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Effect of unilateral nephrectomy on the pharmacokinetics of amikacin in humans

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Abstract

As unilateral nephrectomy is not a rare surgical procedure, it gives rise to the question whether drugs predominantly eliminated through the urinary tract can be handled effectively by the remaining kidney. Amikacin is predominantly excreted via glomerular filtration with only a small fraction undergoing tubular reabsorption, and can be used as a model drug of glomerular elimination. The study was carried out in 28 subjects, 10 one month and 10 one year after unilateral nephrectomy, as well as in 8 healthy subjects. The pharmacokinetics of amikacin was investigated after a 1-h infusion of 5 mg kg^{-1} amikacin. Blood samples were collected for 24 h after the end of infusion. Pharmacokinetic parameters of amikacin were calculated using a one-compartment open model for intravenous administration. Amikacin concentrations were significantly elevated in nephrectomized patients as compared with control subjects, both 1 month and 1 year after the surgery, and were similar at these two time-points following unilateral nephrectomy. Pharmacokinetic parameters of amikacin in patients subjected to unilateral nephrectomy were significantly different from those observed in the control subjects. As compared with the controls, an increase in AUC (area under the serum concentration–time curve) by 81% ($P < 0.001$) and 63% ($P < 0.01$) 1 month and 1 year after nephrectomy was observed, respectively. The λ_z (elimination rate constant) was reduced by 39% ($P < 0.001$) after 1 month and by 38% ($P < 0.001$) 1 year after the operation and $t_{1/2}$ was prolonged by 70% ($P < 0.001$) and by 43% ($P < 0.01$) at the respective time-points following unilateral nephrectomy. CL_T (total body clearance of the drug from plasma) and CL_{BW} (clearance per kg body weight) were both significantly decreased in unilaterally nephrectomized subjects in comparison with the controls. CL_T and CL_{BW} were reduced by 53% ($P < 0.001$) and 42% ($P < 0.01$) 1 month after nephrectomy, and by 45% ($P < 0.001$) and 42% ($P < 0.01$) 1 year after the surgery, respectively. No significant differences among studied groups were found in C_0 (initial serum drug concentration) and V_d (apparent volume of distribution). The results suggest that unilateral nephrectomy impairs elimination of amikacin, and possibly other drugs predominantly eliminated via glomerular filtration.

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Introduction

Unilateral nephrectomy is not a rare surgical procedure, and its incidence rises as the number of living donor nephrectomies increases. Currently, graft survival rates are better when kidneys are obtained from living-related donors than from cadavers (Taramtino 2000). Unilateral nephrectomy is accompanied by an increase in the weight of the remaining kidney. Experimental and human data suggest that the

weight of the contralateral organ increases within 1 to 2 days of surgery, and growth continues until a maximal increase of approximately 40% above the control level is achieved within 1 to 2 weeks. The early phase of compensatory increase in the size of the remaining kidney is due to accumulation of water within tubules and parenchyma. Further increase in the kidney size can be ascribed to cell hypertrophy and hyperplasia (Fine 1986; Argiles et al 1987; Shirley & Walter 1991). Functional adaptation of the remaining kidney accompanies the structural changes, and begins as early as 2 h after nephrectomy. In the rat, 2–5 h after unilateral nephrectomy, there were small increases in glomerular filtration rate and single nephron glomerular filtration rate, which at that stage were not accompanied by an increase in absolute proximal reabsorption. After five days glomerular filtration rate and single nephron glomerular filtration rate had increased further, at which stage absolute proximal reabsorption was also significantly elevated. After 30 days, kidney weight, glomerular filtration rate, single nephron glomerular filtration rate and absolute proximal reabsorption had all increased by approximately 40%, and glomerulo-tubular balance in the proximal tubule had been fully restored (Shirley & Walter 1991). Studies in organ donors have demonstrated a similar response. The functional response of the remaining kidney was apparent as soon as 24 h after unilateral nephrectomy. Creatinine clearance increases by 35% immediately after surgery, peaks 2–6 months postoperatively and then plateaus. This level of renal function is sustained for more than 20 years. However, functional renal reserve capacity after oral protein loading is normal (stable) only during the first decade after unilateral nephrectomy, and then decreases by 50% and 66% 10–20 and 20–30 years later, respectively (Regazzoni et al 1998). Dynamic renal imaging with ^{99m}Tc DTPA (^{99m}Tc-labelled diethylene triamine penta-acetic acid), reflecting changes in glomerular filtration rate, performed by Kakuta et al (1997), indicated that functional compensations in unilaterally nephrectomized subjects are complete within 3 weeks after surgery.

