BAHAGIAN PENYELIDIKAN & PEMBANGUNAN

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Laporan Akhir Projek Penyelidikan Jangka Pendek

1) **Nama Penyelidik:** Prof. Madya (Dr) Mohd. Razali Salleh

Nama Penyelidik-Penyelidik Lain *(Jika berkaitan)* : Prof. Madya (Dr) Rusli Ismail

2) **Pusat Pengajian/Pusat/Unit** : Pusat Pengajian Sains Perubatan, Jabatan Psikiatri.

3) **Tajuk Projek:** KOLERASI RESPONS KLINIKAL DENGAN PARAS PLASMA UBAT - UBATAN ANTIPSIKOTIK DAN ANTIDEPRESI.

Catitan: Kolerasi dengan ubat antidepresi tidak dapat dijalankan kerana kerana kekurangan pesakit.

4) (a) **Penemuan Projek/Abstrak**

*(Perlu disediakan makluman di antara 100 - 200 perkataan di dalam **Bahasa Malaysia dan Bahasa Inggeris** Ini kemudiannya akan dimuatkan ke dalam Laporan Tahunan Bahagian Penyelidikan & Pembangunan sebagai satu cara untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti).*

Tujuan kajian ini ialah untuk menentukan dos terapeutik dan paras plasma Chlorpromazine yang optima bagi merawat penyakit Skizofrenia akut;dan mencari kolerasi diantara paras plasma dan respons klinikal.Lima puluh empat pesakit Skizofrenia dan dan kecelaruan Skizofrenifom (DSM IIIR) yang dimasukkan ke wad psikiatri Hospital USM dipilih untuk kajian ini. Rawatan dimulakan dengan 300mg Chlorpromazine sehari dan dos-nya dipertingkatkan setiap 2 minggu.Paras plasma Chlorpromadiukur dengan cara HPLC.Adalah didapati bahawa dos Chlorpromazine yang selalu dipreskrib kepada pesakit ialah 500mg sehari, 300mg adalah dos terendah dan 900mg yang tertinggi.Hitung panjang paras plasma Chlorpromazine ialah 67.9ng/ml.Tiada kolerasi diantara paras plasma dan respons klinikal;terutama nya pada dos yang tinggi.Oleh itu, kesimpulan dibuat yang majoriti pesakit Skizofrenia memerlukan Chlorpromazine dalam dos yang sederhana tinggi dan paras plasma Chlorpromazine 67.9ng/ml adalah termasuk dalam julat terapeutik.Pengukuran paras plasma ubat - ubatan neuroleptik tidak sesuai untuk dilakukan secara rutin.

4. (a) Penemuan Projek/Abstrak

(Perlu disediakan makluman di antara 100 - 200 perkataan di dalam Bahasa Malaysia dan Bahasa Inggeris. Ini kemudiannya akan dimuatkan ke dalam Laporan Tahunan Bahagian Penyelidikan & Pembangunan sebagai satu cara untuk menyampaikan dapatan projek tuan/puan kepada pihak Universiti).

The aim of this study is to determine the therapeutic dose and the optimum plasma level of Chlorpromazine for treatment of acute Schizophrenia and explored the correlation between plasma level and clinical response. Fifty-four patients diagnosed as Schizophrenia and Schizophreniform disorder (DSM-IIIR) admitted to the psychiatric ward, Hospital USM were selected for the study. The treatment was started with 300mg of Chlorpromazine daily and the dose was increased forthnightly, Chlorpromazine plasma level was measured by HPLC method. It was found that the most frequently prescribed dose was 500mg perday, 300mg being the lowest and 900mg the highest: the mean plasma concentration of Chlorpromazine was 67.9ng/ml. There was a poor correlation between plasma level and clinical response especially at a higher dose. It is concluded that majority of the acute Schizophrenia required a moderate dose of Chlorpromazine and the plasma concentration of 67.9ng/ml is within the therapeutic range. Plasma concentration monitoring of neuroleptic is not recommended for routine used.

