D40/25 for 52 weeks, 44.9% of the stated amount of active ingredient remained. The influence of light seems less harmful than that of humidity (Figure 3).

Methylergometrine (ME)

The level of active ingredient in the product declined under all conditions over time. After 21 weeks under refrigerated storage (D6/83), the level of active ingredient fell below 90%. After 21 weeks at D40/75, only 63.2% of the active ingredient remained, and only 50% after 52 weeks of exposure (Figure 1).

The influence of humidity on stability was stronger than the influence of temperature (Figure 2). After 21 weeks at D30/75 the product had 64.2% of the stated amount of the active ingredient left. At 52 weeks at D40/25, 51.6% of the active ingredient was left.

In all conditions the stability of uncoated E tablets was far less than that of the coated ME tablets. Instability increased under extreme humid conditions (D30/75 or D40/75), and hot conditions (D40/25), for both E and ME. From week 31 onwards the coating no longer seems to protect the compound for stability. This seems to be the case more or less independent of the exposure condition (Figures 1,2).

Oxytocin (OT)

The level of active ingredient in the product declined gradually under all conditions over time. Under refrigerated storage (D6/83) the level of active ingredient remained above 90% for 23 weeks. After that period it fell below this level. At D40/75, OT was less stable, with only 89.4% of the stated amount of the active ingredient left after 14 weeks (Figure 4).

The influence of humidity on stability is stronger than the influence of temperature (Figure 5). At D30/75 the product had only 41.2% of the stated amount of the active ingredient left after 33 weeks. At D40/25, 78.4% of the stated amount of active ingredient was left after 52 weeks. The influence of light seems less harmful than that of humidity (Figure 6). Exposed to light 85% of the stated amount of active ingredient was still left after 52 weeks, whereas after 3 weeks at D20/75 only 85.4% of the stated amount of active ingredient remained. Figure 7 shows the effect of aluminium sealed packages on the level of active ingredient at D30/75.

Desamino-oxytocin (DOT)

The level of active ingredient in the product declined gradually over time under all conditions. In refrigerated storage (D6/83) the level of active ingredient remained above 90% for more than 14 weeks. After that period it fell below this. At D40/75 the product was less stable, with only 67.2% of the stated amount of the active ingredient left after 14 weeks (Figure 4).

The influence of humidity on stability is stronger than the influence of temperature (Figure 5). At D30/75 the product had only 37.2% of the stated amount of the active ingredient left after 33 weeks. At D40/25, 60.9% of the stated amount of active ingredient was left after 52 weeks. For all conditions (except test III) OT was more stable than DOT (Figures 5,6).

Discoloration occurred in tablets, especially stored under humid conditions. Growth of micro-organisms on tablets stored under humid conditions (tests II, IV and VI) was observed. The micro-organisms (moulds) were not analysed.

DISCUSSION

Materials and methods

Simulated tropical conditions

The methods in the protocol "Protocol of the research of the stability of drugs in aqueous solutions" by the Dutch Society of Hospital Pharmacists (19) were adapted and used to serve the objectives of the study. Tropical conditions were simulated, paying attention to the effect of humidity, temperature and light on the concentration of the active ingredient (Table II).

Definitions of these simulated tropical conditions were derived from data from the literature (16,17,28). Hartmann (17) has formulated generally accepted test conditions (calculated storage conditions) to "define" a **climatic** zone. From these data and data from Bos (8) we defined our calculated storage conditions (Table V), which formed the base for the simulated tropical conditions that were actually used (Table II).

Table V: Calculated storage conditions for worldwide stability testing

Temperature °C	Relative humidity (RH %)	Intended for:
4°C	ambient	refrigerator
20°C	60-65%	temperate climate
30°C	<65% >65%	hot and dry climate hot and humid climate
40°C	<40%	recognition of critical quality characteristics, special storage instructions
50°C	<20%	recognition of critical quality characteristics (short-term experiments)

Materials

Drug stability is dependent on many product-related factors (29,30), i.e. the active ingredient, the excipients, the dosage form, the manufacturing process and the nature of the packaging. We chose those manufacturers whose products are actually most widely available in developing countries. ME has been included in our investigation because of the claims that it shows less hypertensive side-effects and less influence on postpartum prolactin levels (31,32). It is as cheap as E. The choice of the manufacturer was based on availability. Although E and ME are being produced on "market demand", in practice they are produced only once a year. More than one freshly produced batch from different manufacturers was therefore unavailable. Comparison

between different brands has therefore not been possible in this study, as Hogerzeil et al (13) had recommended.

Buccal OT tablets have been withdrawn from the market, as greater control was achieved by intravenous or intramuscular administrations of oxytocin, and because buccal absorption had been unpredictable (33). Despite unfavourable pharmacokinetic data (33-37), we still considered it useful to examine whether buccal oxytocin would be an acceptable, non-parenteral prophylactic oxytocic. The pharmacokinetic studies mentioned had been small and not fully convincing in discouraging its use as an alternative non-parenteral oxytocic for active management of the third stage of labour. As buccal oxytocin tablets have been withdrawn from the market, we were fortunate to be able to import samples of OT and DOT. Because the products are no longer manufactured, we could obtain just one brand of both.

Degradation of active ingredient

To assess their stability under tropical climates, we examined tablets for content of active ingredient (29,30). The efficacy of a product may decrease over time, due to degradation of the active ingredient. Loss of potency usually results from a chemical change (38,39). In this study attention was mainly paid to chemical stability.

Sampling points in time

Long-term stability studies in "temperate climate" conditions normally last for five years (17). The tablets in this study were subjected to more extreme conditions. A shorter period of investigation was accepted, as deterioration of tablet quality would probably appear sooner. Therefore, the stability test was performed for a period of only one year. It was assumed that no additional information would be obtained from longer testing, and in any case such tablets are normally used within a year in tropical countries.

Results

Ergometrine and methylergometrine

When stored at D6/83, ergometrine and methylergometrine were not stable and contained less than 90% of the active ingredient within 7 and 21 weeks, respectively. D6/83 is the least harmful condition, although the high humidity factor must be taken into consideration. Packed in a closed tin and stored in a refrigerator, the humidity will be lower and stability probably better. Still, the results are alarming, indicating that storage is such a critical factor that these tablets are in no way suitable for use under (primitive) tropical conditions.

Improvement in stability might be obtained by protecting the tablets from humidity by coating or special packaging, as humidity seems a more harmful factor in the process than temperature. The influence of light is not so striking as for the ampoules (13).

A remarkable difference between the results of E and ME occurs. Under extreme conditions the active ingredient of E quickly reduces to levels below 50% of the stated

amount and finally falls to below 1% (at D40/75), whereas the active ingredient of ME, even at D40/75, does not fall below 45%. Probably ME is converted into a metabolite, which is not separately measured by HPLC. It is known that in an alkaline (methanol) environment E and ME can be converted into their inactive enantiomer: (methyl) ergometrinin. In E and ME ampoules that vulnerability to an alkaline environment has been avoided by dissolving the compound in an acid solution (pH = 1-2). The fact that injectable E and ME are not sensitive to environmental pH-changes (while tablets are prone to these changes) might be one of the factors that unexpectedly makes the stability of E and ME tablets even worse than that of the ampoules.

