FURTHER INVESTIGATIONS ON THE ACTION OF DETERGENTS ON THE EYE * †

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INTRODUCTION

It is well known that the incorporation of wetting agents in drug solutions for local application enhances the penetration of the drug into the tissues (McKee *et al.*, 1943; Bellows and Gutman, 1943; Trim and Alexander, 1946). Ginsburg and Robson (1945) have shown that when dodecyl sodium sulphate is incorporated in solutions of sodium sulphacetamide applied to the cornea, the increase in penetration is due to an action of the detergent on the corneal epithelium. The action of the detergents on the eye has been further investigated and the results are described in the present communication.

METHODS

Penetration of drugs into the eye and the isolated cornea.

The methods used have been previously described by Robson and Tebrich (1943) and Ginsburg and Robson (1945).

Drop size measurements. There is a linear relationship between drop size and the surface tension of a solution provided that the age of the surface is constant (Gaddum, 1931). The size of drops formed at a water/paraffin interface was measured as follows: Ten drops of the solutions were delivered from a 5 ml. micro-burette with the tip immersed 1 cm. below the surface of liquid paraffin B.P. in a large crystallising dish. The total volume of solution delivered was too small to alter appreciably the level of paraffin in the dish so that the drops were formed under a practically constant head of paraffin. The time for delivery of ten drops was adjusted to 200 secs. and the volume of the drops delivered was measured.

Chemical Methods. Sulphacetamide was extracted from the tissues by the method of Bellows and Chinn (1939) and was estimated by the method of Bratton and Marshall (1940).

All experiments were performed on mature rabbits of both sexes and various breeds.

RESULTS

Table I shows the results of 36 experiments on the effect of five wetting agents on the penetration of sodium sulphacetamide into the cornea. In the experiments on the isolated cornea the drug was

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applied for 15 minutes, while in those on the intact animal it was applied for 6 minutes. The results clearly show that dodecyl sodium sulphate is the most effective of the detergents tested in increasing the penetration of the sulphonamide both into the living eye and into the isolated cornea. Thus 0.25 per cent. lissapol N increases penetration by 75 per cent., while 0.1 per cent. dodecyl

TABLE I

The effect of different concentrations of wetting agents on the penetration of 10 per cent. sodium sulphacetamide into and through the cornea.

Wetting Agent	Concentration gms. per cent.	Experiment	No. of Experiments	Conc. of Sulphacetamide mg. per cent.			
				Cornea		Anterior Fluid	
				+ W.A.	Control	+ W.A.	Control
Dodecyl sodium sulphate	0.1	Isolated cornea	3	803	357	29.5	8.3
"	0.5	"	2	1300	342	38.7	8.3
"	1.0	"	2	1915	315	54.4	6.9
"	0.1	In vivo	6	349	191	29.1	6.4
"	1.0	"	1	860	200	77.2	16.1
Ammonium Lorol	1.0	Isolated cornea	2	886	478	17.6	8.9
Aerosol OT	0.1	Isolated cornea	1	434	—	6.9	—
"	0.2	"	1	451	449	8.5	7.6
"	1.0	"	3	398	365	10.2	11.6
"	1.0	In vivo	4	389	108	32.3	8.0
Lissapol N	0.1	Isolated cornea	1	430	372	4.1	3.7
"	0.25	"	1	603	346	10.3	4.0
"	0.5	"	2	850	366	7.3	5.0
"	1.0	"	2	1050	295	19.8	4.7
"	0.1	In vivo	1	114	186	4.2	8.7
"	1.0	"	1	601	155	84.9	13.3
C. 60799	1.0	Isolated cornea	2	288	323	2.3	2.6
"	1.0	In vivo	1	48.8	61.9	3.3	5.5

sodium sulphate increases penetration by 125 per cent. C 60799 has no effect on the penetration of the drug. According to Bellows and Gutman (1943) aerosol OT is highly effective. In the present experiments it had no effect on the isolated cornea, but in the intact eye 1 per cent. of aerosol OT increased the penetration by 260 per cent. compared with 330 per cent. for 1 per cent. dodecyl sodium sulphate and 288 per cent. for 1 per cent. lissapol N.

