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Changes in gentamicin pharmacokinetic profiles induced by mechanical ventilation*

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Summary. The influence of controlled mechanical ventilation (CMV) on the pharmacokinetic profile of gentamicin has been examined in 23 patients after elective open heart surgery. A parallel design was adopted in two groups of patients: 13 patients requiring CMV for at least 32 h after surgery, all of whom were able to breath spontaneously (SB) after 72 h (study group), and 10 patients who required CMV for only a brief period and who showed SB at 32 h postsurgery. Haemodynamic parameters remained stable throughout the study. Apparent volume of distribution (V_z), half-life ($t_{1/2}$), total clearance (CL), peak ($C_{max^{ss}}$) and trough ($C_{min^{ss}}$) plasma levels at steady-state for target levels (6–8 μg/ml), were measured.

In the study group significant differences between CMV and SB conditions were found in V_z (mean 0.36 and 0.25 l/kg), $t_{1/2}$ (mean 3.63 and 2.90 h) and $C_{max^{ss}}$ (mean 4.30 and 5.53 μg/ml) while $C_{min^{ss}}$ (mean 1.06 $\mu g \cdot ml^{-1}$ and 0.92 $\mu g \cdot ml^{-1}$) did not change significantly. In contrast, the pharmacokinetics in the control group showed no differences.

It appears that CMV leads to an increase in gentamicin V_z, which accounts for the fall in $C_{max^{ss}}$ below the therapeutic dose range (< 5 μg/ml) recommended for gentamicin. It seems advisable to use a larger dose of gentamicin in patients receiving CMV, even before the level is assessed.

Key words: Gentamicin; pharmacokinetics, mechanical ventilation, therapeutic dose range

Aminoglycoside antibiotics are an important group in the treatment of serious Gram-negative infections. The range between a toxic and a therapeutic level is very narrow, so it is recommended that peak and trough drug concentrations should be carefully monitored to ensure that a therapeutic range is achieved and to avoid drug accumulation, which may provoke impaired renal function [1, 2]. Moore et al. [3] recently demonstrated a strong correlation between high serum peak concentrations related to the minimal inhibitory concentration for the infecting organism and the clinical response to aminoglycoside therapy, or survival in gram-negative bacteraemia. Others [4] have suggested that breakthrough bacteraemia, the recurrence or regrowth of the infecting organism in blood cultures is most often associated with subinhibitory peak concentrations of gentamicin.

Controlled mechanical ventilation (CMV) increases airway and intrathoracic pressures, decreases cardiac filling pressure and cardiac output, inducing a decrease in central blood volume and a fall in right heart transmural pressure [5–7]. CMV has also been shown to diminish renal blood flow, glomerular filtration rate, tubular sodium excretion and urinary output [8]. These phenomena appear to be more prominent in previously hypovolaemic patients, or when PEEP is added to low compliance lungs and patients are ventilated with a high tidal volume [7].

In addition, CMV increases the plasma vasopressin response to baroreceptor stimulation and the renin-angiotensin system becomes activated [8]. Altered intrarenal blood flow distribution, decline in renal blood flow, increase in renal venous pressure promoting tubular sodium reabsorption, and the stimulated secretion of antidiuretic hormone, are other mechanisms probably involved in fluid retention related to CMV [8]. Recently, the alpha-atrial natriuretic peptide (ANP) has been shown to play an important role in sodium and water homeostasis, stimulating natriuresis and diuresis by an increase in the glomerular filtration rate [9]. Atrial compression caused by high intrathoracic pressure induced by CMV, positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP), may all diminish ANP excretion [10, 11].

All these body fluid changes could influence the distribution and elimination of water-soluble drugs, and they are important factors affecting the classical pharmacokinetic disposition parameters. Whether the use of CMV should lead to modification of dosage recommended to obtain plasma drug levels within the therapeutic range re-

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mains to be elucidated. Although the metabolism of hepatically cleared drugs has previously been studied in mechanically ventilated patients [12], the effect of CMV on the pharmacokinetics of renally excreted drugs has not been well established.