Buccal oxytocin and desamino-oxytocin

As the stability results show, OT and DOT are more stable than E and ME. However, within ± 23 weeks, both products show levels of the active ingredient below 90%. This is too quickly for use in tropical countries, considering that transportation and intermediate storage alone may take several weeks. The negative influence of humidity seems stronger than that of high temperature.

Because of their observed instability under tropical conditions, buccal OT and DOT tablets cannot be considered as an alternative for PPH prevention either. Moreover, their route of administration may pose several problems. Data on their pharmacokinetics when used for preventing PPH are still far from adequate.

CONCLUSIONS AND RECOMMENDATIONS

Oral ergometrine (E) and methylergometrine (ME) tablets and buccal oxytocin (OT) and desamino-oxytocin (DOT) tablets are not stable under simulated tropical conditions, and are therefore not suitable for use in the prevention of PPH in tropical climates. It is unlikely that the serious instability of E and ME under simulated tropical conditions can be improved by a different formulation. Moreover, pharmacokinetic data on buccal OT and DOT seem far from reliable (40). Pharmacokinetic studies on buccal OT and DOT (33-37) and the data obtained in this study on their stability do not justify efforts to improve their stability.

Injectable oxytocin therefore remains the best choice of oxytocic for prophylactic use in the prevention of PPH, although its intramuscular route of administration is not ideal. Investigation of the possibility of formulating and manufacturing a stable non-injectable alternative to oxytocin is recommended.

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ANNEXES

Annex 1: Ergometrine 0.2 mg tablets

Stated amount: 147µg free base ergometrine (= 100%)

test I: D6/83

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.142	96.6	0.008	5.6	20
3	0.148	100.7	0.014	9.5	4
7	0.125	85.1	0.005	4.0	4
14	0.130	88.4	0.005	3.8	4
21	0.096	65.3	0.002	2.1	4
30	0.096	65.3	0.003	3.1	4
40	0.085	57.8	0.002	2.4	4
52	0.079	53.7	0.004	5.1	16

test II: D20/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.142	96.6	0.008	5.6	20
3	0.104	70.7	0.022	21.1	4
7	0.108	73.5	0.002	1.9	4
14	0.095	64.6	0.008	8.4	4
21	0.049	33.3	0.003	6.1	4
30	0.045	30.6	0.002	4.4	4
40	0.032	15.3	0.001	3.1	4
52	0.023	15.6	0.002	8.7	20

test III: D30/45

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.142	96.6	0.008	5.6	20
3	0.093	63.3	0.014	15.1	4
7	0.120	81.6	0.008	6.7	4
14	0.099	67.3	0.001	1.0	4
21	0.074	50.3	0.003	4.1	4
30	0.067	45.6	0.003	4.5	4
40	0.059	40.1	0.000	0	2
52	0.054	36.7	0.003	5.6	20

Ergometrine 0.2 mg tablets

test IV: D30/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.142	96.6	0.008	5.6	20
3	0.124	84.4	0.013	10.5	4
7	0.084	57.1	0.005	8.5	4
14	0.058	39.5	0.004	6.9	4
21	0.034	23.1	0.002	5.9	4
30	0.031	21.1	0.002	6.5	4
40	0.019	12.9	0.001	5.3	3
52	0.013	8.8	0.002	15.4	20

test V: D40/25

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.142	96.6	0.008	5.6	20
3	0.095	64.4	0.012	12.6	4
7	0.113	76.9	0.010	8.8	4
14	0.102	69.4	0.003	2.9	4
21	0.078	53.1	0.005	6.4	4
30	0.077	52.4	0.005	6.5	4
40	0.074	50.3	0.001	1.4	4
52	0.066	44.9	0.010	15.0	20

test VI: D40/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.142	96.6	0.008	5.6	20
3	0.039	26.5	0.008	20.5	4
7	0.018	12.2	0.006	33.3	4
14	0.005	3.4	0.001	20	4
21	0.002	1.4	0.000	0	4
30	0.001	0.7	0.000	0	4
40	0.002	1.4	0.000	0	4
52	0.001	0.7	0.001	100	8

Ergometrine 0.2 mg tablets

test VII: L 20/30

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.142	96.6	0.008	5.6	20
3	0.090	61.2	0.010	11.1	4
7	0.095	64.6	0.008	8.4	4
14	0.077	52.4	0.009	11.7	4
21	0.073	49.7	0.006	8.2	4
30	0.073	49.7	0.003	4.1	4
40	0.068	46.3	0.002	2.9	4
52	0.065	44.2	0.003	4.6	18

Ergometrine 0.2 mg tablets

test VII: L 20/30; packed in aluminium foil

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.142	96.6			20
12	0.095	64.6			4
20	0.087	59.2			2
41	0.087	59.2			4

test VII: L20/30; packed in sealed poly ethylene

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
41	0.079	54.4			11

Annex 2: Methylergometrine 0.125 mg tablets

Stated amount: 95µg free base methylergometrine (= 100%)

test I: D6/83

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.089	93.7	0.008	9.0	20
3	0.093	97.9	0.009	9.7	4
7	0.093	97.9	0.003	3.2	4
14	0.090	94.7	0.001	1.1	4
21	0.088	92.6	0.003	3.4	4
30	0.050	52.6	0.002	4.0	4
40	0.055	57.9	0.004	7.3	4
52	0.056	58.9	0.003	5.4	11

test II: D20/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.089	93.7	0.003	9.0	20
3	0.100	115.8	0.006	6.0	4
7	0.083	87.4	0.004	4.8	4
14	0.078	82.1	0.003	3.8	4
21	0.056	58.9	0.003	5.4	4
30	0.049	51.6	0.002	4.1	4
40	0.053	55.8	0.001	1.9	4
52	0.054	56.8	0.004	7.4	12

test III: D30/45

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.089	93.7	0.008	9.0	20
3	0.089	93.7	0.007	7.9	4
7	0.072	85.2	0.013	18.1	4
14	0.059	62.1	0.001	1.7	4
21	0.042	44.2	0.002	4.8	4
30	0.046	48.4	0.001	2.2	4
40	0.056	58.9	0.001	1.8	4
52	0.050	52.6	0.003	6.0	12

Methylergometrine 0.125 mg tablets

test IV: D30/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	0.089	93.7	0.008	9.0	20
3	0.079	83.2	0.009	11.4	4
7	0.075	78.9	0.005	6.7	4
14	0.077	81.1	0.001	1.3	4
21	0.061	64.2	0.001	1.6	4
30	0.047	49.5	0.000	0	4
40	0.053	55.8	0.001	1.9	4
52	0.047	49.5	0.003	6.4	12

test V: D40/25

time (weeks)	mean conc/tablet HPLC	% HPLC	SD	SD/mean x100% CV%	n
0	0.089	93.7	0.008	9.0	20
3	0.093	97.9	0.008	8.6	4
7	0.090	94.7	0.004	4.4	4
14	0.091	95.8	0.001	1.1	4
21	0.076	80.0	0.004	5.3	4
30	0.046	48.4	0.002	4.3	4
40	0.052	54.7	0.000	0	4
52	0.049	51.6	0.002	4.1	12

test VI: D40/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/GEM x100% CV%	n
0	0.089	93.7	0.008	9.0	20
3	0.084	88.4	0.013	15.5	4
7	0.083	87.4	0.004	4.8	4
14	0.083	87.4	0.004	4.8	4
21	0.060	63.2	0.003	5.0	4
30	0.044	46.3	0.003	6.8	4
40	0.046	48.0	0.002	4.3	4
52	0.040	42.1	0.002	5.0	12

