Paradoxical Increase in Aminoglycoside Body Clearance in Renal Disease When Volume of Distribution Increases

Keyphrases □ Pharmacokinetics—aminoglycosides in renal disease, clearance, volume of distribution □ Aminoglycosides—body clearance in renal disease with increased volume of distribution, pharmacokinetics □ Renal disease—aminoglycoside body clearance with increased volume of distribution, pharmacokinetics

To the Editor:

Recent studies in our laboratory on the disposition of gentamicin in dogs (1) and sheep (2) with glomerular disease indicated that gentamicin's volume of distribution (Vd) increased, while the glomerular filtration rate, as measured by endogenous creatinine clearance, decreased. A re-evaluation of these studies to include a comparison of renal clearance parameters demonstrates that body or systemic clearance of gentamicin (Cl_B) paradoxically increases in the face of a decreased glomerular filtration rate (Table I). The purpose of this communication is to explore the nature of this paradox and to assess its significance in predicting drug disposition from clinical estimates of the glomerular filtration rate.

Volume of distribution generally has been shown to remain constant or decrease in renal failure for drugs that are not extensively protein bound (4–6). Often the decrease in Vd is not physiological, but rather is dependent on the pharmacokinetic parameters used to estimate it. Thus, in a two-compartment open model, a decrease in elimination will result in a decrease in Vd_β, Vd_{area}, and Vd_B, but not Vc or Vd_{ss} which are estimates of the physiologic distribution space of the drug (7). Aminoglycoside antibiotics are not appreciably bound to serum proteins. They are distributed essentially in extracellular water, are eliminated unchanged by the kidney, and a decreased glomerular filtration rate decreases their elimination (8). However, Vd_{ss} and Vc of netilmicin (9, 10) and Vd calculated after constant intravenous infusion of gentamicin (11) increased in patients with a decreased glomerular filtration rate, as measured by creatinine and/or inulin clearance. This is similar to the situation seen in our laboratory in animals with glomerulonephropathy. The mechanism of increased Vd is not known and may be specifically related to the pathophysiology of acute glomerulonephropathy. This condition, which has been associated with sodium retention and concommitantly increased exchangeable body sodium (12), could cause fluid retention and thus an increased physiological Vd. Alternatively, the immunological events occurring at the glomerulus could release a vasoactive factor(s) which might increase tissue binding of drug. Since the etiologic diagnosis of the renal disease is often not reported in pharmacokinetic studies, some of the human patients in the studies cited may have had glomerular disease.

Clearance may be calculated from the following:

$$Cl_B = K_{el}Vc \qquad \text{(Eq. 1)}$$

$$Cl_B = \beta Vd_{area} \qquad \text{(Eq. 2)}$$

where K_{el} is the elimination rate constant, Vc is the volume of the central compartment, β is the overall elimination rate constant, and Vd_{area} is the volume of distribution calculated from the area; all are defined in terms of a two-compartment open pharmacokinetic model (7, 13, 14). Body clearance can also be calculated according to the following model-independent technique:

$$Cl_B = \frac{\text{Dose}}{AUC} \qquad \text{(Eq. 3)}$$

where AUC is the area under the plasma concentration *versus* time curve, and dose is the amount of absorbed drug unchanged in the body (13, 14). Incomplete collection of data points may result in spuriously low values for AUC due to low serum concentrations seen with the expanded Vd, the result being increased Cl_B.

An increase in Cl_B could reflect a physiological increase in drug clearance. Gentamicin Cl_B calculated using Eqs. 1 and 3 increased in animals with glomerulonephropathy (Table I). In the human studies cited (9, 11), the ratio of aminoglycoside clearance to the glomerular filtration rate (fractional urinary excretion) also increased with a decreasing glomerular filtration rate and increasing Vd. In one study (11), actual renal gentamicin clearance even exceeded the glomerular filtration rate in some patients. This finding is supported in a recent micropuncture study in rats (15), which demonstrated that expansion of extracellular fluid volume with saline or bicarbonate caused an increase in the fractional urinary excretion of gentamicin exceeding unity in some cases. Similar findings were also noted when furosemide was administered concurrently with gentamicin (16). In this study utilizing rabbits, gentamicin renal clearance exceeded the glomerular filtration rate, as determined by inulin clearance, when furosemide was coadministered. The authors attributed this to in-

Table I—Selected Pharmacokinetic Data [a] of Gentamicin Disposition in Dogs and Sheep with Normal or Decreased Renal Function Secondary to Glomerular Disease