The aim of the present study was to evaluate the two following issues: 1) to determine whether CMV altered the pharmacokinetic profile of an aminoglycoside, and 2) if a change were observed to propose the dosage adjustment necessary to ensure plasma therapeutic levels.

Materials and methods

Patient population

One hundred patients more than 18 years old, admitted over a 6 month period to the General Intensive Care Unit in the postoperative period after elective open heart surgery, were considered as candidates for the study. All patients received prophylactic Cefazolin and gentamicin for 4 days.

After applying exclusion criteria (haemodynamic instability, use of diuretics, vasopressor and vasodilator agents, changes in gentamicin dosage and inter-dose intervals, cumulative fluid changes >5% body weight, changes in creatinine clearance above 25 ml·min^{-1}, haemoglobin levels below 8 g·dl^{-1} and acid base disturbances) patients were grouped according to their requirement for ventilatory support 32 h after surgery. The study group was composed of patients who were still being mechanically ventilated at that time. All those patients began to breath spontaneously over the following 48 h. The control group consisted of patients who breathed spontaneously within the first 12 h after surgery. In order to avoid differences between patients CMV was maintained for a longer period in the study group, without giving any sedative drugs.

According to these criteria 23 patients were included in the study after informed consent had been obtained from each patient or his legal guardian. Two groups were formed:

a) *Study group* of 13 patients (6 f and 7 m) with a mean age of 55.4 (10.9) y (range 40–72 y), and a mean body weight of 66.9 (6.5) kg (range 57–76.5 kg). Seven patients underwent by-pass coronary surgery, and 6 had had a valve replacement procedure.

b) *Control group* of 10 patients (4 f and 6 m) with a mean age of 58.9 (12.3) y (range 32–76 y), and a mean body weight of 63.05 (10.1) kg (range 46.5–80). Seven patients were submitted to by-pass coronary surgery and 3 to a valve replacement.

Treatment

CMV was performed with a Servo ventilator 900 C (Siemens ELEMA, Sweden), with a positive end-expiratory pressure of 3 cm H_2O, and inspiratory O_2 concentration of 30–40%. A minute volume of 10–12 ml·kg^{-1} was maintained during CMV at a rate of 16 to 18 breaths·min^{-1}. During spontaneous breathing (SB) an oxygen mask was used by all patients.

The adequacy of ventilation in CMV and SB patients was ascertained by arterial blood gas measurements.

All patients were closely and continuously monitored by the nursing staff and one of the investigators during the study period. Throughout the study, in each 8-h period, plasma and urinary electrolytes, blood and urinary urea, and urinary and plasma creatinine concentrations were measured by standard laboratory techniques. Creatinine clearance, free water and osmolar clearance were calculated.

Study stages

The decline in gentamicin plasma levels was studied in both groups. After 32 h during the postoperative period, the study group was still on CMV. Control group patients were extubated at least 20 h before the onset of the protocol. The pharmacokinetic profile of gentamicin was again studied after 72 h during the postoperative period. All patients showed SB, and for the study group, this was achieved at least 24 h before the second phase of the study.

The steady state condition for plasma gentamicin levels was considered to have been achieved by 32 h during the postoperative period.

The study protocol was approved by the Ethical Committee of the hospital.

