Short communications

Central and peripheral effects of propranolol and sotalol in normal human subjects

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No unequivocal central effects were found with either ±-propranolol (120 mg) or ±-sotalol (240 mg) in acute dosage in normal subjects. Subjective feelings of drowsiness and muzziness were found with sotalol and both sotalol and propranolol caused subjects to feel more troubled. These changes were not accompanied by physiological or behavioural evidence of sedation. Adequate β-adrenoceptor blockade was achieved as measured by a significant fall in pulse-rate on both active drugs but no other significant peripheral physiological changes occurred.

Since the initial report that propranolol was therapeutically effective in anxious patients (Granville-Grossman & Turner, 1966), there has been speculation about the mode of action of β-adrenoceptor blocking drugs in treating anxiety. The main possibilities are that propranolol has a central sedative effect or that it acts by peripheral β-blockade alone. Evidence for a central action has been reported in animal studies (Leszkovsky & Tardos, 1965; Bainbridge & Greenwood, 1971) and in human subjects (Gillam & Prichard, 1965; Hinshelwood, 1969). In all these studies, however, the dosage was much greater than that used in therapeutic practice. Evidence for a primary peripheral action is suggested by its effecting significant improvement in anxious patients with respect to autonomic symptoms only (Granville-Grossman & Turner, 1966), and by the absence of therapeutic effects with (+)-propranolol (Bonn & Turner, 1971) which has the same properties as the (−)-isomer with the exception of β-blockade.

Our study was designed to detect central effects in normal subjects after single doses of propranolol and sotalol. Sotalol (MJ 1999) is a β-adrenoceptor blocking agent which has been claimed to have no local anaesthetic or central effects except in very high dosage (Lish, Weikel & Dungan, 1965). It was chosen for comparison because of its relative freedom from other effects. To confirm adequate β-blockade peripheral measures were included.

Methods.—Six subjects (3 male, 3 female) aged between 19 and 29 were each tested on three weekly occasions before, one hour and three hours after taking an aqueous suspension of 120 mg (±)-propranolol (Inderal), 240 mg (±)-sotalol or placebo. Order effects were balanced by a Latin square design and double-blind procedure was used. Subjects were instructed to take no alcohol or psychotropic drugs in the 24 hours before each testing.

To sample a wide range of central effects a battery of tests was carried out on each occasion using a PDP-12A laboratory computer on-line (Bond & Lader, 1972):

1. Subjective self-rating scales. Sixteen linear (visual analogue) 100 mm scales were used to assess mood (Norris, 1971) and 8 similar scales to assess bodily symptoms. Subjects rated themselves by placing a perpendicular mark at the appropriate position on each scale.
2. Physiological measures.

(a) The electroencephalogram (EEG) was recorded from bipolar saline pad electrodes on the vertex and left temporal region during a reaction time task in which the subject was instructed to press a key in response to 32 auditory click stimuli presented at random intervals. The electroencephalogram was fed into 4 parallel band-pass filters to give four frequency ranges: (1) 2·4—4 Hz; (2) 4—7·5 Hz; (3) 7·5—13·5 Hz; (4) 13·5—26·0 Hz. Each waveband was sampled for 5 s epochs between the clicks and then rectified and averaged to yield the mean voltage.

(b) The mean evoked response was measured by averaging the 500 ms epochs of electroencephalogram following each of the 32 auditory click stimuli. The latencies and amplitudes of the main components of the evoked response were quantified.

(c) Power spectral analysis of a 40 s sample of the electroencephalogram was also performed on-line by computing the auto-cross-products function followed by a Fourier analysis to yield the power spectrum between 2 and 32 Hz.

(d) Finger tremor was measured with an Ether BLA-2 sub-miniature accelerometer (Marsden, Meadows, Lange & Wat-

son, 1967). Recording lasted for 40 s and the signals were analysed on-line to yield the power spectrum.

(e) Skin conductance (palmar sweat-gland activity) and the number of spontaneous fluctuations in conductance were measured during the reaction-time task using a standard procedure (Lader & Wing, 1966).

(f) The radial pulse rate was taken by an independent assessor after the subject had been resting for 10 minutes.

3. Psychological measures.

(a) Reaction time. This was measured as the response to each of the 32 clicks presented and the mean reciprocal calculated.

(b) Key-tapping. The subject tapped a key as quickly as possible for 60 s.

(c) Card-sorting. The subject was timed while he sorted 32 cards into 4 compartments according to the number of dots on the card, and also while he dealt blank cards into 4 equal piles ('motor' sort).

(d) Digit symbol substitution test (D.S.S.T.). This subtest of the Wechsler Adult Intelligence Schedule (W.A.I.S.) was given according to the instructions in the W.A.I.S. manual (Wechsler, 1958).

(e) Symbol copying test. The subject copied a series of symbols similar to those used in the D.S.S.T. (Kornetsky, Vates & Kessler, 1959).

