Flupenthixol in Chronic Schizophrenic Inpatients: A Controlled Comparison with Haloperidol

THOMAS S. EHMANN, MA[1], NICHOLAS J. DELVA, MD[2], AND RICHARD J. BENINGER, PHD[1, 2]

Departments of [1]Psychology and [2]Psychiatry, Queen's University, Kingston, Ontario, Canada

Two neuroleptics having different effects at dopamine receptors were administered to chronic schizophrenic inpatients to compare their therapeutic efficacy and ability to produce side effects. Haloperidol appeared to produce lower levels of psychopathology than flupenthixol but similar levels of side effects. No evidence was found that flupenthixol is specifically useful in "activating" chronic patients or in alleviating affective symptoms. Although these are preliminary results, they support the view that D_2 receptors may mediate the antipsychotic effects of neuroleptic drugs.
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SEVERAL studies have reported that flupenthixol possesses specific anxiolytic or antidepressant properties,[1, 2] yet others have failed to find these effects.[3] Rimestad[4] and others have argued that flupenthixol is best suited for chronic, anergic schizophrenics. The contradictory results concerning the effects of flupenthixol on anergia and affective symptoms may derive from such methodological shortcomings as failures to employ double-blind procedures[1, 4, 5] and a lack of standardized outcome assessments.[2]

Pharmacologically distinct subclasses of dopamine (DA) receptors have been identified: at D_1 receptors, DA agonists stimulate adenylate cyclase, but at D_2 receptors they either fail to stimulate or else actively inhibit it.[6] Snyder[7] has suggested that the therapeutic effects of neuroleptics result from D_2 receptor antagonism. Although flupenthixol and haloperidol share similar pharmacological profiles, including potent antagonism of D_2 receptors, their major difference is that flupenthixol has a high degree of D_1 antagonism and haloperidol a low degree.[8, 9] This study was designed to compare the effects of flupenthixol and haloperidol on clinical state and side effects, and to provide further insight into the roles of D_1 and D_2 receptors in the action of antipsychotic medications.

Address requests for reprints to: Thomas S. Ehmann, Department of Psychology, Queen's University, Kingston, Ontario, Canada K7L 3N6.

Methods

Nine inpatients who met DSM-III[10] criteria for schizophrenia and were receiving neuroleptic medication consented to participate. Exclusionary criteria included the regular use of any psychotropic drugs other than neuroleptics and antiparkinsonian agents. The patients (two females and seven males) ranged in age from 24 to 63 years with a mean of 37.9 years and had had multiple psychiatric admissions.

The Rating Scale of the Mental State (RSMS)[11] and the 18-item version of the Brief Psychiatric Rating Scale (BPRS)[12] were employed to assess clinical status. Depression was assessed with a validated version of the Hamilton Rating Scale for Depression.[13] Side effects were assessed by the Simpson-Angus Rating Scale for Extrapyramidal Side Effects (SA)[14] and the Side Effects Scale of Mindham and co-workers,[15] which primarily assesses autonomic side effects. The social interest, cooperation, and irritability subscales from the Nurses' Observation Scale For Inpatient Evaluation (NOSIE) were selected to assess any changes in activity level.[16]

A double-blind, crossover design with each phase lasting for 11 to 14 weeks was used. The crossover point for each subject rested primarily on the judgment of the attending psychiatrist (N.J.D.) that the patient's clinical state was stable. After an orientation period and physical examinations, patients were randomly assigned to receive either flupenthixol or haloperidol during phase 1. Both medications were concealed in identical capsules containing 1- or 6-mg doses. The dosage of neuroleptic was flexible throughout the trial but never was permitted to exceed 84 mg/day or go below 80% of the chlorpromazine equivalent dose of neuroleptic received prior to the phase. There were no drug-free periods. Amylobarbitone was administered for agitation only if additional neuroleptic of the type currently prescribed proved ineffective. Benztropine mesylate was administered for extrapyramidal side effects in the usual doses (2 to 6 mg) on an as-needed basis and, if necessary, on a regular basis until the end of the phase. All evaluations were conducted in the final week of each phase. Analyses were conducted using paired *t*-tests or repeated measures analyses of variance.

Results

The average dose of flupenthixol given at the time of final assessments was 27 mg/day (range, 8 to 84 mg) and of haloperidol, 33 mg/day (range, 10 to 84 mg). The need for extra medication was low with the striking exception of one patient who received the maximum doses of both medications. The means and standard errors of the rating scales are presented in Table 1. The RSMS indicated significantly less psychiatric disturbance when patients were receiving haloperidol [$F(1,8) = 5.73, p < 0.05$]. The total score on the BPRS also showed less psychopathology with haloperidol, but this was not significant [$F(1,8) = 3.51, p < 0.10$]. The BPRS agitation-excitement scale, which also favored haloperidol, was significant [$F(1,8) = 5.26, p < 0.05$].

