75 years who had undergone an operation under general anaesthesia within the previous 48 hours were studied under double-blind conditions, each patient receiving in random order, on request, the active treatment and an identical placebo. The test preparations were substituted for the first two oral analgesics required after operation. Patient volunteers were asked, by means of a multichoice questionnaire, (1) to indicate their initial level of pain immediately before taking the first set of tablets; (2) to rate their pain relief 1 hr after taking each set of tablets and (3) to select their preference, if any, for either set of tablets. Preparations investigated included aspirin and pethidine.

Submission of the results to sequential analysis using the method described by Armitage (1960) showed that it was not possible to demonstrate a significant difference between the test treatments and their corresponding placebo on pain relief if the populations were treated as homogeneous units. When, however, these populations were split into three groups using the initial pain levels as the basis for classification, the sensitivity of the study was greatly increased. Pethidine (100 mg) produced greater analgesia at the more severe pain levels, whereas aspirin (600 mg) had its most significant effect at the mildest level of pain. This difference was confirmed by the mean pain relief scores ($\pm$S.E.) obtained at every level of pain after both drug and placebo. It was also found that with both drugs the number of placebo responses were inversely related to the pain relief obtained. When the patient's preferences were analysed sequentially, similar results were obtained to those using relief scores.

Differences between the two sets of results may be due to the incidence of side effects and their influence on the preference made by the patient. For patients with mild pain the discomfort was often preferred to the side effects produced by the potent analgesic, whereas at the more severe levels of pain the importance of the side effects encountered was relatively small compared with the relief of pain achieved.

The classification of initial pain permits better discrimination between drug and placebo than is achieved using overall comparisons and also enables an estimation of the potency of the drug to be made.

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The effect of triflupromazine on the peripheral and central actions of some anticholinergic drugs

R. W. BRIMBLECOMBE and D. M. GREEN,* *Ministry of Defence, Chemical Defence Experimental Establishment, Porton Down, Salisbury, Wiltshire*

Many authors have shown that atropine and other anticholinergic drugs can produce a pattern of slow wave activity in the electroencephalogram (e.e.g.) inde-

pendent of the behavioural state of the animal. The drugs apparently affect the postulated mesodiencephalic activating system (m.d.a.s.) (Rinaldi & Himwich, 1955) which can be independent of the system involved in wakefulness and sleep. Brimblecombe & Green (1968a) provided quantitative evidence for a cholinergic link in this system by demonstrating a correlation between the central anticholinergic potency of a number of drugs and their potency in elevating the e.e.g. arousal threshold.

Bradley & Hance (1957) reported that the phenothiazine derivatives chlorpromazine and methopromazine acted synergistically with atropine in producing these effects in the e.e.g. of the cat. They suggested that this action of phenothiazines might be related to their weak anticholinergic activity.

The present study investigates the effect of trifluprom azine, another phenothiazine derivative, on the anticholinergic activity of a number of drugs, and their ability to elevate the e.e.g. arousal threshold. Peripheral and central anticholinergic activities were measured by blockade of oxotremorine-induced salivation and tremors in mice respectively. The method used, and the technique for measuring activity in elevating the e.e.g. arousal thresholds in cat *encéphale isolé* preparations, were described by Brimblecombe & Green (1968b).

The results are summarized in Table 1. Trifluprom azine did not potentiate the peripheral anticholinergic activity of any of the drugs and only in four cases out of six was central anticholinergic activity, as measured by blockade of oxotremorine-induced tremors, potentiated. However, trifluprom azine potentiated the effect of all drugs in elevating the e.e.g. arousal thresholds. It seems unlikely that the action of trifluprom azine on the e.e.g. is related to its anticholinergic activity.

TABLE 1. *Summary of results*

Compound	Central				Peripheral	
	Dose for elevation of e.e.g. arousal by 100% in cat *encéphale isolé* μmoles/kg		Antagonisms of oxotremorine induced tremors in mice ED50 μmoles/kg		Antagonism of oxotremorine induced salivation in mice ED50 μmoles/kg	
	Alone	+TFP	Alone	+TFP	Alone	+TFP
1	0·70	0·15	3·2	3·4	2·0	4·0
2	3·00	0·80	4·7	3·1	5·4	10·7
3	0·62	0·20	1·8	3·9	1·0	12·3
4	0·28	0·14	1·1	0·5	0·05	0·12
5	3·40	1·60	16·1	7·1	0·44	0·44
6	48·60	11·00	40·3	15·3	23·5	>100·0
7	42·0	—	>100·0	—	>100·0	—

Compound 1. N-ethyl-2-pyrrolidylmethyl-phencyclopentylglycollate
2. 4′-N-methylpiperidyl 1-phenylcyclopentane carboxylate
3. N-methyl-3-piperidylbenzilate
4. Hyoscine
5. Atropine
6. Caramiphen
7. Trifluprom azine
TFP, Trifluprom azine.

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A comparison of conditional responses induced by various drugs

W. J. LANG* and M. RUSH (introduced by M. J. RAND), *Department of Pharmacology, University of Melbourne, Australia*

Conditional cardiovascular and autonomic responses can be established in experimental animals using drugs of various types as unconditional stimuli (Bykov, 1957; Lang, Brown, Gershon & Korol, 1966; Lang, Ross & Glover, 1967).

Using atropine (0.5 mg/kg, intravenously) and morphine (2 mg/kg, subcutaneously) in dogs, a comparison has been made of the ease of producing conditional changes in the electrocardiogram, salivation and gastric secretion. An electric buzzer and the constant laboratory procedure served as the conditional stimulus which was paired with the unconditional stimulus (drug injection), and tests for conditioning were made after the seventh, fourteenth and twenty-first pairings. Conditional salivation resulted with both drugs after the seventh pairing. Conditional responses in gastric secretion and heart rate resulted in dogs given morphine after the seventh pairing but not in dogs given atropine even by the twenty-first pairing.

In other dogs, conditional cardiovascular changes occurred with yohimbine (0.2–0.8 mg/kg, intravenously) or nicotine (16 mg/kg, intravenously) as unconditional stimuli. When phentolamine (0.5 mg/kg, intravenously) or hexamethonium (10–20 mg/kg, intravenously) was used as the unconditional stimulus, however, the results were inconstant. The findings support the view that conditional responses are more readily established with drugs that have a central component of action than with drugs that act only peripherally.

Using glyceryl trinitrate (0.6 mg, sublingually in humans, or 0.5 mg/kg, intravenously in dogs) as the unconditional stimulus, conditional responses have been established in the heart rate of human volunteers and dogs. Conditional responses occurred in a shorter time in the human subjects.

Conditional responses to drugs may play a part in the placebo response and should be considered in the interpretation of double-blind clinical trials.

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