shaped or needle-like. The X-ray powder diffraction patterns of the anhydrous and trihydrate forms of epicillin are distinguishable (Table I). The X-ray diffraction patterns of epicillin and ampicillin and of epicillin trihydrate and ampicillin trihydrate, respectively, are similar. The amorphous form of epicillin shows no X-ray diffraction pattern.

Epicillin trihydrate contains 13.3% of total volatiles or water, as determined by thermal gravimetric or Karl–Fischer analysis. Differential thermal analysis of the trihydrate shows characteristic endotherms at 92, 102, and 120° and an exotherm peak at about 213–218°; the anhydrate shows only an exotherm peak at about 215–220°. Differential thermal analysis of the amorphous form of epicillin shows only one inflection near 170°. Thermograms of ampicillin and ampicillin trihydrate resemble those of epicillin and epicillin trihydrate, respectively[1].

The solid polymorphic forms of epicillin may also be distinguished by their IR spectra (Fig. 1). Spectra of epicillin anhydrate (A) and epicillin trihydrate (B) differ in the NH and OH stretching regions. A very sharp isolated band at 2.99 μm is characteristic of the anhydrous form, whereas less sharp peaks at about 2.85 and 2.90 μm are found for the trihydrate. The anhydrate also shows distinct bands at 5.65, 5.92, 6.12, 6.32, 6.55, 6.71, 6.86, 7.20, 7.30, 7.37, 7.68, and 7.99 μm; the trihydrate shows corresponding bands at 5.64, 5.95, 6.15, 6.25, 6.36, 6.71, 6.85, 7.02, 7.08, 7.15, 7.25, 7.30, 7.52, 7.68, and 7.99 μm. There are, in addition, striking differences between the two crystalline forms of epicillin evident in the fingerprint region of the IR spectrum (beyond 8 μm). Spectrum C shows the typically poor resolution characteristic of the amorphous form of epicillin. The IR spectra of ampicillin and its hydrated forms were reported previously (11, 14).

Neither the trihydrate nor the anhydrate of epicillin is hygroscopic at 30° when exposed to an atmosphere of 85% relative humidity for 24 hr or to 100% humidity for 2 hr. The amorphous form of epicillin, however, increases in moisture content by 5–8% within 2 hr in air at ambient temperature.

When the epicillin trihydrate is heated *in vacuo* (dehydrated) at 50° for 4 days, the crystal lattice is ruptured and the compound is converted to the amorphous form; under these circumstances, loss of activity (11%) occurs. Similarly, ampicillin trihydrate and monohydrate showed losses in potency after rupture of their crystal lattices (9).

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[1] Details of the differential thermal analysis results are to be published.

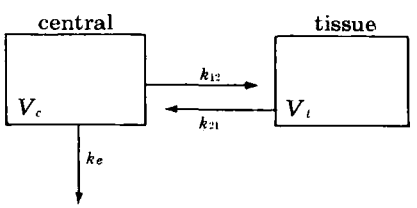
Changes in Pharmacokinetics of Cefazolin due to Stress

Keyphrases □ Cefazolin—pharmacokinetics, changes due to stress □ Pharmacokinetics—cefazolin, changes due to stress □ Stress—effects on pharmacokinetics of drugs, cefazolin

To the Editor:

Several investigators (1–4) have published cefazolin blood level data after intravenous infusion or bolus dose injection. In every case the pharmacokinetics of this drug have been described by a one-compartment model. Inspection of the data indicates that the decline in blood levels is a biexponential process and that the pharmacokinetics of this drug are more appropriately described by at least a two-compartment model, as was confirmed in our laboratories using normal human volunteers.

A 1-g dose of the drug was administered intravenously and serum samples were analyzed for cefazolin concentration as a function of time. The serum samples were assayed by absorbing 20 μl of suitably diluted serum on filter paper disks and placing the disks in bacto antibiotic medium No. 1 agar plates. Nine to 10 ml of agar, previously seeded with *Bacil-*