Although the Hamilton Depression Scale scores indicated that patients were experiencing mild depressive symptoms, no significant differences were found between the medications. Nurses' observations of ward behavior on the NOSIE subscales also revealed no significant differences between the medications.

Four patients did not develop any extrapyramidal side effects during the trial. Each medication generated one case of akathisia. Each of two patients developed parkinsonian symptoms on one medication but not the other. Two patients had parkinsonian effects from both medications, while another experienced oculogyric crises from both medications. No significant differences were found between the drugs on either side effects scale: SA: [$t(8) = -0.48$, not significant (NS); Mindham $t(8) = -1.51$, NS]. The total amount of benzotropine given was comparable for both drugs [$t(8) = 0.61$, NS]. Thus, the side effects generated by both drugs were similar in type and severity. The following case report describes the patient exhibiting the greatest difference in response between the two drugs:

TABLE 1. Outcome measures—mean scores (±1 SEM)

	Flupenthixol		Haloperidol	
	Mean	SEM	Mean	SEM
Rating Scale of the Mental State: total score	19.44	1.26	18.00[a]	0.88
Brief Psychiatric Rating Scale				
Thought disturbance	8.89	1.11	8.56	0.97
Anxiety/depression	5.11	0.89	4.33	0.96
Withdrawal/retardation	5.22	1.23	5.22	1.10
Hostility/suspicion	4.00	1.25	3.33	0.94
Agitation/excitement	3.11	0.63	2.00[a]	0.55
Miscellaneous	3.56	0.85	3.11	0.69
Total score	29.89	3.35	26.56	3.30
Hamilton Depression Rating Scale	12.44	2.12	11.56	1.74
NOSIE subscales				
Irritability	29.22	1.93	29.78	1.52
Cooperation	8.67	1.32	7.55	0.93
Social interest	29.11	4.34	25.55	2.98
Side effects				
SA scale (EPS)	2.67	0.47	3.00	0.71
Mindham et al. scale	1.22	0.59	2.11	0.63

[a]Different from flupenthixol, $p < 0.05$.

Case Report

A 36-year-old man with a family history of schizophrenia was first hospitalized 14 years ago. He started the study on 12 mg/day of flupenthixol, and this was gradually increased over 2 months to 84 mg/day. His condition deteriorated and became of increasing concern to staff as he began swearing, striking out at other patients and staff, pacing, screaming, inappropriately laughing, and continuously whispering and muttering. He expressed delusions that he did not exist and that he had no name and no blood. He also manifested a marked formal thought disorder. He required supplementary treatment with amylobarbitone (400 mg orally) on 25 occasions. He began haloperidol at a dose of 67 mg/day, and this was increased over 3 weeks to 84 mg. Ten more doses of amylobarbitone were needed at the beginning of the phase. After 3 months he was much improved and enjoyed full ward privileges. His scores on the BPRS and RSMS dropped by 13 and 4 points, respectively. Over the following year his dosage of haloperidol was reduced to 45 mg/day without any deterioration.

Discussion

Our results suggest greater psychopathology with flupenthixol than haloperidol, which is consistent with the observation of Carney and Sheffield[5] that the antipsychotic efficacy of flupenthixol was less than expected given its potency in laboratory tests. Because the drugs were used in conventional or slightly higher than conventional doses in this study, it is unlikely that increases in dosage would produce better therapeutic results.[17] In fact, the patient with the most marked clinical differences between the two drugs, with haloperidol being superior, was treated with 84 mg/day of each drug. There is no correlation between antipsychotic efficacy and affinity for α-adrenergic, serotonergic, and histaminergic receptors.[18] Flupenthixol is a potent D_1 and D_2 antagonist, yet it failed to lead to greater therapeutic effects. This supports Snyder's contention that the antipsychotic effects of neuroleptics may be mediated by D_2 receptors. In rats, some behaviors resulting from D_2 receptor blockade have been shown to be antagonized by D_1 receptor blockade,[19] raising the further possibility that D_1 antagonism may reduce the effectiveness of D_2 receptor blockade.

The failure to detect significant differences between drugs on the subscales assessing affective symptoms casts doubt on the purported ability of flupenthixol to exert specific antidepressant effects. Finally, the results from the NOSIE subscales fail to support claims

that flupenthixol possesses special "activating" properties for the apathetic, chronic schizophrenic patient.

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