INTERACTIONS OF ORPHENADRINE AND PHENOBARBITONE WITH CHLORPROMAZINE: PLASMA CONCENTRATIONS AND EFFECTS IN MAN

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1 Two studies were carried out on acutely psychotic patients receiving chlorpromazine (100 mg) 8-hourly.

2 In the pilot study on five patients, plasma chlorpromazine concentrations fell over the course of 3 weeks of treatment and parallel changes were noted in the plasma half-life of antipyrine, salivation rate and handwriting length.

3 In the main study involving twelve patients treated for 15 weeks, the above findings were confirmed and were interpreted as indicating that chlorpromazine accelerated its own metabolism by inducing liver microsomal oxidising enzymes. No metabolites of chlorpromazine were detected in plasma.

4 The addition of phenobarbitone (50 mg) 8-hourly for 3 weeks, or orphenadrine (100 mg) 8-hourly for 3 weeks, resulted in a lowering of plasma chlorpromazine concentrations together with a further shortening of plasma antipyrine half-life.

5 Physiological effects of the additional treatments suggested that phenobarbitone lessens the effects of chlorpromazine by lowering body concentrations. However, orphenadrine acts more by virtue of its anticholinergic effects.

6 It was concluded that phenobarbitone and orphenadrine should not be prescribed routinely in patients receiving major tranquillisers. The need for the addition of orphenadrine should be assessed in each individual case.

Introduction

Of all the major tranquillisers, chlorpromazine, the prototype, is still the only one with which there have been any systematic clinical pharmacological studies. Nevertheless, there are many outstanding questions and the answers to these questions are only slowly forthcoming. This slow progress reflects the difficulties of assaying chlorpromazine, its plethora of metabolites and the problems in clinical assessment of patients and of drug effects in these patients.

In addition, psychiatrists commonly prescribe barbiturates and antiparkinsonian agents in conjunction with major tranquillisers, making interactions with other drugs an important aspect of the clinical pharmacology of chlorpromazine.

In a previous study (Sakalis, Curry, Mould & Lader, 1972), we found quite consistently that

chlorpromazine concentrations rose during the first 8-15 days of treatment but then fell. Despite this fall, clinical improvement continued as did many physiological effects. The assumption was made that chlorpromazine, like many other drugs, induced its own metabolism in the liver.

In the present study, our purpose was to investigate drug interactions with chlorpromazine as well as to seek further evidence of chlorpromazine induction. The two drugs whose interactions with chlorpromazine were studied were phenobarbitone, a well-known inducer of its own and other drugs' metabolism, and orphenadrine. The latter is widely used clinically as an antiparkinsonian agent, and animal experiments have shown it to be a powerful enzyme inducer (Conney, Davison, Gastel & Burns, 1960). Consequently, its

antiparkinsonian action might be due at least in part to induction of chlorpromazine metabolism.

To obtain more detailed information regarding the metabolism of chlorpromazine we estimated the ability of the liver to metabolize antipyrine (Davies & Thorgeirsson, 1971), and we assayed a known major metabolite of chlorpromazine, 7-hydroxychlorpromazine. A battery of physiological tests was also used to give some indication of autonomic effects of the drugs.

Methods

Patients

Pilot study Five patients, four males and one female, suffering from acute functional psychotic episodes and requiring phenothiazine treatment took part. All the available clinical evidence suggested that they had not received medication with psychotropic drugs for at least one month.

Under close nursing supervision, the patients received chlorpromazine (100 mg) as an elixir every 8 h for 3 weeks orally before meals. No other form of medication was permitted except nitrazepam if needed at night. Before treatment and at weekly intervals for three occasions after treatment was started the following testing was carried out: (1) blood samples for estimation of chlorpromazine were taken 2 and 4 h after the morning dose, (2) a test dose of antipyrine was administered and its plasma half-life estimated, (3) blood-pressure, pulse rate, and pupil size were measured at the 2 and 4 h points, (4) salivation was estimated about 1 h after the morning dose, (5) the handwriting test for extrapyramidal effects was given between 2 and 4 h, and (6) clinical ratings were made between 2 and 4 hours.

