the propranolol concentration should not exceed approximately 150 ng/ml (13, 14, 15). Since relatively high propranolol concentrations could have an effect on liver bloodflow because of its β adrenergic receptor blocking properties, which might complicate a quantitative interpretation of the results, experiments were also performed with the pharmacologically inactive dextro-isomer. The mean systemic availability after administration of dextro-propranolol at 0.2 cm from the anus was 50 and 64 % relative to a 0.25 or 0.125 mg i.v. dose, respectively. Since the maximal blood concentration (Fig. 4) and the urinary excretion pattern (Table II) of the rectal administration are similar to the values obtained with i.v. administration of 0.125 mg, this latter experiment has been taken as the reference. The results with the dextro-isomer do not indicate that with the racemate the results are considerably affected by systemic effects of the active isomer.

The rectal route may be used for the high-clearance drug propranolol as a partially non-hepatic route, but avoidance of presystemic elimination is maximal close to the anus only. Previous studies on the rectal absorption of nitroglycerine (16) and lidocaine (7, 11) and the results of this study further support the hypothesis that the venous blood supply of the upper part of the rectum of rats is connected to the portal system and that the far lower part passes directly into the general circulation. This situation is quite comparable to that found in man.

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Improved Delivery Through Biological Membranes. XVII[3]. A Site-Specific Chemical Delivery System as a Short-Acting Mydriatic Agent

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Abstract: O,O-Di(ethylsuccinyl) adrenalone was synthesized and studied as a potential short-acting mydriatic agent. This unsymmetrical tetraester has a very short hydrolytic half-life in biological fluids (approximately 1 minute). The hydrolysis produces the inactive adrenalone. On the other hand, a reduction-hydrolytic sequence resulting in adrenaline was established as the mechanism of action of these types of compounds. The facile activation to epinephrine and fast deactivation to adrenalone of the unreduced chemical delivery system results in a short-acting mydriatic agent, a potentially important diagnostic or surgical agent.

The unexpected and high ocular sympathomimetic activity of a series of diester derivatives of adrenalone (**1**) was recently described (2). While adrenalone is the synthetic precursor of epinephrine, it has very little intrinsic activity of its own (3). The simple diester derivatives of adrenalone, however, were found to produce dramatic mydriasis and decrease in the intraocular pressure following topical administration. The effect was established even with solution concentrations equi-

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valent to 0.05 % of adrenalone, while 2 % adrenalone solutions resulted in only a minimal level of mydriatic activity. On a molar basis, some of the adrenalone diesters, such as the diisovaleryl and dipivalyl derivatives, were found to be more potent (2) than the successful prodrug of epinephrine, dipivalyl epinephrine (4, 5).

This unexpected observation prompted further studies in this field in two directions: first, to determine the mechanism of this unusual finding, and second, to develop a short-acting mydriatic agent. The mechanism of action was determined to be the site-specific formation of adrenaline (6), which takes place only in the iris-ciliary body. Significant concentrations of adrenaline were found in the iris-ciliary body following administration of diisovaleryl adrenalone. While adrenalone was present in all segments of the anterior chamber as a result of ester hydrolysis, adrenaline was found *only* in the iris ciliary body. Note that adrenalone, delivered at high concentrations, will not produce mydriasis, either directly or indirectly; topical administration of adrenalone resulted only in adrenalone delivery, no adrenaline could be detected (6). Therefore, adrenalone is not reduced in the eye to the active adrenaline.

Mydriatic agents are an important class of compounds that are used to dilate the pupil during an ophthalmic examination in order to provide for a more complete examination of the fundus, the vitreous, and the periphery of the lens. These compounds are also important in various surgical procedures (vitrectomy, lens extraction, and intraocular lens implantation) where pupil dilation is a necessity (7).