Methylergometrine 0.125 mg tablets

test VII: L20/30

time (weeks)	mean conc/tablet HPLC	% HPLC	SD	SD/mean x100% CV%	n
0	0.089	93.7	0.008	9.0	20
3	0.097	102.1	0.003	3.1	4
7	0.072	75.8	0.006	8.3	4
14	0.081	85.3	0.001	1.2	4
21	0.061	64.2	0.003	4.9	4
30	0.048	50.5	0.001	2.1	4
40	0.054	56.8	0.002	3.7	4
52	0.054	56.8	0.002	3.7	12

Methylergometrine 0.125 mg tablets

test III: D30/45; packed in aluminium foil

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
12	0.042	44.2			7
41	0.062	65.3			12

test IV: D30/75; packed in aluminium foil

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/GEM x100% CV%	n
12	0.049	51.6			8
41	0.060	63.2			12

test V: D40/25; packed in aluminium foil

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
20	0.049	51.6			4

test VI: D40/75; packed in aluminium foil

tijd (wkn)	gem. HPLC abs	% HPLC	SD	SD/GEM x100%	n
12	0.047	49.5			8
20	0.044	46.3			6

test VII: L20/30; packed in aluminium foil

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
12	0.051	53.7			8
41	0.052	54.7			6

test VII: L20/30; packed in sealed poly-ethylene

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
41	0.057	60.0			24

Annex 3: Buccal oxytocin 200 IU

Stated amount: 200 IU oxytocin (= 100%)

test I: D6/83

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	227.125	113.6	39.854	17.5	4
7	217.825	108.9	15.956	7.3	4
14	195.500	97.8	2.858	1.5	4
23	197.550	98.8	3.077	1.6	4
33	164.050	82.0	4.397	2.7	4
45	158.825	79.4	3.144	2.0	4
53	164.988	82.5	4.618	2.8	20

test II: D20/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	170.825	85.4	2.952	1.7	4
7	105.675	52.8	9.064	8.6	4
14	197.727	98.9	3.23	1.63	4
23	35.000	17.5	2.899	8.3	4
33	3.743	1.9	0.217	5.8	4
45	1.637	0.8	0.091	5.6	4
53	3.062	1.5	0.911	29.7	4

test III: D30/45

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	203.033	101.5	2.914	1.4	3
7	208.725	104.4	16.201	7.8	4
23	2.393	1.2	0.230	9.6	3
33	6.903	3.5	9.732	14.1	4
45	2.023	1.0	0.136	6.7	4
72	124.000	62.0	13.966	11.3	16

Buccal oxytocin 200 IU

test III: D30/45; packed in sealed aluminium package

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	202.600	101.3	8.675	4.3	4
14	194.738	97.4	7.636	3.9	4
23	197.965	99.0	3.183	1.6	4
33	160.725	80.4	3.235	2.0	4
45	157.675	78.8	0.855	0.5	4
72	159.142	79.6	8.024	5.04	12

test IV: D30/75; no package

time (weeks)	mean conc/tablet HPLC	% HPLC	SD	SD/mean x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	188.4750	94.2	12.048	6.4	4
7	190.850	95.4	8.368	4.4	4
14	151.283	75.6	8.982	5.9	4
23	128.478	64.2	9.041	7.0	4
33	82.338	41.2	1.971	2.4	4
45	67.420	33.7	1.137	1.7	4
53	65.045	32.5	2.802	4.3	20

test IV: D30/75; packed in sealed aluminium package

time (weeks)	mean conc/tablet HPLC	% HPLC	SD	SD/mean x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	188.900	94.4	10.280	5.4	4
7	196.825	98.4	13.909	7.1	4
14	205.665	102.8	9.318	4.5	4
23	198.843	99.4	1.607	0.8	4
33	161.450	80.7	2.475	1.5	4
45	104.568	52.3	66.613	63.7	4
53	132.709	66.4	56.711	42.7	19

Buccal oxytocin 200 IU

test V: D40/25; no package

time (weeks)	mean conc/tablet HPLC	% HPLC	SD	SD/GEM x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	201.500	100.8	14.332	7.1	4
7	204.375	102.2	19.652	9.6	4
14	142.405	71.2	7.383	5.2	4
23	144.735	72.4	5.898	4.1	4
33	163.725	81.9	4.757	2.9	4
45	162.723	81.4	1.764	1.1	4
53	165.593	82.8	3.497	2.1	20

test V: D40/25; packed in sealed aluminium package

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	191.550	95.8	3.541	1.8	4
7	187.2	93.6	2.462	1.3	4
14	207.210	103.6	7.130	3.4	4
23	208.110	104.6	4.998	2.4	4
33	117.975	59.0	2.849	2.4	4
45	139.170	69.6	24.271	17.4	4
53	120.069	60.1	1.983	1.7	8
72	121.925	61.0	19.227	15.8	12

test VI: D40/75; no package

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	204.625	102.3	29.545	14.4	4
7	206.850	103.4	7.824	3.8	4
14	178.805	89.4	2.858	1.6	4
23	164.075	82.0	4.347	2.6	4
33	127.325	63.7	2.934	2.3	4
45	128.430	64.2	4.036	3.1	4
53	2.927	1.5	0.120	4.1	13

Buccal oxytocin 200 IU

test VII: L20/30; no package

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	211.135	105.6	17.070	8.1	20
3	227.775	113.9	14.973	6.6	4
7	210.650	105.3	4.812	2.3	4
14	176.904	88.5	19.563	11.1	5
23	185.740	92.9	3.833	2.1	4
33	175.650	87.8	4.608	2.6	4
45	174.958	87.5	1.763	1.0	4
53	169.960	85.0	4.960	2.9	20

Annex 4: Buccal desamino-oxytocin, 50 IU

Stated amount: 50 IU (= 100%)

test I: D6/83

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	49.887	99.7	5.272	10.6	20
3	49.050	98.1	0.901	1.8	3
7	49.671	99.3	2.449	4.9	8
14	48.968	97.9	1.117	2.3	4
23	44.725	89.5	0.746	1.7	4
33	27.55	55.1	2.623	9.5	9
45	29.5	59.0	1.103	3.7	6
53	25.667	51.3	0.945	3.7	3

test II: D20/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	49.887	99.7	5.272	10.6	20
3	45.253	90.5	6.474	14.3	3
14	47.765	95.5	3.638	7.6	4
23	46.9	93.8	1.952	4.2	4
33	7.020	14.0	4.530	64.5	5
45	1.625	3.2	0.417	25.6	4
53	0.563	1.1	0.302	53.6	15

test III: D30/45

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	49.887	99.7	5.272	10.6	20
3	42.007	84.0	2.506	6.0	3
7	43.088	86.2	1.915	4.4	4
14	44.357	88.7	4.636	10.5	3
23	44.29	88.6	3.741	8.4	4
33	22.958	45.9	2.188	9.5	6
45	21.918	43.8	1.342	6.1	11
72	19.421	38.8	1.321	6.8	19