Main study Twelve male schizophrenic patients, aged between 19 and 38 years, took part in the study. All were 'drug-free' as in the pilot study; their clinical states were neither so severe as to preclude testing nor so mild as to render drugs superfluous. They were treated informally in an open ward with a high nurse-patient ratio and extensive occupational therapy facilities were available.

After initial testing, all twelve patients were placed on chlorpromazine elixir (100 mg) 8-hourly, for 15 weeks. The patients were allocated randomly into two groups of six patients. Group 1 received in addition to the chlorpromazine, orphenadrine hydrochloride (100 mg) 8-hourly, during weeks 4, 5 and 6 of the study. During weeks 10, 11 and 12, this group was

given phenobarbitone (50 mg) 8-hourly. The other group received these additional drugs in reverse order—phenobarbitone during weeks 4, 5 and 6, orphenadrine during weeks 10, 11 and 12.

At weekly intervals, testing was carried out as in the pilot experiment—plasma samples, antipyrine plasma half-life, blood-pressure, pulse rate, pupil size, salivation, handwriting and clinical ratings.

Chemical measurements

Chlorpromazine plasma concentration determination This was carried out using gas-liquid chromatography with an electron-capture detector. Full details of this technique have been described previously (Curry, 1968), and the reliability and validity of the technique as currently employed in the laboratories of the London Hospital Medical College have also been presented earlier (Sakalis *et al.*, 1972). The lowest concentration detectable was 5 ng/ml in a 5 ml plasma sample.

7-hydroxychlorpromazine plasma concentration determination This was carried out by a method devised for the purpose of this study. To the plasma sample (1 ml) was added ammonium hydroxide solution (1 ml, N) and ether (10 ml analytical grade). After shaking (10 min) and centrifugation an ether aliquot (7 ml) was removed and added to HCl (2 ml, 0.1 N) solution. After shaking (10 min), and centrifugation, an aliquot (1.8 ml) of the aqueous layer was removed and added to a fresh sample of ether (4 ml), and sufficient ammonium hydroxide solution was added to bring the pH of the aqueous layer to 9 (approx.) After shaking and centrifugation an aliquot (3 ml) of the ether layer was removed and evaporated to dryness on a water bath at 35°C. The residue was redissolved in heptane (50 µl) containing 1% bis-(trimethylsilyl)-acetamide. Samples (10 µl) of the heptane solution were examined by gas-chromatography as described earlier for chlorpromazine. The retention time of the silyl derivative of 7-hydroxychlorpromazine was 1.62 times that of chlorpromazine. There was no interference from other chlorpromazine metabolites, from chlorpromazine itself, or from phenobarbitone or orphenadrine. For analytical purposes, experimental plasmas were compared directly with calibration curves from standard solutions in plasma. Recovery was around 70-80%.

Phenobarbitone plasma concentration determination This was carried out by the method of Goldbaum (1952), as modified by Jatlow (1973).

This method involves extraction of phenobarbitone into chloroform, back extraction into aqueous sodium hydroxide, and differential ultraviolet absorption spectrophotometry of two fractions of the alkaline solution, after adjustment of the pH of one fraction to 10. The method was not affected by the presence of chlorpromazine, its metabolites, or orphenadrine.

