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High Dosage Haloperidol in Chronic Schizophrenia

By ROBIN G. McCREADIE and IAN M. MacDONALD

In a double blind chlorpromazine-controlled trial, high dosage haloperidol (100 mg daily) given for three months, appreciably improved the mental state of male chronic 'drug resistant' schizophrenic in-patients in the rehabilitation/long-stay unit of one psychiatric hospital. The results of a three-month follow-up suggested that the improvement could be maintained in some patients on lower doses of the drug.

Serious extrapyramidal side effects were not seen at high doses. However, the majority of patients on haloperidol showed a deterioration in ward behaviour, possibly related to drowsiness, and developed raised serum alkaline phosphatase levels. These side effects disappeared in the follow-up period when either the drug was discontinued or the dose of haloperidol reduced.

Haloperidol has been used in the treatment of chronic schizophrenia with varying success. Double blind studies suggest that it is more effective than placebo (e.g. Brandrup and Kristjansen, 1961; Okasha and Tewfik, 1964; Ota and Kurland, 1973), no more effective than thioridazine (Prasad and Townley, 1966; Gonier *et al*, 1970), trifluoperazine (Stewart *et al*, 1969), fluphenazine (Hall *et al*, 1968), chlorpromazine and clopenthixol (Serafetinides *et al*, 1972), and less effective than clozapine (Gerlach *et al*, 1974).

In these and other studies, however, the dose range has been fairly limited; the maximum daily dose has not exceeded approximately 30 mg, the average usually being considerably less. Recently it has been shown (Forsman and Ohman, 1974) that the same dose of haloperidol given to patients can produce a ten-fold variation in serum levels; if the free diffusible fraction in serum reflects the concentration at the site of action, it follows that the dose may have to be increased in some patients to produce a therapeutic response. Relevant to this finding is a recent double blind study in an American psychiatric hospital (Howard, 1974) which showed that haloperidol in high doses (on average 104 mg daily) was effective in the rehabilitation of 'intractable treatment-resistant chronic psychotics', the majority of whom were schizophrenics. As there are international differences in the diagnosis of schizophrenia (Cooper *et al*, 1972), and as there has been no controlled trial of high dosage haloperidol in chronic schizophrenia in the United Kingdom, it was decided to carry out a broadly similar investigation in one British psychiatric hospital.

Method

Patient selection

All male in-patients (N = 114) in the long stay/rehabilitation unit of one psychiatric hospital were considered. Seventeen patients in a token economy research project were excluded, as were those who in the opinion of either the medical or nursing staff were controlled on, and benefiting from, medication. A patient was then selected on the basis of the following criteria: (i) he was physically fit and under 65 years of age; (ii) his case record showed that a diagnosis of schizophrenia had consistently been made during his stay in hospital; (iii) either his case record or an assessment interview demonstrated the presence

of one or more 'Schneiderian' first-rank symptoms (Mellor, 1970); (iv) he, and where traceable his next of kin, gave consent. Twenty patients (mean age 52 years, range 38–61; mean length of stay in hospital 20 years, range 1–34) distributed in three wards of the rehabilitation unit survived this selection process and thus could probably be classified as drug-resistant chronic schizophrenics.

Medication

All patients had had many previous courses of psychotropic medication (they had had on average 3·2 different major tranquillizers). All such medication was stopped for at least two weeks before the trial commenced; no deterioration in the patients' mental state was noted during this period. With the sole restraint that equal numbers should get one or other drug, patients were randomly assigned to receive either active liquid haloperidol and placebo chlorpromazine tablets or placebo haloperidol and active chlorpromazine. The dose initially was 15 mg haloperidol or 100 mg chlorpromazine daily; it was increased over twelve days to 100 mg haloperidol or 600 mg chlorpromazine in divided doses and thereafter was constant for the remainder of the twelve-week trial period. Anti-parkinsonian medication was prescribed when required.