Parameter	Units	Dogs [b]		Sheep [c]	
		Normal (n = 11)	Diseased (n = 4)	Normal (n = 6)	Diseased (n = 2)
GFR [d]	ml/min/kg	3.8 ± 0.9	1.9 ± 0.6	1.7 ± 0.3	0.5 ± 0.2
Cl_B	ml/min/kg	4.1 ± 0.6	5.3 ± 1.2	1.0 ± 0.2	1.4 ± 0.5
Vd_{ss}	liter/100 kg	34.1 ± 2.4	51.2 ± 2.5	24.5 ± 2.9	47.0 ± 7.4
Vc	liter/100 kg	19.2 ± 0.7	28.6 ± 4.2	11.3 ± 1.4	14.4 ± 1.8

[a] Mean ± *SD*. [b] Data revised and adapted from Riviere *et al.* (1) and Riviere and Coppoc (3) (two-compartment open pharmacokinetic model). [c] Data revised and adapted from Brown *et al.* (2) (three-compartment open pharmacokinetic model). [d] GFR = glomerular filtration rate (as determined by endogenous creatinine clearance).

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creased gentamicin excretion by a renal tubular process, an event which was not present in the control animals studied. Finally, when water-deprived and hydrated rats were treated with gentamicin (17), the trend in changes seen in Cl_B and Vd with hydration were of similar nature to the animals with glomerulonephropathy. Extrapolation of these findings to the diseased animal is difficult due to the precisely defined experimental conditions of these studies. This is especially true in micropuncture experiments where small quantities of drug are involved. However, these data provide a physiologic basis for the pharmacokinetic changes detected in the dogs and sheep with acute glomerular disease.

It would appear that certain physiologic conditions and disease states associated with volume expansion and/or increased urine flow might lead to increased gentamicin clearance. This response may be modulated through a mechanism triggered by the abnormal fluid status. The increase in drug clearance may be a reflection of nephron heterogeneity (15) or a result of active tubular secretion, decreased proximal tubular reabsorption, or decreased nonionic back diffusion in the distal nephron (16, 18). Alternatively, glomerular disease may specifically increase the drug's ultrafilterability across the glomerular capillary membrane, normally restricted due to the Donnan Effect (18). This functional lesion would be expected to increase the fractional urinary excretion of gentamicin. Mechanistic studies have not been performed in diseased animals, and thus, further speculation is not warranted. This situation may not be seen in the chronic disease situation where individual nephrons have undergone compensatory hypertrophy. This chronic condition is pathophysiologically distinct and is clinically characterized by a different syndrome than is the acute disease process.

In view of these changes, one must be cautious in predicting Cl_B from the glomerular filtration rate, especially when an increased Vd is present, because these methods assume that this relationship does not change with the underlying disease process. However, certain disease conditions may uncouple this association of Cl_B to the glomerular filtration rate. Actual renal clearances of drug should be determined by measuring urinary drug excretion. Note that serum elimination half-life may remain relatively stable in the above situation because the increasing clearance will offset the increased volume of distribution. Dosage nomograms, which correlate elimination half-life or decreasing Cl_B with decreasing creatinine clearance, must be interpreted differently when Vd is known to have increased. Finally, additional studies relating drug disposition to specific pathophysiologic states of renal disease must be conducted to define the effects of various disease processes on drug clearance and volume of distribution, the two physiologic determinants of drug disposition.

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Isosorbide Dinitrate: Pharmacokinetics after Intravenous Administration

Keyphrases □ Pharmacokinetics—intravenous administration of isosorbide dinitrate, bioavailability □ Bioavailability—pharmacokinetics of isosorbide dinitrate after intravenous administration □ Isosorbide dinitrate—pharmacokinetics after intravenous administration, bioavailability

To the Editor:

Isosorbide dinitrate is an organic nitrate found therapeutically useful in its sublingual and oral forms in various cardiovascular diseases such as angina pectoris (1) and congestive heart failure (2). Recently, Distante *et al.* (3) showed that an intravenous infusion of this drug (0.021–0.083 mg/min) was also effective in managing unstable angina. The availability of an intravenous dosage form of isosorbide dinitrate not only affords the opportunity to characterize the pharmacokinetics of this drug after this particular mode of therapy, it also allows the possibility to assess the bioavailability of this drug after other (*e.g.*, oral) routes of administration in patients. This latter subject has been of major controversy since Needleman *et al.* (4) made the assertion that oral nitrate therapy is irrational because of its complete first-pass metabolism.

A preliminary study has appeared which provided some initial information on this important issue. Taylor *et al.* (5) showed that in two normal, young subjects who received

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