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Inland stability study (Sudan)

Pilot study 1989-1991

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Introduction

This pilot study was performed jointly by the WHO Action Programme on Essential Drugs, the International Dispensary Association (IDA) in Amsterdam, The Netherlands, and the Ministry of Health in Khartoum, Sudan. The objectives of the study were (1) to compare the potency and quality of some essential drugs after 16 months storage under extreme climatic conditions in Sudan, in comparison with reference samples; and (2) to pretest the stability of some essential drugs selected for a longitudinal study in the Sudan.

Materials and methods

Samples of essential drugs supplied by IDA to the Nile Province Essential Drugs Programme in Sudan were retrieved sixteen months later from three district hospitals in the area. Quality analysis was carried out both in the governmental drug quality control laboratory in Khartoum and in the IDA quality control laboratory. Test samples were compared with original batch samples kept by IDA since 1989.

Drugs were selected on the basis of an existing suspicion of instability under tropical conditions, high turnover in the essential drugs programme, and medical relevance.

Shipment and transport record

29 May 1989	Sea container leaves Amsterdam to Port Sudan
July 1989	Containers arrive in Port Sudan; remain in port area for eight months, of which the first three months in very high temperatures (> 50°C) but with low relative humidity (RH<30%).
Febr 1990	Containers transported to CMS/Khartoum
Apr-Jun 1990	Drug kits are distributed from Khartoum to several hospitals in the Nile Province; in this period the temperatures are again high (40-48°C) with 80% RH.
Aug 1990	Samples collected from three district hospitals in Nile Province and sent to Khartoum and by air to IDA for testing

Samples

CNTRL	Reference sample, kept since 1989 and tested by IDA
WH	Wad Hamid district hospital (south); tested by IDA
B	Berber district hospital (centre); tested by IDA
AH	Abu Hamad district hospital (north); tested by IDA
Local	Test samples, analyzed in Khartoum laboratory

Results

A summary of the results is given in Table 1. The full analytical data for each of the drug products is given in the last section of this report.

Table 1 Potency of drugs after 16 months in the Sudan, as compared to original batch samples

	Potency (%) cntrl	test	diff*	Degrad. products (%) cntrl	test	diff*	Stability problem
Acetylsalicylic acid tab.	98.0	98.2	+0.2	0.22	0.12	- 0.1	
Ampicillin cap.	97.2	94.6	- 2.6	2.01	3.75	+1.7	
Ampicillin pow.inj.	99.7	98.9	- 0.8	5.13	6.45	+1.3	
Ampicillin susp.		95.3					
Benzylpenicillin inj.	100.3	98.8	- 1.5	2.26	3.71	+1.5	
Chloramphenicol cap.				0.24	0.22	- 0.02	
Chloramphenoicol susp.		105.8					
Epinephrine inj.	88.6	75.8	- 14.4				++
Ergometrine inj.	62.0	50.6	- 18.4				++
Ferrous sulfate tab.		105					
Lidocaine inj.	103.5	103.5	0.0	<10ppm	<10ppm	0.0	
Procain penic.fort inj.	101.7	101.2	- 0.5	0.58	1.09	+0.6	
Quinine inj.		97					
Retinol cap.	110.5	98	- 12.5				(+)
Tetracycline cap.	93.0	93.6	+0.6	5.6	5.7	+0.1	
				0.69	0.71	+0.02	

* Expressed as percentage of active ingredient in control sample

Conclusions

Of the twelve drugs (in 15 presentations), three products show a serious loss of potency. In two cases (epinephrine and ergometrine maleate injection) this loss has serious medical consequences; for the third (retinol) it has not, in view of the wide therapeutic margin of the drug and the high initial amount of active ingredient. It should be noted that the ergometrine control sample may have lost potency as well because it was kept at room temperatures. If this is true, the actual loss of potency in the test sample is more than the 18.4% reported here. For all three drugs the instability in tropical climates has been reported before (1-3).

It is reassuring to see that none of the other drugs showed signs of instability, other than some increase in degradation products which was never more than 2%. These drugs are all very common essential drugs, and they usually constitute a large proportion of the drug budget (36% in the case of this consignment). One product (tetracycline capsules) showed a low potency and elevated levels of degradation products, but there was no difference between control and test samples and therefore no sign of instability.

From this pilot study we may therefore conclude that, with the exception of epinephrine and ergometrine injections, the drug products most commonly used in the Nile Province Essential Drugs Programme did not show signs of instability, despite the extreme climatic conditions they were exposed to.

References

1 Walker GJA, Hogerzeil HV, Hillgren U. Potency of ergometrine in tropical countries. Lancet 1988 (ii); 393

2 Abu-Reid IO, El-Samani SA, Hag Omer AI, Khalil NY, Mahgoub KM, Everitt G, Grundstrom K, Lindgren B and Stjernstrom NE. Stability of drugs in the tropics. A study in Sudan. Int Pharm J 1990; 4: 6-10.

