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# VEHICLE INFLUENCE ON OCULAR DISPOSITION OF CHLORTETRACYCLINE HYDROCHLORIDE AND CHLORAMPHENICOL IN THE ALBINO RABBIT.

M.A. Attia, H.A.El-Sourady and S.M. El-Shanawany
Demaprtment of Pharmaceutics, Faculty of Pharmacy, Assiut University, Assiut , Egypt.

## ABSTRACT

*The effect of four bases on the ocular disposition of chloramphenicol and chlortetracycline hydrochloride in the albino rabbits was investigated. It was found that the highest concentration of chlortetracycline hydrochloride in conjunctiva and cornea obtained from absorption base (A) and emulsion base (C). The absorption base (B) and emulsion base (C) were the only bases that can penetrate through the cornea into aqueous humor and irisciliary body. The emulsion base (D) give the highest chloramphenicol concentration in the conjunctiva in comparison with the other bases studied. Chloramphenicol appeared to be rapid uptake from all formulations and distributed across the cornea to the anterior chamber. Chloramphenicol uptake by conjunctiva from two emulsion bases (C and D) was more than from the other two absorption bases (A&B).*

## INTRODUCTION

Topical application of drugs to the eye is the most frequently employed route of administration for the treatment of various eye disorders. Unfortunately, the disposition of drugs administered by this route is not well understood, although it is generally agreed that the bioavailability of topically applied

drugs is extremely poor[1].

Topically applied drugs may be absorbed into a variety of ocular tissues, most notably the cornea and conjunctiva. To minimize therapy with topically applied ocular drugs, it is necessary to know the amounts and rates at which drugs are lost to these various precorneal routes and the relative contribution of each to the bioavailability.

Numerous vehicles have screened for various drugs toimprove the overall intraocular penetration of topically applied drugs. It has been shown that, depending on the interplay in physicochemical properties between the drug and the base (eye ointments or viscous gels), such preparations can significantly prolong the presence of a drug in various ocular tissues, icluding tear chamber and corneal surface without exploring the distribution patterns of a drug in the precorneal area and intraocular tissues.[2,3,4,5]

The purpose of this study was to evaluate the ability of 4 bases to affect the uptake and retention of chlortetracycline hydrochloride or chloramphenicol in the different ocular tissues (conjunctiva, cornea, aqueous humor, and iris-ciliary body).

## MATERIALS AND METHODS

**Materials:**

Four formulations containing 1% chloramphenicol and 0.5% chlortetracycline hydrochloride separately. The four bases are shown in table 1. Benzalkonium chloride, BDH; Disodium edetate, prolabo; sodium metabisulphite, BDH; Chloramphenicol and chlor-

tetracycline hydrochloride, supplied from CID . Company, Cairo, Egypt.

All bases containing 0.01% w/w banzalkonium chloride (as preservative), 0.5% w/w sodium metabisulphite (as antioxidant), and 0.3% w/w disodium edetate (as chelating agent). All formulations were used within two weeks of preparation.

Preparation of 0.5% w/w chlortetracycline hydrochloride and 1% w/w chloramphenicol eye ointments.

Chlortetracycline hydrochloride and chloramphenicol ointments were prepared in the absorption bases (A & B). The drug was incorporated into the melted base at low temperature with continuous stirring until cold in order to achieve homogenity of the drug in the base. The chlortetracycline hydrochloride and chloramphenicol ointments were prepared in Male albino rabbits, weighing 1.8-2.0 kg, were used throughout the study. They were fed a regular diet with no restrictions on food or water consumed.

Administration of Formulation:

During the experiments, all rabbits were kept in restraining boxes in a normal upright posture. Both eyes of the two rabbits were used at each time interval. Three eyes were used for determination of antibiotic and the fourth one was used as control. Individual doses, of approximately 100mg of each formulation, were weighed on an analytical balance immediately before application to the center of the lower eyelid of an albino rabbit with a microspatula. During dosing, Care was taken not to irritate the eye or touch the corneal surface with the spatula. Immediately following dosing, the lower eyelid was gently moved upward to spread the dose over the corneal surface and then released. No other manipulative technique was used during the run to distribute the formulation in the precorneal area.

emulsion ointment bases (C &D), by dissolving or suspending the drug in the aqueous phase, then warming and stirring in the melted oleoginous phase of the ointment bases.

