Netilmicin pharmacokinetics in Hong Kong Chinese cancer patients

Sophie Chang,¹ Ronald C. Li,¹ Lesley S. Y. Chan,¹ S. Y. Wong,¹ Min Zhu,¹ Anthony T. C. Chan² & Kenneth Raymond¹

Departments of ¹Pharmacy and ²Clinical Oncology, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong

Objectives To study the pharmacokinetics of netilmicin in Chinese haematology-oncology patients and to determine the pharmacokinetic differences, if any, between this patient subpopulation of Chinese and Caucasians.

Methods A prospective study was carried out in the adult oncology unit of a major hospital in Hong Kong. During a 6 week period in 1997, all patients commencing on netilmicin therapy were monitored; the patients' demographics, clinical status, netilmicin dose and regimen, and drug administration/blood sampling time were collected. Pharmacokinetic parameters were generated using the USC*PACK package based on specifics of the patients themselves and Caucasians matched for the same patients' parameters using the Bayesian algorithms.

Results A total of 22 patients were enrolled into the study. Twenty-nine sets of levels were drawn, but only 25 sets from 18 patients (86%) were interpretable. The predicted peak ($7.47 \pm 1.46 \mu\text{g ml}^{-1}$) and trough levels ($1.39 \pm 0.96 \mu\text{g ml}^{-1}$) generated by USC*PACK were found to be significantly higher than the levels observed ($6.01 \pm 1.14 \mu\text{g ml}^{-1}$ and $0.93 \pm 0.71 \mu\text{g ml}^{-1}$, respectively). Netilmicin clearance, volume of distribution and rate of elimination were all significantly higher in this Chinese subpopulation than those predicted for matched Caucasians.

Conclusion Alterations in the netilmicin pharmacokinetics observed in our study population might be related to the disease state and/or ethics of the study patient population. Direct application of Caucasian based population pharmacokinetic parameters to this subgroup of Chinese patients may not be appropriate and may result in underdose.

Keywords: Chinese, pharmacokinetics, netilmicin, cancer patients

Introduction

Aminoglycosides are among the most widely used antimicrobial agents in hospitalized patients and over one million patients receive aminoglycoside therapy each year [1]. Unfortunately, these antimicrobials are known to be nephrotoxic and ototoxic and require therapeutic drug monitoring (TDM). Pharmacokinetics of most aminoglycosides have well been defined in the Caucasian population, and computerized programmes such as USC*PACK and Abbott TDx have been developed for individualization of dosage regimens and prediction of serum levels. However, it is not known whether these programmes are appropriate for Chinese patients. Furthermore, alterations in aminoglycoside pharmacokinetics have been reported for specific patient subpopulations [2–9]. Specifically, haematology-oncology patients

show a higher clearance (CL) and shorter half-life ($t_{1/2}$) compared with noncancer patients. However, no information regarding the pharmacokinetics of netilmicin specific to the Hong Kong Chinese population or patient subpopulations is currently available. Initial dosing of netilmicin depends solely on the manufacturer's recommendations specific to the general Caucasian population, and dosage adjustment is empirically performed. Realizing the high level of usage and possible variations in pharmacokinetics, we set out to determine if alterations in the pharmacokinetics of netilmicin in a Chinese haematology-oncology patient subpopulation also exist as previously reported for the Caucasians [5–9].

Methods

This study was carried out in the adult oncology unit of a major, government hospital in Hong Kong serving a regional population of ≈ 1 million. The oncology unit employs netilmicin and piperacillin as first line antibiotics empirically in patients with neutropenic fever. During

Correspondence: Dr Min Zhu, Department of Pharmacy, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong.

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the period from January 13 to February 28, 1997, all patients started on netilmicin were enrolled into the study. Data pertaining to the patient's demographics, clinical status, serum chemistries, and clinical microbiology testing were collected. Netilmicin dosage and regimen, time of drug administration and blood sampling (on the fourth dose) were also recorded. Serum aminoglycoside concentrations were analysed by a fluorescence polarization immunoassay using a TDx analyser (Abbott Laboratories, Abbott Park, IL). The lowest measurable concentration was $0.09 \mu\text{g ml}^{-1}$ and the maximum level that could be quantified was $10 \mu\text{g ml}^{-1}$. Assay performance conformed to the specifications per manufacturer's recommendations. To verify the appropriateness of this empirical approach on dosing, peak and trough levels were first predicted, based on the physicians' doses and patients' characteristics, using the USC*PACK. This computerized programme utilizes a Bayesian algorithm and built-in pharmacokinetic parameter estimates describing the general Caucasian population. Adjusted body weight (ABW) was used for calculating aminoglycoside dosing for patients whose total body weight (TBW) was greater than their ideal body weight (IBW). For patients weighing less than their IBW, TBW was utilized instead. Measured peak and trough concentrations were subsequently recorded and compared to the predicted concentrations generated using a one compartment pharmacokinetic model. For ease of interpretation, concentrations were extrapolated to obtain the peak (30 min after a 30 min infusion) and trough (just before next dose) concentrations by simple linear regression if needed. Once the peak/trough concentrations and serum creatinine were available, patient-specific pharmacokinetic parameters (V_z , $t_{1/2}$, CL, λ_z) in these Chinese haematology-oncology patients were again generated by USC*PACK.