Orphenadrine plasma concentration determination This was carried out by a method basically that of Bilzer & Gundert-Remy (1973). The plasma sample was mixed with sodium hydroxide (1 ml, N) and heptane (10 ml), and shaken for 30 minutes. After centrifugation, an aliquot (8 ml) of the heptane was shaken with HCl (2 ml, 0.1 N) for 30 minutes. After centrifugation, an aliquot (1.8 ml) of the acid layer was mixed with sodium hydroxide (0.2 ml, N) and heptane (100 μ l). The mixture was shaken for 30 min and centrifuged. The heptane layer was collected in the bottom of a tapered centrifuge tube by a series of centrifugation and aspiration steps. An aliquot (5 ml) of the heptane layer was then examined by gas-liquid chromatography on an OV-17 (5%) column with a flame ionization detector. The orphenadrine signal (retention time 3 min) was compared with those from standard solutions of orphenadrine handled similarly. The concentration of orphenadrine was read directly from a calibration curve obtained from the standards. These results were not affected by the presence of chlorpromazine, its metabolites, or phenobarbitone.

Antipyrine plasma half-life determination A dose of 10 mg/kg body weight of antipyrine (phenazone) was given by mouth with the patient fasting overnight. Blood samples were taken 2, 4, 8 and 24 h later and the plasma separated by centrifugation. The antipyrine concentrations in the samples

were estimated using the spectrophotometric method of Brodie *et al.* (1949). The plasma half-life was calculated using exponential regression equations.

In a preliminary study to assess the stability of the antipyrine half-life, the drug was administered on four successive weekly occasions to ten normal volunteers. The half-lives obtained are displayed in Table 1. No significant trends over time were found and the standard error of the within-subject estimate of half-life was only 30 minutes.

Various preliminary checks were carried out to confirm that the various chemical estimations made were accurate in the presence of the other drugs given.

Physiological measurements

Blood pressure and pulse rate The blood pressure was recorded with a manually operated sphygmomanometer, first with the patient seated comfortably and then after he had been standing for 2 minutes. The pulse rate was taken at the same time.

Pupil size The pupil diameter was recorded in mm using a disc comparison method under two standard illuminations (dim-bright), with the patients fixating a reference point.

Salivary secretion Three dental cotton rolls were placed in a sputum cup and weighed. One roll was placed on each side of the mouth against the parotid duct and the third under the tongue; they were retained for 2 min and then replaced in the cup. This was repeated 3 times at 2 min intervals, and the mean expressed as g/2 minutes. Patients were not allowed to eat, drink, or smoke for 1 h prior to the measurement.

Handwriting test The patients were asked to

Table 1 Plasma antipyrine half-lives (h) estimated on four successive weekly occasions in ten normal volunteers

Subject Number	Age (years)	Sex	Weeks			
			1	2	3	4
1	36	M	11.3	12.2	12.2	12.1
2	27	F	15.1	14.7	14.8	15.2
3	33	M	11.9	11.7	11.8	11.4
4	30	M	9.1	9.6	10.0	10.0
5	30	M	15.0	14.7	14.6	14.8
6	34	M	18.1	18.5	17.4	18.2
7	33	M	13.1	12.9	13.4	12.9
8	26	M	13.8	13.8	13.4	13.9
9	24	M	13.2	13.1	12.8	13.2
10	28	M	19.4	19.2	20.6	20.4

write the same verse ('Jack and Jill') on each occasion using the same type of pencil and sheets of paper of equal size. The length of the script was measured in cm.

Clinical ratings

The In-patient Multidimensional Psychiatric Scale (IMPS) as modified by Goldberg, Cole & Clyde (1963) was used, since this form is sensitive to changes in psychopathology. The rating was carried out by a psychiatrist after a semistructured interview. Scores from 0-8 were given according to degree of severity on fifty-three symptoms covering the following fourteen areas of psychopathology: hostility, disorientation, guilt, auditory hallucinations, agitation and tension, slowed speech and movements, delusions of grandeur, indifference to environment, incoherent speech, pressure of speech, persecution, hebephrenia, delirium, and memory deficit. Factor loadings were applied to the symptom scores to yield fourteen weighted values corresponding to the fourteen areas of psychopathology. These values were then totalled.

