Pharmacokinetic-Pharmacodynamic Modeling of Electroencephalogram Effect of Imipenem in Rats with Acute Renal Failure

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The epileptogenic activity of imipenem was investigated in rats with experimental renal failure induced by uranyl nitrate injection using electroencephalogram (EEG) recording and a pharmacokinetic-pharmacodynamic model including an effect compartment. Results previously obtained with healthy rats were used to estimate the dose of imipenem required to induce an observable but nonlethal EEG effect on the assumption that only the pharmacokinetic parameters of the model would be affected by renal failure. Good agreement was observed between the predicted and observed effects.

Carbapenem antibiotics, in particular, the leading compound imipenem, have relatively high convulsant activity (1–3, 10). This has been investigated experimentally in small laboratory animals by using electroencephalogram (EEG) recording (6), more recently along with pharmacokinetic-pharmacodynamic (PK-PD) modeling (7). A profound counterclockwise hysteresis was observed between the EEG effect of imipenem and its concentration in serum following intravenous administration and was successfully described by a PK-PD model including a compartment effect (7). The robustness of this model was assessed in various experimental settings but always in healthy rats. Because seizures occur more frequently in patients with renal insufficiency (10), it was decided to assess the validity of this PK-PD model in rats with experimentally induced renal failure (RF rats).

Except for renal failure induction, the experiment was conducted as previously described (7). Briefly, this work was done in accordance with the Principles of Laboratory Animal Care (National Institutes of Health). Nine male Sprague-Dawley rats from Depres Breeding Laboratories (St. Doulchard, France), with a mean body weight of 300±10 g, were housed in the Animal Breeding Facilities of the laboratory (authorization no. 0028). Rats received a single intravenous dose (5 mg kg−1) of uranyl nitrate (Merck) as a 5% saline solution via a tail vein 5 days before the experiment in order to induce renal failure (9). They had five cortical EEG electrodes implanted 5 days before the experiment and two permanent polyethylene catheters implanted in the left femoral vein for drug administration and in the left femoral artery for blood sample collection 1 day before imipenem administration (7). On the day of the experiment, rats were maintained in plastic cages and the miniature plugs were connected to a moving connector to record the EEG signal, from 10 min before imipenem infusion started until the signals returned to baseline values. Tienam (imipenem monohydrate-sodium cilastatin salt; Merck, Sharp & Dohme Laboratories) was used to prepare a 15.9 mg ml−1 solution of imipenem in 0.9% NaCl, which was infused by using a motor-driven syringe pump (Program 2; Vial Inc.) at a rate of 3 mg of imipenem per min for 6 min, corresponding to a dose of imipenem equal to 18 mg per rat. Infusions were started between 9:00 and 12:00 a.m. Arterial blood samples (300 μl) were collected in dry tubes immediately before (blank sample) and at 10, 60, 120, 180, 240, and 300 min after the start of the infusion and handled as previously described (7). Serum creatinine and urea concentrations were measured in the blank sample by using a Hitachi 911 instrument (Hitachi). Imipenem concentrations in serum were determined by high-performance liquid chromatography (7). The EEG signal was sampled at 256 Hz and analyzed on line by fast Fourier transform to determine the total EEG power in the 0.5- to 30-Hz frequency band (Brain Wave Systems Co., Thornton, Colo.) as previously described (7). A one-compartment open model with zero order input (R0) was used to characterize the serum concentration-versus-time profiles of imipenem during and after infusion. PK parameters were then fixed, and the PD model was regressed to the EEG data for each individual rat by using the nonlinear least-squares program WinNonlin, version 1.1 (SCI Software, Cary, N.C.). An effect compartment model (11) was applied for analysis of the PK-PD relationship, leading to an estimate of the rate constant for elimination of the drug from the effect compartment (k0) (7). The profile of the EEG effect was described by using a spline function derived from the Hill equation (5): P = P0 + Bn · Cn. In this equation, P is the total power (EEG effect) corresponding to Cn, P0 is the baseline effect value; Bn is the combined parameter Emax/EC50n, and n is a factor determining the steepness of the curve. The goodness of fit of each model was assessed by visual inspection and analysis of the residuals and of the coefficient of variation (%) associated with parameter estimates (8).
On the day of the experiment, serum creatinine and urea levels were, respectively, 43.3 ± 3.8 mg liter⁻¹ and 4.1 ± 0.5 g liter⁻¹, on average, attesting to renal dysfunction (4, 9). The volume of distribution of imipenem was virtually unchanged in RF rats, but its clearance was decreased almost exactly 10-fold compared to that in animals with normal renal function (7). As a consequence, the imipenem elimination half-life was increased in proportion. The pharmacokinetic parameters (mean ± standard deviation) characteristic of imipenem infused intravenously into RF rats at a dose of 18 mg over 6 min were as follows: clearance, 1.40 ± 0.33 ml min⁻¹ kg⁻¹; volume of distribution, 198.7 ± 40.2 ml kg⁻¹; elimination rate constant, 0.0072 ± 0.0024 min⁻¹; half-life, 116.3 ± 38.4 min; maximum concentration of drug in serum, 303.1 ± 76.5 μg ml⁻¹. Overall, limited interindividual variability was observed.

