vascular doses of isosorbide dinitrate, 10^{-5} and 10^{-7} moles, were given 60 min apart, and the rate of elimination was ascertained for each dose. Plots of isosorbide dinitrate radioactivity for the two doses of the drug in one experiment are shown in Fig. 7. Two parallel lines, representing a half-life of 8 min, indicated that there was no increase in the half-life exhibited with the second dose. There was thus no indication from these studies that the mononitrate metabolites could inhibit denitration of isosorbide dinitrate, whether the mononitrates were preformed or formed *in situ*.

In summary, this paper illustrates how access to selected organs or tissues may alter the expected metabolism of a drug. Release of a drug from a precursor in the proximity of metabolizing tissue may lead to more rapid metabolism than seems likely from studies involving presentation of the preformed drug to that organ or tissue.

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Age-Related Pharmacokinetics of *N*-Acetylprocainamide in Rats

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Abstract □ The pharmacokinetics of *N*-acetylprocainamide, administered orally or intravenously, were studied in 3-, 6-, and 12-month-old rats using a two-way crossover study design. At 3, 6, and 12 months of age, the half-life values of *N*-acetylprocainamide were 1.66, 1.82, and 2.29 hr, respectively; the apparent volumes of distribution were 4.75, 3.35, and 1.98 liter/kg, respectively. The elimination rate constant, clearance, and absolute bioavailability of the drug (determined by AUC measurements and the amounts excreted unchanged in the urine) decreased significantly with age. The rate of absorption remained unchanged. The amounts of *N*-acetylprocainamide in the liver and kidneys were significantly higher in the 12-month-old animals. These results clearly demonstrate a significant alteration with age in the bioavailability, distribution, and elimination of *N*-acetylprocainamide in rats. In long-term toxicity studies of this and other drugs that show age-dependent pharmacokinetics, an adjustment in the chronically administered dose is essential.

Keyphrases □ *N*-Acetylprocainamide—oral and intravenous pharmacokinetics in rats, bioavailability, age-related changes □ Pharmacokinetics—*N*-acetylprocainamide in rats after oral and intravenous administrations, age-related changes □ Bioavailability—*N*-acetylprocainamide in rats after oral and intravenous administrations, age-related changes

It has been established that many physiological changes are associated with aging. Lean body mass, plasma albumin, and total body water decrease with age. In humans, the cardiac output decreases 1%/year from ages 19 to 86, and the blood flow to the kidneys is also reduced with age (1). In rats, there are pronounced decreases (>30%) in the cardiac index and in hepatic, renal, and GI tract blood flow at 11–12 months of age (2). These changes can account for significant alterations in the pharmacokinetics and pharmacodynamics of drugs. In toxicity and oncogenicity studies in animals, which are conducted over a long period of time (1 year or more), aging may account for (3, 4): (*a*) diminished absorption of drugs through the GI tract; (*b*) diminished rate of metabolism and renal excretion of drugs; (*c*) accumulation of drugs in blood and receptor sites; (*d*) changes in affinity and sensitivity of the receptor sites to drug molecules; and (*e*) an increased rate of mortality. For these reasons, it was considered prudent to

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Table I—Effect of Age on Pharmacokinetics after Intravenous Administration of *N*-Acetylprocainamide Hydrochloride in Rats [a]

Parameter [b]	Age [c] 3 Months Mean	3 Months CV, %	6 Months Mean	6 Months CV, %	12 Months Mean	12 Months CV, %
Plasma C_0 [d], μg/ml	19.0	12.1	27.7	21.6	46.9	21.8
AUC, μg·hr/ml	45.2	18.2	72.6	27.0	156	51.4
β, hr^{-1}	0.423	11.5	0.388	12.8	0.334	26.2
$t_{1/2}$, hr	1.66	12.1	1.82	14.2	2.29	42.3
V_d, ml/kg	4750	11.2	3350	22.0	1980	24.9
CL_{tot}, ml/min/kg	33.5	14.8	21.5	23.5	11.1	71.4

[a] The dose was 100 mg/kg. [b] Determined by model-independent equations. [c] The values for all parameters were significantly different ($p < 0.05$, Duncan's t test) at 6 months (*versus* 3 months) and 12 months (*versus* 3 and 6 months). The sample size was 7 at 3 and 12 months and 11 at 6 months. [d] Extrapolated time zero plasma concentration.

conduct age-dependent disposition studies in parallel with the long-term oncogenicity testing of *N*-acetylprocainamide in rats.