Statistical analysis

Data are presented as mean $\pm$ s.d. Paired *t*-tests (two-sided) were used for comparisons between the pharmacokinetic parameter estimates established using Caucasian data and those generated based on the Chinese study patient population. The same test was employed for detecting statistically significant differences between predicted and measured levels. A *P* value <0.05 was considered to be the level of significance.

Results

A total of 22 patients (8 male, 14 female) were started on netilmicin therapy during the study period. Mean $\pm$ s.d. (range) for the age, height and body weight of the patients were 47.7 ± 15.3 (17–78) years old, 159 ± 7.9

Table 1 Comparison of predicted and measured netilmicin concentrations (mean $\pm$ s.d., $n = 25$).

	Predicted concentration ^a	Measured/ extrapolated concentration	P value
Peak ($\mu\text{g ml}^{-1}$)	7.47 ± 1.46	6.01 ± 1.14	<0.001
Trough ($\mu\text{g ml}^{-1}$)	1.39 ± 0.96	0.93 ± 0.71	0.006

^aGenerated by USC*PACK using population parameter estimates matched for Caucasians.

($144.5\text{--}176$) cm, and 53.2 ± 8.3 (41–74) kg, respectively. Adjusted body weights ranged from 41 to 69.5 kg with a mean $\pm$ s.d. of 50.8 ± 6.4 kg. The initial serum creatinine concentrations were $76 \pm 26 \mu\text{mol l}^{-1}$. Four patients did not have drug levels monitored throughout the therapy. Among the 18 patients, 29 sets of peak and trough concentrations of the drug were obtained but 4 sets were not interpretable due to missing either blood sampling or drug administration times. Types of malignancies included leukaemia (63%) and lymphoma (23%). Neutropenic fever (63%) and chemotherapy administration (23%) were the two main reasons for the hospital admission. A total of 9 (41%) patients had 22 positive cultures grown with one culture found to be resistant to netilmicin. Although the patient population was heterogeneous as indicated by the baseline assessments, the initial dosage regimen was almost invariably 100 mg every 8 h (20/22, 91%) with only two patients (9%) receiving 100 mg every 12 h. The first set of netilmicin levels was always taken within 48 h after the start of therapy. Peak and trough concentrations predicted by the USC*PACK were found to be significantly higher than the measured/extrapolated concentrations. (Table 1)

Table 2 summarizes the pharmacokinetic parameter estimates obtained by the USC*PACK based on the specifics of the present patient population and those matched for Caucasians. All four pharmacokinetic parameters describing the Chinese study population were significantly different ($P < 0.05$) from those predicted utilizing Caucasian parameters. For example, mean clearance and volume of distribution for the Chinese study population were 31% and 20% higher, respectively, than that of the Caucasian based parameters. Because of these differences, the mean half-life estimate of netilmicin was 19% shorter for the Chinese study patients.

Discussion

The patient population in our pilot study was mainly middle-aged with relatively normal renal functions. Despite wide variations in the patients' demographics, the initial netilmicin dosage regimens used were almost

Table 2 Comparison of pharmacokinetic parameter estimates (mean $\pm$ s.d.) generated based on specifics to Chinese cancer patients ($n = 18$) and those matched for the general Caucasian population^a.

Pharmacokinetic estimates ^b	Caucasian based (Range)	Chinese patient based (Range)
λ_z (h^{-1})	0.26 ± 0.08 (0.12–0.45)	0.30 ± 0.10 (0.16–0.55)
V_z (l)	12.8 ± 1.0 (11.2–15.3)	16.0 ± 2.6 (10.7–21.3)
$t_{1/2z}$ (h)	2.98 ± 1.06 (1.53–5.87)	2.51 ± 0.77 (1.26–4.21)
CL (ml min^{-1})	55.4 ± 18.0 (25.6–97.2)	80.6 ± 25.7 (40.6–125.5)

^aGenerated by USC*PACK using population parameter estimates matched for Caucasians.

^bStatistically significant differences ($P < 0.05$) were detected for all four pharmacokinetic estimates by paired t -test (two sided).

identical. This 'invariant' dosing regimen employed by the physicians could result in widely variable serum concentrations and might expose patients to unnecessary side-effects or treatment failure.

A larger volume of distribution, higher elimination rate constant, shorter half-life and faster clearance for netilmicin have been well documented for haematology-oncology patients in the Caucasian population [7–9]. Our study also demonstrated a similar degree of alterations in these estimates describing the present Chinese cancer patients. Unfortunately, the lack of pharmacokinetic information for netilmicin in the normal healthy Chinese population is a limitation of our study. Nevertheless, a trend of higher clearance for this antibiotic in Chinese haematology-oncology patients was observed. This suggests direct application of pharmacokinetic parameters generated for the general Caucasian population to this subgroup of Chinese patients may not be appropriate and may result in underdosing.

The availability of pharmacokinetic parameters for a specific patient population is essential for a reliable TDM service. Therefore, the development of population-based pharmacokinetic parameters for the Hong Kong Chinese and other subpopulations is of prime importance. This should lead to the earlier achievement of targeted therapeutic levels and thus earlier resolution of infection by susceptible organisms as well as decrease unnecessary drug-related costs.

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