International Journal of Pharmaceutics, 53 (1989) 85–89
Elsevier

IJP 01809

Pharmacokinetic properties of intramuscular gentamicin in Chinese subjects

Oliver Yoa-Pu Hu [1], Wen-Shyong Liou [2], Te-Jung Su [2], Shu-Fei Chiam [3], Jin-Shing Lai [3], Mong-Ling Chu [4] and Ping-Hong Chung [3]

[1] School of Pharmacy, National Defense Medical Center, Taipei, Taiwan (R O C), [2] Clinical Pharmacokinetic Laboratory, Department of Hospital and Clinical Pharmacy, Tri-Service General Hospital, Taipei, Taiwan (R O C), [3] Veterans Pharmaceutical Plant, Taipei, Taiwan (R O C) and [4] Research of Clinical Microbiology Laboratory, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan (R O C)

(Received 22 April 1988)
(Modified version received 20 January 1989)
(Accepted 30 January 1989)

Key words: Gentamicin; Pharmacokinetics; Bioavailability; Chinese

Summary

The pharmacokinetics and relative bioavailability of two different formulated injectable gentamicin products were examined i.m in 12 healthy young Chinese men at intervals of 1 week in a randomized cross-over design Serum concentrations of gentamicin were measured by a fluorescence polarization immunoassay (FPIA) method sensitive to 0 01 μg/ml The urine concentration of gentamicin was measured by the USP bioassay method The serum protein binding of gentamicin was determined by an ultracentrifuge method and the free drug concentration was also determined by FPIA. No differences were found in bioavailability between gentamicin products of two manufacturers (Schering and Veterans) However, longer half-life, larger volume of distribution, slower distribution rate and much higher percentage of gentamicin excreted in the urine were observed in Chinese subjects than in Caucasians Despite the longer half-life which was observed in Chinese, the total body clearance of the antibiotic in Chinese was about the same as that of Caucasians, therefore, the same gentamicin dosage may be needed for Chinese to achieve the desired serum level

Many drugs are routinely administered by intramuscular (i.m.) injection. This route of administration is generally considered to be safer and technically simpler in circumstances where intravenous (i.v.) injection or i.v. infusion is the only acceptable alternative (Koch-Weser, 1974; Pechere, 1979). Studies in healthy volunteers, however, have shown that i.m. administration of drugs is not always associated with rapid or complete absorption (Wilensky and Lowden, 1973; Koch-Weser, 1974). Serum drug concentrations after single or multiple i.m. injections may never equal those reached following i.v. or even oral administration of equivalent doses, such as phenytoin, chlordiazepoxide, diazepam, digoxin, and phenobarbital (Koch-Weser, 1976; Tse and Welling, 1980). Many physiological or biopharmaceutical factors may influence the rate and extent of i.m. drug absorption (Tse and Welling, 1980; Koch-

Correspondence: O Y-P Hu, School of Pharmacy, National Defense Medical Center, P.O Box 90048-508, Taipei, Taiwan, R.O.C.

Weser, 1976). While the bioavailability of drugs administered via the oral or enteral route has been investigated to a great extent, few studies have attempted to address the bioavailability of drugs which are dosed i.m. (Greenblatt et al. 1973; Serrano and Wilder, 1974; Fischer et al., 1984).

In the present study, we administered the same dose of two different injectable gentamicin preparations to 12 healthy young Chinese males and measured the serum and urine concentrations. The serum protein binding was also determined. From these studies, we compared the absorption of the proprietary and the generic gentamicin injections, and the pharmacokinetic properties in Chinese and in Caucasians reported in the literature.

Two gentamicin sulfate injections, from U.S. Schering Pharmaceutical Corporation, Garamycin (batch 4AMK75) and a gentamicin product of Veterans Pharmaceutical Plant (batch I-50290), were used respectively. Analysis of these two preparations, gentamicin and garamycin, using the pharmacopoeia method (USP XXI) showed that garamycin and gentamicin contained $104.8 \pm 0.78\%$ and $101 \pm 0.28\%$ of labeled amount of gentamicin, respectively. The slightly different concentration was corrected by administering adapted volumes to the volunteers.

The subjects of this study were 12 healthy males 18–23 years of age (mean 21.6) weighing between 57 and 73 kg (mean 66.6 kg), who were in good physical condition as determined by complete physical and clinical examinations before and after the study. The study was explained, and informed consent was obtained from each subject. The study was approved by the Institutional Review Board of the National Defense Medical Center.