This report presents *in vitro* and *in vivo* data from studies of the O,O-di(ethylsuccinyl) adrenalone (**2 a**) in ocular tissues of rabbits. This unsymmetrical tetraester represents a new type of chemical delivery system with improved biphasic solubility that allows for more efficient formulation and possibly enhanced corneal penetration. The active component, adrenaline, is formed as a result of a reduction-hydrolysis sequence. On the other hand, the limited duration of mydriatic action of this compound (due to the competing fast hydrolytic deactivation to adrenalone) reduces the time it takes for recovery of normal pupil diameter and vision.

Materials and Methods

Synthesis

The adrenalone hydrochloride was supplied by the Fluka Chemical Corporation.

O,O-di(ethylsuccinyl) adrenalone hydroperchlorate (**2 a**)
To a solution of 2.5 g of adrenalone hydrochloride (**1**) (0.01 mole) in 15 ml ethyl acetate, 15 ml ethyl succinyl chloride and 1.43 g 70 % perchloric acid were added dropwise. The mixture was refluxed for 5 hours and covered with a continuous stream of nitrogen. After cooling to room temperature and removal of solvent, a yellow oil was obtained.

Purification of this compound was accomplished using CC-7 neutral silica and a chloroform/methanol (20 $CHCl_3$: 1 CH_3-OH) mobile phase. A solid white compound was obtained, which was recrystallized from isopropyl alcohol; m. p. 95–98 °C; ^{1}H-NMR ($CDCl_3$) 1.22 (6H, t, J = 8Hz, 2XOCH$_2$C**H**$_3$); 2.50–3.0 (11H, M, 2X-COC**H**$_2$C**H**$_2$CO- and -NHC**H**$_3$), 4.10 (4H, q, J=8Hz, 2X-OC**H**$_2$CH$_3$), 4.60 (2H, brs, -COC**H**$_2$-NH-(CH$_3$)), 7.2–7.8 (3H, M, aromatic proton). IR (KBr) 1750, 1715, 1680, 1400, 1355, 1310, 1250, 1100 (br), 1005 and 800 cm^{-1}. Anal. calcd. for $C_{21}H_{27}NO_9.HClO_4$ (mw = 537.902): C, 46.89; H, 5.25; N, 2.60; Cl, 6.59; Found: C, 46.84; H, 5.23; M, 2.58; Cl, 6.57.

O,O-Bis(N,N-diethylsuccinamyl) adrenalone hydrochloride (**2d**)
To 2.5 g (0.01 moles) adrenalone hydrochloride in 30 ml pyridine, 3.67 g (0.02 moles) N,N-diethylsuccinamic acid were added. To this suspension, 100 mg dimethyl amino pyridine were added followed by 6.6 g dicyclohexyl-carbodiimide, and the mixture was stirred for twenty-four hours. The solution was then filtered and washed with methylene chloride, and 5.25 g dicyclohexyl urea was recovered from the solution.

After removal of the solvent, the greenish oil obtained was resolubilized in methylene chloride and washed twice with a 5 % hydrochloric acid solution. The organic layer was isolated and dried with Na_2SO_4, after which it was filtered and dried under vacuum.

Column chromatography was used to further purify the oil obtained. Using a stationary phase of neutral silica (Silicar CC-7) and a mobile phase of chloroform: methanol (50:1), 410 mg O,O-bis(N,N-diethylsuccinamyl)-adrenalone hydrochloride was obtained as a colorless oil; ^{1}H-NMR ($CDCl_3$) 1.0–1.5 (12H, m, 4X-C**H**$_3$), 2.5–3.6 (19H, m, N-C**H**$_3$, 4XN-C**H**$_2$-CH$_3$ and 2XNCOC**H**$_2$C**H**$_2$COO), 4.72 (2H, brs, COC**H**$_2$-NH(CH$_3$)), 7.0–7.9 (3H, m, aromatic protons); IR (neat) 1770, 1695, 1630 (broad peak), 1490, 1465, 1455, 1435, 1380, 1365, 1305, 1270, 1220, 1130 and 760 cm^{-1}. Anal. calculated for $C_{25}H_{37}N_3O_7$ (mw 258.046): C, 56.87; H, 7.25; N, 7.96; Found: C, 56.18; H, 7.20; N. 7.68.

