NYBERG, G., AXELSON, R. & MÄRTENSSON, F. (1978).

Binding of thioridazine and thioridazine metabolites to serum proteins in psychiatric patients. *Eur. J. clin. Pharmac.*, **14**, 341–350.

ROWELL, F.J., HUI, S.M. & PAXTON, J.W. (1979). Evaluation

of a radioimmunoassay for phenothiazines and thioxanthenes using an iodinated tracer. *J. Immunol. Methods*, **31**, 159–166.

SNYDER, S.H. (1979) Receptors neurotransmitters and drug responses. *New Engl. J. Med.*, **300**, 465–472.

ADRENALINE-THYMOXAMINE INTERACTION AND INTRAOCULAR PRESSURE

In a previous publication (Rushton, (1979), I reported that a topically applied β_1 -adrenoceptor antagonist slightly augmented the ocular hypotensive response to topical adrenaline (1%) in healthy male volunteers. This result suggests that the pressure lowering effects of adrenaline are mediated by α - and/or β_2 -adrenoceptor mechanisms.

With the objective of discriminating further between these alternatives, the effects of a topically applied α -adrenoceptor antagonist on the response to adrenaline were studied. Thymoxamine, which had been previously used in ophthalmic practice and pharmacological studies (Turner & Sneddon, 1968; Mapstone, 1970; Paterson & Paterson, 1972), was selected as the α -adrenoceptor antagonist. Turner & Sneddon (1968) reported that topical administration of 0.1% thymoxamine prevented phenylephrine mydriasis, an established α -effect.

Taking this observation into account, a concentration of 0.2% thymoxamine was chosen and eight healthy male volunteers (age range 24–40 years, mean 32 years) entered a randomized, observer masked cross-over study in which the following single drop ($\approx 50 \mu\text{l}$) treatments were administered to both eyes: (1) placebo, (2) adrenaline 1% (Eppy^(R)), (3) thymoxamine 0.2%, (4) adrenaline 1% and thymoxamine 0.2% (thymoxamine was administered 5 min before adrenaline).

After inducing corneal anaesthesia with Minims benoxinate^(R), intraocular pressure (I.O.P.) was recorded using an Alcon pneumotonograph^(R) at the following time points: pre-dose, +45 min, +90 min, +180 min, +300 min and +420 min. The subjects rested in the supine position for 3 min prior to I.O.P. measurement and avoided strenuous physical exertion and alcohol for 24 h prior to and during the assessment days, which were at least 48 h apart.

One subject withdrew from the study at his own request. Data from the remaining seven subjects were analysed by an analysis of covariance. An *F* test was used to detect overall treatment differences at each time point and the *t*-test was used to test differences between pairs of treatments.

The characteristic post-adrenaline I.O.P. profile was observed and the adrenaline-placebo differences were statistically significant at the +45

Figure 1 Unadjusted mean I.O.P. levels for adrenaline 1% (■), thymoxamine 0.2% (▲) and placebo (○) treatment regimes over a 7 h post-administration period. Levels of statistical significance for the adrenaline-placebo differences are indicated thus: **P* < 0.05, ***P* < 0.01.

and +90 min time (*P* < 0.01 and < 0.05 respectively; see Figure 1). The post-thymoxamine profile did not differ significantly from placebo at any time point. Pre-treatment with thymoxamine did not materially alter the response to adrenaline (Figure 2) although the biphasic nature of the profile was slightly accentuated.

The absence of any interaction between thymoxamine and adrenaline in this study is open to two interpretations. Firstly the concentration of thymoxamine at the relevant anatomical sites may have been inadequate to competitively antagonize adrenaline. The available evidence indicates that α -adrenoceptor agonists lower intraocular pressure primarily by an increase in facility of outflow which may be mediated via vascular mechanisms in the intrascleral plexus (Langham, Simjee & Josephs, 1973; Langham & Palewicz, 1977). If this hypothesis is valid, then a concentration of an antagonist in the

Figure 2 Unadjusted mean I.O.P. levels for adrenaline 1% (■) and combined adrenaline-thymoxamine treatment regimes (●) over a 7 h post-administration period.

aqueous humour, sufficient to inhibit α -mediated mydriasis, could also be reasonably expected to antagonize α -mediated effects in the aqueous veins, although this argument may not be applicable to the afferent intrascleral vessels. The alternative interpretation of the data assumes adequate antagonist concentrations at the relevant sites and therefore it can be argued that the ocular hypotensive

response to a single drop of 1% adrenaline is not mediated via α -adrenoceptor mechanisms.

Data from a concentration response study of topical adrenaline support this latter interpretation. Langham, Kitazawa & Hart (1971) reported that concentrations of 2% or less lowered I.O.P. without producing either pupillary dilatation, an established α -effect, or increasing the facility of outflow, a putative α -effect.

Further interaction studies are required to differentiate between the possible interpretations. Such studies should involve higher topical concentrations and/or oral administration of thymoxamine. I.O.P. recording could be usefully supplemented by pupil size measurement to provide direct evidence of intraocular α -adrenoceptor blockade under the experimental conditions employed.

I gratefully acknowledge the assistance provided by the Clinical Pharmacology Unit nursing staff (Mrs J Young, Miss S. Gambles and Miss A.G. Shields) and I am indebted to Mr N.P. Barker for the statistical analysis and to the Pharmacy Department, Moorfields Eye Hospital, for formulation of the thymoxamine eye drops.

A. RUSHTON

Clinical Pharmacology Unit, Clinical Research Department, ICI Pharmaceuticals Division, Alderley Park, Nr Macclesfield, Cheshire

Received November 8, 1979

References

- LANGHAM, M.E., KITAZAWA, Y. & HART, W. (1971). Adrenergic responses in the human eye. *J. Pharmac. exp. Ther.*, **179**, 47–55.
- LANGHAM, M.E. & PALEWICZ, K. (1977). The pupillary, the intraocular pressure and the vasomotor responses to noradrenaline in rabbits. *J. Physiol.*, **267**, 339–355.
- LANGHAM, M.E., SIMJEE, A. & JOSEPHS, S. (1973). The alpha and beta adrenergic responses to epinephrine in the rabbit eye. *Exp. Eye Res.*, **15**, 75–84.
- MAPSTONE, R. (1970). Safe mydriasis. *Br. J. Ophthalm.*, **54**, 590–692.
- PATERSON, G.D. & PATERSON, G. (1972). Drug therapy of glaucoma. *Br. J. Ophthalm.*, **56**, 288–294.
- RUSHTON, A. (1979). Interaction of adrenaline and atenolol with respect to intraocular pressure. *Br. J. clin. Pharmac.*, **7**, 575–578.
- TURNER, P. & SNEDDON, J.M. (1968). Alpha receptor blockade by thymoxamine in the human eye. *Clin. Pharmac. Ther.*, **9**, 45–49.

EFFECT OF FOOD ON THE BIOAVAILABILITY OF LABETALOL

In the literature there are reports in which food reduces, delays, increases, or has no effect at all on the bioavailability of drugs (Melander, 1978). Food has been found to increase the bioavailability of propranolol and metoprolol (Melander, Danielson, Schersten & Wahlin, 1977). In this study we have

examined the influence of food on the bioavailability of the α - and β -adrenoceptor antagonist labetalol in healthy volunteers.

The subjects were four male and four female healthy volunteers aged between 21 and 45 (mean 28) years and weighing between 50 and 77 (mean 69) kg.