OPTOMETRIC PHARMACOLOGY

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PREFACE

Over the last three decades, the scope of optometry has expanded to encompass many aspects of vision diagnosis and therapy. Perhaps the most profound change in optometry has been an increased emphasis on physiology, anatomy, neurobiology, and particularly on recognition of ocular and systemic disease. As a result, the optometry curriculum has been increased from three to four years in order to accommodate the increased scope of the practice and additional educational material needed to integrate this information into clinical practice.

Among the tools that have become vital to the recognition of ocular disease is the clinician's ability to use certain diagnostic pharmaceutical agents. These agents are an important part of a thorough and comprehensive eye examination. Over the last twenty years, most optometry curricula have come to include courses in general and ocular pharmacology. Since 1968, states have begun enacting legislation to allow optometrists to use diagnostic pharmaceutical agents. Most states today allow optometrists to use mydriatics, cycloplegics, and topical anesthetics for the diagnosis of ocular disease. Unfortunately, this development has not been accompanied by comprehensive textbooks that provide the optometrist with "hands-on" information necessary to the effective clinical use of these pharmaceutical agents. *Optometric Pharmacology* is designed to be a classroom text for the optometry student, a basic text for the practicing optometrist wishing to obtain D.P.A. certification, and a reference for the practicing optometrist. This book is meant to be practical rather than highly theoretical.

In addition to the many topics covered in the text itself, a comprehensive set of appendices provides up-to-date information on diagnostic agents and over-the-counter ocular preparations available to the optometrist. Our plan is to continually update this book to make it a modern text in diagnostic ocular pharmacology for the optometrist.

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Part I

Principles of Ocular Pharmacology

Chapter 1

PHARMACODYNAMICS

The clinical use of a drug is not a simple matter of application followed by a specific predetermined effect. Rather, a complex chain of possible interactions can occur, which may ultimately affect the expected outcome. To understand these interactions, it is necessary to have some background in *pharmacodynamics*, the study of the actions, effects, and interactions of drugs on the body, and in its subdiscipline, *bioavailability*, the study of the rate and extent of drug absorption. This chapter discusses methods of quantifying the drug response, including the dose–response effect, time–response effect, maximum effective dose, and minimum diagnostic dose. In addition, many of the factors that may alter drug action will be covered, such as drug characteristics, individual physiological factors (systemic and ocular), absorption, and drug reactions.

DRUG DYNAMICS

Several important concepts must be understood whenever drugs are applied. The first is the relationship between the amount of drug applied and the measured effect (Fig. 1-1). This relationship is known as the *dose-response effect*. Typically, as the drug's concentration is increased, there is a corresponding increase in effect, up to the point at which no further effect is seen. This point is identified as the *maximum effective dose (MED)*. There is no improvement in therapeutic effect beyond the MED, although the potential for a toxic response does

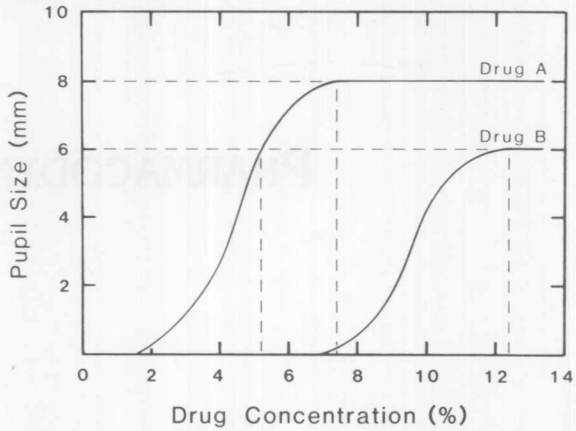

Fig. 1-1. Dose–response curves for two hypothetical mydriatics. Note that MED of drug A is about 7.5 percent, whereas that of drug B is about 12.5 percent. The maximum pupillary dilation produced by drug B is 2 mm less than that produced by drug A. The minimum diagnostic dose for either drug depends upon the pupil size required for the particular technique to be used. If, for example, a 6-mm pupil is desired, the minimum diagnostic dose for drug A is about 5 percent and that for drug B is about 12.5 percent.

increase. An understanding of the dose–response curve is necessary in choosing the correct dosage.

The dose–response curve can also be used to determine the minimum diagnostic dose. The minimum diagnostic dose is the minimum dose necessary for an adequate clinical response. This dose allows for minimum toxic effects while still obtaining the clinical effect desired. The minimum diagnostic dose is generally less than the MED, but its magnitude depends upon the clinical situation. For example, indirect ophthalmoscopy requires a larger pupil with less reactivity to light than the pupil required for direct ophthalmoscopy. The minimum diagnostic dose may therefore differ for these two procedures (Larkin et al., 1980).