Buccal desamino-oxytocin, 50 IU

test IV: D30/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	49.887	99.7	5.272	10.6	20
3	44.90	89.8	6.42	14	3
7	46.538	93.1	3.708	7.9	4
14	37.578	75.2	2.820	7.5	4
23	35.590	71.2	8.334	23.4	4
33	18.608	37.2	1.346	7.2	6
45	19.008	38.0	0.797	4.2	6
53	18.163	36.3	1.040	5.7	16

test V: D40/25

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	49.887	99.7	5.272	10.6	20
3	47.990	96.0	5.141	10.7	3
7	49.963	99.9	0.883	1.8	4
14	36.405	72.8	8.302	22.8	4
23	39.373	78.7	1.783	4.5	4
33	30.925	61.9	2.513	8.1	6
45	31.392	62.8	2.207	7.0	6
53	30.454	60.9	1.582	5.2	12
72	30.348	60.7	1.793	5.9	9

test VI: D40/75

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	49.887	99.7	5.272	10.6	20
3	41.000	82.0	8.516	20.7	3
7	43.250	86.5	2.412	5.6	4
14	33.608	67.2	3.384	10.1	4
23	29.615	59.2	2.282	7.7	4
33	10.500	21	0.711	6.8	6
45	8.100	16.2	0.304	3.8	3
53	6.887	13.8	0.529	7.7	15

Buccal desamino-oxytocin, 50 IU

test VII: L20/30

time (weeks)	mean conc/tablet (HPLC)	% HPLC	SD	SD/mean x100% CV%	n
0	49.887	99.7	5.272	10.6	20
3	48.707	97.4	2.394	4.9	3
7	47.7	95.4	1.863	3.9	4
14	39.21	78.4	1.521	3.9	4
23	41.15	82.3	2.248	5.5	4
33	31.367	62.7	2.513	8.0	6
45	29.387	58.8	1.801	6.1	12
53	27.786	55.6	2.098	7.6	18

Annex 5: Summary of results

Stability of oral ergometrine 0.2 mg

test:	I D6/83	II D20/75	III D30/45	IV D3075	V D40/25	VI D4075	VII L
time (weeks):							
0	100	100	100	100	100	100	100
3	104.2	73.2	65.5	87.3	66.9	27.5	63.4
7	88.0	76.1	71.8	59.2	79.6	12.7	67.0
14	91.5	66.9	69.7	40.8	71.8	3.5	54.2
21	67.6	34.5	52	23.9	54.9	1.4	51.4
30	67.6	31.7	47.2	21.8	54.2	0.7	51.4
40	59.9	22.5	41.5	13.4	52.1	1.4	47.9
52	55.6	16.2	38.0	9.2	46.5	0.7	45.8

Stability of oral methylergometrine 0.125 mg

test:	I D6/83	II D20/75	III D30/45	IV D30/75	V D40/25	VI D40/75	VII L
time (weeks):							
0	100	100	100	100	100	100	100
3	104.5	112.3	100	88.8	104.5	94.4	109
7	104.5	93.3	80.9	84.3	101.1	93.3	80.9
14	101.1	87.6	66.3	86.5	102.2	93.3	91.0
21	99.0	62.9	47.2	68.5	85.4	67.4	68.5
30	56.2	55.1	51.7	52.8	51.7	49.4	53.9
40	61.8	59.6	62.9	59.6	58.4	51.7	60.7
52	62.9	60.7	56.2	53.2	55.5	44.9	60.7

Stability of buccal oxytocin 200 IU (no package)

test:	I D6/83	II D20/75	III D3045	IV D3075	V D40/25	VI D40/75	VII L
time (weeks):							
0	100	100	100	100	100	100	100
3	107.6	80.9	96.2	89.2	95.4	96.9	107.9
7	95.9	-	98.8	90.4	96.8	97.9	99.8
14	92.6	93.6	-	71.6	67.5	84.7	83.8
23	93.5	16.6	1.1	60.8	68.8	77.7	88.0
33	77.7	1.7	3.3	39.0	77.5	60.3	83.2
45	75.2	0.7	0.9	31.9	77.0	60.8	82.9
53	78.2	1.5	-	30.8	78.4	1.4	80.5
72	-	-	58.7	-	-	-	-

Stability of buccal desamino-oxytocin 50 IU

test:	I D6/83	II D20/75	III D30/45	IV D30/75	V D40/25	VI D40/75	VII L
time (weeks):							
0	100	100	100	100	100	100	100
3	98.3	90.7	84.2	89	96.2	82	97.6
7	99.6	-	86.4	93.3	100.1	86.7	95.6
14	98.1	95.7	88.9	75.3	73.0	67.3	78.6
23	89.7	94	88.8	71.3	78.9	59.4	82.3
33	55.2	14	46.0	37.3	62.0	21.0	62.8
45	59.1	3.3	45.9	38.1	62.9	16.2	58.9
53	51.5	1.1	-	36.4	61	13.8	55.7
72	-	-	3.89	-	60.8	-	-

Stability of buccal oxytocin 200 IU, packed in sealed aluminium package

test:	III D30/45	IV D30/75	V D40/25
time (weeks):			
0	100	100	100
3	95.0	89	90.7
7	-	92.8	88.6
14	92.2	97	98.0
23	93.7	94.2	98.6
33	76.1	76.5	55.9
45	74.6	49.5	65.9
53	-	62.8	56.8
72	75.3	-	57.7