Assessment

Before the introduction of medication (week 0), and at the end of weeks 1, 2, 3, 4, 8 and 12, two psychiatrists independently rated the patient's mental state using a modification of the Lorr Rating Scale (Hamilton *et al*, 1960), the 'Hamilton Scale', designed for use with chronic schizophrenics. In one of the three wards two nurses independently rated the patients' behaviour, using the Nurses' Observation Scale for In-patient Evaluation (Nosie-30) designed for use with a long-stay population (Honigfeld and Klett, 1965); in each of the other two wards, because of staff shortages, one nurse only rated the patients. The two psychiatrists also made a joint assessment of extra-pyramidal side effects (tremor, rigidity, dystonia, dyskinesia, akathisia) on a 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe), and recorded other side effects. After the first week, the psychiatrists and nurses independently rated global clinical improvement on a 3-point scale (improved, unchanged, worse).

At week 0, and at the end of week 6 and 12 the patient's weight was taken and full blood count, and liver function tests were carried out.

At the end of week 12, before the code was broken, the two psychiatrists tried to guess which drug each patient was receiving.

Follow-up

At the end of the three month trial period, the patients on haloperidol were followed for a further three months in an open evaluation carried out by the senior psychiatrist (R.McC.) and the nursing staff.

Analysis

The scores obtained with the Hamilton and Nosie-30 scales for the two groups of patients were compared by the Mann-Whitney U test, except in the global ratings, where the Fisher exact probability test was employed. Within each group pre- and post-treatment scores were compared by the Walsh test. Two-tailed tests of significance were used throughout (Siegel, 1956).

Results

Two patients dropped out. The first, never keen to take medication, complained of drowsiness during the second week on chlorpromazine; the second, after the first dose of chlorpromazine, made a psychotic misinterpretation of the word haloperidol; both refused further medication. Therefore, 8 patients on chlorpromazine and 10 on haloperidol completed the trial; the two groups did not differ significantly, statistically speaking, with respect to age, length of stay in hospital, number of different major tranquillizers previously prescribed, and initial severity of illness measured by the Hamilton and Nosie-30 scales.

(i) *Hamilton scale*

The inter-rater correlation was high, the correlation coefficient 'r' being 0·94 $P<0·001$).

The change in the mean scores is shown in Fig 1, a decrease signifying clinical improvement

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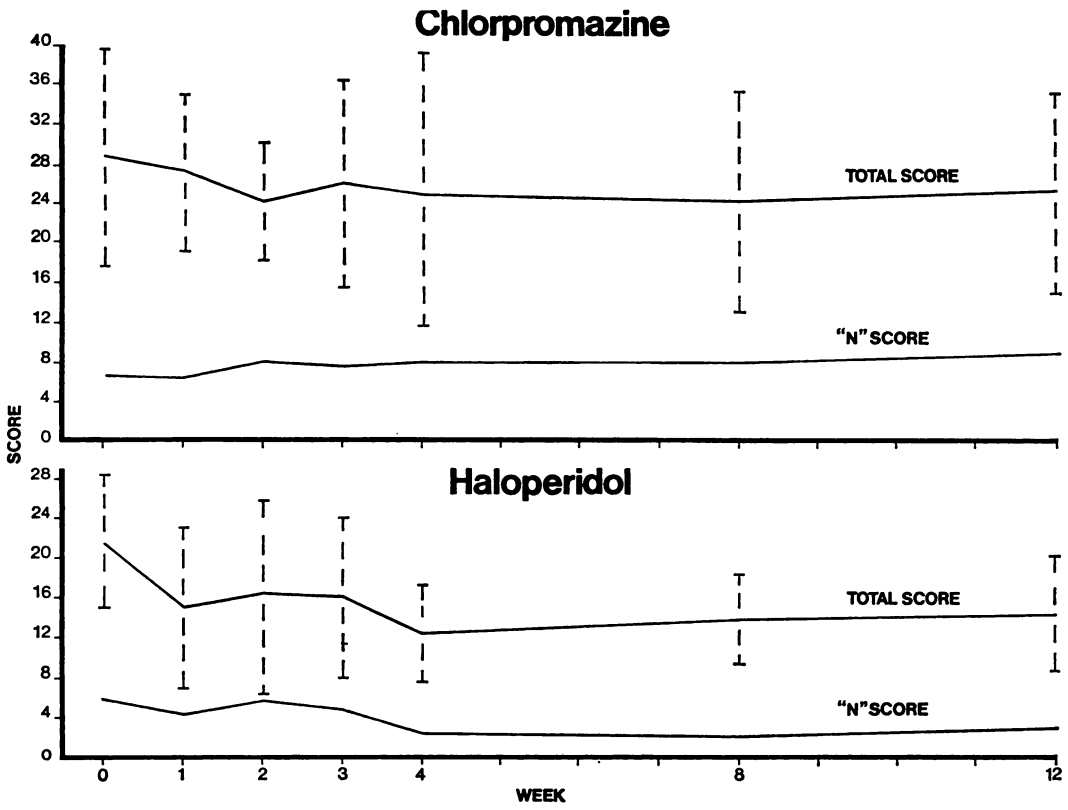

