

Original Article

Disposition Kinetics of Amoxicillin from Urinary Excretion Data in Normal Human Volunteers in Pakistan

Mahmood Ahmad, Nadeem Irfan Bukhari, Naveed Akhtar
Department of Pharmacy, Islamia University, Bahawalpur, Pakistan

Kuwait Medical Journal 2001, 33 (3): 226-228

ABSTRACT

Objectives: To investigate the disposition kinetics of amoxicillin trihydrate by urinary excretion data following oral administration in normal human volunteers.

Design Addressed: Evaluation of disposition kinetics of amoxicillin in local environment using urine data. Urine samples are easy to collect as compared with the blood samples and, therefore, urine data is helpful for the evaluation of disposition kinetics of drugs.

Setting: Faculty of Veterinary Sciences, Agriculture University, Faisalabad-Pakistan and Department of Pharmacy, Islamia University, Bahawalpur-Pakistan.

Subjects/Methods: The study was undertaken in seven normal human volunteers. Urine samples were collected over 12 hours following drug administration and analyzed for the drug by the disc diffusion method using

Sarcina lutea as a test organism. The data was analyzed for computation of pharmacokinetic parameters by standard methods.

Results: A maximum amount of 29.2 ± 3.0 mg of amoxicillin was excreted at four hours and 17.0 ± 1.3 mg at 12 hours. The total amoxicillin cumulative amount excreted and percent cumulative at the 12th hour was concluded to be 183.4 ± 2.6 and $73.3 \pm 1.0\%$, respectively. Elimination rate constant of 0.60 ± 0.03 hr and 1.18 ± 0.05 hours in normal volunteers was observed in this study.

Conclusions: Similarities and differences were both observed when the present findings were compared with the cited results. The urine data may be used as an alternative to the blood data for the estimation of pharmacokinetics of drugs.

KEY WORDS: amoxicillin, blood data, drug parameters, pharmacokinetics, urinary excretion

INTRODUCTION

The disposition kinetics and optimum therapeutic regimen of a drug are best determined in the environment in which it is to be employed^[1]. In this prospective, amoxicillin, a widely used antibiotic in the treatment of upper and lower respiratory tract infections and enteric fever, was selected for pharmacokinetic study under the influence of local environment. Actual data on amoxicillin pharmacokinetics in local environment are scarce, suggesting that an evaluation of pharmacokinetic parameters of the drug would be useful.

Most pharmacokinetic studies are based on the measurement of drug concentrations in blood plasma^[2]. There are, however, drawbacks to this technique. The collection of blood plasma is not entirely without risk and often induces a feeling of inconvenience and discomfort. Patients under study may become fearful with regard to the repeated blood sampling and this may slow the rate of drug absorption from gastrointestinal tract^[3] with possible alterations in the pharmacokinetic profile of drugs under study^[4]. Pharmacokinetic evaluation can also be made using urinary excretion data, a non-invasive technique which could be used as an

alternative to blood sampling. In this study, the disposition kinetics of amoxicillin are assessed by such a study.

SUBJECTS, MATERIALS AND METHODS

Volunteers

Seven healthy human volunteers ranging in age from 23-35 years, weighting 57-75 kg, participated in this study. Volunteers were advised not to take any medication one week prior or during the study. The volunteers were informed about the objectives of the study and a written consent was obtained from each volunteer.

Drug Administration

Each volunteer was given an oral capsule containing 250 mg of amoxicillin trihydrate (Amoxil capsules, manufactured by M/s Smith Kline Beecham Pvt. Ltd., Karachi (Pakistan). Before drug administration, the volunteers emptied their bladders.

Sample collection

The total urine samples were collected at 0.0, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 hours after

Address correspondence to:

Dr. Mahmood Ahmad, Associate Professor, Department of Pharmacy, Islamia University, Bahawalpur, Pakistan. Tel: (92) 0621-876318; fax: (92) 0621-80372; email: ma786@mul.paknet.com.pk

drug administration and their volumes were recorded. The urine samples were immediately used for drug analysis.

