Individual Variability in Response to Haloperidol

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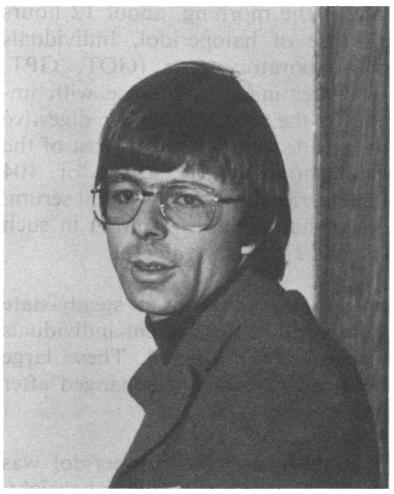
Inter-individual differences in the clinical effect of drugs have been recognized for a long time. Pharmacokinetics can only explain part of this wide variability. This problem was recently reviewed by Michael D Rawlins of the University of Newcastle upon Tyne (1974). He discussed three principal components: (1) Disease. (2) Responsiveness of tissues. (3) Concentration of the drug at its site of action (as reflected by its serum or plasma concentration).



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Different diseases do not necessarily have a common effective therapeutic concentration range for a given drug. If different receptor types, or different 'clusters' of receptors are affected in different diseases, then probably both etiology and pathogenesis are different. A specific disease would then demand not only a particular drug, but also a particular drug concentration to result in a successful clinical outcome. One important implication of this is the necessity of using strict diagnostic criteria when designing trials for testing drugs. To the practitioner it is equally important (in a clinical situation) to use the same strict criteria when looking for the drug of choice and its optimal concentration in serum.

Varying responsiveness of the central neurones probably makes a significant contribution to the variability in the response to a given drug. Animal studies indicate that the affinities of receptors for particular agonists and antagonists are constant within and even between species (Rossum 1968). However, there probably are different amounts of endogenous agonists, like dopamine, noradrenaline and serotonin in the brains of different individuals to compete with the drug. Furthermore, genetically determined differences may exist in the highly complex events interposed between receptor stimulation and drug response. This would of course contribute to the total variability in drug response.

The first two considerations above relate to pharmacodynamics. However, a substantial part of the variability in response to drugs can be explained in terms of pharmacokinetics, which deals with the concentration of drug at its site of action. Constitutional variation in pharmacokinetic parameters, such as apparent volume of distribution, metabolism and excretion may actually explain therapeutic failure as well as side-effects. In fact, adjustment of dosage, according to the steady-state concentration in serum or plasma, has already improved the therapeutic results in the use of anti-epileptic drugs; anti-arrhythmics; digitalis, and in psychiatry, lithium salts and tricyclic antidepressants (Kutt *et al.* 1964, Collste *et al.* 1972, Smith 1969, Schou *et al.* 1970, Sjöqvist *et al.* 1971). Antipsychotic drugs have been studied little in this respect, partly because of methodological difficulties. However, monitoring the serum concentration would be particularly helpful in neuroleptic drug treatment since the clinical effect is often delayed and since embarrassing or even serious side-effects may occur.

At Department III of Lillhagen Hospital in Gothenburg, we developed a specific and highly sensitive method for determining haloperidol in serum and various tissues. It is based on gas chromatography, using an internal standard procedure. The results of some applications will be presented here together with data from studies on protein binding, metabolism and excretion. Methodological questions are not included in this account, since they were, or will be, presented elsewhere (Forsman *et al.* 1974, Forsman & Öhman 1974, 1975).

Steady-state Serum Levels of Haloperidol

During oral administration of haloperidol the serum concentration reached a steady-state level in 7–10 days. Blood samples were obtained from

fasting patients in the morning, about 12 hours after the last dose of haloperidol. Individuals with abnormal laboratory tests (GOT, GPT, serum urea and creatinine) and those with impaired function of the liver, kidney or digestive tract were not included in the study. Most of the haloperidol concentrations in serum of 104 different patients varied from 2 to 4 ng/ml serum. The daily dose of haloperidol, resulting in such concentrations, was 1–8 mg.

A one- to ten-fold variation in steady-state concentration was found in different individuals on identical doses of haloperidol. These large differences remained essentially unchanged after normalization for bodyweight.