FIG 1.—Hamilton Rating Scale. Weekly mean score (±Standard deviation).

(it is to be remembered, however, that the analyses used ranking tests). The mean score of the patients on haloperidol decreased over the three months by a third, but the improvement was only significant at the end of week 12 ($P < 0.05$). No significant changes occurred in patients on chlorpromazine. Although the patients on chlorpromazine tended to have higher initial scores, this inter-group difference was not statistically significant; at the end of week 1, however, it was significant ($P < 0.02$), but not at weeks 2 and 3. By week 4 the significance had reappeared ($P < 0.05$) and then remained through weeks 8 to 12 (both $P < 0.02$).

Hamilton *et al* (1960), on the basis of a factor analysis, have divided the scale into two groups of symptoms, the 'P' and 'N' groups. The former group consists of disturbances of speech and thought, of posture and mannerisms, of affect, and objective evidence of hallucinations; the latter consists of delusions and evidence of hostility. Patients on haloperidol at the end of week 12 had a significantly lower 'N' score than those on chlorpromazine ($P < 0.05$) (Fig 1); examination of the data showed, however, that this was because not only the scores of patients on haloperidol tended to fall, but also the scores of patients on chlorpromazine tended to rise (though neither trend was statistically significant). The 'P' score of patients on haloperidol and chlorpromazine tended to fall, but not significantly, statistically speaking.

(ii) *Nosie-30 scale*

In the ward where two nurses rated the same patients, the inter-rater correlation coefficients for the total score and the six sub-scales ranged from 0·84 to 0·94 (all $P < 0.001$).

In the total score on the Nosie-30 ('total

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assets') there were no significant differences at the end of 12 weeks between the scores of patients on haloperidol and chlorpromazine; neither were there any significant differences between pre- and post-treatment scores of patients on either drug.

Examination of the six sub-scales (social competence, social interest, personal neatness, irritability, manifest psychosis, and retardation) showed that the mean 'social interest' score of patients on haloperidol fell by 54 per cent over the three months. The fall, indicating a deterioration in this aspect of ward behaviour, was statistically significant ($P < 0.01$); no such change was seen in the patients on chlorpromazine. Although the 'social interest' scores of patients on haloperidol were higher, pre-treatment, and lower post-treatment than the scores of patients on chlorpromazine, this inter-group difference was not significant.

(iii) *Global assessments*

The senior psychiatrist rated 5 patients on haloperidol and 2 on chlorpromazine 'improved' after three months; the other rated 2 on haloperidol and 3 on chlorpromazine 'improved'. The other patients, except one on haloperidol, whom both psychiatrists rated 'worse', were 'unchanged'. The nurses rated all patients 'unchanged' except 3 on haloperidol 'worse', and 2 on chlorpromazine 'improved'. None of these results was statistically significant.

The most striking change was in a patient on haloperidol, continuously an in-patient for 27 years, but whose score on the Hamilton scale was low, the main problem being apathy. By the second month he spontaneously asked to become a day-patient, a request which was granted after the trial ended. Passivity phenomena in 2 patients, one on haloperidol, one on chlorpromazine, and auditory hallucinations in one patient on haloperidol markedly diminished. On the other hand 2 patients, one on either drug, had an exacerbation of their auditory hallucinations.

(iv) *Side effects*

A total score was derived at each assessment for the five extrapyramidal side effects. Because of scores on 'rigidity' and 'tremor', few patients scored zero at week 0. There were no significant differences at the end of three months either within or between the two groups of patients. Four patients, 2 on each drug, developed mild akathisia.

