The Amikacin on premature newborn: schema of treatment defined by gestational and postnatal age.

Original Article

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SUMMARY.

Introduction. Amikacin (AMK) is an antibiotic of the aminiglycosides family frequently used against infections caused by gram negative bacteria in the newborn. It is necessary to get defined serum concentrations to obtain the highest efficiency and the lowest toxicity. The classic protocols generally drive to higher plasmatic concentrations than those recommended. That is why, on premature newborn, we used a protocol taking into account weight gestational and the postnatal age, all at the same time, since the physiological constants of the newborn evolve change quickly.

Material and methods. This protocol has been compared to the protocol usually used in our Hospital, that doesn't take those features of the postnatal age into account. The study was carried out on 112 prematures forming four groups, distributed according to their gestational and postnatal age. All received AMK at the dose of 7,5 mg/kg of weight, only the administration rhythms differed. Our schema proposed of AMK administration: every 24 hours to the premature of less than 33 weeks of gestational age an less or more than 7 days of life, every 18 hours to prematures from 33 to 36 weeks with a postnatal age of 6 days or less and every 12 hours to those aged 7 to 21 days.

Results. AMK serum peak and trough concentrations were maintained within recommended limits and the posology did not have to be adjusted more than a few times.

Discussion. These results permit us to recommend this schema in special on those hospitals which don't have the technological support for the serum determination of AMK. *(Rev Biomed 2000; 11:251-256)*

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RESUMEN.
La Amikacina en recién nacidos prematuros: esquema de tratamiento definido por edad gestacional y postnatal.
Introducción. La Amikacina (AMK) es un antibiótico de la familia de los aminoglucósidos, utilizado contra bacterias gram negativas en el recién nacido. En su empleo es necesario obtener concentraciones séricas definidas para obtener la mejor eficiencia con la mínima toxicidad. Generalmente los esquemas clásicos llevan a concentraciones plasmáticas más elevadas que las recomendadas. Por esta razón nosotros utilizamos un esquema que considera el peso, la edad gestacional y postnatal al mismo tiempo, dado que las constantes fisiológicas del recién nacido cambian rápidamente.
Material y métodos. Este protocolo se comparó con el que se emplea de rutina en nuestro Hospital que no considera la edad postnatal. El estudio se realizó en 112 prematuros en el cual se formaron 4 grupos distribuidos de acuerdo a su edad gestacional y postnatal. Todos los RN recibieron AMK a dosis de 7.5 mg/Kg de peso, sólo difirieron los tiempos de administración. En nuestro esquema la administración de AMK fue la siguiente: cada 24 horas para prematuros menores de 33 semanas de gestación mayores o menores de 7 días de vida, cada 18 horas para los prematuros de 33 a 36 semanas de gestación con menos de 7 días de vida y cada 12 horas para aquellos de 7 a 21días.
Resultados. Las concentranciones séricas de AMK pico y valle se mantuvieron dentro de los límites recomendados.
Discusión. Estos resultados nos permiten recomendar este esquema de tratamiento en hospitales donde no se cuenta con soporte tecnológico para la determinación de la AMK.
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INTRODUCTION.
The Amikacin (AMK) is one of the aminoglucoside antibiotic family most frequently used in the treatment of newborn infections caused by gram negative bacteria. But since in neonatal period the physiology changes very quickly. The volume of extracellular liquid and the glomerular filtration rate, play an important role on the pharmacokinetics properties of the AMK (1-4) and in its possible toxicity, since AMK is eliminated mainly through urine (5). Consequently it is recommended to supervise serum peak and trough concentrations to avoid the accumulation and side effects that might result (6-7).

Besides as a direct correlation exist between the glomerular filtration rate on one hand and gestational and postnatal age on the other hand, these last parameters associated to body weight allow an excellent definition of the state of the newborn. It will result logical to take into account all these data to determine the AMK posology, instead of excluding some of them, as has been usual (8-10).

The objective of this study was get a schema of AMK administration that, taking into account gestational and postnatal age and weight, would permit for the maintenance of AMK serum concentrations within the advisable therapeutic limits and would require few adjustments. This may be particularly interesting in situations where technological support is lacking.

MATERIAL AND METHODS.
Patients. This clinical assay was carried out on 112 prematures aged 0 to 21 days, from the Neonatalogy Unit at West National Medical Center. The AMK was administered either for suspected (16 cases) or documented bacteria infection (96 cases) during at least 7 days.

