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Distribution and Pharmacokinetics of Triamterene in Rats

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Abstract □ The tissue distribution of ^{14}C-triamterene was examined in the rat. After intravenous administration of ^{14}C-triamterene, high concentration ratios between tissues and blood were found in most tissues except the brain, fat, and testes. The maximal concentration of the drug was in the kidneys, liver, heart, lungs, and skeletal muscle within the first 20 min, when the maximal natriuresis was observed. No metabolite of triamterene was detected in these tissues. The pharmacokinetics of ^{14}C-triamterene also were investigated. The volume of distribution of the drug was greater in the central compartment (60% of the dose) than in the peripheral compartment (40%). The binding of the drug to skeletal muscle is responsible for the fraction of the dose in the peripheral compartment. Rate constants indicate that slow elimination of triamterene is related to its binding to tissue in the central compartment.

Keyphrases □ Triamterene—distribution and pharmacokinetics, radiochemical analysis, rats □ Drug distribution—triamterene, radiochemical analysis, rats □ Pharmacokinetics—triamterene, radiochemical analysis, rats □ Radiochemistry—analysis, triamterene distribution, rats □ Diuretic agents—triamterene, distribution and pharmacokinetics, radiochemical analysis, rats

Triamterene, in addition to its renal effects, significantly decreases the sodium content of cardiac and skeletal muscle without impairing the potassium content in the rat (1). Although an unusual tissue distribution of triamterene was reported in guinea pigs and baboons (2), its distribution in the rat has not been studied. Previous studies (3, 4) indicated that unchanged triamterene itself, rather than its metabolites, accounts for the observed changes of renal clearance of electrolytes.

It is not known whether the metabolism of triamterene in cardiac and skeletal muscle is similar to that in the kidneys in the rat. The contribution of the drug distributed in the tissue and of its metabolites to the total elimination of triamterene by humans and animals also is not known. The purpose of this study was to determine the tissue distribution and pharmacokinetics of triamterene in the rat to obtain a better understanding of the rate of distribution and elimination of triamterene and its extrarenal action.

EXPERIMENTAL

Animals and Materials—Male Sprague–Dawley rats[1], 200–250 g, were used. ^{14}C-Triamterene[2] (0.92 mCi/mmole) was used as supplied. It was found to be chemically pure by descending paper chromatography in two solvent systems, 1-butanol–acetic acid–water (4:1:1) and 2-propanol–water–ammonia (140:50:10), according to literature methods (4–6). A 4 × 4 countercurrent distribution of ^{14}C-triamterene between ethyl acetate (14 ml) and 0.1 *M* borate buffer at pH 10.00 (7 ml) showed that it behaved like a single compound (6–8).

Other commercially available chemical reagents were used.

Tissue Distribution—Rats were prepared for infusion as described previously (9), and ^{14}C-triamterene[3] (1, 2, or 4 mg/kg; 3.8 μCi/mg) was administered by intravenous infusion for 8 min at 0.5 ml/min/kg. Samples of blood and urine were collected 40 min after the beginning of the infusion, and the rat was then immediately decapitated. Submaxillary and thyroid glands, thymus, aorta, heart, lungs, liver, pancreas, spleen, adrenals, kidneys, ileum, biceps femoris, epididymal fat pads, testes, and brain were dissected, blotted, and weighed. The distribution of ^{14}C-triamterene and its metabolites was determined at 40 min, when the maximal potassium-sparing effect of triamterene was observed (3).

In a second series of experiments, a constant dose of ^{14}C-triamterene (2 mg/kg, 3.8 μCi/mg) was administered by infusion; the rats were sacrificed at intervals of 10, 20, 40, or 60 min thereafter. Plasma, liver, lung, heart, kidney, skeletal muscle (biceps femoris), and urine samples were collected.

The total carbon-14 in the tissues samples was measured[4]. About 200 mg of tissue was placed into a 20-ml glass counting vial. A 2-ml aliquot of liquid scintillation solute[5] was added, and the sample was shaken[6] at 50° until solubilized. To increase the counting efficiency of some heavily colored tissues (blood, liver, lungs, and spleen), 0.6 ml of benzoyl peroxide solution was added to the solubilized sample, and the mixture was shaken for an additional 0.5 hr to obtain a colorless solution.