O,O-Dicinnamoyladrenalone hydrochloride (**2 e**)
Adrenalone hydrochloride (2.5 g, 0.011 moles) was dissolved in 25 ml trifluoracetic acid and 10 ml cinnamoyl chloride was added. The reaction mixture was stirred at room temperature for 1.5 h and then treated with anhydrous ether to obtain fine white crystals. The crystals were recrystallized from isopropyl alcohol; m.p. 219–222 °C; ^{1}H-NMR (CF_3COOH) 3.08 (3H, s. NHC**H**$_3$), 3.85 (2H, s, COOC**H**$_2$NHCH$_3$), 6.5–8.0 (17H, m, 13 aromatic protons and 2XC**H**=C**H**); IR (KBr) 2750, 2660, 2400, 1740, 1720, 1680, 1620, 1590, 1420, 1300, 1250, 1230, 1190, 1100, 960 and 760 cm^{-1}. Anal. calculated for $C_{28}H_{23}NO_5.HCl$ (m. w. 477.944): C, 67.85; H, 5.06; N, 2.93; Found: C, 66.65; H, 5.15; N, 3.09.

Analytical Procedures

High pressure liquid chromatography systems with spectrophotometric (254 nm) and electrochemical detection were used for the determination of the biological stability of the adrenalone diesters **2 a–2 g**, and for the analysis of the regeneration profile of the parent catecholamine. A Spectra-Physics 3500B double piston reciprocating pump with flow feedback control served as the solvent delivery system for all analyses. The chromatographic column used for the stability studies of the diester derivative was a Beckman Ultrasphere C-18, preceded by a 6 cm precolumn which was packed with a C-8 pellicular phase. The mobile phase employed consisted of 65 % acetonitrile, 10 % tetrahydrofuran and a 0.005 M acetate buffer (pH 4.5) with a flow rate of 1 ml/min.

The analytical system used for the analysis of the time course of adrenalone production from its delivery form employed a glassy carbon electrode set at a potential of 0.7 volts, and a BioRad (5 dp.) R. P. C-18 column with a mobile phase of 2 % methanol, 0.1 M potassium phosphate pH (4.4),

70 mg/l of octylsulfonate and 0.3 g of disodium EDTA. Flow rate was 1 ml/min with a column pressure of 2100 PSI at 25°C.

In Vitro Determination of the Enzymatic Hydrolysis Rates

Human Plasma: Freshly drawn human plasma, obtained from the Civitan Regional Blood Center (Gainesville, Florida), was used in the studies of the hydrolysis kinetics of a number of adrenalone diester derivatives. The plasma was used within one week from the date it was collected.

Ten milliliters of the plasma were equilibrated at 37°C for fifteen minutes prior to the introduction of 100 μg/ml (100 mg/ml DMSO x 0.10 ml) of the diester under study. Sampling was performed at various time points by withdrawing 50 μl aliquots from the incubated plasma. Enzymatic activity was stopped and the protein precipitated by adding 200 μl acetonitrile to the 50 μl plasma and vortexing for fifteen seconds. The mixture was filtered through a BAS microfilter system (filter membrane, 0.45 μm regenerated cellulose) and centrifuged at 3000 g for ten minutes. Thirty microliter aliquots were then analyzed selectively by HPLC (254 nm) for the particular diester under investigation. The pseudo first order rate constants for the hydrolysis of the drugs were determined by linear regression of the natural logarithm of their peak height versus time plots. The half-life, correlation coefficient and rate constant were calculated for each ester studied.

Isotonic Saline pH 7.4: Isotonic saline buffer (2.5 mM phosphate pH 7.4) was equilibrated as in previous experiments at 37°C for fifteen minutes prior to the introduction of 100 μg/ml of the ethyl succinyl derivative. Periodically, 50 μl samples were withdrawn from the media and injected directly into the HPLC system at various time intervals. The kinetics were evaluated in a manner similar to that used in previous experiments.