Analysis of data

Appropriate parametric statistics were used throughout. Analyses of variance were carried out to determine the significance of differences between data from the 2 h and 4 h points and changes in the variables over the course of treatment. To examine the latter time course more closely in the main study, trend analyses up to the quintic trend were computed. It was expected that if chlorpromazine alone affected a variable, linear and/or quadratic trends would be significant. If, in addition, one of the other drugs had an effect, cubic trends should be significant. If both additional drugs had effects, quintic trends should be apparent.

Within-patient correlations were calculated between the various variables by computing between-patient and total variance and co-variance matrices and subtracting the former from the latter.

Results

Pilot study

Four variables showed significant changes over the three weeks of treatment: plasma chlorpromazine concentrations, the half-life of antipyrine, salivation rate and handwriting length (Figure 1). The

Figure 1 Mean values of the four parameters for the five patients in the pilot study over 3 weeks of treatment with chlorpromazine (100 mg) 8 hourly. The vertical bar (CD) refers to the 0.05 critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

plasma chlorpromazine values for the 2 and 4 h readings showed no consistent differences so the mean of the two readings was computed. It can be seen from Figure 1 that the highest level was reached in the first week followed by a steady decline. The mean antipyrine half-life was halved over the 3 weeks of treatment. Salivation dropped abruptly with the onset of treatment and remained low. The handwriting length was significantly but not greatly diminished suggesting minimal extrapyramidal effects.

Main study

Plasma chlorpromazine concentrations Preliminary analysis of variance showed no significant difference between the 2 and 4 h estimations. To lessen variability in the plasma readings, the mean of the 2 and 4 h estimations was computed. The

Figure 2 Mean values for the two groups of six patients for plasma chlorpromazine concentrations during 15 weeks of treatment with 100 mg 8 hourly. In group 1 (●) orphenadrine (O, 100 mg) 8 hourly was added during weeks 4, 5 and 6, phenobarbitone (P, 50 mg) 8 hourly during weeks 10, 11 and 12. In group 2 (○), the order of additional drugs was reversed. The vertical bar (CD) refers to the 0.05 critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

means for the two groups of six patients are shown in Figure 2. It can be seen that the plasma concentration in both groups rose to mean values of about 30 ng/ml during the course of the first few weeks. From the fifth to the seventh week the plasma concentration fell significantly in both groups to be followed by a rise particularly noticeable in one of the groups. A second fall in chlorpromazine concentration occurred from the tenth week onwards. Trend analysis suggested an overall quadratic trend to be most important in Group 1 (orphenadrine first) ($F_{1,5} = 86.00$; $P < 0.001$) with some quartic components as well ($F_{1,5} = 6.98$; $P < 0.05$). Group 2 showed a significant quintic trend ($F_{1,5} = 11.26$; $P < 0.05$).

It thus appears that the overall tendency is for a progressive fall in chlorpromazine concentrations over the course of the 15 weeks' treatment. The addition of orphenadrine or phenobarbitone caused a further drop in chlorpromazine concentrations but these drops were unequivocal during the first weeks only and occurred 1-2 weeks after the additional drugs were instituted.

Plasma 7-hydroxychlorpromazine concentration No measurable concentration of 7-hydroxychlorpromazine was found in any sample assayed individually. Pooling of samples which permitted extracts to be prepared from larger volumes of

plasma enabled traces (approximately 1 ng/ml) to be detected. Additionally, no traces of other hydroxylated chlorpromazine metabolites were detected. 7-hydroxychlorpromazine added to pooled plasma assessed earlier was recovered and assayed, the percentage recovery being 70-80.

Plasma phenobarbitone concentrations Phenobarbitone assays were carried out on both 2 and 4 h samples: as there were no significant differences between the samples the mean values were calculated. An analysis of variance revealed no significant differences between Groups 1 and 2 but there was a significant increase in plasma phenobarbitone concentration between weeks 1 and 2 of treatment with a further small but non-significant rise in the third week (means for the 1st, 2nd and 3rd weeks of phenobarbitone treatment respectively: 9.5, 12.0 and 13.0 $\mu\text{g/ml}$; $F_{2,20} = 6.49$; $P < 0.01$).

