

Cooling enhances benzylpenicillin stability during continuous home intravenous administration

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- **OBJECTIVE** — To demonstrate the effects of chilling on the stability of benzylpenicillin sodium in NaCl 0.9% during simulated home IV therapy.
- **DESIGN** — The stability of benzylpenicillin sodium 16 mega units in 100ml NaCl 0.9% both chilled and not chilled was studied over 24 hours under simulated home IV therapy conditions.
- **SUBJECTS AND SETTINGS** — Five volunteers wore reservoirs placed inside a Paragon pump for 24 hours. Two reservoirs were worn for each 24 hour period — one inside a standard home intravenous therapy “belt-bag” (control) and one inside an insulated bag containing frozen packs (chilled). The frozen packs consisted of frozen water or frozen gel and were renewed at 12 hours. A TinyTag thermometer was present in all bags.
- **OUTCOME MEASURES** — Temperatures were recorded each minute, benzylpenicillin samples were taken at timed intervals and concentrations were measured by HPLC.
- **RESULTS** — The mean temperatures recorded were 28.5C (controls, two volunteers), 20C (chilled with frozen water) and 17.4C (chilled with frozen gel). The mean percentages of the initial concentration of benzylpenicillin left at 12 hours were 87.5% (controls), 102.4% (frozen water) and 97.4% (frozen gel). Those at 24 hours were 43.7% (controls), 82.3% (frozen water) and 86.6% (frozen gel). The percentage of the initial concentration of benzylpenicillin left at 24 hours was greater in both the frozen water ($P<0.007$) and the frozen gel bags than in the controls ($P<0.001$).
- **CONCLUSION** — Chilling benzylpenicillin during home IV therapy with insulation and frozen packs increases its stability.

Benzylpenicillin in sodium chloride 0.9 per cent (benzylpenicillin) is useful for home intravenous therapy and has been used extensively in this situation since the introduction of home IV therapy programmes.¹⁻⁴ In one study, conducted in the Netherlands, benzylpenicillin was the second most common antibiotic used in home IV therapy.⁵ In a retrospective review of 957 home IV patients, penicillins were used in 165 cases.⁶ Because penicillins are bactericidal at low concentrations and have a limited post-antibiotic effect there is interest in using them as continuous home IV infusions for specific infections.⁷

In our home IV therapy programme, we prefer to use penicillins rather than ceftriaxone because of concerns about emerging resistance. Unfortunately, benzylpenicillin is subject to temperature-dependent degradation.⁸ When infusion devices are worn next to the body or kept at temperatures approximate to those of the body, significant degradation of benzylpenicillin occurs.⁸ Concentrations of benzylpenicillin reduced to 27 per cent of the initial concentration when an infusion device was worn by volunteers for 24 hours.⁸ Previous studies that suggested benzylpenicillin was stable were carried out at temperatures and concentrations most often encountered in the hospital setting, which were lower than the home IV therapy setting.³

A drug is considered sufficiently stable for clinical use if 90 per cent of the initial concentration is present at the end of the dosing interval.⁷ A method for improving stability to maintain concentrations above 90 per cent of the initial concentration at 24 hours is needed. We postulated that active cooling of the benzylpenicillin infusion would be required to increase the stability of the antibiotic, but this must be practical for clinical use.

Materials and methods

A controlled trial was conducted to stimulate home IV therapy. Five healthy volunteers each wore two different types of bag around their waist continuously for 24 hours (including under their bedclothes at

night). One of these was a standard home IV therapy “belt-bag” made of thin nylon (control) while the other was a foam insulated nylon bag (Kathmandu padded cell) with extra insulation from polystyrene beads and frozen packs (chilled).

Each bag contained a Paragon pump with a plastic infusion reservoir filled with benzylpenicillin (16 mega units in 100ml sodium chloride 0.9 per cent). During the first 24-hour period the frozen packs consisted of nine small sachets of frozen water (total volume approximately 100ml) while in the second 24 hour period they consisted of two large frozen gel packs (Thermogard, total volume approximately 200ml).

The frozen packs were placed around and on top of the pump and renewed after 12 hours. Samples (3ml) were taken from each bag at zero, 12 and 24 hours, stored at 80C until analysis and then assayed in triplicate for benzylpenicillin concentrations by high performance liquid chromatography.⁸ The standard curve was linear ($r^2 > 0.999$) over the range 37.5 to 150 mg/ml. The intra-day coefficients of variation of the assay were 5.8 per cent and 3.0 per cent at the concentrations of 37.5 and 80 mg/ml, respectively. Temperatures were recorded each minute by a TinyTag (Gemini 2) computerised thermometer which was placed next to the Paragon pump in the bags.

