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Notes

Compatibility of phenylmercuric acetate with cefuroxime and ceftazidime eye drops

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Abstract

The compatibility of the antimicrobial preservative phenylmercuric acetate (0.002% w/v) was studied with the cephalosporin antibiotics cefuroxime and ceftazidime (5% w/v), using pre-column derivatisation HPLC. The formulations were stored in amber glass eye drop bottles, at 7 and 25°C. Phenylmercuric acetate was unstable at both temperatures in the presence of either antibiotic. At 25°C, there was complete degradation in 14 days. © 1997 Elsevier Science B.V.

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An eye drop formulation of the second generation cephalosporin antibiotic cefuroxime has been described, which is based on a proprietary viscous vehicle (*Sno Tears*) and contains benzalkonium chloride as the antimicrobial preservative (Hebron and Scott, 1993). A formulation of the third-generation cephalosporin ceftazidime, in the same vehicle, has also been studied (Barnes, 1995). These formulations were found by challenge testing (Barnes and Nash, 1994) to have adequate antimicrobial preservation. However, the same study found that the preservative activity of phenylmercuric acetate (PMA) was markedly reduced in the presence of ceftazidime.

This paper discusses a study of the chemical compatibility of phenylmercuric acetate with 5% w/v cefuroxime sodium and with 5% w/v ceftazidime.

Cefuroxime injection, as the sodium salt, 1.5 g (*Zinacef*) and ceftazidime injection, 1 g (*Fortum*) were from Glaxo, Middlesex, UK. Sterile phenylmercuric acetate 0.002% solution and 10 ml

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amber glass eye drop bottles were from Sterile Fluids, Queen Elizabeth Hospital, Birmingham, UK. Phenylmercuric acetate was from Merck, Poole, UK. 4-Morpholinecarbodithioic acid (MDTA) was from Aldrich, Poole, UK. All other chemicals were of analytical or HPLC grade.

Phenylmercuric acetate was determined by pre-column derivatisation HPLC method (Parkin, 1987). The chromatograph consisted of an Altex 110A pump (Anachem, Luton, UK), LC-3 UV detector (Pye-Unicam, Cambridge, UK), 7125 injection valve (Rheodyne, Palo Alto, USA), and Shimadzu C-R3A integrator (Dyson Instruments, Houghton-le-Spring, UK). A 100×4.6 mm Spherisorb 5 μm ODS column was used with a mobile phase of methanol:aqueous 10^{-4} M disodium edetate (68:32) at a flow rate of 1 ml/min. The injection volume was 20 μl and the detection wavelength 254 nm. To 1 ml sample was added 1 ml derivatisation reagent (prepared daily by dissolving 15 mg MDTA in 12.5 ml water and diluting to 50 ml with acetonitrile). The standard was aqueous phenylmercuric acetate 0.002% w/v, treated as for the sample. Sample and standard solution were derivatised in duplicate and a single injection made from each. Quantification was by measurement of peak height.

Cefuroxime eye drops were prepared by dissolving the contents of a vial of cefuroxime injection, under aseptic conditions, in sterile phenylmercuric acetate 0.002% w/v solution, to give a concentration of 5% w/v. The product was packed in 10 ml sterile amber glass eye drop bottles and stored at 7 or 25°C (both $\pm$ 1°C). Ceftazidime eye drops were prepared in the same way.

The phenylmercuric acetate derivative peak eluted at 9.0 min. Cefuroxime and ceftazidime eluted as large tailing peaks at the void volume. The limit of detection of phenylmercuric acetate was 8×10^{-5}% w/v, based on a peak giving a response of three times the baseline noise.

Peak height was used for quantitation since peak area measurement gave poorer precision. The calibration curve for phenylmercuric acetate was linear, with a negative intercept, in both aqueous solution and spiked into cefuroxime 5% w/v or ceftazidime 5% w/v (for instance, for the preservative spiked into ceftazidime 5% w/v, $y = mx + c$: $m = 4.63$, $c = -30.2$, $r = 0.9999$). Determination of phenylmercuric acetate spiked at 0.002% w/v in cefuroxime sodium 5% w/v gave a recovery of 99.6% and a precision of 1.2% relative S.D. ($n = 6$). For ceftazidime 5% w/v, the recovery was 90.4% and the precision was 2.7% relative S.D. ($n = 6$).

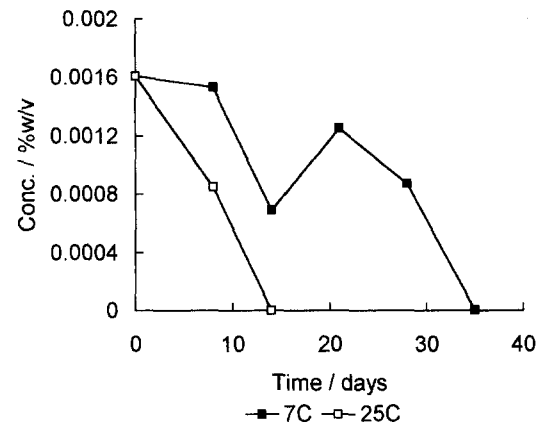

Fig. 1. Phenylmercuric acetate concentration in cefuroxime sodium eye drops.

PMA degraded at 7°C in the presence of both antibiotics (Figs. 1 and 2). At 25°C, degradation was faster, being complete by 14 days in both cases.

The initial concentration of PMA was in agreement with the actual concentration of the vials of sterile PMA used to prepare the formulations.

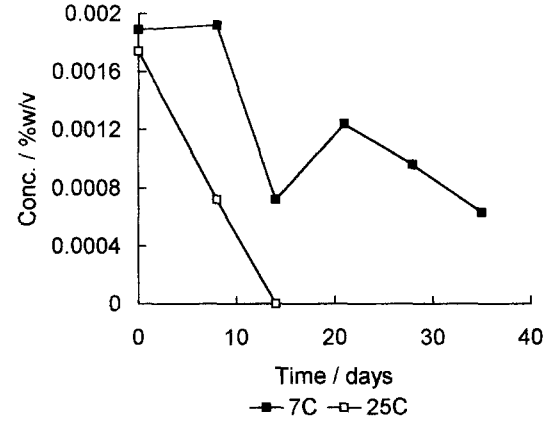

Fig. 2. Phenylmercuric acetate concentration in ceftazidime eye drops.

Antimicrobial challenge testing (Barnes and Nash, 1994) was not performed with PMA in the presence of cefuroxime. However, with ceftazidime, the antimicrobial effectiveness was poor, although aqueous PMA 0.002% w/v solution was confirmed as an effective preservative in the absence of the antibiotics. Degradation of PMA does not completely explain the challenge testing results, since the antimicrobial effectiveness was low even in the first 24 h of challenge, when PMA levels would be expected to be relatively close to the initial values. The results at 25°C (Fig. 2) do, however, correlate with the finding in the challenge testing experiments that preservation was even less effective with ceftazidime in PMA solution which had been stored at 25°C for 14 days before challenge. A combination of a physical interaction of ceftazidime with PMA and chemical degradation of the preservative may explain the challenge testing results.

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