It was previously demonstrated that the range of “epileptogenic but nonlethal” imipenem doses was very narrow in healthy rats and very sensitive not only to the dose itself but also to the infusion duration (7). Therefore, the major problem raised by the present study was to select an appropriate dosing regimen for imipenem administration to RF rats.

Because of the relatively low drug solubility and large drug dose to be infused to provide an EEG effect, a large solution volume (5 ml) and a long duration of infusion (30 min) were necessary for healthy rats (7). This 30-min infusion duration corresponded to almost three elimination half-lives, which is different from what is encountered in clinical practice since imipenem is usually administered as short infusions. It was therefore decided that imipenem should be infused into RF rats over a 6-min period, which corresponds to about 5% of its elimination half-life. The dose to be administered was then selected on the basis of simulations. The 10-fold reduction in imipenem clearance in RF rats was expected from preliminary studies. As a starting point, it was hypothesized that renal failure would have an effect on imipenem PKs but not on its PDs (EEG effect). Accordingly, simulations were conducted by using the PK-PD model previously developed to characterize the EEG effect of imipenem in healthy rats after adjusting PK parameters to account for the renal insufficiency but keeping PD parameters unchanged. These simulations suggested that an 18-mg dose infused over a short period of time would produce a significant but nonlethal effect, whereas a slightly smaller dose (16 mg) would produce an effect reduced by half and a slightly larger dose (20 mg) would be lethal on most occasions. Preliminary experiments confirmed these predictions (data not shown). Interestingly, due to the complexity of the PK-PD relationships governing the imipenem EEG effect, a 10-fold dose reduction according to 10-fold clearance reduction would have completely abolished the EEG effect, illustrating the difficulty of adjusting the imipenem dosing regimen simply on the basis of a creatinine clearance estimate. The first individual spikes appeared several minutes postinfusion. Their frequency and amplitude then increased dramatically, leading to a relatively sudden increase in the total power, accompanied by behavioral troubles, including tremors and partial seizures at about 60 min postinfusion, before the signal came back progressively to the baseline. The temporal delay between the drug concentration in serum and the EEG effect in RF rats was adequately described by the effect compartment model as

in healthy rats (Fig. 1; the pharmacodynamic parameters [mean ± standard deviation] characteristic of imipenem infused intravenously into RF rats at a dose of 18 mg over 6 min were as follows: $P_0$, 0.16 ± 0.03 mV²; zero intercept for β phase, 0.0066 ± 0.0033 mV² ml⁻¹ μg⁻¹; $n$, 2.8 ± 1.8; $k_{oT}$, 0.0259 ± 0.0141 min⁻¹), with comparable $k_{oT}$-estimates in the two populations. As a consequence the $k/k_{oT}$ ratios were very different between healthy and RF rats. Overall, the good agreement between the observed and simulated EEG effects, under the assumption that PD parameters were unchanged, suggests (i) that the PK-PD model successfully used in healthy rats to describe the EEG effect of imipenem applies to RF rats as well and (ii) that the experimental failure induced by uranyl nitrate had an effect on imipenem PKs only.

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