Analysis of amoxicillin

Amoxicillin concentrations in urine samples were measured by employing formerly validated microbiological assay based on the disc diffusion method using *Sarcina lutea* (ATCC 9341) as a test organism^[5].

Data Analysis

The excretion of amoxicillin in urine, expressed in milligrams, was determined by multiplying the drug concentration in samples with the volume of respective urine. The percentage of dose excreted in urine samples was determined for each experimental period as follows:

$$\text{Percentage of dose excreted} = \frac{\text{Total dose excreted (mg)}}{\text{Total dose (mg)}} \times 100$$

The cumulative excretion in milligrams as well as cumulative percentage of the dose excreted in urine at different time intervals after drug administration was determined. Elimination rate constant (K) and half-life from urine excretion data were calculated by standard methods.

RESULTS AND DISCUSSION

The average \pm SEM values for amoxicillin excreted in urine at 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, 10.0, and 12.0 hours after administration of drug to normal volunteers are presented in Table 1. The maximum urinary excretion for the drug was determined to be 29.2 ± 3.3 at four hours post dosing of amoxicillin. The minimum drug excretion was 7.3 ± 1.9 mg at one hour after administration of amoxicillin.

As shown in Table 1, the maximum excretion of amoxicillin was $11.6 \pm 1.3\%$ after four hours of drug administration. The minimum value for drug excretion was $2.3 \pm 0.4\%$ at one hour post administration of drug. The average (\pm SEM) cumulative amount of amoxicillin excreted in urine samples of normal volunteers was 71.4 ± 5.7 mg after three hours, 129.2 ± 6.0 mg after six hours and 183.35 ± 2.38 mg after twelve hours after the drug administration.

After three hours post administration of amoxicillin, $28.6 \pm 2.3\%$ of the drug was cumulatively excreted. This result differs slightly from the literature cited value of $38.6 \pm 2.0\%$ after intramuscular administration of 500 mg of drug^[6]. This variation might be due to the difference in dose and the route of drug administration. After 6 hours of drug administration, $51.7 \pm 2.4\%$ (range

Table 1

Mean \pm SEM (n=7) values of amount excreted, percentage amount excreted, cumulative amount excreted and percentage of cumulative amount excreted in urine of normal volunteers after administration of Amoxil-250 mg capsule.

Time (hrs)	Drug excreted			
	Amount (mg)	Percentage of dose	Cumulative amount (mg)	Cumulative percentage
0.5	7.7 \pm 1.8	2.5 \pm 0.3	6.3 \pm 0.8	2.5 \pm 0.3
1.0	7.3 \pm 2.0	2.3 \pm 0.4	12.1 \pm 1.8	4.9 \pm 0.3
1.5	17.5 \pm 2.5	7.0 \pm 1.0	29.7 \pm 3.3	11.9 \pm 1.3
2.0	19.3 \pm 9.3	7.7 \pm 0.7	48.8 \pm 3.2	19.5 \pm 1.3
3.0	22.6 \pm 2.7	9.0 \pm 1.1	71.4 \pm 5.7	28.6 \pm 2.3
4.0	29.2 \pm 3.0	11.7 \pm 1.2	100.6 \pm 4.8	40.2 \pm 1.9
6.0	28.7 \pm 3.0	11.5 \pm 1.2	129.2 \pm 6.0	51.7 \pm 2.4
8.0	18.8 \pm 2.0	7.5 \pm 0.8	141.0 \pm 4.4	59.2 \pm 1.8
10.0	18.4 \pm 2.1	7.4 \pm 0.8	166.4 \pm 3.2	66.6 \pm 1.3
12.0	17.0 \pm 1.3	6.8 \pm 0.5	183.4 \pm 2.6	73.3 \pm 1.0

41.6 - 61.5%) of the dose was excreted in urine. These values are comparable with the previously reported values of 40.0 and 44.0% following an oral dose of 500 mg and $46.6 \pm 2.9\%$, $48.2 \pm 3.8\%$ and $49.3 \pm 3.9\%$ after 500 and 1000 mg of intramuscularly administered doses, respectively, in separate studies^[6-9].