**Aqueous Humor drug Concentration Time Profile:**

At various times postinstillation (1,2,3, and 4 hours), rabbits were sacrified with an overdose of pentobarbital sodium injected into a marginal ear vein. Eyes were immediately rinsed with distilled water and blotted with tissue, and the queous humor was aspirated from both anterior and posterior chamber. At least 100 μ l of aqueous humor was removed in each case. It is important that the elapsed time from animal sacrifice to removal of the aqueous humor sample be as short as possible.

**Conjunctival and Corneal drug concentration-time profile:**

Following sacrifice of the rabbit, its corneal and conjunctival surfaces were thoroughly rinsed with normal saline and blotted dry in order to remove any residual vehicle. The surgical procedures on each eye were completed within 5 min of sacrificing the rabbit so that any error due to redistribution of drug during the time required to obtain ocular tissue samples were minimized. Each tissue was weighed using an analytical balance. Cornea and conjunctiva was separately grinded with powdered glass in a mortar.

The ground tissues were extracted with 10 ml 0.1 N HCl in case of chlortetracycline hydrochloride and with 10 ml methyl alcohol in case of chloramphenicol. The mixture was filtered and assayed spectrophotometrically at 368 nm for chlortetracycline hydrochloride and 278 nm for chloramphenicol.

**Iris and ciliary body drug concentration-time Profile:**

Immediately after the cornea was excised, the entire iris

and ciliary body were extracted intact and care was exercised to ensure that they were free from chloroidal adhesions. The tissues were then treated in a manner identical to the cornea and coujunctiva.

## RESULTS AND DISCUSSION

Drug release from ointment bases can involve one or more of several processes, including partitioning, diffusion, dissolution and facilitated release. The facilitated release refers to the mechanical rupture of dispersed droplets in emulsion systems (4). With the bases used in this study, drug relase from the absorption bases (A & B) probably involves the penetration of water into the base, dissolution of drug and then outward diffusion to the tear pool. Such mechanism can be expected to affect the rate and duration of drug release and, in turn, the drug concentrations attained in the tears and ocular tissues . As shown in Fig. 1, the highest concentration of chlortetracycline hydrochloride was found in the conjunctiva and the cornea, the two tissues in direct contact with the tear pool, which doses of the drug in ointment bases were placed. An important feature shown in Fig. 1, is the relatively higher level of chlortetracycline hydrochloride in conjunctiva from absorption base (A) than other ointment bases all over the experimental time (4 hours). When chlortetracycline hydrochloride was topically applied to intact eyes, the highest drug concentration in conjunctiva reached 30.7 ug/100 g within four hours from absorption base (A), and the lowest reached 18.3 ug/100 g. from emulsion ointment base (D). During the first two hours after application, the difference in drug concentration in conjunctiva

from absorption base (B) and emulsion base (D) was small, but the difference increased during the lastely two hours. The absorption base (A) and emulsion base (C), by comparison were much more capable of maintaining a high drug concentration in conjunctiva and cornea over a4 hrs period. The absorption base (B) and emulsion base (C), were the only bases that can penetrate through the cornea into aqueous humor and iris-ciliary body. This can be explained on the basis that, the two bases (B & C) liberate chlortetracycline hydrochloride in a concentation higher than the epithelial surface concentration. This finding is in agreement with the results of the other work presumably this behavior[6].

Nevertheless, Fig. 1, shows that the concentration of chlortetracycline hydrochloride in the iris-ciliary body was higher than the aqueous humor, which presumably supplied the iris-ciliary body itself with the drug. This is not surprising in view of the low protein content in aqueous humor that ordinarily will bind some of the drug[7]. Eventually , the binding sites in the iris-ciliary body are saturated, there by allowing chlortetracycline hydrochloride levels in aqueous humor to increase and exceed those in the iris-ciliary body.

