Pharmacology of chlorpromazine: clinical studies

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Chlorpromazine has been in use for nearly 20 years, yet insufficient is known of its clinical pharmacology (Shepherd, Lader & Rodnight, 1968). A new impetus to research in this field has been given by the recent availability of a method for the estimation of the unmetabolized drug in plasma (Curry, 1968). In initial studies in patients treated chronically, plasma concentrations of chlorpromazine measured just before doses varied from 0 to 770 ng/ml. The rises in plasma concentrations after dose ranged from 16 to 225 ng/ml, percentage increases of 3 to 300. After the first 2 h, the calculated half-life of chlorpromazine varied from 2 to 31 h although it was less than 6 h in over 80% of the sample of patients (Curry & Marshall, 1968). The current investigation is an intensive study of variations in concentrations, and also in effects, over a 6 week period.

Patients are eligible for inclusion in the study if: (a) phenothiazines are indicated; (b) they have not received such drugs for at least a month; and (c) their clinical state is not so severe as to preclude testing or so mild as to render drugs superfluous. After an initial dose of 100 mg intramuscularly they receive 100 mg of the drug by mouth every 8 hours. No other medication is given. A battery of tests is carried out on the 1st, 4th, 8th, 15th, 22nd, 29th and 43rd days of treatment. In these investigations: (a) blood samples are taken for chlorpromazine analysis at 0, 2, 4 and 6 h after the dose; (b) blood pressure and pulse (sitting and standing), pupil size, sweat gland activity and electroencephalogram are recorded at each of these times; (c) salivary secretion, EEG evoked response, simple auditory reaction times, and handwriting tests are carried out at the 2 h point only; and (d) detailed clinical ratings are made between 2 and 4 hours.

Preliminary results confirm that chlorpromazine concentrations rise markedly following each dose to fall again within 4 hours. A great variability in concentrations is also found between patients. A consistent finding is that the concentrations rise to the highest maxima in the first 7–14 days of treatment; peak concentrations fall away as treatment is continued. Changes in only some of the physiological measures follow drug concentrations. Tolerance is evident with some of the others. Extrapyramidal effects such as micrographia sometimes become evident after about 15 days. Clinical effects tend to be steadily more noticeable although the rate of improvement may lessen after 3 weeks.

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