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PHARMACOKINETICS OF AMIKACIN, NETILMICIN AND TOBRAMYCIN IN CHILDREN WITH CHRONIC RENAL FAILURE*

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The single-dose pharmacokinetics of amikacin, netilmicin and tobramycin administered intramuscularly at doses of 7.5 mg/kg amikacin, 2.5 mg/kg netilmicin or 3 mg/kg tobramycin were studied in 30 children with chronic renal failure. Serum amikacin, netilmicin and tobramycin levels were measured by a radioimmunoassay method. The correlation between serum creatinine levels and the half-life of the antibiotics was found to be statistically significant. There were interpatient differences in serum aminoglycoside levels among those with the same serum creatinine levels. Thus, monitoring of serum creatinine and aminoglycoside levels is recommended, especially for those with renal failure, in order to maintain an optimal dosage between toxic and noneffective serum aminoglycoside levels. *Key words: chronic renal failure, pharmacokinetics, amikacin, netilmicin, tobramycin.*

Pediatric patients experience unique differences from adults in pharmacokinetic parameters[1]. Medications used in pediatric medicine often lack dosage guidelines for this group. Most drugs and their metabolites are excreted fully or partially by the kidney; therefore accumulation and toxicity can develop rapidly if dosages are not adjusted in patients with impaired renal function[2-4]. The margin between the therapeutic and toxic concentrations for any aminoglycoside antibiotic is narrow. The dosage of aminoglycosides should be adjusted in patients with renal failure to avoid adverse effects and to ensure efficacy[5, 6].

In pediatric chronic renal patients, the use of aminoglycosides carries important risks, such as different pharmacokinetic properties in the patient, the toxic effect of aminoglycosides and drug modification difficulties in renal failure. To our knowledge, pharmacokinetic studies of aminoglycosides have not been reported in the literature on pediatric patients with chronic renal failure (CRF).

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This study was conducted in order to investigate the pharmacokinetics of amikacin, tobramycin and netilmicin in children with CRF.

Material and Methods

Thirty children between two and 13 years of age (median age seven) with CRF were recruited into six groups of five (1a, 1b, 2a, 2b, 3a, 3b) according to their serum creatinine (Scr) levels. Fifteen other children with normal renal function between the ages of two and 15 years undergoing aminoglycoside therapy were chosen at random to comprise the control groups (1c, 2c, 3c) (Table I). A dosage of 7.5 mg/kg of amikacin was administered by intramuscular (IM) injection to group 1a (Scr greater than 4 mg/dl), group 1b (Scr 3-4 mg/dl) and group 1c. A dosage of 2.5 mg/kg netilmicin was administered by intramuscular injection to group 2a (Scr 2-3 mg/dl), group 2b (Scr 1-2 mg/dl) and group 2c. A dosage of 3 mg/kg of tobramycin was administered IM to group 3a (Scr 2-3 mg/dl), group 3b (Scr 1-2 mg/kg) and group 3c.

Serum samples were collected at zero, one, four, and 24 hours postinjection from patients with normal renal function; zero, one, four, eight, 24 and 48 hours postinjection in patients with Scr between 1-3 mg/dl; and at zero, one, four, 24, 48 and 72 hours postinjection in patients with Scr greater than 4 mg/dl.

Serum amikacin, netilmicin and tobramycin were measured by radioimmunoassay method (Coat-A-Count Amikacin, Coat-A Count Netilmicin and Coat-A-Count Tobramycin kits from Diagnostic Products Corporation). Biochemical analyses were performed by standard methods.

Kinetics: Kinetic parameters of the amikacin, netilmicin and tobramycin groups were calculated by linear regression analysis[6]. Serum kinetic parameters were derived after a single dose of amikacin, netilmicin and tobramycin. Calculations were done as follows: the area under curve (AUC) by trapezoidal rule; the elimination rate constant (k_e) by regression analysis of the terminal phase; elimination half-life ($t_{1/2}$) from the reciprocal of the terminal slope (B) time log2; volume of distribution (Vd) by dose/C_0 where C_0 intercepts the elimination slope at time 0; and total body clearance by (Vd.B).

Statistical analyses: values are expressed as means ± SD. To compare the significance between measurements, the Mann-Whitney U test for unpaired data was used. Linear regression analysis was performed to study the relationship between quantitative variables.

