phetamine and placebo on pupil diameter, but the dilatation after 1-benzylpiperazine was greater than that after the placebo ($P < 0.001$).

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Clinical pharmacology of chlorpromazine

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Chlorpromazine has been extensively used in psychiatric treatment over the last 20 years, but its clinical pharmacology remains imperfectly understood. In particular, relationships between plasma concentrations, and physiological and behavioural effects have not been fully evaluated.

In the present study ten drug-free patients requiring phenothiazine treatment received oral chlorpromazine (100 mg) at intervals of 8 h in liquid form. No other drug was given except nitrazepam at night if needed. The patients were first evaluated on the day before treatment, at 10.00 hours. Testing was then carried out on the 4th, 8th, 15th, 22nd, 29th and 36th or 43rd days of treatment and consisted of: (a) blood samples for chlorpromazine estimation at 0, 2, 4 and 6 h after the dose; (b) blood pressure and pulse rate (sitting and standing), pupil size, sweat gland activity and electroencephalogram (e.e.g.) at these times; (c) salivary secretion, e.e.g. auditory evoked response, simple auditory reaction time and handwriting tests at the 2-h point only (10.00 h); and (d) clinical ratings between the 2nd and 4th hours.

After an initial rise in the first 8–15 days, plasma concentrations dropped markedly, as we have previously reported (Curry, Lader, Mould & Sakalis, 1971). The changes were reflected by some of the peripheral measurements. Correlations were computed within each subject, between concentration, physiological measures, and clinical ratings. They were pooled using z transformations (see Table 1). Clinical changes over the first fortnight showed a tenuous relationship with drug concentrations, and there was no correlation during the decreasing phase.

TABLE 1. *Intra-patient correlations between plasma concentration and other variables*

	r	P
Pupil size	−0·4605	<0·001
Pulse rate (standing)	0·3021	<0·001
Blood pressure (sitting systolic)	−0·2603	<0·001
Blood pressure (sitting diastolic)	−0·2114	<0·01
Palmar skin conductance	−0·1906	<0·01
Salivary secretion	−0·3646	<0·05
e.e.g. 4·0–7·5 Hz percentage	0·3912	<0·05

The drop in concentrations after the first fortnight may reflect induction of drug hydroxylase activity in the liver. The correlations with peripheral measurements show that concentration data are useful during appraisal of marked side effects such as postural hypotension, but further studies are needed to evaluate the usefulness of plasma chlorpromazine estimations in the clinical management of psychiatric patients.

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Cardiotoxicity of tricyclic antidepressants

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Since the introduction of psychotropic drugs into medicine, many reports of cardiovascular complications resulting from their administration have appeared in the literature. These effects have ranged from minor electrocardiographic changes to sudden unexplained death in psychiatric patients. Because of the need to confirm or refute a suggestion by the Committee on Safety of Drugs that the administration of tricyclic antidepressants was associated with adverse cardiac effects, a hospital-based drug information system has been used to determine the incidence of sudden death of cardiac origin in patients receiving these drugs. In a preliminary study, the incidence of sudden unexpected death was found to be six out of fifty-three patients with cardiac disease who received amitriptyline compared with no such deaths in a matched control group (Coull, Crooks, Dingwall-Fordyce, Scott & Weir, 1970). This study has now been extended.

All inpatients in the Aberdeen General Hospitals Group who had received amitriptyline during the 40 months' period ending September, 1971 were identified and their hospital records studied. Eight hundred and sixty-four patients had received amitriptyline of whom 119 had cardiac disease. Those patients who had not received the drug during the two weeks immediately before death or discharge were not included. A control group was matched for sex, age, diagnosis and duration of hospital stay. There were twenty-four deaths in the amitriptyline group, thirteen of which were sudden and unexpected (duration of terminal illness <24 h). In the control group there were fifteen deaths, of which only three were sudden unexpected deaths.

All the amitriptyline patients who died apparently received conventional dose regimes and none received any drugs known to interact with tricyclic antidepressants. Thus the association between administration of amitriptyline and sudden death in patients with cardiac disease has been confirmed. No increased incidence of sudden death was found in patients receiving amitriptyline without a diagnosis of cardiac disease or in cardiac patients whose amitriptyline was discontinued at least 2 weeks before death or discharge. The position regarding other tricyclic antidepressants is currently being examined.

We have considered two of the possible factors which might be contributing, alone or in combination, to this cardiotoxicity: (1) interaction with concomitantly administered drugs—we have found that in rats, administration of tricyclic antidepressants for 2 weeks increases the toxicity of digoxin; (2) a decreased rate of drug