PREDICTIVE INDICES FOR CHLORPROMAZINE THERAPY IN SCHIZOPHRENICS

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- 1 Response to chlorpromazine therapy was studied in 24 schizophrenics and 75% reduction in Brief Psychiatric Rating Scale (BPRS) within 4 weeks of treatment was taken to indicate good response.
- 2 Test oral dose of CPZ (200 mg) was administered and serial blood samples and total urine excreted in 6 h were taken for analyses of CPZ and its metabolites.
- 3 Area under the plasma time curve (AUC) showed an inverted U-shaped relationship with % reduction in BPRS.
- 4 Three groups of patients were identified, responders, l- and h-group non-responders.
- 5 l- and h-groups respond on further treatment with haloperidol (30 mg daily) and ECT respectively.
- 6 Responders showed threshold metabolic molar fraction $MMF_{HO-CPZ} \geq 3.0 \times 10^{-5}$ and $MMF_{HO-CPZ}/MMF_{CPZ-SO} \geq 1$.

Introduction

Chlorpromazine (CPZ) is used in the treatment of schizophrenia because of its dopamine receptor blocking activity (Horn & Snyder 1971; Snyder, 1976; Carlsson, 1978), but it has shown wide variability in plasma level with its attendant clinical responsiveness. Drug concentration in plasma seems to be only weakly correlated to the therapeutic effect (Sakalis *et al.*, 1972; Rivera-Calimlim *et al.*, 1973, 1976, 1978) and this low correlation may reside in the inter-individual differences in CPZ metabolism resulting in different levels of active and inactive metabolites in different patients (Sakalis *et al.*, 1973, 1977; Mackay *et al.*, 1974; Sakurai *et al.*, 1975; Phillipson *et al.*, 1977). The high protein binding of CPZ in plasma and the CSF/plasma ratio which seem to be an individual factor (Piafsky *et al.*, 1978; Wode-Helgodt & Alfredson, 1981) may also contribute to this low correlation. The problem is still unresolved as to which pharmacokinetic parameters of CPZ would be best correlated to the therapeutic responsiveness (May & van Putten, 1978).

This work is designed to study possible predictive indices for effective response to CPZ therapy in schizophrenics.

Methods

CPZ and its metabolites, 7-hydroxychlorpromazine (HO-CPZ), chlorpromazine sulfoxide (CPZ-SO), chlorpromazine-*N*-oxide (CPZ-NO), mono- and di-desmethylchlorpromazine (CPZ-nor₁ and CPZ-nor₂) were gifts from Dr A.A. Manian of National Institute of Mental Health, Rockville, U.S.A. The internal standard, 2-4-dichlorpromazine (di-CPZ) was a gift from Dr O. Nemecek of Research Institute for Pharmacy and Biochemistry, Prague.

Patients

Twenty-four hospitalized schizophrenic patients (average age $\pm$ s.d. 25 ± 6 years), admitted to the psychiatric ward of the University Teaching Hospital Complex at Ile-Ife, Nigeria were diagnosed by the method of Spitzer *et al.* (1978). They had not received psychotropic medications for at least 1 month and had no clinical and laboratory evidence of haematological, hepatic or renal dysfunction. Blank blood and urine samples were obtained from the patients. The subjects then received oral administration of CPZ (200 mg) and blood samples (6 ml) were taken hourly for 6 h. The total urine excreted in this period was also

collected. Chlorpromazine was given in four divided doses with a total of 500 mg/day, and treatment in some cases for up to 2 months. At weekly intervals blood samples were taken 3 h after first daily oral administration of 200 mg CPZ. The clinical assessment of clinical response was done with Brief Psychiatric Rating Scale (BPRS) at weekly intervals (Overall & Gorham, 1962). Reduction of 75% of BPRS within 4 weeks of treatment was taken as indication of good response. The non-responders were placed on either haloperidol (30 mg daily) or on electro-convulsive therapy (ECT).

Assay procedure

CPZ and its metabolites were extracted as described by Mackay *et al.* (1974). Analysis of 0.2 μ l injections of the final toluene-isoamyl alcohol (95–15) extract, was performed on a Varian 3740 g.c. using a Ni electron capture detector.

The g.c. was equipped with a glass column (2 m $\times$ 6.35 mm $\times$ 2 mm) packed with 3% OV-17 on chrom W-HP, 80/100 mesh. Injection port temperature was 317°C, column 297°C and detector 346°C. Nitrogen flow rate was 35 ml/min. Retention times (min) of di-CPZ, CPZ, CPZ-nor₁, HO-CPZ, CPZ-NO, CPZ-nor₂, CPZ-SO and HO-CPZ-SO were 2.7, 2.2, 2.4, 5.5, 3.7, 3.1, 6.5 and 9.5 respectively. 7-hydroxychlorpromazine sulphoxide was quantified by difference of HO-CPZ before and after treatment of urine or plasma in acid medium with 12.5% w/v TiCl₃ (0.1 ml). The internal standard (di-CPZ) was added to samples before extraction at a concentration of 5 μ g/ml, and the metabolites were measured by the ratio of their peak heights or areas to that of di-CPZ using a Varian CDSIII integrator.

Results

The results are summarised in Figures 1, 2 and 3 and Table 1. It can be seen from Figure 1 the inverted U-shaped relationship between area under the plasma concentration time curve (AUC_{0-6h}) and % Brief Psychiatric Rating Scale (BPRS).

