Hypoalbuminemia as a risk factor for amikacin nephrotoxicity

GERARD0 GAMBA, ANA MARIA CONTRERAS,* . JORGE CORTES,** FELIPE NARES,** YAFFITA SANTIAGO,* . ANGELES ESPINOSA,* .. JUAN BOBADILLA,* . GERARDO JIMENEZ SANCHEZ,** GUADALUPE LOPEZ,,*** ALBA VALADEZ,* .. * JOSE CARLOS PEÑA**

Abstract

Hypoalbuminemia has been recently informed by us as a risk factor in aminoglycoside nephrotoxicity. Since amikacin has a low serum binding capacity to albumin, the present study was designed to determine if the higher risk of amikacin nephrotoxicity in patients with hypoalbuminemia was due to low serum albumin per se or to malnutrition.

One-hundred and thirteen ward patients who received endovenous amikacin for > 36 hours were studied prospectively. All were evaluated for the following factors: age, sex, diagnosis, serum creatinine, serum albumin, and nutritional status. They were followed with serum creatinine twice a week until cessation of therapy. Amikacin pharmacokinetics was studied in 11 subjects: 6 patients had a serum albumin < 3.0 g/dL and 5 > 3.0 g/dL, but there were no differences in age, sex, weight, diagnosis, arterial pressure and nutritional status.

The overall incidence of toxicity was 11%. In patients with serum albumin < 3.0 g/dL it was 17.3% and in those > 3.0 g/dL it was 2.2%, $p < 0.05$. There was no difference in the nutritional status between toxicity and non-toxicity groups. In the pharmacokinetic study, the peak levels obtained one hour after amikacin administration were higher in patients with serum albumin < 3.0 g/dL than in those with normal serum albumin (12.7 ± 1.6 vs 9.0 ± 1.2, $p < 0.002$).

In conclusion hypoalbuminemia is a risk factor in aminoglycoside nephrotoxicity regardless of the nutritional status.

HIPOALBUMINEMIA COMO FACTOR PREDISPONENTE PARA TOXICIDAD POR AMIKACINA

Resumen

Recientemente informamos que la hipoalbuminemia es un factor predisponente para toxicidad renal por amikacina. No existe explicación para este hallazgo debido a que la amikacina no se fija a la alblimina sérica. El presente estudio se llevó a cabo para determinar si el aumento en el riesgo de nefrotoxicidad en los pacientes con hipoalbuminemia está relacionado directamente a la alblimina sérica o bien con el estado nutricional del enfermo.

Se estudiaron en forma prospectiva 113 pacientes hospitalizados que recibieron amikacina intravenosa por período mayor a 36 horas. En todos los enfermos se valor6 al inicio del tratamiento los siguientes datos: edad, sexo, diagnbstico, creatinina sérica, albúmina sérica y estado nutricional. Todos los enfermos fueron seguidos con determinaciones de creatinina sérica dos veces por semana hasta la suspensión del tratamiento. En once

* Departamento de Nefrología y Metabolismo Mineral.
** División de Medicina Interna.
*** División de Nutrición.
**** Departamento de Medicina Nuclear.
Instituto Nacional de la Nutrición "Salvador Zubirán", Vasco de Quiroga 15, Tlalpan, 14000 México, D.F.

Presentado en parte en la XXXVII reunión anual del Instituto Mexicano de Investigaciones Nefrológicas. Acapulco, Gro., México. 16-20 de noviembre de 1988.

Recibido el 10 de julio de 1989. Aceptado para publicación el 8 de febrero de 1990.

pacientes se estudiaron los niveles de amikacina en sangre durante un periodo de cinco horas: seis tenían alblimina sérica <3.0 g/dL y cinco mayor a esta cifra, pero no habia diferencia en edad, sexo, peso, diagnóstico, presión arterial y estado nutricional entre estos dos grupos.

La incidencia global de nefrotoxicidad fue de 11%. En los pacientes con alblimina sérica <3.0 g/dL la incidencia fue de 17.3%, mientras que en aquéllos con > 3.0 g/dL fue de 2.2% ($p < 0.05$). No existió ninguna diferencia en el estado nutricional entre el grupo que desarrol16 y el que no desarrolld nefrotoxicidad. En el estudio farmacocinético, los niveles pico obtenidos una hora después de la administración de la amikacina, fueron mayores en los pacientes con alblimina sérica <3.0 g/dL (12.7 ± 1.6 vs 9.0 ± 1.2, $p<0.002$).

