J. Pharm Pharmacol. 1990, 42: 566–571
Received April 18, 1990

© 1990 J. Pharm. Pharmacol.

A Pharmacodynamic Model to Predict the Time Dependent Adaptation of Dopaminergic Activity During Constant Concentrations of Haloperidol*

Y. F. CHENG AND L. K. PAALZOW

Department of Biopharmaceutics and Pharmacokinetics, University of Uppsala, BMC, Box 580, S-751 23 Uppsala, Sweden

Abstract—The concentration-response relationship of the accumulation of brain homovanillic acid (HVA) has been studied by giving rats a shorter (12 h) and a longer (76 h) constant intravenous infusion of haloperidol, respectively, at rates aiming at different steady state blood concentrations of haloperidol of 5 to 30 ng mL^{-1}. The observed response on brain HVA concentration vs increasing steady state blood concentration of the drug produced a bell-shaped type of curve during the 12 h infusion. When the infusion proceeded for 76 h a similar type of curve was obtained but it was shifted downwards compared with the 12 h infusion. The dopaminergic activity of the rat brain, as reflected by the HVA levels, therefore adapted to a lower activity during the prolonged exposure to haloperidol. To follow the time course of this adaptation, one steady state level of about 12 ng mL^{-1} was established and kept for 12, 28, 52 and 76 h. The result showed that the accumulation of brain HVA decreased over time compared with control animals given placebo. A pharmacodynamic model was set up to quantitatively describe the time-dependent adaptation of HVA accumulation in the whole rat brain during constant haloperidol administration. By fitting this model to all three sets of experimental data simultaneously, an adaptation half-time of about 38 h $\pm$ 14 (s.d.) and a tolerance potency of about 7 ng mL^{-1} were obtained which could be used to calculate that, for example, at a constant blood level of 10 ng mL^{-1} haloperidol over 5 days the accumulation of brain HVA decreased by approximately 91% of the maximal decrease. Since the therapeutic effects of haloperidol take time to become apparent, the adaptation of HVA-accumulation seen in the present experiments and in the clinical literature could be related to the drug's antipsychotic effect. The adaptation half-time could be a useful parameter to describe and predict the rate of development of the desired therapeutic effect. Furthermore, the observed bell-shaped effect of increasing steady state blood concentrations of haloperidol on the accumulation of brain HVA corresponded to the clinically observed therapeutic haloperidol plasma concentrations of patients with schizophrenia.

When given acutely to experimental animals neuroleptic drugs stimulate brain synthesis, release and metabolism of dopamine (Roth 1983). A feedback increase of central dopamine activity is the secondary result of the blockade of postsynaptic dopamine receptors as explained by Carlsson & Lindqvist (1963). In animal experiments the acceleration of brain dopamine turnover is included amongst criteria of neuroleptic activity (Chang et al 1988). Clinically, however, the antipsychotic effect of neuroleptics is not apparent until after several weeks of therapy (Baldessarini 1985). Several studies have shown tolerance development to the neuroleptically induced stimulatory effect of dopamine (Di Chiara & Imperato 1985; Pickar et al 1986a). This time-dependent decrease of dopamine functional activity has been suggested to be responsible for the antipsychotic effect of neuroleptics (Pickar et al 1986b; Freeman & Bunney 1987).

In the present paper we have studied the effect of different steady state concentrations of haloperidol on the increase of homovanillic acid (HVA), a metabolite of dopamine in the rat brain, and have developed a pharmacokinetic-pharmacodynamic model for the quantitative description of the time-dependent adaptation of dopamine activity after haloperidol.

*Parts of this investigation were presented at the 'International Conference on Pharmaceutical Sciences and Clinical Pharmacology', Jerusalem, 1988.

Correspondence to: L. K. Paalzow, Department of Pharmacokinetics, University of Uppsala, BMC, Box 580, S-751 23 Uppsala, Sweden.

Materials and Methods

Chemicals and drugs

Haloperidol and chlorohaloperidol were kindly supplied by Janssen Pharmaceutica, Västra Frölunda, Sweden. Homovanillic acid (HVA) and vanillic acid were purchased from Sigma Chem. Co. Ltd. All other chemicals and solvents were of HPLC grade.

Animals

Male Sprague-Dawley rats, 243 $\pm$ 10 g (s.d.), were housed under standardized conditions at a room temperature of 22 $\pm$ 1 C, humidity 55 $\pm$ 5% and a 12 h light-dark cycle (6:00 to 18:00 h, light). One week's acclimatization for the rats was allowed. Food and water were freely available.