To the solubilized tissues, 18 ml of counting solution[7] was added. The samples were cooled to 4° for 24 hr prior to counting. All samples were counted twice for 10 min. All data were converted to disintegrations per

[1] Holtzman, Inc., Madison, Wis.
[2] Smith Kline and French Laboratories, Inc.
[3] Triamterene was solublized in Solution A, containing inulin (0.15%), aminohippuric acid (0.2%), and ketamine (8 mg/kg/ml), with the aid of a few drops of 8.5% lactic acid and warming. The total volume administered was 4 ml/kg.
[4] Packard liquid scintillation counter.
[5] Soluene, Packard Instrument Co.
[6] Dubnoff metallic shaker.
[7] Phase Combing System, Amersham/Searle Corp.

Table I—Distribution of Triamterene and Its Metabolites in Various Tissues[a]

Sample	4-mg/kg Dose			2-mg/kg Dose			1-mg/kg Dose		
	nCi/g[b]	T/B[c]	Found[d], %	nCi/g	T/B	Found, %	nCi/g	T/B	Found, %
Blood	4.26 ± 0.16	—	2.56 ± 0.09	2.20 ± 0.01	—	2.12 ± 0.13	1.10	—	2.28 ± 0.16
Submaxillary glands	24.38 ± 1.98	5.72	0.52 ± 0.04	11.07 ± 1.78	5.43	0.48 ± 0.07	7.16 ± 1.26	6.50	0.50 ± 0.08
Thyroid gland	16.42 ± 2.75	3.85	<0.01	8.54 ± 0.80	3.88	<0.01	6.12 ± 0.70	5.56	<0.01
Adrenal glands	23.69 ± 0.85	5.56	0.03	11.44 ± 1.13	5.20	0.03	6.75 ± 1.26	6.13	0.03
Thymus	15.82 ± 0.29	3.71	0.29	7.13 ± 0.68	3.23	0.26 ± 0.02	4.25 ± 0.36	3.86	0.25 ± 0.02
Spleen	13.53 ± 0.62	3.17	0.35 ± 0.01	6.86 ± 0.69	3.11	0.36 ± 0.03	4.24 ± 0.61	3.85	0.36 ± 0.05
Pancreas	16.61 ± 2.73	3.91	0.87 ± 0.14	8.58 ± 0.25	3.94	0.92 ± 0.02	4.80 ± 0.91	4.36	0.83 ± 0.15
Skeletal muscle	9.01 ± 1.10	2.11	40.95 ± 1.68	4.51 ± 0.61	2.05	36.66 ± 0.98	2.70 ± 0.10	2.45	33.79 ± 4.88
Intestine	8.18 ± 0.54	1.92	1.82 ± 0.01	4.32	1.96	1.96 ± 0.01	2.18	1.98	1.58 ± 0.05
Aorta	16.31 ± 1.17	3.83	—	6.79 ± 0.48	3.08	—	3.87 ± 0.15	3.51	—
Testes	2.87 ± 0.56	0.67	0.36 ± 0.07	1.39 ± 0.15	0.63	0.34 ± 0.03	0.72	0.65	0.30 ± 0.02
Brain	1.27	0.30	0.08	0.65	0.29	0.09	0.35	0.31	0.08
Fat	2.82	0.66	4.66 ± 0.26	0.91	0.41	3.24 ± 0.28	0.57	0.51	3.11 ± 0.46
Liver	17.05 ± 0.52	4.00	6.43 ± 0.19	10.18 ± 1.33	4.62	7.78 ± 1.02	5.56 ± 0.43	5.06	6.84 ± 2.05
Heart	10.41 ± 0.52	2.44	0.33 ± 0.01	4.69 ± 0.53	2.13	0.30 ± 0.03	2.71 ± 0.21	2.46	0.28 ± 0.02
Lungs	10.03 ± 0.74	2.35	0.45 ± 0.03	5.15 ± 0.76	3.24	0.47 ± 0.07	2.89 ± 0.45	2.62	0.42 ± 0.06
Kidneys	31.39 ± 3.61	7.36	2.97 ± 0.34	17.25 ± 1.64	7.82	2.41 ± 0.31	9.38 ± 1.41	8.53	2.90 ± 0.45
Urine	—	—	24.22 ± 2.59	—	—	23.38 ± 3.70	—	—	24.04 ± 2.86
Total recovery			86.89			82.71			77.59