La conclusión del estudio es que la hipoalbuminemia es un factor predisponente en la toxicidad renal por amikacina, independientemente del estado nutricional del enfermo.

The aminoglycosides are used in the treatment of severe gram negative bacilli infections'. However, renal toxicity is a frequent complication and requires premature discontinuation of therapy[2]. In order to predict the occurrence of toxicity, clinical studies have identified several risk factors; among the most important are: old age, renal failure, shock, and treatment duration[3-5]. Recently we found, in a prospective study[6], that the incidence of amikacin nephrotoxicity was significantly higher in patients with low serum albumin levels. There is not a satisfactory explanation for this finding because amikacin does not bind to serum albumin[7-8]. Since hypoalbuminemia is one of the indexes used to evaluate the nutritional status[9], the higher incidence of toxicity6 in patients with low serum albumin, might be secondary to malnutrition. On the other hand, different authors found that hypoalbuminemia reduces the glomerular filtration rate (GFR)[10-12]. It is possible to speculate that the higher incidence of nephrotoxicity in these patients is probably due to diminished renal function secondary to hypoalbuminemia.

The purpose of the present study was: 1) to reconfirm if hypoalbuminemia is a risk factor in aminoglycoside nephrotoxicity; and 2) to identify if the higher risk of nephrotoxicity is associated with: malnutrition and low serum albumin or to low serum albumin alone.

Patients and methods

All ward patients treated with intravenous amikacin, for a minimum of 36 hours. alone or in combination with other antibiotics, were included in this three-month prospective study (Apr to Jun 1988). Patients with acute renal failure, end stage renal disease under dialysis, shock, hepatorenal syndrome, and with renal, liver or bone marrow transplantation treated with cyclosporine were excluded from the study[6].

Amikacin is the only aminoglycoside used. in our hospital since 1981[3], and it is usually administered I.V. (15 mg/kg 3 times/day) in a 30 minute period; dose was corrected according to the calculated creatinine clearance with the formula described by Cockcroft and Gault (CrClmale = 140-age/serum creatinine. CrClfemale= 0.9 X CrClmale)[14], and adjusted to maintain plasma levels ranging from 2-9 ug/mL.

Before amikacin was begun the following data were recorded for each patient: age, sex, underlying disease, other antibiotic used, control serum creatinine in mg/dL, serum albumin in g/dL, and calculated and given amikacin dose in mg/day. Weight, height, upper arm circumference, triceps skin fold and arm-muscle circumference were also measured for nutritional evaluation. For the follow up, serum creatinine was measured 2 times per week until cessation of therapy and trough amikacin plasma level once a week.

Nephrotoxicity was defined as an increase in serum creatinine of 0.5 mg/dL or more in patients with serum creatinine <1.9 mg/dl, an increment in serum creatinine >1 mg/dL was required in patients with a serum creatinine level from 2.0-4.9 mg/dL, and finally a rise of 1.5 mg/dL or more for patients with a serum creatinine above 5 mg/dL[6]. In our laboratory the coefficient of variation was 10% for serum creatinine below 2 mg/dL and smaller when serum creatinines were above 2 mg/dL.

For the evaluation of some aspects of pharmacokinetics of amikacin in patients with hypoalbuminemia, eleven patients were studied with blood samples taken before and at 1, 2, 3, 4, and 5 hours after the morning doses in the third day of treatment. Six patients had serum albumin below 3.0 g/dL and the other five >3.0 g/dL. These patients did not have renal disease, diabetes mellitus or arterial hypertension, and were paired by: age, sex, weight, diagnosis, mean arterial pressure, serum creatinine, and nutritional status.

Shock was defined as systolic blood pressure less than 90 mmHg with physical signs of hypo-

perfusion for more than 6 hours. Hepatorenal syndrome was diagnosed if patients with chronic liver disease developed oliguria, azotemia, and urinary sodium concentration below 10 mEq/L[6].

