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Effect of Mannitol on the Pharmacokinetics of Amikacin in Wistar Rats

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ABSTRACT

The study analyzed the effect of mannitol on the pharmacokinetics (PK) of amikacin. Adult Wistar rats were treated as follows: Group 1 (G1) received mannitol for three days, Group 2 (G2) received mannitol plus 10 mg/kg of amikacin simultaneously, and Group 3 only amikacin. The PK study was conducted on the 4th day. For which, blood samples were drawn at fixed times during 24 h and immunoenzymatically analyzed. Results revealed significant differences ($p<0.05$) between the groups, e.g. Cmax were 62.26 ± 15.75 μg/ml for G1, 72.63 ± 24.80 μg/ml for G2 and 68.61 ± 27.40 μg/ml for G3. The AUC also differed in the three groups, being largest for G2, 222.52 ± 47.30 μg/ml/h, and smallest for G1, 135.59 ± 39.00 μg/ml/h. Alteration of the PK parameters observed between the groups must be considered when both drugs are prescribed, although human studies are necessary to confirm the results.

Key words: Pharmacokinetics; interactions; amikacin, mannitol; antibiotics; diuretics

INTRODUCTION

Mannitol is frequently used for severe head trauma (SHT) treatment. Favorable results have been recently reported for the prophylactic use of aminoglycosides in patients with SHT. Medical treatment of SHT aims to prevent or minimize secondary brain damage following injury (Proccacio et al. 2000). Mannitol has substituted other osmotic diuretics in the last 20 years for the treatment of patients with SHT (Kharitonova et al. 1984), especially when increased intracranial pressure (ICP) is suspected, or is in fact present (GTNC 2000, Suarez 2001). In many studies, mannitol has proved to benefit cases of high ICP, deficient blood flow and brain metabolism, and short-term benefit for the patient's neurological prognosis (Mendelow 1985). The immediate plasma expansive factor of mannitol decreases hematocrit and blood viscosity, increasing brain blood flow (BBF) as well as oxygen distribution. This decreases ICP a few minutes after mannitol administration, especially in patients with low perfusion pressure in cerebral (PPC) (< 70 mmHg) (Muizelaar et al. 1984). Mannitol increases the plasma osmolar pressure and is excreted in the urine, which implies significant risk of acute renal failure by acute tubular necrosis when plasmatic osmolarity reaches values above 320 mOsm/l (BTFNS 1996).

Similarly, reports about the prophylactic use of aminoglycosides in patients with severe head

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trauma, especially when there is liquid exposure, have led to adequate outcome in patients (Kolodzeijczyk and Hirsch 1992, Kharitonova et al. 1990). Amikacin is among the most useful aminoglycoside antibiotics with rapid bactericidal effect against many aerobic Gram-negative bacilli and Gram-positive cocci. However, there are no reports on whether the use of mannitol as a volume expander and an ICP hypotensor has an effect on the pharmacokinetics and/or pharmacodynamics of aminoglycosides. Moreover, the simultaneous use of amikacin and mannitol in adults is relatively rare.

The aim of the present study was to analyze the effect of the administration of mannitol, anticipated and simultaneous to amikacin, on amikacin pharmacokinetics in Wistar rats.

MATERIALS AND METHODS

Three groups of eight adult Wistar rats were used mean weight 210 g, the first group (G1) received 0.75 ml/100 g of weight of 20% mannitol for three days, and on the fourth day, a single dose of amikacin (10 mg/kg) was administered for the pharmacokinetic study. Group 2 (G2) received simultaneous mannitol plus amikacin since the first day, and the pharmacokinetics study was done on the fourth day as in G1. Group 3 (G3) received a single dose of amikacin for the pharmacokinetic study. All drugs were administered intraperitoneally (IP). For the pharmacokinetic study, 200 µl of venous blood were drawn from the tail at 15, 30, 60, 90, 120 minutes and 4, 10, 12 and 24 h post-doses, and immunoenzymatically analyzed (TDx-Abbott). This technique determined amikacin concentrations with specificity, precision and exactness, and was previously validated in the laboratory (TDxFLx 1992). The study was approved by the Committee of Animal Care of the Institute. The program Winnonline version 2.1 was used for pharmacokinetic analysis and differences among the groups and between the treatments ($p \leq 0.05$) were determined by the Kruskal-Wallis test.