[a] No metabolites of triamterene were detected in the liver, heart, lungs, kidneys, skeletal muscle, blood, or urine during these short-term studies (40 min after administration of triamterene). Each value is the mean ± *SE* from three rats. When the standard error is smaller than 0.01, it is not shown. [b] Nanocuries per gram of wet tissue. [c] Ratio of the mean value of the concentration in tissues (T) to that in the blood (B). About 50% of the ^{14}C-triamterene present in the blood was in the plasma. [d] Percentage dose was calculated on the basis of total ^{14}C-radioactivity in the whole tissue divided by the administered dose of ^{14}C-triamterene. Organ weights (except for total blood, total fat, and total muscle) were determined in each animal. It was not possible to determine total blood volume, total fat, and total muscle tissue within the same animal in which ^{14}C-triamterene distribution was determined. Therefore, estimated values (12–14) were used in the calculations: total blood, 6%; total fat, 16.5%; and total muscle, 45% of the body weight.

minute, using an automatic external standard and channels ratio technique. The remainder of each tissue was homogenized with 25 ml of aqueous acetone, the homogenate was centrifuged, and the aqueous acetone extract was separated and saved. The pellet was rehomogenized in 25 ml of aqueous acetone and centrifuged, and the supernate was combined with the original extract. After removal of the organic solvent by evaporation, the residue was dissolved in acetone and analyzed by paper chromatography and 4 × 4 countercurrent distribution as described previously (6–8). The procedure was repeated with each tissue.

Pharmacokinetics—Male rats were anesthetized with ketamine[8] (160 mg/kg ip). The femoral vein was cannulated with polyethylene tubing (PE 10) for the injection of ^{14}C-triamterene[9] (2 mg/kg, 3.8 μCi/mg). The femoral artery was cannulated with polyethylene tubing (PE 50) for collection of blood samples (0.3 ml for each) at timed intervals. In a second series of experiments, animals were maintained under light anesthesia with ether during cannulation of the femoral artery and vein. The rats received ^{14}C-triamterene after they recovered from the anesthesia in both series of experiments. Thereafter, blood samples were collected at timed intervals. The second series of experiments was used as a control to examine whether any postanesthetic effect of ketamine would influence the rate of distribution and elimination of triamterene in the first series.

Plasma samples were obtained after centrifuging whole blood samples, which were collected with heparinized syringes. The radioactivity in the samples of plasma was assayed according to the methods described in *Tissue Distribution*. The pharmacokinetic profile of ^{14}C-triamterene was determined in the plasma concentration–time curve, constructed according to the method described by Mayersohn and Gibaldi (10).

RESULTS

Tissue Distribution—In these short-term studies (60 min), no metabolite of triamterene was detected in the plasma, urine, or other tissues (liver, heart, lungs, kidneys, and skeletal muscle) analyzed by paper chromatography and countercurrent distribution. By comparison with the reference material, the single band at R_f 0.47 in 1-butanol–acetic acid–water or at R_f 0.42 in 2-propanol–water–ammonia was identified as unchanged triamterene in all tissues studied.

The distribution of the drug in various tissues after administration of different doses of ^{14}C-triamterene is shown in Table I. For most tissues, the concentration ratio between the tissue and the blood was greater than 1 (range of 1.80–8.53). The descending order of tissue and blood concentration ratios was: kidneys (7.36–8.53) > submaxillary glands > adrenal glands > liver > thyroid gland = pancreas > thymus > aorta = spleen > heart = lungs > diaphragm = biceps femoris > ileum. The ratio for brain was less than 1 (0.29–0.31). It was shown previously that there is a passive diffusion of triamterene into the brain across the blood–brain barrier, but it is actively transported out of the brain. This fact may explain partially the low tissue to blood ratio in the brain (11).

The same fraction of the drug was excreted in the urine irrespective of the size of the dose. The total amount of the drug in the organs was about 78–87% of the dose.

The tissue distribution of ^{14}C-triamterene as a function of time is shown in Fig. 1. The concentration of the drug reached a peak at 20 min in all tissues. The maximum concentration was in the renal tissue within the first 20 min, when the maximal natriuresis was also observed (3). The storehouse of the drug was the skeletal muscle, which contained about 39% of the dose at 20 min.

Pharmacokinetics—The pharmacokinetic profile of ^{14}C-triamterene in the rat was determined utilizing the data obtained following intravenous drug administration. The plasma concentration–time curve[10] of triamterene constructed from these data was biexponential (Fig. 2). The values of the parameters for the biexponential equation ($C_p = Ae^{-\alpha t} + Be^{-\beta t}$) are shown in Table II. The half-lives of the fast and slow components also were obtained. The two-compartment pharmacokinetic model was applied to this study, and its rate constants are shown in Table III.