Undernutrition was established in patients who had weight for height, triceps skin fold, upper arm circunference or arm-muscle circumference below percentile 15 of the Frisancho tables[15].

Triceps skin fold and upper arm circunference were measured and arm-muscle circumference derived according to the Jeliiffe recomendation.[16] The serum creatinine and serum albumin were measured in an Autoanalyzer. Amikacin plasma level was determined by RIA in duplicate using a solid phase kit[17] (Diagnostic Products Co., Los Angeles, CA); with a coefficient of variation inter and intraassay of 6.8% and 7.5% respectively.

All data were saved in a Hewlett Packard PC Vectra-AT. Statistical analysis was performed using the software Stat-Pak NWA. Fisher exact test, chi square square with Yates correction, and two-tailed non paired student t test were used. All data are expressed as mean ± one standard deviation and the difference between means and between proportions with confidence intervals of 95% (CI95%)[18, 19]. A $p<0.05$ was considered statistically significant.

Results

A total of 13 patients fulfilled the criteria for inclusion in the study. The mean age was 50.2 ± 18.5 years; the control serum creatinine 1.2 ± 0.4 mg/dL, and serum albumin 2.8 ± 0.6 g/dL. The group included 50 males and 63 females. Treatment duration was 11.6 ± 7.9 days. Eight patients received amikacin alone, 62 with another antibiotic, and 43 as part of a three drug combination scheme. Some type of penicillin was used in 56 patients, cephalosporin in 36, clindamycin in 43, sulbenicillin in 10, and metronidazole in 20. Underlying diseases in the study group were: diabetes mellitus in 29/113 (25.6%), malignancies in 24/113 (21.2%), chronic liver disease in 14/113 (12.3%), collagen disease in 10/113 (8.8%) and others in 36/113 (31.8%).

Nephrotoxicity developed in 13 of the 113 patients, for an incidence of 11.5%. All cases had non-oliguric acute renal failure, and none had received radiographic contrast material. There was no difference between toxicity and non-toxicity groups in: weight (55 ± 9 vs 58 ± 12 kg, $p>0.05$, CI95% -3.7 to 9.7); serum creatinine (1.33 ± 0.4 vs 1.18 ± 0.4 mg/dL, $p> 0.05$, CI95% 0.1 to 0.4); chronic liver disease (2/13 vs 12/100, $p> 0.05$, CI95% -17 to 23%); diabetes mellitus (6/13 vs 23/100, $p> 0.05$, CI95% -5 to 51%), and cephalothin treatment (4/13 vs 23/100, $p> 0.05$, CI95% -19 to 33%). The mean age of patients with toxicity was 61 ± 14 years and in the group without toxicity was 49 ± 19 years. This difference was significant ($p <0.05$, CI95% 1 to 22).

The serum albumin was lower in patients who developed nephrotoxicity than in those without toxicity (2.40 ± 0.4 vs 2.86 ± 0.6 g/dL, $p< 0.02$, CI95% 0.06 to 0.83). Furthermore, the incidence of nephrotoxicity in patients with serum albumin less than 3.0 g/dL was 17.3% (12/69), while in those with serum albumin equal or more than 3.0 g/dL it was 2.2% (1/44) ($X^2 = 4.6$, $p< 0.05$, difference 15.1 CI95% 5.1 to 25%) with a relative risk of 7.8.

The mean amikacin daily dose was 466 mg ± 201 mg in the group with toxicity and 571 ± 221 in the group without toxicity: this difference did not reach significance ($p> 0.05$, CI95% -22 to 232).

Table 1 shows the mean percentage of: the relation between weight for height, the triceps skin fold, the upper arm circumference, and the arm-muscle circumference in the toxicity and non toxicity groups. The percentile 15 of the

Table 1
MEAN VALUES (± STANDARD DEVIATION) FOR THE PERCENTAGE OF ANTHROPOMETRIC INDEXES IN THE TOXICITY (N = 13) AND NON TOXICITY (N = 100) GROUPS

	Toxicity group	*Non toxicity group*	*p**	*CI 95%*
Weight for height relation	112 ± 31	104 ± 21	NS	5 to 21
Triceps skin fold	125 ± 65	144 ± 76	NS	24 to 62
Upper arm circumference	98 ± 11	102 ± 14	NS	4 to 12
Arm-muscle circumference	95 ± 36	96 ± 34	NS	10 to 20