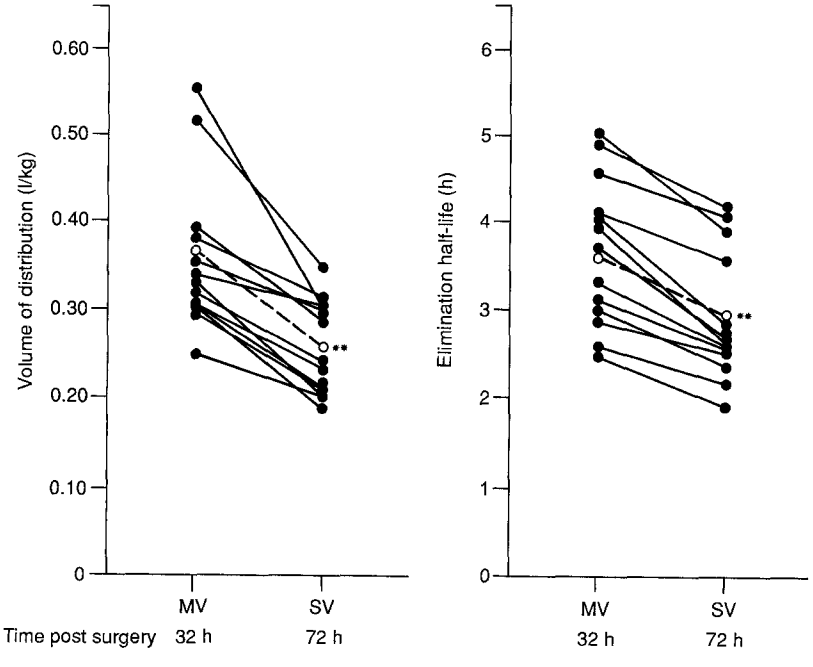

Fig. 1. Changes in volume of distribution and half-life in Study Group patients

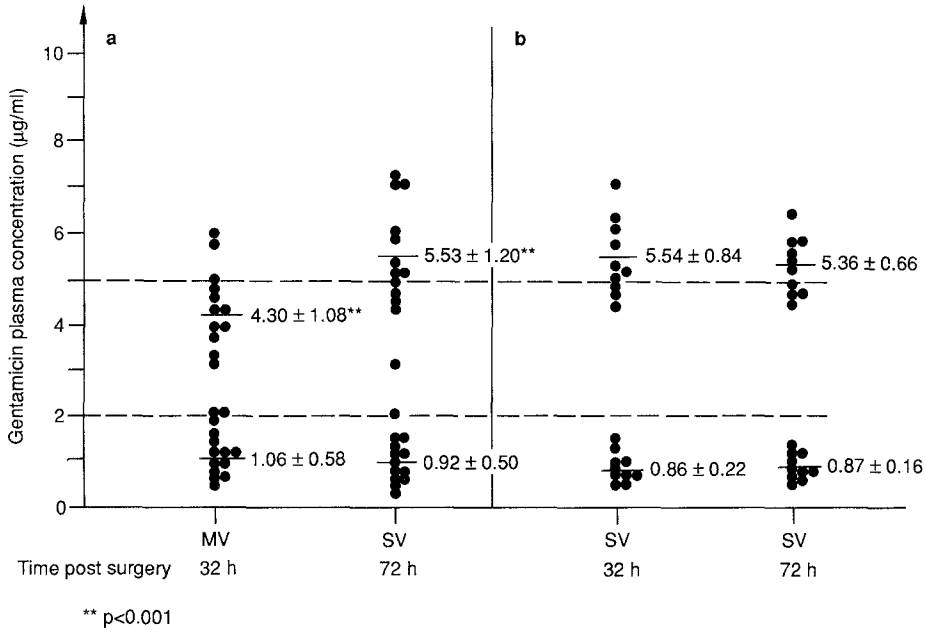

Fig. 2a, b. Distribution of peak-trough plasma levels of gentamicin in both groups of patients **a** Study group ($n = 13$); **b** Control group ($n = 10$)