Testing lasted for 30 min on each occasion. All the variables were analysed using a three way split-plot analysis of variance, drug effects being estimated against within-subject, within-occasion error variance. A

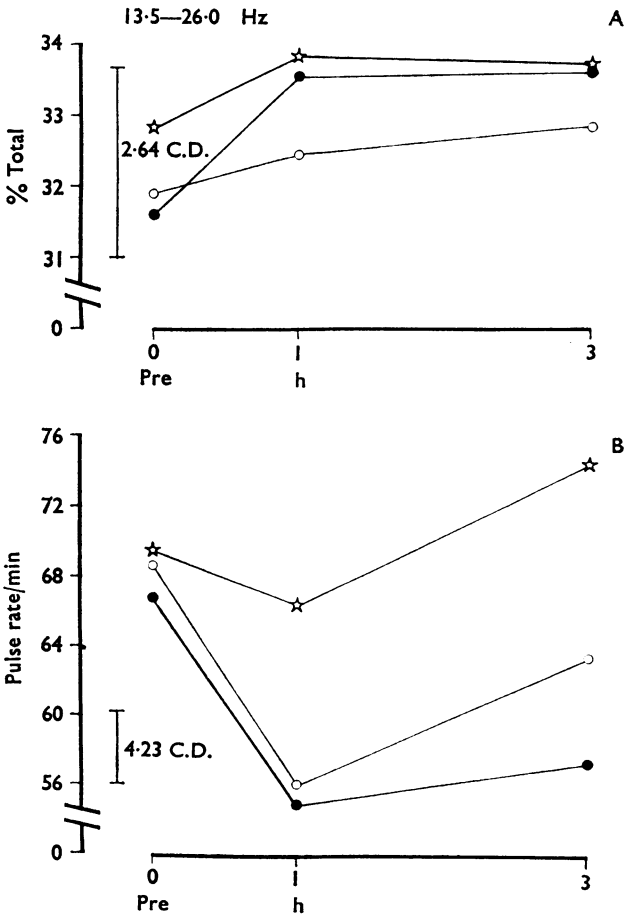

FIG. 1. Effects of propranolol, sotalol and placebo on (A) percentage of fast EEG activity and (B) pulse rate. Any two means further apart than the critical difference (C.D.) are significantly different at the 0·05 level of probability. ◈ Placebo, ● sotalol, ○ propranolol.

subsequent analysis was performed on the change scores between values after 1 and 3 h and pre-drug values. This yielded very similar results. Variables showing significant F-ratios were subjected to Tukey's test (Winer, 1962) to determine the significance of individual drug means.

Results.—Three of the subjective mood analogue scales showed significant drug effects: the alert-drowsy, muzzy-clear-headed and troubled-tranquil scales. Sotalol produced more drowsiness than placebo ($t=3{\cdot}65$; $P<0{\cdot}01$) and propranolol ($t=2{\cdot}57$; $P<0{\cdot}05$), and greater 'muzziness' than placebo ($t=4{\cdot}92$; $P<0{\cdot}01$) and propranolol ($t=6{\cdot}05$; $P<0{\cdot}001$). Both sotalol ($t=3{\cdot}57$; $P<0{\cdot}01$) and propranolol ($t=4{\cdot}0$; $P<0{\cdot}01$) caused the subjects to feel more troubled than when on placebo. These effects were all more marked after three hours.

None of the physiological or behavioural measures showed significant drug effects. One of the most sensitive measures of central drug effects is the percentage of activity in the fastest wave-band of the EEG (13·5–26·0 Hz) and the close similarity of the effects of the three drugs is illustrated (Fig. 1A).

There was a significant drop in pulse rate over time for both sotalol ($t=7{\cdot}17$; $P<0{\cdot}001$) and propranolol ($t=5{\cdot}05$; $P<0{\cdot}01$) as compared with placebo (Fig. 1B). There was some evidence that the effects of sotalol lasted longer than propranolol, the fall in pulse rate after 3 hours being greater for sotalol than propranolol ($t=3{\cdot}23$, $P<0{\cdot}02$). No drug effects were shown with tremor or skin conductance.

Discussion.—The absence of significant drug effects on the central physiological and behavioural measures suggests that neither sotalol or propranolol has central effects in this dosage. Although the number of subjects was small, these measures have been shown to be very sensitive to drug effects in other studies (Walters & Lader, 1971 ; Bond & Lader, 1972). The changes in subjective mood after drug administration are difficult to interpret. The scales do not necessarily measure primary central effects ; it is possible to feel troubled because of a marked fall in pulse rate alone. Nevertheless, the increased drowsiness and muzziness after taking sotalol is unlikely to be entirely secondary to peripheral changes and could be a central effect which is too subtle to be detected by objective measures. These changes were not shown by propranolol, possibly because the drugs were not used in equal potency.

The significant fall in pulse rate after taking both active drugs confirms that adequate β-adrenoceptor blockade was achieved. The absence of drug effects on skin conductance and finger tremor is interesting. There is some evidence that propranolol reduces finger tremor in anxious patients (Marsden, Gimlette, McAllister, Owen & Miller, 1968) but this effect does not seem to occur with normal physiological tremor. Propranolol has been suggested as a treatment for hyperhidrosis (Laurent, 1971) but it is unlikely that β-blockade directly affects the cholinergic secretory mechanism of sweating.

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