Another important concept in the understanding of drug effects is the *time–response curve*, in which the effect is measured as a function of time after application of a specific concentration and volume of the drug. For example, the time–response curve for 2 percent homatropine in Figure 1-2 shows that with this mydriatic drug very little effect occurs during the first 20 minutes, but then the mydriasis begins to increase rapidly. Maximum pupil size is obtained after about 60 min-

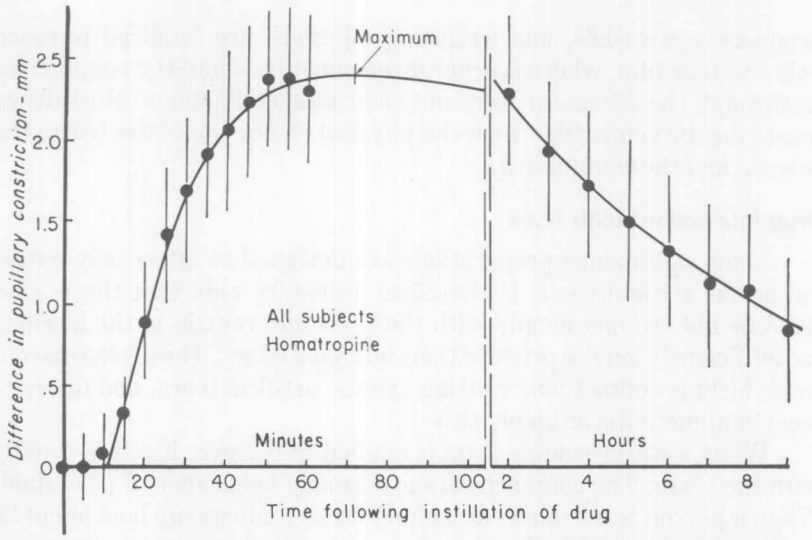

Fig. 1-2. Time–response curve for 2 percent homatropine. Little effect occurs within the first 20 minutes after instillation; then mydriasis increases until it reaches a maximum at about 60 minutes. The pupil remains maximally dilated for about 40 minutes and then begins to recover. Nine to twelve hours after instillation, the pupil returns to its original size. (From Gambill, H. D.; Ogle, K. N.; and Kearns, T. P. (1967) With permission. Mydriatic effects of four drugs determined with pupillograph. *Arch. Ophthal.* 77(6): 743. Copyright 1967, American Medical Association.)

utes and lasts for about 40 minutes, after which the pupil starts to recover. About 9–12 hours after instillation, the pupil returns to normal size.

Time–response curves describe several important aspects of a drug's effect, including the time required to achieve the maximum effect, the time required for recovery, and the magnitude of the expected maximum response for a given concentration of the drug. The time–response relationship provides the information necessary to know when to expect the desired effect and whether additional drops are needed.

BIOAVAILABILITY

Ocular Absorption

An ophthalmic pharmaceutical must be available to the part of the eye it is intended to affect, and it must be available in sufficient concentration to have the desired effect. Some drugs, such as contact lens

products, eyewashes, and irrigating solutions, are required to reach only the tear film, whereas other drugs must pass into the conjunctiva or through the cornea to carry out their intended actions. Most drugs must thus be compatible with the physical chemistry of the tears, the cornea, and the conjunctiva.

Drug Interactions with Tears

Many ophthalmic preparations are designed to affect only external ocular structures. It is therefore necessary only that these solutions be able to mix evenly with the tears and remain in the lacrimal sac sufficiently long to produce their intended effect. These pharmaceuticals include contact lens wetting agents, artifical tears, and drugs to treat conjunctivitis or blepharitis.

When a water-soluble drug is applied to the eye, it mixes rapidly with the tears. The conjunctival sac normally holds about 7 μl of fluid. When a person is not allowed to blink, it can temporarily hold about 25 μl (Fraunfelder, 1976). One drop from a standard eye dropper contains about 50–75 μl of fluid; thus, the majority of the drop that is applied is immediately lost by flowing either over the lid margin or down the nasolacrimal duct. Another cause of rapid drug loss from the external eye is the constant turnover of tears as new tears are secreted, flow over the eye, and are lost down the nasolacrimal duct. Estimates of the tear turnover rate vary between 0.66 (Patton and Robinson, 1975) and approximately 1.2 μl/min (Mishima et al., 1966; Fraunfelder, 1976).

