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Chloramphenicol Pharmacokinetics in Hospitalized Patients

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The apparent body clearance of chloramphenicol was investigated in 21 hospitalized adult patients on 27 occasions. Apparent body clearance was found to be significantly lower (1.99 ± 1.49 ml/min per kg) in patients with total serum bilirubin concentrations of >1.5 mg/100 ml than in patients with serum bilirubin concentrations of ≤1.5 mg/100 ml (3.57 ± 1.72 ml/min per kg; $P < 0.001$). Serum protein binding of chloramphenicol was lower in cirrhotic patients (42.2 ± 6.8% bound) than in normal adults (53.1 ± 5.2% bound; $P < 0.001$). Low binding of chloramphenicol was also found in the serum of premature neonates (32.4 ± 8.2% bound; $P < 0.001$). Reduced binding in neonates implies the need for a lower therapeutic range of total chloramphenicol concentration (3.5 to 13.9 μg/ml) compared with the usual adult range (5 to 20 μg/ml). Finally, three case reports are presented which demonstrate marked abnormalities and intrasubject variation in chloramphenicol clearance.

As a result of the activity of chloramphenicol (CAP) against anaerobic organisms (5) and *Haemophilus influenzae* which are resistant to ampicillin (2), it has gained new popularity. Use of this agent is, however, coupled with serious potential toxicities. Idiosyncratic aplastic anemia is extremely rare (25) but must be weighed as a factor in the choice of this agent. Dose-related, and thus avoidable, toxicities include normocytic bone marrow suppression, which is associated with serum concentrations exceeding 25 μg/ml and prolonged courses of therapy (13, 19, 25), and a syndrome consisting of cardiovascular collapse, gastrointestinal distress, respiratory depression, and coma. This symptom complex, commonly referred to as the grey syndrome, has been reported in neonates (3, 12, 22, 24), infants (4), and adults (11, 23) and is associated with serum CAP concentrations ranging from 40 to 200 μg/ml.

CAP is extensively metabolized. In normal adults approximately 90% of an oral dose is excreted in urine within 24 h (8). Of this quantity, only 5 to 10% is excreted as unchanged drug (7). The principal metabolite is a glucuronide which is formed in the liver and is actively secreted by the kidney (6). It is reasonable to expect decreased clearance of the drug in patients with impaired liver function. McCurdy (13) and Suhrland and Weisberger (20) reported higher CAP serum concentrations in patients with cirrhosis of the liver compared with normal subjects given similar doses of the drug. Reversible hematological toxicity of the drug has been shown to occur with an increased frequency in patients who demonstrate decreased CAP clearance (21). Cardiovascular toxicity and other symptoms of toxicity may also occur with increased frequency in these patients. The symptoms of toxicity may be confused with manifestations of underlying disease states.

It was the goal of this investigation to evaluate CAP clearance in hospitalized patients being treated with the drug, to attempt to correlate these clearance values with total serum bilirubin (used as an index of liver function), and to evaluate the binding of CAP to serum proteins in various patient populations.

During these investigations, three unusual patients were studied. Analysis of CAP serum concentration data in these patients revealed marked deviation from the expected behavior of this drug. These cases have been summarized and are presented as documentation of potential problems which may occur.

MATERIALS AND METHODS

Serum specimens (5.0 ml) were obtained on 27 occasions from 21 adult patients during a course of treatment with CAP. CAP serum concentration determinations had been requested by the physicians of the patients. The patients represented a wide spectrum of medical conditions. They were receiving either oral CAP or intravenous CAP-succinate ester. Specimens were obtained 4 to 6 h after a previous dose and at least 24 h after initiation of therapy, in order to estimate serum concentrations at steady state. The CAP dose corrected for body weight (milligrams per kilogram per day) was recorded.

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CAP clearance was estimated for each patient by dividing the CAP dosage (in milligrams per kilogram per minute) by the serum drug concentration (in milligrams per milliliter). This value has been termed apparent body clearance (ABC) (26). Results were expressed as milliliters per minute per kilogram.