The data in Fig. 2 show that the uptake of chloramphenicol from the 4 ointment bases studied was greatest in the cornea, followed by conjunctiva, the aqueous humor, and the iris-ciliary body in that order. During the first 60 minutes of drug administration, the concentration of drug achieved in the conjunctiva, was not different among the 4 bases. The results, illustrated in Fig. 2, revealed that, the emulsion base(D) gave the highest chloramphenicol concentration in the conjunctiva in comparison with other bases studied. This result can be explained on the basis that in this base (D), chloramphenicol was

concentrated in the external oil phase which is miscible with conjunctiva and consequantely a rapid rate of chloramphenicol uptake by conjunctiva. The data presented in Fig. 2, suggest an extremely rapid rate of chloramphenicol uptake by conjunctiva from the two emulsion bases (C & D), than from the two absorption bases (A & B).

The absorption base (A) gave the highest drug concentration in the cornea in comparison with other ointment bases. Chloramphenicol appeared to be rapidly absorbed from all ointment formulations and is distributed across the cornea to the anterior chamber. The high concentration of chloramphenicol in aqueous humor and in iris-ciliary body is due to the continuing flux of drug from the reservoir in the corneal epithelium. The observation is in agreement with the findings of other investigators[8,9,10], regarding the presence of a depot for pilocarpine in the cornea.

From the previous results, it can be concluded that,the availability of the water-soluble chlortetracycline hydrochloride and water-insoluble chloramphenicol into the different tissues of the eye depends mainly on the composition of the ointment base, the location of the medicament into it, and the nature of the incorporated drug.

Table 1: Formulae of ointment bases

| *Composition (in gram)* | *Ointment No.* | | | |
|---|---|---|---|---|
| | *A* | *B* | *C* | *D* |
| | *Absorption bases* | | *Emulsion bases* | |
| White petrolatum | 70 | 70 | 25 | 30 |
| Liquid paraffin | 15 | 20 | 12 | - |
| Anhydrous wool fat | 15 | - | - | - |
| Cetyl alcohol | - | 10 | 25 | 15 |
| Propylene glycol | - | 10 | 25 | 15 |
| Distilled water | - | - | 33 | 30 |
| $Span_{40}$ | - | - | - | 5 |
| $Tween_{40}$ | - | - | 5 | - |

