0031-3998/85/1911-1191$02.00/0
PEDIATRIC RESEARCH

Vol. 19, No. 11, 1985
Printed in U.S.A.

Nephrotoxicity of Aminoglycosides in Young and Adult Rats[1]

ABRAHAM P. PROVOOST, OLUSANYA ADEJUYIGBE,[2] AND ERIK D. WOLFF

Department of Pediatrc Surgery and Pediatrics, Erasmus University Medical School, Rotterdam, The Netherlands

ABSTRACT. The nephrotoxicity of gentamicin and amikacin was evaluated comparatively in young and adult rats. The aminoglycosides were administered once daily for 14 days, gentamicin in a dose of either 20 or 60 mg/kg, and amikacin in a dose of either 60 or 180 mg/kg. Renal function was measured during and after treatment. In adult rats there was a dose dependent fall in the glomerular filtration rate which was preceded by histopathological changes in the proximal tubules. The nephrotoxicity of gentamicin was more severe than that of amikacin. The nephrotoxicity of either aminoglycoside was less severe in young rats than in adult rats. In the proximal tubules there were less histopathological changes in young rats than in the adult rats. The mechanism underlying this difference in nephrotoxicity was investigated by measuring the renal accumulation of gentamicin and amikacin. The renal uptake after the first dose of either aminoglycoside was similar in young and adult rats. Expressed as a percentage of the injected amount, the uptake decreased as the aminoglycoside dosage increased. The uptake of gentamicin was somewhat greater than that of amikacin. In young rats, the aminoglycoside concentration in total kidney as well as in renal cortex, was significantly less than in adult rats. This difference was due to the larger wet kidney weight relative to body weight in the young rats. The lower renal aminoglycoside levels in the young rats provide an explanation for the difference observed in aminoglycoside nephrotoxicity when comparing young and adult rats. (*Pediatr Res* 19: 1191–1196, 1985)

Abbreviations

Ak, amikacin
BW, body weight
ERPF, effective renal plasma flow
GFR, glomerular filtration rate
Gm, gentamicin

The nephrotoxic side effects of aminoglycoside antibiotics are well known and have been widely investigated in humans as well as in experimental animals (1). A great deal of knowledge concerning the pathogenesis of the aminoglycoside-induced nephrotoxicity has been generated by studies performed in rats (2). Most of this work involved adult animals. Experimentally, there is some evidence for a reduced nephrotoxicity of aminoglycosides in young animals as compared with adults (3, 4). While reversible changes in renal function of infants treated with aminoglycosides have been reported (5, 6), most of the clinical studies seem to indicate that there are few nephrotoxic side effects of aminoglycosides in neonates and children (7–9).

To further investigate the nephrotoxicity of aminoglycosides in the developing individual, we compared the effects of two doses of either gentamicin (Gm) or amikacin (Ak) on the renal function and histopathology in young and adult rats. A ratio of Gm to Ak dosage was chosen to obtain equally potent bactericidal activity. At the same time we examined the difference in renal tissue accumulation of these aminoglycosides in either young or adult rats.

MATERIALS AND METHODS

Rats. Male rats of a Wistar strain (Wistar Cpb/Wu, TNO, Zeist, The Netherlands) were used. Adult rats were about 3 months of age with a body weight (BW) of about 300 g. The young rats were 3–4 wk of age at the time of the first injection with a BW of 50–60 g. The animals had free access to food and water.

Aminoglycoside dosage. The aminoglycosides were administered by subcutaneous injection once daily between 0900 and 1100 h for a maximum of 14 days. Gm (Essex BV, Amstelveen, The Netherlands) was injected in doses of either 20 mg/kg/day (Gm-20) or 60 mg/kg/day (Gm-60), Ak (Bristol Myers BV, Weesp, The Netherlands) was administered in doses of either 60 mg/kg/day (Ak-60) or 180 mg/kg/day (Ak-180).

Renal function studies. The GFR and the effective ERPF were assessed in pentobabital anesthetized (60 mg/kg intraperitoneal) rats. The GFR and ERPF were measured as the plasma clearances of Cr-51-EDTA and of I-125-Iodohippurate, respectively, using a single injection, single sample technique. This method, allowing for repeated use in the same animal, has been described in detail elsewhere (10).

In adult rats, the GFR and ERPF were determined on days 4, 7, 11, and 14 during treatment, and at wk 3, 6, and 9 after cessation of the aminoglycoside administration. The various groups of aminoglycoside-treated rats were compared with a group of saline-treated control rats. Each group consisted of seven to 10 animals.

Due to technical difficulties, the renal function of the young rats could only be measured at the end of the treatment period (day 14) and 3, 6, and 9 wk after cessation of the treatment. In order to determine the effects during treatment, separate groups of Gm-60 (n = 10), Ak-180 (n = 9), and saline (n = 7) treated control rats had their GFR and ERPF measured on day 7 during treatment. There was no further follow-up of these rats.