Annex 6: Figures 1 to 7

Figure 1

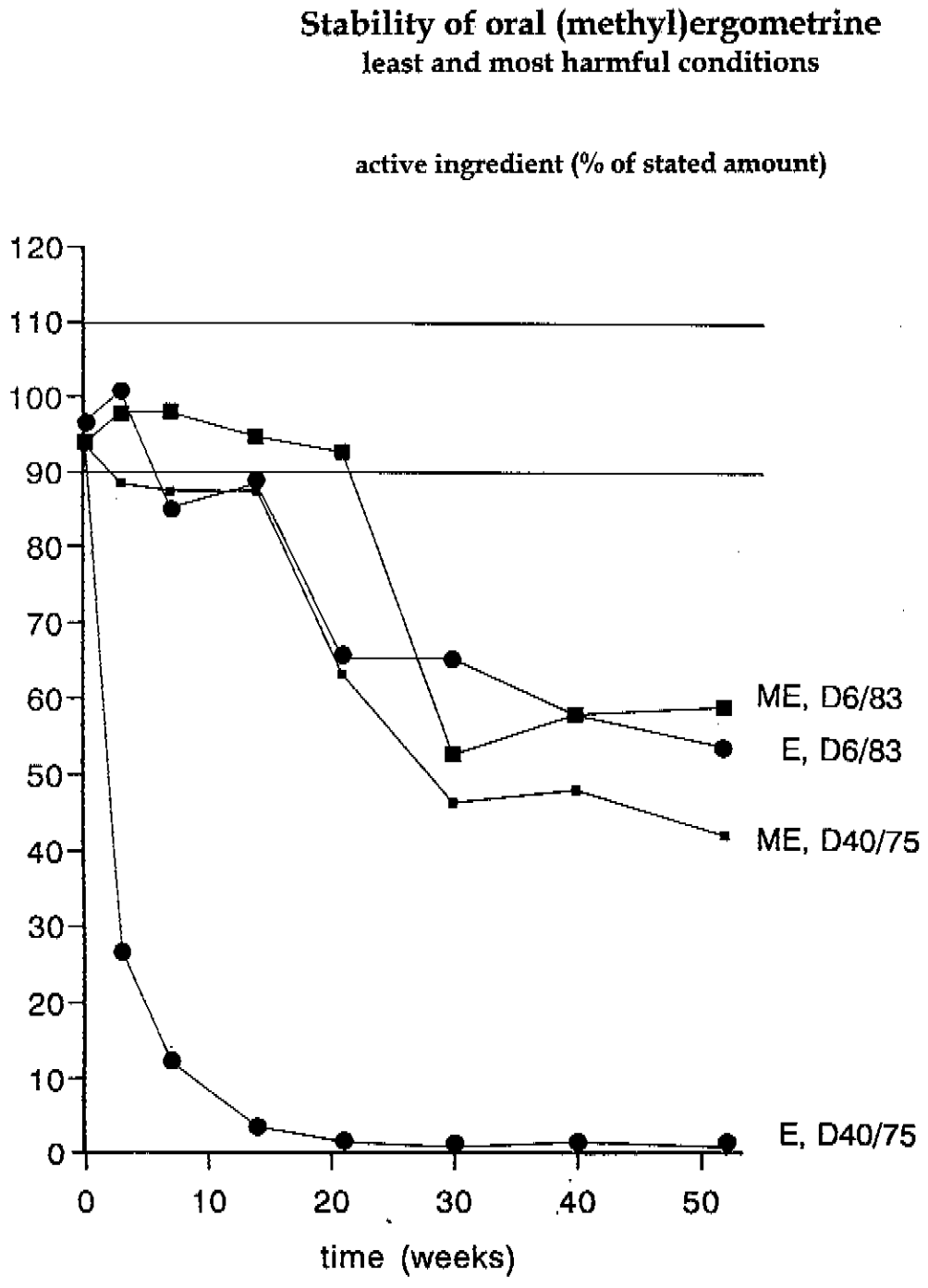


Figure 2

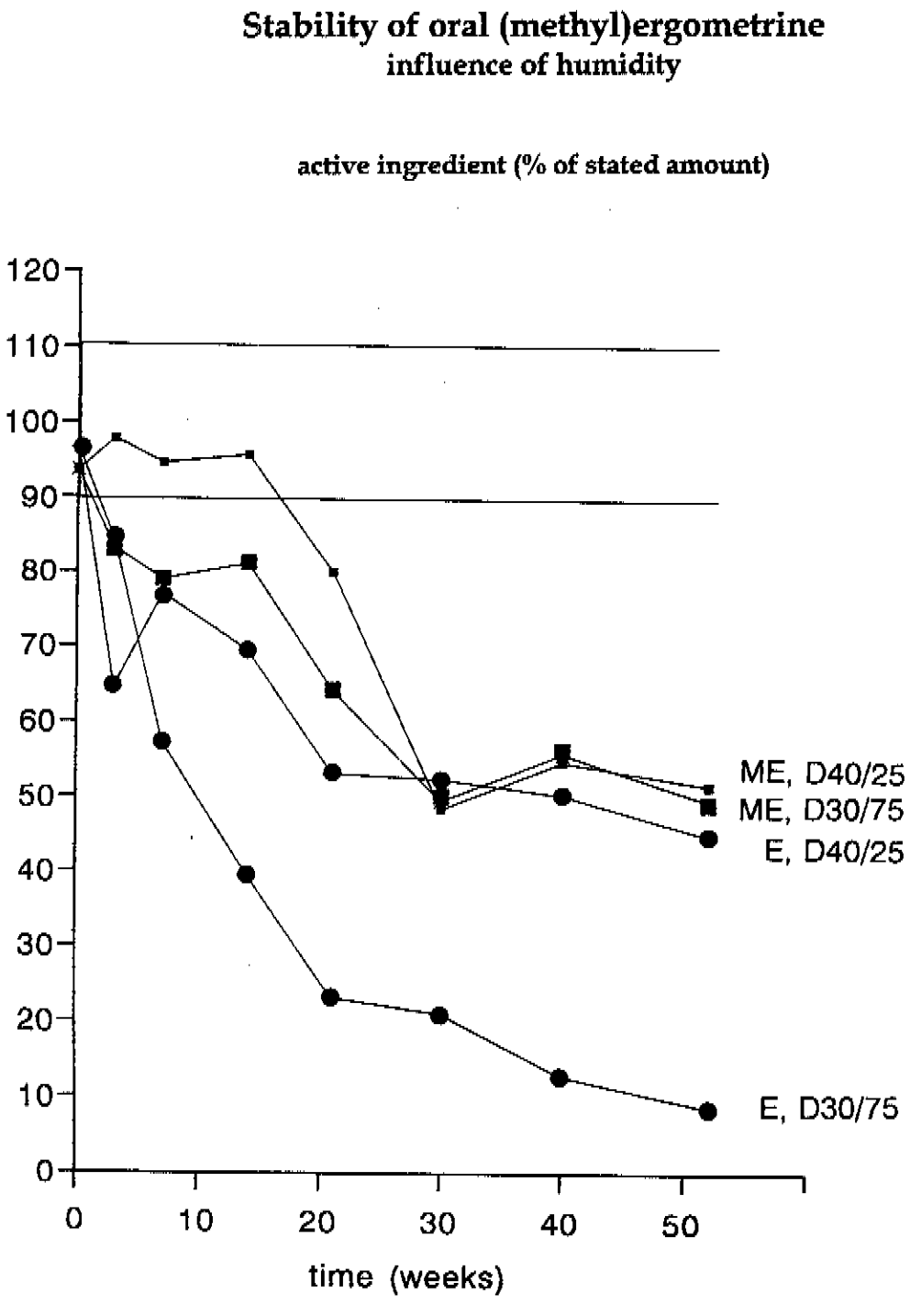

Stability of oral (methyl)ergometrine
influence of humidity
active ingredient (% of stated amount)
120
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
time (weeks)
ME, D40/25
ME, D30/75
E, D40/25
E, D30/75