Plasma orphenadrine concentrations These concentrations were quite inconsistent with no detectable changes over time. Eight of the thirty-six samples were found to contain no detectable orphenadrine, a further ten had concentrations below 100 ng/ml, and the remainder divided equally above and below 200 ng/ml, the highest value being 845 ng/ml.

Figure 3 Mean values for the two groups of six patients for the antipyrine plasma half-life. In group 1 (●), orphenadrine (O, 100 mg) 8 hourly was given during weeks 4, 5 and 6 and phenobarbitone (P, 50 mg) 8 hourly during weeks 10, 11 and 12. In group 2 (○), the order of additional drugs was reversed. Chlorpromazine (100 mg) 8 hourly was administered throughout the trial. The vertical bar (CD) refers to the 0.05 critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

Figure 4 Mean values for the two groups of six patients for standing systolic blood pressure (BP). In group 1 (●), orphenadrine (O, 100 mg) 8 hourly was given during weeks 4, 5 and 6 and phenobarbitone (P, 50 mg) 8 hourly during weeks 10, 11 and 12. In group 2 (○), the order of additional drugs was reversed. Chlorpromazine (100 mg) 8 hourly was administered throughout the trial. The vertical bar (CD) refers to the 0.05 critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

Figure 5 Mean values for the two groups of six patients for standing diastolic blood pressure (BP). In group 1 (●), orphenadrine (O, 100 mg) 8 hourly was given during weeks 4, 5 and 6 and phenobarbitone (P, 50 mg) 8 hourly during weeks 10, 11 and 12. In group 2 (○), the order of additional drugs was reversed. Chlorpromazine (100 mg) 8 hourly was administered throughout the trial. The vertical bar (CD) refers to the 0.05 critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

Antipyrine plasma half-life There was a significant difference between the two groups of patients with respect to the initial antipyrine half-lives (Figure 3). No other initial differences were discernible between the two groups and the difference found is probably a chance finding. In both groups the mean half-lives dropped steadily over the first 6 weeks to about two-thirds of their initial values. The effect of the additional drugs during weeks 4-6 was not apparent but when the drugs were stopped there was an immediate and highly significant increase in plasma half-life. During weeks 7-9 the values were steady but a second drop occurred during weeks 10-12 when the second drug was added to the chlorpromazine. The decrease continued throughout these three weeks to be followed, on cessation of the drugs, by a return to the plateau levels. As seen by the within-group 0.05 critical difference of just over 1 h, the data were very consistent. Trend analyses showed highly significant quartic trends in both groups separately ($F_{1,5} = 37.02$; $P < 0.01$ and $F_{1,5} = 94.11$; $P < 0.001$), and in both groups combined ($F_{1,11} = 117.70$; $P < 0.001$).

Blood pressure and pulse rate There were no significant differences between 2 and 4 h readings for these variables and so little variability that the 2 h readings only are presented. The standing systolic and diastolic blood-pressure values for the

two groups are depicted in Figures 4 and 5. In both, a significant decrease in blood-pressure occurred with chlorpromazine treatment. The decrease was partly reversed by the addition of orphenadrine and phenobarbitone during weeks 4-6 and 10-12. These effects were significant for systolic but not quite so for diastolic blood pressure as judged by the critical differences. The drug effects on the sitting blood-pressure were similar but less apparent.

The mean values for the standing pulse rate showed a marked rise with the institution of chlorpromazine treatment (Figure 6). The addition of either orphenadrine or phenobarbitone during either of the two periods was accompanied by pronounced drops in pulse rate and the withdrawal of these additional drugs was associated with return to tachycardia. Trend analyses revealed highly significant quintic trends for both groups ($F_{1,5} = 19.12$; $P < 0.01$ and $F_{1,5} = 55.02$; $P < 0.001$). Data for the sitting pulse rate were similar but showed less pronounced trends.