Experimental procedure

The experiment was conducted in two phases. In phase one, concentration-response relationships were studied by giving rats a 12 h and a 76 h constant i.v. infusion of haloperidol, at different infusion rates aimed at steady state blood concentrations of haloperidol between 5 and 30 ng mL^{-1}. In phase two, the drug exposure time-response relationship was investigated by giving rats constant i.v. infusions of haloperi-

dol at one infusion rate for 12, 28, 52 and 76 h, aimed at a steady state blood concentration of haloperidol of 12 ng mL^{-1}. In each phase, rats were divided into groups receiving either haloperidol or control solution (phosphate buffer pH 7·4). Haloperidol solution was made by dissolving the drug in a few drops of glacial acetic acid and then diluting with phosphate buffer. All other conditions were the same for the two groups.

A constant infusion pump (Sage Instruments, model 355) was used during 12 h of infusion experiments. An osmotic minipump (Alzet 2 ML 1, Alza Co., Palo Alto, CA), implanted subcutaneously on the right side of the rat, was used in the 28, 52 and 76 h experiments. The polyethylene catheters used to connect the constant infusion pump and the osmotic minipump were sizes PE50 and PE60, respectively.

Polyethylene catheters were inserted into the right jugular vein (PE50 or PE60) and the left carotid artery (PE50) under light ether anaesthesia. The tip of the catheter was lengthened with a 2 cm silicon rubber cannula (Silastic, 0·02 in. i.d.; 0·037 in. o.d.). The free ends of both catheters were exteriorized to the back of the neck and protected by a plastic cover. Haloperidol solution was constantly infused to the rat via the vein and three blood samples were collected via the artery at 10, 11 and 12 h during the 12 h experiment and at 28, 52 and 76 h during the other infusion experiments. Each sample (0·5 mL) was replaced by an equal volume of physiological saline. The blood sample was then quickly mixed with 10 μL 0·4 g mL^{-1} sodium citrate solution and was frozen at -50°C until analysed for haloperidol.

The rat was decapitated immediately following the last blood sample. The whole brain was rapidly removed and placed on an ice-cold dissection plate. The corpus pineale and the cerebellum were discarded. The remaining part was freed from blood vessels, weighed and immediately frozen in methanol at -70°C followed by homogenization in 0·1 M perchloric acid with addition of EDTA and internal standard (vanillic acid). After centrifugation, the supernatant was frozen at -50°C until analysed for HVA content.

Chemical assay

Haloperidol concentrations in the blood were determined by reversed-phase high-performance liquid chromatography (HPLC) with UV detection using chlorohaloperidol as internal standard (Cheng et al 1987). HVA concentration in the brain supernatant was determined by reversed-phase HPLC with electrochemical detection, according to Hefti (1979).

Pharmacodynamic model

As has been previously described for composite dose-(concentration)-response curves of apomorphine (Paalzow & Paalzow 1983a, 1986), clonidine (Paalzow & Edlund 1979; Paalzow & Paalzow 1982), promethazine (Paalzow & Paalzow 1985) and yohimbine (Paalzow & Paalzow 1983b) an observed composite pharmacodynamic effect (E) could be dissociated into its components and described by the sum of activities from at least two functional systems: E_1 and E_2. When each of these was expressed by the Hill equation the following relationship was obtained:

$$E = \frac{E_{max1}\, C^{S_1}}{C^{S_1} + EC50_1^{\,S_1}} + \frac{E_{max2} - C^{S_2}}{C^{S_2} + EC50_2^{\,S_2}} \qquad \text{(eqn 1)}$$

$$E = E_1 + E_2$$

where C is the steady drug concentration and $EC50_1$ and $EC50_2$ are the concentrations producing half of the maximum effects, E_{max1} and E_{max2}, respectively. S_1 and S_2 are constants that create sigmoidicity and exert an influence on the slope of the concentration-response curves. When the two separate effects E_1 and E_2 are opposite one of them should have a negative sign ($E = E_1$-E_2)

The present investigations showed that the observed response on brain HVA concentration at increasing steady state concentrations of haloperidol exhibited a bell-shaped curve. The observed effects on brain HVA levels at different steady state blood levels of haloperidol could thus be described by equation 1 (E_{max2} negative). However, it was found that this time-independent (steady state) composite relationship was changed in relation to the time of drug exposure to the organism. At a fixed steady state blood concentration of haloperidol the brain HVA concentration declined with the increasing duration of the infusion, which can be considered as an adaptation of the system to a constant drug stimulus. From this it follows that a time-component has to be included in equation 1. This was solved by applying the link-model of Sheiner et al (1979) and assuming that the adaptive change, often called tolerance, is obtained by the transfer of drug into a hypothetical and slowly accessible 'tolerance' compartment as shown in Fig. 1.