EXPERIMENTAL

Two-hundred Charles River CD rats[1] were randomly selected from large populations intended for long-term toxicity and oncogenicity testing. Each animal was housed in an individual stainless steel cage with free access to food[2] and water. The animals weighed 260–390 g (mean 320 g) at 3 months, 381–576 g (mean 481 g) at 6 months, and 512–735 g (mean 587 g) at 12 months. At each interval, a group of 12 rats was randomly selected from the population, and the pharmacokinetics of absorption, distribution, and elimination were studied.

A cannula was inserted surgically into a jugular vein of each rat under light ether anesthesia 1 day before drug administration. The preparation of the cannulas and the surgical procedures were described elsewhere (5). Food was withheld for 15 hr prior to drug administration and during the blood sampling period (10 hr). Water was freely accessible to the animals at all times.

The rats were divided into two groups, and the study was conducted according to a balanced two-way crossover design. One group received 100 mg/kg iv of *N*-acetylprocainamide hydrochloride[3] in distilled water through the jugular cannula; the other group received the same amount of drug by oral gavage. After 3 days, the crossover experiment was conducted. A solution containing 100 mg/ml of *N*-acetylprocainamide hydrochloride in distilled water was used for both administration routes. The volume of the administered solution ranged from 0.260 to 0.735 ml. Because of the difficulty in maintaining patent cannulas, the study was completed for 7, 11, and 7 rats at 3, 6, and 12 months, respectively.

Serial blood samples (0.4 ml each) were drawn at 0.5, 1, 1.5, 2, 4, 6, 8, and 10 hr postdose. After collection of each sample, 0.4–0.5 ml of normal saline containing 1% heparin sodium solution (5000 USP U/ml) was infused to flush the cannula and to replace the lost volume. Plasma was separated and frozen immediately. Urine and feces were collected quantitatively at 24 and 48 hr. At each urinary collection time, the animals were induced to empty their bladder by ether inhalation. Feces samples were homogenized[4] in distilled water. Aliquots of urine and feces homogenates were frozen immediately.

After completion of the crossover study, four animals received an additional 100 mg/kg iv of *N*-acetylprocainamide. One-half hour later, the animals were sacrificed by exsanguination *via* the portal vein under ether anesthesia. Plasma, liver, heart, and kidneys were harvested. Immediately after removal, the organs were sliced, blotted in tissue paper to remove excess blood, and weighed. A known volume of saline (3–5 times the weight of the organ) was added to the tissues. The mixture was homogenized[4] in an ice-water bath. An aliquot of each homogenate was frozen immediately.

Concentrations of *N*-acetylprocainamide in plasma, serum, and urine were determined in duplicate by a specific high-performance liquid chromatographic (HPLC) method (6). This procedure was modified for analysis of the drug in tissue homogenates (7) and in feces (8). The pharmacokinetic parameters describing the absorption, distribution, and elimination of *N*-acetylprocainamide were estimated as follows. Biological half-life was calculated from the terminal disposition rate constant (β) which was determined by regression analysis of the logarithm of the plasma concentration *versus* time curve at the postabsorption distribution phase. Area under the plasma concentration *versus* time curve (AUC) was determined by the trapezoidal method. Total clearance (CL_{tot}) was determined by dividing the administered intravenous dose (or amount absorbed) by the AUC. For oral administration, the ratio of AUC_{oral}/AUC_{iv} was used to account for the amount absorbed. The volume of distribution (V_d) was calculated by CL_{tot}/β.

