J. Pharm. Pharmacol. 1998, 50: 1255–1260
Received April 3, 1998
Accepted July 9, 1998

The Kinetic Profile of Vancomycin in Neonates

R. SILVA, E. REIS*, M. A. BISPO*, A. M. ALMEIDA†, I. M. COSTA†, F. FALCÃO, J. M. PALMINHA* AND A. C. FALCÃO†

*Pharmacy Department and *Neonatal Intensive-care unit, São Francisco Xavier Hospital, Estrada do Forte do Alto do Duque, 1495-Lisboa and †Faculty of Pharmacy–University of Coimbra, Largo de D. Diniz, 3000-Coimbra, Portugal*

Abstract

The pharmacokinetic parameters of vancomycin in a neonatal population have been characterized to enable development of optimum dosage guidelines for neonatal intensive-care units and to examine the relationship between these pharmacokinetic parameters and various demographic, developmental and clinical factors which might be associated with changes in the kinetic profile of vancomycin.

Forty-four infants (twenty-five males and nineteen females) with suspected or proven Gram-positive infection and who received intravenous vancomycin between October 1993 and December 1996 were included in this retrospective analysis. Gestational age ranged from 25 to 40 weeks and postconceptional age at the time of the study ranged from 28 to 45 weeks. Sixty case-studies were obtained from the forty-four patients, with one period of study corresponding to one week or one cycle of therapy. Vancomycin pharmacokinetic parameters were determined by use of a one-compartment model. By regression analysis the current weight (g) was shown to be the stronger covariate, and both vancomycin clearance (L h^{-1}) and volume of distribution (L) had to be normalized. The vancomycin volume of distribution depended on the postconceptional age with a cut-off at 32 weeks, whereas vancomycin clearance depended on the presence or absence of concomitant treatment with indomethacin or of mechanical ventilation, or both.

On the basis of the pharmacokinetic parameters obtained we suggest initial dosage guidelines for vancomycin ranging from 10 mg kg^{-1} every 8 h to 10 mg kg^{-1} every 12 h, depending on the demographic and clinical characteristics of the patients. The results obtained enabled application of better *a priori* and *a posteriori* dosage schedules to infants in neonatal intensive-care units by use of the Bayesian approach, although further prospective study is recommended before direct extrapolation to patients in other settings.

Vancomycin is a glycopeptide antibiotic with activity against many Gram-positive pathogens. The use of vancomycin in neonatal intensive-care units has increased markedly over the past decade because of the increasing incidence of staphylococci infection, particularly the coagulase-negative type (Asbury et al 1993). Further potential reasons for this widespread use of vancomycin include the longer survival of preterm and term neonates, expanded intensive-care periods and increased use of intravenous catheters (Rodvold et al 1995).

Although pharmacokinetic parameters have been reported for vancomycin in neonates, the studies have often included small heterogeneous study groups with different demographic and clinical conditions, including serum sampling times and the pharmacokinetic model adopted (Rodvold et al 1997).

Despite the increasing use of vancomycin, stipulation of dosage schedules for the new-born is still based on information regarded as controversial and paediatric patients of all ages are at significant risk of underdosing if vancomycin concentration is not monitored (Miles et al 1997). The purpose of our work was to determine the kinetic profile of vancomycin in a group of neonates for which concentrations were monitored as part of their routine clinical care. The influence of several demographic, developmental and clinical factors on drug disposition was investigated to develop vancomycin dosage guidelines for patients in neonatal intensive-care units.

Correspondence: A. Falcão, Laboratory of Pharmacology, Faculty of Pharmacy, University of Coimbra, 3000 Coimbra, Portugal.

Materials and Methods

Patients

A completely retrospective study was performed on forty-four infants in the neonatal intensive-care unit at the São Francisco Xavier Hospital and receiving intravenous vancomycin for proven or suspected Gram-positive infection between October 1993 and December 1996. Patients were excluded if complete medical records could not be obtained, serum concentration–time data were incomplete or inconsistent with nurse documentation, dose administration times were not documented or postnatal age exceeded 2 months.

