medicines information

Psychiatric Bulletin (2005), **29**, 104–107

DAVID TAYLOR

Establishing a dose–response relationship for haloperidol decanoate

AIMS AND METHOD

The aim of this literature analysis was to establish the range of doses of haloperidol decanoate effective in preventing relapse in schizophrenia. Studies reporting relapse rates in patients treated for longer than 6 months were included. Relapse rate was then plotted against dose or log dose to allow drawing of dose–response curves.

RESULTS

Fifteen publications reporting 13 individual studies were identified. Of these, 6 studies met inclusion criteria and were analysed. Dose–response curves indicated limited effect at 25 mg/4 weeks but near maximal effect at doses of 50 mg/4 weeks. There was no clear evidence that increasing the dose above 100 mg/4 weeks provided additional benefit in preventing relapse.

CLINICAL IMPLICATIONS

The recommended dose range for haloperidol decanoate (50–300 mg/4 weeks) does not reflect the findings of this study. Optimally effective doses appear to be around 50–100 mg/4 weeks. The use of doses above 100 mg/4 weeks is difficult to support given data available.

The *British National Formulary* (Royal Pharmaceutical Society of Great Britain and British Medical Association, 2003) outlines the recommended dose of haloperidol decanoate (HD) thus: 'initially 50 mg every four weeks, if necessary increasing by 50 mg increments to 300 mg every four weeks; higher doses may be needed in some patients'. In practice, clinical doses appear to average 200–300 mg every 4 weeks with higher doses seen in a small but important minority.

Appropriate dosing of HD is made difficult by its complex pharmacokinetic properties (Taylor, 1999) and by a lack of clarity over its dose–response characteristics. Essentially three dose response 'curves' are possible, each based on the assumption that very low doses produce little or no effect and higher ('threshold') doses produce increasingly large effects. At higher doses still, effects may (i) increase still further, (ii) neither increase nor decrease (plateau), or (iii) decrease (see Davis *et al*, 2003 for discussion). With oral haloperidol, there is substantial evidence that its clinical effects plateau at doses above 4–6 mg/day (Hilton *et al*, 1996; Taylor, 2000) and it has been suggested that effectiveness decreases above 12 mg/day (Geddes *et al*, 2000). If these outcomes are accepted then it is possible that some low but recommended doses of HD will be sub-therapeutic and some higher doses unnecessarily supra-therapeutic.

A literature search and analysis was performed in an attempt to establish and describe the dose–response relationship for HD at recommended therapeutic doses.

Method

In December 2003, a literature search was conducted using the terms HALOPERIDOL DECANOATE, HALOPERIDOL DEPOT, HALDOL, HALDOL DECANOATE and HALOPERIDOL LONG ACTING PREPARATIONS. Databases searched were Medline, Embase and PsychLIT. The Cochrane Library and the Cochrane review of HD (Quraishi & David, 2000) were also scrutinised. From the papers retrieved, those describing use of specified doses of HD for at least 6 months and providing relapse outcome data were included. (These factors represented *a priori* inclusion criteria.) Shorter studies and those not describing relapse data were not included.

Results

Fifteen papers describing 13 individual studies were retrieved. From those, 6 studies meeting inclusion criteria were identified. Of those not included, 5 had a duration of assessment of 6 months or less (Zissi *et al*, 1982; Wistedt *et al*, 1984; Bechelli *et al*, 1985; Eberhard & Hellborn, 1986; Dencker *et al*, 1994) and 2 did not provide dosage details (Cookson *et al*, 1986; Meyerowitz *et al*, 1989). Two studies were each published twice – Wistedt (1984) and Wistedt *et al* (1984) described the same study, as did Koskinen *et al* (1991) and Wistedt *et al* (1991). The included studies are described below.

McKane and colleagues (1987) conducted a double-blind trial of HD and fluphenazine decanoate over 60

https://doi.org/10.1192/pb.29.3.104 Published online by Cambridge University Press

weeks (incorporating a 12-week run-in period). Seventeen participants received HD, of whom 6 (35%) relapsed during the 52-week post run-in period. The mean dose of HD was 120 mg every 4 weeks at week 12.

Chouinard and colleagues (1989) conducted a similar comparative double-blind trial over 8 months but with all participants receiving fluphenazine depot for 3 months before study entry. HD was given to 36 participants at intervals of 2, 3 or 4 weeks. The mean dose given per month was 385 mg. On this dose no patient relapsed to an extent requiring readmission and only 2 required additional oral medication (a single oral dose in each case).