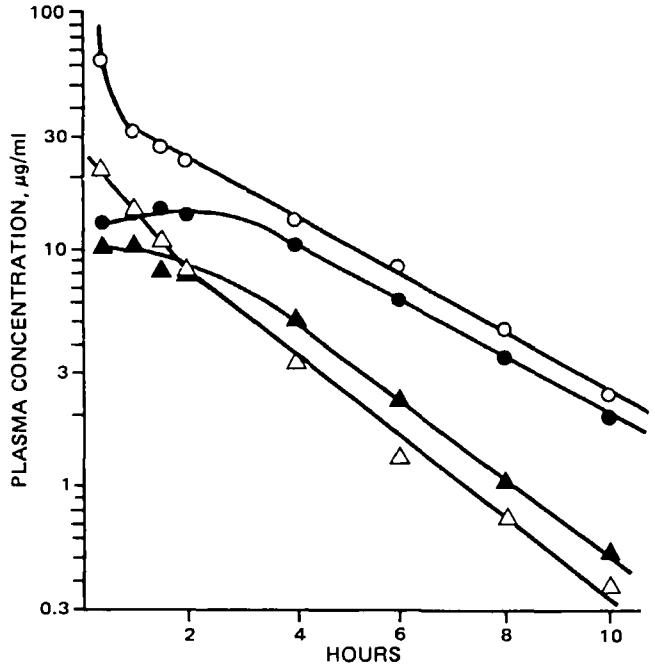

Figure 1—*Time course of* N-*acetylprocainamide in plasma after administration by intravenous injection and by oral gavage. Key: (△) 3-month-old rats, intravenous (n = 7); (▲) 3-month-old rats, oral (n = 7); (○) 12-month-old rats, intravenous (n = 6); (●) 12-month-old rats, oral (n = 6).*

RESULTS

Figure 1 depicts the time course of *N*-acetylprocainamide in plasma after administration by intravenous injection and by oral gavage in 3- and 12-month-old rats. These profiles show: (*a*) higher plasma concentrations of the drug in 12-month-old animals after administration by either route; (*b*) that the ratio of oral–intravenous plasma concentrations decreased with age, suggesting a decline in the bioavailability of *N*-acetylprocainamide; and (*c*) that the rate of decline of the postabsorption distribution plasma concentration was slower in older rats, indicating a longer elimination half-life following administration of the drug by either route.

Table I summarizes the pharmacokinetic parameters for distribution and elimination of *N*-acetylprocainamide in 3-, 6-, and 12-month-old rats following intravenous administration of the drug. The extrapolated time zero plasma concentrations and the AUC values increased significantly with age. Consistent with this, there was a significant decrease (58%) in the volume of distribution, from 4.75 liter/kg at 3 months to 1.98 liter/kg at 12 months of age. There was also a significant elongation of the biological half-life (38%) and a significant decrease in the total clearance (67%) in the 12-month-old animals as compared with the 3-month-old rats. In general, the coefficients of variation in all parameters increased with age: 11–18% in the 3-month-old rats to 22–71% in the 12-month-old animals.

Table II lists the parameters describing the absorption and excretion of unchanged *N*-acetylprocainamide in 3-, 6-, and 12-month-old rats. There was essentially no significant difference in the absorption half-life among the three age-groups. The elimination half-life became significantly longer with age after either intravenous or oral administration of the drug. Also, the ratio of the half-lives (oral–intravenous) increased from 1.05 after 3 months to 1.29 after 12 months, probably impacted by the changes in the absorption of the drug in the older rats. The AUC

[1] Charles River Breeding Laboratories, Inc., Portage, Mich.
[2] Purina Rodent Chow, Ralston Purina, St. Louis, Mo.
[3] American Critical Care Laboratories, McGaw Park, Ill.
[4] Polytron Homogenizer: Brinkmann Instruments, Inc., Westbury, N.Y.

