analysis. Plasma glucose determinations were also done on all samples.

Results. Infusion of epinephrine at the rate of 0.01 μg lb min produced objective symptoms (restlessness and tachycardia) in only one patient, and most subjects were unable to note any subjective difference from the control period. Mean fasting values in normal and obese patients were nearly identical in this series of patients (Table I). It has previously been noted, however, that obese patients tend to have higher fasting NEFA levels than normals, although variable overlapping between the 2 groups has been present(3,5). Mean fasting value in normals in the present study is nearly identical with that reported by Munker in a series of 107 normal patients(5). The rise in plasma NEFA levels following epinephrine infusion ranged from 191-990 μeq l in normals, and from 61-1086 μeq l in overweight individuals. Mean rise and final level attained in each group was identical within the limits of the method. Plasma glucose levels tended to increase much more following epinephrine infusion in the obese group (avg. 30 mg %) than in normal controls (avg 13 mg %), a difference which has statistical significance ($p<0.001$).

Conclusion. These observations suggest, then, that there is no impairment in ability of fat stores in obese patients to release NEFA in response to epinephrine.

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Received March 8, 1960. P.S.E.B.M., 1960, v104.

Mydriatic Half-Life of a New Anticholinergic as Affected by Dose, Route, Quaternization.* (25749)

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It has long been recognized that clearance of many drugs from the bloodstream approximates an exponential relationship with time (1-4), presumably because rate of clearance depends upon concentration of drug in blood. By extension, if degree of pharmacologic response and its rate of disappearance are determined by concentration of the drug on receptor sites, then disappearance of response should also approximate an exponential curve. The negative reciprocal of the slope of this semi-log curve would be the biologic half-life, a very useful index of drug performance (5). Recently, we determined the influence of dose, route, and quaternization on mydriatic half-life in mice of a new tertiary ammonium anticholinergic drug, SKF 5515(6).

Methods. Adult, male, Dierolf mice, in groups of 9-12, were given varying doses i.v., s.c., or p.o. of SKF 5515, 9-methyl-3-oxo-9-azabicyclo-(3,3,1)-nonan-7-yl benzilate maleate(6), or of SKF 5516, the methobromide quaternary derivative, and were observed at intervals for mydriasis. Pupillary diameter was measured in arbitrary units (5 units ≅ 1 mm) under constant illumination, using ocular micrometer. At each interval, the geometric mean increases in pupil size for each group were plotted on semi-log graph paper and least-squares lines fitted to a linear portion of the decay curve. The least-squares equations were in the form of $M = a\ e^{kt}$, where M = change in pupillary diameter in units, a = a constant determining the extrapolated ordinate intercept, t = time in hours, k = a velocity constant in hr^{-1}, and e is the Naperian base. Apparent half-lives ($t_{½}$) in hours were then calculated(5) from $t_{½} = 0.693/k$. The "total drug effectiveness," *i.e.*, areas under time-action curves (F), were cal-

* Presented at Fed. Meetings, Chicago, Ill., April 1960.

