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ORIGINAL PAPER

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D_2-dopamine-receptor occupancy during treatment with haloperidol decanoate

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Abstract We investigated in an open, explanatory study a total of 24 patients meeting DSM-III-R criteria for schizophrenia. Eighteen patients were treated for at least 4 weeks with a fixed dose of orally administered haloperidol for at least 4 weeks (mean daily dosage ranging from 0.07 to 0.35 mg/kg b.w.), and 6 patients received haloperidol decanoate with a fixed dose for at least 4 months (dosage range 50–150 mg/4 weeks; calculated mean daily dosage ranging from 0.02 to 0.09 mg/kg b.w.). One week after injection of haloperidol decanoate, the single photon emission computed tomography examination was performed. Our data suggest that D_2-dopamine-receptor occupancy of 50 mg/4 weeks haloperidol decanoate 1 week after injection corresponds to an oral dose of 4.5 mg/day haloperidol.

Key words Haloperidol decanoate · D_2 dopamine receptor · Dose–response relation · Schizophrenia · SPECT

Introduction

In vivo dopamine-D_2-receptor occupancy under treatment with classical and atypical neuroleptics (Nls) have been performed by means of positron emission tomography (PET) suggesting that a D_2-dopamine-receptor occupancy of 70–89% is expected in patients treated with conventional dosages of classical neuroleptics (Farde et al. 1992). Patients with acute extrapyramidal syndromes (EPS) had a higher D_2 occupancy than those without side effects.

The disadvantages of single photon emission computed tomography (SPECT) in terms of spatial resolution, scatter and attenuation correction lead to a less accurate quantification of tracer uptake as compared with the PET technique. Despite these limitations, SPECT using ^{123}IBZM has been reported to be a specific and safe semiquantitative technique to visualize dopamine-D_2-receptor densities in human CNS. (Brücke et al. 1991; Kung et al. 1990).

In a recent paper (Scherer et al. 1994) we demonstrated by means of ^{123}IBZM-SPECT an exponential dose–response relation between striatal D_2-receptor occupancy and total daily dosage of haloperidol orally in schizophrenic patients, suggesting that it is possible to arrive at a qualitative and quantitative accurate dose–response relation between dopamine-D_2-receptor occupancy and dosage by means of the SPECT technique. This has also been shown by other authors (Brücke et al. 1992). Furthermore, we were able to demonstrate a neuroleptic EPS threshold at approximately striatal frontal cortex ratio (SFCR) = 1.2; above that, extrapyramidal symptoms occurred, which correspond to a mean dose of haloperidol of 0.12 mg in schizophrenic patients. (Scherer et al. 1994). However, the existence of such an EPS threshold is controversial and has not been shown in patients who are poorly responsive to typical antipsychotic drugs.

Given the amount of dopamine-D_2-receptor occupancy and response to treatment, the data published thus far suggest, that dopamine-D_2-receptor occupancy of approximately 70% is sufficient in patients who respond to acute treatment with classical Nls. Because a considerable number of patients are treated with depot medication, it is of special interest to investigate the amount of dopamine-D_2-receptor occupancy in patients treated with depot formulations compared with patients treated orally with antipsychotic drugs.

Nyberg and colleagues (1995) showed by means of the PET technique that 1 week after injection the mean D_2-re-

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ceptor occupancy was comparable to that of patients responding to acute treatment with classic neuroleptics during a 4-week interval of haloperidol decanoate dosage.

In our study, using the IBZM-SPECT technique, we tried to replicate the findings of Nyberg et al. (1995) on the in vivo occupancy of D_2-dopamine receptors by antipsychotic drugs, additionally evaluating if there is an amount of dopamine-D_2-receptor occupancy for the development of extrapyramidal side effects as in patients treated with haloperidol decanoate or haloperidol orally, as we have shown in a previous study (Scherer et al. 1994).