Table II—Effect of Age on Pharmacokinetics Following Intravenous and Oral Administration of *N*-Acetylprocainamide Hydrochloride in Rats [a]

Parameter	Age [b] 3 Months Oral	3 Months iv	3 Months Ratio (Oral/iv)	6 Months Oral	6 Months iv	6 Months Ratio (Oral/iv)	12 Months Oral	12 Months iv	12 Months Ratio (Oral/iv)
Absorption $t_{1/2}$, hr	0.493	—	—	0.563	—	—	0.505	—	—
Elimination $t_{1/2}$, hr	1.74	1.66	1.05	1.92	1.82	1.08	2.66	2.29	1.29
AUC, μg·hr/ml	45.2	45.3	1.01	56.2	72.6	0.835	93.5	156	0.747
X_{tot}, % of Dose	85.1	76.6	1.29	89.2	97.0	0.930	69.0	87.1	0.815
X_u, % of Dose	77.1	76.4 [c]	1.04 [c]	83.6	92.2	0.918	64.3	77.9	0.812
X_f, % of Dose	7.99	10.1	0.674	5.65	4.75	1.29	6.83	6.81 [d]	1.19

[a] The dose was 100 mg/kg. [b] The sample size was 7 at 3 and 12 months and 11 at 6 months. [c] Without one unusually high value ($n = 6$). One urine sample after intravenous injection was very low, presumably due to incomplete collection. [d] $n = 6$.

Table III—Effect of Age on Tissue Distribution Following Intravenous Administration of *N*-Acetylprocainamide in Rats [a]

Tissue	Drug Concentration [b] 3 Months Mean	3 Months *SD*	6 Months Mean	6 Months *SD*	12 Months Mean	12 Months *SD*
Plasma	34.7	5.24	37.8	2.31	43.6	5.44
Liver	83.0	3.00	82.0	4.55	197	12.7
Heart	76.0	5.00	108	12.7	101	8.67
Kidney	294	90.0	299	47.9	528	256
Liver–Plasma Ratio	2.44	0.390	2.12	0.211	4.55	0.552
Heart–Plasma Ratio	2.24	0.370	2.80	0.208	2.33	0.0932
Kidney–Plasma Ratio	8.34	1.27	7.72	0.900	12.0	5.50

[a] The dose was 100 mg/kg. The animals were sacrificed 0.5 hr after receiving the drug. [b] The concentration is expressed as μg/g except for plasma, which is reported as μg/ml. The sample size is 4 at all time intervals.

values increased with age after intravenous and oral administrations. The ratio of the oral AUC to intravenous AUC decreased from 1.01 after 3 months to 0.747 after 12 months, showing a 25% decrease in bioavailability. Consistent with this finding, the oral–intravenous ratio of the percentage of unchanged *N*-acetylprocainamide excreted in the urine (X_u) also showed a decrease (from 1.04 to 0.812), a change of 22%. The oral–intravenous ratio of the amount eliminated in the feces (X_f), however, increased from 0.674 to 1.19 (a change of 77%), which might indicate poor GI absorption in the older rats.

Table III summarizes the effect of age on the distribution in heart, liver, and kidneys following intravenous administration of *N*-acetylprocainamide in rats. There was a significant increase in the tissue concentrations with increasing age, which is consistent with a decrease in the percentage of lean body mass in older rats. The tissue–plasma concentration ratios for liver and kidneys increased significantly ($p < 0.05$, Student's t test) after 12 months. The heart–plasma concentration ratios remained unchanged.

DISCUSSION

This study was conducted in conjunction with a long-term oncogenicity study of *N*-acetylprocainamide in rats. The goal was to determine the age-related changes in the pharmacokinetics of absorption, distribution, and elimination of the drug, which will allow a better understanding of the toxicological effects. For example, if there is a decrease in the GI absorption of the drug, the plasma concentration will decrease accordingly and, thus, a lesser exposure of tissues and organs to the drug will be expected. The opposite situation, however, may occur if the elimination is diminished. In this case, the plasma concentrations will be elevated, which may lead to augmentation of the pharmacological and toxicological response.

Consistent with previous findings in rats (7–9), *N*-acetylprocainamide was found to be: (*a*) primarily eliminated unchanged in the urine (Table II) by an active renal process in rats; (*b*) eliminated in the feces by biliary excretion to a small extent with the remainder eliminated in the urine, presumably after biotransformation to more polar compounds; (*c*) rapidly distributed in the body showing a higher affinity for heart, kidney, and liver tissues than plasma proteins; and (*d*) rapidly and completely absorbed from oral solution in young rats. These parameters were determined repeatedly in the same rats over a period of 12 months.