Due to tear dilution, the concentration of the drug in the tears drops about 50 percent in the first minute and within 8 minutes to about 1/1000th of its initial concentration (Linn and Jones, 1968). As the concentration of the drug falls, the diffusion gradient forcing it into the eye is also reduced. As the tears dilute the drug, more is lost through normal tear drainage; thus, a large proportion of the drug does not remain in the eye. For example, after application of 0.1 ml of a 2 percent solution of radioactive pilocarpine in rabbits, the peak intraocular concentration was measured after 15 minutes, but even at that time, less than 1 percent of the instilled drug could be found in any ocular structure (Harris, 1968). The total amount absorbed depends upon the particular drug used.

The tears consist of three layers (Fig. 1-3). The outermost layer is an oily layer that is secreted by the sebaceous glands and acts to prevent evaporation of the underlying aqueous layer, which is produced by the lacrimal glands. Immediately under the aqueous layer is the mucoid layer secreted by the goblet cells of the conjunctiva. This mucoid layer has both "water-loving" *(hydrophilic)* and "water-fearing" *(hydrophobic)* characteristics. It thus acts as an interface between the hydro-

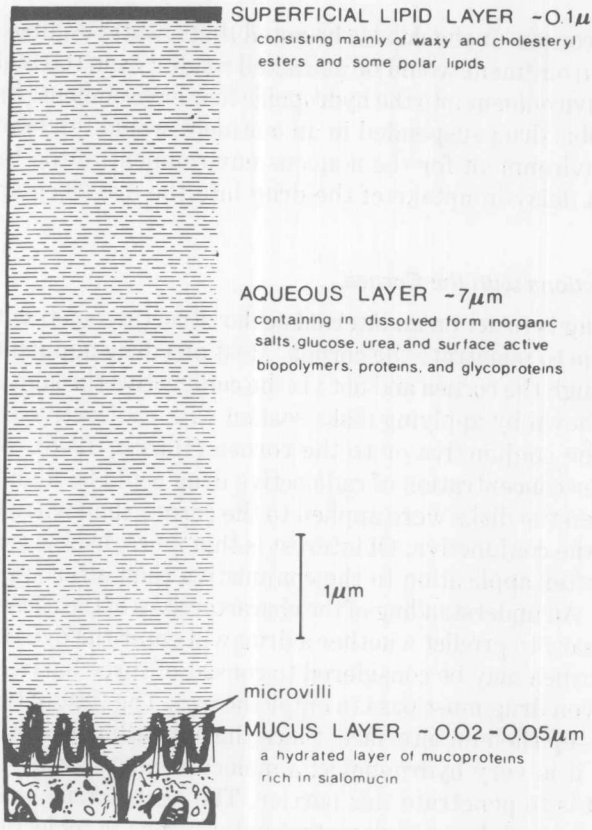

Fig. 1-3. Tear Film. The tear film consists of three layers: 1) the superficial lipid layer (hydrophobic) secreted by the Meibomian glands, 2) the aqueous layer (hydrophilic) secreted by the lacrimal glands and containing some dissolved mucin from the third layer, 3) the adsorbed mucin layer secreted by the goblet cells. (From Holly, F. J. and Lemp, M. A. (1977) Tear physiology and dry eyes. *Surv. Ophthal.* 22(2): 70. With permission.)

philic aqueous layer of the tears and the hydrophobic layer of corneal epithelial cells, allowing the tears to spread evenly over and smooth out the epithelial surface.

The vehicle in which a drug is suspended may have a considerable effect on its ability to mix with the tears and its subsequent uptake into the cornea. For example, water-soluble drugs applied as drops mix rapidly with the aqueous phase of the tears and are thus readily avail-

able to the cornea. It should also be noted that a water-soluble drug suspended in an ointment would be attracted readily from the hydrophobic ointment environment into the hydrophilic tear environment. In contrast, a hydrophobic drug suspended in an ointment would tend not to leave the lipid environment for the aqueous environment of the tears. This can cause a delay in uptake of the drug into the eye (Sieg and Robinson, 1975).

Drug Interactions with the Cornea

If a drug is to act on an internal ocular structure such as the iris, it must be able to penetrate the cornea. Most of a drug applied to the eye enters through the cornea and not via the conjunctiva through the sclera. This was shown by applying disks soaked with radioactive compounds either to the conjunctiva or to the cornea (Harris, 1968). A substantially higher concentration of radioactive drug could be found in ocular tissues when the disks were applied to the cornea than when they were applied to the conjunctiva. Of interest is that more drug was found systemically after application to the conjunctiva than after application to the cornea. An understanding of the characteristics of the cornea is therefore necessary to predict whether a drug will enter the eye readily.

