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# The effect of chlorpromazine on drug metabolism

Curry, Lader & others (1971) have demonstrated a lowering of the steady-state plasma level of chlorpromazine, beginning two weeks after the start of treatment with a constant dose of drug. They suggest that this might result from induction of liver drug-metabolizing enzymes. Certainly, it has been shown that chlorpromazine causes enzyme induction in animals (Conney, 1967). However, in a recent report by Gram & Overø (1972) there are indications that chlorpromazine inhibits the metabolism of imipramine in man. In our work, we have examined the effect of chlorpromazine on drug-metabolizing capacity in two situations—firstly, in schizophrenic patients receiving this drug and secondly, using isolated liver preparations from rats treated with chlorpromazine and, for comparison, with barbitone.

Drug-metabolizing capacity in chlorpromazine-treated patients, in young control subjects and in elderly drug-free patients was assessed using the plasma antipyrine half-life technique, the dose, time of sampling and antipyrine estimations being as previously described (O'Malley, Crooks & others, 1971). Patients included in the study had been receiving chlorpromazine (150–600 mg) for at least 2 months and had not been given other drugs in that time. The phenothiazine was stopped approximately 10 h before ingestion of the test drug. Details of the animal study are as outlined in Table 2.

From Table 1 it can be seen that the mean plasma antipyrine half-life in the chlorpromazine-treated patients was longer than in the younger controls ($P < 0.001$; students $t$-test) and was the same as that found in the elderly control subjects. Had enzyme induction occurred in the drug-exposed group a lower plasma antipyrine

Table 1. *Plasma antipyrine half-life values in three groups of subjects.*

| Subjects | No. | Age | Plasma antipyrine half-life (h) |
|---|---|---|---|
| Young .. .. .. .. | 61 | 26·0 ± 2·5 | 12·0 ± 3·5 |
| Elderly .. .. .. .. | 18 | 77·6 ± 8·7 | 17·4 ± 6·8 |
| Chlorpromazine treated .. | 10 | 61·5 ± 9·3 | 17·7 ± 4·9 |

Results are shown as means ± s.d.

Table 2. *Hexobarbitone oxidation by isolated liver preparations from control and treated animals.*

| | μmol hexobarbitone oxidized/g wet wt liver per h |
|---|---|
| Control .. .. .. .. .. .. | 0·84 ± 0·11 |
| Barbitone (10 mg/kg daily) .. .. .. | 0·95 ± 0·14 |
| Chlorpromazine (10 mg/kg daily) .. .. | 0·89 ± 0·17 |
| Barbitone (50 mg/kg daily) .. .. .. | 2·65 ± 1·10 |
| Chlorpromazine (50 mg/kg daily) .. .. | 1·43 ± 0·42 |

Hexobarbitone oxidation was measured using [$^3$H]-labelled hexobarbitone as substrate. Animals were treated for four days as indicated, the drugs being given in two daily doses. Hexobarbitone oxidation was measured on the fifth day using liver 9000 *g* supernatants. Results are expressed as means and s.d. for groups of six animals.

half-life would have been expected. The finding of identical values in the chlorpromazine group and in the elderly drug-free patients clearly demonstrates that chlorpromazine has not increased drug-metabolizing capacity. This is further emphasized by the fact that the chlorpromazine group are appreciably younger than the elderly control patients and for this reason would be expected to be faster metabolizers of antipyrine (O'Malley & others, 1971). Possible reasons for the discrepancy between the present findings and those of Curry & others (1971) are, firstly, people in the age group of the chlorpromazine patients studied may not be inducible. A second possibility is that chlorpromazine may produce only weak induction in man. This degree of induction might be sufficient to reduce the steady-state plasma level of the drug when administered over a long period but not sufficiently great to affect measurably the plasma half-life of a concomitantly administered drug. Certainly, from our rat studies (Table 2) chlorpromazine while being an inducer, produced only 33% of the stimulation caused by barbitone and must be considered a weak inducer.

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## Spironolactone—a weak enzyme inducer in man

Animal experiments indicate that spironolactone is an inducer of hepatic microsomal oxidizing enzymes. Thus, in mice it increases hexobarbitone metabolism *in vitro* and *in vivo* (Gerald & Feller, 1970) and increases microsomal protein, cytochrome P-450 and cytochrome c reductase activity (Feller & Gerald, 1971). In female, though not in male, rats it has the same effects as in mice (Stripp, Hamrick & others, 1971) and, also in female rats, it shortens the half-life of its main metabolite (Solymoss, Tóth & others, 1970). In view of its widespread clinical use, particularly in combination with drugs known to undergo oxidation in the liver, a study of its inducing potential in man seemed important.

Nine healthy volunteers (1 female), aged 20–30 years, participated in the study. Antipyrine half-lives ($T_{\frac{1}{2}}$) were determined by plasma sampling (6 samples) up to 30 h after an oral load of 600 mg, using the method of Brodie, Axelrod & others (1949). 24-h urinary excretion rates of D-glucaric acid were measured as described by Hunter, Maxwell & others (1971). When control measurements of these parameters had been made, spironolactone 50 mg three times daily was administered for 7 days. Further measurements were started on the day following the end of treatment. After an interval of at least 4 weeks, eight of the subjects received phenobarbitone 120 mg orally each night for seven consecutive nights, following which antipyrine $T_{\frac{1}{2}}$ estimates were repeated.

The results of the experiments are shown in Table 1. In four of the nine subjects there was significant reduction in antipyrine $T_{\frac{1}{2}}$ after spironolactone as assessed by comparison of the slopes of the regression lines. Using paired data for the whole