Materials and methods

Subjects

We investigated in an open, explanatory study a total of 24 patients (19 men and 5 women) with a mean age of 41.5 years (range 20–61 years) meeting DSM-III-R criteria for schizophrenia and 10 healthy controls (5 men and 5 women) matched for age and gender with a mean age of 41.1 years (range 20–61 years). Eighteen patients (group 1) were treated for at least 4 weeks with orally administered haloperidol with a fixed dose for at least 4 weeks (mean daily dosage ranging from 0.07 to 0.35 mg/kg b.w.), and 6 patients (group 2) received haloperidol decanoate treatment with a fixed dose for at least 4 months (dosage range 50–150 mg/4 weeks; calculated mean daily dosage ranging from 0.02 to 0.09 mg/kg b.w.).

One patient treated with haloperidol decanoate and 4 patients treated with haloperidol orally additionally received amitriptyline (dosage range 75–150 mg/day). Two patients treated with haloperidol decanoate and 10 patients treated with haloperidol orally additionally received biperiden hydrochloride (2 mg/day). Besides these drugs, no concomitant medication was administered.

Extrapyramidal side effects were recorded according to the rating scale for extrapyramidal side effects (Simpson and Angus 1970) also used by Farde et al. (1992). In the patients with extrapyramidal side effects, at least one item indicating rigidity on the rating scale for extrapyramidal side effects was rated 2 or more.

One week after injection of haloperidol decanoate, the SPECT examination was performed. Because 1 ml haloperidol decanoate administered every 28 days contains 50 mg haloperidol, the corresponding mean daily dosage (d_c) was calculated with 50 mg/28 days. In patients treated with haloperidol orally, IBZM-SPECT was performed 5 h after the morning dose was given.

Informed consent for ^{123}I-IBZM-SPECT was obtained from every patient. Ethical permission for the study was obtained from the local hospital ethics committee.

Procedure

^{123}I-IBMZ-SPECT was performed 2 h after IV injection of 185 MBq IBZM (3-iodo-6-methoxybenzamide, Cygne BV, Eindhoven, The Netherlands). For data acquisition a rotating double-head gamma camera was used. Data were collected for 60 projections (360° rotation) in a 64 × 64 matrix with an acquisition time of 50 s per projection. Transverse images were reconstructed by filtered back projection with a subsequent computation of coronal slices. Attenuation correction was performed as previously described (Tatsch et al. 1991). Regions of interest (ROI's) were placed over the head of the caudate and over the putamen for each hemisphere. For each time frame, averaged radioactivity of each ROI was determined, and decay was corrected to the start of tracer injection. Specific tracer uptake was calculated for each subject using the ratio: striatal ROI activity/frontal ROI activity which is usually calculated for SPECT studies (Rinne et al. 1990). The investigator who calculated the striatal/frontal cortex ratio (SFCR) was unaware of the patient's diagnoses or drug regimen.

Statistical analysis

To evaluate the relation between daily dose of neuroleptics and SFCR, a nonlinear exponential regression analysis (least-squares method) was carried out (Armitage 1973). To compare two means a Mann-Whitney rank sum test was applied. All reported p-values are based on two-tailed tests.

Results

Demographic and binding data for patients and controls are shown in Table 1. Schizophrenic patients on haloperidol orally and haloperidol decanoate were similar in demographic details, disease duration and lifetime exposure to neuroleptics.

After IV injection of ^{123}I-iodobenzamide patients treated with haloperidol decanoate or haloperidol orally, there was a markedly reduced accumulation of radioactivity in the basal ganglia as compared with the healthy untreated controls (mean SFCR = 1.53, SD = 0.06, range 1.43–1.64). The SFCR of tracer binding in patients treated with haloperidol orally (mean SFCR = 1.19, SD = 0.06, range 1.05–1.29) was comparable to this in patients treated with haloperidol decanoate injections (Mean SFCR = 1.19, SD = 0.08, range 1.09–1.31).

