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Age-related alteration of haloperidol–serum protein binding

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Abstract

Serum haloperidol levels were determined in 59 patients, 50–88 years old, with psychosis, receiving long-term treatment with haloperidol. Although the total (bound and free form) haloperidol level in serum showed a linear correlation with daily dose, there was a larger variation in the relationship between free form and the daily dose compared with total because of inter-individual variation in the serum protein binding of haloperidol. The free fraction of haloperidol in serum increased with age. There was no difference in the ratio of total haloperidol level per daily dose between the adult and elderly groups, whereas the ratio of free haloperidol level per daily dose was significantly higher in the elderly than in the adult group. In the elderly, therefore, the therapeutic window of haloperidol should be assessed using free form level rather than total level, which is influenced by serum protein binding of the drug.

Introduction

Haloperidol, widely used as a neuroleptic to suppress psychiatric disorders, has strong binding characteristics. It has been reported that its plasma protein binding coefficient is very stable at all plasma levels both within and between subjects (Hughes et al 1976; Forsman & Öhman 1977a; Rowell & Hui 1981). Generally, serum protein binding of drugs that have high affinity for serum protein is affected by changes in protein level in serum, mainly albumin. Elderly patients often show decreased serum albumin levels. We reported previously that elderly patients had not only a decreased albumin level but also increased abnormal albumin (%), glycated albumin, which substantially decreased the normal, non-glycated albumin level, inducing elevation of the free fractions of drugs (Koyama et al 1999). Glycation is a reaction in which glucose reacts non-enzymatically with albumin in serum, inducing functional and conformational changes in the serum albumin, affecting drug–serum protein binding. Hence, in the elderly it is assumed that serum protein binding of drugs is decreased, inducing an increase in free drug level in the tissue or site of action. The free, diffusible fraction of a drug, rather than the total serum level, is critical for the pharmacological effect, as the level of this fraction more closely reflects the level at the site of action.

Several groups (Magliozzi et al 1981; Moulin et al 1982; Smith et al 1982; Mavroidis et al 1983; Kelly et al 1990; Doddi et al 1994; Palao et al 1994; Seeman 1995; Volavka et al 1995; Ulrich et al 1998) have investigated the correlations between serum or blood haloperidol levels and clinical response in schizophrenic patients. Smith et al (1982) and Garver et al (1984) suggested that the effective level of haloperidol in blood was in the range 2.5–5.4 and 1.0–2.3 ng mL^{-1}, respectively. On the other hand, with regard to the correlation between therapeutic effect and serum haloperidol level, the effective levels of haloperidol were shown to be 5–10 (Morselli et al 1980), 8–18 (Magliozzi et al 1981), 4.2–11.0 (Mavroidis et al 1983), 5.5–14.4 (Palao et al 1994) or 5–17 (Ulrich et al 1998) by several investigators. These studies, however, included children and adults with psychoses, but did not include elderly subjects. Although haloperidol is frequently

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administered to elderly patients with mood and behavioural problems, there have been no investigations of the effects of ageing on haloperidol–serum protein binding.

It is clinically significant to elucidate whether the effect of ageing on haloperidol–serum protein binding influences the drug treatment in elderly subjects. In addition, determination of the relationship between dose and level of haloperidol in serum would facilitate application of the desired dose to obtain the therapeutic level in the elderly. This would provide some information regarding risk of adverse effects and the safety of drug therapy.

We investigated the influence of ageing on haloperidol–serum protein binding in 59 patients with psychosis, receiving long-term treatment with haloperidol.

Materials and Methods

Subjects

A total of 59 patients with psychosis, chronically treated with haloperidol, were included in the study: 28 men and 31 women, mean age 70±8.4 years (range 50–88 years), body weight 51.7±10.9 kg (31–88 kg) and height 155.1±9.6 cm (135.0–178.0 cm). Twelve adults, aged 50–63 years, and 47 elderly patients, aged 65–88, were included. The subjects had been receiving a constant daily dose of haloperidol for at least one week, and steady-state levels of haloperidol had been achieved (Forsman & Öhman 1977b). Forty-six of the 59 subjects were treated with haloperidol alone, except for biperiden, an anti-parkinsonian drug. The other 13 had been treated with haloperidol, biperiden and other neuroleptics, such as chlorpromazine or methotrimeprazine (levomepromazine).