Evaluation of the Time Course of Regeneration of Adrenalone in Ocular Tissues and Human Plasma

The ethyl succinyl derivative of adrenalone was also used in a series of experiments designed to evaluate the time course of the regeneration of adrenalone. The diester was introduced into the 10 % homogenates of cornea, iris/ciliary body tissue, undiluted aqueous humor and human plasma (75.0 μg/ml in all experiments) previously equilibrated at 37°C. Sampling was performed at various time points by withdrawing 50 μl aliquots from the media under study and adding 200 μl 0.05 M perchloric acid (with 0.05 % NaS_2O_5 antioxidant). Samples were then vortexed, filtered and centrifuged whereupon 20 μl of the filtrate was analyzed by HPLC for adrenalone with electrochemical detection by comparing the peak height to that of a standard curve.

Quantitative Studies of the Ocular Adrenergic Activity of O,O-Di-(ethylsuccinyl) Adrenalone Hydroperchlorate in the Rabbit Eye

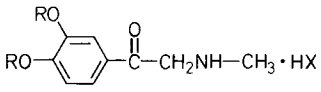
Male albino rabbits weighing 2–3 kg (Kell Farms, Archer Florida) were used in all studies. The animals were placed in fiberglass restraining cages and standard doses of 50 μl were applied to the rabbit eyes, and pupillary changes were measured in a light and temperature controlled room. The pupil diameter was measured with a manostat vernier caliper held at a constant distance at various time points. The differences in the same animals between the pupil diameter in millimeters of the eye with drug applied against the other eye with only saline instilled were recorded. All doses were formulated in 0.9 % saline solutions at concentrations equivalent to 0.04 % to 0.5 % in adrenalone.

Ocular Tissues: Tissues were obtained from NZW albino rabbits weighing 2–3 kg. Animals were sacrificed by cervical dislocation and each eye was immediately enucleated, rinsed in cold saline to remove any traces of blood and dissected. The aqueous humor was obtained by making a single puncture at the limbus using a 25 G x 5/8" needle attached to a 3 cc syringe. Once the aqueous humor was removed, the cornea and the iris/ciliary body tissues were isolated. Homogenates were prepared in isotonic saline with a potassium phosphate buffer, 2.5 mM (pH 7.4). The tissues were weighed and prepared as 10 % homogenates whereas the aqueous humor was used without dilution. The corneal tissue and the iris/ciliary body tissue were homogenized using a Tekmar SDT tissuemizer for two minutes (0°C) at a setting of 20, and then quantitatively transferred to BAS microfilters and centrifuged for ten minutes at 10000 rpm. The homogenates (aqueous humor) were then transferred to stoppered tubes and incubated for fiteen minutes. After equilibration 10 μl of 10 mg/ml (DMSO) solution of 0,0-di-(ethylsuccinyl) adrenalone hydroperchlorate were injected into 1 ml of the homogenate or aqueous humor, and at various time points 50 μl aliquots were removed and treated with 200 μl acetonitrile. Thirty microliter aliquots were then analyzed selectively by HPLC (254 nm) for the ethyl succinyl diester. The pseudo first order rate constants for the hydrolysis of the derivative were determined by linear regression of the natural logarithm of the peak height versus time plots. The half-life, correlation co-efficient and rate constant were calculated for each tissue or fluid studied.