Serum protein binding of CAP was evaluated in serum obtained from 10 normal healthy adult volunteers, 20 premature infants during the first weeks of life, and 15 patients who suffered from cirrhosis of the liver. These additional patient samples were leftover serum which had been obtained for biochemical determinations for other study protocols. Samples were refrigerated immediately and frozen (−4°C) within 8 h of collection. Equilibrium dialysis was performed by placing 0.3 ml of serum and 0.3 ml of phosphate-buffered physiological saline spiked with 30 μg of CAP per ml on opposite sides of dialysis membrane (Spectrapor no. 2; Spectrum Medical Industries Inc., Los Angeles, Calif.). Dialysis cells were shaken in the dark at 37°C for 2 h. Equilibrium had been shown to occur by 1 h in preliminary studies. Samples of both the serum and the buffer sides were assayed for CAP concentration as described below. Percent binding was calculated by the following equation: Percent bound = [1 − (total concentration in buffer/total concentration in serum)] × 100.

Bilirubin (10 mg/100 ml from bovine gallstones; Sigma Chemical Co., St. Louis, Mo.) was added to the sera from normal subjects and premature infants to evaluate the potential displacing effect of bilirubin on CAP binding. CAP binding to high- and low-binding control sera was determined on nine and six separate occasions, respectively, in an attempt to evaluate the precision of binding determinations.

Analysis of total CAP concentration in all samples was performed by high-performance liquid chromatography (8). This method has been shown to be specific for CAP in the presence of metabolites, CAP-succinate ester, and other antibiotics. The analytic procedure was as follows. The sample (0.1 ml) was shaken with an equal volume of 1.0 N sodium acetate buffer, pH 4.6. This solution was extracted with 1 ml of ethyl acetate containing 12.5 μg of 5-ethyl-5-*p*-tolylbarbituric acid (99+% pure; Aldrich Chemical Co. Inc., Milwaukee, Wis.) per ml as an internal standard. The organic phase was evaporated to dryness under a nitrogen stream at 40°C. The residue was redissolved with 0.2 ml of methanol, and 0.02 ml of this solution was injected into the chromatograph. Separation was accomplished by using a 25-cm C-18 μ-Bondapak column (PN-27324; Waters Associates, Milford, Mass.) at 40°C. The mobile phase was 25% acetonitrile (Photrex grade; J. T. Baker Chemical Co., Phillipsburg, N.J.) in 0.1 N acetate buffer, pH 6.0. Ultraviolet absorbance of CAP and the internal standard was determined at 270 nm. Retention times for CAP and the internal standard were 3.0 and 4.8 min, respectively. The procedure demonstrated between-day coefficients of variation of 13.7% on 7.5-μg/ml control samples and 6.1% on 25-μg/ml control samples.

During the above-described studies, three critically ill patients were examined. By appropriate prospective sampling and by obtaining leftover serum from clinical laboratories, a detailed evaluation of the pharmacokinetic characteristics of CAP was possible.

RESULTS

Figure 1 shows CAP serum concentrations as related to weight-corrected dose. Patients were divided into two groups on the basis of normal (<1.5 mg/100 ml) or elevated (≥1.5 mg/100 ml) total serum bilirubin concentration. This parameter was used as a marker for impaired liver function. Extrahepatic factors which cause elevation of serum bilirubin concentration were not present in study patients. In patients with normal liver function, regression analysis demonstrated a significant correlation between concentration and dose correlation coefficient (0.68; $P < 0.01$). No correlation was found for patients with bilirubin ≥1.5 mg/100 ml.

Figure 2 shows the results of ABC calculations. Points joined by a line indicate serial determinations of ABC in the same patient on different days. The mean for patients with normal liver function was 3.57 ± 1.72 ml/min per kg. In patients with impaired liver function, the mean clearance was 1.99 ± 1.49 ml/min per kg. The difference between the mean clearances of the two patient groups was statistically significant ($P < 0.001$).

The results of protein binding studies are shown in Fig. 3. In normal adults, the mean binding was 53.1 ± 5.2%. When bilirubin was added to the serum before dialysis, there was no statistically significant change in binding (50.9 ± 2.7%).

