GENTAMICIN PHARMACOKINETICS IN KWASHIORKOR

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- 1 Single dose intravenous gentamicin kinetics (2.4 mg/kg) were studied in six children with kwashiorkor. It was observed that therapeutic drug concentrations were achieved which should be neither oto- nor nephrotoxic.
- 2 Due to the diminished glomerular filtration and renal plasma flow seen in the acute phase of kwashiorkor, gentamicin half-life was prolonged (229.0 ± 94.8 min) at this time returning to normal (178.5 ± 99.5 min) with nutritional rehabilitation.

Introduction

Infection in protein energy malnutrition (PEM) especially with gram negative organisms, is exceedingly common (Scragg & Appelbaum, 1978) and despite the use of potent antimicrobial agents remains the leading cause of death in children hospitalized with PEM. For this reason it has been postulated that a study of the pharmacokinetics of drugs used in the treatment of PEM may be useful (Buchanan, 1978). To this end a variety of studies have been performed and were recently reviewed by Krishnaswamy (1978). The present report deals with the kinetics of gentamicin in kwashiorkor.

Methods

Six children, mean age 25.6 ± 10.3 months, with kwashiorkor as judged by the Wellcome Classification (FAO/WHO 1971), were studied on admission to hospital and subsequently after a 21 day period of nutritional rehabilitation. The patients were receiving no other drugs at the study times except an oral potassium supplement. Gentamicin sulphate (2.5 mg/kg) was administered intravenously and blood samples were obtained at 10, 20, 30, 60, 120, 180, 240 and 360 min. Serum urea, creatinine and albumin concentrations were estimated on the first blood sample obtained. Serum gentamicin was estimated in duplicate by radioimmunoassay (New England Nuclear, North Billerica, Mass. U.S.A. coefficient of variation 8%). Gentamicin pharmacokinetics were analysed using a two compartment model (Curry, 1974), particular attention was paid to data obtained from the elimination (β) phase. On the subsequent day, *p*-amino hippuric acid (PAH) (1.5 ml 20% solution) was administered intravenously to

ascertain PAH half-life ($T_{1/2}$), blood samples were collected at 30, 60 and 180 min and analysed spectrophotometrically (White, Erickson & Stevens, 1970). This represents an adequate, albeit indirect, assessment of renal plasma flow, more especially as it was felt to be undesirable to introduce urinary catheters for formal PAH clearances in children in whom it is known that asymptomatic urinary tract infection is prevalent (Buchanan, Fairburn, Schmaman & Vos, 1973).

Results

The results obtained revealed normal renal function; serum urea and creatinine were 10.6 ± 3.8 mg/100 ml and 0.37 ± 0.21 mg/100 ml respectively on admission and did not change significantly with recovery. The remaining results are shown in Table 1 where it can be seen that gentamicin $T_{1/2}$ (β phase) was 229.0 ± 94.8 min on admission, falling to 178.5 ± 99.5 min on recovery. This was associated with both an increase in clearance from 13.6 ± 6.0 ml/min to 28.7 ± 21.3 ml/min and an increase in the apparent volume of distribution (V_d) from 3.9 ± 0.461 to 4.35 ± 11 . PAH $T_{1/2}$ also shortened over the same period from 64.3 ± 11.5 min to 48.9 ± 14.7 min, whilst clearance increased from 81.5 ± 22.7 ml/min to 182.3 ± 95 ml/min. The correlation between gentamicin and PAH clearance was poor ($r = 0.35$). Details of the actual serum gentamicin concentrations before and after nutritional rehabilitation are shown in Table 2.

Discussion

The present data has shown a fall in gentamicin $T_{1/2}$ (β) over a 21 day period of nutritional rehabilitation

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associated with an increase in clearance and V_d . In addition, simulation of an 8 hourly multi-dose schedule, as is administered to these patients in the clinical situation showed that at the time of admission to hospital, the predose concentration would be approximately 1.55 mg/l, whilst on recovery it would be approximately 1.15 mg/l.

The half life ($T_{1/2}$) of gentamicin in adults is approximately 2 h (Bochner, Carruthers, Kampmann & Steiner 1978) whilst in children it varies from

26–230 min and is age related (Echeverria, Siber, Paisley, Smith, Smith & Jaffe, 1975). Thus three of the six children reported here, had unduly prolonged $T_{1/2}$ values. The mean $T_{1/2}$ shortened with recovery, probably related to an improvement in renal function which is known to occur in kwashiorkor (Alleyne, 1967) and has been previously documented with penicillin administration in kwashiorkor where $T_{1/2}$ was observed to be 50.7 ± 20.6 min on admission and 31.6 ± 7.4 min on recovery (Buchanan, Eyberg,

Table 1 PAH and gentamicin data obtained on the six patients studied. A = admission, R = recovery.