Received December 7, 1984; accepted July 8, 1985.
Reprint requests Dr. Abraham P. Provoost, Department of Pediatric Surgery, Laboratory for Surgery, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.
Supported by the Sophia Foundation for Medical Research. We thank Mrs. A. Ribbink-Goslinga for her help in editing the manuscript.

[1] These experiments were presented in part at the Sixth International Symposium of Paediatric Nephrology [Eur J Pediatr 1983; 140:167(abstr)] and at a meeting of the Dutch Society of Nephrology [Kidney Int 1985; 27:705(abstr)].

[2] Present address: Pediatric Surgical Unit, Department of Surgery, IFE-University Teaching Hospital, ILE-IFE, Nigeria.

Renal histopathology. Histological examination was carried out in separate groups of three to four rats at various times during and after aminoglycoside treatment. The kidneys were removed and cut sagitally; one half was fixed in 4% formaldehyde solution while the other half, as well as the contralateral kidney, were used for the assessment of renal aminoglycoside levels.

The fixed renal tissue was dehydrated with ethanol and embedded in paramat. Serial sections were cut to a thickness of 3 μm. Sections were stained with hematoxylin and eosin. Pathological changes in the kidney were scored by a pathologist (Dr. W. O. Odesamni, University of Ife, Nigeria) who was unaware of the origin of the specimen. Histological changes in tubules were scored according to criteria given in Table 1.

Renal tissue studies. The amounts of Gm and Ak in renal tissue were measured at days 1, 4, 7, 11, and 14 of the treatment period in separate groups of six to eight rats on days 1 and 14, and of three rats on days 4, 7, and 11.

The animals were killed 4–5 h after receiving the last dose of aminoglycoside. The kidneys were removed and weighed. The right kidney was assayed for the total kidney drug level. The left kidney was cut sagitally. Half a piece of renal cortex was excised and weighed to determine the cortical aminoglycoside concentration. The other half was reserved for histological examination. The kidneys and cortices were homogenized with a Potter-Elvehjem homogenizer in 66.7 mM phosphate buffer (pH 8.0). Both Gm and Ak were determined by an enzyme-immuno-assay (EMIT, Syva, Palo Alto, CA). The samples were diluted not only to obtain an aminoglycoside level within the recommended range, 1–10 μg/ml for Gm and 2.5–30 μg/ml for Ak, but also to have less than 50 mg of renal tissue homogenate per ml of buffer. Previously we have shown that a greater amount of renal tissue interfered with the EMIT assay procedure (11).

Statistics. Statistical differences between the means of the renal function parameters of the various groups of either young or adult rats were assessed by one-way analysis of variance. In case of statistically significant differences, *i.e.* an F value indicating a $p < 0.05$, the Newman-Keuls test was applied to detect which pair(s) of means were different (12). Differences in renal aminoglycosides levels between adult and young rats receiving the same dose of aminoglycosides were compared by Student's *t* test.

RESULTS

Renal Function.

Adult rats. The effects on the GFR and the ERPF of the various doses of Gm or Ak in adult rats are presented in Figure 1. With Gm-20 a small, but significant drop of about 20% in the GFR was noted at the end of the treatment period. With Gm-60 the fall in the GFR was more marked. After 4 days of treatment the GFR had fallen to 80%. The greatest reduction was observed between days 7 and 11. At day 11 the GFR was only 15% of that of control rats. With continuation of the Gm treatment, the GFR showed a small increase between days 11 and 14.

With Ak-60 no significant changes in GFR were observed during the treatment period. With Ak-180 there was a gradual decrease in the GFR to a level of about 50% of that of control rats at the end of the treatment period.

After cessation of aminoglycoside administration, there was a recovery of GFR in all groups of treated rats. The GFR was not significantly different from control rats 3, 6, or 9 wk after cessation in Gm-20-, Ak-60-, and Ak-180-treated rats. However, a small, permanent reduction in GFR persisted in the Gm-60-treated adult rats up to 9 wk after cessation of the drug administration.

During aminoglycoside treatment, the reduction in ERPF was less marked than for GFR. No significant changes were seen after Gm-20 and Ak-60 during the whole treatment period. A severe fall in the ERPF was only noted after Gm-60. As with