In a double-blind comparison of HD and zuclopenthixol decanoate, Wistedt *et al* (1991) found that a mean dose of 92 mg every 4 weeks allowed relapse in only 4 of 27 participants (11%) receiving HD for 9 months. In this study, relapse was defined as withdrawing prematurely 'because of deterioration'. Aside from these withdrawals, 3 participants showed deterioration on clinical assessment scales.

Eklund & Forsman (1991) conducted a rare placebo-controlled, randomised double-blind assessment of HD given for 48 weeks (after a 3-month period in which all subjects received 60 mg every 4 weeks of HD). Out of 18 participants receiving HD, 2 relapsed (11%) compared with 16 out of 23 (69%) of those receiving placebo.

Altamura and colleagues (1995) followed 48 participants given HD for up to 3 years. In the first year 11 participants (23%) relapsed. The mean dose of HD was 120.6 mg every 4 weeks. The study was an open evaluation of naturalistic clinical practice.

In the most recently published study, Kane and colleagues (2002) examined the effect of fixed doses of HD on relapse ('symptomatic exacerbation') in a double-blind, year-long study. Relapse rate was highest for those receiving 25 mg HD every 4 weeks (15 out of 25 participants, 60%) and lowest for 200 mg HD every 4 weeks (4 out of 26, 15%). There was no statistically significant difference in relapse rates between the highest dose and medium doses (50 mg and 100 mg every 4 weeks; 25% and 23% respectively). Oddly, this study took almost 10 years to be fully published (see Davis *et al*, 1993).

Plotting dose–response curves

The above data (see also Table 1) were plotted as mean or fixed dose HD (or, by convention, log dose) against percentage remaining well (100–relapse rate) to estimate a dose–response curve for HD (see Figs 1 and 2). These curves suggest that HD has little effect below 25 mg/4 weeks (anchor point for no HD is placebo effect from Eklund & Forsman, 1991). Effect on relapse seems to increase substantially between >25 mg and 100 mg/4 weeks and then to level off almost to horizontal between 100 mg and 400 mg/4 weeks. Effect could be said to be maximal or near maximal at 50 mg/4 weeks.

Discussion

This analysis of medium-term trials of HD strongly suggests that beneficial effects on relapse peak at around 100 mg/4 weeks and little, if any, therapeutic advantage is provided by higher doses. If accepted, this conclusion has important consequences for clinical practice.

Of course, the exact nature of the dose–response curve beyond 100 mg/4 weeks is a vitally important question. If horizontal, then clearly higher doses can be seen as unnecessary, incurring additional expense and perhaps producing a greater burden of adverse effects

Table 1. Haloperidol decanoate studies, 9–12 months' duration

Reference	Duration and subject details	Dose details	*n*	Relapse *n* (%)
McKane *et al*, 1987	48 weeks (12 week run-in) In-patients with schizophrenia well controlled with antipsychotics	Mean of 120 mg/4 weeks. Range of doses not provided	17	6 (35)
Chouinard *et al*, 1989	8 months (+3 months before study) Patients with schizophrenia already stabilised on depot treatment	Mean equivalent to 385 mg/4 weeks (some received drug at shorter intervals) Range 15–1800 mg/4 weeks.	36	0 (0)
Eklund & Forsman, 1991	48 weeks (15 week run-in) Patients with schizophrenia mostly out-patients	All patients received 60 mg/4 weeks	18	2 (11) 16 out of 23 (69) relapsed on placebo
Koskinen *et al*, 1991; Wistedt *et al*, 1991	9 months Out-patients with chronic schizophrenia	Mean of 92 mg/4 weeks Range 38–200 mg/4 weeks	27	4 (11)
Altamura *et al*, 1995	1 year Out-patients with schizophrenia of mean duration 8 years	Mean 120.6 mg/4 weeks Range 25–375 mg/4 weeks	48	11 out of 48 in year (23)
Kane *et al*, 2003	1 year Patients with schizophrenia of at least 2 years' duration. Out-patients	25 mg/4 weeks 50 mg/4 weeks 100 mg/4 weeks 200 mg/4 weeks	25 28 26 26	15 (60) 7 (25) 6 (23) 4 (15)

https://doi.org/10.1192/pb.29.3.104 Published online by Cambridge University Press

