Pharmacokinetics and Safety of a New Parenteral Carbapenem Antibiotic, Biapenem (L-627), in Elderly Subjects

OSAMU KOZAWA,1 TOSHIHIKO UEMATSU,1,∗ HIROYUKI MATSUNO,1 MASAYUKI NIWA,1 YOSHIHARU TAKIGUCHI,1 SYOYOUZU MATSUMOTO,3 MASAHIKO MINAMOTO,3 YOSHITO NIIDA,3 MASAHIRO YOKOKAWA,1 SATORU NAGASHIMA,4 AND MITSUTAKA KANAMARU4

Department of Pharmacology, Gifu University School of Medicine, Gifu 500, Japan; Department of Clinical Pharmacology, Graduate School of Pharmaceutical Sciences, The Tokushima University, Tokushima 770, Japan; Lederle Japan Ltd., Tokyo 175, Japan; and Shitotro Clinic, Hamamatsu 432, Japan

Received 19 May 1997/Returned for modification 10 November 1997/Accepted 24 March 1998

The pharmacokinetics and tolerability of a new parenteral carbapenem antibiotic, biapenem (L-627), were studied in healthy elderly volunteers aged 65 to 74 years (71.6 ± 2.7 years [mean ± standard deviation], n = 5; group B) and ≥75 years (77.8 ± 1.9 years, n = 5; group C), following single intravenous doses (300 and 600 mg), and compared with those of healthy young male volunteers aged 20 to 29 years (23.0 ± 3.5 years, n = 5; group A). The agent was well tolerated in all three age groups. Serial blood and urine samples were analyzed for biapenem to obtain key pharmacokinetic parameters by both two-compartment model-dependent and -independent methods. The maximum plasma concentration and area under plasma concentration-versus-time curve (AUC) increased in proportion to the dose in all three groups. Statistically significant age-related effects for AUC, total body clearance, and renal clearance (CLR) were found, while elimination half-life (t1/2) and percent cumulative recovery from urine of unchanged drug (%UR) remained unaltered (t1/2, 1.51 ± 0.42 [300 mg] and 2.19 ± 0.64 [600 mg] h [group A], 1.82 ± 1.14 and 1.45 ± 0.36 h [group B], and 1.75 ± 0.23 and 1.59 ± 0.18 h [group C]; %UR, 52.6% ± 3.0% [300 mg] and 53.1% ± 5.1% [600 mg] [group A], 46.7% ± 7.4% and 53.0% ± 4.8% [group B], and 50.1% ± 5.2% and 47.1% ± 7.6% [group C]). A significant linear correlation was observed between the CLR of biapenem and creatinine clearance at the dose of 300 mg but not at 600 mg. The steady-state volume of distribution tended to be decreased with age, although not significantly. Therefore, the age-related changes in parameters of biapenem described above were attributable to the combination of decreased lean body mass and lowered renal function of the elderly subjects. However, the magnitude of those changes does not necessitate dosage adjustment in elderly patients with normal renal function for their age.

Biapenem, (1R,5S,6S)-2-[(6,7-dihydro-5H-pyrazolol[1,2-a][1,2,4]triazolium-6-yl)-thio-6-[(R)-1-hydroxyethyl]-1-methyl carbapenem-3-carboxylate L-627, is a new parenteral carbapenem developed by Lederle (Japan), Ltd. It exhibits antibacterial activity against a wide range of gram-positive and -negative bacteria (14). It is also stable to human renal dehydropeptidase I and therefore does not require the coadministration of a dehydropeptidase I enzyme inhibitor (6).

Single and repeated intravenous doses of biapenem have been shown to be well tolerated in healthy young volunteers, with linear pharmacokinetics exhibited within the dosage range of 20 to 600 mg (9). In normal subjects, biapenem is cleared primarily by urinary excretion. The predominant concern in terms of adverse reactions to the prototype carbapenem antibiotic, imipenem/cilastatin, is the greater tendency to cause seizures than that of other β-lactams. The risk of producing a seizure is highly associated with inadequate dose adjustment in relation to renal function (1).