(b) **Senaraikan Kata Kunci yang digunakan di dalam abstrak:**

Bahasa Malaysia	**Bahasa Inggeris**
Pemonitoran ubat terapeutik	Therapeutic Drug Monitoring
Psikofarmakologi,	(TDM), Psychopharmacology,
Skizofrenia, Chlorpromazine.	Schizophrenia, Chlorpromazine.

5) **Output Dan Faedah Projek**

(a) Penerbitan *(termasuk laporan/kertas seminar)*
(Sila nyatakan jenis, tajuk, pengarang, tahun terbitan dan di mana telah diterbit/dibentangkan).

Abstrak dari laporan ini telah dihantar untuk penilaian sebelum dibentangkan di Kongres Psikiatri Sedunia Yang Ke - 10 (Tenth World Congress of Psychiatry) pada 23 - 28hb. Aug 1996 di Madrid Sepanyol.Salinan abstrak tersebut dan laporan penuh kertas pembentangan (artikel) tersebut disertakan bersama.

(b) Faedah-Faedah Lain Seperti Perkembangan Produk, Prospek Komersialisasi Dan Pendaftaran Paten.
(Jika ada dan jika perlu, sila gunakan kertas berasingan)

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(c) Latihan Gunatenaga Manusia

i) Pelajar Siswazah .....

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ii) Pelajar Prasiswazah: .....

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iii) Lain-Lain : Hasil penyelidikan ini mengingatkan doktor - .....

doktor supaya tidak menggunakan ubat Chlorpromazine dalam .....

dos yang tinggi seperti yang selalu diamalkan bagi mendapat- .....

kan respons yang baik dan mengurangkan kesan sampingan. .....

6. **Peralatan Yang Telah Dibeli:**

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Tiada

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UNTUK KEGUNAAN JAWATANKUASA PENYELIDIKAN UNIVERSITI

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16/7/93

DATO' PROFESOR MUSTAFFA EMBONG
DEKAN/PROFESOR PERUBATAN
PUSAT PENGAJIAN SAINS PERUBATAN
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16150 KUBANG KERIAN
KELANTAN.

NEUROLEPTIC DOSAGE FOR ASIAN PATIENTS

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MALAYSIA

X WORLD CONGRESS OF PSYCHIATRY

MADRID, AUGUST 23-28 , 1996

ABSTRACT

The aim of this study is to determine the therapeutic dose and the optimum plasma level of chlorpromazine for treatment of acute schizophrenia.Fifty-four patients diagnosed as schizophrenia and schizophreniform disorder (DSM - IIIR) admitted to the psychiatric ward in a teaching hospital in Malaysia were selected for the study.The treatment was started with 300 mg of chlorpromazine daily and the dose was increased forthnightly till they improved. The clinical improvement was assessed by BPRS and the chlorpromazine plasma level was measured by HPLC method.It was found that the most frequently prescribed dose was 500 mg perday, 300 mg being the lowest and 900 mg the highest ; the mean plasma concentration of chlorpromazine was 67.9 ng/ml.There was a poor correlation between chlorpromazine dose and plasma level.It is concluded that majority of the acute schizophrenia required a moderate dose of chlorpromazine and the plasma concentration of 67.9 ng/ml is within the therapeutic range.

INTRODUCTION

Determination of the lowest effective dose of neuroleptic is regarded as a critical factor in clinical psychiatry. Too low a dose may result in inadequate blood level and the drug will be ineffective.Too high a dose not only increases side-effect but become less effective especially if the drug has therapeutic window response.As yet,no reliable clinical assessment available to determine the optimum dose of neuro leptic.Measurement of plasma concentration is the ultimate choice.

Control clinical trial had shown that moderate doses of neuroleptic (500 to 600 mg/day of chlorpromazine or its equivalent) were adequate to control acute psychotic episode in majority of patients (1).Lind and Finder(2) found that Asian patients required lower dosage of neuroleptic than caucasians ; however their finding was disputed by the other(3).In clinical practice the tendency to give higher dose of neuroleptic than required is common.Survey of neuroleptic drug utilization in various part of the world showed that many patients were prescribed doses above the recommended level,particularly if high potency drugs were used(4,5,6).