The rate of equilibration of drug between blood and the 'tolerance' compartment is determined by the rate constant k_{a0} (similar to k_{e0} in the link model by Sheiner et al 1979). The effect (E_3) produced by the drug concentration in the 'tolerance' compartment is opposing the naive (non-tolerance) effects (E_1-E_2) produced by the concentration in blood (eqn1) giving the following relationship:

$$E = \frac{E_{max1}\, C^{S_1}}{C^{S_1} + EC50_1^{\,S_1}} - \frac{E_{max2}\, C^{S_2}}{Ca^{S_2} + EC50_2^{\,S_2}} - \frac{E_{max3}\, Ca^{S_3}}{C_a^{S_3} + EC50_3^{\,S_3}} \qquad \text{(eqn 2)}$$

$$E = (E_1 - E_2) - E_3$$

where C_a is the concentration of haloperidol in the compartment responsible for tolerance development and $EC50_3$ is the tolerance potency (the concentration producing half of the maximal tolerance, E_{max3}). S_3 is the slope factor and the other

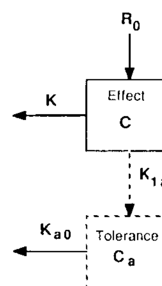

FIG. 1. A compartment model for describing concentration-response and time-response data of haloperidol.

parameters have been defined in equation 1. The haloperidol concentration in the 'tolerance' compartment (C_a) during constant drug input to the blood (one-compartment model) at different infusion times (τ) is described by the following equation (Holford & Sheiner 1981).

$$C_a = \frac{R_0 k_{a0}}{k\,(k_{a0} - k)\,V_c}(1 - e^{-k\tau}) + \frac{R_0\,k_{a0}}{k_{a0}\,(k_{a0} - k_{a0})\,V_c}(1 - e^{-k_{a0}\tau}) \quad \text{(eqn 3)}$$

where R_0 is the i.v. infusion rate, k is the first-order elimination rate constant of haloperidol from blood and V_c is volume of distribution of central compartment. k_{a0} is the rate constant determining tolerance development. The true concentration ('C_a') in the biophase cannot be determined but it can be shown that C_a in equation 3 is equal to 'C_a'/K_p where K_p is the unknown partition coefficient of haloperidol in the biophase (Holford & Sheiner 1981). According to the definition of a partition coefficient:

$$Kp = \frac{'C_a'}{C_{ss}} \quad \text{or} \quad C_{ss} = \frac{'C_a'}{K_p}$$

it follows that the tolerance potency $EC50_3$ in equation 2 is expressing the steady state blood concentration (C_{ss}) producing 50% of E_{max3} since also

$$EC50_3 = \frac{'EC50_3'}{K_p},$$

where '$EC50_3$' is the true and unknown potency of E_3.

Equations 2 and 3 were simultaneously fitted to observed individual data of the effect vs concentration and observed mean data of effect vs time, respectively, using the regression program PCNONLIN (Statistical Consultants, Inc. 1986) and different weighting schemes. The pharmacokinetic parameters k and V_c were used as constants and were obtained from a previous study (Cheng & Paalzow 1990). The calculated, formerly unknown parameters of equations 2 and 3 (E_{max1}, E_{max2}, E_{max3}, $EC50_1$, $EC50_2$, $EC50_3$, S_1, S_2, S_3, k_{a0}) can thus be obtained with their asymptotic standard deviations. Discrimination between different models was based on visual inspection of the fits, standard deviations of estimated parameter values, weighted sum of squares (partial F-test) and residual analysis. The tolerance of adaptation half-time is defined as

$$t_{\frac{1}{2}} k_{a0} = \frac{0.693}{k_{a0}}$$

The statistical analyses were made using Student's *t*-test.

Results

Steady state blood concentrations of haloperidol were obtained by constant i.v. infusions. Different rates of drug input at different infusion times from 12 to 76 h yielded desired steady state blood levels in the range of 5–30 ng mL^{-1} (Fig. 2). Established steady state conditions in the body were confirmed by the blood analyses of haloperidol at different times during the infusion and the samples taken at each steady state level did not differ significantly.

After infusion for 12 h the brain HVA level increased with increasing haloperidol blood concentration up to about 15 ng mL^{-1} (Fig. 2) where a maximal increase of HVA about 5 times (470%) the endogenous level (10 ng g^{-1}) of control animals was obtained. At steady state blood levels above approximately 15 ng mL^{-1} the increase of HVA was less than the maximum and at about 20 ng mL^{-1} the increase was similar to the effect seen at about 5 ng mL^{-1}. A bell-shaped type of concentration-response relationship was obtained (Fig. 2).