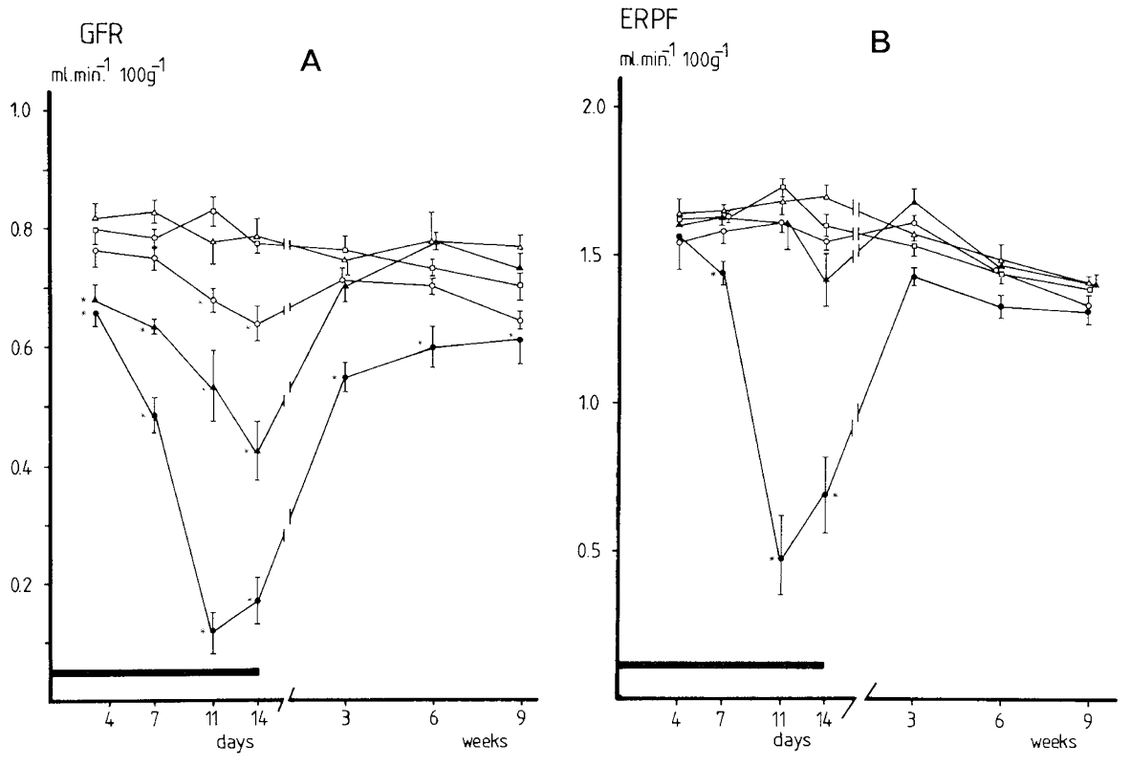

Fig. 1. Longitudinal study of the changes in the GFR (*A*) and effective renal plasma flow (*B*) of adult rats during and after 14 days of aminoglycoside administration. Data represent mean ± SEM. * $p < 0.05$ from saline-treated controls; □, control ($n = 9$); ○, Gm-20 ($n = 8$); ●, Gm-60 ($n = 10$); △, Ak-60 ($n = 8$); ▲, Ak-180 ($n = 9$).

GFR the lowest value was obtained at day 11 of treatment. At that time the ERPF amounted to 20% of that of control rats. When measured 9 wk after cessation of the various treatments, there were no significant differences between the ERPF of previously treated and control rats. Only a small drop in the ERPF was found at day 14 after Ak-180.

Young rats. When compared with control rats, only the Gm-60-treated rats showed a small but significant reduction (about 20%) in GFR after 14 days of aminoglycoside administration. The GFR recovered completely after cessation of treatment (Fig. 2). At the end of the treatment period no significant differences were seen between the ERPF of treated and control rats.

In a separate study of groups of Gm-60, Ak-180, and saline-treated control rats, no significant differences in GFR or ERPF were found among the groups after 7 days of treatment.

Histopathology.

Adult rats. During aminoglycoside treatment tubular damage was dose dependent and, in general, more severe after Gm than after Ak. With the lower doses, Gm-20 and Ak-60, grade 3 damage (see Table 1) was present at day 11. At that time there also was evidence of regeneration of tubular cells. With the higher doses, Gm-60 and Ak-180, the most severe tubular damage (grades 4–5) was present at days 4 and 7. By days 11 and 14 there was tubular regeneration and the degree of necrosis had decreased. During the follow-up period some tubular damage persisted. The degree of damage was somewhat higher in the adult rats receiving the higher doses of aminoglycosides (Table 1).

Table 1. *Pathological scores of kidneys of adult and young rats treated with various doses of Gm or Ak**

	Pathological score						
	During treatment				After treatment		
	Day 4	Day 7	Day 11	Day 14	Wk 3	Wk 6	Wk 9
Adult							
Gm-20	2	3	3	2	2	1	1
Ak-60	2	2	3	2	2	1	1
Gm-60	5	5	3	2	2	2	2
Ak-180	4	4	2	2	2	2	2
Young							
Gm-20	2	2	1	1	1	1	1
Ak-60	1	1	2	2	1	0	0
Gm-60	2	3	3	3	2	2	2
Ak-180	2	3	3	3	2	2	2

* Grading of histopathological changes. Grade 0, normal histological appearance; grade 1, cloudy swelling of proximal tubular epithelium without necrosis; grade 2, necrosis of up to 25% of the tubules; grade 3, necrosis of 25% to 50% of the tubules; grade 4, necrosis of 50% to 75% of the tubules; grade 5, necrosis of 75% to 100% of the tubules.