Patients who responded poorly to neuroleptic treatment usually end up with a high dose of drug.In such patients,the

neuroleptic doses were often inappropriately raised thereby giving the impression that it was the increase in medication that reduced the symtoms when it actually was the passage of time on medication.

The objective of this study is to determine the therapeutic dose and optimum plasma level of chlorpromazine for treatment of acute schizophrenia in a general psychiatric ward. This is a semi-flexible dose design study and thereby the dosage prescribed is expected to be higher than the recommended dose of fixed dose study but lower than the flexible dose design or uncontrolled study

METHODOLOGY

The study was conducted in University Hospital(USM),Kota Bharu on the east coast of peninsular Malaysia. All inpatients diagnosed as schizophrenia and schizophreniform disorder (DSM-IIIR)(7) during the study period were selected for the study if they could follow the treatment regime.Any cases who had been taking neuroleptic in the last two weeks were excluded.Patients sociodemographic and clinical variables were recorded in a standard proforma.

All the selected cases was started with initial dose of 300mg chlorpromazine daily in two divided dose.The dose was

increased by 100mg in every two weeks till the patients improved or developed side-effect.Used of other neuroleptic was not allowed.Benzhexol was only given when necessary. Night sedation was allowed for not more than five consecutive night.Concurrent use of other drugs should be properly documented. If the drug requirement exceeds the above criteria or the medication need to be increased before two weeks,the patients will be automatically discharged from the study.

Blood sample for measurement of chlorpromazine plasma level was taken in every two weeks before increasing the dose The sample was taken 10-12 after the last dose.At the same time patients improvement and side-effect of the drug were measured by Brief Psychiatric Rating Scale(BPRS)(8) and A Rating Scale For Extrapyramidal Side Effect(9) respectively.Drug concentration in the plasma was measured by HPLC(High-performance liquid chromotography) method.

Results

Fifty-four patients were included in the study and their biographical information is shown in Table 1. The racial distribution parallels that of the population in Kelantan.. More than 90% of the patients were Malays, 4% were Chinese and 2% Indians (Table 1).

Race		
	Malay	51
	Chinese	2
	Indian	1
Sex		
	Male	36
	Female	18
Age		
	Mean (± SD)	26.48 (7.96)
	Minimum	16
	Maximum	54
Weight		
	Mean (± SD)	53.81 (14.47)
	Minimum	33
	Maximum	125
Daily Dose (mg/kg)		
	Mean (± SD)	10.916 (4.125)
	Minimum	2.4
	Maximum	22.5
Plasma CPZ (ng/ml)		
	Mean (± SD)	67.89 (57.91)
	Minimum	5.0
	Maximum	561.5

Table 1. Demography of Study Patients

The most frequently prescribed dose was 500 mg per day, 300 mg being the lowest and 900 mg the highest (Fig. 1).

