Brit. J. Psychiat. (1975), 126, 457–61

Observations on the Dose Regime of Fluphenazine Decanoate in Maintenance Therapy of Schizophrenia

By D. A. W. JOHNSON

Summary

An analysis of the drug regimes prescribed to two separate groups of unselected schizophrenic patients indicates certain trends of clinical importance. The results demonstrate a need for the adoption of a personalized dose regime. The scatter of dose regimes found effective is too great to recommend a standardized approach to the prescription of L.A.P. injections.

Two other results of particular significance are that the dose of drug required to control symptoms can be gradually reduced in nearly half of patients, and that helpful trends in prescribing were identified that will help the clinician to abolish side-effects.

Introduction

Though there is wide acceptance of the long-acting depot phenothiazines as a major advance in the treatment of chronic schizophrenia (Denham and Adamson, 1971; Johnson and Freeman, 1972; Hirsch *et al.*, 1973) there is no generally agreed dose regime. So far, because of the difficulties of serum estimations of the minute concentrations present, it has not been possible to evaluate scientifically the duration of action of the long-acting phenothiazines (L.A.P.) in humans. Conditioned avoidance response tests in rats have demonstrated that fluphenazine enanthate inhibits responses for 12 to 21 days, and that fluphenazine decanoate has a longer duration of action (Laffan *et al.*, 1965; Ebert and Hess, 1965). Short-term clinical studies suggest that fluphenazine enanthate is effective for approximately two weeks and that the decanoate acts for a longer period (Neal and Imlah, 1968; Van Praag and Dols, 1973). So far, no study has been published demonstrating the dose range for maintenance therapy or the dose variations likely to occur over an extended period of treatment.

Method

Since it has been shown that both the antipsychotic effect and the principal side-effects are dose-dependent (Johnson, 1973), it is necessary to measure both these variables in any evaluation of a drug regime. This study reports the dose regimes of two groups of patients over separate periods of time, beginning in each case with the start of maintenance therapy following a relapse of acute schizophrenia. Only the first group (Group A) meets the above requirements, but the second group has also been reported because the observations were made while the patients were receiving routine out-patient treatment and it would seem important to identify any differences of prescription under normal clinical conditions from a more rigid research-orientated period of management.

Group A consisted of 140 consecutive patients, under the age of 65 years, diagnosed as suffering from schizophrenia. They were all treated by L.A.P. for an average period of 15 months. Further details concerning this group of patients, their side-effects and the techniques of measurement have already been published (Johnson, 1973).

Group B. A group of 264 unselected schizophrenic patients treated for a minimum period of 12 months following an acute relapse of schizophrenia. These patients were under the care of a number of consultants, although the author was usually the principal clinician responsible for day to day care. All patients were treated as ordinary N.H.S. out-patients; the only selection was the possession of complete records for the period under assessment, and they represent the total sample of patients treated with L.A.P. by the author.

The dose regime of Group A patients was under constant review with the conscious aim of maintaining the patients on the lowest dose thought compatible with their mental state, in order to minimize the incidence of side-effects. The patients were all under regular observation and received immediate attention whenever a change of mental state or the appearance of side-effects was suspected. By contrast, the patients in Group B were treated under normal clinical conditions, and the analysis of their prescription records was retrospective. Some of the patients in Group B have been included in other surveys on L.A.P. treatment (Johnson and Freeman, 1973), but their drug prescriptions were not under special consideration at the relevant time.

The indices used for the estimation of therapeutic gain were the number of hospital admissions and the days spent as an in-patient. Each patient was used as his own control. To do this, the hospital admissions during a period immediately preceding the relevant relapse, and equal in length to the follow-up time, were compared with admissions during the follow-up period. This procedure was adopted to allow comparison with the only other report on the therapeutic gain in a group of unselected schizophrenic out-patients on treatment with L.A.P. (Johnson and Freeman, 1972).

Results

Group A. Table I shows the number of patients on each dose regime at the beginning of the follow-up period to evaluate side-effects. The number of patients on each dose regime at the completion of this period (average 15 months, range 12–20 months) is shown in Table II.

Table I

Number of patients on each dose regime at onset of follow-up to evaluate side-effects—Group A

Dose in mg.	Injection interval in days					
	7	10	14	21	28	35
12·5	1	1	18	2	2	0
25	2	0	56	38	14	2
50	0	0	0	2	2	0

n = 140

Table II

Number of patients on each dose regime at completion of follow-up to evaluate side-effects—Group A

Dose in mg.	Injection interval in days					
	7	10	14	21	28	35
12·5	0	0	15	4	4	1
25	3	2	12	42	48	6
50	0	0	1	1	1	0

n = 140

During this period 67 patients (48 per cent) had their total dose reduced, 18 patients (13 per cent) had the intervals between injections adjusted although their total dose remained unchanged, 7 patients (5 per cent) required an increase in their total dosage, and 48 patients (34 per cent) remained on an unchanged dose regime throughout the period of observation.

