

# Interaction of Chlorpromazine with Tricyclic Anti-Depressants in Schizophrenic patients

Pages with reference to book, From 233 To 234

Azmat Rasheed, Samia Nazir ( Faculty of Pharmacy, Punjab University, Lahore. )

Muhammad Afzal Javed ( Department of Psychiatry, Mayo Hospital, Lahore. )

Obaidullah Khawaja ( Department of Pharmacology, K.E. Medical College, Lahore. )

## Abstract

Interaction of Chlorpromazine with tricyclic antidepressants was investigated in twenty schizophrenic patients after their concurrent administration. A significant increase in serum chlorpromazine concentration was observed when administered in combination with both amitriptyline and imipramine with chlorpromazine. If combined therapy is indicated, the dose of chlorpromazine should be reduced or the time of administration of other two drugs should be adjusted to maintain therapeutic levels of chlorpromazine (JPMA 44:233, 1994).

## Introduction

Chlorpromazine is a versatile, prototype neuroleptic drug having variety of actions. It is a synthetic phenothiazine derivative that affects the pharmacological actions of a number of drugs, e.g., antacid<sup>1</sup>, antimalarial<sup>2</sup>, phenobarbitone<sup>3</sup>, Cimetidine<sup>4</sup> and Lithium carbonate<sup>5</sup> due to different drug interactions. It acts on the hypothalamus and brainstem reticular formation. It has a remarkable ability to control hyperactive and hypomanic states without seriously impairing consciousness. It modifies abnormal behaviours in schizophrenic states associated with increase dopaminergic activity in the limbic system of the brain<sup>6</sup>. Tricyclic antidepressants like amitriptyline and imipramine are chemically and structurally related to phenothiazines. These drugs contrary to chlorpromazine, enhance the neurotransmitter activity in the brain by blocking the reuptake of amine neurotransmitters. They increase the availability of adrenaline, noradrenaline and serotonin in the central nervous system<sup>7</sup>. Although neuroleptics are mainly used in the treatment of schizophrenia, yet antidepressants are also prescribed for the treatment of depression. A number of treatment studies have been undertaken to investigate the utility of adjunctive antidepressant medication in schizophrenia with secondary depression<sup>8,9</sup>. The present study was carried out to investigate the effects/interactions of amitriptyline and imipramine, two commonly used tricyclic antidepressants, on serum concentration of chlorpromazine after their concurrent administration to a group of schizophrenic patients.

## Patients and Methods

### Selection Criteria for Patients

Twenty male (between 30-50 years of age) schizophrenic patients diagnosed as per Diagnostic and Statistical Manual of Mental Health Disorders<sup>10</sup>, were selected for this study. They were resident members of Fountain House, a rehabilitation centre situated in Lahore. Patients enrolled in the study were made drug free and all the medications were discontinued ten days prior to the start of the study. The study was done in three stages. After 10 days of initial drug holiday, Chlorpromazine, Amitriptyline and Imipramine were administered orally in a sequence to the patients.

**Stage I:** Each patient was given chlorpromazine (200 mg). Blood samples were collected at 0,2,4,12 and 24 hours after the administration of drug for the determination of serum chlorpromazine

concentration.

**Stage II:** After a week interval the blood samples from each patient was taken at zero hour in the morning. Each patient was given chlorpromazine (200 mg) and amitriptyline (100 mg) concomitantly. Blood samples were then collected at 0,2,4,12 and 24 hours after the administration of both the drugs for the determination of serum chlorpromazine concentration.

**Stage III:** After an interval of another week the blood samples from each patient was taken at zero hour in the morning. Each patient was given chlorpromazine (200 mg) and imipramine (100 mg) concomitantly; blood samples were then collected at 0,2,4,12 and 24 hours after the administration of both the drugs for the determination of serum chlorpromazine level. Serum chlorpromazine concentration was determined according to the method adopted by Rasheed et al.<sup>11</sup> using Perkin Elmer 1320 Infrared Spectrophotometer at a wave length 273 nm.

## Results

Serum chlorpromazine level increased after concurrent administration of amitriptyline or imipramine and was maximum at 2 hours of administration. Although it gradually decreased at intervals of 4,12 and 24 hours yet its concentration remained consistently high as compared to the group receiving chlorpromazine alone. A significant increase in the serum chlorpromazine concentration was however observed ranging between  $23.44 \pm 1.40$ ,  $32.29 \pm 0.48$  and  $31.36 \pm 0.56$  ug/ml at 2 hours interval after the administration of drugs in stage I, H and III respectively (Table).