In cirrhotic patients, the mean binding was 42.2 ± 6.8%. This was significantly ($P < 0.001$)

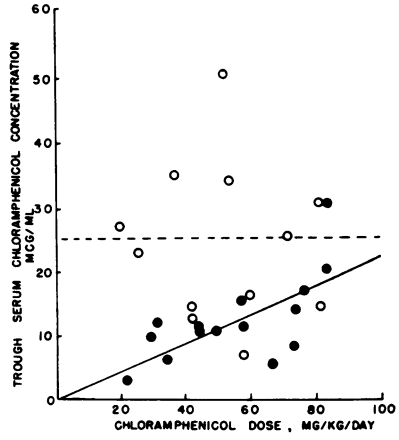

FIG. 1. *Relationship between serum CAP concentrations and daily dosage in patients with normal* (●) *and elevated* (○) *serum bilirubin concentrations.*

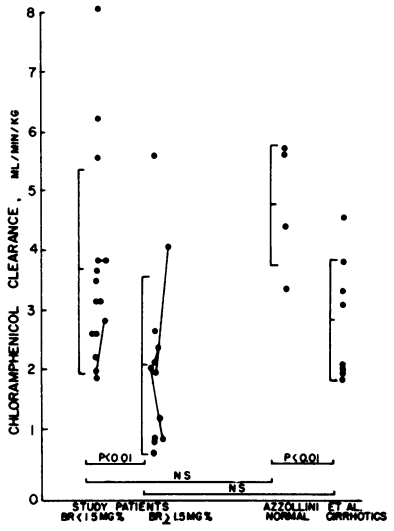

FIG. 2. *Estimated ABC in patients with normal and elevated serum bilirubin (BR). Also shown are data derived from Azzollini et al. (1). Standard deviation for each group is shown. Points joined by lines indicate serial determinations for the same patient on different days. NS, Not significant.*

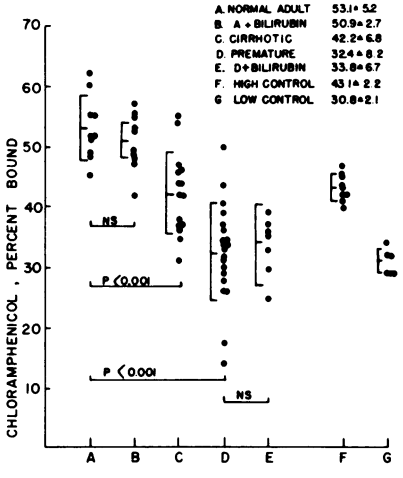

FIG. 3. *Protein binding of CAP in serum from various patient categories. The mean ± 1 standard deviation of percent binding is shown for each category. Statistical significance of differences between groups is demonstrated. NS, Not significant.*

lower than that of normal subjects. Binding in serum from premature infants was also significantly lower than binding in serum from normal adults (32.4 ± 8.2%; $P < 0.001$). Again, in neonatal serum, added bilirubin produced no significant change in binding (33.6 ± 6.7%).

Also shown in Fig. 3 are results of replicate binding determinations performed on the high- and low-binding control sera. The coefficients of variation for these determinations were 5.2 and 6.9%, respectively.

Case studies. (i) Case 1. C.O. was a 67-year-old white male admitted with a diagnosis of sepsis and *E. coli* meningitis. He was a chronic alcoholic. Initial laboratory data indicated normal renal function and cirrhosis of the liver (total bilirubin, 8.5 mg/100 ml; serum albumin, 2.2 g/100 ml). Antibiotic therapy with CAP (75 mg/kg per day, given intravenously) and tobramycin, given both intravenously and intrathecally, was initiated. Total serum, free serum, lumbar, and ventricular concentrations of CAP are shown, along with CAP dose, in Fig. 4. In response to the elevated serum CAP concentrations obtained on day 5, the daily dose was reduced to 50 mg/kg. Despite the reduction in dose, serum concentration continued to rise. On hospital day 10, renal function remained normal, total bilirubin was 4.4 mg/100 ml, and albumin was 4.3 g/100 ml. On hospital day 15, the patient went into low cardiac output septic shock with a blood pressure of 75/50 mm of Hg and a dramatic reduction in urine flow (300 to 40 ml/24 h). The condition of the patient continued to deteriorate. CAP concentration was determined on hospital day 17, and it had continued to increase. The patient expired on hospital day 18.

