high affinity for the estrogenic receptor and a suitable balance of antiestrogenic and estrogenic effects associated with induction of ovulation by IB.

In summary, the establishment of the stereochemistry of isomers of I has corrected an error in the literature, permitted a consistent explanation of the biological and physical data available on isomers of I and IV, and provided insight into the molecular mechanisms of action and direction for additional studies in this area.

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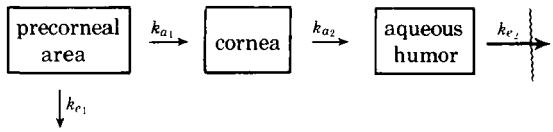
Corneal Drug Absorption: An Illustration of Parallel First-Order Absorption and Rapid Loss of Drug from Absorption Depot

Keyphrases □ Corneal drug absorption—pharmacokinetics, pilocarpine nitrate, rabbits □ Absorption, corneal—pharmacokinetics, pilocarpine nitrate, rabbits □ Pilocarpine nitrate—pharmacokinetics, corneal absorption, rabbits

To the Editor:

While studying corneal drug transport of pilocarpine nitrate, we encountered what at first appeared to be rapid permeation of drug into the cornea and aqueous humor but what, in fact, was a slow absorption process. The short time to achieve peak drug concentration in ocular tissues from an applied dose is caused by a rapid parallel elimination process from the absorption depot. This type of process was reported previously (1–3) but has not been reported as being applicable to the eye. The present communication presents evidence, using pilocarpine nitrate in rabbits, that corneal uptake of this drug and, presumably, other ocular drugs is not as rapid as the ocular tissue drug concentration *versus* time profile appears to indicate.

Ocular tissue drug level *versus* time profiles for most topically applied drugs have two common characteristics relative to the absorption phase: a low fraction of dose absorbed and a short time to achieve a peak drug level in either corneal tissue or aqueous humor (4, 5). The time of peak aqueous humor drug levels is generally in the range of 20–30 min postinstillation of drug, and the fraction of drug absorbed into the anterior chamber is usually less than 0.1 and often less than 0.01. The time of peak drug level in aqueous humor following instillation of an aqueous pilocarpine nitrate solution is around 20 min, and the fraction of dose absorbed is 0.002–0.003 (5). Figure 1 presents the corneal and aqueous humor drug levels *versus* time profiles for pilocarpine nitrate, illustrat-



Scheme I

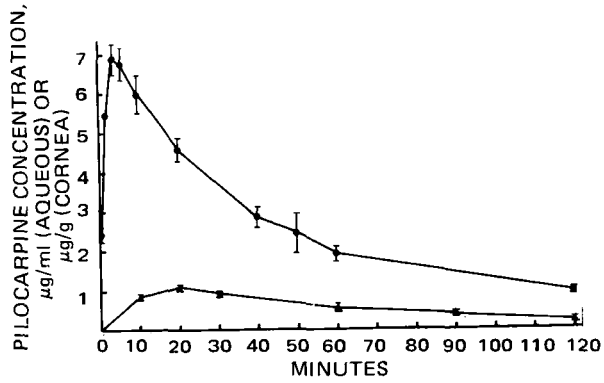


Figure 1—*Concentration of pilocarpine in rabbit aqueous humor (▲) and cornea (●) after dosing with 25 μl of 10^{-2} M pilocarpine in aqueous pH 6.24 buffer. Each point represents a minimum of six eyes, and the standard error of the mean is indicated as vertical bars.*

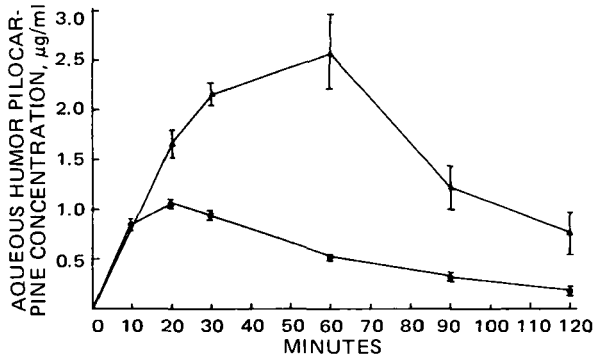


Figure 2—*Concentration of drug in rabbit aqueous humor after dosing with 25 μl of 10^{-2} M pilocarpine in aqueous pH 6.24 buffer. Key: ●, normal drainage; and ▲, drainage duct plugged (8). Each point represents a minimum of six eyes, and the standard error of the mean is indicated as vertical bars.*

ing the apparent rapid absorption.