Pupil size Again 2 h data only are presented (Figure 7). The pupil size under dimly lit conditions diminished with chlorpromazine treatment. When orphenadrine was added, either in group 1 during weeks 4-6 or group 2 during weeks 10-12, reversal of the constriction took place. With phenobarbitone, only small changes in pupil size

Figure 6 Mean values for the two groups of six patients for standing pulse rate. In group 1 (●), orphenadrine (O, 100 mg) 8 hourly was given during weeks 4, 5 and 6 and phenobarbitone (P, 50 mg) 8 hourly during weeks 10, 11 and 12. In group 2 (○), the order of additional drugs was reversed. Chlorpromazine (100 mg) 8 hourly was administered throughout the trial. The vertical bar (CD) refers to the 0.05 critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

were apparent. Trend analyses revealed highly significant quintic effects ($F_{1,5} = 48.55$; $P < 0.001$ and $F_{1,5} = 32.82$; $P < 0.01$ for groups 1 and 2 respectively), suggesting that phenobarbitone effects were indeed present. The results for the pupil size under bright illumination were essentially similar with quintic trends again being the most significant.

Salivary secretion The effects of the drugs on salivation (Figure 8) were rather similar to those on pupil size. Chlorpromazine produced a decrease in salivation, orphenadrine partially reversed this effect, and phenobarbitone had little effect. However, the cubic trends were the most significant ($F_{1,5} = 18.54$; $P < 0.01$ and $F_{1,5} = 19.25$; $P < 0.01$) although significant quintic trends were also present ($F_{1,5} = 10.53$; $P < 0.05$ and $F_{1,5} = 12.86$; $P < 0.05$).

Handwriting length Chlorpromazine produced a significant decrease in handwriting length during the first week (Figure 9). Orphenadrine reversed this micrographia effect in both groups. The

effects of phenobarbitone are more difficult to discern. In group 1 some slight effect is apparent over weeks 11, 12 and 13 and this is confirmed by a significant quintic trend ($F_{1,5} = 36.48$; $P < 0.01$). In group 2, where phenobarbitone was given first, no reversal effect was discernible but the micrographia increased significantly after the phenobarbitone was discontinued. The cubic trend was the most significant in this group ($F_{1,5} = 7.42$; $P < 0.05$).

Clinical ratings As can be seen from Figure 10, the overall IMPS total score decreased steadily in both groups, the linear trend being highly significant for both groups combined ($F_{1,11} = 67.12$; $P = 0.001$) with a just significant quadratic trend ($F_{1,11} = 7.03$; $P < 0.05$). There is a suggestion of some slowing down in the rate of improvement in group 1 when orphenadrine was added but this did not show in the trend analyses.

Within-patient correlations between measures The within-patient correlations matrix for the variables detailed above is set out in Table 2. It can

Figure 7 Mean values for the two groups of patients for pupil size under dim illumination. In group 1 (●), orphenadrine (O, 100 mg) 8 hourly was given during weeks 4, 5 and 6 and phenobarbitone (P, 50 mg) 8 hourly during weeks 10, 11 and 12. In group 2 (○), the order of additional drugs was reversed. Chlorpromazine (100 mg) 8 hourly was administered throughout the trial. The vertical bar (CD) refers to the critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

Figure 8 Mean values for the two groups of six patients for salivary flow rate. In group 1 (●), orphenadrine (O, 100 mg) 8 hourly was given during weeks 4, 5 and 6 and phenobarbitone (P, 50 mg) 8 hourly during weeks 10, 11 and 12. In group 2 (○), the order of additional drugs was reversed. Chlorpromazine (100 mg) 8 hourly was administered throughout the trial. The vertical bar (CD) refers to the critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