AUC_{0-6h} shows a positive correlation when linearly regressed against CPZ plasma concentration 3 h after a test oral dose of 200 mg (Figure 2). These two pharmacokinetic terms were found also to correlate significantly with the mean weekly CPZ plasma concentration 3 h after ingestion of the drug (see Wode-Helgödt & Alfredsson, 1981).

The further examination of Figure 2 shows that patients whose Cp values lie between 40–80 ng/ml were all responders but above 80 ng/ml only one in six (16.7%) while below 40 ng/ml four in ten (40%) were responders. Non-responders with Cp values below 40 ng/ml and above 80 ng/ml were classified as l-group and h-group respectively and their mean plasma concentration and AUC_{0-6h} values are given on Table 1. These values were significantly different for the l-, h-group and the responders ($P < 0.001$).

CPZ and its metabolites HO-CPZ, CPZ-SO, HO-CPZ-SO, CPZ-nor₁, CPZ-nor₂ and CPZ-NO were identified in the urine but showed quantitatively interpatient variation. The molar metabolic fraction (MMF) defined as the ratio of moles of a metabolite excreted in 6 h to the moles of parent drug ingested was calculated for HO-CPZ (MMF_{HO-CPZ}) and CPZ-SO (MMF_{CPZ-SO}). The plot of MMF_{HO-CPZ} against the ratio MMF_{HO-CPZ}/MMF_{CPZ-SO} is shown in Figure 3. The threshold values for responders were MMF_{HO-CPZ} $\geq 3.0 \times 10^{-3}$ and MMF_{CPZ-SO} ratio ≥ 1 .

There were symptoms of severe postural hypo-

Figure 1 The relationship between % reduction of BPRS (after 4 weeks of treatment with CPZ) and AUC_{0-6h} . ● non-responders, □ responders. BPRS = Brief Psychiatric Rating Scale.

Figure 2 The relationship between AUC_{0-6h} and plasma concentration of CPZ (C_p) 3 h post oral administration of 200 mg CPZ. ● non-responders, □ responders. $y = 3.2x + 16.3$, $r = 0.88$ ($n = 24$) $P < 0.01$.

tension and sedation in three of the h-group patients. While h-group patients showed good response to ECT, the l-group responded to a further treatment with haloperidol (30 mg daily).

Discussion

AUC values could be used as the best estimates of drug exposure at the receptor sites (Potter *et al.*, 1980) and this parameter in our data shows the inverted U-shaped (Figure 1) relationship concept of Curry *et al.* (1970) and Rivera-Calimlim *et al.* (1973, 1976) with respect to the responsiveness of CPZ therapy. Our result suggests that intermediate C_p and AUC values appear to be associated more with responders rather than non-responders.

Non-responders are known to have high plasma CPZ-SO (Sakurai *et al.*, 1980) and high CSF CPZ-SO levels (Axelsson *et al.*, 1975) with suggested low levels of HO-CPZ and CPZ. It may be speculated that the

Figure 3 MMF_{HO-CPZ} and $MMF_{HO-CPZ}/MMF_{CPZ-SO}$ values in schizophrenics 6 h after oral administration of 200 mg CPZ. ● non-responders, □ responders. MMF = ratio of the number of moles of metabolite excreted to the moles of parent drug ingested.

use of drugs like chloroquine that suppress the ring sulfoxidation of CPZ (Traficante *et al.*, 1979) or drugs that displace CPZ from plasma protein enhance C_p values in l-group patients with a possible improved response, but this might lead to severe toxicity in h-group patients with predominantly high C_p values for CPZ. This high value of CPZ-SO in non-responders was responsible for the low $MMF_{HO-CPZ}/MMF_{CPZ-SO}$ ratio observed in this study.

Our observation with haloperidol appears to agree with the studies of Sakurai *et al.* (1980). Smith *et al.* (1967) have shown that ECT-chlorpromazine combination to be better than CPZ alone in the treatment of schizophrenia, but Taylor (1980) was of the opinion that the use of ECT alone was superior to the combination of ECT and neuroleptics. These two studies with ECT might have involved a heterogeneous group of patients with different responsiveness to these treatments. These differences in thera-

Table 1 CPZ plasma concentration (3 h post administration) and AUC_{0-6h} values in schizophrenics after oral test dose of CPZ (200 mg).

	Responders	Non-responders	
		h-group	l-group
Plasma concentration (ng/ml)	51 ± 6	98 ± 11	28 ± 11
AUC_{0-6h} (ng/ml ⁻¹ h)	196 ± 19	277 ± 18	130 ± 15
Number of patients	13	5	6

Values are means $\pm$ s.e mean, and these are significantly different for each group ($P < 0.001$).

peutic response to CPZ might be genetic and may lie on the population of different dopamine receptors (Gower & Marriott, 1981; Horn *et al.*, 1981) and their relative affinities to CPZ, haloperidol (Snyder, 1981) or electroconvulsive shock.

The use of MMF was a noninvasive method of differentiating responders from non-responders,

although there was no discrimination between the l- and h-group of patients using this parameter. Furthermore, the MMF and plasma data may be a total reflection of individuals genetic expression, and as such, could be used as indices for classification and treatment of schizophrenics after a test dose of CPZ.

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