In general, it is accepted that adverse drug effects are more frequently encountered in the elderly. The heightened susceptibility to adverse reactions is due to a number of factors, including altered pharmacokinetic properties of many drugs (12, 13). It is well recognized that many physiologic functions including renal function diminish with increasing age (3, 13). In consideration of these observations, full clarification of pharmacokinetic properties of biapenem in the aged is quite essential for its safe application to them.

In the present study, the pharmacokinetics of biapenem were investigated in an elderly group and compared with those of healthy younger subjects. Our results will aid physicians in adjusting the dosage of the new carbapenem antibiotic for this age group.

MATERIALS AND METHODS

Subjects and study protocols. Before the implementation of this study, the research protocol and the consent form were reviewed and approved by the Ethics Committee of Shitotro Clinic, Hamamatsu, Japan. Volunteers were selected for enrollment in the study on the basis of physical examination, medical history, and clinical laboratory tests performed prior to the drug administration. In addition, elderly subjects were enrolled in the study on the basis of criteria such as being self-supporting and medically stable under restriction of other medications for 1 week prior to the beginning of study. Finally, 5 younger healthy male subjects (group A) aged 23.0 ± 3.5 years (mean ± standard deviation [SD]; range, 20 to 29 years) and weighing 59.4 ± 7.2 kg and 10 elderly subjects (three males and seven females) participating in the present study after giving their written informed consent. The elderly subjects were subdivided into two groups based on two age ranges, 65 to 74 years and ≥75 years, namely, group B (71.6 ± 2.7 years, 55.6 ± 7.5 kg of body weight, n = 5) and group C (77.8 ± 1.9 years, 56.5 ± 11.4 kg of body weight, n = 5). Caffeine-containing beverages and smoking were prohibited from 12 h before until 24 h after drug administration. Use of other medications was restricted from 7 days before until 24 h after drug administration.

The safety and pharmacokinetics were examined by single intravenous dosing of biapenem over 1 h. Biapenem was administered first at the dose of 300 mg and then at the dose of 600 mg at a 1-week interval. On each study day, biapenem was administered to the volunteers after overnight fasting. Venous blood samples (5 ml) were collected in heparinized tubes before (0 h) and 1, 1.25, 1.5, 2, 3, 5, 9, 12, and 24 h after the beginning of the 1-h intravenous administration. Urine samples were collected as voided just before administration, and at intervals of 0 to

∗ Corresponding author. Mailing address: Department of Pharmacology, Gifu University School of Medicine, 40 Tsukasa-machi, Gifu 500, Japan. Phone: 81-58-267-2231. Fax: 81-58-267-2959. E-mail: uematsu@cc.gifu-u.ac.jp.
The curve thus obtained was linear in this concentration range (r = 0.9998). Its coefficient of variation (CV) was 1.38%. The mean recovery (n = 6) of biapenem was 99.5%. The detection limit was 0.1 µg/ml in plasma. For urine, the calibration curve was generated by measuring the urine sample with the biapenem concentrations adjusted to 20.0, 50.1, 100.2, 200.4, 501.0, and 1,002.0 µg/ml. The calibration curve thus obtained was linear in this concentration range (r = 0.9999). The CV was 2.44%. The mean recovery (n = 6) of biapenem was 102.5%. The detection limit was 1.0 µg/ml in urine.

### Pharmacokinetic analysis

In the phase I studies using younger healthy subjects (9), concentrations of biapenem in plasma were fitted well to a two-compartment open model. For comparison, the time-sequential concentrations of drug in plasma for each subject were individually fitted to this model by employing the nonlinear least-squares computer program (MULTI) (17). The data apparently fitted better to a two-compartment model than to one-compartment model with a lower Akaike’s information criterion value. The area under the plasma concentration-time curve from 0 h to infinity (AUC∞,0) was calculated by use of the trapezoidal rule until the time of the last quantifiable plasma concentration and then to infinity by using the quotient of the last measurable concentration and the terminal elimination rate constant, which was calculated by the above-mentioned curve fitting. The steady-state volume of distribution (Vss) was calculated by using the distribution volume of central compartment (Vc) and two intercompartmental microconstants (k12 and k21) as follows (11): 

\[ V_{ss} = V_c \times \left[ 1 + (k_{21}/k_{12}) \right] \]

The maximum concentration in plasma (Cmax) was obtained from the simulated value at 1 h. Renal clearance (CLR) was calculated by dividing the amount of drug excreted into the urine by the AUC. Creatinine clearance (ClCR) was determined by dividing the amount of creatinine excreted into the urine in the 1 h prior to drug administration by the creatinine concentration in serum.