This patient demonstrated marked variability of CAP pharmacokinetics. His ABC continually decreased over the course of hospitalization, from 1.95 to 1.02 to 0.67 ml/min per kg. Although his initial value was close to the mean value which was observed in cirrhotic patients (1.99

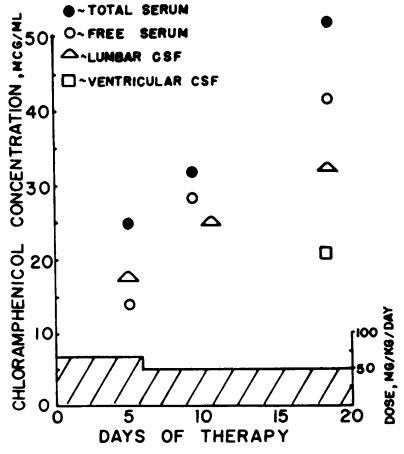

FIG. 4. *Serum, free serum, lumbar, and ventricular concentrations and dosage of CAP at various times during therapy in case 1. CSF, cerebrospinal fluid.*

ml/min per kg), his final clearance value was only about one-third of this value. In addition, the binding of CAP to serum proteins was low and variable in this patient. Adequate penetration of CAP into the cerebrospinal fluid was well demonstrated. The deterioration of cardiovascular status which occurred on day 15 may have adversely affected CAP clearance.

(ii) Case 2. R.P. was a 17-year-old 72-kg white male admitted to the hospital in septic shock on 25 March 1978. Therapy with gentamicin, oxacillin, CAP, methylprednisolone, and dopamine was begun. Three doses of 1.8 g. of CAP, followed by four dose of 1.2 g of CAP, were administered at 6-h intervals. Serum creatinine was 4.2 mg/100 ml on admission and increased to 7.4 mg/100 ml by 50 h, at which time continuous peritoneal dialysis was begun. Serum creatinine stabilized in the range of 7 to 8 mg/100 ml during the period of study. Serum glutamic oxalacetic transaminase, serum glutamic pyruvic transaminase, and lactic dehydrogenase were only mildly elevated during the study (47 to 62 vs. 5 to 19 in normals; 35 to 43 vs. 4 to 25 in normals; and 252 to 274 vs. 55 to 134 in normals, respectively). Arterial oxygen tension remained low (50 to 80 mm of Hg) despite high percentages of inspired oxygen (50 to 90%) during treatment. Initial hypotension was rapidly reversed by the infusion of dopamine (7.5 to 15 μg/kg per min). At 75 h, the dopamine infusion was discontinued, and the blood pressure of the patient remained stable. All CAP doses and serum concentrations obtained during the treatment are shown in Fig. 5. The patient recovered over the course of 2 months and was discharged without sequelae.

The patient demonstrated an unusual degree of accumulation of CAP and a dramatically increased elimination half-life (19.1 h) (Fig. 5). If a normal volume of distribution of 0.92 liters/kg is assumed (1), the calculated CAP body clearance of the patient (volume of distribution times elimination constant) (17) was only 0.55 ml/min per kg, which is a value markedly below those reported previously. At approximately 80 h, his clearance began to increase dramatically, and by 130 h, his ABC had returned to normal (4.28 ml/min per kg). This increased clearance coincided with the discontinuation of dopamine infusion. As dopamine is not expected to decrease mesenteric blood flow at the dose employed, one might expect that the improvement in clearance after the discontinuation of dopamine was coincidental or that dopamine was discontinued in response to an overall improvement in the condition of the patient, which resulted in increased CAP clearance. This patient also demonstrated marked variability in CAP clearance.

(iii) Case 3. K. S. was a 4-month-old 5-kg white female who was admitted to the hospital after suffering respiratory arrest at home. She had been well until 1 day before admission, when she became febrile and listless. Moderate hepatomegaly was noted on admission. Indexes of liver function were only slightly abnormal on admission but became markedly elevated by 72 h after admission (total bilirubin, 5.5 mg/100 ml; serum glutamic oxalacetic transaminase, 394 U; serum glutamic pyruvic transaminase, 129 U; lactic dehydrogenase, 1,399 U). Renal function remained normal during the period of observation. Antibiotic coverage with gentamicin, oxacillin, and CAP was begun. The dosage of CAP employed and the resultant serum concentrations are shown in Fig. 6. At 59 h, the patient suffered a second respiratory arrest and cardiovascular collapse. At this time, a serum sample was assayed for CAP concentration. The result (58.8 μg/ml) was above the desired therapeutic range, and therapy was discontinued. During the subsequent 48-h period, multiple serum samples were assayed. The half-life of CAP elimination was markedly increased (36 h).

