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HALOPERIDOL DECANOATE IN CHRONIC SCHIZOPHRENIA: A STUDY OF 12 MONTHS WITH PLASMA LEVELS

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Abstract

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1. Clinical activity, extrapyramidal side-effects were evaluated in 22 schizophrenic out patients diagnosed according to DSM III and treated with haloperidol decanoate (50-300 mg i.m. monthly dose) for 12 months.
2. BPRS total scores did not show significant fluctuations showing a clinical stability of the patient population.
3. Patients with a duration of illness > 10 yrs (Group 2) showed significant ($p < 0.01$) higher EPSE total scores compared to those with a duration of illness <10 yrs (Group 1).
4. A positive correlation was found between the administered dose and haloperidol plasma levels.
5. Patients from Group 2 reached the steady-state more slowly and showed a lower total L/D ratio compared to those from Group 1.
6. The pharmacokinetic approach seems desirable in order to adjust the dose and avoid schizophrenic relapses.

Keywords: haloperidol decanoate, pharmacokinetics, schizophrenia.

Abbreviations: brief psychiatric rating scale (BPRS), catatonic (C), disorganized (D), diagnosis (DG), extrapyramidal side-effects rating scale (EPSE), haloperidol (HL), haloperidol decanoate (HL-D), level/dose ratio (L/D), not performed (NP), paranoid (P), plasma levels (PL), patient (PT), standard deviation (SD), undifferentiated (U), years (yrs).

Introduction

Haloperidol (HL), a widely used antipsychotic drug, is now available in its depot preparation, haloperidol decanoate (HL-D).

Several clinical studies have demonstrated the efficacy of this ester in reducing

schizophrenic relapses, but fewer studies have considered pharmacokinetic patterns as well (Deberdt et al 1980, De Buck et al 1981, De Cuyper et al 1986, Reyntjens et al 1982, Viukari et al 1982). Concerning pharmacokinetics, the intramuscular injection of HL-D gives subtained high plasma concentrations with a half-life of about 3 weeks (Reyntjens et al 1982). The release from the injection site seems to be a rate limiting step for the duration of action (about 4 weeks) of the injection. The steady-state seems to be achieved within 2-4 months (see Beresford and Ward for review, 1987). Moreover, follow-up studies lasting more than 6 months including evaluations of the clinical efficacy, side-effects and plasma levels monitoring, are scanty for this drug.

The aim of this study was to evaluate clinical activity, extrapyramidal side-effects of HL-D and HL plasma levels in relation to the duration of illness in chronic schizophrenic patients treated with HL-D during a follow-up period of 12 months.

Methods

The study has been performed in a "naturalistic" setting since the HL-D monthly dose and drug combinations were left up to the physicians who had patients in charge. Moreover they were not aware of the aim of the study and of HL plasma levels determination.

i) Population

22 schizophrenic out-patients of both sexes (14 male and 8 female), with age ranging from 16 to 62 years (yrs)(mean age 40.27 ± 12.92 SD), diagnosed according to DSM III (8 disorganized, 9 undifferentiated, 3 paranoid, 2 catatonic), with mean duration of illness of 13.45 yrs ± 8.90 SD, were followed up for 12 months (Table 1). The patients were divided into two groups according to the duration of illness: in Group 1 the duration of illness ranged from 1 to 10 yrs (mean 5.30 yrs ± 3.71 SD) and in Group 2, from 12 to 31 yrs (mean 20.25 ± 5.39 SD).

Patients suffering from organic disorders, drug addiction or alcoholism or tardive dyskinesia were not included in the study.

ii) Drug Administration

Each patient received a monthly HL-D dose ranging from 50 to 300 mg i.m. (158.6 mg ± 5.73 SD; 2.25 mg/kg ± 0.83 SD) for 12 months. Patients from Group 1 were given a mean dosage of 2.04 mg/kg ± 0.62 SD and patients from Group 2 a mean one of 2.42 mg/kg ± 0.97

Table 1

The Characteristics of population Under Survey, Drug Doses (mg/kg), HL Plasma Levels (PL)(ng/ml),Level/Dose Ratio (L/D), the BPRS and EPSE Scores Recorded in the Course of the Study

TIME (Months)