### Statistics

Means of the pharmacokinetic parameters were compared among the three age groups by analysis of variance, followed by Scheffe’s multiple comparison test.

### RESULTS

#### Clinical results

Biapenem was well tolerated by the subjects of all three groups. No adverse clinical effects were noted, and none of the subjects developed any laboratory abnormalities definitely attributable to the test drug.

#### Pharmacokinetic results

Among the three age groups, there was no significant difference in body weight (Table 1). Figures 1 and 2 illustrate the profiles of the biapenem concentration in plasma and of the recovery of unchanged drug from urine, respectively, as a function of time following intravenous administrations of 300 and 600 mg, the clinically expected doses in the elderly. The pharmacokinetic parameters are also shown in Table 1. When the three age groups were examined, statistically significant age-related effects were found for AUC0–t, total clearance (CLR), and ClCR, while the elimination half-life (t1/2β) remained unchanged. Recovery of unchanged drug from urine, expressed as percentages of 300- and 600-mg doses, also remained unaltered: group A, 52.6% ± 3.00% (300 mg) and 53.1% ± 5.1% (600 mg); group B, 46.7% ± 7.4% and 53.0% ± 4.8%; and group C, 50.1% ± 5.2% and 47.1% ± 7.6%. A significant linear correlation was observed between ClCR of biapenem and ClCR of at the dose of 300 mg (Fig. 3; Y' = 0.782 + 0.0645X, r = 0.566, n = 15, P < 0.05) but not at the dose of 600 mg. The value of Vss tended to be decreased with age, although not significantly.

### DISCUSSION

The data from the present study revealed that a new parenteral carbapenem, biapenem, was well tolerated in regimens using clinical doses relevant for all ages and possessed the following different pharmacokinetic properties in elderly subjects as compared with those in younger subjects. Biapenem showed statistically significant age-related effects in AUC0–t, CLR, and ClCR values, while it showed linear pharmacokinetics both age groups and the t1/2β and percent cumulative recovery of unchanged drug from urine remained unchanged.

It is well recognized that subject age affects the disposition of many drugs because of physiological changes associated with aging. Organ functions in the elderly generally decline as a
result of advancing age. For example, cardiac output decreases by 30 to 40% between the ages of 25 and 65 years and the glomerular filtration rate as expressed by CLCR declines progressively with age. Body composition also changes with aging. Total body water and lean body mass are lower in the elderly, both in absolute terms and as percentages of body weight. There is an age-related increase in adipose tissue as a fraction of body weight of 9 to 49% with a concomitant reduction in lean body mass and body water (5). The decrease in the proportion of lean body mass per unit of body weight has been shown to alter the distribution volumes of various drugs (4). In accordance with the above-mentioned observations, such age-related alterations in pharmacokinetics as increases in $t_{1/2}$ and in concentration of drug in plasma are encountered for various types of antimicrobial agents. In fact, we have reported age-related changes in the pharmacokinetic properties of two fluoroquinolones, balofloxacin and grepafloxacin, whose main excretion routes are the renal and hepatic routes, respectively (7): delayed and diminished recovery of balofloxacin from urine, attributed to the reduced renal function of the elderly subjects, and increases in $C_{max}$ and AUC of grepafloxacin, attributed to a decrease in $V_{ss}$ in the elderly.

In the present study, a significant linear correlation was observed between the CLR of biapenem and CLCR, although only at the dose of 300 mg, and $V_{ss}$ tended to be decreased with age, although not significantly. CLCR was calculated on the
basis of urine collection for 12 h during the night instead of over a whole day (24 h). Therefore, the intra- and interindividual variabilities in urine volume during the night might have had a relatively large influence on the accuracy of calculating CL\textsubscript{CR} and, further, on the result that a significant linear correlation between CL\textsubscript{CR} of biapenem and CL\textsubscript{CR} was present and absent at the doses of 300 and 600 mg, respectively. At the dose of 600 mg, no significant correlation was observed (symbols: ○, group A; △, group B; ■, group C; ●, for each group) (straight line, $r = 0.556$ [n = 15], $P < 0.05$). At the dose of 600 mg, no significant correlation was observed (symbols: ○, group A; △, group B; ■, group C).