This investigation was approved by the Health Authority Ethics Committee of Kyoto Prefectural University of Medicine.

Determination of total and free levels of haloperidol in serum

Venous blood was collected into glass centrifuge tubes before administration of haloperidol in the morning. Samples were left to clot for 60 min at room temperature, and were then centrifuged at 3000 rev min^{-1} for 10 min to obtain the serum fraction. To measure the biochemical parameters, samples (2 mL) of serum were stored at −20°C before analysis. Total haloperidol levels in the serum from patients were assayed by enzyme immunoassay using Markit-M Haloperidol kits (Dainippon Pharmaceutical Co. Ltd, Osaka, Japan). The same serum samples were centrifuged at 1500 rev min^{-1} for 5 min using a micropartition system starter kit (MPS-1) (Amicon Div., W. R. Grace & Co. Danvers, MA) with Diaflo ultrafiltration membranes (YMT-membrane) (Amicon Div., W. R. Grace & Co., Danvers, MA). After ultrafiltration, 300-μL samples of the filtrates containing free haloperidol were evaporated. The residues were dissolved by adding 30 μL of 10 mM phosphate buffer, pH 7.4, and assayed with Markit-M Haloperidol. All experiments were performed in duplicate. The adsorption rate (%) for the YMT-membrane was evaluated at two haloperidol saline levels, 1 and 10 ng mL^{-1}, before and after ultrafiltration according to equation 1:

$$\text{Adsorption rate (\%)} = [(\text{Total haloperidol level} - \text{Free haloperidol level})/\text{Total haloperidol level}] \times 100 \quad (1)$$

The biochemical parameters measured were: total protein, albumin, glycated albumin (%), α_1-acid glycoprotein, total bilirubin and free fatty acids. The non-glycated albumin level was calculated from the albumin level and glycated albumin (%).

Assessment of various factors influencing haloperidol–serum protein binding

Both the total and the free haloperidol levels in serum from patients receiving haloperidol were measured, and the relationships between the haloperidol free fraction and the biochemical parameters were evaluated.

To evaluate the effects of glycation on haloperidol–serum protein binding, the 59 patients were divided into 2 groups according to their glycated albumin (%): normal group, 10–15%; high group, 15% and over (James et al 1979). The haloperidol free fractions in each group were compared.

To evaluate the influence of ageing on haloperidol–serum protein binding, the 59 patients were divided into 2 groups according to age: adult group, younger than 65 years; elderly group, 65 and over. The ratios of total or free haloperidol level to daily dose, and the free fraction of haloperidol were compared between each group.

Statistical analysis

The results are represented as the mean±s.d. The comparisons between normal and high groups divided according to glycated albumin (%), between adult and elderly groups and between male and female groups are carried out using the unpaired t-test. Correlations are analysed using Spearman's test.

Results

Characteristics of the subjects in this study are shown in Table 1. There were markedly large inter-individual differences with regard to these values in the population.

There were significant correlations with the haloperidol daily dose per kg body weight ($r = 0.949$, $P < 0.0001$ for the total haloperidol levels; $r = 0.749$, $P < 0.0001$ for the free levels) (Figure 1). Total haloperidol levels showed an excellent linear correlation with the daily dose per kg body weight, whereas the free levels showed large variation with the daily dose per kg body weight.

Table 1 Characteristics of the subjects in this study.