Table I: The Characteristics of the Groups

	Group 1 a Amikacin Scr > 4 mg	Group 1b Amikacin Scr: 3-4 mg	Group 1c Amikacin Scr < 1 mg (control)	Group 2a Netilmicin Scr: 2-3 mg	Group 2b Netilmicin Scr: 1-2 mg	Group 2c Netilmicin Scr < 1 mg (control)	Group 3a Tobramycin Scr: 2-3 mg	Group 3b Tobramycin Scr: 1-2 mg	Group 3c Tobramycin Scr < 1 mg (control)
Age (year)	11.2 ± 1.3	9.8 ± 2.8	6.1 ± 3.9	5.5 ± 2.4	6.1 ± 1.8	9.3 ± 4.9	7.2 ± 2.4	9.9 ± 2.8	6.4 ± 2.6
Sex (F/M)	3/2	2/3	2/3	4/1	3/2	4/1	3/2	2/3	3/2
Weight (kg)	26.9 ± 4.5	21 ± 5.6	20.1 ± 8	17.3 ± 5.2	18.3 ± 4	31.8 ± 17.8	17.3 ± 3.9	22.3 ± 5.6	21.2 ± 5.8
Urea (mg/dl)	19.3 ± 16	151.2 ± 18.4	23.6 ± 3.4	74.8 ± 14	58.2 ± 5.4	24.4 ± 3.2	81.6 ± 7.8	59.8 ± 3	22.4 ± 3.1
Creatinine (mg/dl)	4.8 ± 0.5	3.32 ± 02	0.57 ± 0.2	2.38 ± 0.3	1.44 ± 0.2	0.69 ± 0.2	2.5 ± 0.2	1.57 ± 0.1	0.6 ± 0.2
Creatinine clearance ($ml/min/1.73m^2$)	14.41 ± 0.8	20.1 ± 3	109.2 ± 30	24.74 ± 4.2	42.4 ± 8.9	100.4 ± 9.7	23.6 ± 2.5	36 ± 5.6	102.3 ± 30.1

Results

There was substantial interpatient variation in drug elimination and clearance values in each group (Table II). Peak serum levels (first hour) for amikacin in group 1a ranged from 27 to 60 mg/L, in group 2a for netilmicin from 8.8 to 12 mg/L, and in group 3a for tobramycin from 9.7 to 10.05 mg/L. There was a linear correlation between the serum creatinine and serum half-life of amikacin, netilmicin and tobramycin (r values were 0.82, 0.86 and 0.78, respectively). The serum half-life time values ($t_{1/2}$) of aminoglycosides in each group were found to be as follows: for amikacin 1a = 31h, 1b = 18.7h, 1c = 4.4h; for netilmicin 2a = 13.9h, 2b = 7.3h, 2c = 7.6h; and for tobramycin 3a = 8.2h, 3b = 6.6h, 3c = 3.7h. The linear correlation (r) between serum drug concentration and Scr for the 24th hour was found to be statistically significant for each group; r values were as follows: amikacin 0.79 ($p < 0.05$), netilmicin 0.9 ($p < 0.005$) and tobramycin 0.61 ($p < 0.05$). Other pharmacokinetic parameters are given in Table III.

Table II: Serum Drug Levels (µg/ml) of The Groups

			Hours						
Antibiotic	Groups		0	1.	4.	8.	24.	48.	72.
Amikacin	1a	mean ± SD	0	44 ± 11.9	44 ± 13.1		17.4 ± 9.3	13.9 ± 6.5	9.3 ± 5.8
		range		(27-60)	(32-58)		(14-31)	(7.6-23.5)	(3.5-16)
	1b	mean ± SD	0	36.2 ± 5.4	31.6 ± 2.4		14.2 ± 5.2	6.8 ± 2.8	2.2 ± 1.9
		range		(31-43)	(25-39)		(9-23)	(4-11)	(0.5-5)
	1c	mean ± SD	0	30.3 ± 7.6	6.7 ± 2.3		0.5 ± 0.8		
		range		(19-42)	(3-10)		(0-1.9)		
Netilmicin	2a	mean ± SD	0	9.9 ± 1.2	5 ± 0.18	3.06 ± 0.48	0.96 ± 0.17	0.48 ± 0.3	
		range		(8.8-12)	(4.8-5.2)	(2.5-3.8)	(0.8-1.2)	(0.12-0.8)	
	2b	mean ± SD	0	7.94 ± 1.4	4.14 ± 0.7	2.0 ± 0.23	0.21 ± 0.04	0.08 ± 0.05	
		range		(6.4-9.8)	(3.2-5.1)	(1.7-2.2)	(0.18-0.28)	(0-0.12)	
	2c	mean ± SD	0	9.12 ± 1.08	2.98 ± 0.49	0.9 ± 0.49	0.11 ± 0.07		
		range		(7.6-10.2)	(2.5-3.8)	(0.4-1.12)	(0-0.2)		
Tobramycin	3a	mean ± SD	0	11.31 ± 2.01	6.25 ± 2.45	5.74 ± 2.74	2.35 ± 2.09	0.16 ± 0.08	
		range		(9.7-10.05)	(4.4-10)	(2.7-8.7)	(0.82-5.2)	(0.1-0.26)	
	3b	mean ± SD	0	10.06 ± 0.4	4.56 ± 0.16	2.81 ± 0.89	0.5 ± 0.21	0.06 ± 0.07	
		range		(9.6-10.6)	(4.4-4.8)	(1.85-3.9)	(0.34-0.8)	(0,0.14)	
	3c	mean ± SD	0	6.98 ± 2.64	2.29 ± 0.75	0.58 ± 0.35	0.06 ± 0.1		
		range		(3.8-10.5)	(1.15-3.1)	(0.17-0.9)	(0-0.23)		