Table II shows the penetration of sodium sulphacetamide with

aerosol OT into the eyes of anaesthetised rabbits and under the same conditions into the eyes of dead and cold rabbits.

In the living animal, aerosol OT increases the penetration of the drug, but has no effect when applied to the dead animal. The

TABLE II

The penetration of sodium sulphacetamide with aerosol OT into the eyes of living and dead rabbits.

Tissue	Mg./100 gm. sulphacetamide			
	Living		Dead	
	S	S + A	S	S + A
Conjunctiva	135	416	704	568
Aqueous	8'0	32 3	3'5	4'3
Cornea	108	387	100	148
Iris	11'0	38'9	9'9	16'9
Sclera	42'0	100	42'1	30'2

The figures are the mean of 4 experiments.

S — 10% sodium sulphacetamide.

S + A — 10% sodium sulphacetamide plus 1% aerosol OT.

difference in the action of aerosol OT in the living and dead animals may be due to differences in temperature.

Two of the wetting agents, lissapol N and C 60799 (supplied by I.C.I), are non-ionic and therefore form stable solutions in the

TABLE III

The effect of age of solution on the action on the isolated cornea of lissapol N. and dodecyl sodium sulphate.

Detergent, etc.	Sulphacetamide concentration in Cornea Mg./100 gm.	
	24 hr. old solution	Fresh solution
Lissapol N. 0.5%	668	696
Dodecyl sodium sulphate 0.5% ...	653	1240
None	—	334*

* The figures are the results of one experiment except the control which is the mean of 21 experiments.

presence of high concentrations of sodium sulphacetamide, while the ionic detergents coagulate within an hour after the preparation of the solutions. The results on Table III show that 24 hours after the preparation of the solution the activity on the isolated cornea of dodecyl sodium sulphate is halved while that of lissapol N is unimpaired.

In Table IV the effect of the wetting agents on the interfacial tension at a water/paraffin interface is compared with their effect in increasing the penetration of sulphacetamide into the isolated cornea. It will be seen that the order of the effect of the detergents on the interfacial tension is aerosol, lissapol, dodecyl sodium

TABLE IV

Effect of wetting agents on the interfacial tension at a water/paraffin interface and the percentage increase in the absorption by the cornea of 10 per cent. sodium sulphacetamide.

Wetting Agent	Percentage increases in absorption by cornea	IT. Water/Paraffin Vol. of 10 drops
NIL	0	1.79
Lissapol N 0.1%	14	0.095
" 0.25%	74	0.071
" 0.5%	170	0.063
" 1.0%	290	0.060
Dodecyl Sodium Sulphate 0.1% ...	125	0.148
" " 0.25% ...	—	0.138
" " 0.5% ...	300	0.149
" " 1.0% ...	510	0.144
Aerosol OT 1.0%	10	0.044

sulphate, *i.e.*, the reverse of their effects on sulphacetamide penetration. The interfacial tension of detergent plus drug solutions is not lower than the interfacial tension of solutions of the detergent alone, suggesting that in the concentrations used in these experiments, there is no tendency for complex formation between drug and detergent at the interface.

Effects of detergents on the living cornea.

A mucoid discharge on the surface of the cornea was observed when detergents were applied in concentrations, which increased penetration by 200 per cent. or more. After the application of 0.1 per cent. dodecyl sodium sulphate for 15 minutes *in vivo* the cornea stained with fluorescein, showing that the epithelium over the whole surface of the cornea had been damaged. Examination of eyes with the slit-lamp after six hourly application of drops of detergent solutions, showed oedema of the epithelium and punctate staining of the cornea with fluorescein confined to the anterior surface. These changes were more marked with 1 per cent. than with 0.1 per cent. dodecyl sodium sulphate. One per cent. lissapol N given in the same way produced a slight discharge and very

slight conjunctival oedema, these effects disappearing in 24 hours. Two successive hourly applications of drops of 0.5 per cent. lissapol N produced no abnormalities.