GROUP 1

PT	AGE (yrs)	SEX	DI (yrs)	DG	1 DOSE (mg/kg)	1 PL (ng/ml)	1 BPRS	1 EPSE	1 L/D	2 DOSE (mg/kg)	2 PL (ng/kg)	2 L/D	3 DOSE (mg/kg)	3 PL (ng/ml)	3 BPRS	3 EPSE	3 L/D	6 DOSE (mg/kg)	6 PL (ng/ml)	6 BPRS	6 EPSE	6 L/D	12 DOSE (mg/kg)	12 PL (ng/ml)	12 BPRS	12 EPSE	12 L/D
01	21	M	03	U	1.69	3.3	19	1.1	1.95	1.42	3.9	2.74	1.42	4.2	18	1.2	2.95	1.28	5.5	18	1.3	3.98	1.28	5.4	18	1.2	3.91
02	19	M	01	U	3.12	4.1	35	1.0	1.31	3.12	5.9	1.89	3.12	6.9	30	1.0	2.21	2.50	5.9	25	0.9	2.36	2.50	NP	NP	NP	NP
03	35	M	10	U	2.23	4.2	25	1.1	1.88	1.49	4.0	2.68	1.11	3.8	19	1.1	3.42	2.23	6.6	19	1.1	2.95	2.23	5.9	19	1.0	2.64
04	31	M	06	D	2.45	2.7	24	1.6	1.10	3.68	4.7	1.27	2.45	4.7	23	1.0	1.91	2.45	4.9	NP	NP	2.00	2.45	5.0	NP	NP	2.04
05	16	M	01	C	0.72	1.5	31	1.6	2.08	1.20	3.6	3.00	1.20	3.9	24	1.4	3.25	1.20	4.0	18	1.0	3.30	0.80	2.1	18	0.9	3.87
06	34	F	09	P	2.77	4.0	30	1.7	1.44	2.77	4.9	1.76	2.77	5.4	23	1.3	1.94	0.92	4.1	19	1.0	4.45	0.92	3.6	18	0.9	3.91
07	28	M	10	D	2.80	3.3	27	1.4	1.17	1.35	3.6	2.66	2.02	3.9	26	1.4	1.93	2.02	4.9	NP	NP	2.42	2.02	4.8	NP	NP	2.37
08	27	F	03	U	0.96	1.6	18	1.1	1.86	1.29	3.4	2.63	2.58	5.7	18	1.1	2.20	1.72	4.3	18	1.1	2.50	1.72	4.3	18	0.8	2.50
09	45	M	02	D	1.19	3.2	28	1.1	2.68	1.19	4.3	3.61	2.38	5.5	22	1.1	2.31	2.38	NP	NP	NP	NP	2.38	NP	NP	NP	NP
10	36	M	08	P	2.98	4.9	35	1.1	1.64	2.98	4.2	1.44	2.61	5.2	22	1.6	1.99	2.98	6.0	19	1.5	2.01	2.98	5.3	18	1.4	1.77
Mean	29.2		5.3		2.08	3.2	27.2	1.28	1.71	2.04	4.2	2.36	2.16	4.9	22.5	1.2	2.41	1.97	5.1	19.4	1.1	2.88	1.93	4.6	18.1	1.0	2.87
SD(±)	8.86		3.7		0.90	1.1	5.8	0.26	0.48	0.96	0.7	0.74	0.69	1.0	3.7	0.19	0.57	0.65	0.9	2.5	0.2	0.86	0.71	0.9	0.4	0.2	0.88