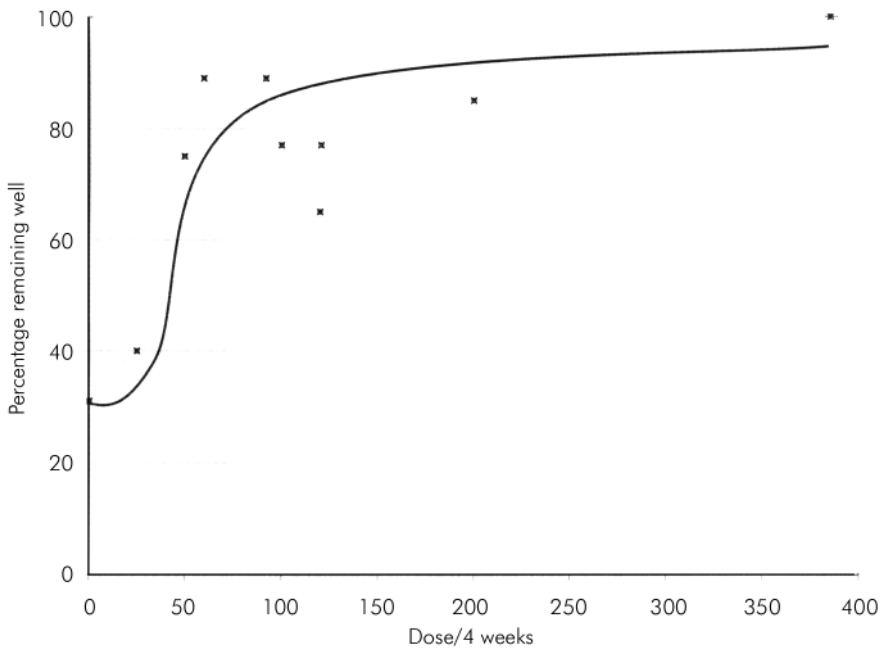

Fig. 1. Dose–response curve for haloperidol decanoate dose v. relapse.

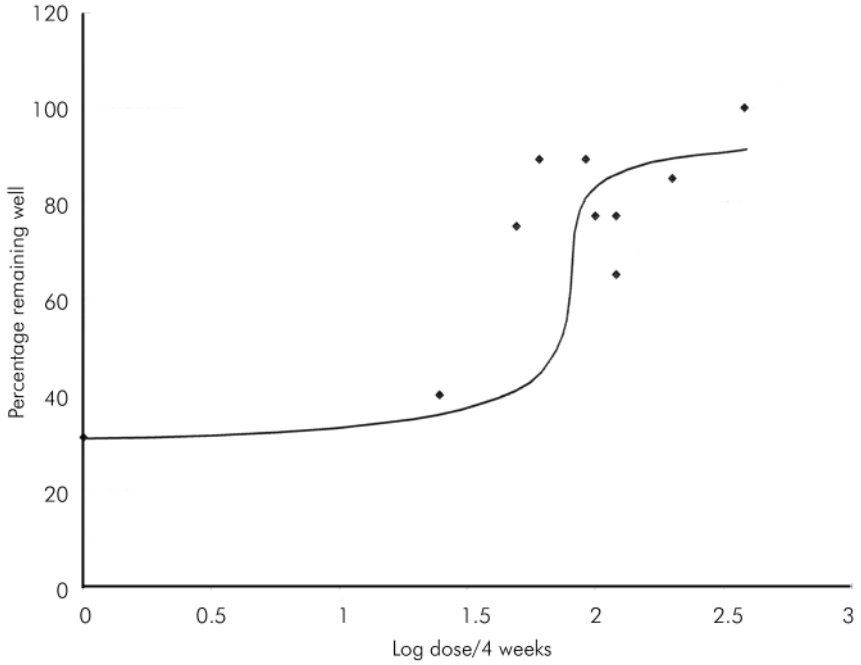

Fig. 2. Log dose–response curve for haloperidol decanoate dose (log) v. relapse.

through greater drug exposure (as with oral haloperidol; Van Putten *et al*, 1990; Stone *et al*, 1995). If the curve rises above the horizontal (as it could be drawn) then many will argue that such negative effects are a suitable price to pay for a small but palpable reduction in risk of relapse. Unfortunately, available data provide few details on the effects of doses above 120 mg/4 weeks and so we cannot be certain about the exact dose–response relationship. It is noteworthy however that the very high doses of HD reported by Chouinard and colleagues (1989) allowed no relapses in 36 patients. Without these data, the curve is clearly flat; with it, it suggests worthwhile reduction in risk of relapse with very high doses. It is also noteworthy that receptor binding studies report near saturation of dopamine receptors at very low doses (5 mg/day) of haloperidol (Tauscher & Kapur, 2001). This might predict a plateau of effect.

