Stability of essential drugs during shipment to the tropics

H V Hogerzeil, A Battersby, V Srdanovic, N E Stjernstrom

Abstract

Objective—To determine whether present methods of international transport of essential drugs by sea adversely affect their quality.

Design—Controlled longitudinal study of drug shipments sent by sea from Unicef in Copenhagen to Lagos; to Mombasa and by land to Kampala; and to Bangkok. 11 essential drugs were stored in four locations on board the ships.

Setting—Main shipping routes from Unicef, Copenhagen, to tropical countries.

Main outcome measures—Temperature and relative humidity in the test packs during the journey. Amount of active ingredient in the drugs before and after shipment.

Results—Temperatures recorded within the test packs range from -3.5°C to 42.4°C and were 3-12°C higher than the ambient temperature. Relative humidity within the packs ranged from 20% to 88%. Differences between the locations on board were negligible. Ergometrine injection, methylergometrine injection, and retino capsules lost 1.5-5.8% of their active ingredient. Among 80 samples having concentrations 60% below those stated: Ampicillin, benzylpenicillin, phenoxymethylpenicillin, and tetracycline were not affected by transport.

Conclusions—Drugs were exposed to a much higher temperature and humidity than is recommended by the manufacturer, especially in tropical harbours and during inland transport. Except for ergometrine and methyl ergometrine the transport would not affect clinical effectiveness.

Introduction

In 1987 Unicef sent over $30 million worth of essential drugs to tropical countries. The stability of medicines distributed and used in hot and humid climates can pose serious problems, but stability studies and storage guidelines usually refer to temperate climates and therefore may not be relevant in extreme climatic conditions. Few studies have described the influence of tropical storage conditions on the quality of medicines. The World Health Organisation and Unicef therefore carried out a joint study on the stability of essential drugs during international transport.

Materials and methods

We used three criteria to select drugs for the study. The first criterion was an indication from WHO accelerated stability tests or other studies that the active substance or the drug product could be unstable in tropical climates. The other criteria were that Unicef has a high turnover of the drug in volume or in medical relevance. Eleven drugs were selected. All samples were taken from normal Unicef stock, and

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products in the test and control packs were taken from the same batch.

Three sea routes were chosen that together cover 35 of the 77 countries served by Unicef and nearly 40% of the total volume of drugs dispatched in 1987. The journeys from Copenhagen to Lagos (Nigeria), to Mombasa and overland to Kampala (Uganda), and to Bangkok (Thailand) took 51, 52, and 27 days respectively 10-30% of the time was spent in the port of destination before customs clearance.

Battery operated "autolog" devices were developed that electronically measured and recorded temperature and relative humidity at three hourly intervals over 100 days. The test packs were the normal Unicef triple wall cardboard boxes containing the selected drugs and the autolog. Four test packs were included in each of the shipments and were put in different locations on board (one pack in the centre and one near the ceiling of two containers, one located in the hold and the other on deck). After arrival and clearance from customs the test packs were sent by air to the chemical laboratories of the Medical Products Agency in Uppsala, Sweden, where control packs had been kept and where the chemical analyses were done. Unfortunately, the test packs from Bangkok were returned by surface mail. The climatic recordings of that journey were used but the drugs were excused from the analysis.

Results

The temperatures recorded within the test packs ranged from −3.5°C to 33.6°C during the journey to Lagos, from −2.5°C to 42.4°C during the journey to Kampala, and from 1.9°C to 37.5°C during the journey to Bangkok. Relative humidity ranged from 20% to 88%. The temperature within the test packs was usually 3-12°C higher than the ambient temperature. Differences between the locations on board were negligible. The figure shows a sample recording from the trip to Mombasa and overland to Kampala.

Three of the 11 drugs (ergometrine injection, methylergometrine injection, and retinol capsules) lost 1-5-5.8% of their active ingredient during the journey (table). Moreover, the individual ampoules of ergometrine varied greatly, with 18 out of 80 (23%) of the test samples having less than 80% of the stated content and three (4%) less than 60%. A similar but less extreme pattern was found with methylergometrine. For all drugs the decomposition products, weight variation, disintegration, and hardness were within pharmacopoeial standards and did not differ between control and test packs.

Discussion

Both the temperature and relative humidity on the three routes showed an identical pattern: steadily rising on approaching tropical waters, then high values and moderate fluctuation in tropical harbours, and high values and large fluctuation during storage and transport on land. The recorded temperature of −3.5°C within the test packs, which occurred in Aarhus harbour in November was unexpected (figure).

Only one study has been published on the climatic pattern during transport of drugs in tropical climates; this study described the temperature within a box of emergency drugs kept in a life raft on board a naval vessel during a voyage in the Indian Ocean.9 The highest temperature recorded in that box was 40-2°C, in Mombasa. Humidity and quality of the drugs were not studied.

The WHO defines normal drug storage conditions as dry, well ventilated premises at temperatures of 15-25°C or, depending on climatic conditions, up to 30°C. In our study the temperature in the drug packs was at times much higher than that, with a maximum of 42.4°C in Mombasa. We also found that the temperature within the packs was 3-12°C higher than the ambient temperature and that periods of great fluctuation occurred in which expansion and contraction could cause drug packages to leak.

The temperature and relative humidity at sea were less of a problem than on land. Extreme climatic conditions occurred especially during time in the harbour and in bond in the port area, and during transport over land. Drugs were exposed to high temperature and humidity for 17 (33%) days on the journey to Lagos and 26 (54%) days on the journey to Kampala.

Three drugs (ergometrine, methylergometrine, and retinol) showed decreased concentrations of active ingredient after international transport. For retinol this had no medical and practical implications: the loss was only 1-5%, the product contained an extra 20% of active ingredient, and the therapeutic margin is wide.