The cornea may be considered to consist of three barriers through which a given drug must pass to enter the eye. The first of these layers is the tear–epithelium interface. Since the epithelium is a multicellular structure, it is very hydrophobic; a molecule must likewise be hydrophobic if it is to penetrate this barrier. The next barrier is created by the stroma, which has a high water content; thus, a molecule that dissolves readily in water will pass through the stroma with ease. The third and thinnest barrier is the endothelium. Since cells are surrounded by lipid membranes, the endothelium is also hydrophobic, but it is a much weaker barrier than the epithelium because it is only 1 cell layer thick (Harris, 1968). Fat-soluble materials pass through the endothelium most readily.

It is thus apparent that molecules with both lipid- and water-soluble characteristics have the potential to enter the eye, whereas those that are strictly water soluble do not. Many ocular pharmaceuticals derive this dual characteristic from the fact that they are either weak acids or, more commonly, weak bases. A strong acid such as hydrochloric acid immediately dissociates and gives up its hydrogen ion (proton) when it is dissolved in water. A strong base readily accepts a proton. In contrast, weak acids or bases do not readily dissociate when they are dissolved in water. When in the charged form (dissociated acid or protonated base), the molecule is water-soluble. In the uncharged form (undissociated acid or unprotonated base), it is lipid soluble.

The ability of a weak acid to give up a proton, or of a weak base to take a proton on, is dependent both upon the pH of the medium in which it is dissolved and upon an intrinsic characteristic of the weak acid or base called the pK_a.

When this pK_a value and the surrounding pH are known, the relative concentrations of the protonated and nonprotonated forms can be determined from the Henderson-Hasselbach equation:

$$pH = pK_a + \log \frac{[\text{concentration of proton acceptor}]}{[\text{concentration of proton donor}]} \tag{1.1}$$

As an example, we will consider atropine, a weak base with a pK_a of about 9.7 compounded by the manufacturer in a solution with a pH of 6.7. Let us designate the atropine as R_3N in its uncharged form and as R_3NH^+ in its charged form. This molecule will take on and release a proton from and to the environment as follows:

$$R_3N + H^+ \longleftrightarrow R_3NH^+ \tag{1.2}$$

We can use the Henderson–Hasselbach equation to determine the relative concentration of the charged and uncharged molecules:

$$6.7 = 9.7 + \log \frac{[R_3N]}{[R_3NH^+]}$$

OR

$$\log \frac{[R_3N]}{[R_3NH^+]} = -3$$

AND

$$\frac{[R_3N]}{[R_3NH^+]} = 1/1000$$

The charged (water-soluble) form is thus much more concentrated than the uncharged (lipid-soluble) form at this pH.

Let us also consider a hypothetical weak acid with a pK_a of 9.7, again compounded at pH 6.7. In this case, we will designate the hydrogen donor as RCOOH and the acceptor as $RCOO^-$. The Henderson–Hasselbach equation now becomes:

$$6.7 = 9.7 + \log \frac{[RCOO^-]}{[RCOOH]}$$

AND

$$\frac{[RCOO^-]}{[RCOOH]} = 1/1000$$

Here, the uncharged (lipid-soluble) form is more concentrated than the charged (water-soluble) form.

Given only the above information, one would expect the weak acid to be more readily absorbed into the eye than the weak base because each must first pass through the strong lipid barrier created by the epithelium. Given the low concentration of the uncharged atropine, one may at first be surprised that it is taken up at all. Other factors obviously must play a role in the absorption of atropine. For instance, in our example, the pH was set by the manufacturer at 6.7. The pH of the tears, however, is closer to 7.4. When the atropine is applied to the eye, the buffering capacity of the tears rapidly brings its pH to 7.4, thus increasing the relative concentration of the uncharged form of the drug.

Of interest is a study by Lee and Hammarlund (1974) in which it was found that instilling a buffer into the eye to raise the pH before instilling an alkaline drug substantially increased drug uptake. This is not presently an accepted clinical procedure, but it could potentially allow for the use of weaker concentrations to obtain the same effect.

A more important factor is that when atropine is applied to the eye, its concentration within the eye is zero. The diffusion gradient pulls any available uncharged atropine into the eye, thereby reducing the amount of the uncharged drug in the tears. The law of mass action then drives Equation 1.2 to the left, generating more of the uncharged molecule to be drawn into the eye.

If the epithelium is removed from the cornea, the uptake of a water-soluble drug is substantially enhanced. This can be demonstrated by the use of fluorescein, which is charged at the pH of the tears. The lipids surrounding the epithelial cells and the interdigitations between the cells create a barrier impermeable to fluorescein. When this barrier is disrupted (such as after corneal abrasion), the fluorescein can pass between the cells and into the deeper layers of the epithelium. If several layers of epithelium are lost, the fluorescein can penetrate into the stroma. Many conditions can cause epithelial loss. For example, application of an anesthetic to the cornea will chemically disrupt the interdigitations and allow penetration of greater amounts of topically applied