Results and Discussion

Kinetic rate data for the enzymatic hydrolysis of a series of diester derivatives of adrenalone are shown in Table I. Since it was not possible to obtain human ocular tissues and fluids, plasma was chosen as a model system for the hydrolytic activity found in human aqueous humor. The primary difference between plasma and aqueous humor is the much larger protein content found in plasma (7.0 % total protein, vs 0.01–0.02 % in

Table I. Kinetics of the disappearance of adrenalone esters[a] in human plasma at 37°C



2

No.	R	k (min^{-1} x 10^{-1})	r	t ½ (min)
2a	$C_2H_5OCCH_2CH_2CO$-	6.68	0.9998	1.01
	O			
2b	$CH_3CH_2CH_2CO$-	3.26	0.9970	2.13
2c	$CH_3(CH_2)_4$-CO-	2.34	0.9969	2.96
2d	$(C_2H_5)_2NCCH_2CH_2CO$-	0.81	0.9993	8.55
	O			
2e	C_6H_5-CH–CH-CO-	0.69	0.9971	10.1
2f	$(CH_3)_2CHCH_2CO$-	0.36	0.9956	19.2
2g	$(CH_3)_3CCO$-	0.12	0.9991	57.8

[a]Compounds **2 b, c, f, g** were synthesized according to the method previously described (6).

aqueous humor). However, considering the ubiquitous distribution of esterase activity in a wide assortment of tissues and fluids, and the demonstration of enzymatic hydrolysis of pilocarpine and dipivalyl epinephrine in aqueous humor (8, 9), the model system appears to be reasonable.

Among the diesters tested, the straight chain compounds were the most labile, with the ethylsuccinyl diester **2a** having the shortest half-life of all compounds. The remaining ester linkages appeared to display a steric order of reactivity which has previously been demonstrated for esterase catalyzed hydrolysis of phenyl acetates (10). The effect of chain branching and the presence of a tertiary carbon in the pivalyl compound can be seen to significantly reduce the rate of hydrolysis.

Based on its facile hydrolytic cleavage, the O,O-di(ethylsuccinyl) ester (**2a**) was selected as a potential short-acting mydriatic agent.

The hydrolytic behavior of **2a** in ocular tissues, human plasma, and isotonic saline-buffer pH 7.4 is shown in Table II.

Table II. Kinetics of the disappearance of O,O-di(ethylsuccinyl) adrenalone hydroperchlorate (**2a**) in various media at 37°C

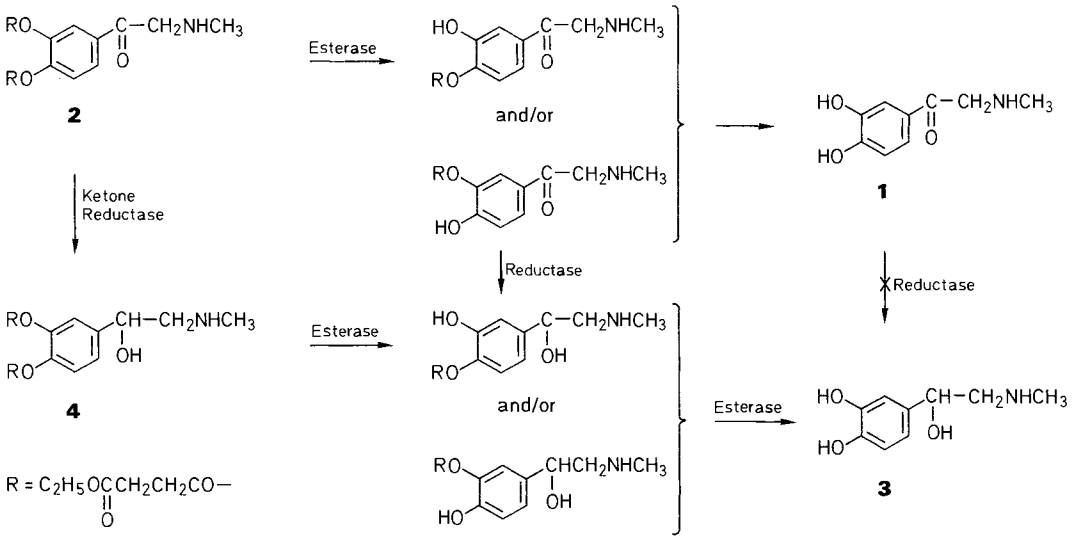
Media	k (min^{-1} x 10^{-1})	r	t ½ (min)
Iris/cilicary body 10% homogenate	7.91	0.9900	0.88
Aqueous humor	5.09	0.9995	1.36
Corneal tissue 10% homogenate	3.08	0.9929	2.25
Human plasma	6.68	0.9998	1.01
Isotonic saline pH 7.4	0.04	0.9988	173