Clinical studies reported in the literature have mostly characterized excretion of endogenous substances in patients subjected to unilateral nephrectomy. The problem of drug elimination in those patients has not been addressed, except for one report on rolitetracycline pharmacokinetics (Wojcicki et al 1981a). There have been a few reports giving experimental data concerning the elimination of gentamicin (Drozdzik et al 1993a, b), rolitetracycline (Wojcicki et al 1981b), and salicylate (Wojcicki et al 1981c), suggesting that there is an impairment of drug excretion in unilaterally nephrectomized subjects.

This study was designed to evaluate the pharmacokinetics of amikacin, which can serve as a model drug excreted primarily through glomerular filtration, like other aminoglycosides. A slight tubular secretion of the drug may also occur. It was demonstrated that amikacin levels parallel changes in renal function measured as creatinine clearance or glomerular filtration rate (Sarubbi & Hull 1978; Elting et al 1990). This study was designed to evaluate the pharmacokinetics of amikacin 1 month and 1 year after unilateral nephrectomy, since at 4–6 weeks following the procedure a new glomerulotubular balance is established, with a slight increase during the subsequent year. The remaining kidney then functions without deterioration for 25–30 years as measured by standard renal function tests (Fine 1986; Wesson 1989; Shirley & Walter 1991; Regazzoni et al 1998).

Materials and Methods

Subjects

The study was carried out in 28 subjects (group 1 – 10 patients 1 month after nephrectomy (4 males, 6 females) aged 48.0±5.21 years, body-mass index (BMI) 24.0±2.8; group 2 – 10 patients 1 year after nephrectomy (6 males, 4 females) aged 43.2±5.81 years, BMI 24.1±2.1; and group 3 – 8 healthy (4 males and 4 females) age-matched subjects aged 42.8±6.24 years, BMI 25.6±2.1). All patients from groups 1 and 2 underwent unilateral nephrectomy due to renal injury or carcinoma clarocellulare with tumour size not exceeding 5 cm. During the study period, all the subjects remained on normal diet and were free of any medication for at least 1 week leading up to the study. The study protocol was approved by the Pomeranian Academy of Medicine Ethics Committee on human research. The aim of the study was fully explained to all patients and informed consent was obtained in each case. All study subjects underwent a thorough physical examination, and the following laboratory tests were carried out one day before the kinetic studies: haemoglobin, haematocrit, white blood cell count, platelets, sedimentation rate, fasting blood sugar, plasma sodium and potassium, plasma uric acid, total protein and albumin, as well as activity of alanine and aspartate aminotransferases, alkaline phosphatase and urinalysis. Plasma creatinine and blood urea nitrogen were measured twice with a three day interval, and plasma creatinine clearance was

calculated for each creatinine value using the following formula:

$$CL_{cr}\ (mL\ min^{-1}) = UV/P \quad (1)$$

where U is urine creatinine concentration (mg%), V is diuresis for 1 min (mL min^{-1}) and P is plasma creatinine concentration (mg%). Standard plasma creatinine clearance was also calculated from equation 2.

$$CL_s\ (mL\ min^{-1}) = CL_{cr} \times 1.73/S \quad (2)$$

where S is body surface (m^2, evaluated from Du Bois' equation). All the above mentioned laboratory parameters were defined using the apparatus RA 1000 (Technikon and Hema-Line-Baker Instruments).

Pharmacokinetic studies of single-dosed amikacin were performed in patients 1 month and 1 year after unilateral nephrectomy, and in the control subjects. During the study period all subjects of the study were given a standard diet.

Sample collection and analytical method

Subjects received amikacin (Biodacyna, Bioton, Poland) 5 mg per kilogram of actual body weight as a single intravenous dose administered over 1 h. Blood samples of 5 mL were obtained from an indwelling catheter in the forearm vein immediately before the infusion and then 5 min and 0.5, 1, 2, 4, 6, 8, 12 and 24 h after the end of the drug infusion, and then were centrifuged. Sera were stored at −20°C until the assays were done. Serum amikacin was measured by fluorescence polarization immunoassay (TDx, Abbott Laboratories, Diagnostic Division, USA). The sensitivity of the method for amikacin determination defined by the manufacturer was 0.8 $\mu g\ mL^{-1}$.