RESULTS

Results showed significant differences in the pharmacokinetic parameters of amikacin in rats under different treatments. Table 1 shows the different study modalities. Differences were found in amikacin concentration after 15 minutes as follows: for G1, 62.26 ± 15.75 µg/ml; G2, 72.63 ± 24.80 µg/ml and 68.61 ± 27.40 µg/ml for G3. Similarly, the area under the curve (AUC) was different for the three groups, the largest AUC was for G2 with 222.52 ± 47.30 µg/ml/h and the smallest for Group 1 with 135.59 ± 39.00 µg/ml/h. Pharmacokinetic parameters and statistical analyses are shown in Table 1.

Table 1 - Effect of mannitol on the pharmacokinetic parameters of amikacin in Wistar rats.

Pharmacokinetic Parameters	**Group 1***	**Group 2 ****	**Group 3 *****	**Comparison (KW)**
Cmax (µg/ml)	62.26 ± 15.75	72.63 ± 24.80	68.61 ± 27.40	$p \leq 0.05$
AUC (µg/ml/h)	135.59 ± 39.00	222.52 ± 47.30	144.40 ± 31.60	$p \leq 0.03$
α (l/h)	- 0.07 ± 0.01	- 0.07 ± 0.01	- 0.04 ± 0.01	$p \leq 0.03$
ß (l/h)	- 0.21 ± 0.03	- 0.71 ± 0.11	- 0.90± 0.16	$p \leq 0.03$
$t_{1/2}$ (h)	3.30 ± 0.49	0.97 ± 0.33	0.76 ± 0.25	$p \leq 0.02$
Vd (l)	20.39 ± 21.85	13.21 ± 8.65	17.55 ± 12.40	$p \leq 0.05$
Cl (l/h)	0.78 ± 0.22	0.45 ± 0.08	0.75 ± 0.31	$p \leq 0.05$

* Mannitol for 3 days, then amikacin

** Mannitol plus amikacin for 3 days

*** Amikacin only

KW: Kruskal-Wallis test, Cmax: Maximum concentration; AUC: Area under the curve; α and β are the rate constants and represent fast and slow phases of drug loss from plasma; $t_{1/2}$ Half-life; Vd: Distribution volume; Cl: Clearance.

The pharmacokinetic profiles were built with amikacin concentration values. Figure 1 (Group 1) shows the average pharmacokinetic profile observed in the group of rats treated with mannitol previous to amikacin and pharmacokinetically analyzed on the last day of treatment. The figure also shows the pharmacokinetic profile of rats that received simultaneous mannitol plus amikacin for three days (Group 2), although the elimination parameters tended to increase, they were different to those of Group 1. The average pharmacokinetic profile of the group of rats treated with a single dose of amikacin for the pharmacokinetic study (Group 3) is also shown.

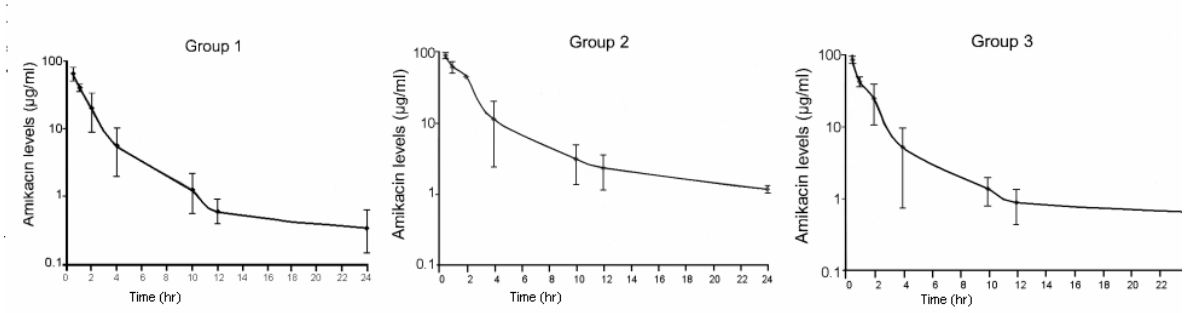

Figure 1 - Pharmacokinetic profiles of amikacin affected by mannitol in Wistar rats. G1: Mannitol previous to amikacin, G2: Mannitol plus amikacin, G3**:** Amikacin, single dose.

It should be noted that all the pharmacokinetic profiles showed an open two-compartment model, fitted to the data, i.e. α and β, which were the rate constants, represented fast and slow phases of drug loss from the plasma. The half-life values for each treatment show statistically significant differences. The distribution volume values were affected by each treatment, which also modified the amikacin clearance values significantly.

