Influence of a Circadian-Stage-Dependent Dosing Schedule on the Pharmacokinetics of Isepamicin in Humans

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These experiments were conducted in order to determine the influence of the time of day of drug administration on the pharmacokinetics of isepamicin. Six healthy volunteers were given 400 mg isepamicin IM, on 2 separate occasions, either in the morning (8 AM) or in the evening (8 PM). Within-subject differences in the pharmacokinetic parameters between the morning and evening dosing regimens were evaluated. The plasma concentrations of isepamicin were not significantly different between the morning and evening trials, but significant time-dependent changes were found with a lower elimination rate constant and a longer elimination half-life in patients administered isepamicin at night. Our finding suggests that isepamicin may have the same clinical effects irrespective of whether dosing takes place in the morning or in the evening, but its clearance tends to be depressed when taken in the evening. Therefore, morning therapy is desirable because of possible interference from aminoglycoside toxicity.

Key words: Isepamicin, chronopharmacokinetics, human

INTRODUCTION

The susceptibility of mice to the acute toxicity of aminoglycosides dependent on circadian rhythms was first reported by our group.¹ Since aminoglycosides are excreted via the kidneys, the pharmacokinetics of these drugs are strongly influenced by renal function. The chronopharmacokinetics of antibiotics are known to be associated with circadian-dependent changes of renal function, as measured by the glomerular filtration rate.² A new aminoglycoside antibiotic, isepamicin (ISP), has recently been introduced commercially. Plasma ISP concentrations have been used for monitoring the efficacy of drug therapy, however, no data are available which demonstrate the chronopharmacokinetics of ISP in people. The present study was undertaken to elucidate possible effects of the time of day of drug administration on the pharmacokinetics of ISP in humans.

METHODS

Six healthy young volunteers, three men and three women, with a mean (± SD) age of 22.2 years (± 1.2 years), and a mean weight of 63.5 kg (± 15.3 kg) participated in this randomly-assigned crossover study which was approved by our institutional Ethical Committee for Clinical Research after the subjects gave written informed consent. Two of the 6 subjects were moderately morning-types, 1 of the 6 subjects was moderately an evening-type and the other 3 were neither type as determined by a self-assessment questionnaire.³ They were free of identifiable medical or psychiatric disease, had normal laboratory parameters, and were not taking therapeutic drugs. The subjects maintained a regular lifestyle with diurnal activity and nocturnal rest, with sleep time from 11 PM to 7 AM. For standardization, all subjects rested for 3 hours in a sitting position after ISP administration, and non-strenuous activity was allowed thereafter.

Subjects were given a single 400 mg dose of ISP intramuscularly (Excacin Injection; Asahi Chemical Industry Co Ltd, Osaka, Japan), on 2 occasions, either in the morning (8 AM) or in the evening (8 PM), in an experimental design using Latin squares. One week elapsed between trials. Heparinized blood samples (3 mL) were obtained at 0.25, 0.5, 0.75, 1, 1.5, 2, 4, 8 and 12 hours after ISP administration. The tubes were centrifuged and the plasma stored at -20°C until assayed.

Plasma ISP levels were measured by a fluorescence polarization immunoassay (TDX Isepamicin, Dinabot Co Ltd, Tokyo, Japan). The detection limit was 0.4 μg/mL. The interday coefficients of variation were 3.7 % at
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5.1 μg/mL, 2.5% at 15.3 μg/mL and 1.8% at 25.6 μg/mL. The plasma concentrations were plotted against time, and a one-compartment open model was employed to calculate the following kinetic parameters: peak concentration (C_{max}), time to peak concentration (t_{max}), clearance (CL), absorption rate constant (ka), distribution volume (Vd), elimination rate constant (ke), elimination half-life (t_{1/2}) and area under the plasma concentration-time curve (AUC). Within-subject differences in the pharmacokinetic parameters between the morning and evening trials were evaluated by the paired t test.

RESULTS

The mean ISP plasma concentration after the injection in either the morning or evening is shown in Fig. 1. Peak plasma concentrations were attained within 1 hour in both groups, and there were no significant differences between the time to achieve peak plasma concentrations or the rate of clearance of ISP. The pharmacokinetic measurements yielded several significant different parameters between subjects given ISP in the morning and those given ISP at night. There was a lower elimination rate constant and a higher elimination half-life in patients given ISP in the evening (Table 1). The time required to reach the specified range of plasma ISP levels was significantly different between the morning trial and the evening trial (P < 0.01 respectively, Table 2).

DISCUSSION

Circadian-dependent changes in pharmacokinetics and nephrotoxicity have been demonstrated for a variety of drugs including aminoglycoside antibiotics in humans and rodents. ISP has recently been introduced commercially, and has clinical merits such as low nephrotoxicity and a once-daily dosing regimen. Since aminoglycosides are excreted via the kidneys, the pharmacokinetics of these drugs are strongly influenced by renal function, where a minimal change in kinetics can result in significant nephrotoxicity. A correlation of plasma aminoglycoside concentrations with therapeutic responses has been reported. The monitoring of plasma aminoglycoside concentrations to achieve optimal therapeutic levels has been stressed because of the apparent existence of a therapeutic window. From a pharmacokinetic standpoint, few studies have been published evaluating the dosing schedule of ISP. The point in the circadian cycle at which a drug is administered is important for evaluating exactly the predictive accuracy. However, no data are available demonstrating the chronopharmacokinetics of ISP in humans. The aim of the present study was to examine the influence of a circadian stage-dependent dosing schedule on the pharmacokinetics of ISP in humans.

When ISP was administered intramuscularly, the mean plasma ISP concentrations showed no statistical difference between the morning and evening administration schedules. However, there were significant differences between the 2 groups in terms of a lower absorption rate constant, a lower elimination rate constant and a higher elimination half-life in subjects administered ISP in the evening. These findings indicate that the rate of elimination of ISP in people is greater after a morning dose, which is similar to findings with gentamicin where the drug is eliminated more rapidly in morning trials than in evening trials in healthy people.

Generally, factors including exercise, body position, site of injection, volume and concentrations of injection, osmolarity, pH, and carriers play an important role in the kinetics of antibiotics after an intramuscular injection. To standardize the test results, all subjects rested for 3 hours after ISP administration and only non-strenuous activity was allowed thereafter. Renal function, as measured by the glomerular filtration rate, is known to increase significantly during the day and decrease during the night among day-active individuals. The circadian rhythm of renal function may contribute to the chronopharmacokinetics of ISP, particularly since the drug is excreted via the kidneys.

Aminoglycosides exhibit bactericidal activity which is dependent on blood concentrations, so that the clinical effects are also dependent upon the peak drug concentration. Our findings suggest that the clinical efficacy may not be different in these 2 groups as the peak