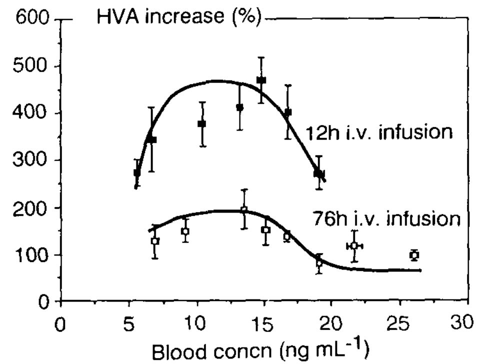

FIG. 2. The observed and calculated relation between the steady state blood concentrations of haloperidol and brain HVA response following 12 and 76 h i.v. infusion, respectively, to the rat. Each point is the mean ± s.e.m. of 4–10 rats.

When the infusion proceeded for 76 h the same type of curve was obtained but it was shifted downwards compared with the 12 h infusion with a maximum increase of about 200% (Fig. 2). The dopaminergic activity of the rat brain, if reflected by HVA concentrations, is thus adapted to a lower activity during the prolonged exposure to haloperidol. To follow the time course of this adaptation or tolerance in more detail, one steady state level of about 12 ng mL^{-1} was established in all animals and maintained for 12, 28, 52 and 76 h, at which time they were killed and the brain analysed for HVA and the blood for haloperidol concentration.

As shown in Fig. 3, the brain concentrations of HVA decreased over time during a constant drug level of haloperidol compared with control animals. The endogenous HVA level remained essentially constant during the 76 h i.v. infusion in the control group (Fig. 3). Equations 2 and 3 were then simultaneously fitted to all the data of animals given

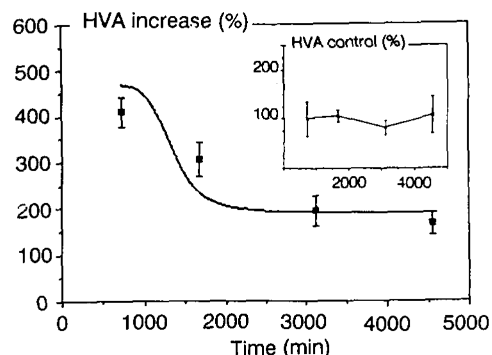

FIG. 3. The observed and calculated relation between the exposure time of haloperidol and brain HVA response following i.v. infusions to the rat. Each point is the mean of 12–22 rats (± s.d.).

haloperidol, as shown in Figs 2, 3. The unknown parameters of equations 2 and 3 were calculated with acceptable precision (Table 1). The solid lines in Figs 2, 3 show the best fits to the data.

The parameter estimates obtained were then used to plot the separate concentration-effect curves of E_1, E_2, and E_3 as shown in Fig. 4. E_1 represents the pure increase of brain HVA with increasing steady state blood levels of haloperidol with an EC50 value of $5{\cdot}5 \pm 0{\cdot}27$ (s.d.) ng mL^{-1} and a maximum increase of about 470 % (Table 1). This increase in dopaminergic activity is counteracted by another separate system E_2 appearing at steady state blood levels above about 14 ng mL^{-1} and with an EC50 value of $17{\cdot}4 \pm 1{\cdot}1$ ng mL^{-1} and a maximum decrease of 130% (Table 1).

The observed adaptation of dopaminergic activity to a lower level (as expressed by decreased brain HVA concentrations) during a constant haloperidol concentration could be described by the slow equilibration of haloperidol (k_{a0}) in the 'tolerance' compartment. In this compartment the negative effect E_3 resides and its magnitude is developed at a rate in relation to the concentration of haloperidol in the 'tolerance' compartment (C_a) according to equations 2 and 3. The maximum effect of E_3 was found to be −280% (Fig. 4, Table 1).

The rate constant of tolerance development (k_{a0}) was found to be $0{\cdot}0182 \pm 0{\cdot}0065$ h^{-1} which corresponds to a half-time of $38{\cdot}1 \pm 13{\cdot}6$ (s.d.) h. The sum of the calculated E_{max} values (E_1-E_2-E_3) when complete adaptation has developed after infinite infusion time yields an increase of brain HVA levels of about 60% at steady state haloperidol concentrations of about 25 ng mL^{-1} (Fig. 4). On the other hand, lower haloperidol concentrations at about 12–14 ng mL^{-1} will yield a higher maximal response of about 190% (E_1–E_3) at infinite infusion, since E_2 appears first at concentrations above this range.

Table 1. Pharmacodynamic parameters obtained by fitting equations 2 and 3 simultaneously to the observed data.