It was possible to abolish the side-effects while still maintaining a positive anti-psychotic action in 36 of the 47 patients experiencing unwanted symptoms, though in 4 patients the side-effects subsequently returned (Johnson, 1973). In 20 of these cases the abolition of side-effects was achieved by a simple lengthening of the interval between injections, in 3 the dose at each injection was reduced but the interval between injections kept constant, and in 13 an adjustment of both the dose at each injection and the interval between injections was found necessary. However, in this latter group, the net result in 6 cases was that the patient was receiving the same total dose over a given unit of time.

The dose regime that each patient was receiving at the time of first developing side-effects is shown in Table III. An absolute comparison of the incidence of side-effects on

Table III

Number of patients experiencing side-effects on each dose regime—Group A

Dose in mg.	Injection interval in days					
	7	10	14	21	28	35
12·5	1	1	0	0	0	0
25	1	0	24	13	4	0
50	0	0	1	1	1	0

n = 140

https://doi.org/10.1192/bjp.126.5.457 Published online by Cambridge University Press

different dose regimes is very complex, since a patient may at different times experience side-effects on quite different regimes; further, a comparison of dose prescriptions only ignores other possibly relevant factors, such as the duration on a particular dose regime. Within these limitations, certain trends may be demonstrated. The incidence of new side-effects in patients receiving an injection dose of 50 mg. is likely to be 75 per cent, irrespective of the interval between injections. The incidence on 25 mg. injections is likely to be 60–65 per cent if the interval between injections is two weeks or less, but only 25 per cent if the interval between injections is three weeks or longer. The risk of side-effects on 12·5 mg. injections appears to be very small, and is virtually absent unless the interval between injections is reduced to less than two weeks.

Group B. Tables IV and V illustrate the scatter of dose regimes prescribed at the onset of maintenance therapy and again after a 12 month period of continuous treatment under normal clinical conditions as an out-patient. During this period 41 per cent of patients had their total dose reduced, 11 per cent had the interval between their injections adjusted although their total dosage remained unchanged, 9 per cent required an increase in their total dose, and 39 per cent remained on an unchanged dose regime.

An analysis of the intervals between injections (Table VI) suggests that the longer a patient remains on maintenance therapy with L.A.P. the more possible it becomes to control his symptoms with injections given at less frequent intervals. After 12 months, 29 per cent of patients received their injections every three weeks, and a further 33 per cent at even less frequent intervals.

The clinical gain in Group A was a reduction in the re-admission rate of 38 per cent, and in the duration of in-patient stay of 56 per cent.

TABLE IV
Number of patients on each dose regime at onset of maintenance therapy—Group B

Dose in mg.	Injection interval in days					
	7	10	14	21	28	35
12·5	6	2	34	2	6	0
25	8	0	82	40	36	2
37·5	0	0	12	2	2	0
50	0	0	24	2	0	0

n = 264

TABLE V
Number of patients on each dose regime after 12 months —Group B

Dose in mg.	Injection interval in days					
	7	10	14	21	28	35
12·5	0	0	34	8	12	2
25	6	4	40	56	62	6
37·5	0	0	10	2	2	0
50	0	0	6	10	2	0

n = 264

TABLE VI
Interval between injections of patients on maintenance therapy—Group B

	Injection interval in days					
	7	10	14	21	28	35
Onset of therapy	14	2	154	46	44	2
After 12 months	6	4	90	76	78	8

n = 264

DISCUSSION

The clinical gain was not significantly different from that reported in the only other survey of unselected schizophrenic out-patients (Johnson and Freeman, 1972), and the incidence of side-effects (Johnson, 1973) was very similar to the reported incidence in studies on oral medication. These comparisons can only be considered as rough guides, but they would seem to indicate the validity of the treatment regimes prescribed. The close similarity of the prescriptions used in the two groups reported, although under quite different clinical conditions, would seem a further indication of the usefulness of the reported regimes.

These results suggest important trends for the use of these long-acting injectable depot neuroleptics. Perhaps the most clearly demonstrated

https://doi.org/10.1192/bjp.126.5.457 Published online by Cambridge University Press

fact is that there is no such thing as a proper or even recommended dose in maintenance therapy; each patient must have his prescription determined on an individual basis. The possible variations of dose per injection and of interval between each injection are considerable, but only if this personalized approach is adopted can the side-effects be minimized with the greatest possible therapeutic gain.