Figure 3

Stability of oral (methyl)ergometrine
influence of light

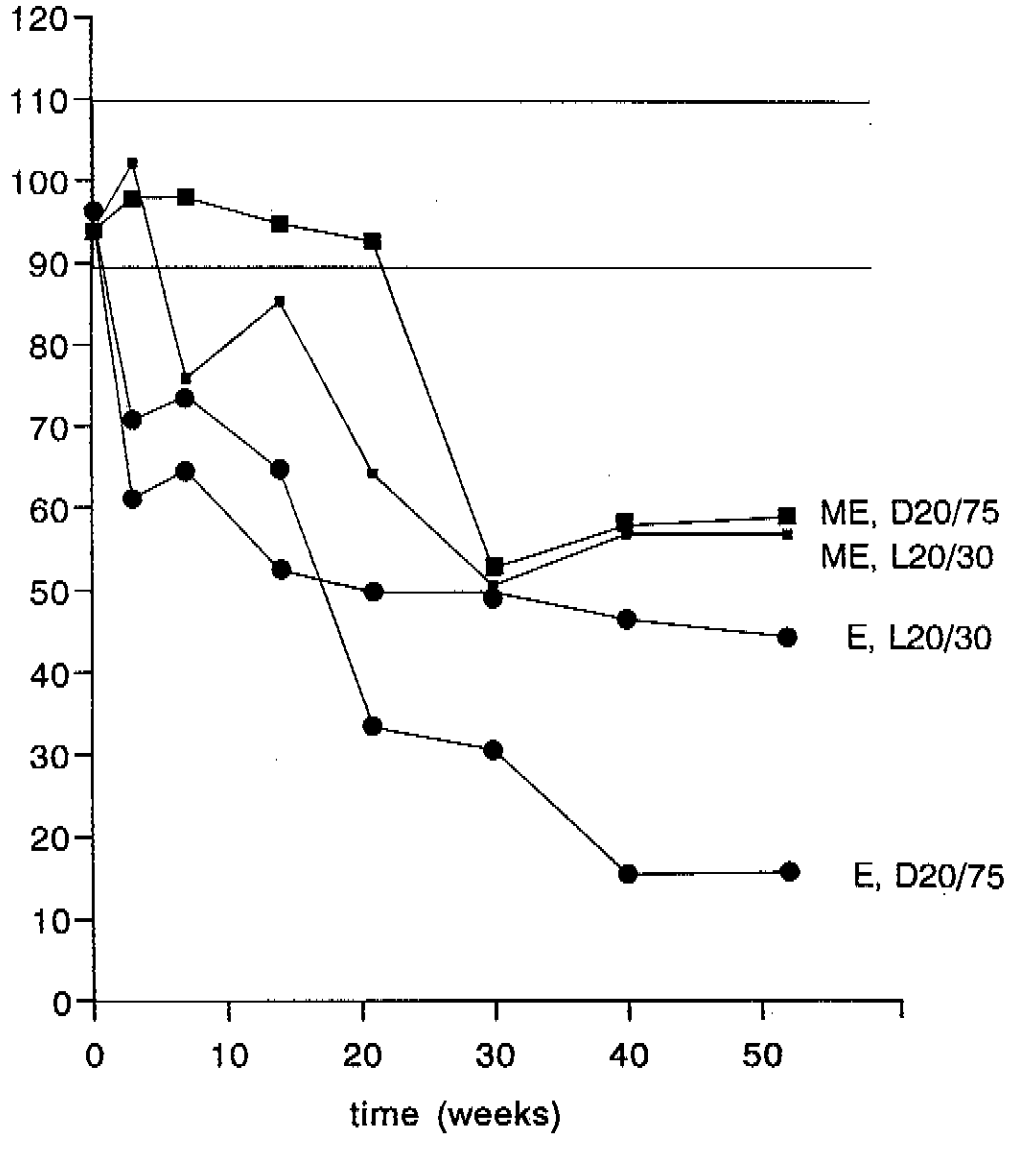


Figure 4

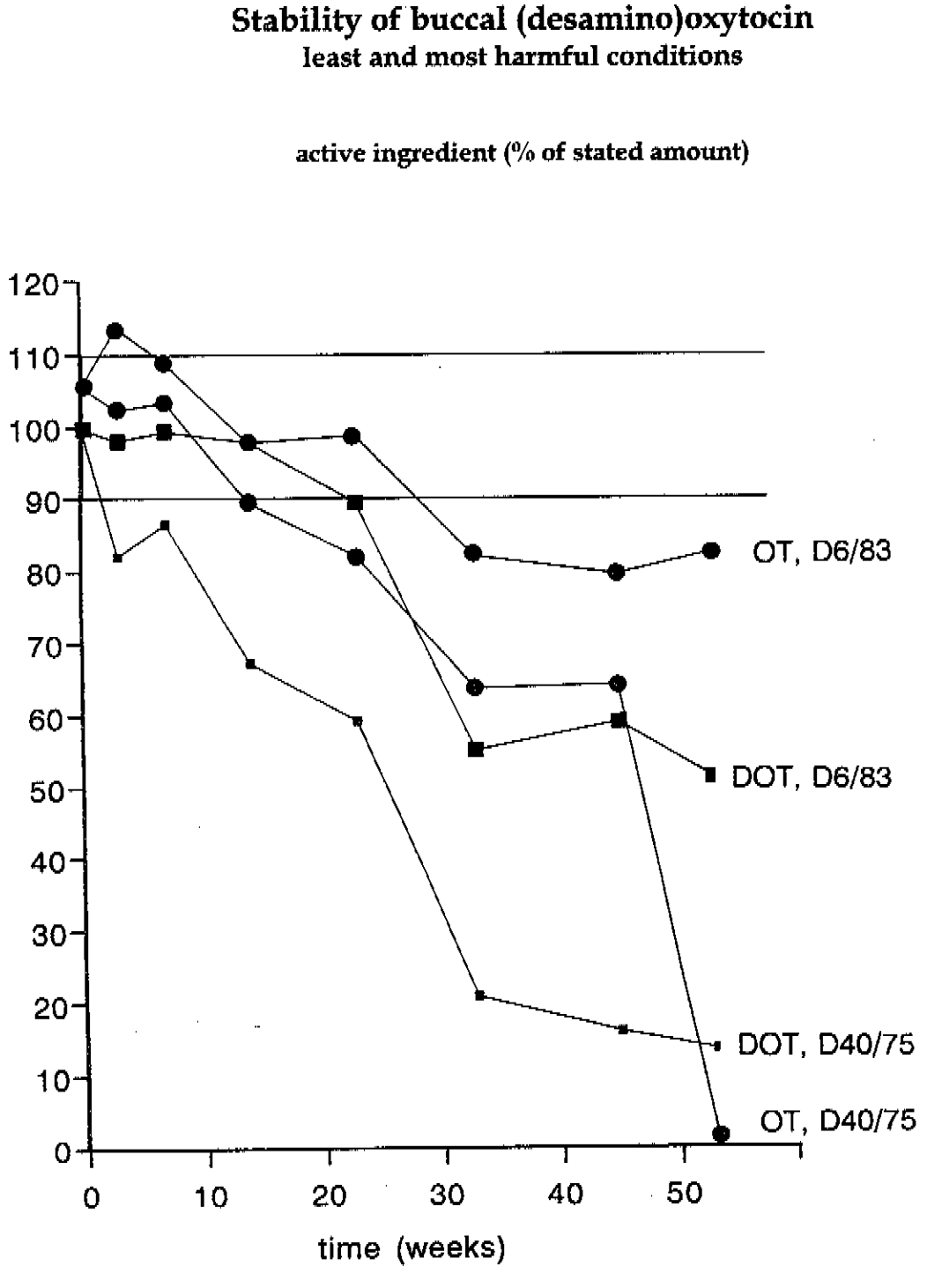

Stability of buccal (desamino)oxytocin
least and most harmful conditions
active ingredient (% of stated amount)
120
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
time (weeks)
OT, D6/83
DOT, D6/83
DOT, D40/75
OT, D40/75