DISCUSSION

Tissue Distribution—There are several interesting aspects to the distribution of ^{14}C-triamterene in the rat. After intravenous drug administration, the highest concentration was present in the kidneys at all timed intervals and dosage levels, whereas the largest fraction of the administered dose was deposited in the skeletal muscle. No metabolite was detected in these tissues. Therefore, the extensive accumulation of unchanged triamterene probably is responsible for its inhibitory action on sodium transport in skeletal muscle (1) as well as in kidneys (3).

A high concentration of the drug in all tissues analyzed, except the testes, brain, and fat, was maintained against a low concentration in the

[8] Bristol Laboratories.

[9] ^{14}C-Triamterene was suspended in 0.9% sodium chloride with a few drops of 8.5% lactic acid and warming until a clear solution was obtained.

[10] A nonlinear program was used for fitting the plasma concentration–time curve. The program was kindly provided by Dr. James Kao, Department of Chemistry, University of Georgia, Athens, Ga.

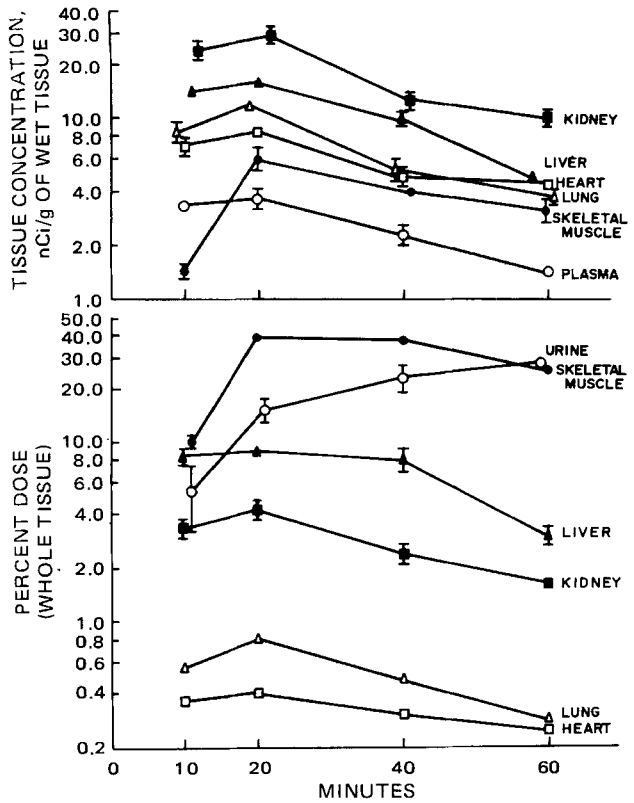

Figure 1—*Tissue distribution of ^{14}C-triamterene as a function of time. The upper panel indicates tissue concentration* versus *time; the lower panel shows percent dose* versus *time. The dose of ^{14}C-triamterene was 2 mg/kg iv. No metabolites of triamterene were detected in these tissues during the timed intervals. Each value is the mean ± SE from three rats. When the standard error is smaller than the dimension of the symbol, it is not shown.*

blood. Higher concentrations of triamterene were found inside dialysis bags in association with tissue homogenates (2). Therefore, the extensive accumulation of the drug in those tissues probably is a consequence of its binding by them.

Although the relationship of the tissue concentration of ^{14}C-triamterene to its effect on tissue electrolytes is not known, the data indicate that secretory (adrenal, submaxillary, and thyroid glands; liver; and kidneys) and lymphoid organs (thymus, spleen, and pancreas) accumulate the drug in higher concentrations than other tissues.

