Table I—Renal Clearance (ml/min/kidney) of *R*- and *S*-Epimers of Moxalactam in Anesthetized Male Beagle Dogs

	Dog 1		Dog 2	
	Control phase[a]	Probenecid phase[b]	Control phase[a]	Probenecid phase[a]
Apparent clearances				
R-epimer, total	16.29 ± 0.68[a]	10.81 ± 0.17[b]	17.32 ± 1.18	15.90 ± 0.58
S-epimer, total	9.21 ± 0.52	6.97 ± 0.85[b]	10.48 ± 0.43	10.76 ± 0.25
Clearance ratio *R*/*S*, I	1.81 ± 0.11	1.59 ± 0.19[b]	1.66 ± 0.10	1.48 ± 0.07
Corrected clearances				
R-epimer, 23.7% binding	21.73 ± 0.74	14.19 ± 0.20[b]	22.57 ± 1.55	20.01 ± 0.26
S-epimer, 44.9% binding	16.68 ± 0.95	12.67 ± 1.56[b]	19.03 ± 0.82	19.52 ± 0.44
Clearance ratio *R*/*S*, II	1.32 ± 0.09	1.16 ± 0.14[b]	1.19 ± 0.07	1.07 ± 0.05
Statistical differences[c] of *R*/*S* values between I (total) and II (unbound)	$p < 0.05$	NS	$p < 0.01$	$p < 0.01$
Glomerular filtration rate (Creatinine clearance)	18.16 ± 0.19	14.33 ± 0.88[b]	18.67 ± 0.37	17.04 ± 0.44

[a] Value represents mean ± *SE* (number of samples: $n = 4$). [b] Number of samples: $n = 3$. [c] Student's t test.

nohippuric acid (6), and moxalactam (7). The ratios of *R*- to *S*-epimer in plasma and urine were determined using high-performance liquid chromatography (8). The fractions of the *R*- and *S*-epimers of moxalactam bound to dog plasma were determined at 37° by an ultrafiltration method[4].

The renal clearances of the moxalactam epimers in Table I were calculated by dividing the urinary excretion (micrograms per milliliter) by the total (bound and unbound) concentrations of the epimers. Clearance of the *R*-epimer was 1.4–1.8 times that of the *S*-epimer. The clearance ratios of *R*- and *S*-epimers to creatinine were less than unity. Since only unbound moxalactam would have been available for glomerular filtration, the clearance value based on the total concentration of the epimer in plasma may be underestimated. To determine the actual glomerular filtration, the protein binding of moxalactam epimers was determined at concentrations of 25, 50, and 100 μg/ml of dog plasma. The mean percentage of the bound fraction calculated from these values was 23.7 ± 1.6% *SEM* ($n = 3$) for the *R*-form and 44.9 ± 0.4% ($n = 3$) for the *S*-form.

As indicated in Table I, the data were corrected for the binding of the *R*- and *S*-epimers, *e.g.*, the clearances were calculated by dividing the urinary excretion (micrograms per minute) by the concentrations of the unbound epimers. The calculated renal clearances of the epimers were nearly equal to the glomerular filtration rate (creatinine clearance) and the *R*-epimer/*S*-epimer clearance ratio was closer to unity. When probenecid was given to Dog 1, the *p*-aminohippurate clearance decreased from 55.3 ± 0.6 to 17.0 ± 1.0 ml/min/kidney (mean ± standard error, $n = 3$), but the *R*- or *S*-epimer/creatinine clearance ratio was not affected.

Stereospecific differences in protein binding have been reported for other drugs (9–12) and vary from one animal species to another (3, 13). Our findings indicate that in the dog, both epimers of moxalactam are excreted by glomerular filtration, and the striking difference in renal clearance of the *R*- and *S*-epimers is due mainly to differences in binding to plasma protein.

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[4] Centriflo CF25, Amicon Corp., Lexington, Mass.

