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Prediction of stability of cefazolin sodium in perfusion fluids

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Summary

The stability of cefazolin sodium in commonly used intravenous solutions was studied by accelerated degradation. The methods of analysis were thin layer chromatography and an hydroxylamine method for cephalosporins. The shelf life of all the samples studied allows its clinical utilisation.

Cefazolin sodium is a semisynthetic cephalosporin that is not absorbed orally, so it is only used parenterally. Because of the clinical importance of parenteral solutions we studied the kinetics of degradation of cefazolin sodium in commonly used intravenous infusion fluids. Among the solutions studied those containing carbohydrates may undergo perceptible alterations in stability, as reported by Borstein et al. (1974). Degradation of cefazolin sodium follows a first-order rate constant as our previous studies and bibliographical references have shown (Bundgaard et al., 1983).

Solutions included in the study were:

- 0.9% sodium chloride
- 10% mannitol in water
- 1/6 sodium lactate
- Ringer's solution (F.E. 1954)
- Lactated Ringer's solution (Hartmann)
- 5% glucose in water
- 10% glucose in water
- 5% fructose in water
- 10% fructose in water
- 5% glucose in lactated Ringer's solution.

For the solutions containing no carbohydrates we used the Mays method (Mays et al., 1975) which is based on the reaction between cefazolin sodium and hydroxylamine with cleavage of the β-lactam ring and formation of the hydroxamic acid which forms a coloured complex with ferric ion that can be determined spectrophotometrically.

For the solutions containing carbohydrates we could not use this method because of the reaction between aldehydes and hydroxylamine, so we used the thin-layer quantitative chromatography method based on the technique of Bolós (Bolós et

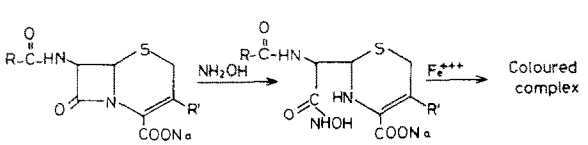

Fig. 1. Reaction between cetazolin sodium and hydroxylamine.

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TABLE 1

Cefazolin sodium rate constants (first order) with their confidence range at 40, 50 and 60 °C in perfusions containing no carbohydrates

	40 °C	50 °C	60 °C
0.9% NaCl	0.0040 ± 15.4%	0.0134 ± 5.5%	0.0312 ± 9%
0.9% NaCl (buffer pH = 5.6)	0.0042 ± 11%	0.0101 ± 7.4%	0.0330 ± 6.3%
10% Mannitol	0.0064 ± 8.8%	0.0141 ± 20%	0.0383 ± 30%
10% Mannitol (buffer pH = 5.6)	0.0060 ± 2.1%	0.0103 ± 7.7%	0.0474 ± 18.8%
1/6 Sodium lactate	0.0045 ± 6.3%	0.0155 ± 17%	0.0447 ± 12.2%
1/6 Sodium lactate (buffer pH = 5.6)	0.0056 ± 10.5%	0.0096 ± 20%	0.0596 ± 5.8%
Ringer's solution	0.0074 ± 5.4%	0.0123 ± 9%	0.0276 ± 6.8%
Ringer's solution (buffer pH = 5.6)	0.0053 ± 3.4%	0.0095 ± 10.2%	0.0289 ± 9.7%
Hartmann's solution	0.0064 ± 16.5%	0.0101 ± 12.2%	0.0368 ± 11.8%
Hartmann's solution (buffer pH = 5.6)	0.0071 ± 19.6%	0.0152 ± 20.5%	0.0441 ± 9.5%

al., 1977), using cut-away aluminium sheets developed by fluorescence inhibition. The cut away aluminium sheet pieces were eluted in methanol for 2 h, and the titrates were determined spectrophotometrically; they also may be determined by a special spectrophotometer for turbid samples.

Kinetics of degradation of each solution were studied simultaneously. In the first case the antibiotic is diluted in a parenteral solution controlling the pH variation to register its oscillations. In the second case the experiment was carried out at a constant pH using an acetate buffer pH = 5.6 (maximal stability) and ionic strength of 0.5 (Gallardo, 1985). To find the specific rate constant at 25 °C (k_{25}) and shelf life we have studied these solutions at different temperatures; in the cases of saline infusions these were 40, 50 and 60 °C and the remaining ones we also studied at 35 °C.

When the analytical method of Mays is used concentration of cefazolin sodium is 4.5 mg/ml and in chromatographic method is 5.0 mg/ml.

Statistical data processing follows Bolós (Bolós et al., 1986) procedure using 90% probability.

Table 1 shows the values of the rate constants with their confidence range for infusion fluids without carbohydrates. Table 2 gives the values for carbohydrate-containing solutions. Table 3 shows the values of k_{25} and t_{90} (shelf-life or time needed for a degradation of 10% at 25 °C) obtained using the Arrhenius equation with data from Tables 1 and 2. In both cases we also state confidence ranges. The pH variation is not meaningful when no buffer is used. The values were in the 5.10–6.70 range.