Vancomycin was administered intravenously by means of a syringe pump set to deliver each dose at a constant rate over 60 min. Initial doses were in accordance with institutional guidelines practised in our neonatal intensive-care unit. A standard 20 mg kg^{-1} dose was administered and the interval between doses was selected on the basis of the patients' postconceptional ages; 24, 18, 12, 8 and 6-h intervals for postconceptional ages ≤ 29, between 30 and 33, between 34 and 37, between 38 and 44 and ≥ 45 weeks, respectively.

Subsequent dosage regimens, based on the first set of vancomycin concentrations (peak and trough pairs) obtained in general between 24 and 48 h after starting the therapy, were optimized by the pharmacy service by applying pharmacokinetic criteria. Periodic dosage adjustments were performed according to the results obtained from drug monitoring and clinical evaluation. Duration of vancomycin therapy varied from four to 17 days.

Pharmacokinetic analysis

The determination of pharmacokinetic parameters was performed by assuming a one-compartment model with zero-order absorption and first-order elimination. Peak and trough concentrations, respectively, were defined as the concentrations obtained 1 h after the end of the 60-min infusion and 1 h before the next administration, to enable eventual dosage readjustments in time.

All samples were obtained via heel capillary prick, and serum samples were analysed by a fluorescence polarization immunoassay technique (TDx; Abbott Diagnostics). Intra- and interday coefficients of variation were $< 5\%$ in our institution.

Vancomycin pharmacokinetic parameters were determined by fitting the data using a weighted least-squares non-linear regression method (PKS; Abbott Diagnostics).

Covariates

Several covariates were assessed to explain the pharmacokinetic behaviour of vancomycin: birth weight, current weight, gestational age, postnatal age, postconceptional age, creatinine clearance (CL_{cr}), and concomitant treatment with indomethacin or mechanical ventilation, or both. For the purposes of data analysis, by "concomitant treatment with indomethacin" it should be understood that neonates received indomethacin concomitantly with vancomycin within two weeks before our study because, as was pointed out by Asbury et al (1993), the time-course of the interaction between vancomycin and indomethacin in infants with successful and unsuccessful closure of the patent ductus arteriousus must be considered because of its potential interference on the clearance of vancomycin.

To reduce and characterize the intravariability associated with the use of birth weight, current weight, postnatal age, postconceptional age and CL_{cr} as covariates, the periods of study were confined to a week. Patients subjected to longer therapies were considered as different individuals, one individual corresponding to one week or one cycle of therapy. In this way we obtained 60 case studies from the 44 patients. We considered each cycle of therapy as an independent observation.

Statistical analysis

The information available (pharmacokinetic parameters and covariates) was initially studied by linear regression analysis to assess the strength of correlation between the variables. Subsequent analysis involved stepwise multiple regression, enabling the identification of the most important covariates for explaining the pharmacokinetic profile of vancomycin in our population. Other statistical tests, applied when appropriate during the statistical analysis, included the *t*-test, analysis of variance and correlation analysis. A value of $P < 0{\cdot}05$ was regarded as indicative of significance. All population variability values are reported as plus or minus one standard deviation. Statistical assessment was performed by use of the Statistica software package, which is appropriate for this kind of analysis.

Results

Forty-four patients (twenty-five males and nineteen females) were included in the study: birth weight ranged from 766 to 3835 g, current weight ranged from 775 to 3740 g, gestational age ranged from 25 to 40 weeks, postnatal age ranged from 0·39 to 7·43 weeks, postconceptional age ranged from 28 to 45

Table 1. Summary of patient data.