The data indicate a high level of enzymatic activity in ocular tissues and fluids. The half-life of the disappearance of **2** was found to be the shortest in the iris-ciliary body tissue, followed by the aqueous humor and the corneal tissue. The ability of ocular tissues to metabolize a wide variety of drugs and foreign chemicals has only recently begun to receive attention. Like many other non-hepatic tissues such as the lung, kidney, and spleen, the eye possesses a powerful metabolic system for the biotransformation of exogenous substances. The ability of ocular tissues to carry out such processes can be rationalized in terms of its anatomical position and structure. The eye is a relatively isolated organ that tends to retain or concentrate compounds within itself (11). Consequently, drugs and other chemicals that are either carried to the ocular tissues by the circulating blood or come into contact with the eye directly must be detoxified in order to avert deleterious effects on the visual apparatus. Considering that the uveal tissues have the largest relative blood flow of any tissue in the body, it seems reasonable that these tissues would have the best developed drug metabolizing system found in the eye (12). This has been substantiated by a number of research groups who have found well developed endoplasmic reticulum and P-450 activity in the ciliary body (13) and have identified a number of other enzyme systems in uveal tissues associated with drug metabolism. Only relatively low levels of these various enzymes have been found in the avascular tissues of the eye (lens, cornea).

The rate of hydrolysis of the ethyl succinate diester in human plasma was found to be similar to that of the aqueous humor of rabbits. This suggests that the use of plasma as a model for hydrolytic activity in the aqueous humor was reasonable. In addition, it also helps to further establish the feasibility of using rabbits as models of human ocular systems.

The stability of the ethyl succinyl derivative in isotonic saline buffer was determined in order to contrast the rates of hydrolysis of a chemical system with those of the ocular enzymatic systems. It is apparent that the diester is fairly stable even at pH 7.4 and 37 °C. Similar to the adrenaline esters (**4**), the corresponding adrenalone esters **2** are expected to be much more stable at pH around 4.5.

The time course of the appearance of the active drug in target tissues is an important parameter that must be determined in the evaluation of a drug delivery system. The present situation, though, is more complex. First, adrenalone is not the active species; it is not a drug. The hydrolysis of the diester **2a** is, presumably, competing with the reduction-hydrolysis processes (Scheme 1) leading to the active species, epinephrine (**3**), but the fast hydrolysis-deactivation of **2a** will contribute to the desired short-acting feature of this delivery system.



Scheme 1 Transformation of the adrenalone diester (**2a**) into adrenalone (**1**) and adrenaline (**3**), respectively.

The data from such a series of experiments are shown in Table III. The results represent selective monitoring of the production of adrenalone with time in ocular tissues and fluids and human plasma. The data indicate not only a rather rapid

Table III. *In vitro* enzymatic hydrolysis of the O,O-di(ethylsuccinyl) adrenalone hydroperchlorate at 37°C

Minutes	Per cent hydrolysis in corneal tissue	iris/ciliary body	Aqueous humor	human plasma
0	0	0	0	0
3	12.7	47.6	15.4	30.0
5	28.0	76.0	28.9	44.3
7	45.1	92.7	48.1	58.0
10	61.2	100	69.8	75.1
15	85.5	–	91.5	88.9
30	94.0	–	100	100
45	100	–	–	–
60	–	–	–	–

production of adrenalone from its transport form, but also reflect the relative levels of enzymatic activity in each of the tissues and fluids studied. The mechanism of enzymatic hydrolysis of the ethyl succinyl derivative most likely involves esterase attack at the phenolic positions of the molecule. The evidence for this, although indirect, is based on the fairly similar rates of disappearance of the diester and the appearance of adrenalone. (It is possible, however, that some intramolecular cleavage of the ester anion takes place). These rates were found to be comparable in all the media tested. Since the compound contains four different ester functions, it is not surprising that the *in vitro* rate of production of adrenalone cannot be described by pseudo first order kinetics (Fig. 1).