A randomized double-blind cross-over design with 7 days washout period was used. Subjects were randomly assigned to each group and instructed to abstain from any drug for at least 2 weeks before, and during the study. Subjects with a history of drug or alcohol abuse or drug sensitivity were excluded. A single dose of gentamicin sulfate (80 mg) was administered (right arm) i.m. following an overnight fast.

Following drug administration, 3 ml blood samples (except 30 and 45 min when 5 ml blood was drawn for protein binding study) were collected from a forearm vein (left arm) before each dose and at 15, 30, 45, 60 min and 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h without using any anticoagulant. Urine was collected before and at appropriate intervals after drug administration, up to 48 h.

All serum and urine samples were stored at $-10\,^{\circ}C$ and assayed within 3 days. Subjects stayed in the hospital for 24 h and maintained a low level of physical activity. Blood pressure, heart rate and any possible side effects were closely monitored for the entire study. The serum samples were assayed for gentamicin concentration using Fluorescence Polarization Immunoassay (FPIA), (Abbott Laboratories, North Chicago, IL 60064). The lower detection limit in our laboratory was about 0.01 μg/ml. Numerous good correlations between the FPIA and other available assay methods were reported (Jolley et al., 1981a and b; Ratcliff et al., 1981; Rotschafer et al., 1983; Oeltgen et al., 1984; Tayeb et al., 1986). These indicated that the FPIA can accurately determine serum gentamicin concentration.

The urine samples were assayed for gentamicin concentration according to USP microbiological assay. Serum protein binding was also determined for each volunteer by ultracentrifugation. By means of the computer program NEWLIN (CSTRIP and NONLIN), the serum data was fitted to a two-compartment model with first-order absorption and first-order elimination.

Pharmacokinetic parameters such as: area under the serum concentration–time curve (AUC_{∞}), the distribution and elimination half-lives, the volume of distributions and total body clearance were calculated for each individual subject according to the standard formulae (Gibaldi and Perrier, 1982). Analysis of variance (ANOVA), power analysis and 95% confidence intervals were used to make statistical evaluation of these data.

The mean serum concentration–time data for each preparation and the bioavailability parameters are shown in Fig. 1 and listed in Table 1. The average of the individual peak time, the average of the maximum serum concentration, the AUC, and the percentage of gentamicin excreted in the urine (ΣU_{∞}) for gentamicin and Garamycin had statisti-

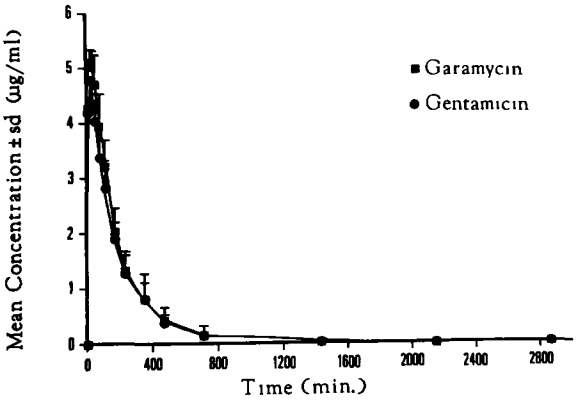

Fig. 1. The mean serum concentration time plot following gentamicin and Garamycin administration.

cally non-significant differences ($1 - \beta > 0.9$). In other words, the rate and extent of gentamicin absorbed were not significantly different between these two brands. The pharmacokinetic parameters for each preparation were listed in Table 2. The results show that intrasubject variation was not significant. As for the unbound fraction of serum protein binding, there was no difference between these two preparations (86.8 ± 1.40 and 85.2 ± 3.40 for gentamicin and Garamycin, respectively). From urinary data, in Table 3, almost all the drug was eliminated in the urine within 48 h, $94.1 \pm 11.7\%$ and $105.7 \pm 14.6\%$ for gentamicin and Garamycin, respectively. No significant difference in percent excreted in urine was observed between these two preparations. Aside from pain on injection, none of the subjects experienced any adverse effects following two single injections of gentamicin.