Aside from difficulties relating to the plotting of the dose–response curve, other caveats should be noted. First, the plotting of mean HD doses as single data points

https://doi.org/10.1192/pb.29.3.104 Published online by Cambridge University Press

is problematic since each value conceals a range of doses given to participants. These data might be better represented as horizontal lines on the graph, describing the range of doses used. It is notable, however, that fixed dose studies (Eklund & Forsman, 1991; Kane *et al*, 2003) provide data-points which fit with the general trend of mean dose data. Second, there is clearly a time-effect when considering rates of relapse and studies used to generate data-points ranging in total duration from 9 months (Wistedt *et al*, 1991) to 60 weeks (McKane *et al*, 1987). Data generated from studies conducted do not allow standardisation of relapse data at a particular time point. It should be understood therefore that shorter studies probably underestimate relapse by 1 year (perhaps important for Chouinard *et al*, 1989) and longer studies probably over estimate relapse at 1 year (for example, McKane *et al*, 1987). Third, criteria used to define relapse varied somewhat from one study to another: some used the administration of additional oral antipsychotics, some admission to hospital; others leaving the study early. Such variation is likely to have an important effect on data interpretation but the fixed dose study of Kane *et al* (2002) used the same relapse criteria for each dose and produced results broadly in line with the trend.

A major advantage of attempting to define dose–response of a depot formulation is that, it is assumed, full compliance with treatment is certain. With oral forms, assessment of dose–response is confounded by partial or non-compliance which may well be unknown to the study investigators. It might be argued that the use of depots allows more accurate assessment of dose–response relationships.

This analysis might be strengthened still further by the inclusion of unpublished pre-licence data, but these were not available. Nevertheless, this secondary analysis serves to strengthen impressions gained from single studies. The overall impression given by data analysed here, it can tentatively be concluded, is that there is little to be gained by increasing the dose of HD above 100 mg/4 weeks. Individual clinicians will need to decide whether or not the use of doses above this level can be justified when there is little or no expectation of improved efficacy and well grounded expectation of higher cost and worsened adverse effect burden.

Declaration of interest

None.

References

ALTAMURA, A. O., TACCHINI, G. I., MAES, M. (1995) Haloperidol plasma 'threshold' levels for relapse prevention in schizophrenia: a study with haloperidol decanoate. *European Neuropsychopharmacology Supplement*, 55–58.

BECHELLI, L. P. C., IECCO, M. C., ACIOLI, A., *et al* (1985) A double-blind trial of haloperidol decanoate and pipothiazine palmitate in the maintenance treatment of schizophrenics in a public out-patient clinic. *Current Therapeutic Research*, **37**, 662–671.

BRITISH MEDICAL ASSOCIATION AND THE ROYAL PHARMACEUTICAL SOCIETY OF GREAT BRITAIN (2003) *British National Formulary*. London: British Medical Association and the Royal Pharmaceutical Society of Great Britain.

CHOUINARD, G., ANNABLE, L., CAMPBELL, W. (1989) A randomised clinical trial of haloperidol decanoate and fluphenazine decanoate in the outpatient treatment of schizophrenia. *Journal of Clinical Psychopharmacology*, **9**, 247–253.

COOKSON, J. C., KENNEDY, N. M. & GRIBBON, D. (1986) Weight gain and prolactin levels in patients on long-term antipsychotic medication: a double blind comparative trial of haloperidol decanoate and fluphenazine decanoate. *International Clinical Psychopharmacology* (suppl1), 41–51.

DAVIS, J. M., McKANE, J. M., MARDER, S. R., *et al* (1993) Dose reponse of prophylactic antipsychotics. *Journal of Clinical Psychiatry*, **54** (suppl), 24–30.