The use of a pH = 5.6 buffer (maximal stability of the antibiotic) is not necessary because it has

TABLE 2

Cefazolin sodium rate constants (first order) with their confidence range at 35, 40, 50 and 60 °C in perfusions containing carbohydrates

	35 °C	40 °C	50 °C	60 °C
5% glucose	0.0016 ± 10.6%	0.0028 ± 6.4%	0.0081 ± 28.5%	0.0250 ± 9.6%
5% glucose (buffer pH = 5.6)	0.0013 ± 10%	0.0023 ± 6.4%	0.0078 ± 31%	0.0303 ± 20.8%
10% glucose	0.0025 ± 28.7%	0.0036 ± 5.7%	0.0076 ± 12.4%	0.0160 ± 22%
10% glucose (buffer pH = 5.6)	0.0019 ± 23%	0.0038 ± 7.5%	0.0074 ± 12.9%	0.0128 ± 12.2%
5% fructose	0.0039 ± 21%	0.0038 ± 15%	0.0086 ± 9.6%	0.0458 ± 15.4%
5% fructose (buffer pH = 5.6)	0.0014 ± 6.5%	0.0032 ± 15%	0.0060 ± 14%	0.0227 ± 23.5%
10% fructose	0.0025 ± 9.7%	0.0033 ± 6.6%	0.0091 ± 13%	0.0609 ± 11.6%
10% fructose (buffer pH = 5.6)	0.0016 ± 12.6%	0.0029 ± 7.4%	0.0082 ± 18%	0.0580 ± 20%
5% glucose in Hartmann's solution	0.0021 ± 9.3%	0.0036 ± 20%	0.0108 ± 21.4%	0.0588 ± 4.5%
5% glucose in Hartmann's solution (buffer pH = 5.6)	0.0018 ± 14%	0.0026 ± 10%	0.0078 ± 6.9%	0.0390 ± 9.9%

TABLE 3

Cefazolin sodium solutions values of k_{25} and t_{90}

	k_{25} (h^{-1})	t_{90} (h)
0.9% NaCl	$(9.93 \pm 2.86)10^{-4}$	$(1.17 \pm 0.34)10^{2}$
0.9% NaCl (buffer pH = 5.6)	$(6.43 \pm 1.53)10^{-4}$	$(1.77 \pm 0.34)10^{2}$
10% Mannitol	$(16.13 \pm 3.70)10^{-4}$	$(0.70 \pm 0.16)10^{2}$
10% Mannitol (buffer pH = 5.6)	$(15.46 \pm 28.14)10^{-4}$	$(0.70 \pm 0.16)10^{2}$
1/6 Sodium lactate	$(6.76 \pm 0.82)10^{-4}$	$(1.62 \pm 0.19)10^{2}$
1/6 Sodium lactate (buffer pH = 5.6)	$(8.07 \pm 3.80)10^{-4}$	$(1.71 \pm 0.81)10^{2}$
Ringer's solution	$(25.25 \pm 3.26)10^{-4}$	$(0.42 \pm 0.05)10^{2}$
Ringer's solution (buffer pH = 5.6)	$(13.92 \pm 2.55)10^{-4}$	$(0.79 \pm 0.14)10^{2}$
Hartmann's solution	$(12.45 \pm 5.00)10^{-4}$	$(1.02 \pm 0.41)10^{2}$
Hartmann's solution (buffer pH = 5.6)	$(14.96 \pm 5.11)10^{-4}$	$(0.81 \pm 0.27)10^{2}$
5% Glucose	$(4.83 \pm 0.48)10^{-4}$	$(2.20 \pm 0.21)10^{2}$
5% Glucose (buffer pH = 5.6)	$(3.00 \pm 0.50)10^{-4}$	$(3.69 \pm 0.62)10^{2}$
10% Glucose	$(10.95 \pm 1.60)10^{-4}$	$(0.98 \pm 0.14)10^{2}$
10% Glucose (buffer pH = 5.6)	$(12.91 \pm 2.47)10^{-4}$	$(0.85 \pm 0.16)10^{2}$
5% Fructose	$(9.38 \pm 5.84)10^{-4}$	$(1.83 \pm 0.46)10^{2}$
5% Fructose (buffer pH = 5.6)	$(12.91 \pm 2.47)10^{-4}$	$(1.83 \pm 0.46)10^{2}$
10% Fructose	$(5.02 \pm 1.80)10^{-4}$	$(2.40 \pm 0.86)10^{2}$
10% Fructose (buffer pH = 5.6)	$(4.98 \pm 1.52)10^{-4}$	$(2.33 \pm 0.71)10^{2}$
5% Glucose in Hartmann's solution	$(4.99 \pm 1.03)10^{-4}$	$(2.26 \pm 0.46)10^{2}$
5% Glucose in Hartmann's solution (buffer pH = 5.6)	$(3.74 \pm 1.34)10^{-4}$	$(3.31 \pm 1.20)10^{2}$

little influence on the stability of the solution. Shelf-life of all studied infusion fluids was sufficient for clinical use; there was no significant loss of activity. In the mannitol solution the degradation of cefazolin sodium is accelerated. This effect can be explained by the rate-accelerating effect of the hydroxy compounds on the β-lactam antibiotics. Ringer's solution and lactated Ringer's solution also have an accelerating effect. This may be due to a catalytic effect of the Ca^{2+} ions present in both solutions.

The glucose solutions containing the antibiotic show a decrease in stability when the glucose concentration is increased at low temperatures (35,40 °C) but this effect is reversed at 60 °C. Solutions containing 5% glucose show a significantly greater stability than the solutions with 0.9% sodium chloride. However, when the concentration of glucose is 10% the stability is clearly below 0.9% sodium chloride.

Solutions containing levulose and sodium lactate show no significant changes in stability compared to a solution of 0.9% sodium chloride.

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