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SHORT COMMUNICATIONS

The effect of antipyretic analgesics on the metabolism of chlorpromazine in man*

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THE DEVELOPMENT of analytical methods for the identification and quantification of some of the major chlorpromazine metabolites, namely, unchanged chlorpromazine (CP), chlorpromazine sulfoxide (CPO), hydroxychlopromazine (CPOH), and chlorpromazine glucuronides (CPGL) has made available a technique for determining the blood levels and urinary excretory patterns of these metabolites in patients. Blood levels of chlorpromazine were found to be generally low but almost parallel to the urinary excretions, and are fairly proportional to the dosages.[1] Chlorpromazine glucuronides were found to be the major metabolites in blood and in urine[2] which accounted for nearly 44 per cent of the administered dose.

The unchanged chlorpromazine has been regarded as the active form of this drug in accordance with reports that its oxidation products have less pharmacological effect than chlorpromazine[3] and that CPGL possess a negligible effect.[4] It is speculated that if the blood level of the unchanged chlorpromazine could be raised, it might favor the rate of transport of this drug through the blood–brain barrier, which would in turn enhance the clinical effect of this drug on patients. A metabolic approach is therefore designed to provide further insight into the effect of a second drug which would compete with chlorpromazine for the hydroxylation or glucuronidation processes that occur in the liver. Such competing agents should yield quantitative differences in the excretion pattern of chlorpromazine and possibly produce further clinical changes.

Antipyretics such as acetylsalicylic acid, salicylamide, and acetanilid are known to be prone to oxidation in biological systems to form hydroxy derivatives and glucuronides.[5–7] When one of these drugs is administered concomitantly with chlorpromazine, it competes with chlorpromazine in the formation of hydroxy derivatives or glucuronides. It was observed that, as a result of the competing effect of these substrates, formation of hydroxychlorpromazine and chlorpromazine glucuronides diminished as evidenced by the fact that the blood levels of non-polar metabolites increased and the urinary excretion of polar metabolites decreased significantly compared with the control levels. Of the three competing agents used in this study, acetanilid was found to be the most powerful metabolic competitor against chlorpromazine, followed by salicylamide; acetylsalicyclic acid was the weakest.

METHODS

Subjects selected for this study were male psychotic patients between the ages of 21 and 45. Patients with complicating organicity and subnormal intelligence were screened from the study. Psychometric procedures such as the In-patients Multidimensional Psychiatric Scale (IMPS), were employed as a method of evaluating patients' symptomatology. In addition, the Psychotic Reaction Profile (PRP) was recorded by the nursing personnel. All such evaluations were continued on a weekly basis throughout the course of the study. Upon selection for study, patients were placed on a chlorpromazine medication administered in the form of a liquid concentrate. Along with this medication they also received a simulated placebo capsule, in accordance with the double-blind design[8] of the study. In all cases, the dosage was adjusted to individual needs until such time as acute symptomatology abated and the patient's clinical course showed signs of stabilization. The oral dosage necessary to achieve such a state for these patients was between 0·3 and 0·4 g, t.i.d. During this conditioning period, kidney function was tested by applying the phenolsulfonphthalein excretion test; liver function was

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checked by analyzing the serum bilirubin, serum glutamic-oxaloacetic transaminase (SGOT) and serum glutamic-pyruvic transaminase (SGPT).

Daily urine specimens were collected during the 12-hr period from 7 a.m. to 7 p.m. and analyzed throughout the study. Baseline for the excretion of the four groups of metabolites (CP, CPO, CPOH, and CPGL) was established by analyzing the urine specimens according to the procedure described in a previous communication.[2] After the baseline control was established for each patient, a combination of 1 g acetylsalicyclic acid plus 0·2 g chlorpromazine was administered three times a day for a period of 3 days. The results of the urinalysis obtained during the combination drug period was compared with that of the baseline control period for each patient.