Figure 5

Stability of buccal (desamino)oxytocin
influence of humidity

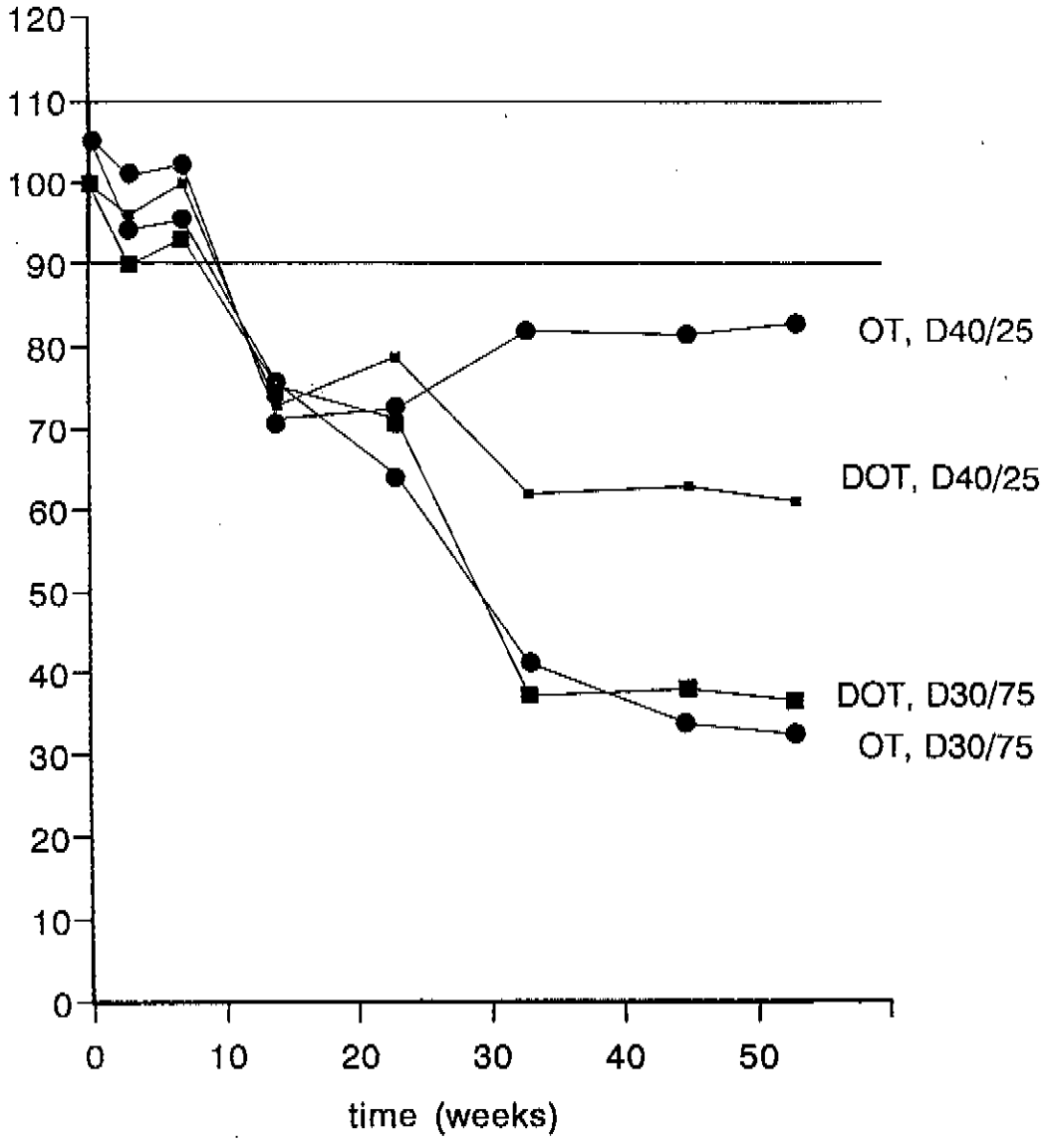


Figure 6

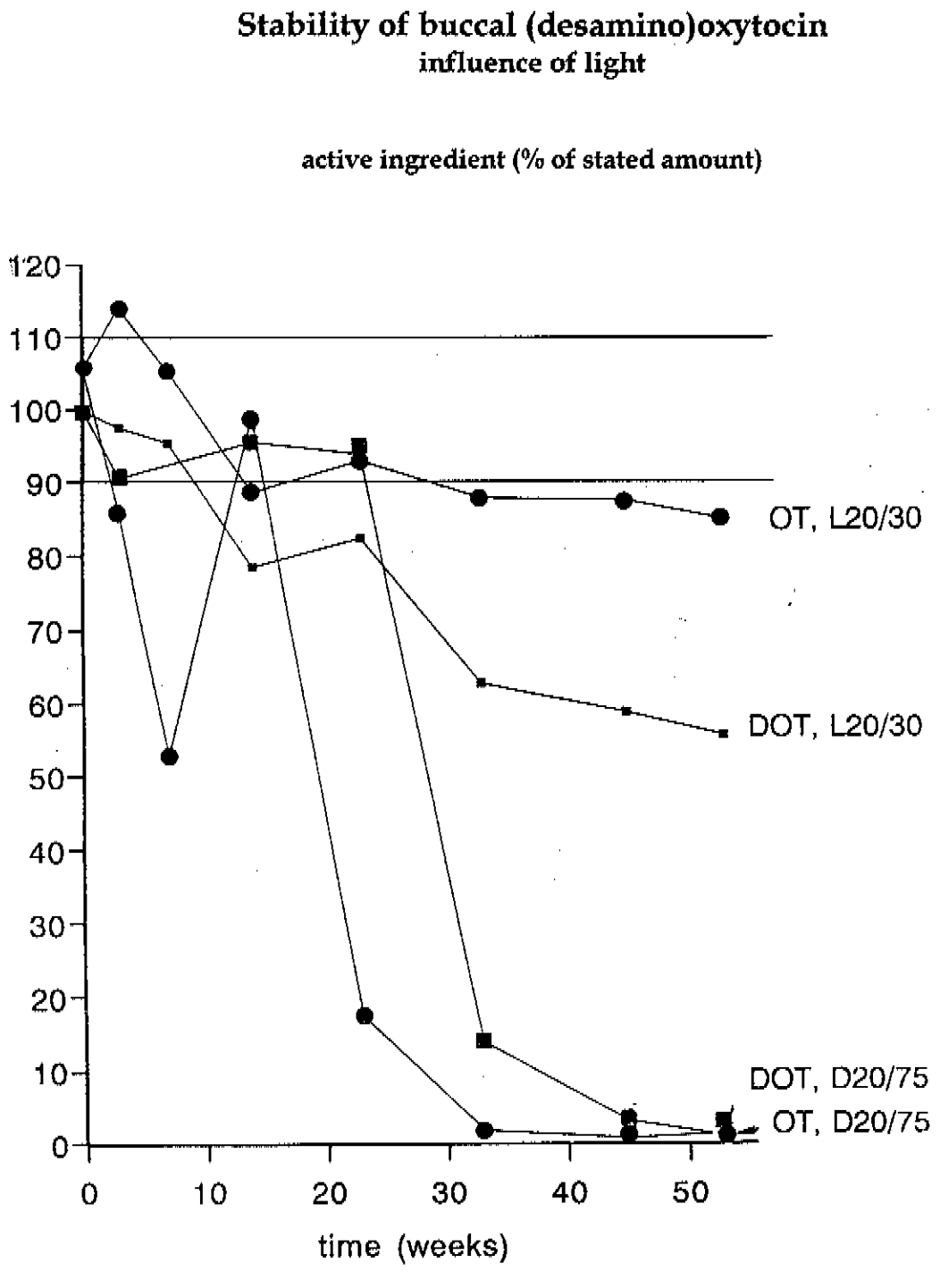
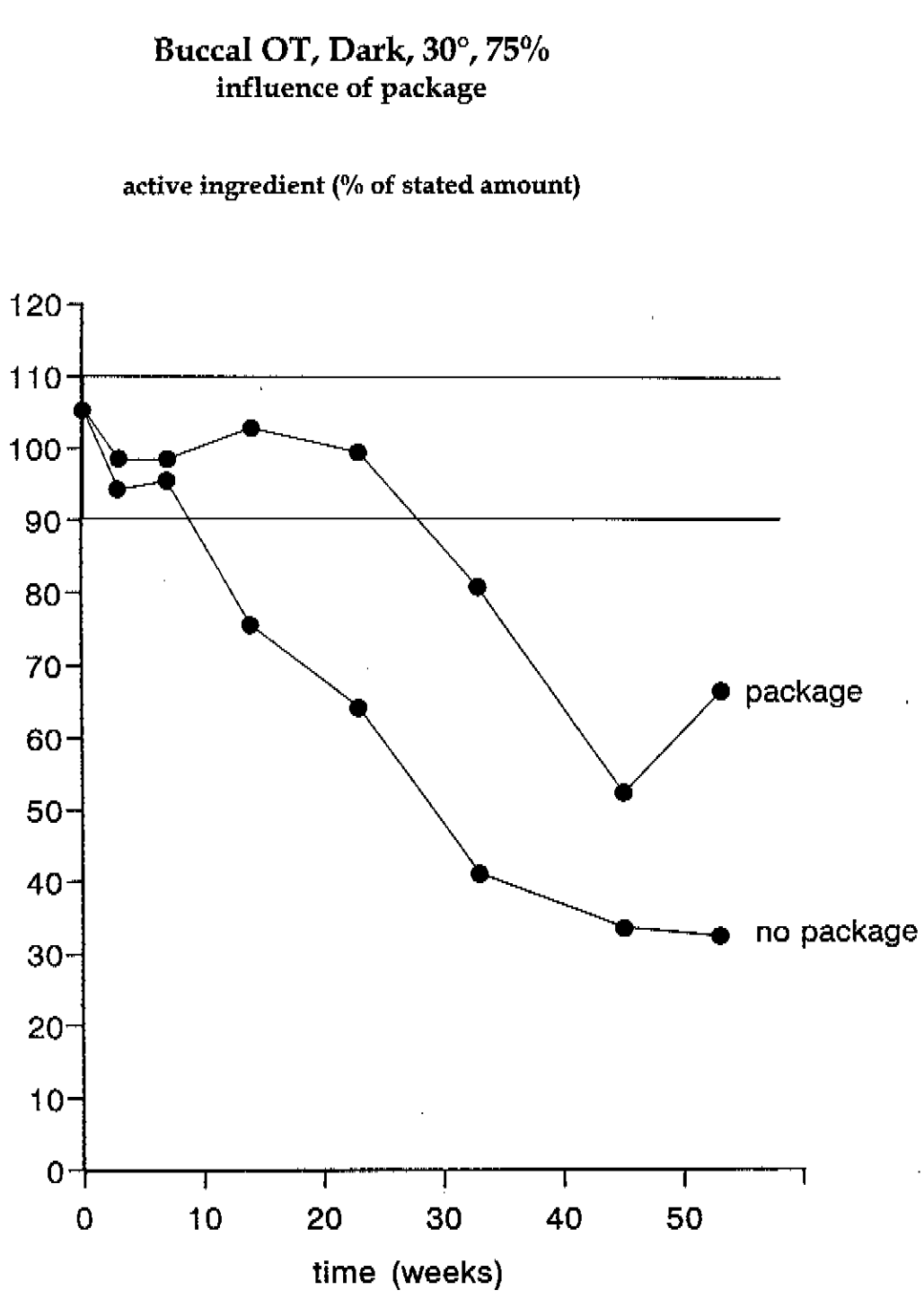

Stability of buccal (desamino)oxytocin
influence of light
active ingredient (% of stated amount)
120
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
time (weeks)
OT, L20/30
DOT, L20/30
DOT, D20/75
OT, D20/75

Figure 7


Buccal OT, Dark, 30°, 75%
influence of package
active ingredient (% of stated amount)
120
110
100
90
80
70
60
50
40
30
20
10
0
0
10
20
30
40
50
time (weeks)
package
no package

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☆ ☆ ☆

In 1981 WHO's Action Programme on Essential Drugs was established to provide operational support to countries in the development of national drug policies based on essential drugs and to work towards the rational use of drugs.

The Programme seeks to ensure that all people, wherever they may be, are able to obtain the drugs they need at a price that they and their country can afford; that these drugs are safe, effective and of good quality; and that they are prescribed and used rationally.

Research analysing the impediments to developing and managing sound national drug policies and programmes is an important element of country support activities. The Programme undertakes and promotes operational research aimed at filling some of the many gaps in existing knowledge about the best means of selecting, procuring and distributing drugs, and their use by prescribers and consumers.

This document is part of a series reporting on Action Programme research activities and guidelines.

Research that leads to breakthroughs in pharmaceutical technology or in highly sophisticated and expensive techniques of biomedical practice may superficially appear to be more "glamorous". But the operational research that WHO's Action Programme on Essential Drugs undertakes has a direct bearing on the ways in which vital medicines can be made available and accessible to the greatest number of people.

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