The serum concentration of haloperidol was divided by the given dose per kg of bodyweight. This was called the relative steady-state concentration. It is a measure of concentration achieved per daily dose. The relative steady-state concentration was higher in a group of patients above 45 years of age, as compared to younger patients.

The large variation in serum steady-state concentration in different patients on identical doses of haloperidol may be due to individual differences in drug bioavailability, volume of distribution and metabolizing capacity. Furthermore, such differences may well be the background of therapeutic failure or unexpected side-effects in several patients.

Pharmacokinetics and Bioavailability

Haloperidol was given intravenously to 10 healthy volunteers. Six of these individuals again took the same dose of 10 mg haloperidol orally (i.e. as tablets) six weeks later, after a fasting period of about six hours. After intravenous administration there was a steep fall in concentration, lasting for about one hour, followed by a slower exponential decay. Sedative effects reached a maximum during the first distribution period of one hour. In contrast, there was an apparent delay of 12–16 hours in the onset of extrapyramidal side-effects. This delay may be explained by a gradual onset of metabolic changes in the CNS, caused by the drug. It may equally well be due to a local delay in the distribution of the drug in the CNS.

After oral administration of haloperidol there was a time-lag of almost 1.5 hours between ingestion of the tablets and appearance of the drug in blood. The serum concentration increased to a maximum after four to six hours. The concentration curve then gradually turned into a slow exponential decay, similar to that after intravenous infusion. However, there was a second concentration peak after about 18 hours (i.e. when the individuals had lunch). Presumably this indicates excretion of the drug into the bile. The second peak would then result from reabsorption of the drug after emptying of the gall bladder. After oral administration of haloperidol, there was a gradual onset of sedation, lasting for several hours.

The bioavailability was calculated by comparing the surface under the concentration curve after intravenous and oral administration. It ranged from 44% to 74% with a mean value of 60% in the 6 patients studied in this respect. This means that only approximately 60% of an oral dose of haloperidol finally reached the systemic circulation.

The serum half-life after intravenous infusion varied from 10.1 to 19 hours with a mean value of 15.6 hours. The estimated serum half-life was several hours longer after oral administration, indicating delayed absorption, or possibly enterohepatic recirculation of haloperidol. After determining C_0, which would be the concentration at time zero if the distribution were instantaneous, the apparent volume of distribution could be calculated. When determined in this way it ranged from 1280 to 2130 litres.

The equation describing the serum concentration as a function of time was also calculated for each oral and intravenous experiment, using multiple regression analysis. This was performed using the BMDX 85 programme in an IBM computer. After testing various pharmacokinetic models, we found that an open three-compartment model, according to Gibaldi *et al.* (1971) would best fit the results. In this model the body is supposed to consist of a central compartment, a hepatoportal compartment and a tissue compartment. Intravenous doses arrive in the central compartment immediately, while oral doses must pass first through the hepatoportal compartment before distributing into the body.

This model can explain the shape of the serum concentration curves after intravenous and oral administration. It can also explain why bioavailability is reduced despite even complete absorption of the drug. This phenomenon is sometimes referred to as a 'first-pass effect' in the liver. Finally it is possible to calculate the numerical values of the equilibrium constants in the model and thus the volume of the different compartments and the haloperidol content in them. Adopting this model one can show that a sub-

stantial extrahepatic elimination of haloperidol is likely to occur. Further pharmacokinetic data will be published elsewhere.

Haloperidol Concentration in Serum, Plasma, Whole Blood and Red Blood Cells

Steady-state concentrations of haloperidol were of the same order in serum, plasma, whole blood and red blood cells of different patients and healthy volunteers. After intravenous administration the serum concentration exceeded that in red blood cells during the distribution phase. When distribution was completed the concentrations in serum and red blood cells were identical and they remained so during the metabolic phase.

Free and Bound Fraction of Haloperidol in Serum

Protein binding of haloperidol was determined using three independent techniques, one based on ultrafiltration, the other two on equilibrium dialysis. The protein binding was very close to 92% in 4 different healthy volunteers using these methods, in the concentration range of 0.5 – 20 ng/ml serum. The inter-individual differences were negligible between these 4 individuals. Interestingly, there was an inter-individual variation in the protein binding of haloperidol in the serum of different patients at steady state. The higher the serum concentration, the higher was the degree of protein binding. Thus, the free and diffusible fractions of haloperidol in serum showed less inter-individual variation as compared to the total concentration of haloperidol in serum. Presumably this diffusible fraction reflects the drug concentration at its site of action, i.e. the receptors of the central neurones.