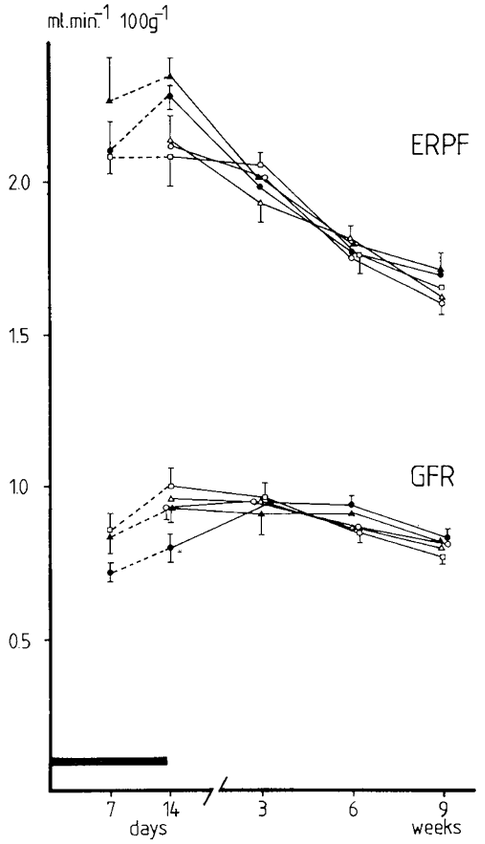

Fig. 2. Longitudinal study of the changes in effective renal plasma flow (*upper portion*) and GFR (*lower portion*) of young rats during and after 14 days of aminoglycoside administration. Data represent mean ± SEM. * $p < 0.05$ from saline-treated controls; □, control ($n = 8$); ○, Gm-20 ($n = 9$); ●, Gm-60 ($n = 10$); △, Ak-60 ($n = 10$); ▲, Ak-180 ($n = 7$). The data at day 7 represent single data obtained in separate groups of young rats, control ($n = 7$), Gm-60 ($n = 10$), and Ak-180 ($n = 9$).

Young rats. During treatment the degree of tubular necrosis was less than observed in the adult rats treated with similar doses of aminoglycosides. Again the lower doses of Gm and Ak were associated with less damage than the higher ones. After 7 days of treatment, in Gm-60 and Ak-180, grade 3 tubular damage was present. The accompanying interstitial reactions were most pronounced in the Gm-60-treated rats. By day 7 there was a concurrent regeneration of epithelial cells, which was even more marked on days 11 and 14. After cessation of the drug treatment some damage remained, especially in animals given higher dosage (Table 1).

Renal tissue levels. The tissue aminoglycoside levels for total kidney and renal cortex determined in adult and young rats are depicted in Figure 3. In both age groups the cortical concentrations of both Gm and Ak were higher than that of total kidney. In adult rats, initially, the tissue drug levels were dose related. After 7 days of treatment, the lowest level was found after Gm-20, intermediate levels after Gm-60 or Ak-60, while the highest levels were found after Ak-180. A steady state level was achieved after 11–14 days of treatment. However, after Gm-60, no steady state level was found. From day 7 the amount of Gm in renal tissue decreased. At day 14 the renal tissue Gm levels after Gm-60 were almost identical to those measured after Gm-20.

In young rats dose-related steady state levels were reached during the 2nd wk of aminoglycoside treatment. As in adults the drug concentration in renal cortex was significantly higher than that of total kidney. With an identical dose, aminoglycoside concentrations in the kidneys always were significantly less in young rats than in adult rats. This difference probably related to differences in kidney weight relative to BW between adult and young rats. As indicated in Table 2, the wet kidney weight per 100 g of BW of young rats on the 1st day of aminoglycoside administration averaged about 170% of that of adult rats.

The total amount of Gm or Ak taken up by the kidney from the first administration increased with dose in both adult and young rats. However, this increase was not proportional to the increase in dosage. The renal uptake (as a percentage of the injected dose) in adult rats amounted to 4.1% after Gm-20 and decreased to 1.5% after Ak-180. In the young rats these figures were 3.6 and 1.5%, respectively. At day 1 the renal uptake after Ak-60 was less than after Gm-60 in both adult and young rats (Table 2).