	Mean±s.d.	Range
n (male/female)	59 (28/31)	
Haloperidol		
Dose (mg)	4.7±6.4	0.75–30
Dose (mg kg^{-1})	0.09±0.13	0.01–0.71
Total level in serum (ng mL^{-1})	6.57±8.53	0.56–48
Total level in serum per dose (ng mL^{-1} mg^{-1})	1.64±0.71	0.50–4.54
Free level in serum (ng mL^{-1})	0.58±0.37	0.13–2.25
Free level in serum per dose (ng mL^{-1} mg^{-1})	0.22±0.11	0.03–0.52
Free fraction (%)	15.0±10.0	2.9–63.1
Biochemical parameters		
Albumin (g dL^{-1})	3.8±0.3	3.1–4.6
Glycated albumin (%)	18.2±6.4	12.1–45.3
Non-glycated albumin (g dL^{-1})	3.1±0.4	1.9–4.0
Total protein (g dL^{-1})	6.7±0.5	5.8–8.1
α_1-Acid glycoprotein (mg dL^{-1})	79.4±28.4	30–167
Total bilirubin (mg dL^{-1})	0.5±0.2	0.3–0.9
Free fatty acids (mEq L^{-1})	0.4±0.1	0.3–0.9

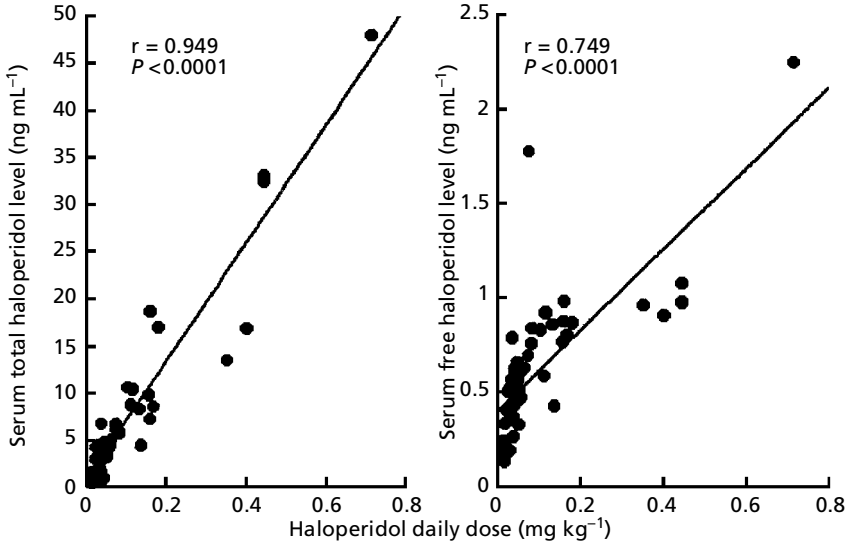

Figure 1 The relationship between serum level (left, total; right, free) and dose of haloperidol.

Table 2 Correlation coefficients between age or haloperidol free fraction, and drug-binding proteins or endogenous substances in serum.

	Age (years)	*P*	Haloperidol free fraction (%)	*P*
Glycated albumin (%)	0.062	0.644	0.005	0.969
Albumin (g dL^{-1})	−0.168	0.208	−0.017	0.899
Non-glycated albumin (g dL^{-1})	−0.138	0.303	−0.031	0.819
Total protein (g dL^{-1})	−0.248	0.061	0.057	0.672
α_1-Acid glycoprotein (mg dL^{-1})	−0.043	0.751	0.110	0.413
Total bilirubin (mg dL^{-1})	0.050	0.709	−0.120	0.370
Free fatty acids (mEq l^{-1})	−0.075	0.579	−0.068	0.615
Haloperidol free fraction (%)	0.338	< 0.05	–	–

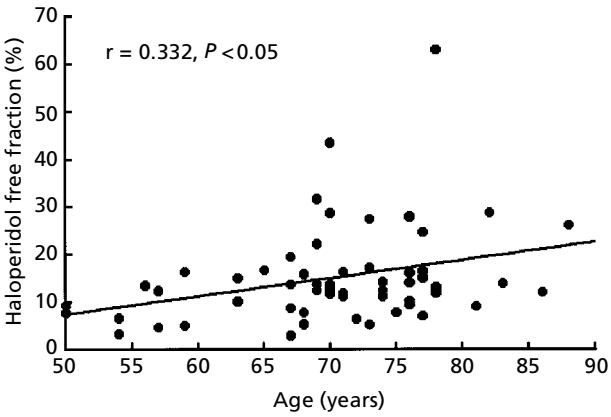

Figure 2 The relationship between age and free fraction of haloperidol in serum from 59 subjects.