Table I. Gasometric and fluid balance (mean with (SD)) parameters

Condition/Parameter	Study group ($n = 13$)		Control group ($n = 10$)	
	CMV (32 h)	SB (72 h)	SB (32 h)	SB (72 h)
pH	7.44 (0.03)	7.43 (0.03)	7.44 (0.04)	7.44 (0.04)
PaO_2 (mm Hg)	112.7 (22.1)	96.1 (18.8)	87.1 (5.6)	88.9 (9.6)
$PaCO_2$ (mm Hg)	33.7 (5.6)	38.2 (3.2)	35.4 (5.6)	38.2 (2.8)
FIO_2 (%)	31.7 (5.9)	25.7 (1.97)	37.5 (4.2)	25.1 (1.4)
Tidal Volume (ml/kg)	10.2 (2.55)	–	–	–
Urinary output (ml/min)	1.10 (0.11)	1.35 (0.05) *	1.32 (0.02)	1.33 (0.01)
CL H_2O (ml/min)	−1.12 (0.2)	−1.67 (0.04) *	−1.50 (0.29)	−1.56 (0.37)
CL_{osm} (ml/min)	2.10 (0.15)	2.63 (0.30) *	2.55 (0.21)	2.49 (0.18)
CL_{CR} (ml/min)	60.8 (18.9)	60.5 (16.5)	71.4 (12.1)	71.7 (13.4)

Significance * $P < 0.05$

Procedures

Doses of gentamicin were diluted in 50 ml 5% dextrose solution and were administered intravenously (3.5 mg · kg^{-1} per day) over 30 min, by a metered-chamber delivery system using gravity flow. The i.v. tubing was flushed with 15 ml 5% dextrose solution after the drug solution had been empted from the chamber. Any variation in this procedure was recorded. Cefazolin was administered at a different time, so as to avoid any interaction with gentamicin.

Blood samples were taken in steady state conditions in the 32 and 72 h phases. Blood samples were obtained immediately before the next scheduled dose (trough level), 30 min after the end of the infusion (peak level), and 2, 4, 6 and 8 h in the postinfusion period.

All samples were immediately centrifuged and frozen until analyzed to minimize interday analytical variability. Plasma concentrations were measured in duplicate by fluorescence immunoassay (TDX, Abbott Diagnostics, Irwing, Tx). The between and withinrun coefficients of variation were below 10% for values ranging from 0.5 to 16 µg · ml^{-1}.

Calculations

Pharmacokinetic disposition parameters, apparent volume of distribution (V_z), elimination half-life ($t_{1/2}$), total body clearance (CL), were calculated by the Sawchuk and Zaske method [13], which assumes a one-compartment model for gentamicin and accounts for drug disposition during the infusion period. V_z data were obtained according to the following equations:

$$V_z\,(l) = k_o\,(1\text{-}e^{-ke\,t'})/k_e\,(C_{max}^{ss}\text{–}C_{min}^{ss\ -ke\,t'})$$

k_e (h^{-1}): elimination constant rate calculated by least-squares linear regression analysis of the slope of the log serum concentration-time curve.

(C_{min}^{ss} (µg/ml): Trough gentamicin level measured just before infusion of the dose at steady-state.

(C_{max}^{ss} (µg/ml): Peak gentamicin level measured at the end of the infusion dose in steady-state conditions.

C_{max}^{ss} d: desired peak gentamicin level around 6 to 8 µg · ml^{-1}

k_o (h): Infusion rate
t' (h): Duration of the infusion
T (h): Dosing interval

Statistical analysis

The analysis was one way repeated measures with five variables (C_{min}^{ss}, C_{max}^{ss}, V_z, $t_{1/2}$, CL) MANOVA, using Hotelling/T^2 test for evaluating multivariate differences in order to avoid Type I errors with inflated degrees of freedom.

Correlations between the different pharmacokinetic variables were also assessed by means of Pearson's r.

Paired Student's t-test was used to compare renal function values in each group of patients.

In all cases $P < 0.05$ was considered significant. The data were evaluated using the Standard Statistical Package for Social Sciences (SPSS-PC$^+$) program.

Results

The results of arterial blood gas analysis and the fluid balance measurements are summarized in Table I. In the study group, the fluid balance was positive during CMV and negative when patients breathed spontaneously, due to reduced urine output and negative free water clearance during CMV. Osmolar clearance changed in the opposite direction, ($P < 0.05$). The creatinine clearance remained within normal values throughout the study period. In the control group, renal function and gasometric parameters were similar in both study phases (Table I).