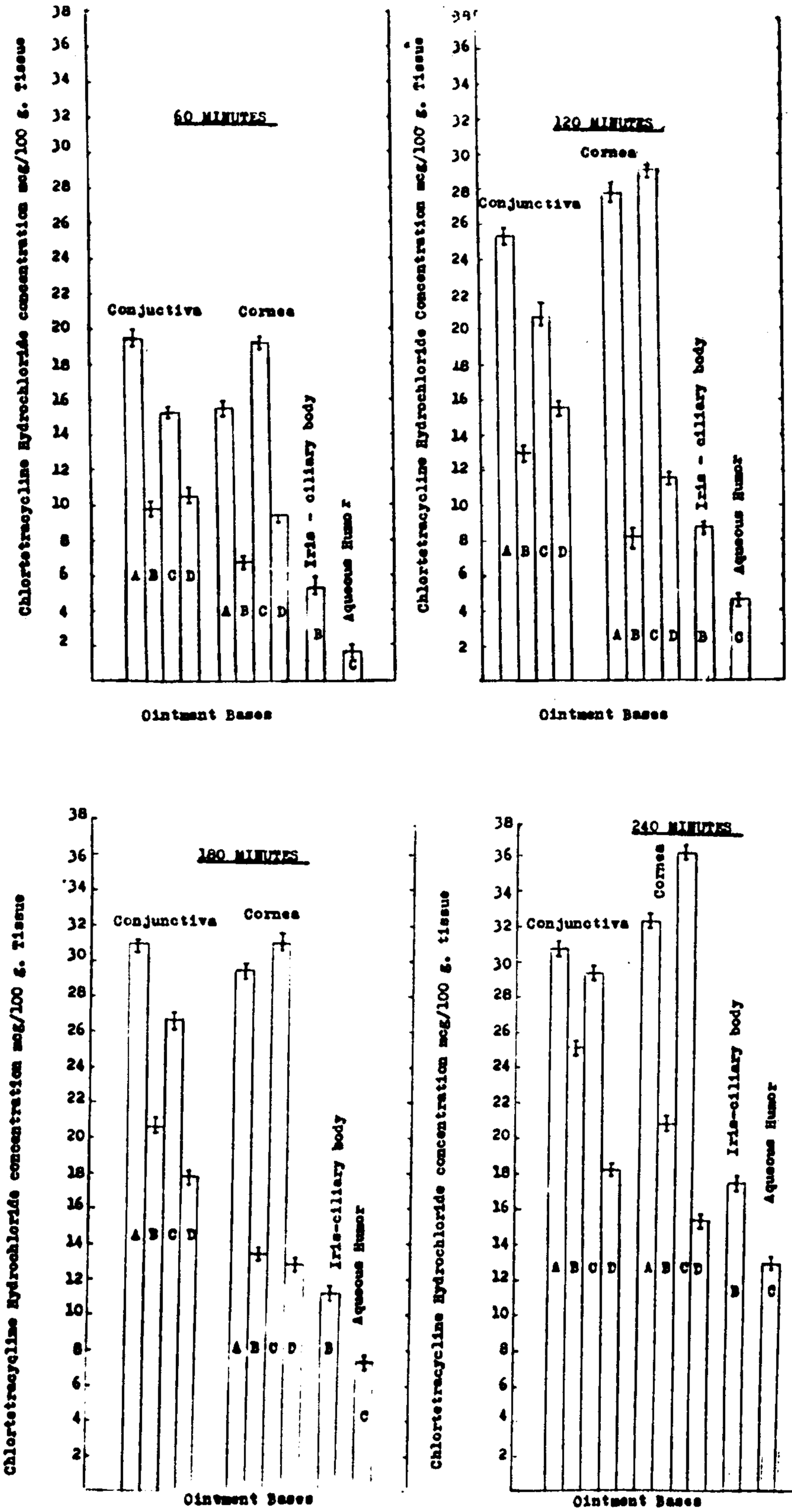


Fig. 1 Chlortetracycline hydrochloride concentration in various ocular tissues and fluids at 60, 120, 180 and 240 min. Following application of drug in various vehicles. Between 8 and 12 eyes were used for each tissue or fluid. Error bars represent standard error of the mean.

*Vehicle influence on ocular disposition of chlortetracycline hydrochloride and chloramphenicol in the albino rabbit.*