Table 3 Effects of glycation on haloperidol binding to serum protein.

	Normal	High
Glycated albumin (%)	10–15	>15
n	14	45
Age (years)	67.8±10.3	70.9±7.7
Total protein (g dL^{-1})	6.7±0.5	6.7±0.5
Non-glycated albumin (g dL^{-1})	3.4±0.3	3.0±0.4*
α_1-Acid glycoprotein (mg dL^{-1})	71.6±19.1	81.8±30.5
Total bilirubin (mg dL^{-1})	0.4±0.2	0.5±0.2
Free fatty acids (mEq L^{-1})	0.4±0.1	0.4±0.1
Haloperidol free fraction (%)	11.8±6.0	16.0±10.8

Values are presented as the mean±s.d.; *$P < 0.0001$ vs normal group (unpaired t-test).

The correlation coefficients between haloperidol free fraction or age, and serum components that may influence drug–serum protein binding are shown in Table 2. These endogenous substances in serum showed no statistically significant correlations with the free fraction or age. To assess the relative effect of each variable on free fraction of haloperidol, step-wise multiple linear regression analysis was performed using the biochemical parameters such as total protein, α_1-acid glycoprotein, free fatty acids and total bilirubin. No variables were selected.

Figure 2 shows that the free fraction was significantly correlated with age (r = 0.338, $P < 0.05$), and that the haloperidol free fraction in elderly psychotic patients was increased compared with that in adult psychotic patients.

Table 3 summarizes comparison of the haloperidol free fraction in normal (10–15) and high groups (>15) divided according to glycated albumin (%). In the glycated albumin (%)-high group, although there were no differences in total protein, α_1-acid glycoprotein, total bilirubin or free fatty acid levels between the 2 groups, a statistically significant decrease in non-glycated albumin level ($P < 0.0001$) was observed, and the free fraction of haloperidol tended to be higher than that in the normal group.

Table 4 summarizes comparison of the ratio of haloperidol total and free levels in serum to daily dose, and free fraction in 12 adult and 47 elderly psychotic patients. There were no differences in total levels to daily dose between the 2 groups, whereas the free levels to daily dose and free fraction in the elderly group were significantly higher ($P < 0.05$) than those in the adult group. The ratio of total levels to dose in the elderly female group was significantly higher ($P < 0.01$) than in the elderly male group. The ratio of free level to dose in the elderly female group was significantly higher ($P < 0.0005$) than in the adult male group and ($P < 0.05$) the elderly male group. These ratios in both adult and elderly groups showed that the female group tended to be higher than the male group. The free fraction in the elderly female group was significantly higher ($P < 0.05$) than in the adult male group.

The adsorption rates (%) for the YMT-membrane were 11.5±3.5 and 8.6±2.0% at 1 and 10 ng mL^{-1} of haloperidol, respectively. The adsorption rates at the two levels were about 10%.

Discussion

Several previous studies have indicated a triphasic relationship between total haloperidol level in serum or blood and clinical efficacy, and suggested the existence of a therapeutic window of the drug (Mavroidis et al 1983; Palao et al 1994; Ulrich et al 1998). There have, however, been few investigations of the relationship between serum haloperidol level and clinical response in elderly patients, and the therapeutic window for treatment of elderly subjects is not clear. On the other hand, it is well known that the level of serum albumin, which binds to most drugs, is decreased in the elderly. Our previous study (Koyama et al 1999) showed that a decrease in normal (non-glycated) albumin level due to progressive glycation of albumin as a result of ageing resulted in a markedly elevated free fraction of carbamazepine in serum, which may affect the clinical effects of drugs. Pang et al (1978) and Cheng et al (1987) investigated the pharmacokinetics of haloperidol in detail. They reported that the changes in the free fraction of haloperidol in blood, free intrinsic hepatic clearance and the hepatic blood flow can affect the total blood clearance and the extent of oral bioavailability of haloperidol. Hepatic clearance and hepatic blood flow are influenced by ageing, whereas it is not clear whether ageing influences drug–serum protein binding. Consequently, we investigated whether ageing influences haloperidol–serum protein binding.