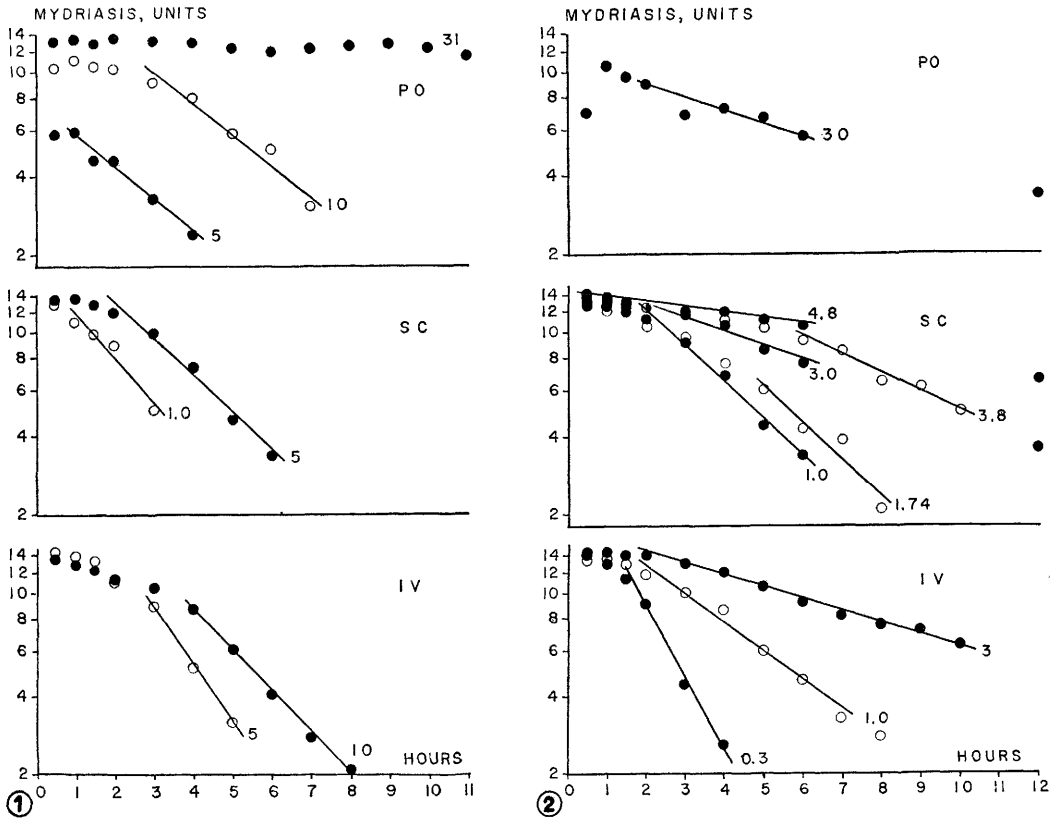

FIG. 1. Time-action curves for SKF 5515-induced mydriasis in mice. Ordinate: geometric mean change in pupillary diameter in arbitrary units; logarithmic scale. Abscissa: time after treatment in hr. Numbers adjacent to curves denote dosage in mg/kg. No. of animals/group given in Table I.

FIG. 2. Time-action curves for SKF 5516-induced mydriasis in mice. Other notes as in Fig. 1.

culated according to Dost's formula†(7) as

$$F = \int_0^\infty f(t)dt = a/k,$$

in terms of unit-hours.

Results. The effect of highest oral dose of SKF 5515 was not followed for a sufficiently long time to observe disappearance of mydriasis (Fig. 1). For other routes and doses of SKF 5515, disappearance appeared exponential. The harmonic mean half-life, weighted by number of mice and observations/group, was 2 hr (Table I). Comparison of F-values for the same doses given by different routes reveals a reasonably efficient absorption of the drug as the number of absorptive barriers is increased, *i.e.*, as route changes from i.v. to s.c. to p.o. SKF 5516 was poorly absorbed orally (Fig. 2, Table I). In fact, at highest dose, 50 out of 60 mice displayed no mydriasis; the remaining 10 were pooled and graphed. Unexpectedly, the apparent half-life following i.v. or s.c. treatment changed with dose level: $t_{1/2}$ was roughly correlated with log dose. Comparison of F-values for SKF 5516 shows little difference between parenteral routes. Comparison between SKF 5515 and SKF 5516 suggests a greater parenteral effectiveness of the latter, attributable in part to dependence of $t_{1/2}$ on dose. Orally, of course, the tertiary compound is much more effective. Nothing can be said of the relative mg potencies of the 2 compounds, because, under this experimental design, almost all

† Although Dost proved this relationship for single and double consecutive first-order reactions, it can be shown by mathematical induction to hold in general for *n*-consecutive reactions.

TABLE I. Mydriatic Responses.*

Drug	Route	Dose, mg/kg	No. mice	Total No. observations	α	k	$t_{1/2}$	F
SKF 5515	i.v.	5	12	36	43.4	.53	1.3	80
	"	10	10	50	36.7	.36	1.9	100
	s.c.	1	"	40	17.9	.40	1.7	45
	"	5	"	50	25.3	.33	2.1	75
	p.o.	5	"	"	7.7	.28	2.5	25
	"	10	"	"	22.2	.27	2.6	80
	"	31	"		Not mensurable			
SKF 5516	i.v.	.3	12	48	30.5	.62	1.1	50
	"	1.0	"	72	20.5	.25	2.8	80
	"	3.0	"	108	17.7	.10	6.6	170
	s.c.	1.0	10	50	22.9	.32	2.2	70
	"	1.74	"	40	31.8	.33	2.1	100
	"	3.0	"	50	17.1	.13	5.3	130
	"	3.8	"	"	26.9	.17	4.1	160
	"	4.8	9	72	14.2	.045	15.3	315
	p.o.	4.8	10			No effect		
	"	10.0	"			" "		
	"	30.0	10/60	70	11.2	.11	6.2	100

* See text for definitions and units of α, k, $t_{1/2}$, and F.

doses caused maximal mydriasis.