The SFCR was plotted against the daily dosage of haloperidol orally or haloperidol decanoate and the exponential dose–response function could be well fitted to the data (Fig. 1). Our data show that the striatal D_2-dopamine-receptor occupancy during treatment with orally administered haloperidol follows approximately the function

$$(SFCR_H - 1) = 0.5 \times \exp(-7 \times dw_H),$$

where H denotes haloperidol orally, dw_H = d/w the daily dosage (mg) per kilogram of body weight, d the daily dosage (mg) and w the body weight (kg); and during treatment with haloperidol decanoate

$$(SFCR_{HD} - 1) = 0.5 \times \exp(18 \times dcw_{HD}),$$

Table 1 Characteristics of patients treated with haloperidol and haloperidol decanoate

	Haloperidol (n = 18)[a]	Haloperidol decanoate (n = 6)[a]	P[b]
Age (years)	43.0 (13.0)	36.8 (8.5)	0.30
Duration of disease (months)	89.0 (72.0)	132.0 (46.8)	0.19
Lifetime exposure to neuroleptics (months)	29.83 (37.6)	49.7 (37.3)	0.28

[a] Mean (SD)
[b] Group 1 vs group 2

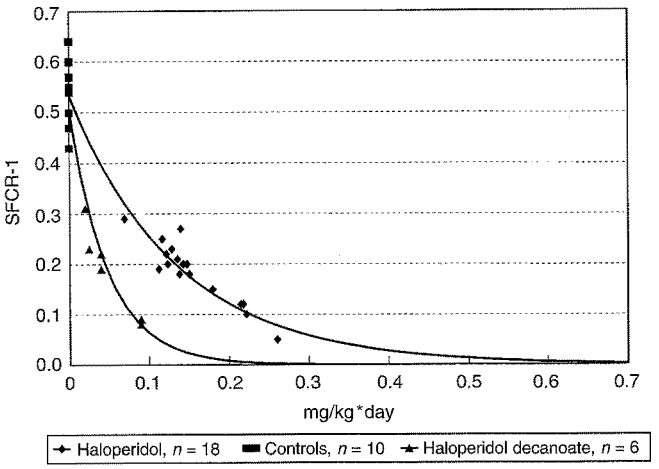

Fig. 1 Dose-response relationship between striatal D_2 receptor blockade and daily dose of haloperidol and haloperidol decanoate

where HD denotes haloperidol decanoate, $dcw_{HD} = d_c/w$ the corresponding mean daily dosage (mg) per kilogram of body weight, d_c the corresponding mean daily dosage and w the body weight (kg).

This exponential dose–response function allows the calculation of the dose equivalent of haloperidol decanoate and haloperiodol orally with regard to the amount of D_2-dopamine-receptor occupancy. If we assume that $SFCR_H = SFCR_{HD}$, we get, $-dw_H \times 7 = -18 \times cdw_{HD}$ and $dw_H = (18 \times cdw_{HD})/7$.

Our data suggest that D_2-dopamine-receptor occupancy of dw_{HD} = 50 mg/4 weeks of haloperidol decanoate 1 week after injection corresponds approximately to an oral dose of dw_H = 4.5 mg/day haloperidol.

Discussion

A D_2-dopamine-receptor occupancy 50 mg/4 weeks of haloperidol decanoate 1 week after injection corresponds to an oral dose of 4.5 mg/day haloperidol. Our data suggest a calculation factor of 11 from daily oral dose to monthly depot dose. This finding is in concordance with the results of Beresford and Ward (1987). The monthly depot doses used in this study correspond to a calculated oral dose range of 4.5–13.5 mg.

Extrapyramidal symptoms in patients treated with haloperidol decanoate were present in 2 patients (SFCR: 1.08; 1.09) and absent in 4 patients (SFCR: 1.19, 1.22, 1.23, 1.31). Concerning the presence of a neuroleptic EPS threshold, we refer to the sample of the 18 patients treated with haloperidol orally. These data have already been reported elsewhere. In patients treated with haloperidol decanoate we achieved a neuroleptic EPS threshold of SFCR = 1.2. This finding corresponds to the neuroleptic EPS threshold found in the other sample (Scherer et al. 1994) in patients treated with haloperidol orally.

The SFCR in patients treated with haloperidol orally was comparable to that in patients treated with haloperidol decanoate injections. Our data suggest an exponential dose-response relationship between striatal D_2-receptor blockade and total daily dosage of both, haloperidol and haloperidol decanoate. Thus, for haloperidol decanoate we could confirm the results of Nyberg et al. (1995).

To our knowledge, this is the first study with the IBZM-SPECT technique, a simple and clinically easily applicable method demonstrating that it is possible to arrive at a qualitative and quantitative accurate dose–response relation between D_2-receptor occupancy and dosage of haloperidol decanoate in vivo.

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