All serum creatinine values were between normal limits according to Guinar criteria (11).

Newborns showing a congenital malformation or if they showed increments above of 0.3 mg/dL of initial creatinine serum values; as well as those whose state had required an exanguino-transfusion or a peritoneal dialysis were excluded of the study.

Four groups were formed (Group I to IV) in function of the gestational and postnatal age (12). Inside each group, two subgroups (A and B) with 14 newborn each one were constituted by random distribution. Features of each of the 4 groups with its corresponding subgroups are indicated on table 1.

Treatment. The A schema of AMK administration, is the schema that we proposed, this schema was established in function of prior observations obtained in a pilot study (not reported) and the B schema, is the one usually employed in our Hospital.

All prematures received the same dose of AMK 7,5 mg/kg of body weight by i.v. injection. According to the A schema, the AMK was given every 24 hours to those of the subgroups I and II; every 18 hours to those of the subgroup III and every 12 hours to prematures of the subgroup. IV. To prematures from the B schema of AMK administration, the antibiotic was given every 12 hours of the other subgroups I and III, and every 8 hours to those of the other subgroups II and IV.

AMK determination. AMK serum concentrations were determinated using an Amikin kit from laboratories Abbot System assays. Values were expressed in µg/mL. From the third administration, peak values were measured 20 minutes after the antibiotic injection and trough values 20 minutes before the following injection. These two parameters were also determined on the 5th and 7th day of treatment.

AMK serum concentrations were considered adequate when peak values were found between 15 and 25 µg/mL and those of the trough between 2 and 5 µg/mL (13-14). If the aminoglucoside serum concentrations were not in these limits, intervals of administration were decided to be modified.

Creatinine determination. It was carried out, in the same samples, with the help, of a commercial kit into Hospital routine.

Statistical analysis. In order to guarantee a risk of mistake of 5% and to have a strength of 90%, 56 patients were included in each therapeutic schema. Variables were compared by the correspondace X^2 and/or by Student´s "t" test.

RESULTS AND DISCUSSION.

Table 1 shows that, all newborns, independently of the group or schema of AMK administration (A or B) that they were submitted

TABLE 1
CHARACTERISTICS OF PREMATURES AND GROUPS

Group	Gestational Age (Weeks)	Prematures Age (Days)	Gestational Age Mean ± SD*		Postnatal Age Mean ± SD	
			A†	B†	A†	B†
I	<33	0 to 6	29.7 ± 1.5	30.4 ± 1.6	3.5 ± 1.6	3.4 ± 1.4
II	<33	7 to 21	30.0 ± 1.3	30.4 ± 1.3	10.2 ± 2.1	10.3 ± 3.2
III	33 to 36	0 to 6	35.3 ± 1.2	35.0 ± 1.3	4.6 ± 1.2	4.5 ± 0.9
IV	33 to 36	7 to 21	34.8 ± 0.9	34.8 ± 0.9	9.7 ± 3.1	11.9 ± 4.9

*SD = Standard deviation.   † = schema

to, were strictly comparable on gestational and postnatal age. To verify the renal function, we measured serum creatinine on newborn from different groups: Groups that received the therapeutic A schema had a creatinine average of 0.69 ± 0.15 mg/dL whereas those that received the therapeutic B schema had a creatinine average of 0.71 ± 0.15, these values remained practically without variations during all treatment, suggesting a good renal function and permitting a valid comparison between the different treatment schema.

AMK dose was the same for all children (7.5 mg/kg of body weight and administration), thus taking into account the child weight.

Premature newborns with less than 33 weeks gestation age groups I (postnatal age from 0 to 6 days) and II (postnatal age from 7 to 21 days), according to the A schema, AMK was given every 24 hours. We found that peak and trough AMK levels were perfectly in the desired limits at the first determination (table 2), as well as those of the determination made at 5th and 7th day of AMK administration (as there were not differences between 5th and 7th day of treatment only are show the corresponding values to the 7th day). With the B schema, the AMK was given every 12 hours to newborn of the group I (postnatal age

from 0 to 6 days) and every 8 hours to newborn with a postnatal age from 7 to 21 days (group II), contrastingly on these groups AMK peak and trough serum concentrations were higher on a rank 1.3-2.2 and 2.9-5.8 times respectively that the superior values recommended as efficients and not toxics (table 2). As to determinations made the 5th and 7th day of treatment, they have not interest because the treatment schema was adjusted to be adapted several times, as it is indicated on table 3.

