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.

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
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.

In the most recently published study, Kane and colleagues (2003) 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 4–25 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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Duration and subject details</th>
<th>Dose details</th>
<th>n</th>
<th>Relapse n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mckane et al, 1987</td>
<td>48 weeks (12 week run-in) In-patients with schizophrenia well controlled with antipsychotics</td>
<td>Mean of 120 mg/4 weeks. Range of doses not provided</td>
<td>17</td>
<td>6 (35)</td>
</tr>
<tr>
<td>Chouinard et al, 1989</td>
<td>8 months (+3 months before study) Patients with schizophrenia already stabilised on depot treatment</td>
<td>Mean equivalent to 385 mg/4 weeks (some received drug at shorter intervals) Range 15–1800 mg/4 weeks</td>
<td>36</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Eklund &amp; Forsman, 1991</td>
<td>48 weeks (15 week run-in) Patients with schizophrenia mostly out-patients</td>
<td>Mean of 92 mg/4 weeks Range 38–200 mg/4 weeks</td>
<td>18</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Koskinen et al, 1991; Wistedt et al, 1991</td>
<td>9 months Out-patients with chronic schizophrenia</td>
<td>Mean of 120.6 mg/4 weeks Range 25–375 mg/4 weeks</td>
<td>48</td>
<td>11 out of 48 in year (23)</td>
</tr>
<tr>
<td>Altamura et al, 1995</td>
<td>1 year Out-patients with schizophrenia of mean duration 8 years</td>
<td>Mean of 92 mg/4 weeks Range 38–200 mg/4 weeks</td>
<td>27</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Kane et al, 2003</td>
<td>1 year Patients with schizophrenia of at least 2 years’ duration. Out-patients</td>
<td>Mean of 92 mg/4 weeks Range 38–200 mg/4 weeks</td>
<td>25</td>
<td>15 (60)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean of 100 mg/4 weeks Range 25–375 mg/4 weeks</td>
<td>26</td>
<td>7 (25)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mean of 200 mg/4 weeks Range 25–375 mg/4 weeks</td>
<td>26</td>
<td>6 (23)</td>
</tr>
</tbody>
</table>
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
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 point. It should be understood therefore that shorter allow standardisation of relapse data at a particular time 1987). Data generated from studies conducted do not


efficacy and well grounded expectation of higher cost when there is little or no expectation of improved 4 weeks. Individual clinicians will need to decide whether


tionships.

allows more accurate assessment of dose-response rela-

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


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David Taylor
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