The data observed in this study show that the rate of absorption of *N*-acetylprocainamide from the GI tract is not age dependent. Similar results have been reported for intestinal absorption of sulfamethazole, paracetamol, amino acids, and glucose (10–14). The data from the present study, however, also indicate that the extent of absorption of *N*-acetylprocainamide (as reflected by the decrease in the oral–intravenous ratios of AUC values and the amounts of unchanged drug excreted in the urine) decreased significantly in the older rats. The fact that the GI blood flow diminished significantly would suggest that the rate of drug absorption should be affected proportionally. These conflicting results, however, may be due partially to the effect of changes in gastric pH, permeability of the GI wall, gastric emptying, and GI motility and, in part, to the simplified pharmacokinetic model used to analyze the data. In any case, the lower bioavailability did not result in a decrease in plasma concentrations of *N*-acetylprocainamide. The elimination rate and the clearance of the drug declined to a greater extent, and this presumably caused a pronounced accumulation of the drug in the body.

The age-related changes in the pharmacokinetic parameters obtained in this study are consistent with the age-related changes in other physiological parameters (2), *e.g.*, significant diminution in renal function in older rats (15, 16). Yates and Hiley (2) reported several hemodynamic parameters in young-adult (3–4 months) and middle-aged rats (11–12 months). Table IV summarizes some of these parameters as well as

Table IV—Effect of Age on Tissue Blood Flow and Related Pharmacokinetic Parameters of *N*-Acetylprocainamide

Parameters	Young Adult Rats 3–4 Months n	Young Adult Rats 3–4 Months Mean	Young Adult Rats 3–4 Months *SD*	Middle-Aged Rats 11–12 Months n	Middle-Aged Rats 11–12 Months Mean	Middle-Aged Rats 11–12 Months *SD*	Ratio of Means Middle-Aged/ Young Adult
Physiological [a]							
Cardiac index, ml/min/kg	10	210	63.2	10	123	34.8	0.586
Heart blood flow, ml/min	10	4.26	1.71	10	3.74	2.59	0.878
Liver blood flow [b], ml/min	10	0.13	0.063	10	0.09	0.032	0.692
Kidney blood flow, ml/min	10	5.70	1.26	10	3.00	1.26	0.562
Hepatosplanchnic [c], ml/min	10	1.10	0.32	10	0.44	0.095	0.400
Pharmacokinetics							
Volume of distribution, ml/kg	7	4750	530	7	1980	493	0.417
Total clearance, ml/min/kg	7	33.5	5.00	7	11.1	7.90	0.330
Renal clearance, ml/min/kg	7	22.2	7.87	6	7.13	1.55	0.322
Nonrenal clearance, ml/min/kg	7	11.3	9.42	6	5.02	2.88	0.444
AUC Ratio (Oral/iv)	7	1.01	—	7	0.747	—	0.740
X_u Ratio (Oral/iv)	6	1.04	—	6	0.841	—	0.809

[a] Physiological parameters taken from Ref. 2. [b] Hepatic artery. [c] Hepatic artery, spleen, pancreas, and GI tracts.

pharmacokinetic parameters, which might have been impacted directly by the physiological changes. There were significant decreases in the cardiac index (41%), hepatic blood flow (31%), renal blood flow (44%), and GI tract blood flow (60%) in older animals. These changes may account for the decreased renal clearance (68%), total clearance (67%), volume of distribution (57%), and bioavailability (25%). The renal clearance values were 3.9 and 2.4 times larger than the respective renal blood flow in young-adult and middle-aged rats indicating a significant active renal secretion of *N*-acetylprocainamide, consistent with previous findings (9). The nonrenal clearance values were 82 and 52 times larger than the respective hepatic blood flow in young-adult and middle-aged rats, indicating a combination of active biliary secretion and biotransformation of the drug in the liver. The decrease in the volume of distribution might have been due also to a change in body composition in the older animals. While the fatty tissue and skin account for a larger percentage of the body weight in older animals, the percentages of lean body mass and body water decrease.