After twelve hours of drug administration, the total amoxicillin excreted in urine was $73.3 \pm 1.0\%$ (range 70.1 - 76.0%) was also comparable to the previous findings where the recovery of amoxicillin was 68% after an intravenous administration of amoxicillin.

The mean volume of urine passed by the volunteers over 12 hours was 1210 ml. Therefore, the high rate of urine flow in normal volunteers prevented any possible back diffusion and caused higher elimination of the drug^[10].

Elimination rate constant

The value for the elimination rate constant (K) in normal volunteers is 0.60 ± 0.03 hr. The literature for this parameter is scarce. However, in foals this value is reported to be 0.65 ± 0.12 hr^[11] which is comparable with the present value.

The half-life ($t_{1/2}$) of 1.18 ± 0.05 hours was observed in this present study. The present $t_{1/2}$ value is comparable with 60.0 ± 9.0 and 71 minutes in normal human subjects^[12,13] and surprisingly, with 73 minutes in patients with renal impairment^[14]. There are very limited literature cites that report this parameter in normal human volunteers. This value is slightly more prolonged than 0.88 hr in sick children after a 30 min. i.v. infusion of 50 mg/kg amoxicillin^[15]. In another study in elderly in-patients, $t_{1/2}$ was observed to be 1.6-3.0 hours^[16]. In a subsequent study in pre-term infants with gestational ages of less than 32 weeks^[17], Huisman-De and coworkers observed $t_{1/2}$

of 6.7 ± 1.7 hours after administration of drug twice daily in a 25mg/kg i.v. dose.

Although studies of the $t_{1/2}$ of amoxicillin in humans are limited, data are available for a number of other animal species. The value of $t_{1/2}$ of 2.15 ± 0.20 and 1.20 ± 0.16 hours was observed in goats after oral and intravenous routes, respectively^[18], 1.05 ± 0.09 hours in goat after i.v. administration^[19] and 66 minutes in *Columbia livia* pigeons^[20]. In sheep and goats, the half lives of amoxicillin were 1.43 ± 0.16 and 1.13 ± 0.19 hours, respectively^[21]. In a preceding study in same animals, $t_{1/2}$ were determined to be 46.3 minutes in sheep and 66.9 minutes in goats^[22]. In healthy adult horses after i.v. administration, the half life was determined to be 1.43 hours^[23].

Previous literature is deficient in disposition and pharmacokinetic parameters observed particularly from urine data. Some similarities were, however, observed when present values were compared with the values obtained by blood data in available literature.

The pharmacokinetics of amoxicillin may be unaffected under the local environment, however, more studies are needed to substantiate this claim. The urinary excretion data is likely to be used as an alternative to blood sampling for the evaluation of pharmacokinetics of drugs for comparing different dosage forms, routes of administration and for bioequivalence studies. More experimentations are imperative for a certain end point.