Scheme I

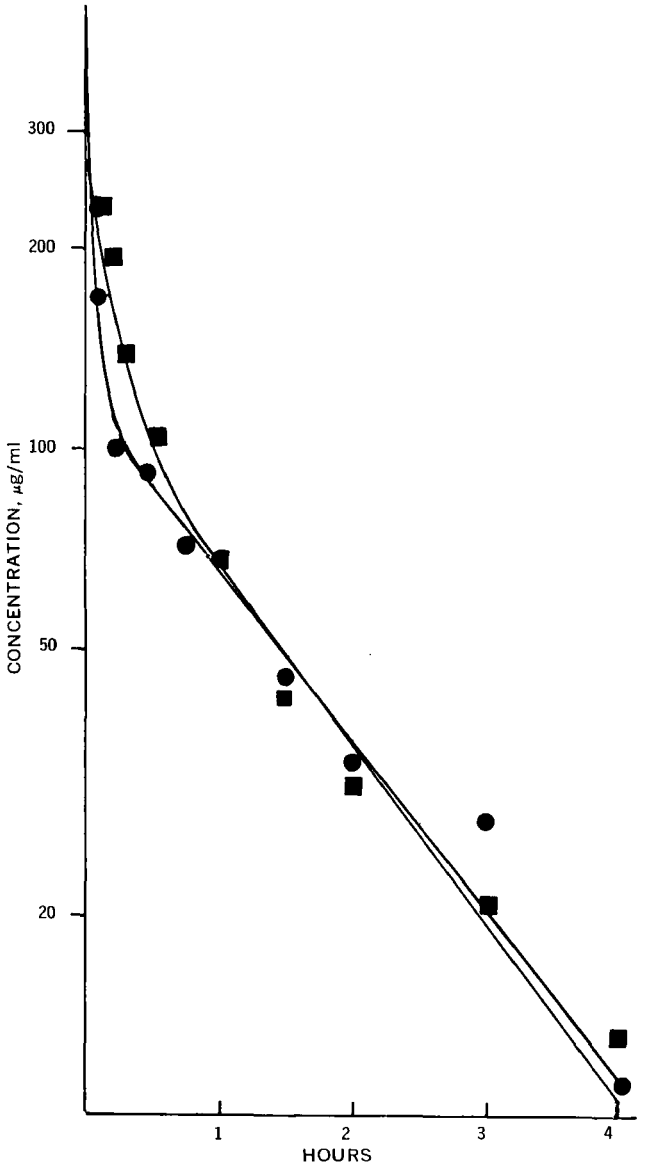


Figure 1—*Cefazolin serum concentrations. Key:* ■, *mean data, four subjects; and* ●, *Subject BEV.*

lus subtilis spores, was used in each 100-mm plate. The plates were incubated for 16–18 hr at 37°. Zones of inhibition were measured and compared to similarly assayed standards prepared in pooled human serum.

The data were fit to a two-compartment open model (Scheme I) with the aid of a nonlinear curve-fitting program (5). For such a model, the serum concentration at any time can be expressed by:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}$$

where:

$$C_p^0 = A + B \qquad \text{(Eq. 2)}$$

$$A = \frac{C_p^0(k_{21} - \alpha)}{\beta - \alpha} \qquad \text{(Eq. 3)}$$

$$B = C_p^0\frac{(k_{21} - \beta)}{\alpha - \beta} \qquad \text{(Eq. 4)}$$

and k_{12} and k_{21} are first-order distribution constants

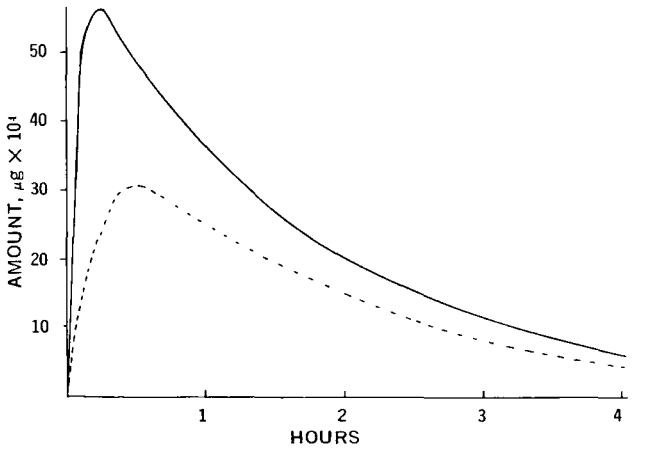


Figure 2—*Cefazolin tissue levels. Key: - - - -, mean data, four subjects; and ——, Subject BEV.*

and k_e is a first-order elimination rate constant [$(\alpha\beta)' = k_{21}k_e$, $\alpha + \beta = k_e + k_{12} + k_{21}$]. Then:

$$(V_d)_{ss} = V_c\left(\frac{k_{21} + k_{12}}{k_{21}}\right) = V_c + V_t \qquad \text{(Eq. 5)}$$

where V_t = volume of the tissue compartment, and V_c = volume of the central compartment = dose/(A + B). Then:

$$(V_d)_\beta = \frac{k_e V_c}{\beta} \qquad \text{(Eq. 6)}$$

$$V_{d(\text{extrap})} = \frac{\text{dose}}{B} \qquad \text{(Eq. 7)}$$

An excellent fit to the data was obtained as can be seen in Fig. 1. The correlation coefficient was never less than 0.996. Analysis of the available published data (1–4) gives pharmacokinetic parameters that are similar to the results of this study (Table I).