One week after the last dose of the above combination of drugs was administered, patients were conditioned by maintaining them on a medication of 0·3 to 0·4 g chlorpromazine, t.i.d. for a period of 4 weeks. During this conditioning period, observation of the patients' clinical conditions continued to see if any after-effect was produced by the prevous combination drug treatment. In the second phase of this study, patients were given 1 g salicylamide plus 0·2 g chlorpromazine three times a day for a period of 3 days. Daily observation of patients and urinalysis contined for another 4 weeks to evaluate changes in the clinical state of the patients and the excretory patterns of the chlorpromazine metabolites.

In the third phase, patients were assigned to a 3-day treatment interval of a combination of 1 g acetanilid plus 0·2 g chlorpromazine three times a day. Repetitive observations of patients and urinalysis continued for 4 weeks to evaluate the combined effect of these drugs.

Blood specimens were obtained during the conditioning period (control) and at the end of the 3-day period of the combination drug treatment. Blood specimens were obtained at a predetermined peak level, i.e. 3 hr after the second medication. The serum was separated by centrifugation and a 5-ml aliquot was analyzed for the nonpolar and polar metabolites of chlorpromazine, according to the method described in a previous communication.[1]

RESULTS AND DISCUSSION

In the first phase of this study with the combination of the acetylsalicyclic acid plus chlorpromazine, patients showed no significant change in the excretion of the chlorpromazine metabolites nor was there any observable change noted in their clinical state before and after the tests. The results of these indicated that acetylsalicylic acid was not an effective glucuronidation-competing substrate.

In the second phase of this study, with the combination of salicylamide plus chlorpromazine, patients showed no particular clinical change. It was found that patients 3 and 4 showed little or no change in the urinary level of chlorpromazine metabolites; however, patients 1, 2, and 5 exhibited a significant descrease in the urinary level of the metabolites, especially the glucuronides.

In the third phase of this study, with the combination of acetanilid plus chlorpromazine, a moderate change in the patients' clinical state and a remarkable change in the urinary excretory pattern of the chlorpromazine metabolites were observed.

TABLE 1. EFFECT OF ACETANILID ON SERUM LEVEL OF CHLORPROMAZINE METABOLITES*

	Serum	
Patient	Before medication	After medication
	CP & CPO (μg/5 ml)	CP & CPO (μg/5 ml)
M.S.	5·2 ± 0·5	17·3 ± 1·4
E.K.	5·4 ± 0·3	9·2 ± 1·0
W.K.	4·3 ± 0·4	2·2 ± 2·1
B.P.	2·4 ± 0·3	11·4 ± 1·5

*Data expressed as mean ± mean S.E.; CP = unchanged chlorpromazine; CPO = chlorpromazine sulfoxide.

As shown in Table 1, all 5 patients showed a decrease in the excretion of chlorpromazine glucuronides by 25–63 per cent, and the unchaged chlorpromazine increased by 22–160 per cent of the control level. The chlorpromazine sulfoxide level showed a significant rise; however, the hydroxychlorpromazine level showed little or no change. Clinically, 4 patients, who had a long history of hospitalization and medical treatment, showed a moderate degree of improvement in their condition compared with other control period. The remaining patient showed little or no response to the treatment. These centrally acting antipyretic analgesics might have a potentiating effect on chlorpromazine, but further studies would be needed to evaluate the clinical effects of this drug combination because of the small number of patients involved in this study.

It appears that acetanilid possesses a greater ability to compete with chlorpromazine in the formation of glucuronide, as indicated by the decreased level of chlorpromazine glucuronides and increased excretion of the unchanged chlorpromazine found in urine when acetanlid was administered to the patients concomitantly with chlorpromazine. The increase in the blood level (Table 2) of the unchanged chlorpromazine was reflected in the increased urinary excretion of this drug, as indicated in the