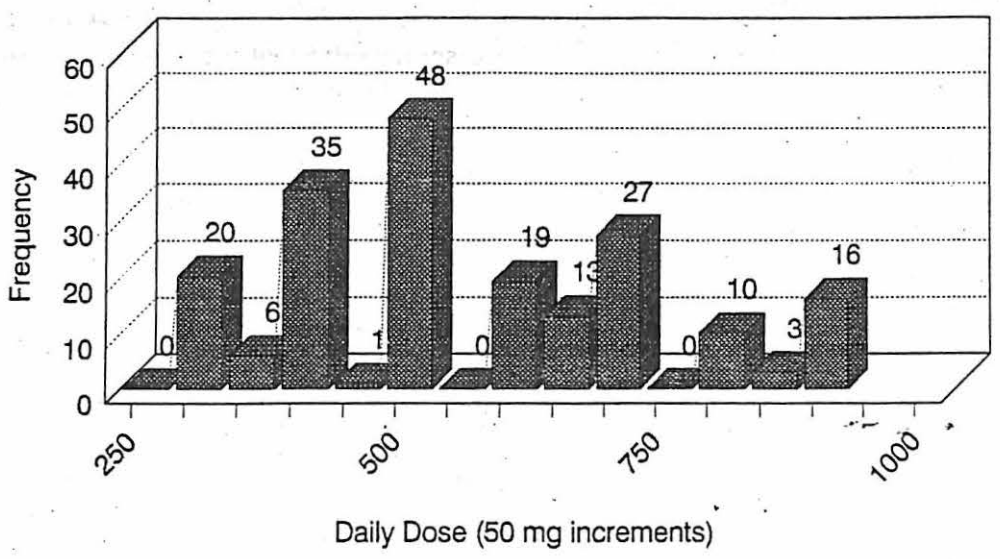

Fig. 1. Histogram Frequency of Daily Doses

Mean plasma concentration of chlorpromazine (plasma CPZ) obtained was 67.89 but many patients had concentrations below the sometimes recommended minimum of 50 ng/ml (Fig. 2).

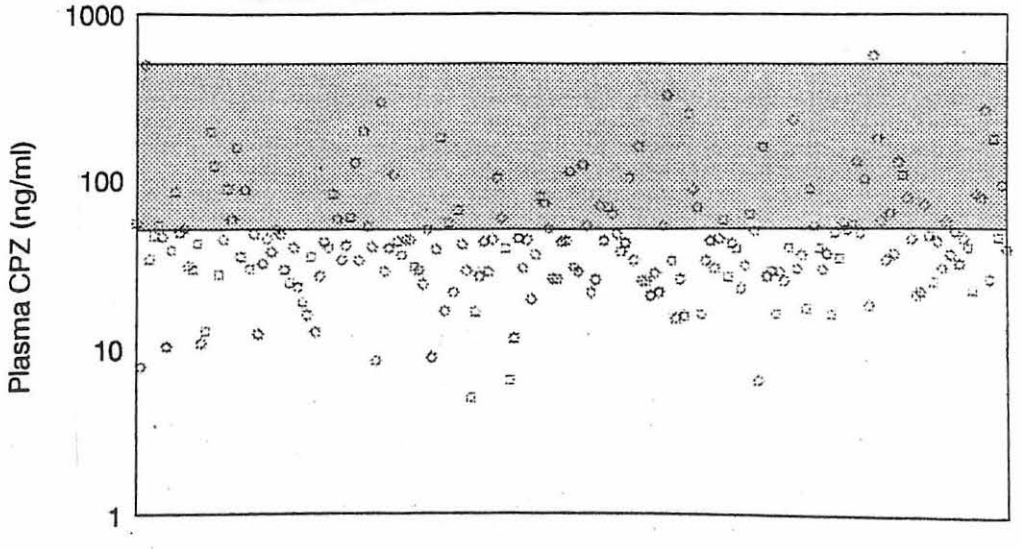

Fig.2. Scatter of Plasma CPZ (Log Scale, Target Range Shaded)

Plasma CPZ correlated poorly with daily doses, both total and in terms of body weight (Figs. 3a & 3b). A wide scatter of plasma CPZ ocurred with any given dos and a prediction is thus not possible. Plasma CPZ however tend to cluster around the regression line at doses below about 15 mg/kg/day. Above that, the increase in concentrations with increasing doses occur less proportionately.