Rowell et al (1981) and Moulin et al (1982) reported that total haloperidol levels in serum were correlated well with daily doses administered. Our result (Figure 1) was in agreement with the observation reported by Rowell et al. It is possible to calculate the desired total level of haloperidol in serum at steady state from the patient's body weight and dose. On the other hand, the free levels of haloperidol were

Table 4 Age-related increase in serum free haloperidol levels per daily dose and free fraction of haloperidol.

Group	Sex	n	Total level/Dose (ng mL^{-1} mg^{-1})	Free level/Dose (ng mL^{-1} mg^{-1})	Haloperidol free fraction (%)
Adult	All	12	1.631±0.401	0.159±0.095	9.5±4.2
	Male	8	1.571±0.299	0.127±0.065	8.2±4.2
	Female	4	1.751±0.595	0.225±0.119	12.2±3.1
Elderly	All	47	1.621±0.800	0.233±0.110[a]	16.4±10.5[a]
	Male	20	1.258±0.561	0.192±0.121	17.0±13.3
	Female	27	1.890±0.852[b]	0.263±0.065[c,d]	15.9±8.1[e]

[a]The elderly group is significantly different ($P < 0.05$, unpaired t-test) to the adult group. [b]The elderly female group is significantly different ($P < 0.01$, unpaired t-test) to the elderly male group. [c]The elderly female group is significantly different ($P < 0.0005$, unpaired t-test) to the adult male group. [d]The elderly female group is significantly different ($P < 0.05$, unpaired t-test) to the elderly male group. [e]The elderly female group is significantly different ($P < 0.05$, unpaired t-test) to the adult male group. Values are presented as the mean±s.d.

increased with increases in daily dose, whereas a large variation of free level was observed compared with the total level. Despite the linear relationship between total levels of haloperidol and daily dose, a large variation of free haloperidol level is considered to be induced by variable serum protein binding of haloperidol. Previous studies (Hughes et al 1976; Forsman & Öhman 1977a; Rowell & Hui 1981) demonstrated minor inter-individual variations of serum protein binding of haloperidol (about 90%), whereas a large inter-individual variation was observed in this study (36.9–97.1%). This result suggested that in elderly patients it is difficult to predict therapeutic effects by monitoring of total levels of haloperidol in serum. Consequently, investigation of serum protein binding of haloperidol in elderly patients was considered to be clinically important.

The large inter-individual variation of haloperidol–protein binding in serum observed in this study is not caused by concomitant drugs such as methotrimeprazine (levomepromazine) and biperiden because there is no interference with haloperidol–protein binding (Forsman & Öhman 1977a), although it may depend on variable albumin level. No correlation, however, was observed between the free fraction of haloperidol and albumin level. Although the relationships between the free fraction and several serum constituents were evaluated, no correlation was observed with free fraction. We failed to find any factors influencing the free fraction of haloperidol. This result suggested that the free fraction of haloperidol is influenced not only by quantitative, but also by qualitative differences in serum constituents. Forsman & Öhman (1977a) also described qualitative rather than quantitative differences in serum constituents with regard to the individual variation of haloperidol free fraction. Our previous studies (Koyama et al 1997a, b) showed that glycation of albumin decreased the binding capacity of albumin and its affinity for drugs, and we observed an age-related decrease in non-glycated albumin level due to progressive glycation of albumin in elderly patients, and a substantially increased free fraction of carbamazepine in elderly patients compared with children and adults (Koyama et al 1999). Although the result of this study showed a significant increase in the free fraction of haloperidol in the elderly group, the free fraction of haloperidol and age were not correlated with the non-glycated albumin levels. It was considered that the population had a narrow range of non-glycated albumin level because most of the subjects were elderly.

The group with a high proportion of glycated albumin had a significantly decreased non-glycated albumin level and tended to have an increased free fraction of haloperidol, suggesting that non-glycated albumin may be an important factor influencing haloperidol–serum protein binding. The free fraction of haloperidol was not correlated with any serum constituents, whereas we observed an age-related increase in the free fraction of haloperidol, suggesting that glycation may influence not only albumin but also other binding proteins in serum. Unfortunately, in this study, we measured glycated albumin (%) only, and so the possible effects of glycation on other serum proteins were not clarified.