The Pharmacokinetic data from the Study Group are shown in Table 2. The V_z (mean with (SD) was significantly larger ($P < 0.001$) in CMV (0.36 (1.20) $l \cdot kg^{-1}$) than during SB (0.25 (0.05) $l \cdot kg^{-1}$). The differences in $t_{1/2}$ between CMV (3.63 (0.90) h) and SB (2.90 (0.80) h) was significant ($P < 0.001$). CL in CMV (0.075 (0.034) $l \cdot kg^{-1} \cdot h^{-1}$) was not different from in SB (0.063 (0.020) $l \cdot kg^{-1} \cdot h^{-1}$).

After gentamicin infusion, the C_{max}^{ss} values obtained were significantly lower ($P < 0.0001$) in CMV (4.30 (1.08) $\mu g \cdot ml^{-1}$) than during SB (5.53 (1.20) $\mu g \cdot ml^{-1}$). No difference in C_{min}^{ss} was found between CMV (1.06 (0.58) $\mu g \cdot ml^{-1}$) and SB (0.92 (0.50) $\mu g \cdot ml^{-1}$).

There was a significant correlation between V_z and C_{max}^{ss} ($r = 0.767$; $P < 0.001$).

None of the pharmacokinetic parameters in the control group (Table III) showed any differences between the two phases of the study.

Discussion

The present data strongly suggest that CMV alters the pharmacokinetic disposition of gentamicin, producing a significant increase in its V_z. This probably accounts for the lower than desired peak serum concentrations. Therefore, there is the need to adjust gentamicin dosage under those conditions.

Aminoglycoside antibiotics are primarily distributed to a pharmacological space very similar to the physiological space of the extracellular fluid compartment, since binding to serum proteins is low and is not considered clinically important. They are eliminated unchanged by glomerular filtration.

The efficacy of aminoglycosides is well correlated with the peak serum concentration obtained shortly after institution of therapy [14]. These antibiotics have a low therapeutic index, and the concentrations necessary for optimal efficacy are close to those associated with a risk of toxicity [14]. Due to the large inter- and intrapatient differences in pharmacokinetic parameters, the serum concentration produced by the recommended dosage regimens varies substantially. It has been demonstrated that initial aminoglycoside serum levels are too low in at least 40% of patients treated according to the manufacturer's dosage recommendations [15–17]. Measuring serum concentrations and adjusting the dosage regimen in individual patients are often necessary to achieve the desired (therapeutic) serum concentration.

Table II. Pharmacokinetics of gentamicin in study group patients

Parameter	V_z (l/kg)		$t_{1/2}$ (h)		CL ($l \cdot kg^{-1} \cdot h^{-1}$)		C_{max}^{ss} ($\mu g \cdot ml^{-1}$)		C_{min}^{ss} ($\mu g/ml$)	
Patient/condition	CMV	SB	CMV	SB	CMV	SB	CMV	SB	CMV	SB
1	0.39	0.28	4.61	4.15	0.058	0.048	4.04	4.94	1.31	1.41
2	0.55	0.30	2.51	1.92	0.153	0.109	3.16	5.02	0.40	0.33
3	0.31	0.23	4.94	4.26	0.044	0.037	6.07	7.33	2.12	2.16
4	0.32	0.23	4.11	2.89	0.054	0.056	4.39	5.31	1.24	0.88
5	0.34	0.30	5.01	3.91	0.047	0.053	5.85	5.21	2.07	1.38
6	0.31	0.18	3.13	2.36	0.070	0.053	4.65	7.24	0.88	0.80
7	0.39	0.31	3.72	2.70	0.073	0.079	3.92	4.45	0.97	0.65
8	0.52	0.34	2.81	2.56	0.013	0.092	2.17	3.28	0.34	0.43
9	0.30	0.21	2.50	2.39	0.083	0.060	4.40	6.15	0.55	0.70
10	0.25	0.19	3.96	2.70	0.043	0.048	5.22	6.02	1.40	0.88
11	0.31	0.19	3.34	2.53	0.064	0.053	4.83	7.17	1.01	0.92
12	0.35	0.30	4.05	3.58	0.059	0.058	4.02	4.65	1.11	1.09
13	0.37	0.20	2.50	1.87	0.010	0.074	3.21	5.21	0.40	0.39
mean	0,36	0,25	3,63	2,90	0,059	0,063	4,30	5,53	1,06	0,92
(SD)	(0,08)	(0,05)	(0,90)	(0,80)	(0,035)	(0,020	(1,08)	(1,20)	(0,58)	(0,50)
Significance	**		**		NS		**		NS	