Case	Weight (kg)	Serum albumin (g/100 ml)	$T_{1/2}$ PAH (min)	PAH clearance (ml/min)	Gentamicin		
					$T_{1/2}$ β phase (min)	V_d (l)	Clearance (ml/min)
1-A	13.2	2.0	70.8	87.1	144.6	4.7	22.5
1-R	14.0	2.6	49.3	319.1	119.9	8.1	46.8
2-A	10.5	2.1	80.5	68.4	256.0	3.6	9.7
2-R	12.0	3.6	76.8	71.7	68.9	6.1	61.35
3-A	5.6	2.4	53.1	60.0	125.3	3.4	18.8
3-R	5.8	3.9	34.6	248.4	120.1	4.8	27.7
4-A	9.3	1.8	49.5	123.2	204.3	4.0	13.6
4-R	10.1	3.8	40.7	219.6	176.3	4.5	17.7
5-A	7.0	1.6	67.9	82.4	256.6	3.9	10.5
5-R	7.3	4.25	41.3	126.2	245.7	4.3	12.1
6-A	6.8	1.8	63.7	67.9	387.2	3.65	6.5
6-R	7.8	4.1	49.1	108.7	340.3	3.35	6.8
<i>Admission</i>							
Mean	8.7	1.95	64.3	81.5	229.0	3.9	13.6
$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
s.d.	2.8	0.3	11.5	22.7	94.8	0.45	6.0
<i>Recovery</i>							
Mean	9.5	3.87	48.9	182.3	178.5	4.53	28.7
$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$	$\pm$
s.d.	3.1	0.26	14.7	95.1	99.5	1.4	21.3
P value	—	—	<0.01	<0.025	<0.1	<0.05	<0.1

Table 2 Serum gentamicin concentrations (μ g/ml) in the patients studied. A = admission, B = recovery

Case	Time (min)							
	10	20	30	60	120	180	240	360
1-A	13.2	9.9	7.0	6.6	3.7	3.4	1.9	1.3
1-R	13.5	9.9	7.0	3.0	2.2	1.5	1.1	0
2-A	5.5	5.5	5.0	2.95	2.2	1.7	1.2	1.1
2-R	10.5	10.5	8.0	6.4	2.95	1.95	1.3	0.2
3-A	14.0	11.9	—	9.8	6.0	3.45	2.85	1.5
3-R	12.4	11.0	6.6	6.1	4.0	1.5	1.2	1.2
4-A	19.5	19.0	17.5	10.1	9.0	5.3	2.8	2.6
4-R	16.2	14.5	11.0	8.4	4.4	2.1	2.0	1.4
5-A	11.4	9.5	8.2	7.7	6.8	5.8	4.4	3.5
5-R	14.5	12.6	11.5	8.7	6.2	4.4	3.8	3.0
6-A	15.5	14.0	13.5	10.3	8.7	7.3	6.3	5.6
6-R	17.0	15.5	15.1	14.2	9.9	7.7	6.4	2.4

Robinson & Koornhof, (in preparation). In addition an amelioration in renal function was demonstrated in the present study by a shortening of PAH T_1 . The apparent volume of distribution (V_d) was calculated to be 45% of body weight on admission and 48% on recovery. These values are very similar to those described by McCracken & Nelson (1977) in neonates. The reasons for the increase in V_d are unclear, however they cannot be related to changes in protein binding as gentamicin is to all intents and purposes is not protein bound (Buchanan, 1978). It may be related to the observation that TBW increases in the early phase of rehabilitation from malnutrition (Alleynes, Hay, Picou, Stanfield & Whitehead, 1977).

Peak gentamicin concentrations (C_0) varied from 5.7–10.3 mg/l on admission and from 2.7–14.8 mg/l on recovery, however there was a large inter-individual variation. Predicted trough concentrations

during an 8 h dose schedule are such that this would have been 1.5 mg/l at the time of admission and 1.15 mg/l at the time of recovery. Thus the possibility of either ototoxicity or nephrotoxicity, at least from these single dose studies, seems remote (Barza & Lauermann, 1978). However bearing in mind recent data on the tissue persistence of gentamicin and other aminoglycosides in man (Schentag, Jusko, Plaut, Gumbo, Vance & Abruytn, 1977) and the known depression of renal function in kwashiorkor, multiple dose studies serially measuring peak and trough levels need to be carried out in these children.

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