Before the assessment at the end of the first week, however, 2 patients on 15 mg haloperidol daily developed a marked short-lived dystonic reaction, which responded rapidly to 2 mg intra-muscular benztropine. No dystonic reactions were seen at the higher doses. These 2 patients and 2 others, one on each drug, were the only 4 prescribed antiparkinsonian medication.

Eight patients on haloperidol and 3 on chlorpromazine at some time during the twelve weeks either exhibited drowsiness or complained of it at interview; with the patients on haloperidol, this began in 2 on 30 mg daily, in 6 on 100 mg. Three patients on chlorpromazine developed photo-sensitivity reactions. In both groups there was no significant change in the patient's weight or full blood count.

Liver function tests (Table I)

At the end of three months raised serum alkaline phosphatase levels were found in 7 of the 10 patients on haloperidol. The levels in 4 of the 7 were well within normal limits before the trial began; in 2 of the other 3, whose pre-

TABLE I

Serum alkaline phosphatase levels (in King-Armstrong units: normal range 3–13)

Week 0	Week 12
Haloperidol	Haloperidol
16·2	24·1
14·9	21·0
14·8	15·0
11·1	17·4
10·0	14·2
8·8	16·2
8·4	15·1
Chlorpromazine	Chlorpromazine
11·5	14·0
9·8	14·7

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treatment levels were slightly elevated, the levels rose further over the three months. Two patients on chlorpromazine developed raised levels.

Blindness of trial

Both psychiatrists guessed correctly in the same 8 and wrongly in the same 6 patients which drug the patient was receiving. Although this success rate is no higher than that expected by chance, the significantly high inter-rater agreement (14 out of 18, $P < 0{\cdot}02$) suggests that the psychiatrists were responding to cues in a similar way. The successes were due largely to correct guesses being made in the two patients on haloperidol who developed dystonic reactions and the three on chlorpromazine with photosensitivity reactions, the failures largely to wrong guesses in four patients on haloperidol with marked drowsiness.

Follow-up Evaluation

Of the 10 patients on haloperidol, 4 had their medication stopped as there was no improvement in the mental state; in the other 6 the score on the Hamilton scale had fallen by at least 30 per cent. In a further 2 cases, the medication was stopped because of persistently raised serum alkaline phosphatase levels. One of the two, the patient discharged to attend as a day patient, sought (and obtained) readmission while still on haloperidol; the nursing staff suspected that he had not been taking his medication regularly. The improvement in the other patient was maintained on no medication during the follow-up period.

Of the remaining 4 patients, one had the drug stopped at the end of the fourth month because his mental state had reverted to pre-treatment severity although he was still receiving 100 mg daily. With the other 3 the dose was steadily reduced from the end of the fourth month in order to determine, through appreciable change in the Hamilton scale, the minimum maintenance dose, which proved to be 20, 30 and 60 mg daily. The patient on 20 mg daily required an anti-parkinsonian agent for considerable rigidity.

Drowsiness was less apparent in the follow-up period. By the end of the follow-up the scores on the 'social interest' subscale of the Nosie-30 in the 10 patients had improved significantly in comparison with the ratings at the end of the initial three months ($P < 0{\cdot}01$); in all but one patient, whose haloperidol had been stopped, the scores rose to pre-treatment levels.

Of the 6 patients on haloperidol in whose case there was a clear rise in the serum alkaline phosphatase level (Table I), the values fell to pre-treatment levels in 5 within four to six weeks of stopping medication, and in one on 100 mg haloperidol daily. The value in one of the 2 patients on chlorpromazine fell to within normal limits while still on 400 mg daily, and in the other within five weeks of stopping medication.

Discussion

The study was probably not entirely 'double-blind' because of recognizable side effects but it is unlikely that any drug trial examining potent neuroleptics achieves complete 'blindness'. If placebo rather than chlorpromazine had been used in the present study, the side effect of drowsiness noted in 8 of the 10 patients on haloperidol would probably have revealed more certainly what preparation each patient was receiving.