DISCUSSION

The establishment of accepted parameters of care for patients with severe head trauma has led to medical treatment guidelines that include fundamental aspects in the management of physiological changes. The generally used therapies include agents such as barbiturates (Eisenberg et al. 1988), corticosteroids (French and Galicich 1964), mannitol (Kirkpatrick et al. 1996), hypertonic saline solutions (Freshman 1993), hyperventilation (Muizelaar et al.1984), anticonvulsant drugs (McNamara 1996) and nutrition (BTFNS 1996). According to the BTNFS Patient Management Guide (BTFNS 1996), certain patients are initially treated with mannitol before starting prophylactic treatment with the selected antibiotic. Aminoglycosides, such as amikacin administered as monotherapy, are used either to treat diagnosed infections, or prophylactically, even if no infectious problem has been precisely defined. However, amikacin is a potentially nephrotoxic and ototoxic drug. It has a narrow therapeutic range and, therefore, amikacin blood levels should be monitored.

Amikacin has potentially damaging properties which may increase by treatment with an additional compound, such as a diuretic or a volume expander (Visweswaran et al. 1997). In the present study, this possibility was analyzed, and found that some pharmacokinetic parameters such as the AUC differed in the three groups with different treatment. Group 2, to which amikacin was administered simultaneously with mannitol, showed the largest AUC; the smallest AUC was found in the group that received a single dose of amikacin. A pharmacokinetic analysis of all traced pharmacokinetic profiles with the Winnonline program showed that the data always adjusted to an open two-compartment model. In the literature, this has been concluded to be due to extensive distribution towards deep tissues. In the present study, the absorption process occurred rapidly since, in all cases, maximum concentrations were reached after the first recorded time, 15 minutes. Thus, if the absorption process was about to be determined, it would be necessary to reduce the

sampling periods. In spite of this inconvenience, only small differences were observed regarding drug availability by either the intraperitoneal or intravenous route of administration, as described by other authors (Flessner and Dedrick 1994, Kalmus et al. 1989). The half-life elimination values, as well as the distribution volume and clearance value showed significant differences between the treatments. Results of the pharmacokinetic parameters obtained in Group 3 were similar to those reported in the literature when the drug was administered alone. However, in the results for Groups 1 and 2, pharmacokinetic parameters such as half-life elimination and distribution volume were prolonged by the effect of mannitol. The employed statistical analysis discerned the differences between the three groups clearly; however, the AUC results tended to be similar between the groups that received a single dose of amikacin and (groups 1 and 3). In general terms, aminoglycoside dose regimes must be based on creatinine clearance, and therefore the variables that modify clearance may directly affect therapeutic management. Based on these results, constant assessment of renal function is necessary because of its possible relation to intracranial damage (Brandis 1975), and amikacin must be monitored, especially if combined with mannitol, since its presence may alter some pharmacokinetic parameters and the expected pharmacological parameters of both.

We concluded that alteration of the pharmacokinetic parameters observed between the groups must be considered when both mannitol plus amikacin are prescribed simultaneously, although human studies are necessary to confirm these findings.

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RESUMO

O estudo analisa o efeito do manitol na farmacocinética (PK) da amicacina . Ratos adultos Wistar foram tratadas da seguinte maneira: o grupo 1 (G1) recebeu manitol durante três días. Ao grupo 2 (G2) se administrou manitol e 10 mg/kg de amicacina, ao mesmo tempo. Finalmente, o grupo 3 (G3) recebeu somente amicacina. No quarto día se realizou o estudo de PK nos três grupos. Para isso, foram retiradas amostras de sangue, em tempos pre-determinados, durante 24 horas, que foram analisadas por métodos imuno-enzimáticos. Os resultados mostraram diferencas significativas ($p < 0.05$) entre os grupos. Po exemplo, os valores obtidos de Cmax foram 62.26 ± 15.75 μg/ml para G1, 72.63 ± 24.80 μg/ml para G2 e 68.61 ± 27.40 μg/ml para o Grupo 3. A AUC foi também diferente entre os três grupos: a maior para G2, com, 222.52 ± 47.30 μg/ml/h, e a menor para G1, com um valor de 135.59 ± 39.00 μg/ml/h. A alteração dos parámetros de PK entre os grupos debe ser considerada quando se administram os dois farmacos simultaneamente. No entanto, é necessario realizar estudos em seres humanos para confirmar os nossos resultados.

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