Parameter		Estimate	±s.d.
E_{max1}	(% of control)	473·7	26·7
$EC50_1$	(ng mL^{-1})	5·5	0·2
S_1		6·2	2·2
E_{max2}	(% of control)	132·2	40·9
$EC50_2$	(ng mL^{-1})	17·4	1·0
S_2		15·4	11·5
E_{max3}	(% of control)	279·9	30·3
$EC50_3$	(ng mL)	6·9	1·8
S_3		8·3	5·8
k_{a0}	(h^{-1})	0·0182	0·0065

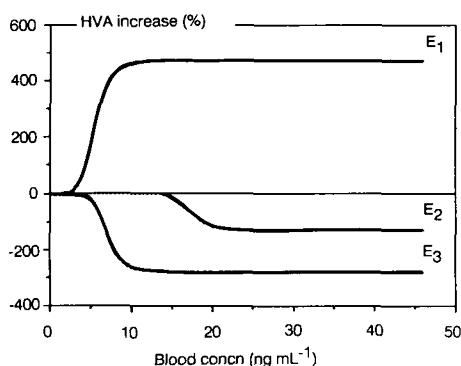

FIG. 4. The calculated pharmacodynamic effects (E_1, E_2) and adaptive effect (E_3) at different concentrations of haloperidol using the parameters from Table 1.

Discussion

Acute effects

Haloperidol is one of the most widely used neuroleptic drugs in the treatment of schizophrenia. Although there are large individual variations in pharmacokinetics and pharmacodynamics, there seems to be a clear indication of a therapeutic range of plasma concentrations below and above which the effects are not beneficial (Forsman & Öhman 1977; Magliozzi et al 1981; Extein et al 1982; Mavroidis et al 1983; Smith et al 1985).

Neuroleptic drugs are considered to block central postsynaptic dopamine receptors, resulting in an accelerated turnover of dopamine (Carlsson & Lindqvist 1963) with increased brain levels of acid metabolites such as HVA (Andén et al 1964). Accumulation of HVA has been considered as an index of increased dopamine activity and this effect has been used in animal screening models to reflect neuroleptic potency (Asper et al 1973; Bowers & Rozitis 1974; Chang et al 1988). Although acute administration of haloperidol blocks dopamine receptors, long-term treatment is required for effective antipsychotic treatment (Baldessarini 1985; Pickar et al 1986b; Davidson et al 1987).

In the present investigation, constant haloperidol concentrations were achieved by intravenous administration using implanted osmotic minipumps or an external constant infusion pump, and steady state conditions throughout body tissues were assured by measurements of the blood concentrations of haloperidol. The experiments were designed to avoid altered distribution kinetics of haloperidol during treatment or fluctuating drug levels as a consequence of repeated single doses. Infusion for 12 h produced a concentration dependent elevation of HVA levels at increasing blood concentrations of haloperidol up to about 15 ng mL^{-1}. Higher concentrations, however, resulted in a decrease of HVA accumulation and a bell-shaped (inverted U-shaped) concentration-response curve was obtained (Fig. 2) similar to that observed in humans for the antipsychotic effects (Mavroides et al 1983; Smith et al 1985). It was interesting that the therapeutic window observed in plasma of patients corresponds to the steady state blood concentrations needed for the maximal accumulation of HVA in the rat. The bell-shaped curve can be described as being composed of the sum of two separate and opposing concentration-effect curves, E_1 and E_2 (eqn 1) (for review see Paalzow et al 1985). E_1 dominates at low and moderate haloperidol concentrations and E_2 appears at haloperidol blood concentrations above approximately 14 ng mL^{-1} in addition to E_1 (Fig. 4). As to the mechanistic explanation of the effects E_1 and E_2, the increase of dopamine metabolism (E_1) would reflect the postsynaptic dopamine receptor blockade while, with increasing dose, E_2 would gradually counteract it. E_2 then

dominates at high steady state blood concentrations of haloperidol and as yet there is no clear-cut explanation of the mechanism available. Although Asper et al (1973) and Matsumoto et al (1983) noted a ceiling of the HVA increase with increase of the haloperidol dose, and Chang et al (1986), like us, found a bell-shaped dose-response curve of haloperidol on HVA accumulation in the rat brain, no further explanatory biochemical or functional studies have been made. The decline of HVA after high doses is concentration-dependent and thus represents little nonspecific toxicity. It also agrees with the therapeutic range reported with haloperidol during increased doses in schizophrenic patients (Rivera-Calimlim & Hershey 1984) and would be an effect unfavourable to antipsychotic activity. It is well known that haloperidol shows affinity for a number of receptor systems (Seeman 1987) and further studies are necessary to clarify high-dose elicited effects on dopamine metabolism.