Figure 9 Mean values for the two groups of six patients for handwriting length. In group 1 (●), orphenadrine (O, 100 mg) 8 hourly was given during weeks 4, 5 and 6 and phenobarbitone (P, 50 mg) 8 hourly during weeks 10, 11 and 12. In group 2 (○), the order of additional treatments was reversed. Chlorpromazine (100 mg) 8 hourly was administered throughout the trial. The vertical bar (CD) refers to the critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

Figure 10 Mean values for the two groups of six patients for total IMPS score. In group 1 (●), orphenadrine (O, 100 mg) 8 hourly was given during weeks 4, 5 and 6 and phenobarbitone (P, 50 mg) 8 hourly during weeks 10, 11 and 12. In group 2 (○), the order of additional treatments was reversed. Chlorpromazine (100 mg) 8 hourly was administered throughout the trial. The vertical bar (CD) refers to the critical difference, i.e. means further apart than this are significantly different at the 0.05 level of significance at least.

Table 2 Within-patient correlations between measures

Chlorpromazine concentration	1	—										
Antipyrine plasma half-life	2	-0.32	—									
Standing systolic BP	3	-0.31	0.16	—								
Standing diastolic BP	4	-0.17	0.02	0.68	—							
Standing pulse rate	5	-0.15	-0.03	-0.37	-0.30	—						
Pupil size (dim)	6	-0.29	0.31	0.39	0.30	-0.30	—					
Salivation rate	7	-0.25	0.27	0.48	0.34	-0.24	0.43	—				
Handwriting length	8	-0.12	-0.06	0.16	0.11	-0.22	0.34	0.35	—			
Total IMPS score	9	0.02	0.35	0.04	0.05	-0.17	0.33	0.09	0.22	—		
		1	2	3	4	5	6	7	8	9		

$r > 0.15; P < 0.05$

$r > 0.19; P < 0.01$

$r > 0.24; P < 0.001$

be seen that almost all the correlations among the autonomic measures reach significant levels. Handwriting length also correlates significantly with several of the autonomic measures. A low but significant correlation exists between handwriting length and clinical rating score, low scores being associated with micrographia. Clinical scores also correlate with standing pulse rate and pupil size.

The antipyrine half-life correlates positively with some of the autonomic measures and with clinical ratings suggesting that the chlorpromazine effects on the liver parallel those on the autonomic measures and on clinical status. Plasma chlorpromazine levels correlate strongly (-0.32) with antipyrine half-life and with most of the autonomic measures. There is no within-patient correlation between plasma chlorpromazine level and clinical rating score.

Discussion

The results of this study confirm our original observations of the rise and then fall of plasma chlorpromazine levels over the first few weeks of treatment (Sakalis *et al.*, 1972). We previously proposed that the fall was caused by enzyme induction in the liver, and this appears to be so inasmuch as the plasma half-life of antipyrine is an estimate of liver microsomal oxidase activity. Such activity is almost certainly responsible for the processes of demethylation, sulfoxidation and hydroxylation of chlorpromazine. The utility of antipyrine half-life estimations was re-assessed in this study and confirms previous studies (e.g. Davies & Thorgeirsson, 1971) in showing the high reliability of repeated estimations in any individual.

In spite of enzyme induction, however, no significant quantities of any chlorpromazine metabolites were found in the plasma. Demethylated and sulfoxidized derivatives would have been found in the extracts in which chlorpromazine was assessed. Hydroxylated metabolites were sought with a method designed for the purpose of this study. Although pharmacologically this lack of material was surprising, it is not altogether unexpected from the biochemical viewpoint when the role of metabolism in facilitating excretion of drugs is considered. Nevertheless, certain other investigators have reported the presence of 7-hydroxychlorpromazine in the plasma of patients treated for longer periods than those in the present study (Iverson, personal communications; Sakalis, Chan, Gershon & Park, 1973; Kaul, Conway & Clark, 1974). Additionally, moderate quantities of the sulfoxide, together with small quantities of demethylated metabolites

have been detected in patients treated for long periods (Curry & Marshall, 1968).