Pharmacokinetic analysis

Amikacin data were analysed using a one-compartment open model. Pharmacokinetic parameters were estimated by weighted non-linear least-squares regression of serum concentration versus time by use of the Statistica 5.0 computer program. The parameters of the pharmacokinetic model were the post-infusion slopes and intercepts. The following pharmacokinetic parameters were considered: the area under the serum concentration–time curve (AUC; $\mu g\ mL^{-1}\ h$), initial serum drug concentration (C_0; $\mu g\ mL^{-1}$), the elimination rate constant (λ_z; h^{-1}), the elimination half-life ($t_{1/2}$; h), the apparent volume of distribution (V_d; L kg^{-1}) and the total body clearance (CL_T; L h^{-1}), as well as the clearance per kg body weight (CL_{BW}; L $kg^{-1}\ h^{-1}$).

Statistical analysis

Statistical comparisons of blood amikacin concentrations and pharmacokinetic parameters were performed by analysis of variance or Kruskal–Wallis test. Correlations between plasma creatinine concentration (C_{cr}), plasma creatinine clearance (CL_{cr}), standard plasma creatinine clearance (CL_s) and $t_{1/2}$, λ_z or total body clearance of the drug from plasma (CL_T) were determined by calculating the Pearson's coefficient (r). A P value less than 0.05 was considered significant.

Results

General observations

For age and BMI, none of the study groups differed significantly. Physical examination, ECG and the results of all general laboratory tests were within the normal range. Blood urea nitrogen, plasma creatinine clearance and standard plasma creatinine clearance were comparable in evaluated patient groups, whereas plasma creatinine concentration was significantly elevated in patients nephrectomized one year before the study (1.24 ± 0.25 mg mL^{-1}) as compared with the controls (0.95 ± 0.08). Plasma creatinine level in subjects one month after nephrectomy was 1.13 ± 0.25, which was not significantly different from the other study groups; all the values were, however, within the normal range.

Pharmacokinetics

The mean plasma concentrations of amikacin in the serum are outlined in Figure 1. Amikacin concentrations were significantly elevated in nephrectomized patients as compared with the control subjects. Comparison of healthy controls and patients nephrectomized 1 month before the study revealed significantly higher amikacin concentrations for up to 6 h after drug infusion ceased. In patients 1 year after nephrectomy, amikacin concentration levels were elevated throughout the whole period of observation (i.e. for 24 h) with respect to the controls. Amikacin blood serum concentrations were similar in the two groups of nephrectomized patients, except for concentrations measured 12 and 24 h after the end of infusion, which were significantly higher in patients who had been unilaterally nephrectomized 1 month previously.

