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Haloperidol Decanoate
A Preliminary Review of Its Pharmacodynamic and Pharmacokinetic Properties and Therapeutic Use in Psychosis

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Synopsis

Haloperidol decanoate[1] *is a depot preparation of haloperidol, a commonly used butyrophenone derivative with antipsychotic activity. Haloperidol decanoate has no intrinsic activity: its pharmacodynamic actions are those of haloperidol – primarily that of central antidopamine activity. The monthly administered depot formulation has several clinical and practical advantages over oral haloperidol: better compliance and more predictable absorption; more controlled plasma concentrations; fewer extrapyramidal side effects; less frequent reminders of condition; and reduced medical workload. In open and controlled studies, haloperidol decanoate has produced adequate maintenance or improvement of the condition of patients with psychoses (mainly schizophrenia) when an abrupt change from orally administered haloperidol or other antipsychotic drugs has been instituted. Limited comparative studies indicate that the depot and oral forms of haloperidol are equally effective, and that haloperidol decanoate is at least as effective as depot forms of fluphenazine, pipothiazine, flupenthixol and perphenazine in controlling the symptoms of psychosis. Extrapyramidal side effects and the need for concomitant anti-Parkinsonian drugs may be a problem, but may be less frequent than with oral haloperidol or other depot antipsychotics. Thus, haloperidol decanoate offers a useful alternative in the treatment of psychoses to orally administered haloperidol or to other depot antipsychotic drugs.*

Pharmacodynamic Studies

Haloperidol decanoate is a depot form of haloperidol with no intrinsic activity. Its pharmacodynamic effects are those of haloperidol; it has a central antidopamine action, antagonising the effects of apomorphine and amphetamine and releasing prolactin. Dopamine turnover is also increased and dopamine metabolites accumulate. Glutamic acid decarboxylase activity in the substantia nigra is reduced (an event which may be associated with the production of tardive dyskinesia). Like haloperidol, haloperidol decanoate has little effect on the cardiovascular system or on the motility of smooth muscle.

Pharmacokinetic Studies

Haloperidol decanoate is injected in a sesame oil vehicle into muscle. It is then hydrolysed relatively slowly to haloperidol and decanoic acid. Peak plasma concentrations are not reached for 3 to 9 days and are proportional to the administered dose. Steady-state plasma concentrations are reached within 2 to 3 months (compared with 7 days for the oral preparation). The pharmacokinetic disposition appears to be essentially the same as that of oral haloperidol, which is approximately 92% bound to plasma proteins, crosses the blood-brain barrier and passes into the milk of nursing mothers. Haloperidol is metabolised mainly by oxidative dealkylation to inactive metabolites. The plasma elimination half-life of the depot preparation (about 3 weeks) is considerably longer than that of the oral form (about 24 hours).

Therapeutic Trials

Haloperidol is a widely used antipsychotic drug in the treatment of psychotic disorders. Haloperidol decanoate is a depot formulation of haloperidol, usually administered monthly, which has recently been used in the treatment of psychoses (mainly schizophrenia) in an attempt to minimise side effects and compliance problems while maintaining clinical efficacy. Open and controlled studies have shown that haloperidol decanoate is more effective than placebo, and at least as effective as oral haloperidol and a number of other depot antipsychotic agents, including fluphenazine decanoate, pipoth-

1 'Haldol Decanoate' (Janssen; McNeill).

iazine palmitate, flupenthixol decanoate and perphenazine enanthate. Symptoms of schizophrenia, such as emotional withdrawal, conceptual disorganisation, depression, paranoia, hallucinatory behaviour and catatonia, are well controlled and indeed may be improved in most patients even when previous medication, upon which they are usually stabilised, has been abruptly discontinued. Dose-ranging studies to determine the optimum dose for clinical efficacy and improved tolerance originally used a protocol of high initial doses (usually 20 times the previous daily oral haloperidol dose) which were reduced as necessary. Currently, initial doses are often lower (10 to 15 times the previous daily oral dose) and are increased if required.

Side Effects

The major unwanted effect of antipsychotic therapy, including haloperidol decanoate, is the production of extrapyramidal symptoms. The incidence and intensity of symptoms may be less with haloperidol decanoate than other antipsychotic drugs, especially when the dose is not too high. The concomitant use of anti-Parkinsonian drugs also tends to be less with the depot preparation. Other side effects reported with haloperidol decanoate, apart from 2 cases of neuroleptic malignant syndrome, have been mild and short-lived.

Dosage and Administration

Haloperidol decanoate is usually given as a monthly intramuscular injection. Although earlier investigators gave an initial dose which was 20 times the daily oral haloperidol dose, more recent investigations have tended to give a lower initial dose, often between 10 and 15 times the daily oral haloperidol dose (i.e. about 50 to 100mg). This may be increased during subsequent injections as required, and tends to maximise antipsychotic effects and minimise extrapyramidal effects.