An analysis of the dose regimes at the onset of maintenance therapy in both groups (Tables I and IV) demonstrates not only the scatter of dose regimes prescribed at this time but also that short intervals between injections and injection doses of above 25 mg. are prescribed relatively more frequently then than at other times. A comparison with the dose regimes in use at the completion of the periods under observation (Tables II and V) shows that with the passage of time, in a substantial proportion of patients, there can be both a reduction in the total dose and an increase in the intervals between injections, so that 62 per cent of patients need only receive their injections at intervals of three weeks or longer (Table VI). The finding that the total dose of L.A.P. required to control symptoms is reduced in 40–50 per cent of patients after a time is of particular clinical importance. A proper adjustment of medication will not only reduce the risk of dose-dependent side-effects, such as extrapyramidal symptoms, but will, even more importantly, reduce the total drug administered to the patient and further minimize the possible long-term and largely unknown dangers, without loss of therapeutic benefit. The results give no clear indication as to when such a reduction can safely take place, but the trend is firmly established after six months on treatment. It is important to notice that the trend towards using injections at less frequent intervals seems partly independent of the reduction in the total dose administered.

The considerable variation in the individual response of patients to drugs is clearly demonstrated in the analysis of the drug regimes producing side-effects (Table III). However, trends can again be demonstrated that are likely to be of clinical importance. The use of injections of more than 25 mg. increases the risk of extrapyramidal side-effects quite dramatically. Equally, the use of an interval of two weeks or less is accompanied by a significant rise in the incidence of side-effects, irrespective of the injection dose used. The results would suggest that the clinician should try and keep the dose per injection at a minimum, even though this will require an increase in the frequency of injections. He should aim at giving no more than 25 mg. at any one injection, though it is doubtful if there is any clinical gain in reducing the injection dose once the frequency is reduced to two weeks, unless the injection dose is reduced to 12·5 mg. The knowledge that the total dose required is likely to be reduced with time should encourage clinicians and patients alike to persevere when side-effects require patients to have small dose injections at frequent intervals during the initial stages of treatment.

The author has already made a plea for the dose regimes of L.A.P. to be personalized, and for the regime to remain under constant review because of the development of new side-effects after long intervals on treatment (Johnson, 1973). The results of this study again demonstrates the need for careful individual consideration of each patient. The habit of some clinicians of prescribing a 'recommended maintenance dose' that is continued for an indefinite period is likely to result in the over-treatment of patients with drugs in nearly 50 per cent of cases. The lack of a personalized dose regime is also a likely cause for the high incidence of side-effects reported by some authors. The use of the long-acting injectable neuroleptics requires careful supervision, which can be time-consuming, but the results would seem to suggest that the potential therapeutic gains justify this effort.

ACKNOWLEDGEMENT

The author wishes to thank Dr. A. A. Schiff of E. R. Squibb and Sons Ltd. for his helpful criticisms of both the results and the manuscript.

REFERENCES

DENHAM, J. & ADAMSON, L. (1971) The contribution of fluphenazine enanthate and decanoate in the prevention of readmission of schizophrenic patients. *Acta Psychiatrica Scandinavica*, **47**, 420–27.

EBERT, A. G. & HESS, S. M. (1965) *Journal of Pharmacology and Experimental Therapeutics*, **148**, 412.

HIRSCH, S. R., GAIND, R., ROHDE, P. D., STEVENS, B. C. & WING, J. K. (1973) Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: double-blind placebo trial. *British Medical Journal*, *i*, 633–7.

JOHNSON, D. A. W. (1973) The side-effects of fluphenazine decanoate. *British Journal of Psychiatry*, **123**, 519–22.

—— & FREEMAN, H. L. (1972) The long-acting tranquillizers. *The Practitioner*, **208**, 395–400.

—— —— (1973) Drug defaulting by patients on long-acting phenothiazines. *Psychological Medicine*, **3**, 115–19.

LAFFAN, R. J., HIGH, J. P. & BURKE, J. C. (1965) The prolonged action of fluphenazine enanthate in oil after depot injection. *International Journal of Neuropsychiatry*, **1**, 300–306.

NEAL, C. D. & IMLAH, N. W. (1968) Fluphenazine decanoate: a second long-acting phenothiazine. *British Journal of Social Psychiatry*, **2**, 178–86.

VAN PRAAG, H. M. & DOLS, L. C. W. (1973) Fluphenazine enanthate and fluphenazine decanoate: a comparison of their duration of action and motor side-effects. *American Journal of Psychiatry*, **130**, 801–804.

A synopsis of this paper was published in the December 1974 *Journal*.

D. A. W. Johnson, M.Sc., M.R.C.Psych., *Consultant Psychiatrist and Lecturer in Psychiatry, Crumpsall Hospital, Manchester 8, and University of Manchester*

(*Received 15 July 1974*)