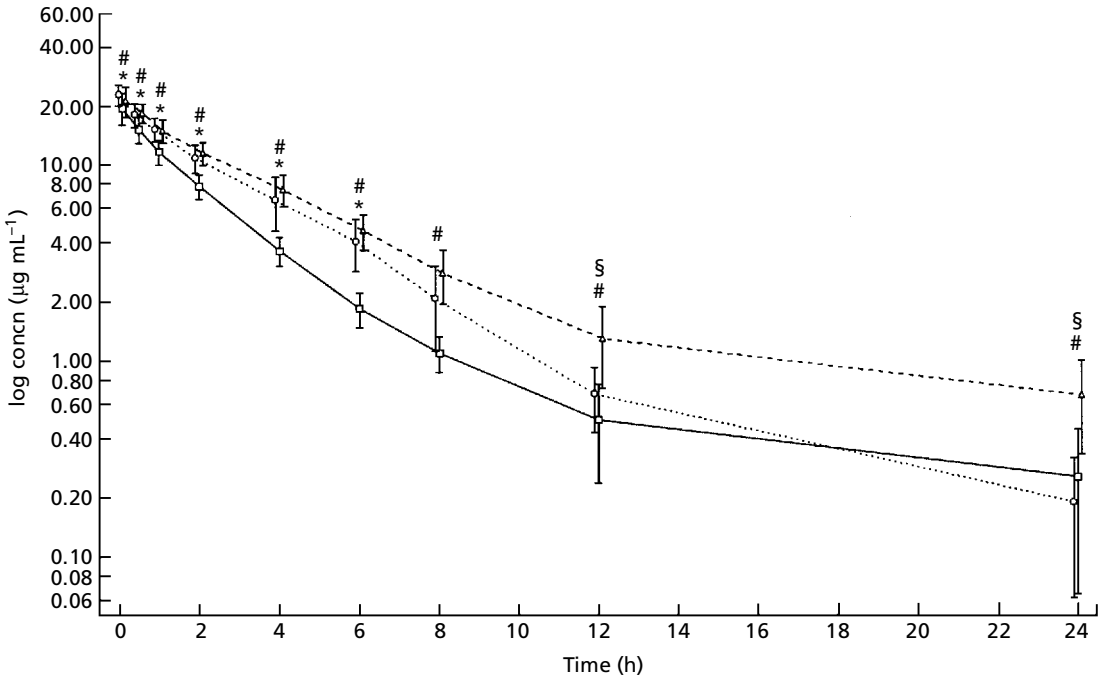

Figure 1 Mean serum amikacin concentrations (±s.d.) versus time in patients 1 month (△) or 1 year (○) after unilateral nephrectomy and in healty subjects (□). Amikacin (5 mg kg^{-1}) was administered as a single intravenous dose over 1 h. $P < 0.05$ *control vs 1 month, #control vs 1 year, §1 month vs 1 year.

Table 1 Pharmacokinetic parameters of amikacin in patients 1 month and 1 year after unilateral nephrectomy, and in healthy controls.

Parameter	1 month (n = 10)	1 year (n = 10)	Controls (n = 8)	Statistical significance ($P < 0.05$)
AUC (μg mL^{-1} h)	77.7±14.2	69.9±13.0	42.9±5.8	1 month vs control, 1 year vs control
C_0 (μg mL^{-1})	21.6±3.7	22.3±2.5	19.7±3.4	–
λ_z (h^{-1})	0.28±0.06	0.33±0.07	0.46±0.06	1 month vs control, 1 month vs control
V_d (L kg^{-1})	0.24±0.04	0.23±0.03	0.26±0.05	–
Cl_T (L h^{-1})	4.36±0.83	5.15±0.76	9.34±3.00	1 month vs 1 year, 1 month vs control, 1 month vs control
CL_{BW} (L h^{-1} kg^{-1})	0.067±0.015	0.074±0.016	0.118±0.016	1 month vs control, 1 month vs control
$t_{1/2}$ (h)	2.61±0.52	2.19±0.44	1.53±0.18	1 month vs control, 1 month vs control

Values are means±s.d. Amikacin (5 mg kg^{-1}) was administered as a single intravenous dose over 1 h.

Pharmacokinetic parameters of amikacin in patients subjected to unilateral nephrectomy were significantly different from those observed in the control subjects (Table 1). Compared with the controls, an increase in AUC by 81% ($P < 0.001$) and by 63% ($P < 0.01$) 1 month and 1 year after nephrectomy, respectively, was observed. Elimination of amikacin was altered in nephrectomized patients. The λ_z was reduced by 39% ($P < 0.001$) and 38% ($P < 0.001$) 1 month and 1 year, respectively, after the operation and $t_{1/2}$ was prolonged by 70% ($P < 0.001$) and 43% ($P < 0.01$), as compared with healthy volunteers. The difference in $t_{1/2}$ values between the operated groups was statistically insignificant ($P = 0.082$). CL_T and CL_{BW} were both significantly decreased in unilaterally nephrectomized subjects in comparison with the controls. CL_T and CL_{BW} were lower by 53% ($P < 0.001$) and 42% ($P < 0.01$), respectively, 1 month after nephrectomy, and by 45% ($P < 0.001$)

and 42% ($P < 0.01$) 1 year after the surgery. No significant differences among studied groups were found in C_0 and V_d.

Significant correlation between CL_s and λ_z (0.75, $P < 0.05$), $t_{1/2}$ (-0.74, $P < 0.05$) or CL_T (0.79, $P < 0.05$) were found in the control subjects. In these a correlation was also seen between CL_{cr} and CL_T (0.87, $P < 0.01$). No other significant correlations were determined in the controls or unilaterally nephrectomized patients 1 month and 1 year after the surgery.