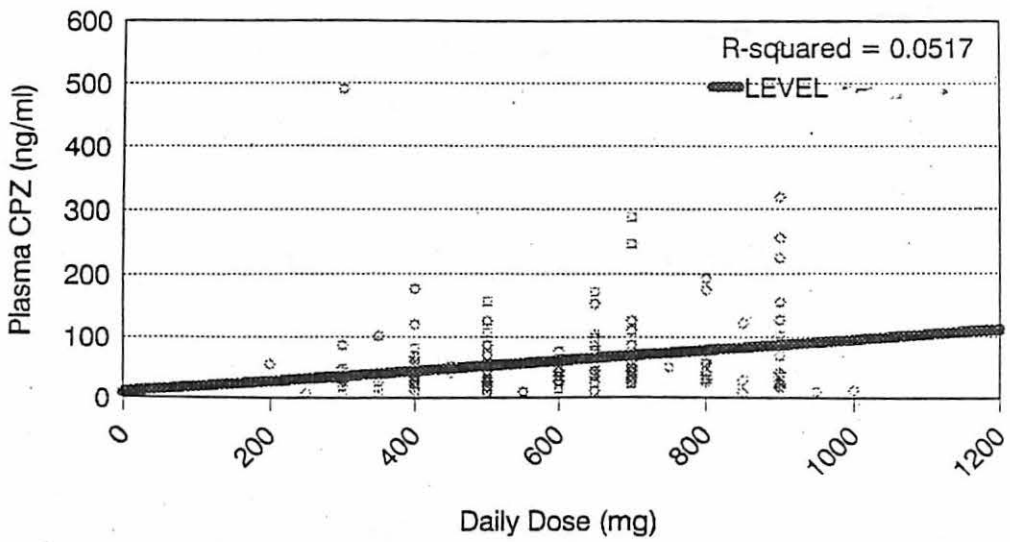

Fig. 3a. Plasma CPZ As A Function of Daily Dose

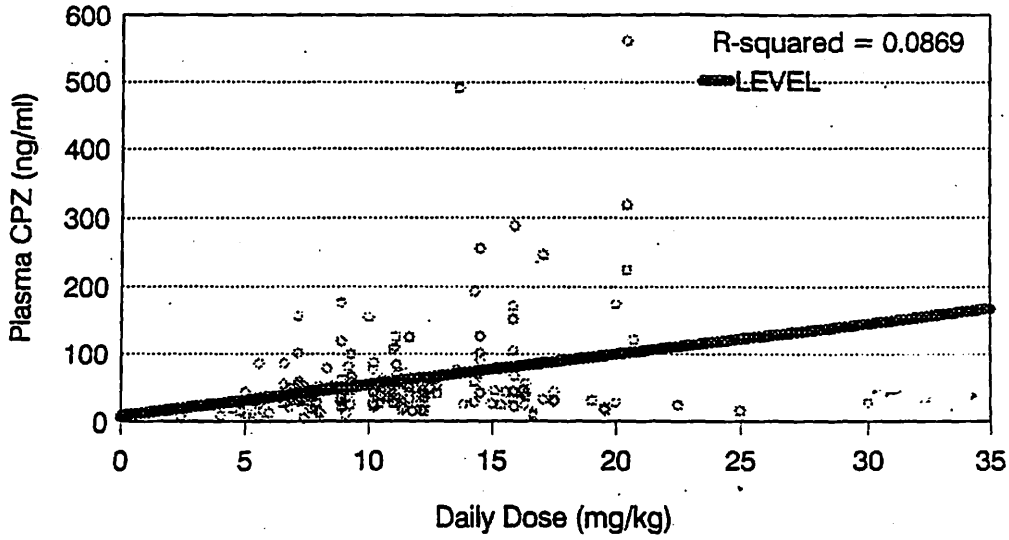

Fig. 3b. Plasma CPZ As A Function of Daily Dose

DISCUSSION

Although the study was a semi-flexible dose design,the mean daily dose of chlorpromazine to treat acute schizophrenia was within the range of fixed dose study of 500 to 600mg perday(1).However the dose was much lower than the mean daily dose of chlorpromazine or its equivalent to treat schizophrenic inpatients in uncontrolled studies in Australia,1126 mg(4); United States, 2653 mg(5) and Spain,1290 mg(6).

The much lower dose of chlorpromazine used in this study as compared with the three previous studies were related to differences in methodology and sample selection.In this study the dose could not be increased before two weeks, while the dose of neroleptic in the previous studies were determined from the patients clinical state.Majority of the patients in this sample were neither aggressive nor chronic.Most likely the aggressive patients were excluded from the study in the beginning because they could not comply with treatment regime.

As a teaching hospital we were able to select the patient for admission.Chronic cases were sent to a nearby psychiatric unit in General Hospital.Thus, majority of the cases selected for the study were less problematic and expected to require lower dosage of medication.The other pos

sibility was the patients might require less amount of drug due to lower body weight as compared with caucasians.Body weight for caucasians were generally 30-50% higher than Asians.