	Number	Mean ± s.d.	Range
Case studies	60	–	–
Male/female	33/27	–	–
Indomethacin/mechanical ventilation (yes/no)	35/25		
Birth weight (g)	–	1926 ± 988	766–3835
Current weight (g)	–	1940 ± 954	700–3800
Gestational age (weeks)	–	32·6 ± 4·8	25–40
Postnatal age (weeks)	–	2·6 ± 1·3	0·14–7·43
Postconceptional age (weeks)	–	35·6 ± 4·6	28–45
Creatinine clearance (mL min^{-1} kg)*	–	2·04 ± 0·8	0·8–4·8

*Estimated by use of the method of Schwartz et al (1976).

weeks and clearance of creatinine ranged from 0·86 to 4·8 mL min^{-1} kg^{-1}. Twenty-six of these patients had received concomitant treatment with indomethacin or mechanical ventilation, or both. Two cycles of therapy were derived from twelve patients, and three cycles of therapy from two patients. Mean weights (birth and current weights), ages (gestational, postnatal and postconceptional) and clearance of creatinine and incidence of concomitant treatment with indomethacin or mechanical ventilation, or both, for the 60 case studies are listed in Table 1.

The best correlations were obtained between current weight (CW, g) and both vancomycin clearance (CL, L h^{-1}) and volume of distribution (Vd; L), indicating that current weight is the best covariate for explaining the kinetic profile of vancomycin in our population (Figures 1 and 2). Equations expressing these relationships are:

$$CL\,(L\,h^{-1}) = 0{\cdot}007 + 6{\cdot}875 \times 10^{-5} \times CW\,(g) \quad (1)$$

$$Vd\,(L) = 0{\cdot}034 + 4{\cdot}991 \times 10^{-4} \times CW\,(g) \quad (2)$$

Significant correlations were also obtained between birth weight (g), gestational age (weeks) and postconceptional age (weeks) for both vancomycin CL (L h^{-1}) and Vd (L). Although no correlation was found between postnatal age (weeks) and vancomycin CL (L h^{-1}), when normalized by the current weight (g) a moderate correlation was found between postnatal age (weeks) and vancomycin CL (L h^{-1} kg^{-1}); this could be a sign of the effect of time-dependency on its kinetic profile. There was no significant correlation between either gestational age (weeks) or postconceptional age (weeks) with vancomycin CL (L h^{-1} kg^{-1}), which suggests that the current weight (g) absorbed some of the variability explained through these covariates and the remaining time-influence was represented by the weak but significant correlation between postnatal age (weeks) and vancomycin CL (L h^{-1} kg^{-1}). The correlation between clearance of creatinine (mL min^{-1} kg^{-1}) and vancomycin CL (L h^{-1} or L h^{-1} kg^{-1}) was weak, despite being statistically significant, indicating that clearance of creatinine (mL min^{-1} kg^{-1}) was not an important covariate in explaining vancomycin clearance in this kind of population. Finally, the only significant, but weak, correlation shown between the selected covariates and vancomycin Vd (L kg^{-1}) was the gestational age (weeks), which suggests

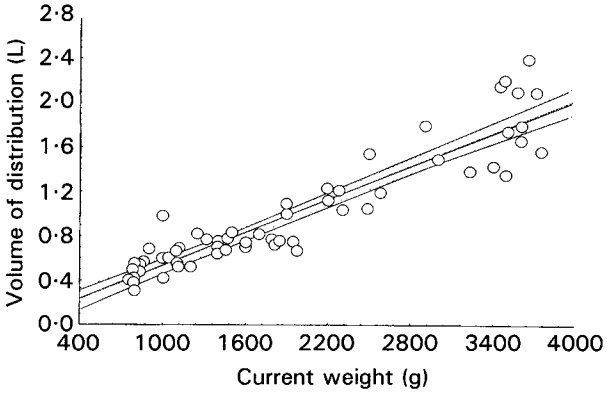

Figure 1. Relationship between current weight and vancomycin volume of distribution, Vd (L) = 0·034 + 4·991 × 10^{-4} × CW (g); r = 0·928, $P < 0{\cdot}05$.