** $P < 0.001$

Table 3. Pharmacokinetics of gentamicin in control patients

Parameter	V_z (l/kg)		$t_{1/2}$ (h)		CL ($l \cdot kg^{-1} \cdot h^{-1}$)		C_{max}^{ss} ($\mu g \cdot ml^{-1}$)		C_{min}^{ss} ($\mu g/ml$)	
Patient/condition	32 h	72 h	32 h	72 h	32 h	72 h	32 h	72 h	32 h	72 h
1	0.24	0.26	2.58	2.95	0.064	0.062	4.86	4.70	0.65	0.80
2	0.19	0.21	2.35	2.52	0.055	0.058	7.12	6.53	0.78	0.83
3	0.24	0.25	2.87	2.72	0.059	0.061	5.84	5.76	0.95	0.85
4	0.15	0.19	2.34	2.55	0.046	0.051	6.47	5.59	0.70	0.73
5	0.32	0.26	4.46	3.96	0.050	0.046	4.44	4.81	1.38	1.29
6	0.28	0.29	3.11	3.08	0.062	0.066	5.54	5.26	1.04	0.97
7	0.28	0.32	2.97	3.22	0.066	0.070	4.91	4.45	0.85	0.88
8	0.21	0.22	2.22	2.47	0.065	0.062	6.16	6.00	0.59	0.73
9	0.26	0.27	3.00	2.86	0.061	0.065	4.93	4.82	0.87	0.79
10	0.22	0.21	2.78	2.78	0.055	0.052	5.21	5.66	0.80	0.87
mean	0.24	0.25	2.86	2.91	0.058	0.059	5.54	5.36	0.86	0.87
(SD)	(0.05)	(0.04)	(0.64)	(0.44)	(0.007)	(0.008)	(0.84)	(0.66)	(0.22)	(0.16)
Significance	NS		NS		NS		NS		NS	

Aminoglycoside pharmacokinetics have been studied in many disease states and patient groups [18–22]. Interpatient differences have previously been documented, but intrapatient variations have only recently been described [17], and their causes, are not certain, although several hypotheses have been proposed. In stable patients, 80 to 90% of the variance in aminoglycoside elimination can be accounted for by changes in renal function [23]. In patients with sepsis renal function is unable completely to explain the observed variability in aminoglycoside pharmacokinetics [16]. A substantial error may occur in predicting drug clearance or elimination rate from estimates of glomerular filtration rate, even though renal function is the most important variable.

Many factors that are commonly present in critically ill patients affect aminoglycoside pharmacokinetics [15, 16]. The V_z of these drugs has been reported to be between 0.20 to 0.25 $l \cdot kg^{-1}$ in stable patients, although an increase in V_z can be seen in many situations, e. g. in the early stages after extensive burns, surgical patients in the postoperative period, peritonitis, congestive heart failure and ascites [16, 19, 24].

In the present trial 23 patients during the postoperative period after elective open heart surgery were studied to evaluate possible changes on gentamicin pharmacokinetic parameters related to CMV. The patients were enrolled in two different groups, depending on whether they were still undergoing CMV at the onset of the study. Three days later, when all patients were breathing spontaneously, the pharmacokinetic evaluations were repeated.

During CMV the mean V_z was 0.36 $l \cdot kg^{-1}$, similar to results in other critically ill surgical patients, while, during SB, the mean V_z was 0.25 $l \cdot kg^{-1}$, similar to widely reported data for stable patients [24, 25–27].