The highest concentration of the drug was found in the kidneys, liver, heart, lungs, and skeletal muscle within the first 20 min, when maximal

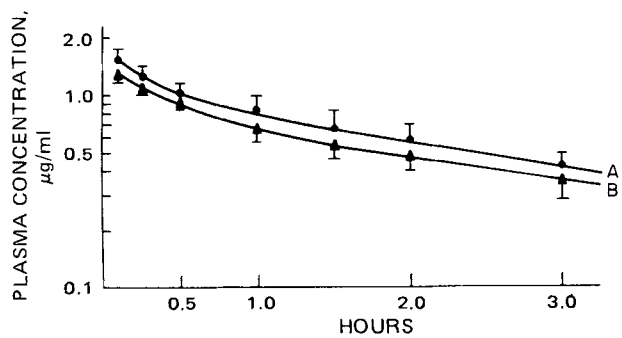

Figure 2—*Semilogarithmic plot of the plasma concentration of ^{14}C-radioactivity as a function of time after administration of ^{14}C-triamterene (2 mg/kg iv). Key: A (●), control group of animals that received light ether anesthesia during cannulation; and B (▲), group of animals that received ketamine instead of ether. Each point represents the mean ± SE for four animals in A and three animals in B. The plasma half-life of the fast component was 0.28 hr in A and 0.27 hr in B; the plasma half-life of the slow component was 2.77 hr in A and 2.78 hr in B. There was no significant difference between A and B in the plasma half-life of either the fast or slow component* ($p > 0.05$).

Table II—Values in the Equation[a] $C_p = Ae^{-\alpha t} + Be^{-\beta t}$ for Triamterene[b]

Parameter	Ketamine Anesthesia	Control[c]
A, μg/ml	0.68 ± 0.27	0.72 ± 0.17
α, hr^{-1}	2.61 ± 0.11	2.49 ± 0.22
B, μg/ml	0.79 ± 0.10	0.95 ± 0.14
β, hr^{-1}	0.25 ± 0.02	0.28 ± 0.03

[a] C_p is the drug concentration in the plasma at any time t, A and B are the ordinate axis intercepts, α is the fast disposition rate, and β is the slow disposition rate. [b] Each value is the mean ± SE for three rats in ketamine anesthesia and four rats in control experiments. [c] Control refers to the group of rats under light ether anesthesia during cannulation of the femoral artery and vein.

natriuresis was also observed (3). Since no metabolite of triamterene was detected in these tissues, there was a good correlation between the tissue concentration of the unchanged drug and its inhibitory effect on sodium transport. These data suggest that the extrarenal effect of triamterene on the tissue content of sodium deserves further investigation.

Pharmacokinetics—The rats were anesthetized with either ketamine or ether during surgery, and they received ^{14}C-triamterene only after they recovered from anesthesia. Although the pharmacology of ketamine is different from that of ether (5), the rate of distribution and elimination of triamterene was not significantly affected by any postanesthetic action of ketamine (Table III). Apparently, ketamine is as suitable as ether as an anesthetic agent in the pharmacokinetic study of triamterene.

The pharmacokinetic profile of triamterene was evaluated by the two-compartment open-model system (10). According to the biexponential plasma concentration–time curve of the drug, the first exponent is the fast disposition rate constant (α) and the second exponent is the slow disposition rate constant (β). The magnitudes of α and β indicate that triamterene ought to be distributed at a fairly rapid rate and be eliminated at a relatively slow rate. The ratio of β/k_{el} indicates that approximately two-thirds of the drug in the body would be in the central compartment available for elimination at any time.

The distribution volume of the drug was greater in the central compartment (*e.g.*, highly perfused tissues such as kidney and liver) than in the peripheral compartment (*e.g.*, poorly perfused tissues such as fat and muscle). These values reflect the high affinity of triamterene for binding substances in the central compartment. The result is well correlated with the present finding on the tissue distribution of ^{14}C-triamterene. A high drug concentration ratio between tissue and blood was found in kidney, liver, and other highly perfused tissues. Furthermore, the sum of the fractions of the dose found in skeletal muscle (37%), smooth muscle (2%), and fat (3%) was close to the value (38%) from pharmacokinetic studies in the peripheral compartment. Apparently, the high affinity of the drug

Table III—Distribution and Elimination Parameters of the Two-Compartment Open Model for Triamterene[a]

Parameter	Ketamine Anesthesia[b]	Control[b]
Distribution volume[c], ml		
V_c	311.1 ± 19.2	317.8 ± 64.2
V_p	175.5 ± 62.8	150.9 ± 17.5
V_d	486.7 ± 48.3	468.7 ± 74.4
Clearance[c], ml/min, C_t	2.27 ± 0.51	2.17 ± 0.39
Rate constants[d], hr^{-1}		
k_{12}	0.81 ± 0.18	0.79 ± 0.12
k_{21}	1.59 ± 0.03	1.56 ± 0.09
k_{el}	0.46 ± 0.13	0.46 ± 0.06
Constant ratio[e], β/k_{el}	0.61 ± 0.10	0.63 ± 0.05