1. Pharmacodynamic Studies

Haloperidol decanoate (fig. 1) is a depot antipsychotic agent, an ester of haloperidol and decanoic acid. After injection it is released gradually from muscle tissue and hydrolysed slowly into free haloperidol which then enters the systemic circulation.

1.1 Pharmacodynamic Properties of Haloperidol

Haloperidol is a butyrophenone derivative with a therapeutic effect (like that of other antipsychotic agents) thought to be the result of its central antidopamine activity. It antagonises the effects of apomorphine (a direct dopamine agonist) and amphetamine (an indirect dopamine antagonist), its activity being similar to that of trifluoperazine and fluphenazine, slightly greater than chlorpromazine and much greater than that of thioridazine. The turnover rates of striatal dopamine and its metabolites, particularly homovanillic acid, are increased and the concentration of dopamine reduced by haloperidol at doses ranging between 3 and 15mg. However tolerance to this effect of haloperidol develops after 7 days. Receptor binding studies show that haloperidol is equivalent to fluphenazine and about twice as active as chlorpromazine as an inhibitor of dopamine binding to central dopamine receptors (Pakes 1982a).

Animal studies have shown that haloperidol has low antiadrenergic activity and thus has little tendency to produce orthostatic hypotension and/or tachycardia. It also has low anticholinergic activity, and is less sedative than many other antipsychotic agents. However haloperidol does produce motivational, emotional and behavioural changes, although it is less likely than chlorpromazine, for example, to produce ptosis or catalepsy in rats or to potentiate thiopentone narcosis. Studies carried out in humans have shown that haloperidol alters patterns of sleep by increasing stages 1 and 2 and reducing stages 3 and 4 without affecting REM sleep. In addition, in computerised EEG studies, it reduces the energy level of the EEG in schizophrenia patients but increases it in healthy subjects (Pakes 1982a).

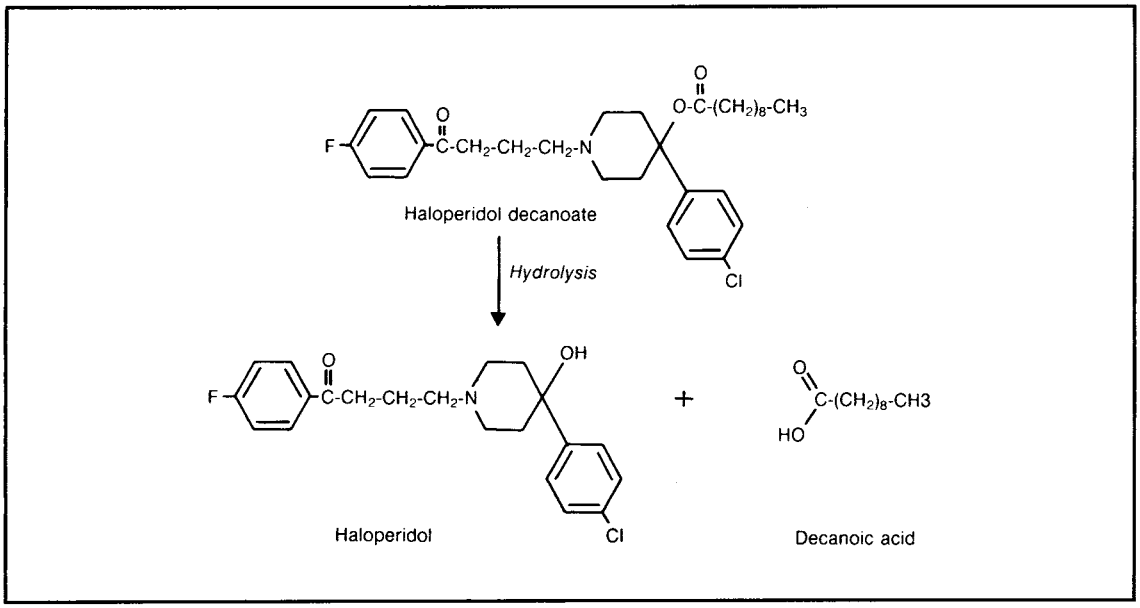

Fig. 1. Structural formula of haloperidol decanoate and its hydrolysis into haloperidol and decanoic acid.

Haloperidol can produce any of the 5 different types of extrapyramidal syndrome: Parkinsonism, akathisia, acute dystonic reactions, tardive dyskinesia and (rarely) perioral tremor. These side effects are dose-related and common, but variable. However, the drug has very little tendency to produce jaundice (Baldessarini 1980).

1.2 Pharmacodynamic Properties of Haloperidol Decanoate

1.2.1 Central Effects

Since haloperidol decanoate is a depot preparation of a long-established drug, it was used clinically (and found to be valuable) before many animal studies had been carried out to validate its use as a haloperidol prodrug. However, subsequent studies have been undertaken to elucidate the pharmacological activity of the drug.