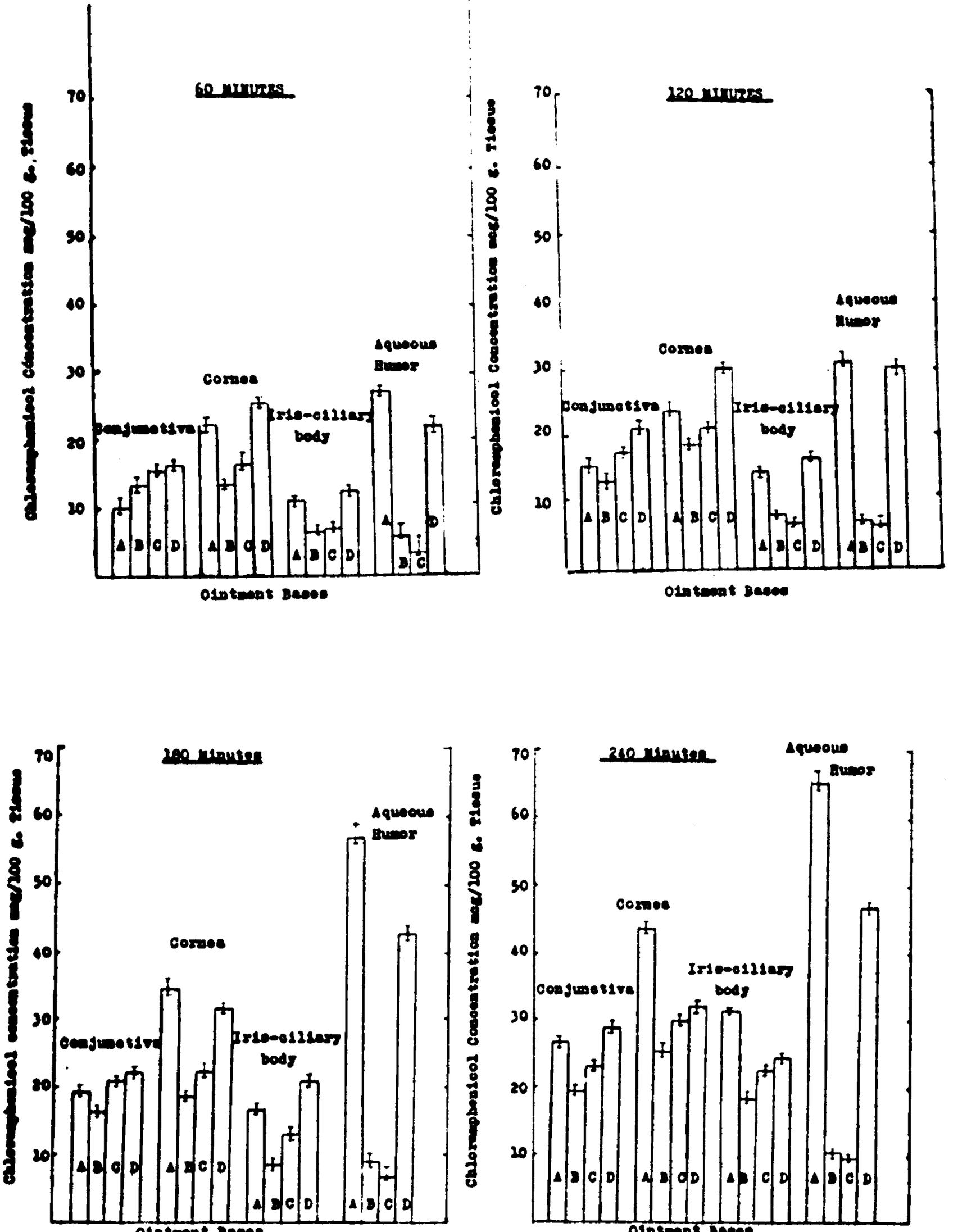


Fig. 2 Chloramphenicol Concentration in various ocular tissues and fluids at 60, 120,180 and 240 min. Following application of drug in various vehicles. Between 8 and 12 eyes were used for each tissue or fluid. Error bars represent standard error of the mean.

## REFERENCES

1) T.F. Pattoh, J.R. Robinson, J. Pharm. Sci., 65, 1295 (1976).

2) J.W. Sieg, J.R. Robinson, ibid, 64, 931 (1975)

3) J.W. Sieg, J.R. Robinson, ibid, 66, 1222 (1977)

4) J.W. Sieg, J.R. Robinson, ibid, 68, 724 (1979).

5) M.F. Saettone, B. Giannaccini, P. Savigni, J. Pharm. Pharmacol., 32, 519 (1980).

6) J.W. Sieg, J.R. Robinson, J. Pharm. Sci., 65, 1816 (1976).

7) N. Asahara, Acta Soc. Ophthalmol. Jpn., 84, 673 (1980)

8) R.F. Jones, D.M. Maurice, Exp. Eye Res., 5, 208 (1966)

9) S. Yoshida, S. Mishima, Jpn. J. Ophthalmol., 19, 121 (1975).

10) D.M. Maurice, Sight-Saving Rev., 42, 42 (1972).

# تاثير القواعد على ترسيب أيدروكلوريد الكلورتتراسيكيلين والكلورامفينكول فى أنسجة عين الأرانب

محمد على عطيه - حمدى عبد الستار الصردى سهير مصطفى الشنوانى

كلية الصيدله - قسم الصيدلانيات - جامعة أسيوط

تم دراسة تاثير أربع قواعد على ترسيب أيدروكلوريد الكلورتتراسيكلين والكلورامفينكول فى أنسجة عين الأرانب . ومن الدراسه وجد أن أعلى تركيز من أيدروكلوريد الكلورتتراسيكلين موجود فى الملتحمه ثم القرنيه وذلك من القاعده المحتويه على شمع صوف الغنم ومن القاعده القابله للأستحلاب . وكذلك وجد أن ترسيب العقارين وصل الى الأنسجه الأعمق ( السائل المائى وأهداب قزحية العين ) من القواعد المحتويه على الكحول الأسيتيلى والمستحلبه .

ومن الدراسه وجد أن القواعد المستحلبه ( ماء فى زيت ) تعطى أعلى نسبة ترسيب للكلورامفينكول فى الملتحمه .

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