TABLE 2. EFFECT OF ACETANILID ON THE EXCRETION OF URINARY CHLORPROMAZINE METABOLITES*

	Control Period (%)				Combination drug period (%)			
Patient	CP	CPO	CPOH	CPGL	CP	CPO	CPOH	CPGL
W.H.	0·96 ± 0·14	10·15 ± 2·25	2·52 ± 0·65	27·62 ± 3·81	1·18 ± 0·32	12·37 ± 2·55	2·49 ± 0·43	21·50 ± 3·31
B.P.	0·56 ± 0·12	4·47 ± 1·19	4·65 ± 0·83	25·98 ± 3·33	1·15 ± 0·29	6·38 ± 1·23	4·25 ± 0·85	17·84 ± 3·63
W.K.	0·24 ± 0·08	3·33 ± 0·75	2·67 ± 0·78	17·78 ± 3·30	0·62 ± 0·11	5·16 ± 1·29	3·05 ± 0·81	13·34 ± 2·67
E.K.	1·86 ± 0·33	5·60 ± 1·40	3·25 ± 0·54	29·29 ± 5·62	2·26 ± 0·32	6·65 ± 0·72	3·16 ± 0·72	20·66 ± 2·12
M.S.	1·66 ± 0·43	11·75 ± 1·21	5·64 ± 0·86	48·43 ± 8·03	2·16 ± 0·41	13·37 ± 1·43	5·24 ± 0·79	17·92 ± 4·44

* Data expressed as mean percent of administered daily dose ± S.E. CP = unchanged chlorpromazine; CPO = chlorpromazine sulfoxide; CPOH = hydroxychlorpromazine; CPGL = chlorpromazine glucuronide.

report[1] that the urinary excretion of chlorpromazine nearly parallels its blood level. It is therefore speculated that as a result of the elevated blood level the quantity of the active form of the drug to cross the blood-brain barrier would be increased. Quantitatively, the decreased excretion of CPGL was not directly reflected in the increased excretion of CP. Whether there is any increase in the rate of fecal excretion of CPGL as a result of the combination with these drugs is not known at present, there is no evidence to show that the clinical improvement of these patients was due to the synergistic effect of acetanilid and chlorpromazine.

Combination effects of antipyretic analgesics (acetylsalicylic acid, salicylamide, and acetanilid) plus chlorpromazine were tested on 5 psychotic patients who had been on maintenance doses of chlorpeomazine for some time. These tests were conducted on a double-blind basis and daily clinical observation of the patients as well as daily urinalysis was carried out. The results indicated that acetanilide is a potent hydroxylation-competing substrate against chlorpromazine, as evidence by the fact that urinary excretion of chlorpromazine glucuronides decreased remarkably with a significant rise in the level of the unchanged chlorpromazine in blood and urine. Chlorpromazine sulfoxide in urine also increased; however, the hydroxychlorpromazine level did not change appreciably. Salicylamide demonstrated a mild competing effect on glucuronidation of chlorpromazine so that only half of the patients tested showed a significant decrease in the urinary level of chlorpromazine glucuronides. Acetylsalicyclic acid exhibited almost no effect on either the clinical condition or metabolite pattern of these patients.

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Metronidazole and atypical human alcohol dehydrogenase

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IT IS well known that human enzymes may exist in a variety of forms. Further, these forms may differ in their response to various inhibiting agents (e.g. the inhibition of various forms of cholinesterase by dibucaine). Two varieties of human liver alcohol dehydrogenase are known, the *typical* and the *atypical* forms.[1]

Recently[2] we reported our finding that metronidazole was a non-competitive inhibitor of a crude preparation of typical human liver alcohol dehydrogenase. We have now had the opportunity of investigating the effect of metronidazole on a crude preparation of atypical human liver alcohol dehydrogenase, using identical methods.

The liver was obtained at laparotomy (which was negative) for a suspected peptic ulcer from a 59 yr old male who had no clinical evidence of liver disease. An homogenate was subjected to the screening test of von Wartburg *et al.*[1] and typed as atypical on the basis of results set out below:

Assay conditions	Relative activity	
	Atypical enzyme	Mean of 24 typical enzyme samples
Sodium pyrophosphate buffer (pH 8·8) = control = 1	1·0	1·0
Glycine-NaOH buffer (pH 11·0)	0·53	1·92 ± S.D:0·30
Sodium pyrophosphate buffer (pH 8·8) + $6{\cdot}6 \times 10^{-1}$ M thiourea	0·39	1·29 ± S.D:0·15