Table III: Pharmacokinetic Parameters of the Groups

Antibiotic	Groups	k_e (h^{-1})	$t_{1/2}$ (h)	Vd (l/kg)	AUC (µg.h/ml)	Cl (ml/kg.h)	C_0 (mg/l)
	1a	0.022	31	0.19	1534	4.9	39.8
Amikacin	1b	0.037	18.7	0.2	990.3	7.6	37.1
	1c	0.16	4.4	0.34	131.6	57	22
	2a	0.05	13.8	0.39	97.5	25.4	6.47
Metilmicin	2b	0.095	7.25	0.47	51.8	48.1	5.26
	2c	0.095	7.26	0.37	35.1	71.1	6.75
	3a	0.08	8.1	0.3	148.2	20.2	11
Tobramycin	3b	0.1	6.6	0.39	70.3	42	7.8
	3c	0.18	3.7	0.59	25.3	117.9	5.1

k_e : Elimination rate constant. $t_{1/2}$: Elimination half-life time.
Vd : Volume of distribution. AUC : Area under the curve.
Cl : Drug clearance. C_0 : the value which intercepts the elimination slope at time 0.

In patients with CRF, drug peak values were higher than those of the control group, but the differences were not statistically significant, No toxicity was observed after the single dose of antibiotics.

Discussion

The present study shows that amikacin, netilmicin and tobramycin have in common a prolonged half-life (proportional to the serum creatinine level) in pediatric patients with reduced renal function. Pediatric patients with normal serum creatinine levels demonstrated a significantly enhanced clearance and a shorter half-life compared to those patients with impaired renal function. Although there is a good correlation between serum creatinine and the half-life of aminoglycoside antibiotics, it was not absolute. Indeed the clinician can use the serum creatinine level for pediatric patients as a guideline for dosage modification if other pharmacokinetic dosage calculations are not available[7-10].

All patients in the study received the usual intial dose for a patient with normal renal function, since in practice the same loading dose is used for both groups. The drug peak values were higher in patients with CRF than in the control groups, but the difference was statistically insignificant. In the amikacin group, one patient with a creatinine level greater than 4 mg/dl had a peak serum level of 60 µg/ml. In conventional aminoglycoside treatment with three times daily dosing, therapeutic peak serum levels between 6 and 12 µg/ml generally recommended for both tobramycin and netilmicin. The corresponding value for amikacin is 24 to 48 µg/ml[11]. This study suggests that in patients with severe renal impairment, peak serum levels may be higher than those in the study group and reduction of the loading dose could be necessary. This result should be interpreted with caution because our sample groups were small. The data requires confirmation by further studies involving more patients.

Results showed that the adjustment of dose intervals in patients with renal failure should be the mode of choice. This usage is associated with improved antibacterial activity and reduced risk of adverse effects[12].

Large inter-individual variations of the pharmacokinetics and serum concentrations were observed in both children with normal renal function and those with chronic renal failure. Drug dosages needed for optimal therapeutic effects differ widely among individuals[13, 14]. The "usual dose" of most potent drugs can accomplish little in some individuals it can cause serious toxicity in some, and is fully satisfactory in few. Obviously large individual differences exist regarding the various half-lives of aminoglycosides. The habitual administration of the conventional dose can be satisfactory only when a drug's therapeutic margin is very large and when its full therapeutic potential is not required. On the contrary,

the therapeutic margin of aminoglycosides is very narrow, and a certain level is necessary for antibacterial effect[15]. Therefore the standard dose schedule of the aminoglycosides is to be considered only as a clinical guideline and should be supplemented with serum concentration measurements whenever possible. Although drug level monitoring may provide a more precise tool to ensure therapeutic efficacy and safety, this service is expensive and not available in every hospital.

In conclusion, dose schedules suggested for adults can also be used for pediatric patients. But they should only serve as crude clinical gudelines and should be supplemented with serum concentration measurements whenever possible[2]. In pediatric patients with CRF, this drug monitoring is especially mandatory for therapy with aminoglycosides.

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