The distribution of *N*-acetylprocainamide in the liver and kidneys was also affected by age. The liver–plasma and kidney–plasma concentration ratios increased with age (86 and 44%, respectively). This elevation of the drug level in the organs seems to be inversely proportional to the decrease in liver and kidney blood flow (31 and 44%, respectively) in the older rats. The drug accumulation in the organs of the older rats probably is caused by: (*a*) higher plasma levels of *N*-acetylprocainamide (initial concentrations of 19 and 46 μg/ml in 3- and 12-month-old animals, respectively); (*b*) the diminution in the blood flow to the organs (the redistribution of *N*-acetylprocainamide from the tissues was affected to a greater extent by this than by the actual distribution of the drug in the organs); and (*c*) changes in the composition of the liver and kidney tissues which favored a larger drug uptake. Interestingly, with the minor change in heart blood flow (12%), the heart–plasma concentration ratio did not change much with age.

In conclusion, the data show an age-dependent reduction in the bioavailability of orally administered *N*-acetylprocainamide solution in rats. The elimination of the drug, however, is impaired to a greater extent with age, which results in significant accumulations in the plasma and tissues after chronic administration. This finding indicates that in long-term toxicity testings of this and other drugs which show age-dependent pharmacokinetics, an adjustment in the chronically administered dose is essential.

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Synthesis and Antiallergenic Properties of 3-*n*-Pentadecyl- and 3-*n*-Heptadecylcatechol Esters

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Abstract □ A synthetic procedure is described for the preparation of 3-*n*-pentadecyl- and 3-*n*-heptadecylcatechols and their acetate and alaninate esters. The Wittig reagent prepared from 2,3-dimethoxybenzyltriphenylphosphonium bromide (III) was coupled with 1-tetradecanal or 1-hexadecanal to give the olefins IV and V, respectively. Catalytic reduction of IV and V followed by demethylation with boron tribromide afforded VIII and IX. The acetates were prepared using acetic anhydride and pyridine, while the alaninates were prepared using *N*-(*tert*-butoxycarbonyl)-L-alanine and dicyclohexylcarbodiimide followed by removal of the *tert*-butoxycarbonyl group with hydrogen chloride gas. The esters were active in guinea pigs in the production of tolerance and desensitization or hyposensitization to poison ivy-type contact dermatitis.

Keyphrases □ Synthesis—3-*n*-pentadecyl- and 3-*n*-heptadecylcatechols, acetate and alaninate esters □ Urushiols—poison ivy and poison oak, synthesis of saturated congeners □ 3-*n*-Pentadecylcatechol—synthesis, acetate and alaninate esters □ 3-*n*-Heptadecylcatechol—synthesis, acetate and alaninate esters

Poison ivy (*Toxicodendron radicans*), poison oak (*T. diversilobum*), and poison sumac (*T. vernix*) are the primary cause of occupational dermatitis in the United States. Other genera of the plant family Anacardiaceae with dermatogenic constituents include *Anacardium* (cashew nuts), *Semicarpus* (india ink tree), *Metopium* (poison wood), and *Mangifera* (mango). The allergenic components in most of these plants are 3-*n*-alk-(en)-yl catechols with C-15 or C-17 side chains and different degrees of unsaturation (0–3 olefinic bonds) (1–5).

Extracts of poison ivy, poison oak, and poison sumac have been used for diagnosis and prophylactic treatment of poison ivy, oak, and sumac dermatitis (6–8). However, the efficacy of these extracts in producing desensitization is questionable (9). Kligman (10) found that, in humans, only hyposensitization was possible by oral or intramuscular injection of either poison ivy oleoresin or pentadecylcatechol. Oleoresin produced hyposensitization after intramuscular injection of 2–2.5 g or after oral administration of 3.5–4.0 g in multiple doses. The hyposensitization was temporary, and the individuals regained their original sensitivity within 6–10 months after cessation of the treatment.

A previous publication (11) reported a new method for

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