The process of patient selection isolated a group of schizophrenics in which an improvement would be a stiff test for the efficacy of any drug. Nonetheless, the patients on haloperidol, as a group, improved appreciably as regards their mental state; the tendency was for all aspects of psychopathology to diminish in severity. It took three months, however, with high doses of haloperidol for the improvement to become statistically significant. The patients given a standard dose of chlorpromazine did not improve. Symptoms such as formal thought disorder tended to decrease and delusions and hostility increase in severity; the overall result was no statistically significant change in the mental state. Although the difference was not statistically significant the severity of the mental state of patients on chlorpromazine was initially slightly greater than that of patients on haloperidol. This pre-treatment difference largely accounts for the statistically significant inter-group difference appearing at the end of the

first week, as the scores had only to diverge slightly further to achieve significance.

The overall results for individual patients, the global assessments, are more difficult to interpret. The senior psychiatrist rated 5 patients on haloperidol and 2 on chlorpromazine improved, while the other rated 2 and 3 respectively as improved. Both psychiatrists found the global assessment difficult to make. It involved giving, almost intuitively, varying weights to changes, both for the better and worse, in different aspects of the mental state in an attempt to arrive at an overall assessment. As the senior psychiatrist had had considerably longer experience of chronic patients, it may be that his results are more valid; if this is the case the global assessments would tend to suggest that haloperidol is more effective than chlorpromazine.

The fact that 2, possibly 3, patients on chlorpromazine did improve suggests, however, that unless this was a placebo effect or a spontaneous fluctuation in a chronic condition, the label, 'drug resistant', need not be permanently affixed to any individual patient.

It must be emphasized that high dosage haloperidol has been compared with a standard dose of chlorpromazine. There is some evidence that high doses of chlorpromazine are more effective than the standard dose in some chronic schizophrenic patients (Prien and Cole, 1968).

The three-month follow-up suggested that the initial improvement in the mental state could be maintained in some patients on lower doses of haloperidol; the fact that one remained well after withdrawal of haloperidol is a reminder that intermittent instead of continuous maintenance medication may profitably be used in some patients.

The improvement was much less dramatic than that found in the American study (Howard, 1974), where 47 per cent of patients were discharged from in-patient care. That study, however, combined drug treatment with an enthusiastic rehabilitation programme; in the present study no change was made in the patient's ward routine.

Accompanying the improvement in the mental state of patients on haloperidol was a marked deterioration in ward behaviour as measured by the 'social interest' subscale of the Nosie-30; the deterioration was reflected in the nurses' global assessments. This deterioration might have been produced by the drowsiness noted in 8 of the 10 patients, a side effect not widely reported in patients on haloperidol. The follow-up suggests, however, that when either the haloperidol is stopped or the dose reduced drowsiness and loss of social interest become much less evident.

Extra-pyramidal signs, mainly tremor and rigidity, were present before the trial began. These were presumed to be secondary to previous administration of major tranquillizers; one study (Hershon *et al*, 1972) has shown that such side effects can persist for 16 weeks after discontinuation of a neuroleptic (trifluoperazine). Although at low doses (15 mg daily) dystonic reactions were seen in 2 patients, high dosage haloperidol did not produce serious extrapyramidal signs, which indeed were no more noticeable than those recorded in patients on chlorpromazine. This finding has been documented previously (Sangiovanni, 1973), but the underlying mechanism is not clear; it is possible that in high doses haloperidol has a considerable anticholinergic effect.

A noticeable side effect was the development of raised serum alkaline phosphatase levels in the majority of patients on haloperidol. The values, however, fell back to pre-treatment levels when the drug was discontinued and in one patient when the dose remained the same. This side effect has not previously been reported, although there have been few studies where haloperidol has been prescribed in high doses for lengthy periods of time. In the study previously cited (Howard, 1974), the average dose was 104 mg daily over a maximum 12-week period, yet no abnormalities were noted in the liver function tests. In another study, however (Gerlach *et al*, 1974), raised serum glutamic oxalacetic transaminase levels were found in 4 out of 20 patients on haloperidol at doses between 3 and 32 mg for twelve weeks. It is clear that if high doses of haloperidol are given over a period of time frequent assessments of liver function must be carried out.

We conclude that haloperidol in high doses appears to produce beneficial changes in the

mental state of some chronic schizophrenics. Against this improvement, however, must be balanced drowsiness, deterioration in ward behaviour and possible liver damage, side effects which appear to diminish when either the haloperidol is stopped or the dose reduced to maintenance levels.

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