Table 3 summarizes the recently published single-dose gentamicin pharmacokinetic parameters in healthy volunteers. Slower distribution ($t_{1/2}(\alpha) = 1.5$ h), longer terminal half-life (6.5 ± 2.7 h), larger volume of distribution of central compartment (13.0 ± 1.97 liter), and much higher percentage of gentamicin excreted in the urine ($98.6 \pm 14.1\%$) were observed in Chinese, when compared with those of values in the literature which only concerned Caucasians. Besides the possible genetic difference between Chinese and

TABLE 1

Bioavailability parameters for two brands of gentamicin sulfate

	Gentamicin	Garamycin	Statistics (ANOVA)
Average of the individual peak serum conc. (μg/ml)	4 82 ± 0.58	5.21 ± 0 78	n.s
Average of the individual peak time (min)	32.4 ± 14.3	36.5 ± 12 0	n.s
AUC_∞ ($\mu g \cdot$ min/ml) (95%) confidence interval	986 ± 171 (877.4–1094 6)	1 127 ± 237	n s.

Values are mean ± S D

TABLE 2

The fitted pharmacokinetic parameters (mean ± S D) in subjects following i m administration of gentamicin sulfate

Parameter	Gentamicin	Garamycin	Overall (24 subjects)
$t_{1/2}(\alpha)$ (min)	88.6 ± 23.1	90.8 ± 29.4	89 7 ± 25 9
$t_{1/2}(\beta)$ (min)	412.7 ± 195.8	367.8 ± 129 3	390.2 ± 163 9
$t_{1/2}(k_a)$ (min)	7.01 ± 3 58	7 80 ± 2 94	7.40 ± 3 23
V_c/F (liter)	13.6 ± 1 95	12.4 ± 1.88	13.0 ± 1.97
V_{dss}/F (liter)	22.1 ± 6 30	18.8 ± 4.02	20 4 ± 5.44
Cl_t/F (ml/min) (D/AUC_∞)	83 0 ± 12.1	73.1 ± 11.3	78 0 ± 12 5

TABLE 3

Comparison of recently published single-dose gentamicin pharmacokinetic parameters in Caucasian healthy volunteers with those in Chinese

Parameters Source/race	Compartment	$t_{1/2}$ (α) (h)	$t_{1/2}$ (β) (h)	$t_{1/2}$(γ) (h)	V_c (ml/kg)	V_d(ss) (ml/kg)	Cl_t (m/min·kg)	Cl_r (ml/min kg)	T_{max} (h)	$t_{1/2}(k_a)$ (min)	ΣU^{∞} (%)	Method
Chung et al (1980) i.m (Caucasian)	2	–	2.23	–	101.6	156 3	64 3 ± 12 4	50 8 ± 20 0	0 65 ± 0 17	2.64	78.2 (24 hr)	Bioassay
Bauer and Blouin (1982) (Caucasian)	2	–	2 2 ± 0 51	–	–	230	1 29 ± 0 52	–	–	–	–	RIA
Laskin et al (1983) (Caucasian)	3	0.56	3.98	94 3	108 ± 25	450	1 02 ± 0 35	–	–	–	67 4 ± 18.7 (8 hr)	RIA
Matzke et al (1983) (Caucasian)	1	–	–	–	–	226	69.0 ± 25 8 (ml/min)	–	–	–	–	RIA
Fischer et al (1984) (Caucasian)	2	–	1 60 ± 0 21	–	–	–	1 35 ± 0.12	–	0.78 ± 0 14	–	62 1 ± 17 0 (4 hr)	EMIT
Our data (Chinese)	2	1 5	6 5 ± 2 71	–	13 0 ± 1 97(1) (195 ml/kg)	20 4(1) (300 ml/kg)	78 ± 12 5 (ml/min)	76.3 ± 30.9	0.9 ± 0 54	9 50 ± 5 80	98.6 ± 14.1 (48 hr)	FPIA (plasma) Bioassay (urine)

Caucasians, many reasons may explain the observed phenomena, such as different serum sampling time intervals, different length of time for urine collection and different treatment of pharmacokinetic data among studies. Good correlations between the FPIA and other assay methods were observed from previous reports (Rotschafer et al., 1983; Oeltgen et al., 1984; Jolley et al., 1981a and b; Ratcliff et al., 1981; Tayeb et al., 1986); therefore, different gentamicin assay methods did not affect the parameters. The much higher urinary excretion may well be explained by the 48 h urine collection in our study rather than 24 h or even 4 h urine collection in other reports. (Chung et al., 1980; Laskin et al., 1983; Fischer et al, 1984).