The mean plasma concentration of chlorpromazine found in this was 67.9ng/ml.This was within the therapeutic range of 50 to 300 ng/ml (10,11);other workers suggested a wider therapeutic range of 35-350 ng/ml(12).Poor clinical response was associated with both very high (>500 ng/ml) and very low (<10 ng/ml) plasma concentration(13).The greatest improvement was seen in patients with chlorpromazine plasma of 100-300 ng/ml(11). A few studies attempted to find a therapeutic window response of chlorpromazine but so far no concensus was reached.The suggested large range of therapeutic response did not benefit the clinician.It was likely that the upper end represent drug toxicity while the lower end probably reflex a minimal amount of drug necssary to achieve some therapeutic effect.However our study design was not aimed for detecting therapeutic window;ideally it should be a fixed dose design with adequate treatment period.

There was a poor correlation between chlorpromazine dose and plasma level(14).It is most likely that the same dosage of medication will produce different plasma level

and clinical response in each patient.For example, Alfredson et al (15) found that the steady-state serum chlorpromazine concentration showed a 20-fold variation in 25 patients receiving chlorpromazine 400 mg daily. As expected this study found the same, especially if the dose was more than 15 mg/kg.

Among the factors that may cause the discrepancy between dosage and plasma level are the individual pharmacokinetic variables such as absorption, first-pass effect,enzyme induction and bioavailability.According to Dahl(16),a major reason for the interindividual variation in plasma level of phenothiazine drug was due to large interindividual variation in the extent of presystemic metabolism of the drug.These factors also explained the difference of dose requirement between caucasians and Asians patients.

ACKNOWLEDGMENT

The authors acknowledge the research grant provided by Universiti Sains Malaysia that has resulted in this article.

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NEUROLEPTIC DOSAGE FOR ASIAN PATIENTS

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35mm SLIDES ☑
PROJECTOR
OVERHEAD ☐

LANGUAGE OF PRESENTATION
(Subject to availability of translators, see page 12).

ENGLISH ☑ SPANISH ☐ GERMAN ☐
FRENCH ☐ RUSSIAN ☐ JAPANESE ☐

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Title:

Neuroleptic dosage for Asian patients

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Educational Objectives (type single-space, 50 words or less): At the conclusion of this presentation, the participant should be able to (e.g. demonstrate, recognize, diagnose, treat...).

recognise that majority of the acutely psychotic patients in an Asian country required a moderate dose (300 - 900 mg daily) of Chloropromazine.The mean plasma concentration of 67.9 ng/ml was within the therapeutic range (50 - 300 ng/ml).

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35 mm Slide Projector (w/Remote Control) and Screen

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Literature References (list two)

1.Baldessarini RJ,Cohen BM,Teicher MH.Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses.Arch Gen Psychiatry 45:79-91,1988.
2.Lin KM,Finder E.Neuroleptic dosage for Asians.Am J Psychiatry 140:490-491,1983.

ABSTRACT: DOUBLE-SPACED TYPEWRITTEN SUMMARY OF PAPER SUBMISSION, INCLUDE OBJECTIVE, METHOD, RESULTS AND CONCLUSION (DO NOT EXCEED 200 WORDS). All copy must be contained in this box.

The aim of this study is to determine the therapeutic dose and the optimum plasma level of chlorpromazine for treatment of acute schizophrenia.All patients diagnosed as schizophrenia and schizophreniform disorder (DSM - III R) admitted to the psychiatric ward in a teaching hospital in Malaysia during the study period were included in the study.The treatment was started with 300 mg of chlorpromazine daily and the dose was increased forthnightly till they improved. The clinical improvement was assessed by BPRS and the chlorpromazine plasma level was analysed by HPLC.It was found that the most frequently prescribed dose was 500 mg perday, 300 mg being the lowest and 900 mg the highest ; the mean plasma concentration of chlorpromazine was 67.9 ng/ml.It is concluded that majority of the acute schizophrenia required a moderate dose of chlorpromazine and the plasma concentration of 67.9 ng/ml is within the therapeutic range.