The loss of active ingredient is more important for ergometrine. In a study of 24 field samples from Bangladesh, South Yemen, and Zimbabwe only nine complied with British Pharmacopoeia requirements and seven contained less than 20% of the stated amount of active ingredient.4 Recent data from WHO on samples from Gambia, Malawi, and Zimbabwe confirm this finding. In a longitudinal study in Sudan the drug preparation lost 10% of its active ingredient during the first few months in Port Sudan and was found to contain only 53% of the stated contents after 25 months in the country.

The large variation we found between individual ergometrine ampoules is worrying, with three out of 80

<table>
<thead>
<tr>
<th>Drug</th>
<th>Control pack</th>
<th>Transported pack</th>
<th>Difference*</th>
<th>Significance (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin (acetylsalicylic acid) (tablet) (brand a)</td>
<td>101-0 (99-7 to 102-2)</td>
<td>100-7 (99-9 to 101-4)</td>
<td>−0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Aspirin (acetylsalicylic acid) (tablet) (brand b)</td>
<td>100-0 (99-9 to 100-2)</td>
<td>100-2 (99-7 to 100-8)</td>
<td>0.2</td>
<td>NS</td>
</tr>
<tr>
<td>Ampicillin trihydrate (capsule)</td>
<td>96-4 (92-5 to 100-3)</td>
<td>96-1 (95-4 to 96-4)</td>
<td>0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Ampicillin trihydrate (injection)</td>
<td>84-1 (83-4 to 84-8)</td>
<td>83-7 (82-9 to 84-6)</td>
<td>0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Benzylpenicillin (injection)</td>
<td>96-6 (92-8 to 100-5)</td>
<td>96-2 (95-6 to 96-8)</td>
<td>0.4</td>
<td>NS</td>
</tr>
<tr>
<td>Ergometrine (injection)</td>
<td>87-1 (86-0 to 88-1)</td>
<td>82-0 (80-5 to 83-8)</td>
<td>−5.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Methylerygometrine (injection)</td>
<td>100-7 (100-0 to 101-4)</td>
<td>99-0 (98-4 to 99-5)</td>
<td>−1.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ferrous salt (tablet)</td>
<td>100-0 (98-5 to 101-4)</td>
<td>100-1 (99-2 to 101-0)</td>
<td>0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Folic acid (tablet)</td>
<td>108-8 (101-2 to 125-9)</td>
<td>106-6 (103-1 to 110-0)</td>
<td>−1.8</td>
<td>NS</td>
</tr>
<tr>
<td>Phenoxymethylpenicillin (tablet)</td>
<td>96-3 (94-9 to 98-5)</td>
<td>96-0 (95-6 to 96-4)</td>
<td>−0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Retinol (capsule)</td>
<td>120-8 (120-2 to 121-4)</td>
<td>119-0 (118-1 to 119-9)</td>
<td>−1.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Tetracycline (tablet)</td>
<td>101-0</td>
<td>101-5 (99-9 to 100-3-4)</td>
<td>−0.3</td>
<td>NS</td>
</tr>
</tbody>
</table>

*As percentage of control value. **Combined with ferrous salt in one tablet.

Mean (95% confidence interval) amount of active ingredient in essential drugs after international transport as percentage of stated content.
Variability in serial CD4 counts and relation to progression of HIV-I infection in AIDS in haemophilic patients

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Abstract

Objective—To examine the CD4 count and its near term changes relative to progression to AIDS within 30 months and to subsequent CD4 counts.

Design—Longitudinal clinical and laboratory study.

Setting—Haemophilia treatment centres in six large American cities.

Patients—555 people with congenital clotting disorders who were infected with HIV, initially without AIDS, and seen at follow up for 6-30 months in 1986-9.

Main outcome measures—Absolute CD4 counts and incidence of AIDS.

Results—Outset CD4 count and age were independently related to progression to AIDS (p<0.0001 and p<0.005 respectively). Patients with CD4 counts of 0-30·0-49 x 10⁶ cells/l had an age adjusted risk of AIDS within 30 months of only 9% that of patients with counts 0-20·0-30 x 10⁶. Children under 10 years old had only 16% of the CD4 adjusted risk of AIDS of people aged 15-45 years. Analysis of 149 patients' CD4 counts at the beginning and end of two successive six month intervals showed an average decrease of 11% in each six months regardless of the outset count (0-20 x 10⁶). For individual patients the decrease in the second six month period was unaffected by the decrease in the first six month period.

Conclusions—Antiviral treatment of asymptomatic people, particularly children, with CD4 counts ≥0.03 x 10⁹/l is questionable if predicated on near term progression to AIDS. Because of individual CD4 count variability and the low rate of progression to AIDS the near term declines in individual CD4 counts are a poor index for identifying people who will rapidly progress to AIDS.

Introduction

The absolute CD4 count has repeatedly been found to be either the best predictor or among the best predictors of the rapidity with which HIV-I infection progresses to clinical manifestations, especially AIDS disclosed by opportunistic infections. Consequent antiretroviral treatment is presently being administered to some people who are asymptomatic but whose CD4 counts are considered indicative of approaching AIDS. Values that have been suggested for initiation of AIDS prophylaxis are 0.0-2.0·5 x 10⁶ cells/l, which if implemented could mean treatment for some 50 000 to 650 000 people in the United States alone.

Although the appreciable toxic effects of zidovudine are now more manageable with regimens with reduced dosage, the residual incidence of bone marrow depression, the cost of the drug, the need for an increased amount of medical supervision, and the...