An active metabolite of haloperidol in man (Shostak et al 1987) does not occur in the rat (Korpi et al 1985) and is not thought to contribute to the effect described here.

Time-dependent effects

When the infusion was continued to 76 h the accumulation of HVA decreased with the time course of infusion. Thus, the relationship between steady state blood concentrations of haloperidol and the effect on HVA accumulation changes with time and a function (model) to account for this time-dependency (tolerance) has to be included in equation 1. To describe the time component of development of this adaptive system we needed an additional kinetic component to be included in the naive composed (E_1-E_2) pharmacodynamic model (eqn 1). This was achieved by using the link-model of Sheiner et al (1979) according to which a hypothetical effect compartment is linked to a pharmacokinetic model so as to describe the distribution disequilibrium between blood concentrations and effect site(s). We presumed a hypothetical 'adaptation' or 'tolerance' compartment (Fig. 1) and that the rate of drug equilibration between blood and this compartment is determined by the loss of drug from this tolerance compartment (k_{a0}) in the same manner as the elimination constant of a drug from blood (k) determines the time to reach steady state conditions. The effect produced in the tolerance compartment (E_3) is then related by a Hill equation to the drug concentration in this compartment (C_a in eqn 3), while the naive composed effects E_1-E_2 are related to the steady state blood concentrations of haloperidol. Accordingly, the rate of tolerance (adaptation) development can be calculated and defined by the tolerance or adaptation half-time of the specific drug ($t\frac{1}{2}$ k_{a0}). The potency of tolerance development is defined by its EC50 value i.e. the steady state blood concentration at which the original or naive effects are decreased to 50%. It has been shown that this model is also capable of describing rebound effects often seen on drug withdrawal (Paalzow et al 1988).

By fitting equations 2 and 3 simultaneously to all experimental data of brain HVA concentrations seen during continuous exposure to different steady state concentrations of haloperidol, we were able to calculate the characteristic pharmacodynamic parameters of E_1, E_2 and E_3. A tolerance half-time of about 38 h was obtained with a tolerance potency of about 7 ng mL^{-1} (Table 1), which means that, for example, at a constant blood level of 10 ng mL^{-1} of haloperidol over 5 days (3·3 half-lives) the accumulation of HVA decreased wth approximately 91% of the maximal decrease.

In the calculations we assumed that the effects E_1 and E_2 remained unchanged during prolonged exposure to haloperidol. Extensive research is needed to prove or refute such an assumption. Several known characteristics of haloperidol are, however, in favour of this assumption. Tolerance to the antipsychotic effect has never been observed (Baldessarini & Tarsy 1980), but instead, since the therapeutic effect develops after prolonged exposure to haloperidol (Baldessarini 1985), it is tempting to speculate that the adaptation of HVA-accumulation seen in our experiments could be related to the antipsychotic effect of this drug. The adaptation half-time calculated in the present investigation could be a parameter describing and predicting the rate of development of the desired therapeutic effect, rather than the loss (tolerance) of it. Following prolonged treatment with haloperidol basal dopamine release in rat brain decreases (Lane & Blaha 1987) and after three days of repeated administration, HVA concentrations are significantly decreased compared with controls (Chang et al 1986). Others have shown that differences exist in tolerance development to HVA increase in discrete areas of the rat brain (Bowers & Rozitis 1974; Matsumoto et al 1983).

In the present paper we have provided a quantitative description of the adaptation of HVA accumulation occurring in the whole rat brain during long-term haloperidol administration. The adaptation is described by its maximum effect (E_{max}), potency (EC50) and its slope factor (S). Furthermore, the developed model is able to describe the time-component of this adaptation as defined by its adaptation half-time ($t\frac{1}{2}$ k_{a0}). These quantifications could serve as a useful tool in comparative descriptions of neuroleptics, especially since this time-dependent adaptation may be considered to reflect therapeutic efficacy. Furthermore, if applied to man, these quantitative parameters could be used to calculate optimal dosing of neuroleptic drugs in individual patients in order to obtain a rapid onset of the therapeutic response.

From our results and from other clinical and experimental studies it can be inferred that acute effects of haloperidol on dopamine metabolism do not themselves reflect antipsychotic efficacy. There is a concentration dependent range for postsynaptic dopamine receptor blockage as reflected by HVA levels. Rather, the time-dependent depression of basal dopamine activity after haloperidol should relate to the therapeutic effect. The findings suggest that moderate blood concentrations should be attained in patients as quickly as possible and be kept constant in order to develop adaptation of dopamine activity rapidly.

Acknowledgements

The present study has been supported by grants from the Swedish Medical Research Council (B89-04X-07469-04B).

