tention was rapid, complete, and independent of the dosing volume up to 50 μl, which is about the limit for a rabbit eye without spillage over the lids. Presumably, the larger diameter and greater particle mass resulted in faster deposition so that the suspending vehicle was drained away independently of the particles. The possibility that the observed retention for the larger particles was due to physical obstruction of the drainage apparatus was checked by subsequent instillation of a radioactive solution of [^{67}Ga]gallium citrate. The mean drainage rate constant obtained for a 25-μl dose of this solution in the presence of the 25-μm spheres was 0.52 min^{-1}, and this value corresponds well with the normal value of 0.545 min^{-1} reported previously for the rabbit (5). Particle size clearly plays a significant role in the rate and extent of particle retention for ophthalmic suspensions.

Studies also were carried out beyond the times indicated by Fig. 1. Only the early postinstillation time intervals are shown to define the washout process clearly. Individual runs lasting several hours were performed, and the presence of particles in the conjunctival sac was demonstrated for at least 12 hr. However, studies are continuing to determine the precise kinetics of the gradual loss of particles that follows the initial washout process, particularly for the 3-μm particles. Preliminary evidence shows that blinking and the associated movement of the tear film play a major role in redistributing small particles within the ocular sac. A blink normally pulls a fresh layer of the precorneal film up from the conjunctival sac and over the corneal surface. Lighter particles are pulled up with the film, and this process leads to gradual loss *via* the drainage apparatus during normal tear turnover.

The data from these studies indicate that a lower limit probably exists for particle-size retention in the eye, in addition to the previously recognized upper limit for irritation. This evidence suggests that caution should be used regarding the extent to which the particle size is reduced for such systems and also may explain the recently documented successes of so-called "economy suspensions," systems characterized by somewhat larger particle sizes than more traditional ophthalmic microsuspensions. Presumably, the smallest particles of the distribution range of a micronized suspension are lost rapidly with the washout of the suspending vehicle and contribute minimally to the ocular drug levels. Thus, the observed *in vivo* performance of an ophthalmic suspension probably is due mainly to the larger particles in the size distribution. Further studies are being conducted to establish more definitively the role of particle size for ocular retention and the influences of suspension concentration and vehicle pH.

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Half-Life of *N*-Acetylprocainamide in Rats

Keyphrases □ Procainamide—metabolism to *N*-acetylprocainamide, half-life of *N*-acetylprocainamide in rats □ *N*-Acetylprocainamide—half-life in rats □ Antiarrhythmic agents—*N*-acetylprocainamide, half-life in rats

To the Editor:

Procainamide is eliminated from the body by renal excretion as unchanged drug and through metabolism to *N*-acetylprocainamide. This metabolite has been shown to have antiarrhythmic activity in animals (1, 2) and humans (3, 4) and is eliminated from the body by urinary excretion. Many patients receiving procainamide chronically have shown plasma levels of *N*-acetylprocainamide in excess of the unmetabolized drug (5).

A most significant therapeutic advantage of *N*-acetylprocainamide is that it does not cause development of lupus erythematosus in patients (6). Additionally, the biological half-life of *N*-acetylprocainamide in humans is more than twice that of procainamide (7, 8), which allows less frequent dosing. We showed previously that *N*-acetylprocainamide decreased the heart rate in rats when the plasma concentration was 16.8 μg/ml, which is quite similar to the therapeutic concentrations in humans (9).

Schneck *et al.* (10) investigated the disposition of procainamide and *N*-acetylprocainamide in rats and found biological half-lives of 55 and 51 min, respectively. These results are in contrast to the data obtained in our laboratory. Therefore, the purpose of this communication is to report our preliminary results showing that the half-life of *N*-acetylprocainamide is two to three times longer than that of procainamide in the same rat and that the disposition of both drugs is qualitatively similar to that in humans.

Eight male Charles River[1] rats, 250–450 g, were selected. A cannula was inserted surgically into the jugular vein of each rat 1 day before the experiment (11). Procainamide hydrochloride (75 mg/kg) and *N*-acetylprocainamide hydrochloride (86 mg/kg) were administered intravenously through the cannula in a randomized crossover design. A 3-day washout period was allowed between administration of the two drugs.

Serial blood samples (0.4 ml) were withdrawn at 0 (just before drug administration), 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 hr following dosing, and the plasma was separated immediately. Urine and feces were collected for 48 hr. The concentrations of procainamide and *N*-acetylprocainamide in plasma and urine were determined by a specific high-pressure liquid chromatographic method (12). Plasma concentrations of the unchanged procainamide and *N*-acetylprocainamide were fitted to one-and two-compartment open models, respectively, using a nonlinear re-

[1] Charles River Breeding Laboratories, Wilmington, Mass.