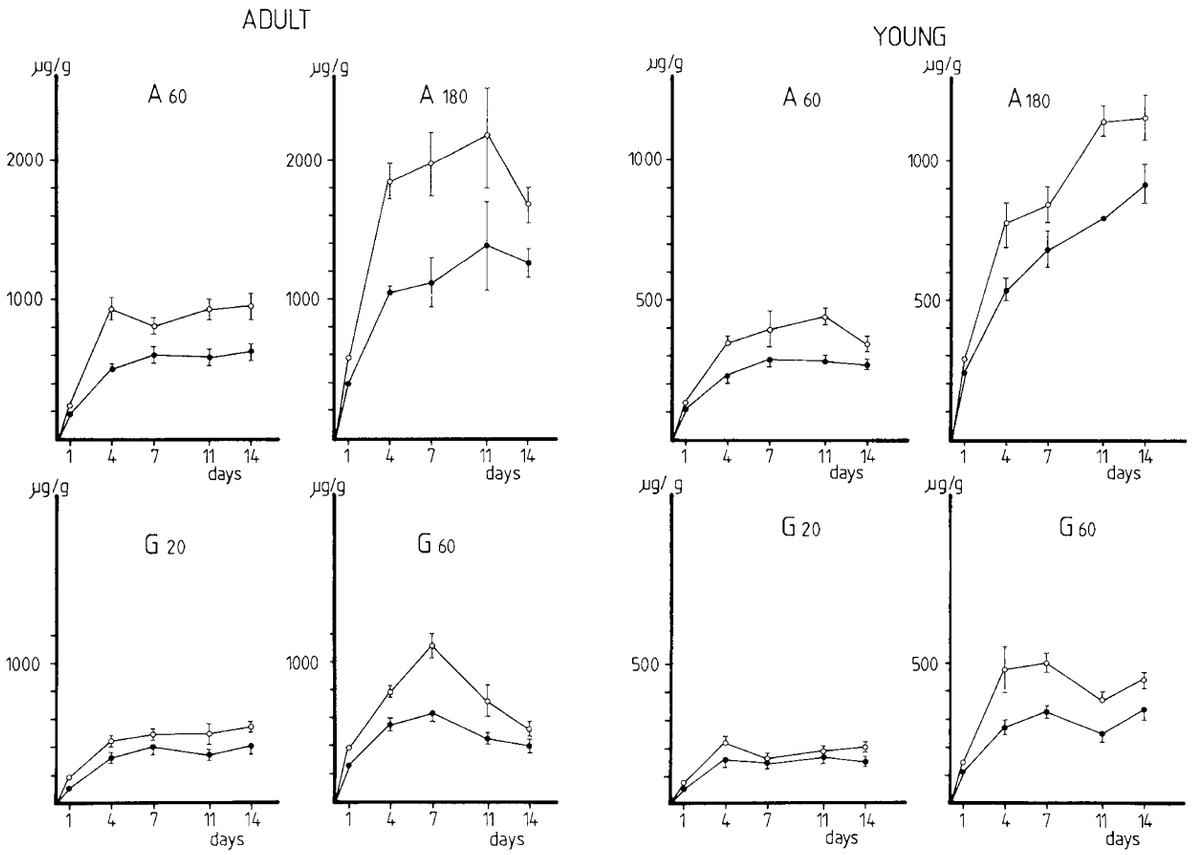

Fig. 3. Aminoglycoside concentration in total kidney and renal cortex of adult (*left*) and young rats (*right*) at various intervals during the administration of various does of Gm or Ak. Data represent mean ± SEM. ●, total kidney; ○, renal cortex; *A*, Amikacin, *G*, Gentamicin. The *figures* behind *A* and *G* indicate the dosages in mg/kg/day. Note the difference in scale of the concentration between adult and young rats.

Table 2. *Pharmacokinetic parameters of renal aminoglycoside uptake in adult and young rats (mean ± SD)*

	(*n*)	BW (g)	Wet kidney wt (mg/100 g)	Accumulation (µg)	Concentration (µg/g)	Uptake (% injected dose)
Adult						
Gm-20	(6)	294 ± 4	704 ± 28	240 ± 18	117 ± 7	4.1 ± 0.3
Gm-60	(6)	296 ± 3	644 ± 21	522 ± 58	273 ± 17	2.9 ± 0.3
AK-60	(6)	297 ± 4	700 ± 46	378 ± 24	189 ± 12	2.1 ± 0.2
AK-180	(6)	294 ± 6	704 ± 52	816 ± 90	394 ± 36	1.5 ± 0.2
Young						
Gm-20	(6)	62 ± 4	1226 ± 58	46 ± 14	59 ± 14	3.6 ± 0.9*
Gm-60	(6)	63 ± 2	1210 ± 88	88 ± 10	115 ± 10	2.3 ± 0.2
Ak-60	(6)	64 ± 2	1088 ± 52	76 ± 10	109 ± 14	2.0 ± 0.2*
Ak-180	(6)	66 ± 4	1108 ± 76	176 ± 30	244 ± 36	1.5 ± 0.3*

* All data of young rats are significantly different ($p < 0.05$) from those of adult rats, except those marked with an asterisk.