DAVIS, J. M., CHEN, N. & GLICK, I. D. (2003) A meta-analysis of the efficacy of second generation antipsychotics. *Archives of General Psychiatry*, **60**, 553–564.

DENCKER, S. J., GIOS, I., MARTENSSON, E., *et al* (1994) A long term cross-over pharmacokinetic study comparing perphenazine decanoate and haloperidol decanoate in schizophrenic patients. *Psychopharmacology*, **114**, 24–30.

EBERHARD, G. & HELLBORN, E. (1986) Haloperidol decanoate and flupenthixol decanoate in schizophrenia. *Acta Psychiatrica Scandinavica*, **74**, 255–262.

EKLUND, K. & FORSMAN, A. (1991) Minimal effective dose and relapse – double blind trial: haloperidol decanoate vs. placebo. *Clinical Neuropharmacology*, **14**, S7–S15.

GEDDES, J., FREEMANTLE, N., HARRISON, P., *et al* (2000) Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. *BMJ*, **321**, 1371–1376.

HILTON, T., TAYLOR, D. & ABEL, K. (1996) Which dose of haloperidol? *Psychiatric Bulletin*, **20**, 359–362.

KANE, J. M., DAVIS, J. M., SCHOOLER, N., *et al* (2002) A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. *American Journal of Psychiatry*, **159**, 554–560.

KOSKINEN, T., WISTEDT, B. & THELANDER, S. (1991) Zuclopenthixol decanoate vs. haloperidol decanoate: A double blind comparative study. *Biological Psychiatry*, **1**, 563–565.

McKANE, J. P., ROBINSON, A. D. T., WILES, D. H., *et al* (1987) Haloperidol decanoate v. fluphenazine decanoate as maintenance therapy in chronic schizophrenia in-patients. *British Journal of Psychiatry*, **151**, 333–336.

MEYEROWITZ, W., JARAMILLO, J. D. C., DENSON, D., *et al* (1989) Optimum therapeutic dosing with haloperidol decanoate. *Current Therapeutic Research*, **46**, 1174–1178.

QURAISHI, S. & DAVID, A. (2000) Depot haloperidol decanoate for schizophrenia (Cochrane Review). In: *The Cochrane Library*, issue 4. Chichester, UK: John Wiley & Sons, Ltd.

STONE, C. K., GARVER, D. L., GRIFFITH, J., *et al* (1995) Further evidence of a dose–response threshold for haloperidol in psychosis. *American Journal of Psychiatry*, **152**, 1210–1212.

TAUSCHER, J. & KAPUR, S. (2001) Choosing the right dose of antipsychotics in schizophrenia. *CNS Drugs*, **15**, 671–678.

TAYLOR, D. (1999) Depot antipsychotics revisited. *Psychiatric Bulletin*, **23**, 551–553.

TAYLOR, D. (2000) Low dose typical antipsychotics – a brief evaluation. *Psychiatric Bulletin*, **24**, 465–468.

VAN PUTTEN, T., MARDER, S. R. & MINTZ, J. (1990) A controlled dose comparison of haloperidol in newly admitted schizophrenic patients. *Archives of General Psychiatry*, **47**, 754–758.

WISTEDT, B. (1984) A comparative trial of haloperidol decanoate and fluphenazine decanoate in chronic schizophrenic patients. *International Clinical Psychopharmacology*, **1** (suppl 1), 15–23.

WISTEDT, B., PETSSON, T. & HELLBORN, E. (1984) A clinical double-blind comparison between haloperidol decanoate and fluphenazine decanoate. *Current Therapeutic Research*, **35**, 804–814.

WISTEDT, B., KOSKINEN, T., THELANDER, S., *et al* (1991) Zuclopenthixol decanoate and haloperidol decanoate in chronic schizophrenia; a double blind multicentre study. *Acta Psychiatrica Scandinavica*, **84**, 14–16.

ZISSI, N. P., PSARAS, M. & KYKETSOS, G. (1982) Haloperidol decanoate, a new long-acting antipsychotic in chronic schizophrenia: a double blind comparison with placebo. *Current Therapeutic Research*, **31**, 650–655.

David Taylor Pharmacy Department, Maudsley Hospital, London SE5 8AZ. E-mail: David.taylor@slam.nhs.uk

https://doi.org/10.1192/pb.29.3.104 Published online by Cambridge University Press