A dose response study of the ethyl succinyl derivative **2a** was performed in order to determine the effectiveness with which this derivative was able to deliver an active pharmacon. The iris can be considered to be the target tissue of such a delivery system, and its response with time can be assumed to reflect the amount of drug present. The pupillary dose response data are summarized in Table IV and shown in Figure 2. The average pupil diameter and standard error (difference in pupil diameter between the eye with drug versus the eye with saline) are presented. The maximal mydriatic response is observed sixty minutes following topical administration. The pupil diameter returned to normal after approximately 2 hours. This is in contrast to our previous results with dipivalyl adrenalone; 3–4 hours are needed to achieve < 1 mm mydriasis, while dipivalyl adrenaline produces greater than 2 mm enlargement of the pupil even after 5 hours (2). There is also a

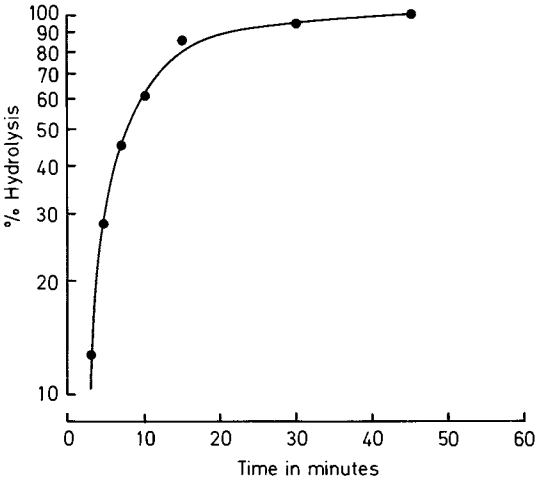


Fig. 1 Time course of appearance of adrenalone following incubation of O,O-di(ethylsuccinyl) adrenalone hydroperchlorate in 10% corneal homogenate at 37°C.

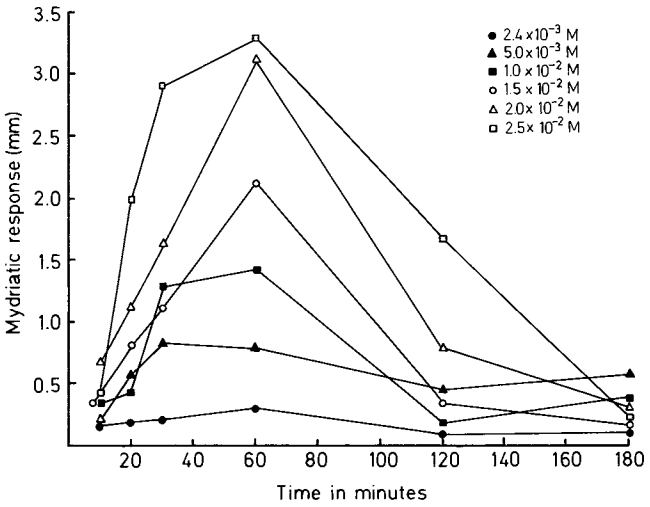


Fig. 2 Dose-response evaluation of the mydriatic activity of O,O-di-(ethylsuccinyl) adrenalone hydroperchlorate in the eyes of New Zealand white rabbits.

linear relationship between the dose and maximal effect over a portion of the dose range studied. The shortened mydriatic response with the ethyl succinyl derivative **2a** suggests that the active compound is rapidly generated and metabolized within the iris tissue. This behavior *in vivo* may provide certain advantages because of the faster recovery of normal vision.

