Stability of benzylpenicillin during continuous home intravenous therapy

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Objectives: The aim of this study was to investigate the temperature profile of home intravenous (iv) antibiotic reservoirs and the stability of 16 megaunits of benzylpenicillin sodium in 120 mL of sodium chloride 0.9% at constant and variable temperatures.

Methods: A Tinytag computerized thermometer recorded temperatures every minute in the home iv antibiotic reservoir pouches of nine patients over a 24 h period. Similar bags containing benzylpenicillin sodium (16 megaunits) were maintained either at a constant 36°C, 26°C or 21–22°C or were worn in a pouch by five healthy volunteers for a 24 h period. Other bags were stored at 3–5°C for 10 days. The bags were sampled at timed intervals and benzylpenicillin concentrations assayed by HPLC.

Results: Median temperatures recorded in the infusion bags worn by the nine patients were in the range 16.7–34.1°C. For infusion bags maintained at 36°C, 26°C and 21–22°C, the concentrations of benzylpenicillin dropped below 90% of the initial concentration at a mean time of 5 h 18 min, 12 h 54 min and 13 h 20 min, respectively, whereas for bags worn by the healthy volunteers the mean time for 10% loss of benzylpenicillin was 9 h 20 min. In contrast, at 3–5°C, concentrations of benzylpenicillin only dropped below 90% of the initial concentration at 8 days.

Conclusions: Significant temperature-dependent degradation of benzylpenicillin occurs during continuous home iv antibiotic programme infusions, which could result in loss of efficacy.

Keywords: benzylpenicillin, home iv therapy, stability, temperature

Introduction

Benzylpenicillin sodium has been used internationally in home intravenous (iv) therapy, where patients can be managed at home but require prolonged therapy.1–4 The use of home iv programmes decreases length of hospital stay and has high patient acceptability.1 However, much of the available data on antibiotic stability relates to hospital application, where the antibiotics are infused at much lower concentrations and temperatures than those during home iv therapy.2 The concentration of antibiotics in home iv pumps is higher, as the volume of fluid that can be given is restricted by the size of the pump reservoir. Similarly, the temperatures reached during the home iv therapy are likely to be higher than those in the hospital setting, as the reservoir of antibiotic is attached to the patient’s body. Consequently, the literature relating to drug stability generated from constant-temperature studies may not be relevant to the way in which these agents are used in the home iv setting.

The purpose of this study was to document the profile of temperatures in the antibiotic reservoir in the home iv therapy setting and to determine the stability of benzylpenicillin sodium over this range and also at refrigerator temperatures (3–5°C).

Materials and methods

A Tinytag (Gemini 2) computerized thermometer was used throughout the study to record temperatures every minute. These data were then downloaded to a Microsoft Excel spreadsheet.

The thermometer was carried next to the antibiotic reservoir in a pouch for 24 h by nine consecutive patients recruited into the home iv antibiotic therapy programme. Six patients kept the pouch attached to the
body around their waists for the whole 24 h. The remaining three patients kept the pouch outside the bed at night. The groups are uneven as patients were enrolled consecutively and asked to continue their lives as usual, to gain a representative sample of actual practice in this group of patients.

The stability of benzylpenicillin sodium at room temperature (21–22°C), 26°C and 36°C was studied based on the temperatures recorded in the pouches carried by the patients above. Triplicate plastic (IntraVia, Baxter Healthcare Corporation) bags containing 16 megunits (9600 mg) of benzylpenicillin sodium (CSL) in 120 mL of sodium chloride 0.9% (Baxter Healthcare Corporation) were made up in the pharmacy bench, and an incubator oven was used to maintain constant temperatures of 26°C and 36°C. Single (3 mL) samples were taken from each of the bags immediately after dispensing (time 0) and every 2 h during waking hours (0600–2200 h). All samples were stored at –80°C until analysis. Each sample was analysed in triplicate by HPLC. A Tinytag (Gemini 2) computerized thermometer was used to record temperatures every minute at each of the temperatures.