Scheme I shows, in abbreviated form, the major pathways of disposition for pilocarpine following topical application, where k_{a_1} and k_{a_2} represent the apparent absorption constants into the cornea and aqueous humor, respectively; k_{e_1} represents elimination of drug from the precorneal area through drainage and nonproductive absorption; and k_{e_2} represents elimination of drug from the aqueous humor. This highly simplified scheme is not a complete representation for pilocarpine disposition in ocular tissues but is useful for describing limited data such as those presented in Fig. 1.

Graphical analysis of the corneal and aqueous humor drug data generates an apparent k_{a_1} of 0.8 min^{-1} and an apparent k_{a_2} of 0.08 min^{-1}. These rather large rate constants are considerably larger than published data from perfusion studies (6) and data generated from this laboratory[1] for small solute molecules.

Computer fitting the data in Fig. 1 to Scheme I generates a corneal absorption rate constant of approximately 0.006 min^{-1} for pilocarpine nitrate, which is considerably smaller than the 0.8-min^{-1} apparent rate constant that would be obtained by ignoring the parallel elimination step, *i.e.*, k_{e_1}. The parallel elimination step, consisting primarily of drainage and tear turnover, which has a first-order influence on drug concentration (7), and first-order nonproductive absorption (8) have been studied and demonstrate that loss of drug from the absorption depot is extensive with a large associated rate constant.

Evidence supporting this interpretation of the data is available from the following considerations:

1. Increasing the contact time of the drug with the cornea through the use of viscosity-inducing agents generates only nominal increases in aqueous humor drug levels in animals (9, 10) and almost none in humans (11). If the corneal absorption rate constant was indeed large, significantly higher levels would be expected. That only small increases are observed can be attributed to the large loss of drug to nonproductive absorption, *i.e.*, conjunctival absorption, as well as to the reduced, but appreciable, drainage loss of drug. Thus, long contact times are needed to overcome the small corneal uptake rate constant.

2. Pharmacokinetic equations predict that increasing the magnitude of the parallel elimination step rate constant, k_{e_1}, should shorten the time to achieve a maximum drug level with a corresponding reduction in peak height. Conversely, reducing the magnitude of k_{e_1} should prolong the peak time and increase the peak level. Patton (8) blocked the drainage ducts of rabbits prior to instilling drug solution and found that the time to achieve the maximum level of drug was lengthened from the normal 20 min to about 60 min. The shift in peak time is apparent in Fig. 2 and can only occur through a change in absorption mechanism or by fluctuating the magnitude of the parallel elimination rate constant.

Further aspects of corneal absorption, as well as the ramification of slow corneal absorption on drug delivery and vehicles, will be reported later. However, it is important to recognize, as one would intuitively expect for a sensitive tissue such as the cornea, that drug penetration is relatively slow and that the large apparent absorption rate constant, as evidenced by the short time to achieve a peak drug level, is caused by the appreciable parallel elimination step in the absorption depot.

[1] Perfusion studies with propionic and *n*-octanoic acid, where the cornea is bathed with drug solution, yield corneal uptake constants in the range of 0.001–0.002 min^{-1}.

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Elimination of Alcohol from Human Blood

Keyphrases □ Alcohol—kinetics of elimination from human blood, Michaelis–Menten equation □ Elimination kinetics—alcohol from human blood, Michaelis–Menten equation

To the Editor:

Traditionally, it has been assumed that the kinetics of elimination of alcohol from the blood of animals and humans can be described as zero order, *i.e.*, independent of the blood concentration (above about 2–3 m*M* or 0.09–0.14 mg/ml). Some investigators make this assumption simply because part of the alcohol concentration–time curve appears to be linear, while others believe that liver alcohol dehydrogenase is saturated at low concentrations of alcohol (1–5). Although some work (6–9) suggested non-zero-order elimination kinetics for alcohol in both animals and humans, the concept of zero-order kinetics persists (4, 5).