Discussion

The aminoglycosides continue to be used in the treatment of Gram-negative, enterococcal and staphylococcal infections. Similar to other aminoglycosides, amikacin is primarily excreted through the kidney where it undergoes mainly glomerular filtration and slight tubular reabsorption (Clarke et al 1974). In subjects with normal and impaired renal function, a linear relationship between levels of creatinine in serum and elimination parameters of amikacin has been reported (Pijck et al 1976; Sarubbi & Hull 1978; Elting et al 1990). Elting et al (1990) documented that amikacin paralleled the daily changes in kidney function measured by urine volume and glomerular filtration rate. Amikacin levels measured in the evening after the day-time increase in renal function were unexpectedly low. Conversely, higher levels were seen in the early morning, following the night-time decrease in renal function, and thus, clearance of amikacin. As amikacin is excreted via the urinary tract, the need to modify amikacin dosage for patients with impaired renal function has been pointed out, since in those patients accumulation of the drug was observed (Pijck et al 1976; Lanao et al 1981; Vanhaeverbeek et al 1993).

There is no available data on the pharmacokinetics of amikacin in unilaterally nephrectomized patients, and only a few data related to other drugs (i.e. rolitetracycline (Wojcicki et al 1981b) and salicylate (Wojcicki et al 1981c), as well as experimental studies on gentamicin (Drozdzik et al 1993a, b). The elimination of amikacin depends on its renal excretion and any alteration of the kidney function may lead to accumulation of the drug, which is a potentially nephrotoxic agent. So, information about its proper dosing in unilaterally nephrectomized patients is useful. Our previous studies have demonstrated an impaired elimination of gentamicin in unilaterally nephrectomized rabbits both after a single dose (Drozdzik et al 1993b) and at steady state (Drozdzik et al 1993a). As reported by Kirby et al (1976) the pharmacokinetics of gentamicin and amikacin are essentially the same. A somewhat greater renal tubular reabsorption and higher non-renal clearance rate for amikacin than gentamicin was suggested. However, as stated by the authors, this difference could have been due to variations in experimental procedure, since the comparative studies were done with different study groups at different times (Kirby et al 1976). The findings of Sarubbi & Hull (1978) support the concept that these agents are pharmacokinetically identical. Although animal data cannot be extrapolated directly to man, gentamicin studies in rabbits do suggest an alteration in aminoglycoside pharmacokinetics in unilaterally nephrectomized subjects.

The results of this study demonstrated an impairment of amikacin elimination in unilaterally nephrectomized subjects, both 1 month and 1 year after the surgery. The serum concentrations of the drug were significantly elevated in nephrectomized subjects as compared with healthy controls, with no significant differences between the two groups of patients after nephrectomy, except for the concentrations 12 and 24 h following the end of infusion. These levels were significantly higher in patients nephrectomized 1 month previously. Impaired elimination of amikacin was reflected in the values of pharmacokinetic parameters calculated. Significant increase in AUC, prolongation of $t_{1/2}$ and reduction in λ_z, as well as decrease in CL_T and CL_{BW}, were noted in unilaterally nephrectomized patients as compared with the controls. There were no significant differences between the two groups of patients after nephrectomy, except for the CL_T value, which was significantly reduced in patients 1 month after surgery in comparison with those whose nephrectomy was performed 1 year ago.

A linear relationship between serum levels of creatinine and elimination parameters of amikacin in patients with normal or impaired renal function was reported (Pijck et al 1976). In this study we found that only in healthy volunteers did CL_s significantly correlate with CL_T, as well as with λ_z and $t_{1/2}$. However, such a correlation was not observed in unilaterally nephrectomized patients, either 1 month or 1 year after the surgery. The above characteristics may depend on the different handling of xenobiotics in nephrectomized subjects due to the development of compensatory changes following nephrectomy.

In the light of this study, it can be concluded that amikacin elimination in unilaterally nephrectomized patients is impaired, leading to increased serum levels of the drug. This leads to an increased risk of nephro- and ototoxicity. It can also be assumed that the data on

amikacin elimination in these patients could be extrapolated to other drugs predominantly eliminated via the glomerular filtration.

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