The increased V_z in patients undergoing CMV cannot be related just to the perioperative period, because the control group did not show any difference in the V_z of gentamicin in the two phases of the study. The aminoglycoside V_z here was not correlated with fluid administration, since patients had already received a large quantity of fluids during surgery, and the volume of fluid administered in the ICU was similar in each groups.

The V_z of water-soluble drugs is a physiological marker of the extracellular fluid compartment, and so is an indirect measure of the state of hydration. During CMV, the decrease in urine volume and negative free water clearance have been related to increased ADH release, inducing water retention and hyponatraemia [8].

Recently, decreased release of α-ANP as a consequence of atrial compression by the distended lungs and of reduced venous return has been described in CMV patients [9, 10]. Those authors suggested that the decline in plasma α-ANP levels contributes to the fluid retention and renal dysfunction that frequently occurs in CMV. Moreover, α-ANP influences salt and water homoeostasis by inhibition of aldosterone secretion, suppression of antidiuretic hormone release, and inhibition of the aldosterone II-induced drinking response. However, the role of all these factors in promoting an "overhydrated state", which could increase the V_z of water soluble drugs, such as gentamicin, is unknown.

Thus, the cause of the larger V_z seen in patients submitted to CMV remains controversial, but it is clear that standard, empirical aminoglycoside dosage recommendations, using an estimated V_z of 0.20 to 0.30 $l \cdot kg^{-1}$, tended to produce under-dosing in mechanically ventilated patients.

Due to low peak gentamicin plasma levels achieved during CMV, the theoretical dose needed to reach the target levels was higher in CMV than in SB. During SB, the dose required by the study patients was equivalent to that in the control group.

SB patients showed Vd, CL, $t_{1/2}$ peak and trough plasma concentrations within the expected values, and no significant differences were found in the control group.

The intrapatient pharmacokinetic variability described here might partly be due to variation in drug delivery, flushing of the intravenous line, the assay method, sampling strategies and the inability of the one-compartment model to account for two-compartment accumulation. Because of these possible errors, the variation may represent apparent rather than real changes in the intrapatient pharmacokinetic variables. To quantify the true intrapatient pharmacokinetic variation, and in order to avoid the standard limitations of the Sawchuk and Zaske

method, an analysis was made of five serum samples obtained during the drug elimination phase under strict adherence to the protocol in terms of data collection and handling, time of drug administration and length of dosage infusion.

In conclusion, the pharmacokinetics of gentamicin was substantially affected by CMV, leading to inadequate peak plasma levels when a conventional schedules was used. As the drug was administered prophylactically, the clinical impact of the findings is not known. Further studies are required to assess the underlying mechanism and the clinical response in critically ill patients of the CMV-induced amino changes in the pharmacokinetics of aminoglycoside antibiotics.