Table IV. Mydriatic effect of O,O-di(ethylsuccinyl) adrenalone hydroperchlorate*

Time (min)	2.4×10^{-3}M	5.0×10^{-3}M	1.0×10^{-2}M	1.5×10^{-2}M	2.0×10^{-2}M	2.5×10^{-2}M
10	0.15±0.06	0.20±0.06	0.34±0.14	0.33±0.08	0.69±0.11	0.44±0.16
20	0.18±0.06	0.56±0.10	0.43±0.11	0.80±0.10	1.12±0.27	1.99±0.18
30	0.20±0.12	0.82±0.22	1.27±0.53	1.10±0.04	1.64±0.21	2.90±0.16
60	0.30±0.10	0.78±0.36	1.42±0.31	2.13±0.15	3.11±0.15	3.29±0.16
120	0.08±0.02	0.46±0.27	0.18±0.09	0.34±0.12	0.79±0.30	1.66±0.11
180	0.11±0.06	0.58±0.21	0.37±0.31	0.16±0.06	0.31±0.12	0.22±0.07

*Mydriatic response mm ($\overline{X}\beta$ S. E.) for each dose of 50 μl.

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Rectal Motility and Bioavailability

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Abstract: The contractile activity of the canine rectal wall exhibits a positive influence on the behaviour of fatty suppositories *in vivo* with respect to both spreading abilities and rate and extent of release of the readily water-soluble compound phenazone. This influence on bioavailability was marked when the drug was suspended in a large particle size (100–125 μm). When used in small particles ($< 35\mu$m), far less influence of contractile activity was found. Small particles were equivalent to coarse particles with respect to the bioavailability. The addition of colloidal silicium oxide has a marked influence on spreading and bioavailability. Enhanced rectal motility exhibits an influence on the absorption only when a coarse fraction of the drug is suspended. It was concluded that rectal motility might be a cause of variation in bioavailability of drugs from rectal suppositories. For this reason only well-trained animals should be used when bioavailability of drugs from suppositories is tested in an animal model.

The bioavailability of a drug administered rectally in fatty suspension suppositories might be influenced by various factors related to the suppository base, the drug incorporated and the rectal environment (1). Among these factors the properties of the physiological environment may play an important role. However, until now this role is of a yet unknown extent.

Especially the forces exerted on the suppository in the rectal cavity may have a marked impact on the spreading characteristics of the suppository mass. These forces result from 1) the pressure caused by the weight of the intra-abdominal organs, which may be further increased by respiratory activity and exercise, and 2) the contractions of the muscular layers in the rectal wall.

The influence of pressure caused by the weight of the abdominal organs has been recognized for valproic acid/cocoa butter suppositories (2): in sitting volunteers the maximum plasma concentration reached significantly higher levels than in supine persons. Furthermore, administration of freshly prepared and aged aminophylline suppositories to sitting volunteers caused no significant difference in bioavailability (3). Yet, the viscosity of the aged suppositories was increased considerably, probably due to the formation of high melting diamides (4).

These results lead to the hypothesis that the intraluminal rectal pressure, caused by the weight of the abdominal organs and exerted on the molten suppository mass might promote spreading of this mass, thus enhancing the bioavailability of the suspended drug.

Another factor that increases the intraluminal pressure in the rectal cavity is the contractile activity of the rectal wall. Until now, rectal pressure, caused by motility of the rectal wall, has not been studied extensively, in contrast to the numerous studies on the motility of other parts of the gastrointestinal tract (5). Most dynamic changes in the anorectum are believed to be due to the change in intra-abdominal pressure and the entry of material from the colon into the rectal cavity (6).

In order to elucidate the possible impact of rectal motility on the spreading and subsequently on the bioavailability of drugs from fatty rectal suppositories, we investigated the rectal motility pattern in dogs and the influence of this activity on the performance of suppositories.

The dog was chosen as an experimental animal, since other laboratory animals, like rats, are more difficult to train for experiments like the ones presented here. We found a considerable influence on rectal intraluminal pressure in rats, due to manipulation or even to the approach of the researcher. For this reason we concluded that the rat is not useful for experiments on rectal bioavailability.

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