Niemegeers (1981) reported that the administration of haloperidol decanoate produced plasma concentrations of haloperidol which paralleled the antagonism to apomorphine-induced emesis in dogs. Oka and colleagues (1985) found that haloperidol decanoate had no intrinsic activity in a model of antipsychotic-like behaviour in rats and mice, and had only 2.5% of the activity of haloperidol in *in vitro* dopamine receptor binding. Intracerebroventricular injections of haloperidol and haloperidol decanoate resulted in an increased accumulation of the dopamine metabolites homovanillic acid and 3,4-dihydroxyphenylacetic acid after haloperidol but little change after haloperidol decanoate. After a single injection of haloperidol decanoate, the concentration of haloperidol in dopamine-rich areas of the brain (frontal cortex, limbic forebrain, striatum) peaked at day 2, remained high for 7 days and then fell slowly.

Oka et al. (1985) found that the time courses of the behavioural and biochemical events following intramuscular haloperidol decanoate injection in rodents were variable. Haloperidol decanoate reduced the conditioned avoidance rate for a long period. The effect peaked 24 hours after injection, remained high for up to 9 days and then declined slowly, returning to its predrug level by the twenty-eighth day. Similarly, the concentrations of homovanillic acid and 3,4-dihydroxyphenylacetic acid in the frontal cortex peaked after 8 hours and remained significantly higher than normal 21 days

after injection. The prolactin-releasing and the antiapomorphine activity of haloperidol decanoate did not last as long. Both effects peaked within 24 hours but returned to pretreatment levels within 7 days.

Accumulation of dopamine metabolites in the striatum peaked 8 hours after injection of haloperidol decanoate, but returned to normal within 21 days. The differential accumulation of dopamine metabolites might help explain why haloperidol decanoate has a long-lasting antipsychotic clinical effect but a less prolonged extrapyramidal effect since it is widely accepted that extrapyramidal side effects are due to dopamine receptor blockade in the nigrostriatal dopamine system (Oka et al. 1985). However, this is disputed by Molloy and Waddington (1985) and O'Boyle and Waddington (1985) whose experiments in rats indicate that something other than dopamine receptor blockade may be involved in such reactions. Orofacial dyskinesias could be produced in rats by both fluphenazine decanoate and haloperidol decanoate (Molloy & Waddington 1985). Despite the similar behavioural effects produced by the 2 drugs, haloperidol decanoate increased striatal dopamine receptor density whereas fluphenazine decanoate did not. In older rats there was less increase in dopamine receptor density and a lessening of the effect of haloperidol decanoate (O'Boyle & Waddington 1985).

There may be a connection between one particular form of extrapyramidal activity, namely tardive dyskinesia, and the GABA-ergic neuron system. Haloperidol decanoate can produce a corresponding disorder in rats. Vacuous mouth movements persisted during an 8 month study period and reappeared on challenge with a single dose of haloperidol. This effect was associated with a reduction in glutamic acid decarboxylase activity in the substantia nigra (Gunne & Growdon 1982; Gunne & Häggström 1983; Gunne et al. 1982, 1984).

Computerised pharmacodynamic studies of the EEG in man have shown that haloperidol decanoate 75 to 300 mg/month increased the theta spectrum power of psychotic patients during the first week after injection, the increase being correlated with clinical improvement (De Buck et al. 1981). Haloperidol decanoate 50 to 180 mg/month also increased serum prolactin concentration in some geriatric patients during a 6-month study (Viukari et al. 1982).

1.2.2 Other Effects

Other pharmacodynamic actions of haloperidol decanoate are similar to those of haloperidol itself. Doses of 25 mg/kg had little effect on locomotor activity in mice whereas very high doses (200 mg/kg) produced catalepsy and piloerection. Doses of 50 to 200 mg/kg did not affect the haemodynamic responses or electrocardiograph of rats, cats or dogs. Neither did it affect the *in vitro* motility of guinea-pig ileum or motility of the uterus of non-pregnant rats (Matsuno et al. 1985).

Like haloperidol, haloperidol decanoate reduced intestinal transport, increased gastric emptying and reduced acid output in rats. It also increased the urine volume in saline-loaded rats without affecting sodium/potassium excretion. It did not affect the response to acetylcholine or serotonin and had a weaker (32%) antihistamine effect than did haloperidol (Matsuno et al. 1985).

2. Pharmacokinetic Studies

2.1 Pharmacokinetics of Haloperidol

The pharmacokinetics of haloperidol have been reviewed by Pakes (1982b). Haloperidol is absorbed rapidly after oral administration but the extent of absorption is very variable. When it was given as a solution, bioavailability ranged from 38 to 86% (Bianchetti et al. 1980); given as tablets, it ranged from 44 to 74% (Forsman & Öhman 1976). Two plasma concentration peaks were observed after oral administration, the first occurring within 3 to 6 hours and the second (probably the result of enterohepatic cycling) at 12 to 20 hours (Forsman & Öhman 1976). Multiple dose studies have shown that steady-state is achieved in about 7 days (Bianchetti et al. 1980), the steady-state serum concentration increasing linearly with increasing dose (Forsman & Öhman 1976).

Haloperidol is distributed rapidly to extravascular tissues such as the liver (where its concen-

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