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References

1. Dasta JF (1986) Drug use in a surgical intensive care unit. Drug Intell Clin Pharm 20: 752–756
2. Zaske DE (1986) Aminoglycosides. In: Evans WE, Schentag JJ, Jusko WJ (eds) Applied pharmacokinetics. Spokane, Applied Therapeutics, INC, 331–381
3. Moore RD, Lietman PS, Smith CR (1987) Clinical response to aminoglycosides therapy: Importance of the ratio of peak concentration to minimal inhibitory concentration. J Infect Dis 155: 93–99
4. Anderson ET, Young LS, Hewitt WL (1976) Simultaneous antibiotic levels in "breakthrough" gram-negative rod bacteremia. Am J Med 61: 493–497
5. Braunwald E, Binion JT, Morgan WL, Sarnoff SJ (1957) Alterations in central blood volume and cardiac output induced by positive pressure breathing and counteracted by metaraminol (Aramine). Circ Res 5: 670–675
6. Morgan BC, Crawford EW, Guntheroth WG (1969) The hemodynamic effects of changes in blood volume during intermittent positive pressure ventilation. Anesthesiology 30: 297–305
7. Suter PM (1983) Intermittent and continuous positive pressure ventilation. In: Tinker J, Rapin M (eds) Care of critically ill patients. Springer, Berlin, pp 371–387
8. Berry AJ (1981) Respiratory support and renal function. Anesthesiology 55: 655–667
9. Burnett JC, Granger JP, Opgenorth TJ (1984) Effects of synthetic atrial natriuretic factor on renal and renin release. Am J Physiol 247: 863–868
10. Leithner C, Frass M, Pacher R, Hartter E, Pesl H, Woloszczuk W (1987) Mechanical ventilation with positive end-expiratory pressure decreases release of alpha-atrial natriuretic peptide. Crit Care Med 15: 484–488
11. Frass M, Popovic R, Hartter E, Avinger C, Woloszczuk W, Leither C (1988) Atrial natriuretic peptide decrease during spontaneous breathing with continuous positive airway pressure in volume-expanded healthy volunteers. Crit Care Med 16: 831–835
12. Richard C, Berdeaux A, Delian F, Rion B, Rimailho A, Giudicelli JF, Auzépy P (1986) Effect of mechanical ventilation on hepatic drug pharmacokinetics. Chest 90: 837–841
13. Sawchuk RJ, Zaske DE (1976) Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: Gentamicin in burn patients. J Pharmacokin Biopharm 4: 183–195
14. Moore RD, Smith CR, Lietman PS (1984) The association of aminoglycoside plasma levels with mortality in patient with gram-negative bacteremia. J Infect Dis 149: 443–448
15. Zaske DE, Cipolle RJ, Rotschafter JC et al. (1982) Gentamicin pharmacokinetics in 1640 patients: Method for control of serum concentrations. Antimicrob Agents Chemother 21: 407–411
16. Zaske DE, Ciopolle RJ, Strate RJ (1980) Gentamicin dosage requirements: wide interpatient variations in 242 surgery patients with normal renal function. Surgery 87: 64–69
17. Mann HJ, Fuhs DW, Awang R et al. (1987) Altered aminoglycoside pharmacokinetics in critically ill patients with sepsis. Clin Pharm 6: 154–159
18. Bosso JA, Relling MV, Townsed PL et al. (1987) Intrapatient variation in aminoglycoside disposition in cystic fibrosis. Clin Pharm 6: 54–58
19. Niemiec PW, Allo MD, Miller CF (1987) Effect of altered volume of distribution on aminoglycoside levels in patients in surgical intensive care. Arch Surg 122: 207–212
20. Kloth DD, Tegtmeier BR, Kong C et al. (1985) Altered gentamicin pharmacokinetics during the perioperative period. Clin Pharm 4: 182–185
21. Carr MR, Dick SP, Bordley J, Bertino IS (1988) Gentamicin dosing requirements in patients with acute pancreatitis. Surgery 103: 533–537
22. Fuhs DW, Mann HJ, Kubayak CA, Cerra FB (1988) Intrapatient variation of aminoglycoside pharmacokinetics in critically ill surgery patients. Clin Pharm 7: 207–213
23. Kaye D, Levisan ME, Labovitz ED (1974) The unpredictability of serum concentrations of gentamicin: Pharmacokinetics of gentamicin in patients withnormal and abnormal renal function. J Infect Dis 130: 150–154
24. Pancoast SJ (1988) Aminoglycoside antibiotics in clinical use. Med Clin North Am 72: 567–580
25. Pechere JC, Dugal R (1979) Clinical pharmacokinetics of aminoglycoside antibiotics. Clin Pharmacokinet 4: 170–179
26. Triginer C, Izquierdo I, Fernández R, Rello J, Torrent J, Benito S (1990) Gentamicin volume of distribution in critically ill patients. Intensive Care Med 16: 303–306
27. Rodvold KA, Pryka RD, Kuehl PG, Blum RA, Donahue P (1990) Bayesian forecasting of serum gentamicin concentrations in intensive care patients. Clin Pharmacokinet 18: 409–418

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