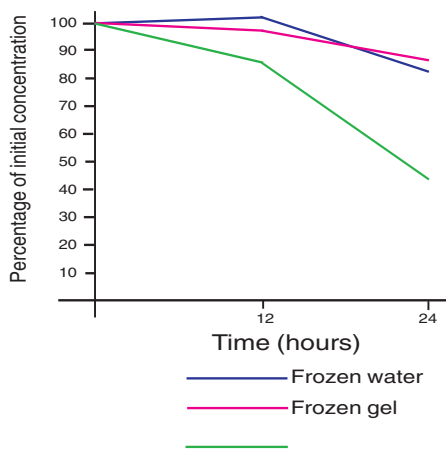
Student's *t*-test (paired) was used to analyse the significance of the differences in benzylpenicillin concentrations between the control and chilled bags and between the temperatures recorded at 24 hours and 12 hours.

Results

The benzylpenicillin concentrations are shown in Figure 1 (p57). The mean percentages of the initial concentration of benzylpenicillin left at 12 hours and 24

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Figure 1: Percentage of initial concentrations of benzylpenicillin infusion (mean)



hours in the controls were 87.5 per cent (range 78 to 97 per cent) and 43.7 per cent (range 24 to 60 per cent), respectively. Those in the frozen water bags were 102.4 per cent (range 92 to 114 per cent) and 82.3 per cent (range 74 to 100 per cent) at 12 hours and 24 hours, respectively, and those in the frozen gel bags were 97.4 per cent (range 80 to 102 per cent) and 86.6 per cent (range 76 to 97 per cent). The percentage of the initial concentration of benzylpenicillin left at 24 hours was greater in both the frozen water ($P<0.007$) and the frozen gel bags than in the controls ($P<0.001$). There was no significant difference in concentrations between benzylpenicillin in the frozen water and the frozen gel bags.

Temperatures recorded over 24 hours are listed in Table 1. The mean temperatures

recorded over 24 hours were 28.5C in the controls ($n=4$, 2 volunteers), 20.1C in the frozen water bags ($n=5$) and 17.4C in the frozen gel bags ($n=5$). The mean temperatures recorded over the first 12 hours and the second 12 hours, respectively, were 27.1C and 29.9C in the controls. There was a significant difference between the mean temperatures recorded over 24 hours in the control bags compared with those recorded in the chilled bags ($P<0.001$) and between the two methods of chilling ($P<0.05$).

Discussion

Chilling the infusion markedly increased benzylpenicillin stability. Benzylpenicillin concentrations remaining were significantly higher in the chilled bags compared with the control bags at 24 hours but not at 12 hours. Much of the degradation occurred in the second half of the 24 hour period, when the bags were worn under bedclothes at night, resulting in higher temperatures. Further studies would be required, but placing the chilled bags outside the bed over night is likely to maintain concentrations above 90 per cent of the initial concentration for the whole 24 hour period.

Technical problems prevented the recording of temperatures in all five volunteers. However the control temperatures that were recorded are similar to those seen in our previous study where five volunteers and nine patients had temperatures recorded in standard home IV therapy conditions.⁸ This indicates that the temperatures reached in the controls were typical of those seen during home IV therapy.

This study is supportive of another study of the use of chilling to enhance the stability of antibiotics, in which the use of insulated and chilled bags successfully extended the stability of ampicillin infusions from six hours to 24 hours.³ This method may be applicable to other antibiotics considered too unstable for use in home IV therapy programmes, eg, imipenem, meropenem and amoxicillin.

Potential drawbacks of using a chilled system for drug delivery include a sensation of coldness caused by the bag and the possibility of pain from the infusion of cooled liquid into a blood vessel in clinical practice. The coldness was reported by the volunteers in this study but was easily tolerated for the 48-hour study period. Patients exposed to weeks of therapy, however, may find this unacceptable. In addition the chilled bags used in this study were cumbersome and uncomfortable to wear. A purpose-designed device may improve stability further and result in improved patient tolerability.

Our results confirm the influence of temperature on benzylpenicillin degradation in the home IV therapy environment and that efforts to reduce these temperatures improved stability. This study has produced a practical method of active cooling of benzylpenicillin that could be used effectively in the home IV therapy setting.

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Table 1: Temperatures recorded in the home IV bags of the five volunteers studied over 24 hours

	Mean (C)	Min(C)	Max(C)
Controls			
Volunteer 1 (1st 24 hours)	28.2	19.1	34.5
Volunteer 2 (1st 24 hours)	29.4	18.4	34.5
Volunteer 1 (2nd 24 hours)	29.6	23.4	34.9
Volunteer 2 (2nd 24 hours)	26.6	12.4	32.6
Overall mean	28.5	18.3	34.1
Frozen gel			
Volunteer 1	18.2	5.0	29.9
Volunteer 2	17.8	8.8	25.2
Volunteer 3	19.3	13.5	27.0
Volunteer 4	16.8	11.0	25.2
Volunteer 5	15.0	7.3	23.7
Overall mean	17.4	9.1	26.2
Frozen water			
Volunteer 1	20.7	8.4	28.1
Volunteer 2	19.7	10.2	27.0
Volunteer 3	19.7	9.9	27.7
Volunteer 4	22.7	14.5	31.4
Volunteer 5	17.8	9.5	28.4
Overall mean	20.1	10.5	28.5