DISCUSSION

The present study clearly shows that aminoglycosides, when administered relative to BW, are less nephrotoxic in young rats than in adult rats. Young rats have a larger body surface area relative to BW than adult rats. Consequently, if the drugs had been administered relative to body surface area the differences in nephrotoxicity between young and adult rats might have been less. For example, the average drug dose per square meter in adult rats was about 1.5 times that in young rats. In adult rats prolonged administration of either Gm or Ak was associated with well-known, aminoglycoside-induced dose-dependent changes in GFR. In contrast, very little change in renal function was observed in young rats. Our data confirm and extend earlier experimental studies indicating that aminoglycosides are less nephrotoxic in young animals than in adult ones (3, 4). Clinical studies also have suggested less nephrotoxicity of aminoglycosides in neonates and children (7–9).

In adult rats the changes in the GFR observed after Gm or Ak were both dose and time dependent. When compared with the histopathological changes in the renal tubules, the fall in GFR was a late nephrotoxic event. Even with the higher dose of Gm, the GFR was only moderately reduced after 7 days of treatment. The most severe drop in GFR was noted during the 2nd wk of treatment, in agreement with the findings reported by others (13–16). The GFR increased again at the end of the Gm treatment period. Such a recovery of function during prolonged Gm administration has been reported earlier (13, 17, 18).

Despite numerous experimental investigations the pathophysiological mechanisms for the decrease in GFR after aminoglycoside administration remain controversial. Changes induced by Gm in glomerular ultrastructure, which may directly lead to a reduction in the GFR, have been reported (19, 20). On the other hand, the fall in GFR might result indirectly from severe damage to other parts of the nephron, especially the proximal tubule. In our study tubular cell necrosis preceded the changes in GFR.

The mechanism by which tubular damage diminishes the GFR was not examined in the present study. There are, however, three possibilities. First, there could be backleak of the radioactive marker used to measure the GFR; this would lead to underestimation of the actual GFR (20). There has been no evidence of backleak. Second, tubular obstruction causing an elevation of tubular pressure and a reduction in the filtration pressure gradient is possible. However this is not very likely (15, 20). Third, activation of the tubuloglomerular feedback mechanism may be of importance in reducing the GFR. This possibility seems most likely. Aside from increased urinary excretion of marker enzymes from proximal tubular cells, polyuria and a fall in urine osmolality are among the earliest signs of aminoglycoside nephrotoxicity. The fall in GFR may then be regarded as a protective mechanism of the kidney to prevent further massive fluid losses. Tubuloglomerular feedback is thought to function through renal vasoconstriction, predominantly preglomerular, by activation of the renin-angiotensin system (22). Both the increase in renal vascular resistance (20, 23, 24) and an activation of the renin-angiotensin system (23, 25) have been found to be present after prolonged aminoglycoside administration in rats.

Most of the experimental results on aminoglycoside nephrotoxicity in rats have been obtained using Gm. Comparative studies usually have examined the nephrotoxic effects of another aminoglycoside in relation to that of Gm. When comparing the nephrotoxicity of Gm and Ak it should be kept in mind that the therapeutic dosages used clinically differ for these two aminoglycosides. In general, the therapeutic dose of Ak is about three times the daily dose of Gm to achieve equal bactericidal activity. Using this difference in dosage we found that in rats Ak was less nephrotoxic than Gm. Similar experimental findings have been reprted (26, 27). In humans, a reduced incidence of nephrotoxic reactions has been reported after Ak in comparison with Gm, but most clinical trials comparing the nephrotoxicity of Gm and Ak do not provide evidence that effective doses of Ak are less nephrotoxic than Gm (28, 29).

The present study also demonstrated that the differences in nephrotoxicity between the low and the high doses of Gm or Ak can be explained by differences in the renal aminoglycoside concentration. In adult Gm-treated rats, the renal drug level was dose related and, when measured at day 7, before the most severe fall in GFR had occurred, predictive for the subsequent functional changes. A relationship between an increased nephrotoxicity and an increase in the amount of aminoglycosides administered has been well established (20, 27, 30, 31). However, there is less certainty concerning a relationship between the dose of aminoglycoside or aminoglycoside nephrotoxicity and the renal accumulation of the drug. In a number of studies such a relationship could not be established (27, 30). In agreement with others, we did find increasing renal aminoglycoside levels when the dose was increased (32). A relationship between the renal drug accumulation and nephrotoxicity can best be established by correlating an early drug level with the subsequent changes in renal function (33).