3 Hogerzeil HV, Battersby A, Srdanovic V, Hansen L, Boye O, Lindgren B, Everitt G, Stjernstrom NE. WHO/UNICEF study on the stability of drugs during international transport. Geneva, WHO, 1991; WHO/DAP/91.1

Acetylsalicylic acid tablets 300 mg

Germany
Batch 9106
MNF 1/89
EXP 1/94

Sample 8/90	CNTRL	WH	B	AH	Local
Potency (%)	98.0	97.7	97.6	99.2	103.1
Degradation products (%)					
Salicylic acid	0.22	0.12	0.12	0.13	

Conclusions

1 Potency remained within BP requirements (95-105%).
2 Level of free acids shows no increase and is within BP specifications.
3 There are no signs of instability in tropical climates.

Ampicillin 250 mg capsules

Ampicillin trihydrate
Czechoslovakia
Batch 300688
MNF 6/89
EXP 6/92

Sample 8/90	CNTRL	WH	B	AH	Local
Potency	97.2%	95.5%			93.7%
Degradation products	2.01%	3.75%			
Dissolution					12 min
Average weight	327.6 mg per caps				

Conclusions

1 Potency of test sample is within BP specifications (92.5-107.5%).
2 Degradation products (in only one sample) increased from 2.0% to 3.75%. However, freshly prepared ampicillin capsules usually contain 0.9-3% degradation products and this level is not regarded as toxic.
3 There are some signs of slight instability in tropical climates, but this is of no clinical relevance (potency loss <2%).

Ampicillin injection 500 mg

Ampicillin trihydrate
Bulgaria
Batch 62
MNF 3/89
EXP 6/89

Sample 8/90	CNTRL	WH	B	AH	Local
Potency	99.7%	99.4%	99.3%	98.0%	
Degradation products	5.13	6.60	6.32	6.43	
Average weight	577.4 mg per vial				

Conclusions

1 Degradation products increased from 5.1% to 6.5%. This is just around the BP limits of acceptability, but in practice few manufacturers are able to produce ampicillin injection much below this limit. The 1.5% increase is acceptable.
2 There are some signs of slight instability in tropical climates, but this is of no clinical relevance (potency loss <2%).

Ampicillin oral suspension

Ampicillin trihydrate
Germany
Batch 320 389
MNF 3/89
EXP 3/92

Sample 8/90	CNTRL	WH	B	AH	Local
Potency					
After reconstitution:					123.1mg/5ml (98.5%)
After 7 days:					119.1mg/5ml (95.3%)

Conclusions

1 Potency of the test samples has remained within BP requirements (80-120%).
2 There are no signs of instability in tropical climates.

Benzylpenicillin injection 1 MU

DDR
Batch 150289
MNF 2/89
EXP 2/94

Sample 8/90	CNTRL	WH	B	AH	Local
Potency	100.3%	98.7%	98.8%	98.9%	
Degradation products	2.26%	3.80%	3.68%	3.65%	
Average weight	631.5 mg per vial				

Conclusions

1 Degradation products have increased from 2.3% to 3.7%.
2 Degradation of the reference sample is higher than normal; normal value on fresh products from Jenapharm and other manufacturers is < 1%.
3 There are some signs of slight instability in tropical climates, but this is of no clinical relevance (potency loss <2%).

Chloramphenicol capsules 250 mg

Chloramphenicol palmitate
Belgium
Batch 88K23
MNF 9/88
EXP 9/91

Sample 8/90	CNTRL	WH	B	AH	Local
Degradation products	0.24%	0.21%	0.23%		
Impurities (TLC)	not detectable				

Conclusions

1 No degradation found. Product is stable under tropical conditions.

Chloramphenicol oral suspension

Chloramphenicol palmitate
Belgium
Batch 89C 15
MNF 3/89
EXP 3/92

Sample 8/90	CNTRL WH	B	AH	Local
Potency				132.3mg/5ml (105.8%)
Degradation products polymorph "A"				within USP'85
Packing				In most samples leakage through the cap of the container had occurred

Conclusions

1 Potency of suspension well within USP limits (95-110% of stated amount).
2 Level of degradation products within USP limits.
3 No signs of instability in tropical climates except leakage through cap of the container.

Epinephrine injection (adrenaline)

France
Batch 82688
MNF 9/88
EXP 9/91

Sample 8/90	CNTRL	WH	B	AH	Local
Potency (HPLC)	88.6%	73.9%	77.8%	75.8%	90%

Conclusions

1 Potency of control and test samples are below BP specifications (90-110%).
2 Loss of potency from 88.6% to 75.8% (-14% of control value).
3 Epinephrine injection is unstable under tropical conditions.

NB Average potency is 92% for fresh production samples from the same manufacturer. This value is a bit low, probably due to the use of a selective HPLC assay rather than the aselective colorimetric method that is included in the BP.

