Effect of a mixture of dexamphetamine and amylobarbitone on critical flicker fusion frequency

SIR,—A proprietary mixture of dexamphetamine sulphate 5 mg and amylobarbitone 32·4 mg (Drinamyl) is claimed by its manufacturers to produce a therapeutic effect "without the drowsiness that accompanies the use of barbiturates alone, and without the irritation or anxiety that may accompany the use of stimulants alone". The opposing action of these drugs has been studied in man (Dickens, Lader & Steinberg, 1965) using simple mental and motor tasks, but no reference could be found to an investigation of their effect on a purely sensory modality such as the critical flicker fusion frequency (c.f.f.f.).

In a double-blind procedure, six normal subjects were given amylobarbitone 100 mg, amylobarbitone 100 mg + dexamphetamine sulphate 15 mg, and a placebo in random order based on a latin square design. Ascending and descending thresholds of c.f.f.f. at 2 and 4 hr were compared with readings before administration. C.f.f.f. was determined by exposing the subjects to intermittent light at 20 and 50 c/sec for 1 min before measuring the c.f.f.f. threshold using a neon lamp driven by a square wave oscillator as the light source. This has been found to increase the sensitivity of the method, and to allow a study of the effect of drugs not only on mean c.f.f.f. but also on the recently recognised adaptation phenomenon (Alpern & Sugiyama, 1961; Turner, 1964).

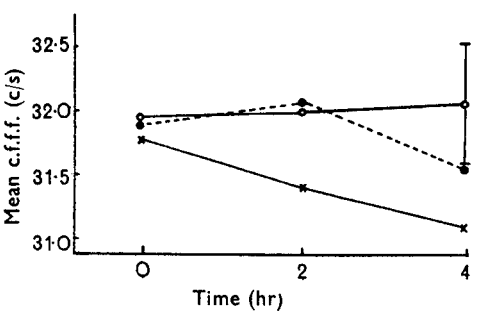

FIG. 1. Mean c.f.f.f. before and at 2 and 4 hr after administration of a placebo (● — ●), amylobarbitone 100 mg (× — ×) and a mixture of amylobarbitone 100 mg and dexamphetamine 15 mg (○ — ○) in 4 subjects. 95% confidence limits were all of the same order and are shown only for the mixture at 4 hr.

The results are shown in Fig. 1. There is a significant fall in mean c.f.f.f. over 4 hr after amylobarbitone 100 mg. The mixture of amylobarbitone and dexamphetamine, on the other hand, does not produce any significant change in c.f.f.f. during the period of the experiment, and it does not differ significantly from the placebo, although at 4 hr the difference between them is almost significant at the 5% level.

Neither amylobarbitone alone or in combination with dexamphetamine produced any change in the adapting effect of light at 20 and 50 c/sec.

This experiment demonstrates that dexamphetamine sulphate, 15 mg, abolishes the depressant action of amylobarbitone, 100 mg, on c.f.f.f. The difference in threshold at 4 hr between the mixture and the placebo, although not quite significant at the 5% level, suggests that at this time dexamphetamine may be having a dominant action. This may not only be due to the dose of dexamphetamine used in the combination but also to its rate of excretion which is

markedly dependent on changes in urinary pH (Beckett, Rowland & Turner, 1965). The duration of action of dexamphetamine in opposing depressant actions of amylobarbitone is probably closely related to urinary pH.

Roback, Krasno & Ivy (1952) found that dexamphetamine sulphate was effective in preventing the depression of c.f.f.f. produced by antihistamine drugs. It is equally effective in combination with amylobarbitone.

I am grateful to Mr. J. V. Smart for statistical help in this experiment which was carried out during the tenure of a Wellcome Senior Research Fellowship in Clinical Science. Smith Kline and French Laboratories Ltd. provided tablets of amylobarbitone, dexamphetamine and placebo.

PAUL TURNER
St. Bartholomew's Hospital,
Medical Professorial Unit,
London, E.C.1.
April 6, 1965.

References

Alpern, M. & Sugiyama, S. (1961). *J. opt. Soc. Amer.*, **51**, 1379–1385.
Beckett, A. H., Rowland, M. & Turner, P. (1965). *Lancet*, **1**, 303.
Dickens, D. W., Lader, M. H. & Steinberg, H. (1965). *Brit. J. Pharmacol.*, **24**, 14–23.
Roback, G. S., Krasno, L. R. & Ivy, A. C. (1952). *J. appl. Physiol.*, **4**, 566–574.
Turner, P. (1964). *J. Physiol.*, **171**, 6–8P.

Use of time-response relationships in assessing pharmacological activity

SIR,—In many pharmacological experiments it is possible to obtain a continuous record of drug activity. Time-response curves provide an ideal basis for determining quantitative estimates of potency since they include a consideration of onset, peak and duration of action of the compounds under investigation. However, the use of time-response curves to obtain such estimates is seldom made. We would like to describe a quick and easy means of processing data for estimating the potency of compounds from integration of time-response curves.

There are two types of curve: one in which an effect is elicited in a single group of animals and its intensity assessed at several different times later, and an alternative in which different groups of animals are each examined once but at a variety of times, a relationship being built up between drug effect and time. For the purpose of this letter the method is applied to the assessment of anti-inflammatory activity of compounds in the guinea-pig ultraviolet erythema test described by Winder, Wax, Burr, Been & Rosiere (1958) but could be equally applied to many other pharmacological test procedures.

Male albino guinea-pigs of 250–400 g had an area 3 inches square on one dorsal flank depilated. Next day the guinea-pigs, in groups of 5, had test compounds administered orally, either dissolved or suspended in 5% w/v gum acacia, in a volume of 5 ml/kg. Control animals received gum acacia only. Two hr after drug administration, the flank of each animal was exposed to ultraviolet light for 30 sec. The head of the lamp was covered with a mask in which 3 holes of 6 mm diameter had been cut. The average intensity of the three resulting erythematous circles was estimated 1, 2 and 3 hr later using an arbitrary scoring system (slight erythema, 1; moderate erythema, 2; severe erythema, 3). For control animals and with each dose of test compound the responses from the group of 5-guinea-pigs were summed (group inflammatory score) and plotted against time. The relationship between group inflammatory score and time for a typical group of control animals is illustrated in Fig. 1A.

The area under the graph (integral) represents the continual level of inflammation over the 3 hr period of the test and is given by the formula overleaf, obtained from Fig. 1B.