Discussion

The application of drugs with detergents to the eye enables the drug to penetrate the corneal epithelium and hence therapeutic concentrations may be established more rapidly and maintained for longer periods in the posterior layers of the cornea and in the anterior chamber. Of the detergents tested, dodecyl sodium sulphate is the most effective, but lissapol N has the advantage that it forms stable solutions in the presence of high concentrations of sodium sulphacetamide.

Trim and Alexander (1946) have shown that the effect of detergents in increasing the penetration of hexyl resorcinol into ascaris is due to the formation of a complex between the drug and the detergents, and that the order of effectiveness of detergents is the same as for their effect in lowering the interfacial tension at paraffin/water interfaces. In the present work, no evidence of compound formation between the detergents and sodium sulphacetamide was found, and the order of effectiveness of detergents in increasing the penetration of sodium sulphacetamide into the cornea is the reverse of their order for the lowering of the interfacial tension at paraffin/water interfaces.

The detergent increases the penetration of sodium sulphacetamide into the cornea by an effect on the corneal epithelium, possibly by solubilising the intercellular cement. After the prolonged application of detergents the epithelial cells may become completely dispersed. Detergents should not therefore be applied to the cornea for long periods and in high concentrations, and where the epithelium is damaged they offer no advantages as they only increase penetration through an undamaged epithelium.

Summary

The effect of five detergents on the penetration of sodium sulphacetamide into the eye was investigated. Sodium dodecyl sulphate was found to be the most effective.

There is no relation between this action of the detergents and their effect on the interfacial tension at a water/paraffin interface.

Effects of detergents on the cornea are described limiting their possible clinical uses, which are discussed.

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REFERENCES

- ALEXANDER, A. E. and TRIM, A. R. (1946).—*Proc. Roy. Soc.*, **B**, **133**, 220.
 BELLOWES, J. G. and CHINN, A. (1939).—*Jl. Amer. Med. Assoc.*, **112**, 2023.
 BELLOWES, J. G. and GUTMAN, M. (1943).—*Arch. Ophthalm.*, **30**, 352.
 BRATTON, A. C. and MARSHALL, E. K. (1939).—*Jl. Biol. Chem.*, **128**, 537.
 GADDUM, J. H. (1931).—*Proc. Roy. Soc.*, **B**, **109**, 115.
 GINSBURG, M. and ROBSON, J. M. (1945).—*Brit. Jl. Ophthalm.*, **29**, 185.
 MCKEE, H. F., BAER, K. L. and SULZBERGER, M. B. (1943).—*Jl. Lab. Clin. Med.*, **28**, 1642.

 THE ARTIFICIALLY PRODUCED RETINAL PULSE

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It is a well-known phenomenon that if the disc and its neighbourhood are observed while external pressure is applied on any part of the globe, at a given moment the arteries in the disc start to pulsate. The artery empties and blanches corresponding to diastole, and fills up with blood corresponding to systole, or as Duke-Elder well puts it: "The blood column flashes across the disc." It is possible by greatly increased pressure to abolish completely the pulsation of the arteries on the disc—a procedure very unpleasant to the patient and rather dangerous. The veins on the disc are behaving in a peculiar way. When the first arterial pulsations appear on the disc, the venous pulse is accentuated, but usually does not change its character. With increased pressure on the eye, just before the arterial pulsation is completely abolished, the veins gradually become narrower, exhibit first a trickle of blood and then this trickle becomes beaded; finally the vein blanches completely. This is a summary of the general description of the artificially-produced arterial retinal pulse as given by such distinguished authorities as Baillart and Duke-Elder.

Some important details may now be added. Baillart (p. 28, ed., 1923) wrote that normally the retinal arteries look immobile. He mentions the opinions of Kummel and of Dr. Steyer, that they personally saw the pulsation of the light reflex (the retinal pulse), but not that of the central artery. I described some years ago that in red-free light one can easily see the pulse wave in nearly all primary and in some secondary branches of the central artery in a normal person, if the waves formed by those branches