Metabolism and Excretion of Haloperidol

The metabolism of haloperidol in man has not previously been studied in detail. We isolated and identified a fluorobenzoyl carbonic acid and fluorophenyl uronic acid from human urine as metabolites of haloperidol. A pathway for the biodegradation of haloperidol in man could therefore be proposed (Forsman & Öhman 1974, 1975). As in the rat, the haloperidol molecule is split by oxidative dealkylation, resulting in hydrophilic fluorocarbonic acids, ultimately conjugated with glycine. Since the carbon-nitrogen bond is split, one does not expect the products to be psychopharmacologically active. Thus, the pharmacokinetics of the drug are equivalent to that of the one and only active substance.

Haloperidol is a lipid-soluble compound with a high protein binding. According to our studies only 1–4% of haloperidol given orally, is excreted with urine. Conjugates of haloperidol have not been found in the urine. Biliary excretion (and reabsorption) might occur, at least after oral administration, as part of a first-pass effect.

These results cannot explain that more than one third of haloperidol elimination seems to be extrahepatic, according to the open three-compartment model described earlier. The suggestion that metabolism also takes place in extrahepatic organs would solve this problem.

Concluding Remarks

Variability in clinical response to haloperidol is probably due to three main factors: the disease in question, variability in responsiveness of tissues and variability in pharmacokinetic parameters, influencing the concentration of the drug at its site of action. It seemed logical to start determining the extent of variability due to the third factor, pharmacokinetics.

Haloperidol is considered to be mainly a dopamine-receptor blocking agent, acting almost exclusively on the CNS. Until recently, studies on the pharmacokinetics and the metabolism of this drug were not possible because of methodological difficulties. The well-defined effects in the CNS; the absence of psychopharmacologically active metabolites and the small variation in the free fraction of haloperidol in serum should be helpful in the search for a correlation between haloperidol in serum (total concentration or free fraction) and clinical effects, provided that homogenous diagnostic groups are studied.

The one- to ten-fold variation in serum levels after comparable doses of haloperidol means that monitoring the drug concentration into a therapeutic range may be essential, particularly in long-term treatment of the chronically ill patient. Since the serum half-life was approximately 16 hours, administration twice daily is sufficient in most instances. According to our studies, extrapyramidal side-effects are not to be expected during the first 12 hours in previously untreated individuals. Blood pressure and pulse rate did not change significantly during the single dose experiments. Despite the absence of serious side-effects, the dose given to elderly patients should be reduced, since serum levels reached in this group are comparatively high.

Further studies on the pharmacokinetics of haloperidol may provide more detailed guidelines for the clinician to reduce therapeutic failure, as well as unnecessary side-effects. Such studies are

presently carried out at Department III of Lillhagen Hospital in Gothenburg. We are also looking beyond the concentration of drug and trying to determine the degree of receptor blockade in the central neurones. This may give an opportunity to quantify the influence of disease and of varying responsiveness of tissues on the total variability in clinical response to haloperidol. When trying to design the clinical profile of a drug, such variability should also be taken into account.

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DISCUSSION

Dr G J Rockley (*Manchester*) said that phenothiazines in urine could be detected by relatively simple tests. He wondered whether thin-layer chromatography could be used in ordinary pathological practice. Such equipment was currently being used for the detection of amphetamines, for example.

Dr Forsman said that only 1–4% of the haloperidol molecule was found in the urine and that was easily detected by gas–liquid chromatography. The metabolites could be detected by thin-layer chromatography although the process was more complicated. The procedure could probably be simplified if anyone was interested in doing so. His own analysis for metabolites was purely qualitative. Only with haloperidol itself had it been quantitative.

Dr A Hordern (*London*) commented that giving haloperidol intramuscularly to patients with excitement had various advantages. For example, the literature claimed that it worked quicker when given in this way than by oral dosage. He asked Dr Forsman whether his studies on the build-up of serum concentration of haloperidol had included the intramuscular route as well as the intravenous and oral routes.

