Effects of oral thymoxamine on blood pressure and pupillary response in normal subjects

Thymoxamine [4-(2-dimethyl-aminoethyl)-5-isopropyl-2-methylphenyl acetate] is a selective adrenergic α-receptor blocking agent. Birmingham, Rubenstein & Latimer (1969) have shown that an intravenous infusion of 0·4 mg/kg to 5 hypertensive patients reclining (3 males and 2 females) produced a statistically significant mean fall of 35 mm Hg in the systolic and 16 mm Hg in the diastolic pressure ($P < 0{\cdot}001$), but no significant effect in healthy normotensive males.

Myers, Hobbs & Irvine (1968) found that rapid intravenous injection of thymoxamine (10 mg) was accompanied by a transient fall in systemic arterial pressure with an increase in cardiac output and minimal tachycardia. The drug's α-blocking action has been shown in the eye by the antagonism of mydriasis induced by local sympathomimetic amines (Turner & Snedden, 1968).

We have investigated the effect of thymoxamine on the systolic and diastolic blood pressures and pupillary responses in healthy, normotensive individuals (3 males and 3 females, aged 20–36 years) both reclining and standing. Under double blind conditions, oral doses of thymoxamine (50 and 100 mg) and matching placebo in identical capsules were given at weekly intervals in a randomized order based on latin squares half an hour after food on 3 occasions, at the same time of day. One h after administration of the capsules, subjects' pupils were photographed five times at 1 s intervals by a Nikon single lens reflex camera with fixed magnification (Turner & Snedden, 1968). The negatives were projected onto a calibrated white ground glass screen at a magnification of ×8. Pupil diameters were measured and expressed as the transverse diameter to the nearest mm. Blood pressure recordings were taken from subjects on a couch who had rested for 5 min. Each subject, while in this position, had instilled 2 drops of a buffered solution (pH 6·8–7·2) of 5% phenylephrine into the right eye and 2 drops of 2% tyramine into the left eye. Blood pressure was recorded 2 min after the subject stood up. Measurement of blood pressure, and pupil photography were repeated at 15, 30, 45 and 60 min after instillation of the eye drops. The mean value of the five blood pressure readings from each subject was calculated together with the mean percentage mydriasis at 60 min in both pupils after oral thymoxamine treatment. There was no significant difference between treatments in systolic and diastolic pressures in the subjects reclining or in the systolic pressures of the subjects when standing, but a statistically significant fall was observed in the diastolic blood pressure of standing subjects when placebo values were compared with those after thymoxamine 100 mg (mean difference = 6·3 mm Hg, s.e. 2·24, $t = 2{\cdot}8$, $P < 0{\cdot}05$).

Resting pupil diameter was not decreased by thymoxamine, unlike antihypertensive drugs such as reserpine and α-methyldopa given by mouth (Snedden & Turner, 1969). A significant reduction in percentage mydriasis was observed in the phenylephrine-treated eye after thymoxamine 50 mg (mean difference 13·01%, s.e. = 4·17, $t = 3{\cdot}11$, $P < 0{\cdot}05$).

These results demonstrate that thymoxamine, 100 mg, in capsule form taken after food produces a significant fall in diastolic blood pressure in standing, but not reclining normal subjects. In view of the difference in response to intravenous thymoxamine of hypertensive patients compared with normal subjects (Birmingham & others, 1969), a study of the effects of oral thymoxamine in this formulation in patients with hypertension would seem to be indicated.

Changes in mydriatic response to sympathomimetic amines were small and not comparable with those obtained by local administration of thymoxamine (Turner

& Snedden, 1968). There was a large variation in the changes produced but the significant fall in phenylephrine mydriasis after thymoxamine, 50 mg, compared with the placebo value indicates that sufficient drug or metabolite reached the pupillary tissue to produce some degree of receptor blockade.

We thank the Mental Health Research Fund for providing apparatus used, and William Warner & Sons Ltd. for the capsules of thymoxamine and placebo. A. G. Arbab is supported by a Colombo Plan Scholarship.

Clinical Pharmacology Division,
Medical Professorial Unit,
St. Bartholomew's Hospital,
*London, E.C.*1, *U.K.*

A. G. ARBAB
P. TURNER

April 10, 1970

REFERENCES

BIRMINGHAM, A. T., RUBENSTEIN, D. & LATIMER, R. D. (1969). Basel 305, 4th Int. Pharmac. Congress.
MYERS, K. A., HOBBS, J. T. & IRVINE, W. T. (1968). *Cardiovascular Res.*, **4**, 360.
SNEDDEN, J. M. & TURNER, P. (1969). *Clin. Pharmac.Ther.*, **10**, 64–71.
TURNER, P. & SNEDDEN, J. M. (1968). *Ibid.*, **9**, 45–49.

The stability of glyceryl trinitrate tablets

Tablets of glyceryl trinitrate based on mannitol may be expected to retain their potency for at least two years, as long as they are protected from light and stored in cool and dry conditions (British Pharmaceutical Codex, 1968). Nevertheless, it is sometimes implied that mannitol-based tablets deteriorate rapidly, and are of little use in the relief of anginal pain unless used within a year (Laurence, 1966) or even a few months (Mathews & Turck, 1969) of preparation. Any reduction in therapeutic effectiveness will be reflected in the hypotensive response to glyceryl trinitrate (Bernstein, Friesinger & others, 1966; Carson, Wilson & others, 1969). The effectiveness of mannitol-based glyceryl trinitrate tablets has been objectively assessed by measuring the hypotensive response of healthy young medical students to the same batch of tablets over three years.

Glyceryl trinitrate tablets (0·5 mg), prepared with a mannitol base, were stored in a capped brown glass bottle on an open shelf at room temperature. No special precautions were taken to protect the tablets from light. Placebo tablets, identical in appearance but containing only mannitol, were prepared at the same time (in 1967) and were similarly stored.

Each subject was given glyceryl trinitrate and the placebo at different times, and the effect on systolic blood pressure was measured with a sphygmomanometer by auscultation. The difference between the initial blood pressure and the value 6 min after sublingual administration of the drug or placebo was recorded; from these values, the hypotensive effect of glyceryl trinitrate in each subject was calculated.

The results (Table 1) are based on measurements in 133 sitting and standing subjects. In sitting subjects, the mean decrease in blood pressure produced by the drug declined from 10 mm Hg in 1967 to 7 mm Hg in 1969; differences between