Cefepime Compatibility

Cefepime is widely used in clinical practice, yet only limited data are available on the safety and efficacy of this drug when administered by continuous infusion along with other parenteral drugs. Concomitant administration may lead to unintentional physical, chemical, or therapeutic incompatibilities and may eventually result in loss of cefepime's antibacterial activity. The objective of our study was to investigate the compatibility of cefepime (prepared for IV administration) with selected parenteral drugs commonly used in clinical practice (Table 1).

Cefepime (Maxipime, Bristol Myers-Squibb, Egypt) at concentrations of 10 mg/mL and 20 mg/mL was dissolved in Ringer's solution and combined with each of 5 other drugs at concentrations commonly used in clinical practice. Each combination was maintained at room temperature (25°C) in glass containers (supplied by Bristol Myers-Squibb) under normal fluorescent room light. Immediately after preparation and after 1, 6, and 24 h, each admixture was visually examined for formation of precipitate, change in colour, and evolution of gas; the pH was determined, and the concentration of cefepime was determined by a first-derivative spectrophotometric stability-indicating method. Cefepime was considered compatible with the second drug in each admixture if more than 90% of its initial concentration was retained.[1]

The therapeutic activity of cefepime in the admixtures was evaluated microbiologically against *Escherichia coli, Staphylococcus aureus*, and *Pseudomonas aeruginosa* just after preparation and 24 h later. Using the agar dilution method,[2] we tested cefepime alone (as a control) and cefepime in combination with each drug, with incubation at 37°C for 18 h. In cultures of cefepime alone, the lowest concentration of the antibiotic for which there was either no visible growth of the tested microorganism or fewer than 4 colonies was designated as the minimum inhibitory concentration (MIC). This MIC was compared with the MIC for cultures of cefepime combined with a second drug, and the combination was judged as synergistic (lower MIC), antagonistic (higher MIC), or indifferent (no change in MIC).

Mixtures of cefepime with drotaverine HCl immediately produced a precipitate; infrared spectral investigation revealed that the precipitate was an insoluble complex between the two drugs. Mixtures of cefepime with metoclopramide HCl, pheniramine maleate, tranexamic acid, and salbutamol sulphate were physically and chemically compatible. For example, the pH changed by less than 1 pH unit when cefepime was mixed with any of these 4 drugs. However, our finding of physical compatibility between cefepime and metoclopramide contradicts a previous publication, which reported that a precipitate formed immediately when cefepime was mixed with IV metoclopramide HCl.[3] Our finding may be related to the lower concentration of cefepime used in the current study.

The microbiological study revealed that cefepime did not lose its therapeutic activity when combined with any of the 4 drugs; all but one of the cultures were judged as "indifferent" because they had the same MIC as cefepime alone; the exception was tranexamic acid tested with *E. coli*, for which there was some antagonism at time zero.

We concluded that cefepime at 10 mg/mL and 20 mg/mL in Ringer's solution was physically, chemically, and therapeutically compatible for up to 24 h at room temperature in glass containers in admixtures with any of the following

Table 1. Drugs Tested for Compatibility with IV Cefepime 1% and 2% in Ringer's Solution

Drug	Manufacturer*	Mean Daily Dose†	Initial Drug Concentration	Amount Added (mL) to 10 mL of Admixture	Final Concentration in Admixture (mg/mL)
Drotaverine HCl	Alexandria	120 mg	40 mg/2 mL (20 mg/mL)	0.12	0.24
Pheniramine maleate	Aventis	68.25 mg	45.5 mg/2 mL (22.75 mg/mL)	0.06	0.1365
Salbutamol sulphate	Glaxo Wellcome	1500 mg	500 µg/mL	0.06	0.003
Tranexamic acid	Amoun	2.25 g	500 mg/5 mL (100 mg/mL)	0.45	4.5
Metoclopramide HCl	Memphis Chemical‡	20 mg	10 mg/2 mL (5 mg/mL)	0.08	0.04

*All manufacturers located in Cairo, Egypt.
†To be administered in 500 mL IV fluid.
‡Affiliated with Delagrange, France.

drugs: metoclopramide HCl, tranexamic acid, pheniramine maleate, and salbutamol sulphate. Therefore, these compounds can be combined with cefepime for IV infusion therapy.

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The Formulary System Reconsidered

I read with interest the Point Counterpoint column in the April issue entitled, "Do Formularies Enhance Patient Safety?"[1,2] First, let me say that I believe this column will provide an opportunity to examine or re-examine many of our practices and perspectives, and the editorial team is to be congratulated on developing it.

The first edition of the column provides just such an opportunity. Formulary systems intended to do what Kevin Hall[1] suggests they can accomplish require major investments of resources, personnel, and systems, and even with those investments, there is no guarantee for success. Furthermore, given the dynamic nature of contemporary medical care, the formulary system needs to be responsive to new information and changes in therapy in a timely fashion—no easy task. Unfortunately, as with many complex tasks, we tend to "cherry pick" the aspects of the formulary system that we will implement, rather than offering the complete package. So one facility will do a good job of documenting allergy status, while another will perform prospective drug-use evaluations while still maintaining outdated automatic stop order policies. But rarely are all aspects of the ideal formulary system put into practice in a single institution.

Even for the aspects selected, there may be very limited supporting evidence of their effectiveness. One of our past residents assessed the effect of prescribing reservations on drug use.[3] Yes, the project was difficult, and its success and subsequent publication of the project report in *CJHP* were attributable to the efforts of the principal investigator. Nonetheless, this is the type of work that is needed to develop an evidence base. Unfortunately, papers such as these are relatively rare, to the point that Hall is left to conclude that use of formulary system for patient safety is built on "belief".

The counterargument is more convincing,[2] in part because it challenges the notion of the age-old structure, originally built with little thought of patient safety, but focusing instead on cost containment. Given that data are available to indicate that pharmacist-provided services do enhance patient safety,[4] we should deploy our staff to provide those services or evaluate our own formulary systems to enhance this evidence base. Continuing to offer and support a system based on "beliefs" reflects poorly on the profession.

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