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Table I—Pharmacokinetic Parameters of Procainamide and *N*-Acetylprocainamide

Parameter	Rats				Humans	
	Our Study		Ref. 10			
	Procainamide	*N*-Acetylprocainamide	Procainamide	*N*-Acetylprocainamide	Procainamide[a]	*N*-Acetylprocainamide[b]
Elimination half-life ($t_{1/2}$), hr	0.66	2.13	0.92	0.85	3.5	6.0
Plasma clearance, ml/min/kg	80.7	20.7	64.0	22.0	7.99	3.09
Apparent volume of distribution, liters/kg	4.60	3.82	4.92	1.64	1.91	1.61

[a] From Ref. 7. [b] From Ref. 8.

gression analysis program available in a statistical analysis system package[2].

The biological half-life ranged from 0.54 to 0.83 hr for procainamide and from 1.72 to 2.92 hr for *N*-acetylprocainamide. The ratio of the biological half-life of *N*-acetylprocainamide to that of procainamide in the same rat averaged 3.3. Table I summarizes the values of the pharmacokinetic parameters obtained by Schneck *et al.* (10), those obtained in our study, and values reported for normal subjects.

Determination of the biological half-lives of procainamide and *N*-acetylprocainamide in the same animal, with sufficient time for elimination of the drugs from the body, allowed a more meaningful comparison of the pharmacokinetic parameters of the two drugs. The discrepancy between these results and those reported by Schneck *et al.* (10) may be due to the study design and to the method of determination of pharmacokinetic parameters. Schneck *et al.* sacrificed groups of rats and followed the blood sampling for 4 hr, which appears to be inadequate for *N*-acetylprocainamide. In our study, a distribution phase of ~1 hr was noticed when *N*-acetylprocainamide was administered intravenously. Furthermore, Schneck *et al.* (10) calculated the volume of distribution by dividing the total body clearance by the elimination rate constant, which obviously results in an underestimated value (Table I).

The results of our study were qualitatively similar to those observed in normal human subjects. The ratio of the half-lives, volumes of distribution, and body clearances of procainamide and its metabolite in these two species are similar. These results have important implications in interpretations of metabolism data from acute and chronic toxicity studies.

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Assignment of ^{13}C-NMR Spectra of Strychnine and Brucine

Keyphrases □ Alkaloids—strychnine and brucine, ^{13}C-NMR spectral analyses, chemical shifts assigned □ ^{13}C-NMR spectroscopy—brucine and strychnine, chemical shifts assigned □ Brucine—^{13}C-NMR spectral analysis, chemical shifts assigned □ Strychnine—^{13}C-NMR spectral analysis, chemical shifts assigned

To the Editor:

Singh *et al.* (1) recently reported on the ^{13}C-NMR spectroscopy of the alkaloids strychnine (I) and brucine (II). In this communication, I shall comment on the spectral data and assignments reported by these authors.

Wehrli (2, 3) previously reported on the ^{13}C-NMR spectrum of brucine. The complete assignment of the brucine spectrum (3) was accomplished by using common

Table I—Assignment of ^{13}C-NMR Spectra of Strychnine

Carbon	Ref. 1	Ref. 4	Ref. 5	Ref. 7	Ref. 6	Ref. 8
1	124.2 d	124.25 d	124.12 d	124.99 d	122.3 d	121.9 d
2	122.3 d	122.31 d	122.17 d	122.67 d	124.3 d	123.8 d
3	128.6 d	128.62 d	128.41 d	128.61 d	128.6 d	128.1 d
4	116.3 d	116.24 d	116.12 d	116.52 d	116.2 d	115.8 d
5	142.3 s	142.21 s	142.21 s	142.21 s	142.2 s	141.8 s
6	132.7 s	132.52 s	132.75 s	132.91 s	132.6 s	132.4 s
7	52.0	51.93 s	51.89 s	52.33 s	51.9 s	51.7 s
8	60.2 d	60.06 d	60.08 d	60.42 d	60.1 d	59.9[a] d
10	169.3 s	169.39 s	169.18 s	170.31 s	169.4 s	168.8 s
11	48.2	42.34[a] t	50.28 t	42.46 t	42.3[a] t	42.2 t
12	77.2 d	77.53 d	77.54 d	77.73 d	77.5 d	77.3 d
13	42.9 d	48.17 d	48.18 d	48.44 d	48.2 d	48.0 d
14	42.5 d	31.54 d	31.60 d	31.83 d	31.5 d	31.4 d
15	31.7 t	26.81 t	26.87 t	26.92 t	26.8 t	26.7 t
16	60.2 d	60.06 d	60.08 d	60.42 d	60.1 d	59.8[a] d
17	26.9 t	42.83[a] t	42.43 t	43.05 t	42.8 t	42.6 t
18	52.6	50.23 t	52.67 t	50.49 t	50.2 t	50.1 t
20	50.4	52.65 t	42.87 t	52.76 t	52.7 t	52.4 t
21	140.5 s	140.27 s	140.56 s	140.04 s	140.3 s	140.2 s
22	127.5 d	127.65 d	127.09 d	128.99 d	127.7 d	125.8 d
23	64.6 t	64.55 t	64.57 t	64.84 t	64.6 t	64.3 t

[a] Interchangeable.

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