Ergometrine injection 0.2 mg

Ergometrine maleate
France
Batch 92172
MNF 3/89
EXP 3/91

Sample 8/90	CNTRL	WH	B	AH	Local
Potency	62%	44%	47%	44%	66.9%
Appearance	B5 *	B2	B3	B2	yellow brown
pH					3.2

Conclusions

1 The test samples showed, on average, only 50.6% potency (BP limits 90-110%) and a yellow-brown discoloration (B2-4).
2 The pH of the samples is within BP limits of 2.7-3.5.
3 It should be noted that the control sample is also far below BP specifications. It is difficult to assess whether this is due to sub-standard initial quality of the drug, or (partly) to storage of the control sample at room temperature. In another study, with ergometrine from the same manufacturer, potency of samples of two different batches kept for one year at 21 °C decreased to 47-53% respectively (and to 83-86% when kept refrigerated).
4 Ergometrine injection is unstable under tropical conditions.

* Dilutions of standard color B(rown); B-9 is colorless, B-1 is undiluted

Ferrous sulphate tablets 200 mg

Manufacturer
Batch
MNF
EXP

Sample 8/90	CNTRL	WH	B	AH	Local
Potency					63mg (105%)
Disintegration					28 min

Conclusions

1 Content of active ingredient within BP limits (85-105%).
2 Disintegration just within BP limit of 30 minutes.
3 Product shows no signs of instability in tropical climates.

Lidocaine 2%, injection 50 ml

France
Batch 978
MNF 1/89
EXP 1/92

Sample 8/90	CNTRL	WH	B	AH	Local
Potency (HPLC)	103.5%	102.8%	104.2%	103.4%	
Degradation products 2,6 xylidine	<10 ppm	<10 ppm	<10 ppm	<10 ppm	

Conclusions

1 Potency of control and test samples are well within BP specifications (95-105%).
2 No increase in degradation products (upper limit 400 ppm).
3 The product is stable under tropical conditions.

Procaine penicillin inj. fortified
(Procaine benzylpenicillin 3MU plus benzylpenicillin sodium 1 MU)

DDR
Batch 310289
MNF 2/89
EXP 2/94

Sample taken 8/90		CNTRL	WH	B	AH	Local
Potency	Total	101.7%	101.2%	101.2%	101.2%	
	ProcP					2.56 g (67.1%)
	BenzP					1.0 g (36%)
Degradation products		0.58	1.09	1.12	1.06	

Conclusions

1 Active ingredients comply with BP 88 (95-105% active ingredient, with 60-70% ProcP and 36-44% BenzP).
2 Degradation products increased from 0.6% to 1.1%. There are no official limits but this amount has no effect on efficacy or toxicity.
3 No signs of instability in tropical climates.

Quinine Injection

Quinine dihydrochloride
Germany
Batch 580872
MNF 1/89
EXP 1/92

Sample 8/90	CNTRL WH	B	AH	Local
Potency				291mg (97%)
Appearance				Yellow coloured

Conclusions

1 Potency of the product is within BP limits (95-105%).
2 Discolouration of the product is more than BP 1980 specification ("almost colourless to slightly yellow").
3 There are no signs of instability in tropical climates other than a slight discoloration of the product.

Retinol capsules 50.000 IU

The Netherlands
Batch 881101
MNF 11/88
EXP 10/91

Sample 8/90	CNTRL	WH	B	AH	Local
Potency *	110.5%	100.4%	95.7%		
Peroxide value (meq/g)		5.3	3.3		

Conclusions

1 Potency decreased from 110.5% to 98% (loss of 12.5% of original content).
2 Potency remained within BP limits (>97%); color and taste were still good.
3 The product is moderately unstable under tropical conditions but the clinical consequences are not serious in view of the extra amount of active ingredient included in the original product and the wide therapeutic margin.

* Analysis was carried out by the manufacturer. No control sample was tested, but the manufacturer's assay value at production was taken as a reference.

Tetracycline 250 mg capsules

Tetracycline hydrochloride
Yugoslavia
Batch 097489
MNF 12/88
EXP 12/91

Sample 8/90	CNTRL	WH	B	AH	Local
Potency (HPLC)	93.0%	93.9%	93.4%		111.2%
Degradation products					
epi-TTC (HPLC)	3.1%	2.9%	2.8%		
epi-anhydro TTC (HPLC)	0.4%	0.8%	0.6%		
anhydro TTC (HPLC)	2.1%	2.2%	2.1%		
light-abs.impurities (BP method)	0.706	0.712	0.723		0.690
Dissolution (45 m)					96.6%

Conclusions

1 The amount of active ingredient is outside BP limits (95-110%) but within USP limits (90-125%).
2 No decrease in active substance was observed.
3 Degradation products in control and test samples are above the BP limits (light-absorbing impurities are above 0.620 for anhydro and epi-anhydro TTC, which corresponds roughly with 1% of each). Especially the 2.1% anhydro-TTC is too high: the upper limit in the raw material is 0.5%. There is no difference between test and control samples.
4 There are no signs of instability in tropical climates.