Effects of General and Local Anesthesia on the Pharmacokinetics of Cefazolin in Patients Undergoing Orthopedic Surgery

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The pharmacokinetics of cefazolin in patients undergoing orthopedic surgery with either general (enflurane) or local (lidocaine or marcaine) anesthesia were studied. No differences in either mean serum levels at 30, 60, or 120 min after the intravenous injection of cefazolin or serum half-lives were seen between the two groups of patients.

Cephalosporin antibiotics such as cefazolin are frequently given to surgical patients before their operations for prophylaxis against possible infection. General (volatile) anesthetic agents used during surgical operations are known to depress liver function by 40% and to reduce renal blood flow and the glomerular filtration rate to 50% of normal levels (3). Because of the potential alteration in the levels of cefazolin in serum during surgical anesthesia, we studied the pharmacokinetics of these antibiotics in orthopedic patients anesthetized with the popular general anesthetic enflurane. The pharmacokinetics of cefazolin in patients anesthetized with enflurane were compared with those in patients given an identical dose of cefazolin but who underwent local anesthesia (marcaine or lidocaine) for their surgery. These local anesthetic agents, in contrast to general anesthetics, have no significant effect on liver function or glomerular filtration rate (8).

Serum specimens were obtained from 20 consenting healthy male patients aged 19 to 40 (this study was approved by the Institutional Human Subjects Review Committee) undergoing surgery for either open or closed reduction/intertabular fixation of fractures of the upper and lower extremities or arthroscopies/arthrotomies of the knee joint. All subjects had normal renal and hepatic functions.

All of the operations required the use of a tourniquet, were performed without transfusion, and lasted from 2 to 4 h. The anesthesia regimen used was as follows: induction, Pavulon (ca. 0.06 mg/kg) and Pentothal (3 mg/kg); maintenance, N2O and O2 (3 and 0.5 liters per min, respectively) with either Ethrane (enflurane) at 1.5% (vol/vol) or marcapl (or lidocaine) for the local maintenance of anesthesia; ventilation (during general [enflurane] anesthesia), 8 liters per min with a minimum volume of 100 ml/kg; intravenous fluids, preloading volume was 500 ml of 5% glucose with a maintenance level of approximately 4 ml of plasmolyte per kg per h. After the induction of anesthesia, a 2-g intravenous bolus injection of cefazolin was given. Serum specimens were collected at intervals of 30, 60, 120, and 240 min.

Levels of cefazolin in serum were measured by high-pressure liquid chromatography with a μBondapak C18 column and an ALC/GPC 204 liquid chromatograph (Waters Associates, Inc., Milford, Mass.) as previously described (9).

The serum half-life ($t_{1/2}$) of cefazolin in the orthopedic patients was calculated by dividing 0.693 by the slope of the regression line. The regression line was derived from a semilogarithmic plot of cefazolin concentration versus time. Analysis of covariance to test the equality of slopes was calculated according to the method of Zar (11). Statistical analysis of the mean levels of cefazolin in serum at various times was determined by analysis of variance (11).

The mean levels of cefazolin in serum in orthopedic patients with enflurane or local anesthesia at 30, 60, 120, and 240 min after injection of a 2-g bolus of cefazolin are shown in Table 1. No significant differences were observed between the two kinds of anesthesia on cefazolin levels in serum at the times indicated. The correlation coefficients for enflurane and local anesthesia were 0.79 and 0.90, respectively, as determined by Pearson's R method (11). Analysis of covariance to test the equality of the enflurane-cefazolin and local anesthesia-cefazolin slopes revealed no significant differences ($P > 0.5$). Hence, the half-lives of cefazolin are not different in patients receiving enflurane ($t_{1/2} = 95$ min) or local ($t_{1/2} = 83$ min) anesthesia (analysis of variance $P$ value is equal to 0.33).

Pharmacokinetic studies of antimicrobial agents are most often performed in healthy, awake human subjects. Because the physiology of the anesthetized surgical patient is very different from that of the unanesthetized patient, we examined the pharmacokinetics of cefazolin in orthopedic patients administered general or local anesthesia. These two kinds of anesthetic agents were studied because general anesthetics (volatile agents, e.g., enflurane) significantly

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reduce liver and kidney function (3), whereas local anesthetics (such as marcaine or lidocaine) do not (8).

Because cefazolin is rapidly excreted into the urine primarily by glomerular filtration (its rate of renal clearance is almost 80% that of its simultaneous creatinine clearance [6, 7], it was surprising that enflurane anesthesia did not increase the half-life of cefazolin compared to that of local anesthesia. The half-life of cefazolin in serum in (mean ± standard deviation) healthy awake subjects after an intravenous injection is 104 ± 29 min (1, 2, 4–6, 10), which is not significantly different from the half-lives reported here in patients treated with enflurane or local anesthetic. To determine whether such a relationship exists for other antimicrobial agents, the pharmacokinetics of additional drugs of surgical and prophylactic importance should be studied in patients receiving local and general anesthesia.

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