**Table. Serum chlorpromazine concentration alone and after its concurrent administration with Amitriptyline and Imipramine (Mean $\pm$ SEM).**

Drugs ug/ml	Time 2	Interval 4	In 12	Hours 24
Chlorpromazine	$23.44 \pm 1.40$	$20.78 \pm 1.28$	$8.60 \pm 1.48$	$4.21 \pm 1.09$
Chlorpromazine after Amitriptyline	$32.29 \pm 0.48^*$	$22.60 \pm 1.15^{**}$	$10.54 \pm 0.98$	$5.21 \pm 0.56$
Chlorpromazine after Imipramine	$31.36 \pm 0.56^*$	$23.10 \pm 0.36^{**}$	$12.65 \pm 0.37$	$6.45 \pm 0.47$

\*P<0.001

\*\*P<0.05

## Discussion

A significant increase in chlorpromazine was observed as compared to the base line levels at 2,4,12 and 24 hours among patients taking chlorpromazine and amitriptyline or imipramine concurrently than patients taking chlorpromazine alone. These results correlate with the findings of Grammer and Rolfe<sup>12</sup> and Lofa et al<sup>13</sup> that the concurrent administration of Chlorpromazine with tricyclic antidepressants significantly increase the serum chlorpromazine concentration in Schizophrenic patients at all time intervals. There may be many explanations for this increase, since chlorpromazine shares a common pathway for metabolism involving hepatic microsomal enzymes with imipramine and amitriptyline. Concurrent administration of these agents slows down the degradation of chlorpromazine resulting in

prolongation of its plasma half life and a rise in therapeutic level of drug in the blood. It can be speculated that the levels of the active drug in the blood may also be elevated on account of its displacement from its binding sites with plasma albumin. Chlorpromazine, imipramine and amitriptyline are lipophilic drugs and have a high binding capacity and are thus capable of binding with plasma albumin to a significant extent. As the total binding capacity of plasma albumin is limited, concurrent presence of the drugs may result in mutual displacement of each other from their binding sites. As a result of which the fraction of active drug is elevated and the pharmacological or therapeutic effect of chlorpromazine is potentiated. The increase in serum Chlorpromazine concentration observed after concurrent administration of Chlorpromazine and antidepressants might also be due to similarity of chemical structure. Chlorpromazine is metabolized in liver to cause induction of hepatic microsomal enzyme. It is more firmly bound to plasma protein and replaces the less bound tricyclic antidepressants resulting in its accumulation in the body. The practical implication of the interaction between chlorpromazine and amitriptyline or imipramine need special attention. Such type of drug interaction may enhance the therapeutic effects of chlorpromazine. Care should, therefore, be taken when chlorpromazine is prescribed with amitriptyline or imipramine. It is therefore recommended that when chlorpromazine and tricyclic antidepressants are prescribed together, the dose of chlorpromazine may be reduced or the timing of the administration of both the drugs should be adjusted in order to achieve the intended therapeutic response with minimum side effects.

## References

1. Pinch, O.C., Fenimore, D.C., Daris, C.M. and Fann, W.E. Drug- drug interaction of chlorpromazine and antacid. *Clin. Pharmacol. Ther.*, 1978;23: 125.
2. Mankuola, K.O.A., Dixon, P.A.F. and Oforah, E. Effects of antimalarial agents on plasma levels of chlorpromazine and its metabolites in schizophrenic patients. *Trop. Geogr. Med.*, 1988;40:31-3.
3. Logs, S., Cony, S. and Lader, M. Interactions of orphenadrine and phenobarbitone with chlorpromazine plasma concentrations and effects in man. *Br. J. Clin. Pharmacol.* 1975;2: 197.
4. Flower, C.A., Pullar, T., Sourindhrin, I. et al. Reduced steady-state plasma concentrations of indomethacin and chlorpromazine in patients receiving cimetidine. *Soc. J. Clin. Pharmacol.*, 1983;24:99-102.
5. Yassa, R. A case of lithium-chlorpromazine interaction. *J. Clin. Psychiatry*, 1986;47:90-1
6. Carlsson, A. Antipsychotic drugs, neurotransmitters and schizophrenia. *Am. J. Psychiatry*, 1975;135:164-73
7. Graves, D.L. and Davis, J.M. Biogenic amine Hypotheses of affective disorders (Mini review) *Life Sci.*, 1979;24:353-94.
8. Sins, E.G., Morgan, V., Fagersform, R. et al. Adjunctive imipramine in the treatment of post-psychotic depression. A controlled trial. *Arch. Gen. Psychiatry*, 1987;44:533-39
9. Kramer, M.S., Vogeh, W.H., Dijoson, C. et al. Antidepressants in depressed schizophrenic patients: A controlled trial. *Arch. Gen. Psychiatry*, 1989;46:922-28.
10. American Psychiatric Association. Diagnostic and statistical manual of mental health Disorders. 3rd revised edition. Washington, D.C., APA, 1987; P.p.194-95.
11. Annat Rasheed, M. Riz and Shsbhir Hussain Qureshi. Interaction of chlorpromazine with aspirin in schizophrenic patients *Pat J. Clin. Psychiatry*, 1992;2:81-86.
12. Grannmer, J.L. and Rolfe, B. Pharmacokinetics of imipramine: and chlorpromazine in man. *Psychopharmacologia*, 1972;26(Suppl):80.
13. Logs, S., Curry, S. and Lathe, M. Interaction of chlorpromazine and nortriptyline in patients with schizophrenia. *Clin. Pharmacokinet.*, 1981;6,454-62.