Triplicate bags of benzylpenicillin sodium in 120 mL sodium chloride 0.9% were prepared as above and stored at 3°C for 10 days. Samples (3 mL) were taken at time 0 and every 24 h for 10 days and stored at –80°C until analysis by HPLC.

To simulate home iv therapy, five healthy volunteers each carried a single plastic bag containing 16 megunits of benzylpenicillin sodium in 120 mL of sodium chloride 0.9% in a home iv antibiotic therapy pouch for two consecutive 24 h periods. During the first 24 h, the bag was worn around the waist by the volunteers for the whole period, whereas during the second 24 h period the bag was removed and placed by the bed at night. Two consecutive 24 h periods were chosen to establish the difference in temperature, and therefore stability, between positioning the antibiotic in bed overnight and leaving it outside the bed. Samples (3 mL) were taken at time 0 and every 4 h during waking hours, stored at –80°C until analysis and analysed in triplicate for benzylpenicillin concentrations by HPLC.

The Student’s t-test (paired) was used to analyse the differences in temperatures and the concentrations between the first and second 24 h periods in the experiments where volunteers wore the pouches. To determine the time taken for benzylpenicillin concentrations to drop below 90% of the initial concentration, linear interpolation was used. The value of 90% was chosen on the basis of clinical relevance, since a 10% loss of potency was not considered significant.

**Assay**

Benzylpenicillin concentrations were determined using an HPLC method. The standard curve (37.5, 75.0 and 150 mg/mL) was freshly prepared in water using benzylpenicillin sodium powder (CSL). The internal standard was mycophenolic acid (Sigma, St Louis, MO, USA). Mycophenolic acid solution (50 μg/mL) was prepared by diluting the stock solution (1.0 mg/mL) with water. To 20 μL of benzylpenicillin standard or unknown sample, 2.0 mL of 50 μg/mL mycophenolic acid solution was added. The mixture was vortexed and 50 μL aliquots were injected into the HPLC system. HPLC analysis was performed on the Agilent 1100 Series system equipped with a quaternary pump, a variable wavelength detector set at 254 nm and an autosampler (Hewlett-Packard, Waldbronn, Germany). An Aqua C18 5 μm, 4 × 3.0 mm internal diameter guard column and an Aqua C18 5 μm, 75 × 4.6 mm internal diameter analytical column (Phenomenex, Torrance, CA, USA) were used for separation. Data were collected and analysed by the Agilent ChemStation (Hewlett-Packard, Waldbronn, Germany). The mobile phase was a mixture of 0.05% phosphoric acid and acetonitrile (70:40, v/v) and the flow rate was 1.5 mL/min. The standard curve was linear (r² > 0.999) over the range 37.5–150 mg/mL. The intra-day coefficients of variation of the assay were 5.8% and 3.0% at the concentrations 37.5 and 80 mg/mL, respectively.

Temperatures recorded in each of the nine patients’ bags are outlined in Table 1. The three patients who took their bags off at night recorded significantly lower median temperatures than those who did not [20.2°C versus 32°C, P < 0.001 (Student’s t-test)].

The percentages of the initial concentrations of benzylpenicillin sodium stored at 36°C, 26°C and room temperature (21–22°C) for 24 h are shown in Figure 1. At 36°C, concentrations dropped to below 90% of the initial concentration at a mean of 5 h 18 min. At 26°C, this occurred at 12 h 54 min and at room temperature this occurred at 13 h 20 min. By 24 h, concentrations had dropped to 5%, 61% and 83% of initial concentrations at 36°C, 26°C and room temperature (21–22°C), respectively.