There have been many previous studies on the therapeutic window of haloperidol in schizophrenic patients (Forsman & Öhman 1977b; Morselli et al 1980; Magliozzi et al 1981; Smith et al 1982; Mavroidis et al 1983; Garver et al 1984; Palao et al 1994; Volavka et al 1995; Ulrich et al 1998). For the therapeutic window of haloperidol in patients with schizophrenia, previous studies showed that the effective levels of total haloperidol in serum were approximately 4–15 ng mL^{-1}. In contrast, Moulin et al (1982) and Doddi et al (1994) reported that there was no relationship between the total level of haloperidol in serum and clinical effectiveness. Moulin et al (1982) observed a good relationship between the total decrease in scores on the Brief Psychiatric Rating Scale during the first 3 weeks of treatment and the half-life calculated during an 8-h period after the first injection of 5 mg of haloperidol, and concluded that this half-life mainly expressed the rate of transfer of haloperidol from serum to tissues and

particularly to the therapeutic effector sites: shorter half-life was associated with better disease improvement. We think that their patients with shorter half-life had an increased free fraction of haloperidol, so that the free form was transferred rapidly to the site of action. Doddi et al (1994) failed to find any relationship between total or reduced haloperidol levels in blood and clinical response. Their subjects may have included several non-responders. Assessment of the therapeutic window is skewed by the inclusion of non-responders with a resultant high dose on chronic treatment of haloperidol. On the other hand, Forsman & Öhman (1977a) reported patients with high serum protein binding of haloperidol (above 99%). Their report suggests that non-responders may be patients who have a high ratio of serum protein binding with the drug. The high ratio of the drug–serum protein binding results in decreased free levels, and so the free levels of the drug may not achieve the therapeutic levels despite high-dose administration. Unfortunately, Doddi et al (1994) and Moulin et al (1982) did not determine the free levels of haloperidol in serum, so that the relationship between the free level of haloperidol and clinical response is not clarified.

Seeman (1995) investigated the relationship between the clinical response and the blocking potencies of various antipsychotic drugs at D_2 receptors, and reported that the therapeutic response to haloperidol was obtained when the drug occupied approximately 75% of dopamine D_2 receptors. Moreover, they reported that the haloperidol therapeutic level required for 75% blockade of D_2 receptors was approximately 2–3 nM in the brain, corresponding to 1–3 nM (0.376–1.128 ng mL^{-1}) of free form in serum. In this study, 1 patient showed no response to haloperidol treatment despite having a high level of total haloperidol (32.5 ng mL^{-1}). This patient was thought to be a non-responder to haloperidol treatment, but the free haloperidol level in this patient was 1.075 ng mL^{-1} and lower than the upper limit of 1.128 ng mL^{-1}, and so this patient may have been administered an insufficient daily dose of haloperidol.

As shown in Table 4, the elderly group showed a significant increase in the free level of haloperidol per daily dose compared with the adult group, although there was no difference in the total level per daily dose between the two groups, suggesting that the elderly require lower doses compared with adults. In fact, daily doses per body weight of adult and elderly groups were 0.172 ± 0.207 and 0.071 ± 0.095 mg kg^{-1}, respectively. In elderly patients, especially female, the risk of development of adverse effects caused by administration of haloperidol was suggested to be higher than that in adult patients.

The total level of haloperidol in serum can most easily be calculated from daily dose. However, it was confirmed that assessment of total haloperidol level-clinical response was not precise because of the large inter-individual variation of haloperidol–protein binding in the elderly patients. The ratio of the free level to dose of haloperidol in the elderly patients was larger than that of adult patients, implying that in the elderly a slight increase in dose of haloperidol may cause a marked increase in the free level in serum. In conclusion, in elderly patients, free haloperidol monitoring should be performed to determine the appropriate haloperidol treatment regimen and to avoid adverse effects of the drug.

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