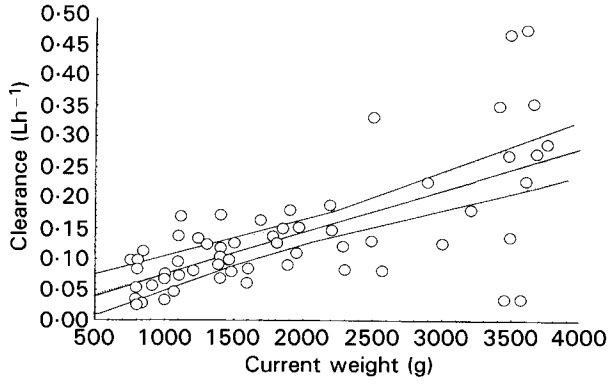

Figure 2. Relationship between current weight and vancomycin clearance, CL (L h^{-1}) = 0·07 + 6·875 × 10^{-4} × CW (g); r = 0·675, $P < 0{\cdot}05$.

Table 2. Significant correlations (r values) between vancomycin pharmacokinetic parameters and several covariates.

	Clearance ($L\ h^{-1}$)	Clearance ($L\ h^{-1}\ kg^{-1}$)	Volume of distribution (L)	Volume of distribution ($L\ kg^{-1}$)
Birth weight (g)	0·58*	N.A.‡	0·71*	N.A.
Current weight (g)	0·68*	N.A.	0·93*	N.A.
Gestational age (weeks)	0·48*	N.S.†	0·58*	0·29*
Postnatal age (weeks)	N.S.	0·46*	N.S.	N.S.
Postconceptional age (weeks)	0·57*	N.S.	0·76*	N.S.
Creatinine clearance ($mL\ min^{-1}\ kg^{-1}$)	0·27*	0·31*	N.S.	N.S.

*$P < 0·05$. †Not statistically significant. ‡Not assessed.

some relationship between Vd ($L\ kg^{-1}$) and the physiological maturation process (Table 2).

These relationships were further explored by stepwise multiple regression analysis. Both vancomycin clearance ($L\ h^{-1}$) and volume of distribution (L) served as dependent variables and the available covariates were used as independent variables. To investigate the possible time-dependency and maturation-dependency of the kinetic profile of vancomycin, we adopted discrete values for postconceptional age (applied as a dichotomous variable), which represent at the same time the possible influence of the gestational period and the postnatal age. Concomitant treatment with indomethacin or mechanical ventilation, or both, were also shown to be a categorical variable. The results obtained (mean and coefficient of variation), confirmed by use of statistical criteria, suggest that vancomycin clearance depends on the presence ($CL = 0·07$ L $h^{-1}\ kg^{-1}$; c.v. = 41%) or absence ($CL = 0·086$ L $h^{-1}\ kg^{-1}$; c.v. = 35%) of concomitant treatment with indomethacin or mechanical ventilation, or both, whereas the volume of distribution is related to postconceptional age with a value of 0·562 L kg^{-1} (c.v. = 15%) for ≤ 32 weeks postconceptional age and 0·498 L kg^{-1} (c.v. = 16%) for > 32 weeks postconceptional age.

Discussion

Although a multicompartmental model might best describe the pharmacokinetic profile of vancomycin, it has been reported that a one-compartment model is adequate for describing the pharmacokinetics of vancomycin in neonates, because the alpha distribution phase in determining clearance did not seem to be important in these patients (Gabriel et al 1991). The use of such a model leads to the assumption or knowledge that all the measured serum concentrations used to calculate pharmacokinetic parameters reflect postdistribution (Fernandez de Gatta et al 1996). Failure to consider this limitation might result in overestimation of the elimination constant, k_e, underestimation of the volume of distribution, Vd, and, perhaps, overestimation of total body clearance (Asbury et al 1993). In the current study, samples for measurement of peak concentration were drawn 1 h after the end of the 60-min infusion to minimize the effect of incomplete drug distribution (McDougal et al 1995).