The median temperatures recorded in the infusion bags worn by the five healthy volunteers were in the range 28–31°C in the first 24 h (in bed overnight) and 26–28°C in the second 24 h (out of bed overnight). The percentages of the initial concentrations of benzylpenicillin from the bags worn by the five healthy volunteers are plotted in Figure 2. The mean time at which the concentration dropped below 90% was 9 h 20 min (range 4 h 40 min to 15 h 22 min). Concentrations dropped significantly more (to a mean of 27%) during the 24 h when the bag was worn continuously than when the bag was left outside the

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**Table 1. Temperatures (°C) recorded in the home iv therapy pouches of the nine patients studied over 24 h**

<table>
<thead>
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<th>Median</th>
<th>Mean</th>
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<td>16.5</td>
<td>9.9–26.6</td>
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<tr>
<td>2</td>
<td>20.9</td>
<td>21.8</td>
<td>16.7–27.4</td>
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<td>23</td>
<td>23.3</td>
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<td>29.4</td>
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<td>34.1</td>
<td>33.2</td>
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*Attached to body for full 24 h period.

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**Figure 1. Percentages of the initial concentrations of benzylpenicillin stored at 36°C, 26°C and room temperature (21–22°C) for 24 h (means ± S.E.M.).**
bed at night (to a mean of 54%, \( P < 0.001 \)). The difference between the concentrations before bed and after bed as a percentage of initial concentrations was statistically significant.

At refrigerator temperatures (3–5°C), benzylpenicillin concentrations only dropped below 90% of the initial concentration by day 8.

**Discussion**

The temperatures reached in the antibiotic reservoir during home iv antibiotic therapy are sufficient to cause significant degradation of benzylpenicillin, which could have clinical significance. In both patients and healthy volunteers, over much of a 24 h period the antibiotic reservoirs were maintained at temperatures approximating to body temperature. The highest temperature recorded when attached to a body was 36.1°C.

When benzylpenicillin sodium was maintained at constant temperatures of 21–22°C (room temperature), 26°C and 36°C, significant breakdown occurred, suggesting that benzylpenicillin sodium may not be a good candidate for home iv antibiotic therapy using standard delivery systems, especially if ambient or likely temperatures are high.

Our results differ significantly from previous studies of the stability of benzylpenicillin sodium in portable pump reservoirs.\(^1\)\(^3\) These studies found that at a constant temperature the percentages of benzylpenicillin sodium left after 24 h were 83.9% at 37°C and 98.9%–100.7% at 25°C, as compared with 5% and 61% observed in this study at 36°C and 26°C, respectively. This may reflect differences in concentrations of solutions studied, pH of the solutions or some other aspect of study design. Interestingly, though, our data agree well with other data presented by Stiles et al.\(^1\) where in a specificity check they observed a drop to 68% of the initial concentration after 24 h at 25°C. Unfortunately, the authors did not propose an explanation for the apparent discrepancy between their two sets of data on the stability of benzylpenicillin at 25°C. The concentration studied here reflects the highest concentrations used in our clinical practice. Although replicating the concentrations in the above studies would have been useful, we chose to study a concentration applicable to our clinical practice.

The lack of stability of benzylpenicillin sodium in the simulated home iv therapy part of this study suggests that benzylpenicillin sodium may not be sufficiently stable to be used as a 24 h continuous infusion in this setting. As far as we are aware, no other studies of concentrations of benzylpenicillin during home iv therapy have been published. The time at which concentrations dropped below 90% of the initial concentration shows considerable inter- and intra-individual variation, ranging from 4 h 40 min to 15 h 22 min (mean 9 h 20 min).

Concentrations of benzylpenicillin stored in the refrigerator (3–5°C) remained above 90% of the initial concentration until day 8, suggesting an refrigerated shelf-life of around 6–7 days. This indicates that the use of insulated pouches, perhaps with freezer packs, may improve the stability of benzylpenicillin during home iv therapy. If the temperature in the pouch could be maintained lower than normal room temperature, the stability of benzylpenicillin may be improved. In one study, the use of such a pouch successfully extended the stability of ampicillin infusions from 6 h to 24 h.\(^2\)

In summary, significant degradation of benzylpenicillin sodium occurs at temperatures encountered in the reservoir solution during home iv antibiotic programmes. This lack of stability of benzylpenicillin sodium suggests that it may be unsuitable for continuous infusion in the home iv antibiotic therapy setting in uncontrolled conditions. The implementation of a ‘cool bag’ carrying system may improve the stability of benzylpenicillin sodium and should be studied further.

**Acknowledgements**

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**References**