One patient (BEV), a white 27-year-old female weighing 56.3 kg, fainted upon drug administration and when blood samples were removed. It can be seen from Table I and Fig. 1 that this patient's data

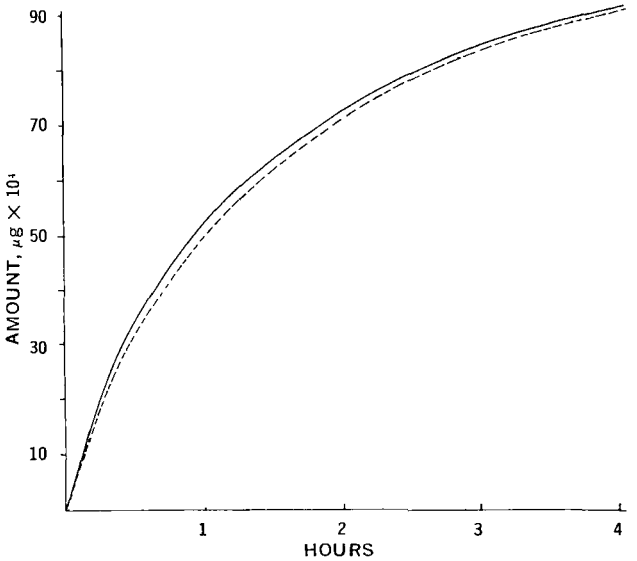


Figure 3—*Cefazolin excretion. Key: - - - -, mean data, four subjects; and ——, Subject BEV.*

Table I—Pharmacokinetic Parameters of Cefazolin[a]

Parameter	Present Study[b]	Literature Values[c]	Subject BEV
α, hr^{-1}	4.832 ± 1.784	3.451 ± 1.489	18.841
β, hr^{-1}	0.573 ± 0.116	0.434 ± 0.083	0.586
k_{12}, hr^{-1}	1.961 ± 0.943	1.291 ± 0.674	11.933
k_{21}, hr^{-1}	2.148 ± 0.914	1.683 ± 0.846	5.481
k_e, hr^{-1}	1.299 ± 0.226	0.907 ± 0.266	2.013
$(t_{1/2})_\alpha$, hr	0.167 ± 0.082	0.245 ± 0.142	0.037
$(t_{1/2})_\beta$, hr	1.248 ± 0.255	1.642 ± 0.322	1.184
V_c, ml	3,482 ± 357	4072 ± 1199	2260
$(V_d)_{ss}$, ml	6,791 ± 1873	6918 ± 1014	7181
$(V_d)_\beta$, ml	8,145 ± 2609	8082 ± 1157	7769
$(V_d)_{(extrap)}$, ml	10,113 ± 3755	9757 ± 670	8429
Clearance, ml/hr			
$(V_d)_\beta \times \beta$	4667	3508	4552
$V_c \times k_e$	4523	3693	4549

[a] Mean ± *SD*. [b] Mean of four subjects. [c] Data obtained from Refs. 1–4.

were significantly different from those of the other patients in this study. The value for α was nearly four times higher than normal, while the volume of the central compartment was reduced by approximately 50% to a value corresponding to the plasma volume for a female of BEV's weight and age (6), indicating that distribution to the tissue compartment was increased. This should be expected since fainting was probably due to decreased blood pressure or flow in the brain resulting from peripheral vasodilation.

If the muscle, a tissue associated with only moderate blood flow, is in the tissue compartment, peripheral vasodilation would result in a faster rate of drug distribution. One would not expect $(V_d)_{ss}$ to change under these circumstances, since this parameter represents the sum of the central and tissue compartment volumes ($V_c + V_t$). It can be seen from Table I that $(V_d)_{ss}$ for BEV was essentially identical to that of the other subjects in this study as well as to the mean values obtained from the literature. Similarly, peripheral vasodilation would not affect the overall elimination of cefazolin as is seen by the almost identical values for β. In addition, the total body clearance, which for this drug also represents renal clearance since the drug is virtually nonmetabolized, was not changed between BEV and the other patients in this study (Table I).

A theoretical plot of cefazolin tissue levels and the cumulative amount excreted into the urine, based on the data of Table I, is shown in Figs. 2 and 3. The tissue levels rose rapidly and peaked significantly sooner for BEV than for the other patients. Differences in urinary excretion, however, were not considered significant.

In terms of antibiotic therapy, the differences in pharmacokinetic parameters induced by this type of stress is probably not significant, because in actual therapy cefazolin must be administered in a constant infusion or multiple-dose regimen. This study illustrates that changes in drug distribution can occur in the clinical situation. These changes would be significant when therapeutic tissue levels must be obtained rapidly and the drug has a narrow therapeutic index, *i.e.*, in the treatment of cardiac arrhythmias. In these cases, the patient is under a stress situation and the clinician is advised to be aware of potential adverse effects due to drug "redistribution" as the patient's condition improves.

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