REFERENCES

- Nawaz M, Shah BH. Genetical consideration in quality assurance of pharmaceuticals. Intern. Seminar on Policies, Management and Quality Assurance of Pharmaceuticals. Karachi, Pakistan. 1985.
- Mehta AC. Pharmacokinetic and analytical chemist. Talanta 1987; 34:535-560.
- Rowland M, Riegelman S, Harris PA, Sholkoff SD. Absorption kinetics of aspirin in man following oral administration of an aqueous solution. J Pharm Sci 1972; 61:379-385.
- Graham GG. Non invasive chemical methods of estimating pharmacokinetic parameters. In: Roland M, Tucker G, editors. Pharmacokinetics: theory and methodology. 1986.
- Arret B, Johnson PD, Kirshbaum A. Outlines of details of microbiological assays of antibiotics. J Pharm Sci 1971; 660:1689-1694.
- Mastrandrea V, Ripa S, La-Rosa F, Tarsi R. Human intravenous and intramuscular pharmacokinetics of amoxicillin. Int J Clin Res 1984; 4:209-212.
- Eshelman FN, Spyker DA. Pharmacokinetics of amoxicillin and ampicillin: Cross over study of the effect of food. Antimicrob Agents Chemother 1978; 14:539-543.
- Arancibia A, Guttman J, Gonzales G, Gonzales C. Absorption and disposition kinetics of amoxicillin in normal human subjects. Antimicrob Agents Chemother 1980; 17:199-202.
- Naoichi I, Taneda Y, Shivata M, Mizoguchi S, Katayama M. Fundamental and clinical study on BRL-25000 (Clavulanic acid-amoxicillin) in the pediatric field. Jpn J Antibiot 1985; 38:342-358.
- Vree TB, Hekster YA, Baars AM, Damsma JE, Van der Klijin E. Pharmacokinetics of sulfamethoxazole in man. Effect of urinary pH and urine flow on the metabolism and renal excretion of sulfamethoxazole and its metabolites, N-acetyl sulfamethoxazole. Clin Pharmacokinetics 1978; 3:319-329.
- Kent CG, Martens RJ, Brown SA, Martin MT. Pharmacokinetics of sodium amoxicillin in foals after intramuscular administration. Am J Vet Res 1986; 47:2126-2129.
- Maudgal DP, Maxwell JD, Lees LJ, Wild RN. Biliary excretion of amoxicillin and ceftriaxone after intravenous administration in man. Br J Clin Pharmacol 1982; 14:213-217.
- Gouyette A, Kitzis MD, Guiber J, Acar JF. Pharmacokinetic study of three amoxicillin formulations for intramuscular injection. Therapie 1982; 37:269-274.
- Humbert G, Spyker DA, Fillastre JP, Loroy A. Pharmacokinetics of amoxicillin dosage monogram for patients with impaired renal function. Antimicrob Agent Chemother 1979; 15:28-33.
- Jones AE, Barnes ND, Tasker TC, Horton R. Pharmacokinetics of intravenous amoxicillin and potassium clavulanate in seriously ill children. J Antimicrob Chemother 1990; 25:269-274.
- Janknegt R, Boogaard-Van den Born J, Hameleers BA, Hooymans PM, Rang J, Smits CA, Willems-Thissen ME. Pharmacokinetics of amoxicillin in elderly in-patients. J Pharm Weekbl Sci 1992; 14:27-29.
- Huisman-de Boer JJ, Van den Anker JN, Vogel M, Goessens WH, Schoemaker RC, de Groot R. Amoxicillin pharmacokinetics in preterm infants with gestational ages of less than 32 weeks. Antimicrob Agents Chemother 1995; 39:431-434.
- Carceles CM, Escudero E, Vicente MS, Serrano JM, Carli S. Pharmacokinetics of amoxicillin/clavulanic acid combination after intravenous and oral administration in goats. Vet Q 1995; 17:134-138.
- Escudero E, Carceles CM, Vicente S. Pharmacokinetics of amoxicillin/clavulanic acid combination and of both drugs alone after intravenous administration to goats. Br Vet J 1996; 152:551-559.
- Soenens J, Vermeersch H, Baert K, Vermeulen B, Nelis H, Butaye P, De Herdt P, Remon JP, De Backer P. Pharmacokinetics and efficacy of amoxicillin in the treatment of an experimental Streptococcus bovis infection in racing pigeons (*Columbia livia*). Vet J 1998; 156:9-65.
- Carceles CM, Escudero E, Baggot JD. Comparative pharmacokinetics of amoxicillin/ clavulanic acid combination after intravenous administration to sheep and goats. J Vet Pharmacol Ther 1995b; 18:132-136.
- Craigmill AL, Pass MA, Wetzlich S. Comparative pharmacokinetics of amoxicillin administered intravenously to sheep and goats. J Vet Pharmacol Ther 1992; 15:72-77.
- Ensink JM, Klein WR, Mevius DJ, Klarenbeek A, Vulto AG. Bioavailability of oral penicillins in the horse: a comparison of pivampicillin and amoxicillin. J Vet Pharmacol Ther 1992; 15:221-230.