Assuming that drug administration can be approximated by a constant infusion, the volume of distribution was estimated by the method of Sawchuk and Zaske (18); a value of 1.42 liters/kg was obtained. This volume distribution and the elimination rate constant were used to simulate serum concentration which would be ex-

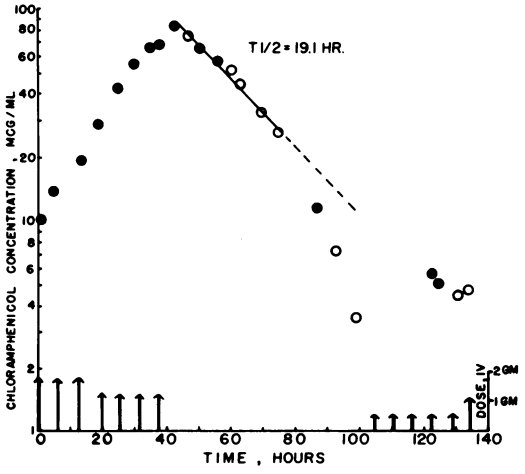

FIG. 5. *Serum concentration and dosage of CAP at various times during therapy in case 2. Symbols: ○, prospectively obtained samples; ●, scavenged serum samples, as explained in text. The solid line is the least-squares fit of the observed serum concentrations (45 to 75 h), and the broken line is the expected continuation of this curve if elimination had remained constant. T 1/2, Half-life; IV, intravenous.*

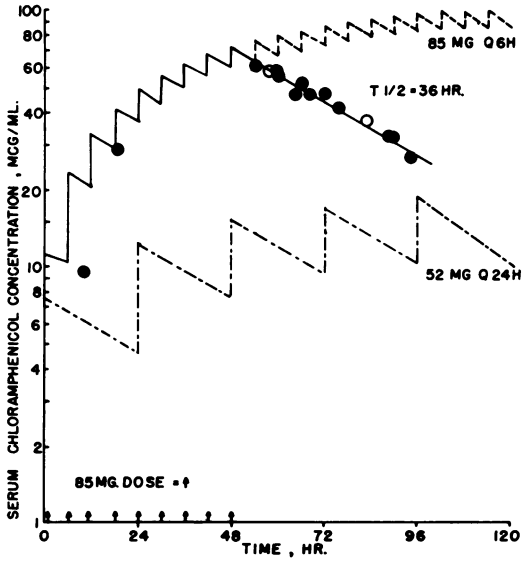

FIG. 6. *Serum CAP concentration at various times during therapy in case 3. Symbols: ○, prospectively obtained samples; ●, scavenged serum samples. Also shown are simulated curves, as explained in the text. T 1/2, Half-life; Q 6H, doses given every 6 h; Q 24H, dose given every 24 h.*

pected from an 85-mg dose of CAP administered every 6 h. The close agreement between observed and predicted values (Fig. 6, upper curve) indicates that the low clearance which this patient demonstrated (0.45 ml/min per kg) was present on admission. Also shown is a simulation (Fig. 6, lower curve) of the dosage regimen which would have been required in this patient to produce serum concentrations in the range of 10 to 20 μg/ml (52-mg doses, given every 24 h). The patient expired at 100 h after admission. Autopsy revealed massive necrosis of the liver with fatty infiltration. The exact etiology of this injury was not found. This case demonstrated the extreme to which CAP elimination can be reduced in patients with severe liver impairment.

DISCUSSION

A significant correlation (correlation coefficient, 0.68) was found between serum trough concentration and dose in patients with normal liver function (Fig. 1). We were unable to observe a correlation in patients with elevated bilirubin concentrations. Compromised liver function may have a variable effect upon CAP metabolism in different individuals.

Our observations indicated that patients with normal liver function receiving usual doses generally have serum concentrations below 25 μg/ml. In one-half of our patients with impaired liver function, however, serum concentrations were above 25 μg/ml. An increased incidence of reversible bone marrow toxicity is associated with serum concentrations that exceed 25 μg/ml (13, 19, 25), and grey syndrome has been reported in patients with somewhat higher serum concentrations (3, 4, 11, 12, 22–24). Thus, monitoring of CAP serum concentrations may not be needed in patients with normal liver function, but it would appear to be of value in patients with cirrhosis.

