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A COMPARATIVE STUDY OF SIDE-EFFECTS OF LITHIUM, CARBAMAZEPINE AND HALOPERIDOL IN ACUTE MANIA

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ABSTRACT

In an open trial on manic patients, side-effects of carbamazepine, lithium and haloperidol were evaluated weekly over a 4-week period. The total side-effects with the three drugs were not significantly different, but the rate of amelioration of the same was best for lithium and least for haloperidol. It was indicative that lithium was better tolerated drug than the other two.

Key Words : Side - effects, Lithium, Carbamazepine, Haloperidol, Acute mania.

INTRODUCTION

Lithium (Li) and carbamazepine (CBZ) are the accepted first line anti-manic drugs (Kaplan et al 1994). Haloperidol (HP) previously, was one of the accepted modes of treatment for mania (Shopsin et al 1975) and is being still used widely for the acute treatment of mania. All these agents have annoying and obtruding side-effects . The side-effect profile of these agents often dictates their use in patients, as they can prevent further raising of the doses and/or affect the compliance of the patient. As part of the study dealing with their efficacy (the results of which have been sent for publication elsewhere), we aimed to study their side-effect profile, and thereby the comparative tolerability of these agents.

MATERIAL AND METHODS:

In an open study, adult patients from the out patient section of the Department of Psychiatry, K.G.'s Medical College, Lucknow diagnosed as bipolar disorder - mania according to DSM-III-R criteria (APA,1987) were randomly allocated to one of the three treatment groups - Li, CBZ and HP. Informed consent was taken from all the patients. Baseline investigations included complete hemogram, liver function and renal function tests. The selected patients were rated on Bech-Rafaelson Mania Scale (Bech et al 1978) on days 0,7,14,21and 28 and side - effect checklist on days 7,14,21, and 28. The side-effect checklist consisted of pooled items from three sources - WHO Multicentric Collaborative Study (WHO 1986) for HP, role of hereditary, clinical and pharmacokinetic factors for prediction of lithium (WHO 1988) for Li and Myler's Textbook of side-effects (1988) for CBZ.

On day 'O' the selected patients were started on either CBZ (200mg/d, which was built upto 800 mg/d by the end of first week), or HP (15 mg/d) or Li (900mg/d). Oral trihexyphenidyl (6mg/d) was given with haloperidol, and in all the groups oral diazepam was given on SOS basis. The patients continued on the same medication, subject to appearance of serious side-effects when the dosage were reduced, till day 21. By this time, if a reduction of 50% of the initial BRMS score was not achieved, the doses of CBZ, Li and HP were increased to 1200 mg/d, 1200 mg/d and 20mg/d respectively.

To compare the changes in side-effect ratings for both intragroup and intergroup comparisons paired 't' test was used.

RESULTS AND DISCUSSION:

Out of 61 patients selected for the study only 43 (Males =35, female =8) completed the study. The 18 patients dropped out for various reasons (left against medical advice = 10, required other medication = 4, withdrew their consent = 4), but none due to serious side-effects.

The majority of side-effects with all the 3 agents, were observed during the initial week of therapy and their frequency and intensity progressively decreased with the duration of the

trial. CBZ commonly produced drowsiness, diplopia/nystagmus, constipation and ataxia during the first week, and also slurred spech and vertigo during the second week. This probably was due to the fact that the maximum dosage of CBZ were reached only by the end of first week.

Nausea/vomiting, diarrhea and tremors were seen in the Li group in the first week, and toxic confusional state, ataxia and constipation in the 2nd week. However, all these symptoms subsided within the next week and by day 28 none of the patients reported any adverse effects.

The anticholinergic property of haloperidol was responsible for producing dry mouth, constipation, rigidity, akathisia and slurred speech.

The dosage that was started on day 0 for HP and Li and those reached at day 7 for CBZ, were maintained till the end of the trial, and no decrements had to be made for the side -effects. Thus the drugs were well tolerated and this is borne out by statistical analysis which showed that there was no statistically significant difference in the adverse effects at weekly intervals between the groups.

The intragroup comparisons show that the side -effects diminished over the weeks. This was highly significant for Li ($p>.001$) at all levels of comparison and moderately so for HP and CBZ (table -1). A faster reduction of side-effects speaks of better compliance and more flexibility in dosage regime which appears best for Li followed by HP and CBZ.

Table-1 : CHANGES IN SIDE-EFFECT SCORES FROM BASELINE

		7-14		7-21		7-28	
Drugs	df	Mean (S.D)	t	Mean (S.D)	t	Mean (S.D)	t
CBZ	14	0.6 (1.9)	1.16	2.3 (3.4)	2.7*	0.9 (2.4)	2.7*
Li	11	1.1 (1.1)	3.46***	2.3 (1.5)	5.2**	1.8 (2.1)	5.8**
HP	15	0.9 (2.4)	1.42	2.6 (1.6)	3.5**	2.0 (2.9)	2.7*

For all values N for CBZ= 15, Li=12, HP=16

* $p > .01$

** $p > .001$

In our study we were handicapped by non-availability of serum levels of the drugs, which constrained us in correlating the appearance of side-effects with it. Secondly, the sample size was small, this being a time bound study.

The authors have not come across any study which directly deals with the issue and therefore are not able to compare their results with any other study. However, as the side-effects of any drug are as important as its therapeutic efficacy, it was considered an issue important enough to address separately.

REFERENCE:

American Psychiatric Association (1987) *Diagnostic and Statistical Manual of Mental Disorders III edn. - Revised.* Washington, American Psychiatric Association.

Bech, P., Rafaelson, O.J., Kramp, P.and Bolwig, T.W. (1975) The mania rating scale : Scale construction and interobserver agreement. *Neuropharmacology,* 17, 430-431.

George , M., Simpson, A., Edmond, H.P. and John, J.S. (1988) in *Myler's text book of side effects of drugs.*

Kaplan, H.I., Sadock, B.J. and Grebb, J.A. (1994) Kaplan and Sadock's *Synopsis of Psychiatry.* 7th ed. pp 516 - 555. New Delhi, B.I. Waverly Pvt (Ltd).

Shopsin, B., Gershon, S., Thompson, H. and Collins, P. (1975) Psychoactive drugs in mania : A control comparison of lithium carbonate, chlorpromazine and haloperidol. *Archives of General Psychiatry,* 32, 34-42.

World Health Organization (1986) *WHO Multicentric Collaborative Study.* WHO, Geneva.

World Health Organization (1988) *Role of hereditary, clinical and pharmacokinetic factors for prediction of Lithium.* WHO, Geneva.

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