References

Andén, N. E., Roos, B. E., Werdinius, B. (1964) Effects of chlorpromazine, haloperidol and reserpine on the levels of phenolic acids in rabbit corpus striatum. Life Sci. 3: 149–158

Asper, H., Baggiolini, M., Burki, H. R., Lauener, H., Ruch, W., Stille, G. (1973) Tolerance phenomena with neuroleptics catalepsy, apomorphine stereotypies and striatal dopamine metabolism in the rat after single and repeated administration of loxapine and haloperidol. Eur. J. Pharmacol. 22: 287–294

Baldessarini, R. J. (1985) Drugs and the treatment of psychiatric disorders. In: Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F. (eds) The Pharmacological Basis of Therapeutics. Macmillan, New York, pp 387–445

Baldessarini, R. J., Tarsy, D. (1980) Dopamine and the pathophysiology of dyskinesias induced by antipsychotic drugs. Ann. Rev. Neurosci. 3: 23–41

Bowers, M. B., Rozitis, A. (1974) Regional differences in homovanillic acid concentrations after acute and chronic administration of antipsychotic drugs. J. Pharm. Pharmacol. 26: 743–745

Carlsson, A., Lindqvist, M. (1963) Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. Acta Pharmacol. Toxicol. 20: 140–144

Chang, W. H., Yeh, E. K., Hu, W. H., Tseng, Y. T., Chung, M. C., Chang, H. F. (1986) Acute and chronic effects of haloperidol on plasma and brain homovanillic acid in the rat. Biol. Psychiatry 21: 374–381

Chang, W. H., Chen, T. Y., Wu, H. S., Hu, W. H., Yeh, E. K. (1988) Dose-response curves of homovanillic acid in pre-frontal cortex and caudate following antipsychotic drugs: relation to clinical potencies. Psychopharmacology 95: 459–462

Cheng, Y. F., Paalzow, L. K. (1990) Linear pharmacokinetics of haloperidol in the rat. Biopharm. Drug Dispos. (in press)

Cheng, Y. F., Paalzow, L. K., Bondesson, U., Ekblom, B., Eriksson, K., Eriksson, S. O., Lindberg, A., Lindström L. (1987) Pharmacokinetics of haloperidol in psychotic patients. Psychopharmacology 91: 410–414

Davidson, M., Losonczy, M. F., Mohs, R. C., Lesser, J. C., Powchik, P., Freed, L. B., Davis, B. M., Mykytyn, V. V., Davis, K. L. (1987) Effects of debrisoquin and haloperidol on plasma homovanillic acid concentration in schizophrenic patients. Neuropsychopharmacology 1: 17–23

Di Chiara, G., Imperato, A. (1985) Rapid tolerance to neuroleptic-induced stimulation of dopamine release in freely moving rats. J. Pharmacol. Exp. Ther. 235: 487–494

Extein, I., Augusthy, K. A., Gold, M. S., Pottash, A. L. C., Martin, D., Potter, W. Z. (1982) Plasma haloperidol levels and clinical response in acute schizophrenia. Psychopharmacol. Bull. 18: 156–158

Forsman, A., Öhman, R. (1977) Applied pharmacokinetics of haloperidol in man. Curr. Ther. Res. 21: 396–411

Freeman, A. S., Bunney, B. S. (1987) Chronic neuroleptic effects on dopamine neuron activity: a model for predicting therapeutic efficacy and side effects? In: Dahl, S. G., Gram, L. F., Paul, S. M., Potter, W. Z. (eds) Clinical Pharmacology in Psychiatry (Psychopharmacology Series 3). Springer-Verlag Berlin Heidelberg, pp 225–235

Hefti, F. (1979) A simple, sensitive method for measuring 3, 4-dihydroxyphenylacetic acid and homovanillic acid in rat brain tissue using high-performance liquid chromatography with electrochemical detection. Life Sci. 25: 775–782

Holford, N. H. G., Sheiner, L. B. (1981) Understanding the dose-effect relationship: clinical application of pharmacokinetic-pharmacodynamic models. Clin. Pharmacokinet. 6: 429–453

Korpi, E. R., Costakos, D. T., Wyatt, R. J. (1985) Interconversions of haloperidol and reduced haloperidol in guinea pig and rat liver microsomes. Biochem. Pharmacol. 34: 2923–2927

Lane, R. F., Blaha, C. D. (1987) Chronic haloperidol decreases dopamine release in striatum and nucleus accumbens in vivo: depolarization block as a possible mechanism of action. Brain Res. Bull. 18: 135–138

Magliozzi, J. R., Hollister, L. E., Arnold, K. V., Earle, G. M. (1981) Relationship of serum haloperidol levels to clinical response in schizophrenic patients. Am. J. Psychiatry 138:365–367