For premature newborns, from 33 to 36 weeks of gestational age, AMK was given every 18 hours, if they were aged from 0 to 6 days (group III) and every 12 hours if they were aged from 7 to 21 days (group IV). Values of the peak and the trough of the first AMK determination as well as the values obtained at the end of 7th day of treatment were inside the advisable limits. According to the B schema, the AMK was given every 12 hours to newborn aged from 0 to 6 days (group III) and every 8 hours to those aged from 7 to 21 days (group IV). Peak values came closer to desired values, but those of the trough AMK concentrations were higher than the recommended values, thus for group IIIB and IVB were superior on a rank of 1.94- 4.85 and 1.42-3.5 times respectively (table 2).

It is worthwhile to underline, to get the

TABLE 2
PEAK AND TROUGH SERUM LEVELS OF AMK EXPRIMED IN µg/mL.

Group	Administration Schema	First Determination (Mean ± S D*)		Determination At 7th day (Mean ± S D)	
		Peak	Trough	Peak	Trough
I	A: each 24 hours	22.6 ± 7.4	4.4 ± 1.3	20.3 ± 3.4	4.0 ± 1.0
	B: each 12 hours	33.6 ± 5.6	11.8 ± 3.3		
II	A: each 24 hours	19.3 ± 2.4	4.2 ± 1.8	18.1 ± 1.1	4.4 ± 0.2
	B: each 8 hours	32.9 ± 6.6	13.7 ± 5.9		
III	A: each 18 hours	20.6 ± 5.5	5.3 ± 3.5	20.3 ± 4.4	5.0 ± 1.5
	B: each 12 hours	28.2 ± 5.8	9.7 ± 6.4		
IV	A: each 12 hours	17.8 ± 1.1	5.2 ± 3.1	18.6 ± 4.4	4.4 ± 1.2
	B: each 8 hours	24.6 ± 6.9	7.1 ± 4.9		

*= Standard deviation.

14 prematures by each subgroup A or B.

TABLE 3
NUMBER AND RELATIVE RISK OF MODIFICATIONS OF THE AMIKACIN SCHEMA OF TREATMENT.

Group	Schema	Number of Modifications to Schema	p value A vs B	Relative Risk	Confidence Intervals at 95 %
I	A	1	<0.002	13	1.96 - 86.42
	B	13			
II	A	0	<0.002	-	-
	B	14			
III	A	2	<0.002	5.5	1.48 - 20.42
	B	12			
IV	A	1	<0.002	13	1.96 - 86.42
	B	13			

14 prematures in each subgroup A or B.
Relative risk = considered like more times that it is needed to modified the schemaa

desired values, it was sometimes necessary to modify intervals of administration. Table 3 shows that for newborns that were submitted to the A schema, it was done once upon group I, 0 times upon group II, twice upon group III and once upon group IV.

In contraposition with the B schema was done 13 times in the group I, 14 times in group II, 12 times in group III and 13 times in group IV. Let us recall that every group counted 14 newborn.

In order to be more clear, we calculated the relative risk (RR) and its confidence intervals at 95%, that means in this case, how many more times the schema B needs to be modified versus schema A (see table 3)

It is important to remark that in some works, the AMK is administered once a day, however these works have been mainly directed to adult and pediatric patients, and no differences were found on AMK serum levels, the authors on those studies have not yet concluded whether this schema is better that the schema based on multiple daily AMK administrations, and could not result adequate for prematures due to its physiologic characteristics (15-17). The schema we propose takes into consideration newborn weight, and it is a function of gestational and postnatal age thus having a more comprehensive idea of the newborn physiologic state. Thus we got and maintained, desired antibiotic serum concentrations, on the peak as well as on the trough values, with a reduced number of adaptations, in intervals of AMK administration. These observations are important because the assayed therapeutic schema diminish the toxic potential of the AMK, probability of making mistakes and the work load. In addition, it constitutes an important advantage particularly in conditions where it is not possible to follow the pharmacokinetics of the antibiotic by routine measurment of its blodd level.

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