LETTER OF THE EDITOR

ALTERATION IN GENTAMICIN PHARMACOKINETICS IN ACUTE TRAUMATIC PARAPLEGICS

Sir,

Interruption of the neuraxis in the 'spinal cord injured' (SCI), brings about several pathophysiological changes in human body such as increase in total extracellular fluid volume, loss of venomotor tone, venopooling, and a change in the body adipose tissue consistency (1,2). To what extent these changes affect drug disposition kinetics and metabolism in the acute spinal man has not been clearly elucidated (3). SCI patients frequently develop urinary tract infection and gentamicin which is commonly used for treatment of such cases was chosen to study the pharmacokinetics in the acute spinal cord injured. Following intravenous administration, the elimination kinetics of gentamicin are accurately characterised by a first order process and a one compartment-open model once equilibration has occurred at the end of the distribution phase.

Three paraplegics, participated in the study within 10 days of sustaining spinal cord injury. None of them were receiving heparin. aminoglycosides or carbenicillin which could alter gentamicin metabolism. Liver function tests and renal function tests were normal in all the patients. By studying each patient at the same time of day, possible influence of normal or disrupted circadian rythms on gentamicin disposition kinetics was kept constant (4). Three ml of blood was withdrawn from antecubital vein before administering gentamicin (1.5 *mg/kg*) intravenously as a bolus. Blood samples were drawn from antecubital vein of the contralateral extremity immediately, 30, 60, 90, 120, 150, 180, 240, 300, 360, 420 and 480 minutes after drug administration. Serum was separated and stored at -20^0C until assayed the next day.

Serum gentamicin levels were estimated in duplicate by solid phase radioimmunoassay (RIA)*. The minimum detectable level is 0.1 $\mu g/ml$. Kinetic parameters viz. volume of distribution (Vd), half life ($t_{\frac{1}{2}}$) and clearance (Cl) were derived from analysis of plots of the time course of log serum gentamicin concentrations obtained from a weighted, iterative, non-linear least-squares regression analysis (5,6).

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The pharmacokinetic parameters (Vd, $t_{\frac{1}{2}}$ and Cl) for gentamicin in the acute paraplegics are given in the Table I. There is a considerable increase in the volume of distribution and drug clearance rate with a decrease in the half-life of gentamicin as compared to the normal values (7).

TABLE - I

Patient's Serial No.	*Volume of distribution Vd (ml/kg)*	*Half life of drug $t_{\frac{1}{2}}$ (min)*	*Drug clearance rate (ml/kg/min)*
1	914.6	135.88	4.66
2	582.3	91 18	4.42
3	650.48	68.61	6.57
Mean	715.79	98.56	5.22
Normal Value	260 ± 20	126 ± 6	1.46 ± 0.08

Pathophysiological changes ocourring in SCI patients influence drug disposition kinetics. Analysis of the time course of serum gentamicin levels in the acute spinal man revealed a pharmacokinetic profile which differed in a significant way from experimentally derived values in normal subjects. Similar observations have been reported in the chronic spinal cord injured (7).

The wide expansion of the volume of distribution (Vd) of gentamicin in SCI as compared to normal subjects is probably due to an increase in extracellular fluid volume, attributed to an alteration in venomotor tone and vascular resistance, tissue trauma giving rise to subclinical odema and changes in body adipose tissue consistency following spinal cord injury. Interruption of neuraxis leads to sympathetic hypoactivity and loss of vascular resistance, thereby resulting in venous pooling and tissue oedema.

This study shows that the gentamicin clearance is greater in SCI than in normal subjects. If gentamicin is administered in the conventional dosage regimen, it could result in underdosing this population with resultant decrease in its therapeutic efficacy.

The alteration in the pharmacokinetic parameters of gentamicin in SCI and a greater inter-subject variability in gentamicin disposition kinetics in the SCI makes it imperative for individualization of drug dosing and spacing of dose to achieve optimum therapeutic effect. Similarly, pharmacokinetics of other life saving and potentially dangerous drugs should be studied in the SCI as a spinal man constitutes a discreet population and pharmacokinetic parameters of drugs in subjects with intact neuraxia cannot be extrapolated to the spinal cord injured.

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REFERENCES

1. Claus-walker, J., R.E. Carter, N.M. Diferranie and J. Singh. Immediate endocrine and metabolic consequences of traumatic quadriplegia in a young woman. *Paraplegia*, **15** : 202-208, 1977.
2. Greenway, J., R.E. Houser and Q. Lindan. Long-term changes in gross body composition of paraplegic and quadriplegic patients. *Paraplegia*, 7 : 301-318, 1970.
3. Livshirts, A.V. and V.P. Iakoviev. Dynamics of doxycycline levels in cases with trauma of the spinal marrow. *Antibiotiki*, **17** : 844-847, 1972.
4. Claus-walker, J.L., R.E. Carter and H.S. Lipscomb. Analysis of daily rhythms of adrenal function in men with quadriplegia due to spinal cord section. *Paraplegia*, **6** : 195-207, 1969.
5. Hartley, H.O. and A. Booker. Non linear test squares estimation. *Ann. Math. Stat.*, **36** : 638-650, 1965.
6. Sawchuk, R.J., D.E. Zaske, R.J. Cipolle, W.A. Wargin and R.G. Strate. Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin. Pharmacol. Ther.*, **21** : 362-369, 1977.
7. Segal, J.L., D.R. Gray, S.K., Gordon, I.M. Eltorai, F. Khansari and J. Patel. Gentamicin disposition kinetics in humans with spinal cord injury. *Paraplegia*, , **23** ; 47-55, 1985.