Despite the longer half-life of gentamicin which was observed in Chinese, the total body clearance was relatively the same as that of Caucasians. Therefore, the same gentamicin dosage may be needed for Chinese to achieve the same therapeutic serum level.

References

Bauer, L-A and Blouin, R A., Gentamicin pharmacokinetics: effect of aging in patients with normal renal function *J Am Geriat Soc*, 30 (1982) 309–311

Chung, M., Costello, R. and Symchowicz, S, Comparison of netilmicin and gentamicin pharmacokinetics in humans. *Antimicrob Agents Chemother*, 17 (1980) 184–187.

Fischer, J.H., Hedrick, P J and Riff, L J, Pharmacokinetics and antibacterial activity of two gentamicin products given intramuscularly *Clin. Pharm*, 3 (1984) 411–416.

Gibaldi, M. and Perrier D., *Pharmacokinetics*, 2nd edn, Dekker, New York, 1982.

Greenblatt, D.J., Duhme, D.W., Koch-Weser J and Smith, T.W., Evaluation of digoxin bioavailability in single dose studies. *N Engl J Med*, 289 (1973) 651–654

Jolley, M E, Stroupe, S.D., Schwenzer, K.S., Wang, C.-H J., Lu-Steffes, M., Hill, H.D, Popelka, S.R., Holen, J.T and Kelso, D.M., Fluorescence polarization immunoassay III. An automated system for therapeutic drug monitoring. *Clin Chem.*, 27 (1981a) 1575–1579

Jolley, M.E., Stroupe, S.D., Wang, C-H.J., Lu-Steffes, M, Hill, H D, Popelka, S.R., Holen, J.T. and Kelso, D.M, Fluorescence polarization immunoassay. I. Monitoring aminoglycoside antibiotics in serum and plasma *Clin Chem*, 27 (1981b) 1190–1197.

Koch-Weser, J., Bioavailability of drugs (two parts) *N Engl J Med*, 291 (1974) 233–237, 291 (1974) 503–506.

Koch-Weser, J., Intramuscular injection of drugs. *N Engl J Med*, 295 (1976) 542–546

Laskin, O L, Longstreth, J.A, Smith, C.R. and Lietman, P.S., Netilmicin and gentamicin multidose kinetics in normal subjects *Clin Pharmacol Ther*, 34 (1983) 644–650.

Matzke, G R, Jameson, J. and Halstenson, C H, Gentamicin pharmacokinetics in the elderly *Clin Pharmacol Ther.*, 34 (1983) 258 (abstract)

Oeltgen, P.R., Shank, W A Jr, Blouin, R.A. and Clark, T., Clinical evaluation of the Abbott fluorescence polarization immunoassay analyzer *Ther Drug Monit*, 6 (1984) 360–367

Pechere, J-C, and Dugal, R., Clinical pharmacokinetics of aminoglycoside antibiotics. *Clin Pharmacokin*, 4 (1979) 170–199

Ratcliff R M., Mirelli, C, Moran, E, O'Leary, D and White, R, Comparison of five methods for the assay of serum gentamicin *Antimicrob Agents Chemother*, 19 (1981) 508–512

Rotschafer, J C, Berg, H G, Nelson, R B, Strand, L. and Lakatna, D J, Observed differences in gentamicin pharmacokinetic parameters and dosage recommendations determined by fluorescence polarization immunoassay and radioimmunoassay methods *Ther Drug Monit*, 5 (1983) 443–447

Serrano, E.E. and Wilder, B.J, Intramuscular administration of diphenylhydantoin *Arch Neurol*, 31 (1974) 276–278.

Tayeb, O S., El-Tahawy, A.T. and Islam, S.I., Comparison of the fluorescence polarization of gentamicin concentration in human serum *Ther Drug Monit.*, 8 (1986) 232–235.

Tse, F-L S and Welling, P G, Bioavailability of parenteral drugs I. Intravenous and intramuscular doses *J Parent, Drug Assoc*, 34 (1980) 409–421.

Wilensky, A J and Lowden, J A., Inadequate serum levels after intramuscular administration of diphenylhydantoin *Neurology*, 23 (1973) 318–324