The relationship between demographic data and vancomycin pharmacokinetic parameters in this study is comparable with those found by other authors (Naqvi et al 1986; Kildoo et al 1990; Asbury et al 1993; Seay et al 1994; McDougal et al 1995; Rodvold et al 1995). The attention of most studies has been focused on the relationships between both vancomycin CL ($L\ h^{-1}$) and Vd (L) and weights (birth and current weights) and ages (gestational, postnatal and postconceptional ages). Such positive correlations were also found in our study, although current weight proved to be the stronger covariate for both CL ($L\ h^{-1}$) and Vd (L). These relationships are inherent and should generally be taken for granted for this patient population (Rodvold et al 1995). When normalized by the current weight (g), we observed that vancomycin Vd ($L\ kg^{-1}$) depends on the postconceptional age (weeks) with a cut-off at 32 weeks, whereas vancomycin CL ($L\ h^{-1}\ kg^{-1}$) seems to be influenced by the presence or absence of concomitant treatment with indomethacin or mechanical ventilation, or both.

Additional variation in distribution volumes would also be expected to occur with increases in postnatal age because major changes in body water compartments occur in babies during the first few weeks to months. (Besunder et al 1988). In the current work the effect of postconceptional age on volume of distribution was incorporated into the model as a dichotomous variable. This was done in response to a clear bimodal distribution in our data with a cut-off at 32 weeks.

The gradual age-dependent increase in clearance of creatinine ($CL\ (L\ h^{-1}\ kg^{-1}) = 0·052 + 0·012 \times CL_{cr}\ (mL\ min^{-1}\ kg^{-1})$; $r = 0·31$, $P < 0·05$) reflects

Table 3. Recommended initial regimens for vancomycin in neonates.

Postconceptional age	Indomethacin or mechanical ventilation or both	
	Yes	No
≤ 32 weeks	10 mg kg^{-1} every 12 h	12·5 mg kg^{-1} every 12 h
> 32 weeks	7·5 mg kg^{-1} every 8 h	10 mg kg^{-1} every 8 h

Doses given intravenously over 60 min irrespective of dose or interval.

the improvement in renal function and is consistent with the improvement in vancomycin elimination. During the first weeks of life clearance of creatinine might not be an ideal indication of renal function, because the infant is born with maternal levels of creatinine, and it takes several days or several weeks for excretion of exogenous creatinine and balance of creatinine production and secretion to be achieved. For this reason the utility of clearance of creatinine as a marker for renal function in neonates remains controversial, depending on the studies considered; some authors found a significant correlation between clearance of creatinine and vancomycin clearance (Kildoo et al 1990; Ginovart et al 1993), whereas several investigations did not prove the strength of that relationship and, in consequence, did not consider clearance of creatinine as the main variable when explaining vancomycin clearance (Naqvi et al 1986; Seay et al 1994).

The function of the ductus arteriosus in the foetus is to supply oxygenated blood via the placenta, thereby bypassing the foetal lungs. Patent ductus arteriosus is a congenital problem not uncommon in premature infants; its incidence is inversely related to birth weight and gestational age. Nowadays treatment of patent ductus arteriosus includes fluid restriction and the use of a prostaglandin synthetase inhibitor such as indomethacin. Non-steroidal, anti-inflammatory drugs that inhibit prostaglandin synthesis might cause acute deterioration of renal function associated with hyperkalaemia. The influence of indomethacin on vancomycin clearance has already been pointed out by other authors (Asbury et al 1993; Ginovart et al 1993).

Reduced renal function as a result of mechanical ventilation would be important for agents, e.g. vancomycin, digoxin, β-lactam antibiotics and the aminoglycosides, whose clearance is predominantly dependent on glomerular filtration rate. Although a change in glomerular filtration rate is generally recognized as a cause of altered drug clearance, more research is needed in this area to provide clinicians with specific guidelines on the use of drugs in patients receiving mechanical ventilation (Perkins et al 1989). An attempt was made by Ginovart et al (1993), who concluded that vancomycin clearance was influenced by concomitant treatment with indomethacin and mechanical ventilation, suggesting close monitoring of renal function and posological individualization when the above factors are present.