The interactions with orphenadrine and phenobarbitone were clear. Chlorpromazine concentrations were lowered by both drugs to about the same extent. In parallel, antipyrine plasma half-lives were further shortened by the addition of these drugs with a prompt return to previous levels when the added drugs were discontinued. The effects of chlorpromazine on blood-pressure and pulse rate were reduced by both drugs to a similar extent, presumably reflecting a diminution in the α -adrenoceptor blocking actions of chlorpromazine, consequent on its reduction in plasma concentration. Other physiological effects of chlorpromazine were also attenuated by orphenadrine and phenobarbitone, but to a much greater extent with the former drug. This could be interpreted as a mixed effect, a reduction in plasma chlorpromazine concentration by both drugs, together with a further anticholinergic effect possessed by orphenadrine alone. Unlike our previous study (Sakalis *et al.*, 1972), handwriting length was a particularly sensitive measure.

The correlations between the autonomic measures were all significant and often substantial, and chlorpromazine concentrations correlated with these measures, confirming our previous study (Sakalis *et al.*, 1972). Handwriting length also correlated with most autonomic measures, suggesting similar time courses of drug action between central and peripheral effects.

As expected there was a significant within-patient correlation between antipyrine half-life and plasma chlorpromazine concentrations. Furthermore, there were appreciable correlations between antipyrine half-life on the one hand and the autonomic measures and clinical scores on the other. This obviously reflects the close relationship between antipyrine half-life and plasma chlorpromazine level. However, this relationship might be interpreted as meaning that the factors governing the antipyrine half-life are themselves altered as an effect of chlorpromazine rather than being just correlates of it. As previously, clinical improvement within-patient did not correlate with chlorpromazine levels. Finally, there was a significant relationship between handwriting length and clinical ratings, supporting the clinical impression that minimal extrapyramidal effects are an unavoidable concomitant of the therapeutic actions of most major tranquillisers.

Thus, it appears that chlorpromazine induces its own metabolism due to induction of liver microsomal oxidase enzymes. Its plasma concentration drops with time but clinical improvement continues. In our previous study (Sakalis *et al.*, 1972), we postulated the formation of an active

metabolite, perhaps 7-hydroxychlorpromazine, but in the present study we could find no evidence for this or any other potentially important metabolite. Another possibility is that chlorpromazine exerts its action in a remote pharmacokinetic compartment in the brain, but this is unlikely as the brain is highly vascular, and there is no evidence for such a compartment (Curry, Derr & Maling, 1970). The mechanism of chlorpromazine action might involve slowly reversible binding of small quantities of drug to active sites, or slowly reversible changes in receptors, but there is no evidence for such phenomena. Finally, chlorpromazine is administered within a behavioural and social context, the patient in the ward, in this instance. One cannot ignore the behavioural components of the response, and the chlorpromazine treatment might act more in the nature of interrupting a vicious circle than of chronic suppression of symptoms.

In practical clinical terms there appear to be no advantages in combining chlorpromazine and phenobarbitone (and presumably other barbitu-

rates), and possible detriments. The combinations will result in lowered plasma chlorpromazine concentrations, paralleled by increased urinary excretion of chlorpromazine metabolites (Forrest, Forrest & Serra, 1970). Orphenadrine and also trihexyphenidyl (Rivera-Calimlim, Castañeda & Lasagna, 1973) also lower plasma chlorpromazine concentrations when given in conjunction. However, orphenadrine acts more by virtue of its anticholinergic effects than by lowering chlorpromazine concentrations. Whether the advantages of administering an antiparkinsonian agent are outweighed by its disadvantages—increased autonomic effects and the danger of a toxic psychosis—still has to be assessed in each individual case. But there is no scientific case for prescribing such compounds routinely in all patients receiving major tranquilisers.

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