Dr Forsman had not himself done this work. It had been performed in the McNeil Laboratories in the United States. They had given very small doses and found peak levels at one to two hours. To give higher dosages it would be appropriate to give for example, 5 mg each in a number of different sites. Dr Forsman did not know what would happen if a large amount was given at one site. Absorption into the systemic circulation might be delayed. It was his clinical impression that a very rapid clinical response followed intramuscular administration of haloperidol, although he had not followed serum concentrations for the drug given by that route.

Dr G Silverman (*Southall*) said that drug metabolism appeared to involve two stages, one an oxidative dealkylation; the other β-oxidation. He wondered which of these involved the B-450 cytochrome system. He also wondered whether anyone had investigated the effect of induction of this system upon the clearance of haloperidol. Finally, did haloperidol itself cause any induction of the system or self-induction?

Dr Forsman had not himself studied the first two topics. He believed that β-oxidation should take place in the mitochondria, where cytochrome B-450 was found. His feeling was that the dealkylation did not take place within the mitochondria. He had never seen self-induction. He studied patients who had never had haloperidol and followed their steady state concentrations It remained constant until he changed the dosage, at which time a new steady-state concentration ensued.

Dr A M van Leeuwen (*Amersfoort*) was interested in the correlation between serum concentrations and clinical effects, particularly since ten-fold differences in serum concentrations could be found from a standard dose of haloperidol.

Dr Forsman said he was studying precisely this question but results were not so far available. He was giving haloperidol in three dosages on three levels, following serum concentrations and clinical

responses. He was also looking at more objective correlates of behaviour that were produced by the brain. For example, he was analysing the cerebrospinal fluid for metabolites of transmitters and for prolactin. In addition, he was studying the electroencephalogram and analysing it by computer. He was trying to correlate all of these endpoints both with behaviour and with serum concentration.

Dr S J Dencker (*Gothenburg*) returned to the question of variations in serum concentration. For haloperidol this had been reported to be a roughly ten-fold difference. Dr Dencker considered this rather low in comparison with some other neuroleptic and antidepressant agents which showed a 30–40-fold difference. He also considered the first-pass effect with haloperidol to be rather low. With many drugs it was as high as 70%.

Dr Forsman agreed. The variation had been ten-fold in the 6 individuals whom he had studied in detail and so far reported, but he was aware that the real variation was larger. So far he had found (though not reported) twenty-fold variations. He agreed that the bioavailability was surprisingly low: 44–84%. He felt that one possible explanation would be retention of oral haloperidol in the liver. The gall-bladder would gradually deliver its retained haloperidol when the concentration curves were no longer being studied. He believed this release effect of the orally given drug was also a reason why oral dosages showed a longer half-life than intravenous dosages. He did not believe the effect was due to delayed absorption. He was currently studying this enterohepatic recirculation in Gothenburg.

He believed that he had identified some patients who were fast metabolizers of the drug and who still required a large amount in their receptors. With them, he did not obtain any antipsychotic effects (or side-effects) below a dose of 100 mg daily. This could be the new profile being discussed today.

Dr P Kristjansen (*Roskilde*) asked if Dr Forsman had any experience of the association of anti-parkinsonian drugs with haloperidol. He said that many clinicians gave an injection of an anti-parkinsonian drug together with a haloperidol injection on the presumption that it might prevent a dystonic reaction. Since extra-pyramidal reactions would appear only 12 hours after the injection of haloperidol such anti-parkinsonian injections would be ridiculous. He wondered nonetheless if the injection of anti-parkinsonian drugs affected serum levels of haloperidol.

Dr Forsman never gave an anti-parkinsonian drug in advance. He always waited for clinical effects. If the drugs were combined from the beginning, then another concentration range would be found where the extra-pyramidal side-effects occurred. But if large doses were given from the start, the extra-pyramidal symptom range seemed to be exceeded, a topic to be described by Dr Dencker. Coming down the concentration range symptoms occurred. At lower levels, however, they vanished again.

Dr P Kristjansen (*Roskilde*) completely agreed, though he believed that some clinicians insisted on administering the two drugs together.

Dr B Alapin (*St Albans*) asked if there was any known influence of anti-parkinsonian drugs on the level of haloperidol in blood.

Dr Forsman said that he was currently studying that problem but so far he had no reportable data.