Effect of Ascorbic Acid on Renal Excretion of Lead in the Rat

Keyphrases □ Ascorbic acid—effect on renal excretion of lead, rats □ Lead—effect of ascorbic acid on renal excretion, rats □ Renal excretion—effect of ascorbic acid, lead, rats

To the Editor:

Lead poisoning is currently treated by chelation therapy using edetate disodium and dimercaprol, both of which have serious side effects. Few studies have been carried out

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on the use of natural compounds such as ascorbic acid to remove heavy metals from the body, and these few studies and anecdotal observations have not provided any direct evidence for ascorbic acid on the excretion of lead from the body (1–4).

In the present communication we report a direct effect of ascorbic acid on the excretion profile of lead in the rat. The control group of rats (weight 300–450 g) were given demineralized water for 4 weeks; the treatment group received 4% ascorbic acid (pH 7.4) as drinking water. Food was given *ad libitum* to both groups ($n = 16$). Lead was administered as lead acetate solution in 5% dextrose intravenously at a dose of 0.637 μg of lead/g of body weight. The treatment group also received a bolus dose of ascorbic acid (1 mg/g of body weight) following administration of lead acetate solution. This was followed by 0.25 mg of ascorbic acid/g of body weight given subcutaneously every 6 hr. The blood samples were collected from the tail vein periodically for up to 163 hr, and urine samples were collected in 24-hr pools for up to 1 week. All samples were analyzed for total lead using a flameless atomic absorption spectrophotometer with graphite furnace[1].

The initial blood levels in the treatment group were higher than the control in accordance with previous findings (3). The urinary clearance of lead was calculated from the plots of blood concentration (C_b) against the urinary excretion (X_u) rate:

$$\text{Control: } \frac{dX_u}{dt} = 0.0049 + 0.1932\ C_b \quad (r > 0.92) \qquad \text{(Eq. 1)}$$

$$\text{Treatment: } \frac{dX_u}{dt} = -0.02089 + 0.4261\ C_b \quad (r > 0.99) \qquad \text{(Eq. 2)}$$

[1] Atomic Absorption Spectrophotometer model 503, Perkin-Elmer, Norwalk, Conn.

The good linear correlation coefficient signifies the relationship between blood concentration and the urinary excretion according to clearance principles; the slopes of Eqs. 1 and 2 were statistically different ($p < 0.05$). An increase of almost 120% in the urinary clearance of lead was recorded as a result of treatment with ascorbic acid. This finding was also reflected in a similar increase in the total amount of lead excreted in the urine (6.5 *versus* 12.8%) within 1 week (difference significant at $p < 0.05$).

Despite the complications involved in the disposition kinetics of lead in the body, such direct observation of the effect of ascorbic acid attests to the many anecdotal uses of ascorbic acid in the treatment and prevention of lead poisoning.

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BOOKS

REVIEWS

The International Pharmacopoeia, Third Edition, Vol. 2: Quality specifications, Health and Biomedical Information Programme, World Health Organization, 1211 Geneva 27, Switzerland. 1981. 342 pp. 16 × 24 cm. Price 36 Sw fr.

By virtue of a resolution of the Third World Health Assembly, the *International Pharmacopoeia* is published to improve the quality control of all drugs and pharmaceutical substances. The quality specification establishment and revision process was carried out with the help of members of the World Health Organization's Expert Advisory Panel on the International Pharmacopoeia and Pharmaceutical Preparations and other specialists.

The present (third) edition of the *International Pharmacopoeia* will appear in five volumes. This volume, the second, contains quality specifications for 126 individual drugs widely used in health care. The first volume was published in 1979 and describes 42 general methods of analysis and should be used along with the general notices given in the present volume. The remaining three volumes will contain further specifications.

Specifications included in the second edition of the *International Pharmacopoeia* have been subjected to thorough revision. For other substances, no international quality specifications have been previously issued. While these specifications have no legal status in any country, unless expressly introduced into the national legislation, they are intended to serve as references for national authorities; it is expected that they will be applied by many developing countries for pharmaceuticals used by their health systems.

As for the monographs themselves, for substances used in more than one form (*e.g.*, anhydrous and hydrated, or noninjectable and sterile) the requirements for the relevant forms have been put together in a single monograph, but separate tests have been provided, as required, for each specific form. Also, IR spectra are mentioned in a number of monographs; however, a separate publication containing reproductions of such spectra will be issued at a later date.

Staff Review