[a] Each value is the mean ± SE as described in Table I. The evaluation of kinetic parameters was according to the methods described in Refs. 10 and 15. [b] Mean values for ketamine anesthesia and control were not significantly different in all parameters, $p > 0.05$ (calculated by the Student t test). Average weights of rats in ketamine and control groups were 210 and 230 g, respectively. [c] V_c = volume of central compartment, V_p = volume of peripheral compartment, V_d = total volume of distribution, and C_t = clearance of a drug from the central compartment. Distribution volume and clearance were calculated per rat. [d] The individual rate constants k_{12} and k_{21} reflect the rate of distribution into and out of the peripheral compartment from the central compartment; k_{el} is the sum of all rate constants governing the elimination process, including metabolism and urinary excretion. [e] Fraction of dose in the central compartment.

for skeletal muscle is responsible for its accumulation in the peripheral compartment.

The ratio of k_{21}/k_{12} ranged from 1.4 to 3.0, with a mean of 2.2, indicating that the drug returns rapidly from distribution sites for elimination from the body. However, the low k_{el}, with a mean of 0.46, indicates that the elimination of triamterene would not be as rapid as the ratio predicts. This situation could be related to the binding of the drug to tissue substances in the central compartment and to the ability of the rat to metabolize a limited amount of the drug (6). According to the plasma half-life of the slow component obtained in the present experiments, after intravenous administration of triamterene there will be a negligible concentration of the drug in the plasma within about five half-lives (13.9 hr).

In conclusion, the present observations illustrate the tissue binding property of triamterene in the rat. Although these data provide limited information about the nature of this property, they reveal the possibility of the effect of unchanged triamterene on the tissue content of sodium. A pharmacokinetic interpretation of the present study appears to be well correlated with the experimental results. Apparently, the tissue binding property of triamterene is an important factor in controlling its rate of distribution and elimination in the rat.

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Effect of Sodium Salicylate on Renal Elimination of a Quaternary Ammonium Compound

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Abstract □ Administration of sodium salicylate inhibited elimination of the tetraethylammonium ion in rats. A two-compartment open model was used to describe plasma decline of tetraethylammonium bromide administered intravenously. The rate constant describing elimination from the central compartment was decreased by 25 and 40% in rats predosed with sodium salicylate at 30 and 50 mg/kg, respectively. Salicylate also enhanced the distribution of the tetraethylammonium ion to the peripheral compartment. Urinary excretion is the principal route of elimination for the tetraethylammonium ion, and studies of the effect of sodium salicylate on the uptake of the tetraethylammonium ion by rat renal cortical tissue indicated noncompetitive inhibition by salicylate.

Keyphrases □ Sodium salicylate—effect on renal elimination of tetraethylammonium bromide, rats □ Tetraethylammonium bromide—pharmacokinetic model, effect of sodium salicylate on renal elimination, rats □ Elimination, renal—tetraethylammonium bromide, effect of sodium salicylate, rats □ Pharmacokinetics—two-compartment open model for tetraethylammonium bromide, rats □ Quaternary ammonium compounds—tetraethylammonium bromide, pharmacokinetic model, effect of sodium salicylate on renal elimination, rats

Quaternary ammonium and other strongly basic compounds are actively secreted by the renal tubule. The secretory pathway for the basic compounds is similar, but not identical, to the anion transport mechanism. Both mechanisms are known to be saturable, specific, and subject to inhibition by structural analogs and antimetabolic compounds and to require energy for their operation. In general, tubular transport of basic compounds is not known to be inhibited by acidic compounds; conversely, the transport of acidic compounds is not known to be inhibited by basic compounds (1).

The recently reported, partly noncompetitive nature of the inhibition of *p*-aminohippurate tubular transport by salicylate (2) prompted investigation of the effect of salicylate on the renal tubular transport of a quaternary ammonium compound. The effect of sodium salicylate on renal elimination kinetics of the tetraethylammonium cation was investigated in *in vitro* and *in vivo* models. Rat renal cortical slice studies were used to determine the nature of the inhibitory effect of salicylate on the active uptake of the tetraethylammonium ion by cortical tissue. The significance of the salicylate effect on renal elimination of the ^{14}C-tetraethylammonium ion was then evaluated in pharmacokinetic studies in anesthetized rats.