In our opinion, the lower renal aminoglycoside concentration, found in young rats in comparison with adult rats with equal drug dosage, provide a good explanation for the observed attenuated nephrotoxicity in the young animals. Lower aminoglycoside levels in the kidneys of young animals when compared to adults have been noted previously (3, 4, 34). These differences have been explained either by a diminished ability to accumulate Gm (4) or by a different distribution of the renal blood flow (3) in the young kidney. The final renal tissue level is the result of an equilibrium between renal uptake and release and the total amount of renal tissue available for the drug distribution. We found no marked differences between the young and adult rats in the percentage of the dose taken up. The only significant difference was the higher wet kidney weight relative to BW in the young rats when compared with adult rats. In a previous cross-sectional study we found that the wet kidney weight per 100 g BW decreased linearly when the rats grew from 35 to more than 350 g (10). Due to this larger wet kidney weight per 100 g BW and the almost identical renal uptake in the young rats when compared with adults, lower renal drug concentrations will result when the aminoglycosides are administered in a dose relative to BW.

The fact that the high kidney weight in relation to BW effectively attenuates the nephrotoxicity of aminoglycosides may prove to be important in humans. When renal autopsy data from children are related to BW, relative renal weight falls from about 8–10 g/kg BW at birth and during the first year of life, to 4–5 g/kg BW in adults (35). Consequently, the low incidence of aminoglycoside nephrotoxicity in neonates and infants (7–9) may well be the result of lower renal aminoglycoside concentration. In one case the post mortem renal Gm concentration was measured in a 2-day-old infant who had received a single dose of 2 mg/kg. The Gm concentration in the renal cortex was only 10% that of an adult who had received two times 2 mg/kg of Gm (36). This supports the view that renal aminoglycoside concentrations in human neonates may indeed be less than in adults and consequently give rise to less nephrotoxicity.

The attenuating effect of the high kidney weight to BW ratio on nephrotoxicity in young rats is not limited to aminoglycosides. Recently, we carried out a study comparing the nephrotoxicity of the antineoplastic agent cis platin in adult and young rats. As with Gm and Ak, we found that when cis platin was administered per kg BW, the nephrotoxicity after equal dosages was less in young rats. This reduced nephrotoxicity was associated with lower renal platinum concentrations, while the renal uptake, as a percentage of the dose, was similar in young and adult rats (37).

In conclusion, by studying the nephrotoxicity of Gm and Ak in both young and adult rats we found that Ak was less nephrotoxic than Gm. Comparing young and adult rats, we found that both aminoglycosides were less nephrotoxic in the young rats. This reduced nephrotoxicity could be explained by the lower renal drug concentration found in the young rats, which is most probably due to the higher kidney weight relative to BW in these animals.

Acknowledgment. The authors thank Mrs. A. Ribbink-Goslinga for her help in editing the manuscript.

REFERENCES

1. Whelton A, Neu HC 1982 The Aminoglycosides. Marcel Dekker Inc, New York
2. Kaloyanides GJ, Pastoriza Munoz E 1980 Aminoglycoside nephrotoxicity. Kidney Int 18:571–582
3. Cowan HR, Jukkola AF, Arant BS Jr 1980 Pathophysiologic evidence of gentamicin nephrotoxicity in neonatal puppies. Pediatr Res 14:1204–1211
4. Marre R, Tarara N, Louton T, Sack K 1980 Age-dependent nephrotoxicity and the pharmacokinetics of gentamicin in rats. Eur J Pediatr 13:25–29
5. Elinder G, Aperia A 1983 Development of GFR and excretion of beta-2-microglobulin in neonates during gentamicin treatment. Acta Paediatr Scand 72:219–224
6. Feldman H, Guignard JP 1982 Plasma creatinine in the first month of life. Arch Dis Child 57:123–126
7. McCracken GH Jr, Chrane DF, Thomas ML 1971 Pharmacologic evaluation of gentamicin in newborn infants. J Infect Dis 124 (suppl):S214–S223
8. Landers S, Berry PL, Kearns GL, Kaplan SL, Rudolf AJ 1984 Gentamicin disposition and effect on development of renal function in the very low birth weight infant. Dev Pharmacol Ther 7:285–302
9. Parini R, Rusconi F, Cavanna G, Vigliani E, Cornacchia L, Assael BM 1982 Evaluation of the renal and auditory function of neonates treated with amikacin. Dev Pharmacol Ther 5:33–46