On the basis of these results, recommended initial regimens for vancomycin in neonates (Table 3) are suggested according to the kinetic parameters obtained and assuming the one-compartment model with target peak and trough concentrations of 18–21 g mL^{-1} and 5–10 g mL^{-1}, respectively. The suggested therapeutic window is appropriate bearing in mind the assumed pharmacokinetic model and the efficacy/safety ratio usually adopted under similar physiopathological conditions (Fernandez de Gatta et al 1996). Although caution must be exercised in extrapolating this information to patients in other settings, the qualitative information relating to postconceptional age and the presence or absence of concomitant treatment with indomethacin or mechanical ventilation, or both, could be important in the individualization of vancomycin therapy in neonates. Finally, an *a priori* and *a posteriori* Bayesian approach could be used with these results to individualize the therapy.

References

Asbury, W. H., Darsey, E. H., Rose, W. B., Murphy, J. E., Buffington, D. E., Capers, C. C. (1993) Vancomycin pharmacokinetics in neonates and infants: a retrospective evaluation. Ann. Pharmacother. 27: 490–495

Besunder, J. B., Reed, M. D., Blumer, J. L. (1988) Principles of drug biodisposition in the neonate. A critical evaluation of the pharmacokinetic–pharmacodynamic interface (Part I). Clin. Pharmacokinet. 14: 189–216

Fernandez de Gatta, M. M., Fruns, I., Calvo, M. V., Lanao, J. M., Dominguez-Gil, A. (1996) Influence of pharmacokinetic model on vancomycin peak concentration targets. Ther. Drug Monit. 18: 145–148

Gabriel, M. H., Kildoo, C. W., Gennrich, J. L., Modanlou, H. D., Collins, S. R. (1991) Prospective evaluation of a vancomycin dosage guideline for neonates. Clin. Pharmacol. 10: 129–132

Ginovart, G., Duat, M. D., Riba, R. F., Mangues, M. A., Guasch, X., Torrent, F. R., Valls, O. A. (1993) Sepsis por estafilococo coagulase negativo en recién nacidos. Aspectos clínicos y terapéuticos. An. Esp. Pediatric. 38: 488–492

Kildoo, C. W., Lin, L. M., Gabriel, M. H., Folli, H. L., Modanlou, H. D. (1990) Vancomycin pharmacokinetics in infants: relationship to postconceptional age and serum creatinine. Dev. Pharmacol. Ther. 14: 77–83

McDougal, A., Ling, E. W., Levine, M. (1995) Vancomycin pharmacokinetics and dosing in premature neonates. Ther. Drug Monit. 17: 319–326

Miles, M. V., Li, L., Lakkis, H., Youngblood, J., McGinnis, P. (1997) Special considerations for monitoring vancomycin concentrations in pediatric patients. Ther. Drug Monit. 19: 265–270

Naqvi, S. H., Keenan, W. J., Reichley, R. M., Fortune, K. P. (1986) Vancomycin pharmacokinetics in small, seriously ill infants. Am. J. Dis. Child. 140: 107–110

Perkins, M. W., Dasta, J. F., DeHaven, B. (1989) Physiologic implications of mechanical ventilation on pharmacokinetics. DICP 23: 316–323

Rodvold, K. A., Gentry, C. A., Plank, G. S., Kraus, D. M., Nickel, E., Gross, J. R. (1995) Bayesian forecasting of serum vancomycin concentrations in neonates and infants. Ther. Drug Monit. 17: 239–246

Rodvold, K. A., Everett, J. A., Pryka, R. D., Kraus, D. M. (1997) Pharmacokinetics and administration regimens of vancomycin in neonates, infants and children. Clin. Pharmacokinet. 33: 32–51

Schwartz, G. J., Haycock, G. B., Edelmann, C. M., Spitzer, A. A. (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58: 259–263

Seay, R. E., Brundage, R. C., Jensen, P. D., Schilling, C. G., Edgren, B. E. (1994) Population pharmacokinetics of vancomycin in neonates. Clin. Pharmacol. Ther. 56: 169–175