CI 95% = confidence intervals of 95%
* = Student t test

Table 2
CLINICAL AND ANTHROPOMETRIC INDEXES OF PATIENTS WITH (N = 69) AND WITHOUT (N = 44) f IYPOALBUMINEMIA

	Serum albumin	
	< 3.0 g/dL	*> 3.0 g/dL*
Age (years)	52.3 ± 18.6	d-i.5 ± 20
Weight (kg)	57.2 ± 12.1	59.6 ± 12.6
Serum creatinine (mg/dL)	1.19 ± 0.44	1.21 ± 0.47
Treatment duration (days)	12.8 ± 6.9	10.52 ± 5.27
Amikacin dose (mg/day)	549 ± 241	604 ± 274
Weight for height relation	1.05 ± 0.22	1.04 ± 0.22
Triceps skin fold	1.45 ± 0.82	1.33 ± 0.57
Upper arm circumference	1.02 ± 0.14	1.00 ± 0.12
Arm muscle circumference	0.96 ± 0.33	0.95 ± 0.26

Frisancho tables[14] was taken as the reference index to calculate the percentage of the anthropometric values.

Table 1 shows that there was no difference in the nutritional status between both groups according to the anthropometric indexes. Furthermore, the incidence of nephrotoxicity in the group of patients with malnutrition was 11/98 (11.2%) and in the other group it was 2/15 (13.3%).

Table 2 shows that there were no significant differences among the 69 patients with serum albumin <3.0 g/dL and the 44 with >3.0 g/dL in: age, serum creatinine, treatment duration, weight, amikacin dose, and the anthropometric indexes.

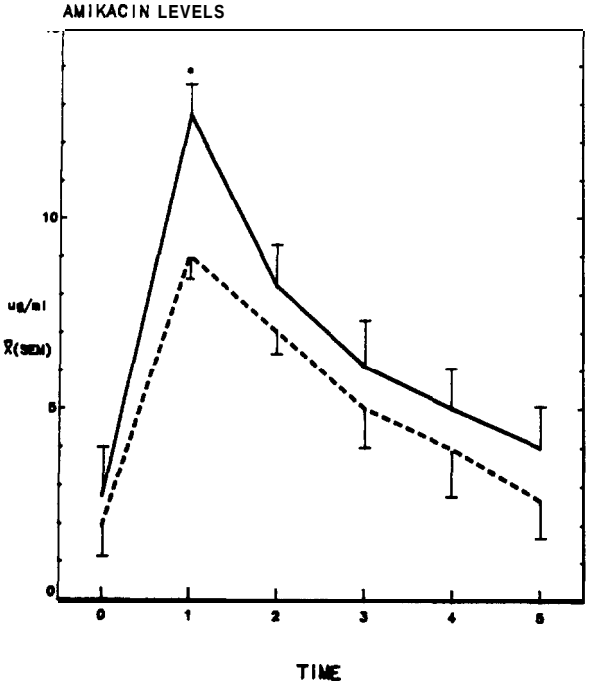

Figure 1. Concentration of serum amikacin versus time postinfusion (hours) in 6 patients with serum albumin <3.0 g/dL (continuos line) and in 5 patients with >3.0 g/dL (deshed line). SEM = standard error of the mean.

Figure 1 shows the concentration of serum amikacin versus time (in hours) in six patients with serum albumin below 3.0 g/dL and in five patients with more than 3.0 g/dL. There was no difference in age, weight, sex, nutritional status and arterial pressure between these two groups. No patient had underlying renal disease. The group with low serum albumin had l-hour post dose levels significantly higher than those with normal serum albumin (12.7 ± 1.6 vs 9 ± 1.2 ug/mL, p<0.002, CI95% 1.6 to 5.7). The group of patients with serum albumin below 3.0 g/dL (continuous line) had higher amikacin levels at 2,3,4, and 5 hours than the group with normal serum albumin (dashed line) but the differences were not significant.