Newman *et al.* (6) gave various doses of alcohol to dogs, covering a wide range of concentration in blood, and found that there was a more rapid decrease in concentration at higher levels and doses than at the lower levels and doses. Eggleton (7) reported that Widmark's β value [the slope of the pseudolinear decline in blood alcohol concentration, expressed as milligrams of alcohol/(gram of blood × minutes)] in cats increased about 30% for every 1-mg/ml increase in alcohol concentration. If elimination kinetics were truly zero order, then the slope of the pseudolinear decline of blood alcohol concentration should be independent of dose or the C_0 value (the initial alcohol concentration at the beginning of the decline). Lundquist and Wolthers (8) showed that terminal serum alcohol concentrations in humans obeyed the integrated form of the Michaelis–Menten equation:

$$C_0 - C + K_m \ln C_0/C = V_m t \qquad \text{(Eq. 1)}$$

The corresponding Michaelis–Menten equation is:

$$-dC/dt = V_m C/(K_m + C) \qquad \text{(Eq. 2)}$$

In Eqs. 1 and 2, C_0 is the initial alcohol concentration, C is the alcohol concentration at time t, K_m is the Michaelis constant, V_m is the maximal velocity, and t is time. Studies in 10 normal subjects (8) gave an average K_m value of 2.03 m*M* (0.093 mg/ml) and an average V_m value of 0.22 mg of alcohol/ml of serum water/hr. Korsten *et al.* (10) reported a mean K_m value of 2.3 m*M* (0.11 mg/ml), estimated from terminal portions of alcohol disappearance curves derived from measurements of alcohol in whole blood from the arm veins of humans.

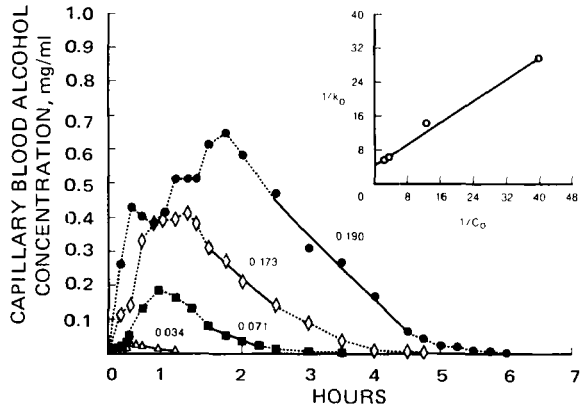

Figure 1—*Time courses of capillary blood alcohol concentrations in one of eight subjects following oral doses of 15, 30, 45, and 60 ml of 95% alcohol under fasting conditions. The absolute values of the slopes of the pseudolinear declines are shown above the declines (solid lines). Inset: double reciprocal plot of* $1/k_0$ *versus* $1/C_0$, *based on Eq. 3.*

As indicated previously, if elimination of alcohol from the blood of humans may be described by zero-order kinetics, then the absolute value of the slope of the linear decline of blood alcohol concentration, k_0, would be independent of dose or the C_0 value. If elimination kinetics are those of Michaelis and Menten, then the apparently linear segment of the alcohol concentration–time curve is actually slightly curved. Furthermore, evaluation as a linear component should disclose an increase in the absolute value of the slope with an increase in dose (or C_0) and a linear relationship between the reciprocal of the slope, $1/k_0$, and the reciprocal of the initial concentration, $1/C_0$ (11).

We followed the time course of alcohol concentrations in whole capillary blood of humans after administration of four different oral doses of alcohol in the fasting state. Capillary blood was used since: (*a*) the concentration of alcohol in capillary blood would be closer to the concentration in arterial blood than the concentration in venous blood, and the brain concentration would be determined by the concentration in arterial blood (12); (*b*) results with the Breathanalyzer are highly correlated with capillary blood alcohol concentrations (13); and (*c*) the large number of blood samples (20–40/subject/treatment) required to define adequately the entire time course makes use of capillary blood more desirable than venous blood, plasma, or serum. Alcohol was measured in 50-μl samples of capillary blood by a new head-space GLC method (14).

Eight normal male volunteers were given oral doses of 15, 30, 45, and 60 ml of 95% alcohol, made up to a volume of 150 ml with orange juice, in crossover fash-