Our CAP clearance values (ABC) were compared with clearance values calculated by conventional means in which the data of Azzollini et al. (1) were used. These authors reported serum CAP concentrations after administration of a single intravenous dose of 10 mg/kg. Their serum concentration data were fit to either a one-compartment or a two-compartment pharmacokinetic model by NONLIN computer program (14) to yield the best fit to observed concentrations. The volume of distribution (V_D), elimination constant (K), and clearance (Total body clearance = $V_D \times K$) were calculated (Table 1). Their clearance data also appear in Fig. 2.

Their normal subjects demonstrated a significantly higher ($P < 0.01$) clearance value than their cirrhotic patients (4.70 ± 1.11 versus 2.78 ± 1.02 ml/min per kg). There was no significant difference between their normal subjects and our patients with normal liver function; nor was there a significant difference between our cirrhotic patients and the patients studied by Azzollini et al. (1). The agreement between ABC and total body clearance values seen in Fig. 2 supports the use of the ABC parameter as an initial clearance estimate in the patient population studied. Azzollini et al. (1) also reported a significant correlation between the half-life of CAP and serum bilirubin concentration. Our observation of reduced clearance in patients with total bilirubin concentrations of ≥1.5 mg/100 ml confirms their results. As approximately 90% of the drug is metabolized by the liver (8), compromised liver function would be expected to diminish clearance and increase serum concentrations. This is consistent with our observations (Fig. 1 and 2).

Protein binding was found to be decreased in serum from patients suffering from liver disease. This phenomenon may be due to a lower total serum protein concentration in cirrhotic patients. Binding in premature infants was also significantly lower, compared with that in normal adults. This is consistent with observations by Kurz et al. (9), who reported a mean binding of 66.0% in their pooled adult plasma and 45.9%

TABLE 1. *Chloramphenicol pharmacokinetics in patients*

Patient type	Volume of distribution (liters/kg)	Elimination constant (h^{-1})	Total body clearance (ml/h per kg)
Normal (n = 4)	0.92 (0.83–1.14)[a]	0.308 (0.226–0.404)	4.70 (3.30–5.62)
Cirrhotic (n = 8)	0.98 (0.59–1.20) (t = 0.52; NS[b])	0.175 (0.106–0.282) (t = 3.27; $P = 0.005$)	2.78 (1.78–4.52) (t = 2.98; $P = 0.01$)

[a] Mean values are given; numbers in parentheses are ranges.
[b] NS, Not significant.

in pooled cord plasma collected immediately after delivery. The ratio of adult to cord serum binding reported by these investigators (1.6) was identical to the value obtained in our study.

These authors determined that some other factor in addition to reduced total protein concentrations in neonatal serum was responsible for the reduced binding in these patients. Nonprotein constituents which may be present in the cord plasma were implicated (9). Different albumin properties which have been reported in newborns (15) may be responsible for the altered binding characteristics. Bilirubin has been shown to displace certain acidic drugs from albumin binding sites (10). Our study, however, demonstrated no such effect on the binding of neutral CAP.

The decreased binding observed in the sera of our cirrhotic patients would be expected to result in a mean free serum CAP concentration which is 23.4% higher than that observed in normal adults (42.2 versus 53.1% bound). This difference is probably not clinically significant. In premature infants, however, the mean free concentration was 44.1% higher than in normal adults (32.4 versus 53.1% bound). The recommended therapeutic range for total serum concentration is 5 to 20 μg/ml (16). This range of total concentrations would generate a free concentration range of 2.3 to 9.4 μg/ml in normal adults (53.1% bound). In premature infants, total serum concentrations of only 3.5 to 13.9 μg/ml would yield the same free drug concentrations (32.4% bound). This significant difference in therapeutic range should be appreciated when interpreting serum concentration data.

The case reports presented are self explanatory. It is of significance that in the rather limited observation of CAP usage in this study, three cases with dramatic alterations in the pharmacokinetic behavior of this drug should appear. It is likely that such unusual behavior may occur with a previously unsuspected frequency. If shock plays a major role in these changes, one could predict a cycle in which shock produces elevated levels of CAP which, in turn, produce cardiovascular collapse and respiratory arrest.

The degree of intrapatient variation observed in the present study indicates that evaluation of CAP pharmacokinetic parameters and dosage prediction in individual patients may not be reliable. It appears that the best approach to therapy is frequent monitoring of serum CAP concentrations, with empirical adjustment of dosage when indicated.

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