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Method of studying anticonvulsant properties of drugs in man

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The efficacy of anticonvulsant drugs is commonly assessed by observing their effect upon the convulsive threshold in experimental animals; it is clearly unacceptable to use this method of evaluation in man. However, the use of flurothyl as a therapeutic convulsant for the treatment of patients suffering from endogenous depression affords a means of observing the effect of drugs upon a seizure in progress.

Flurothyl (Indoklon: Ohio Chemical Co.) is a hexa-fluoryl-diethyl-ether; administered by inhalation it causes reproducible grand mal seizures in animals and man in concentrations as low as 32 parts per million (Krantz, Truitt, Speers & Ling, 1957). The epileptiform response occurs in three distinct phases; there is a preliminary myoclonic phase of irregular movements which is succeeded by tonic and clonic phases similar to those in electro-convulsive therapy (ECT), the tonic lasting for about 15 s and the clonic of varying duration but much longer than that seen with ECT. Establishment of the tonic phase is invariably followed by the clonic and may be regarded as the criterion of a successful treatment.

In these studies each subject was his own control, and since in a series of treatments the duration of the seizure progressively diminishes (Ottosson, 1960), the drug under test was given at the patient's third treatment and control observations made on the next, that is shorter, convulsion. The techniques of anaesthesia and administration of the standard dose of flurothyl (0·35 ml) with oxygen as the carrier gas have been described in detail by Rose & Watson (1967). At the onset of the tonic phase the test drug was given rapidly into an antecubital vein. Cerebral activity and heart-rate were monitored throughout on a Grass polygraph; in some cases, after the induction of anaesthesia, blood pressure was monitored by percutaneous puncture of a radial artery. Times were marked on the polygram of the administration of all drugs and of the clinical observation of anaesthesia, depolarization, phases of the seizure and post-ictal waking.

Anticonvulsants were not used more than twice in the course of any patient's treatment for depression, and we have no evidence that recovery from this illness was in any way prejudiced.

Our results will be published elsewhere (Watson, Harrison & Rees, 1970), but in summary, diazepam 15 mg, nitrazepam 15 mg and thiopentone sodium 250 mg all produced marked reduction in the length of seizures. An example of polygraphic records on test and control days in the same patient will be shown.

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Effect of propranolol on lactate induced phenomena in normal subjects

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Granville-Grossman & Turner (1966) found that propranolol reduced somatic symptoms which may accompany anxiety states. Pitts & McClure (1967) produced symptoms of panic in susceptible subjects by lactate infusion. The present study investigated the possible modification by propranolol of the effects of intravenous lactate in normal subjects.

Six normal subjects received 1 M DL sodium lactate (5 ml/kg) by intravenous infusion over 20 min, having been pretreated 10 min earlier with intravenous propranolol (10 mg) or normal saline. Blood samples were taken before and 15, 20 and 80 min after the beginning of the lactate infusion. Heart rate, skin temperature and forearm muscle-action potentials were recorded continuously and subjective physical and psychological effects noted.

Blood lactate (L isomer) was measured enzymatically (Marbach & Weil, 1967) and increased during lactate infusion from a mean resting level of 0·866 mM (S E.M. $\pm$0·13) to 4·31 mM (S.E.M. $\pm$0·32) after propranolol and from 0·837 mM (S.E.M. $\pm$0·06) to 4·26 mM (S.E.M. $\pm$0·34) after saline. Plasma propranolol concentration was measured fluorimetrically (Shand, Nuckolls & Oates, 1970) and the mean level at the end of the lactate infusion was 65·2 ng/ml (S.E.M. $\pm$4·53).

Propranolol produced a significant fall in mean heart rate before lactate infusion from 86·7 to 66·2 beats/min (d=20·5, S.E.M. $\pm$4·04, t=5·07, $P<0·01$) but the rise in heart rate during lactate infusion was not significantly different following propranolol (66·2–90·0 beats/min, d=23·8, S.E.M. $\pm$4·7, t=5·07, $P<0·01$) and following saline (74·1–102 beats/min, d=27·8, S.E.M. $\pm$5·85, t=4·75, $P<0·01$).

All subjects noted unpleasant effects during lactate infusion but no preference in modifying them was established for propranolol or saline either by the subjects or clinical observer. This would suggest that β-adrenoceptor stimulation is not the primary mechanism responsible for the unpleasant effects of lactate infusion.

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