When a β-lactam antibiotic is prescribed for an elderly patient, precautions should be taken with regard to age-related changes in pharmacokinetic properties. However, in consideration of the safety and tolerance profiles of β-lactam antibiotics including carbapenem, the magnitude of age-related changes observed in the pharmacokinetics of biapenem does not necessitate dosage adjustment in elderly patients with renal function normal for their age.

ACKNOWLEDGMENT

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture in Japan.

REFERENCES

1. Alvan, G., and C. E. Nord. 1995. Adverse effects of monobactams and carbapenem. Drug Saf. 12:305–313.
2. Barbhaiya, R. H., C. A. Knupp, and K. A. Pitman. 1992. Effects of age and gender on pharmacokinetics of cefepime. Antimicrob. Agents Chemother. 36:1181–1185.
3. Crome, P., and R. J. Flanagan. 1994. Pharmacokinetic studies in elderly people. Are they necessary? Clin. Pharmacokinet. 26:243–247.
4. Crowley, J., S. Echaves, B. Cusak, and R. Vestal. 1990. The elderly, p. 141–174. In R. Williams, D. Brater, and J. Mordenti (ed.), Rational therapeutics: a clinical pharmacologic guide for the health professional. Marcel Dekker, Inc., New York, N.Y.
5. Forbes, G. B., and J. C. Reina. 1970. Adult lean body mass declines with age: some longitudinal observations. Metabolism 19:653–663.
6. Hikida, M., K. Kawashima, K. Nishiki, Y. Furukawa, K. Nishizawa, I. Saito, and S. Kuwao. 1992. Renal dehydropeptidase-I stability of 3C, a new carbapenem antibiotic. Antimicrob. Agents Chemother. 36:481–483.
7. Kozawa, O., T. Uematsu, H. Matsuno, M. Niwa, S. Nagashima, and M. Kanamaru. 1996. Comparative pharmacokinetic studies of two newer fluoroquinolones, balofloxacin and grepafloxacin, in elderly subjects. Antimicrob. Agents Chemother. 40:2824–2828.
8. Meyers, B. R., and P. Wilkinson. 1989. Clinical pharmacokinetics of antibacterial drugs in the elderly. Implications for selection and dosage. Clin. Pharmacokinet. 17:385–395.
9. Nakashima, M., T. Uematsu, K. Ueno, S. Nagashima, H. Inaba, M. Nakano, K. Kosuge, M. Kitamura, and T. Sasaki. 1993. Phase I study of L-627, biapenem, a new parenteral carbapenem antibiotic. Int. J. Clin. Pharmacol. Ther. Toxicol. 31:70–76.
10. Norbry, S. R. 1995. Carbapenem. Med. Clin. N. Am. 79:745–759.
11. Regazzi, M. B., R. Rondanelli, and M. Calvi. 1993. The need for pharmacokinetics protocols in special cases. Pharmacol. Res. 27:21–31.
12. Rowland, M., and T. N. Tozer. 1988. Clinical pharmacokinetics: concepts and applications, 2nd ed. Lea & Febiger, Philadelphia, Pa.
13. Salom, I. L., and K. Davis. 1995. Prescribing for older patients: how to avoid toxic drug reactions. Geriatrics 50:37–40.
14. Sloan, R. W. 1992. Principles of drug therapy in geriatric patients. Am. Fam. Physician 45:2709–2718.
15. Ubuakata, K., M. Hikida, M. Yoshida, K. Nishiki, Y. Furukawa, T. Tashiro, M. Kono, and S. Mitsuhashi. 1990. In vitro activity of 3C, a new carbapenem antibiotic with high stability to dehydropeptidase I. Antimicrob. Agents Chemother. 34:1094–1100.
16. Walker, J., and H. Wynne. 1994. Review: the frequency and severity of adverse drug reactions in elderly people. Age Ageing 23:255–259.
17. Yamashita, K., Y. Tanigawara, T. Nakagawa, and T. Uno. 1981. A pharmacokinetic analysis program (MULTI) for microcomputer. J. Pharmacobiodyn. 4:879–885.