Discussion

The 11.5% incidence of amikacin nephrotoxicity in the present study was similar to our previous report (6). Again the main risk factors detected were old age and hypoalbuminemia, while the control serum creatinine was the same in the groups with and without toxicity. As in our previous observation, the patients with diabetes mellitus had a higher incidence of nephrotoxicity, but the difference did not reach significance (x^2 = 2.13), probably because of a type II error. if this is true, the higher incidence of toxicity might be associated with the high incidence of chronic renal disease in patients with diabetes mellitus. There was no difference in the incidence of renal toxicity in the patients with chronic liver failure and in those who were treated with amikacin

plus cephalotin.

Our previous[6] and current data confirm hypoalbuminemia as a risk factor for aminoglycoside nephrotoxicity. The higher risk seems to be associated with low concentration of serum albumin since the nutritional status of both groups was similar according to the weight for height relation, the triceps skin fold, the upper arm circumference, and the arm-muscle circumference. In fact, the incidence of toxicity was equal between patients with and without malnutrition. Furthermore, obsesity has been recently recognized as a risk factor for aminoglycoside toxicity[20].

The higher risk in patients with low serum albumin may be due to low serum protein binding or to an impaired renal function during hypoalbuminemia. Data in the literature regarding the extent of aminoglycoside serum protein binding is conflicting with reports ranging from 0 to 30%[8, 9]. Thus, it is difficult to sustain the hypothesis that patients with hypoalbuminemia had significantly more serum free amikacin, and that this was the cause of the higher incidence of renal toxicity.

There is some evidence in the literature that low serum albumin lower CFR due to a fall in the ultrafiltration coefficient (Kf)[10-12, 21-25]. Klahr and Alleyne in adults[10] and Gordillo et al[25] in children with protein malnutrition found that those with serum albumin below normal had a significant lower GFR than those with normal or near normal serum albumin; when the serum albumin returned to normal after treatment, the GFR increased substantially. We found that patients with serum albumin <3.0 g/dL had a significantly higher l-hour post-dose levels of amikacin than those with normal serum albumin (figure 1): furthermore, at 2, 3, 4, and 5 hours the hypoalbuminemic patients had higher levels, but the differences were not significant, probably due to the low number of patients studied (type II error). This finding support the contention that the higher risk of amikacin nephrotoxicity in patients with hypoalbuminemia was secondary to an impaired renal function induced by the low serum albumin. This hypothesis may explain why the patients of the toxicity group developed acute renal failure even though they received a lower daily dose of amikacin than patients of the non-toxicity group.

that dose or dosage prescription of amikacin taking into account the serum albumin may help to reduce the incidence of nephrotoxicity.

REFERENCES

1 Lietman PS Aminoglycoside and spectinomycin aminocyclitols In Mandel GL Douglas RG Bennett JE (eds) Principles and practice of Infectious diseases Second Ed New York Wiley Medical Pub 1 985 192-4

2 Lietman PS Smith CR Aminoglycoside nephrotoxicity in humans Rev Inf Dis 1983 5(Suppl 2) S284-93

3 Moore RD Smith CR Lipsky JJ Risk factors for nephrotoxicity in patients treated with aminoglycosides Ann Int Med 1984 100 352-7

4 Meyer RD Risk factors and comparisions of clinical nephrotoxicity of aminoglycosides. Am J Med 1986; 80(suppl 68): 119-25.

5 Sawyers CL, Moore RD, Lerner SA, et al. A model for predicting nephrotoxicity in patients treated with aminoglycosides J Ii fect Dis 1 986 153 1062-8

6 Gamba G Arizpe D Ferral H et al Amikacin nephrotoxicity incidence clinical course and risk factors A prospective study in a teaching hospital Rev Invest Clin 1988 40 135-40

7 Humes HD Weinberg JM Knauss TC Clinical and pathophysiologic aspects of aminoglycoside nephrotoxicity Am J Kid Dis 1982 2 5-29

8 Myers DR DeFehr J Bennett W et al Gentamicin binding to serum and

Effects of angiotensin-converting enzyme inhibition on altered renal hemodynamics induced by low protein diet in the rat. J Clin Invest 1987; 80: 1045-9.

25. Gordillo G, Soto AR, Metcoff J, et al. Intracellular composition and homeostatic mechanism in severe chronic infantile malnutrition. III. Renal adjustment. Pediatrics 1957; 20: 303-8.