10. Provoost AP, De Keijzer MH, Wolff ED, Molenaar JC 1983 Development of renal function in Rats. Renal Physiol 6:1–9
11. Provoost AP, Van Schalkwijk WP, Adejuyigbe O, Van Leeuwen WB, Wagenvoort JHT 1984 Determination of aminoglycosides in rat renal tissue by enzyme immunoassay. Antimicrob Agents Chemother 25:497–498
12. Zivin JA, Bartko JJ 1976 Statistics for disinterested scientists. Life Sci 18:15–26
13. Eliott WC, Houghton DC, Gilbert DN, Baines-Hunter J, Bennett WM 1982 Gentamicin nephrotoxicity. I. Degree and permanence of acquired insensitivity. J Lab Clin Med 100:501–512
14. Gilbert DN, Plamp C, Starr P, Bennett WM, Houghton DC, Porter G 1978 Comparative nephrotoxicity of gentamicin and tobramycin in rats. Antimicrob Agents Chemother 13:34–40
15. Kosek JD, Mazze RI, Cousins MJ 1974 Nephrotoxicity of gentamicin. Lab Invest 30:48–57
16. Luft FC, Patel V, Yum MN, Patel G, Kleit SA 1975 Experimental aminoglycoside nephrotoxicity. J Lab Clin Med 86:213–220
17. Gilbert DN, Houghton DC, Bennett WM, Plamp CE, Reger K, Porter GA 1979 Reversibility of gentamicin nephrotoxicity in rats: Recovery during continuous drug administration. Proc Soc Exp Biol Med 160:99–103
18. Luft FC, Rankin LI, Sloan SA, Yum MN 1978 Recovery from aminoglycoside nephrotoxicity with continued drug administration. Antimicrob Agents Chemother 14:284–287
19. Avasthi PS, Evan AP, Huser JW, Luft FC 1981 Effect of gentamicin on glomerular ultrastructure. J Lab Clin Med 98:444–454
20. Baylis C, Rennke HR, Brenner BM 1977 Mechanism of the defect in-glomerular ultrafiltration associated with gentamicin administration. Kidney Int 12:344–353
21. Cohen L, Lapkin R, Kaloyanides G 1975 Effect of gentamicin on renal function in the rat. J Pharmacol Exp Ther 193:265–273
22. Wright FS, Briggs JP 1979 Feedback control of glomerular blood flow, pressure, and filtration rate. Physiol Rev 59:958–1006
23. Fernandez-Repollet E, Finn W 1984 Relative importance of volume expansion and tubular damage in gentamicin induced acute renal failure. In: Solez K, Whelton A (eds) Acute Renal Failure. Marcel Dekker Inc, New York, pp 235–247
24. Schor N, Ichikawa I, Rennke HG, Troy JL, Brenner BM 1981 Pathophysiology of altered glomerular function in aminoglycoside-treated rats. Kidney Int 19:288–296
25. Luft FC, Aranoff GR, Evan AP, Connors BA, Weinberger MH, Kleit SA 1982 The renin-angiotensin system in aminoglycoside-induced acute renal failure. J Pharmacol Exp Ther 220:433–439
26. Hottendorf GH, Gordon LL 1980 Comparative low-dose nephrotoxicities of gentamicin, tobramycin, and amikacin. Antimicrob Agents Chemother 18:176–181
27. Luft FC, Bloch R, Sloan RS, Yum MN, Costello R, Maxwell DR 1978 Comparative nephrotoxicity of aminoglycoside antibiotics in rats. J Infect Dis 138:541–545
28. Smith CR, Lietman PS 1982 Comparative clinical trials of aminoglycosides. In: Whelton A, Neu HC (eds) The Aminoglycosides. Marcel Dekker Inc, New York, pp 497–509
29. Whelton A 1985 Therapeutic initiatives for the avoidance of aminoglycoside toxicity. J Clin Pharmacol 25:67–81
30. Luft FC, Yum MN, Kleit SA 1976 Comparative nephrotoxicites of netilmicin and gentamicin in rats. Antimicrob Agents Chemother 10:845–849
31. Sugarman A, Brown RS, Silva P, Rosen S 1983 Features of gentamicin nephrotoxicity and effect of concurrent cephalothin in the rat. Nephron 34:239–247
32. Aronoff GR, Pottratz ST, Brier ME, Walker NE, Fineberg NS, Glant MD, Luft FC 1983 Aminoglycoside accumulation kinetics in rat renal parenchyma. Antimicrob Agents Chemother 23:74–78
33. Bennett WM, Plamp CE, Gilbert DN, Parker RA, Porter GA 1979 The influence of dosage regimen on experimental gentamicin nephrotoxicity: Dissociation of peak serum levels from renal failure. J Infect Dis 140:576–580
34. Milner RDG, Milner GR, Lancaster D 1979 Tissue gentamicin concentrations in the newborn and adult rat. Pediatr Res 13:161–166
35. Chantler C 1979 The kidney. In: Godfrey S, Baum JD (eds) Clinical Paediatric Physiology. Blackwell Scientific Publications, Oxford, pp 356–398
36. Edwards CQ, Smith CR, Baughman KL, Rogers JF, Lietman PS 1976 Concentrations of gentamicin and amikacin in human kidneys. Antimicrob Agents Chemother 9:925–927
37. Jongejan HTM, Provoost AP, Wolff ED, Molenaar JC 1984 Nephrotoxicity of Cis-platin in young and adult rats. Pharm Weekbl [Sci] 6:228 (abstr)