Matsumoto T., Uchimura, H., Hirano, M., Kim, J. S., Yokoo, H., Shimomura, M., Nakahara, T., Inoue, K., Oomagari, K. (1983) Differential effects of acute and chronic administration of haloperidol on homovanillic acid levels in discrete dopaminergic areas of rat brain. Eur. J. Pharmacol. 89:27–33

Mavroidis, M. L., Donald, R. K., Hirschowitz, J., Garver, D. L. (1983) Clinical response and plasma haloperidol levels in schizophrenia. Psychopharmacology 81: 354–356

Paalzow, L. K., Edlund, P. O. (1979) Multiple receptor responses: a new concept to describe the relationship between pharmacological effects and pharmacokinetics of a drug: studies on clonidine in the rat and cat. J. Pharmacokinet. Biopharm. 7: 495–510

Paalzow, G. H. M., Paalzow, L. K. (1982) Separate noradrenergic receptors could mediate clonidine induced antinociception. J. Pharmacol. Exp. Ther. 223: 795–800

Paalzow, G. H. M., Paalzow, L. K. (1983a) Opposing effects of apomorphine on pain in rats. Evaluation of the dose-response curve. Eur. J. Pharmacol. 88: 27–35

Paalzow, G. H. M., Paalzow, L. K. (1983b) Yohimbine both increases and decreases nociceptive thresholds in rats: evaluation of the dose-response relationship. Naunyn-Schmiedeberg's Arch. Pharmacol. 322: 193–197

Paalzow, G. H. M., Paalzow, L. K. (1985) Promethazine both facilitates and inhibits nociception in rats: effect of the testing procedure. Psychopharmacology 85: 31–36

Paalzow, L. K., Paalzow, G. H. M. (1986) Concentration-response relations for apomorphine effects on heart rate in conscious rats. J. Pharm. Pharmacol. 38: 28–34

Paalzow, L. K., Paalzow, G. H. M., Tfelt-Hansen, P. (1985) Variability in bioavailability: concentration versus effect. In: Rowland, M., Sheiner, L. B., Steimer, J. L. (eds) Variability in Drug Therapy: Description, Estimation, and Control. Raven Press, New York, pp 167–185

Paalzow, L. K., Bredberg, E., Cheng, Y. F., Sunzel, M. (1988) Time dependent change in pharmacodynamic effects (Abstract). Symposium on Variability in Pharmacokinetics and Drug Response, Gothenburg, Sweden

Pickar, D., Labarca, R., Doran, A. R., Wolkowitz, O. M., Roy, A., Breier, A., Linnoila, M., Paul, S. M. (1986a) Longitudinal measurement of plasma homovanillic acid levels in schizophrenic patients. Correlation with psychosis and response to neuroleptic treatment. Arch. Gen. Psychiatry 43: 669–676

Pickar, D., Breier, A., Wolkowitz, O. M., Kelsoe, J., Doran, A. R., Paul, S. M. (1986b) Time-dependent effects of neuroleptic treatment on positive and negative symptoms: relationship to levels of plasma homovanillic acid (HVA). Clin. Neuropharmacol. 9: 412–414

Rivera-Calimlim, L., Hershey, L. (1984) Neuroleptic concentrations and clinical response. Ann. Rev. Pharmacol. Toxicol. 24: 361–386

Roth, R. H. (1983) Neuroleptics: functional neurochemistry. In: Coyle, J. T., Enna, S. J. (eds) Neuroleptics: Neurochemical, Behavioral and Clinical Perspectives. Raven Press, New York, pp 119–156

Seeman, P. (1987) Dopamine receptors and the dopamine hypothesis of schizophrenia. Synapse 1: 133–152

Sheiner, L. B., Stanski, D. R., Vozeh, S., Miller, R. D., Ham, J. (1979) Simultaneous modelling of pharmacokinetics and pharmacodynamics: application to d-tubocurarine. Clin. Pharmacol. Ther. 25: 358–371

Shostak, M., Perel, J. M., Stiller, R. L., Wyman, W., Curran, S. (1987) Plasma haloperidol and clinical response: a role for reduced haloperidol in antipsychotic activity? J. Clin. Psychopharmacol. 7: 394–400

Smith, R. C., Baumgarter, R., Shvartsburd, A., Ravichandran, G. K., Vroulis, G., Mauldin, M. (1985) Comparative efficacy of red cell and plasma haloperidol as predictors of clinical response in schizophrenia. Psychopharmacology 85: 449–455

Statistical Consultants, Inc. (1986) 'PCNONLIN and NONLIN84: Software for the Statistical Analysis of Nonlinear Models. 'The American Statistician 40: 52