Discussion. If we assume that true mydriatic half-life of both drugs is approximately ½ hr, then the apparent increase seen with increasing doses of SKF 5516 suggests that the data to which logarithmic curves were fitted had not yet become truly exponential. This is, of course, an inherent danger in fitting physical curves to biologic data(1). In the present case, we may theorize that kinetic reactions before or after pupillary reaction are responsible, *e.g.*, an initial sequestering of SKF 5516 in peripheral tissues coupled with a slower release of the drug therefrom, a decreased penetrability of absorptive barriers resulting in penetration rates less than that expected on a monomolecular basis, or a concentration-dependent inhibition of drug removal from the eye. It is well-known that mydriasis itself physically impedes drainage of the aqueous humor by compression of the Canal of Schlemm, and that, therefore, mydriasis lasts longer than peripheral anticholinergic effects(8). This, however, cannot explain the present results, because the half-life of SKF 5515 was independent of dose and route. If we assume that the passage of SKF 5516 across absorptive membranes was hindered by the ionic charge and that ante-pupillary kinetic reactions were involved, the data become explicable, even though our assumptions may be incorrect or incomplete. Naturally, the situation is further complicated by the greater ganglion-blocking potency of SKF-5516.

The foregoing thoughts have been based on the assumption of a first-order disappearance of pharmacologic response. This may not be exactly true even though our data may fit such a hypothesis. As has been shown by others(9-11), the drug-receptor reaction may theoretically and experimentally be described by a reversible second-order reaction. In this case, if the dissociation constant for the drug-receptor complex(9) is sufficiently large in comparison to first-order rate constant for detoxication/elimination, then disappearance of pharmacologic activity will rapidly approximate the exponential curve determined by the latter constant. On the other hand, if the dissociation constant is not sufficiently large, the disappearance curve will depart from exponentiality and this departure may become detectable graphically or it may be inferred thermodynamically(10). In general, however, pharmacologic data are obtainable with insufficient accuracy to allow exact description of the underlying kinetic reactions, thus forcing us, for practical purposes, to accept data that appear to fit the simplest assumption, *viz.*, first-order disappearance, with the realization that this is in the nature of an approximation.

Realizing that a drug may have not only different affinities and intrinsic activities for different target organs(9), but, reciprocally and as a result thereof, also different apparent

half-lives, we endeavored to quantitate the time-action curves of these 2 drugs using tachycardia and salivary-suppression in mice. However, difficulties of obtaining precise time-action curves led us to abandon these experiments and to pursue our studies of these 2 drugs using different species. Current approaches also include anticholinergic Q_{10}'s in poikilotherms and simulation of experimental curves on an electronic analog computer.

Summary. The mydriatic half-life in mice of SKF 5515, a new tertiary ammonium anticholinergic drug, was independent of dose and route within the limits of experimental error. The apparent half-life of the methobromide quaternary derivative was dependent upon log dose and route, possibly as a result of decreased rate of penetration of membrane barriers by the charged ion.

I am grateful to Gordon Black for technical assistance, and to Dr. Joseph Swintosky, who initially stimulated my interest in pharmacokinetics. The 2 compounds reported above were synthesized by Dr. Charles Zirkle.

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Received March 9, 1960. P.S.E.B.M., 1960, v104.

Comparison of Heparin Induced Lipid Clearing Activity in Human Thoracic Duct Lymph and Plasma.* (25750)

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Plasma from humans and other species after intravenous heparin administration (post-heparin plasma) when incubated with lipemic serum or milky lymph, produces a decrease in optical density, or "clearing" of fat(1). Rate of decrease in optical density (clearing activity) of such lipemic substrates has been used as index of lipoprotein lipase activity in post-heparin plasma(1,2,3). We tested for clearing activity in human thoracic duct lymph to compare it with that in plasma of the same individual.

Methods. Five patients were studied. Two had disseminated cancer, 2 had Laennec's cirrhosis, and the 5th had dyspeptic symptoms following cholecystectomy 3 years previously. The thoracic duct was cannulated in the neck by technic of Linder and Bloomstrand(4). The observations were made on 1st or 2nd post-operative day. Samples of plasma were collected before and 5 and 10 minutes after administration of 10 mg of heparin to 2 patients and 50 mg to the other 3. Consecutive 10 minute samples of lymph were collected continuously before, during and after heparin administration. Furthermore 3 received intravenous heparin 1 day prior to operation, and these post-heparin plasma samples were assayed for clearing activity. Specimens were collected in chilled test tubes containing oxalate and were kept in ice bucket until centrifuged at 30,000 rpm for 15 minutes in refrig-

* This work supported by grants from U.S.P.H.S. Pancreas Study and N. Y. City Dept. of Health. Technical assistance of Amalia Martelli is gratefully appreciated.