GROUP 2

PT	AGE (yrs)	SEX	DI (yrs)	DG	1 DOSE (mg/kg)	1 PL (ng/ml)	1 BPRS	1 EPSE	1 L/D	2 DOSE (mg/kg)	2 PL (ng/ml)	2 L/D	3 DOSE (mg/kg)	3 PL (ng/ml)	3 BPRS	3 EPSE	3 L/D	6 DOSE (mg/kg)	6 PL (ng/ml)	6 BPRS	6 EPSE	6 L/D	12 DOSE (mg/kg)	12 PL (ng/ml)	12 BPRS	12 EPSE	12 L/D
11	40	F	12	U	2.63	2.6	43	1.9	0.98	2.63	2.9	1.10	2.63	3.8	39	1.7	1.44	2.63	4.7	40	1.8	1.78	2.63	4.9	35	1.5	1.86
12	45	F	17	D	2.63	2.5	48	2.4	0.95	3.50	4.0	1.14	3.50	4.5	49	2.0	1.28	3.50	5.8	31	2.1	1.65	3.50	7.0	46	1.8	2.00
13	50	M	20	U	3.40	3.1	61	1.7	0.91	3.40	4.3	1.26	3.40	5.2	56	1.5	1.52	3.40	5.5	57	1.9	1.61	3.40	5.6	55	1.5	1.64
14	54	F	22	U	1.26	2.1	26	1.6	1.66	1.89	3.1	1.64	1.89	3.9	28	1.6	2.06	1.26	3.7	27	1.4	2.93	1.26	3.8	31	1.7	3.01
15	62	M	31	D	0.80	1.9	24	1.6	2.37	0.80	2.2	2.75	0.80	2.5	25	1.4	3.12	0.80	2.4	28	1.7	3.00	0.80	2.3	30	1.1	2.87
16	49	M	23	D	3.94	2.9	41	1.7	0.73	3.94	4.2	1.06	3.94	4.7	39	1.9	1.19	3.94	5.8	46	2.0	1.47	3.94	7.2	44	1.3	1.82
17	42	F	20	D	1.34	2.0	44	2.0	1.49	2.01	3.2	1.59	2.01	4.1	49	1.5	2.03	2.01	4.9	42	2.3	2.43	2.01	4.7	51	1.7	2.33
18	45	M	17	C	1.85	3.4	50	1.8	1.83	2.77	4.1	1.48	2.77	4.7	60	1.9	1.69	2.77	5.1	58	1.8	1.84	2.77	4.6	50	1.4	1.66
19	55	M	24	U	2.43	2.4	44	2.2	0.98	2.43	3.7	1.52	2.43	4.3	30	1.5	1.76	2.43	5.7	46	2.1	2.34	2.43	4.6	52	1.4	1.89
20	41	F	20	D	1.22	2.7	23	1.5	2.21	2.45	5.6	2.28	2.45	5.6	22	1.9	2.28	2.45	7.4	21	1.2	3.02	2.45	5.9	19	1.1	2.40
21	53	M	25	U	3.27	4.2	31	1.6	1.28	3.27	5.0	1.52	3.27	7.7	31	1.7	2.35	3.27	8.2	22	1.2	2.50	3.27	7.4	20	1.2	2.26
22	58	F	12	P	1.25	1.8	18	1.8	1.44	1.25	2.3	1.84	1.25	2.9	18	1.4	2.32	0.93	2.3	18	1.2	2.47	0.93	2.1	18	1.1	2.25
Mean	49.5		20.2		2.16	2.6	37.7	1.8	1.40	2.52	3.7	1.59	2.52	4.4	37.1	1.6	1.92	2.44	5.1	36.3	1.7	2.25	2.44	5.0	37.5	1.4	2.16
SD(±)	7.07		5.3		1.02	0.6	13.1	0.2	0.53	0.93	1.0	0.49	0.93	1.3	13.7	0.2	0.55	1.03	1.7	13.7	0.3	0.56	1.03	1.7	13.8	0.2	0.44

PT = Patients

DG = Diagnosis (D = Disorganized; C = Catatonic; P = Paranoid; U = Undifferentiated)

DI = Duration of illness

NP = Not Performed

SD. No other drugs were associated except for anticholinergics in case of dire necessity.

All patients had been receiving conventional neuroleptics (mostly HL) for at least 3 months before starting treatment with HL-D. In Group 2, all patients had previously received neuroleptic associations.

iii) Clinical Assessment

Psychopathological features and extrapyramidal side-effects were evaluated at months 1, 3, 6, 12 using the Brief Psychiatric Rating Scale (BPRS)(Overall & Gorham 1962) and Extrapyramidal Side Effects Rating Scale (EPSE)(Simpson & Angus 1970) respectively.

iv) HL Determination

HL plasma levels were monitored using a gaschromatographic method (Abernethy et al 1984) at months 1, 2, 3, 6, 12. From patient 21 and 6 HL plasma levels were obtained also during the first month of treatment, at times 1, 2, 3, 6, 12, 24, 28 days after the injection.

v) Statistical Analysis

The analysis of variance was performed using the ANOVA procedure of SAS package (1979) completed by the SNK test (Student-Newman-Keuls) for multiple comparisons. Regression analysis was performed on data from months 1, 6 and 12.

Results

i) Clinical Data

In all patients, BPRS total scores did not show significant fluctuations over the lenght of the study (Fig 1).

Drop-outs were 4 (patients 4, 7, 9 after 6 months and patient 2 after 8 months) all due to lack of compliance in coming to the scheduled check-up visits.

Basal BPRS values did not differ significantly in the two Groups. Concerning positive (grandiosity, suspiciousness, hallucinations, unusual thought content) and negative (emotional withdrawal, depressive mood, motor retardation, blunted affect) symptoms, the former were more present in patients from Group 1 and the latter in patients from Group 2 (negative/positive total score ratio: 0.96 vs 1.23). During the study BPRS total scores from Group 1 showed a significant amelioration ($p \leq 0.01$) from the third month,

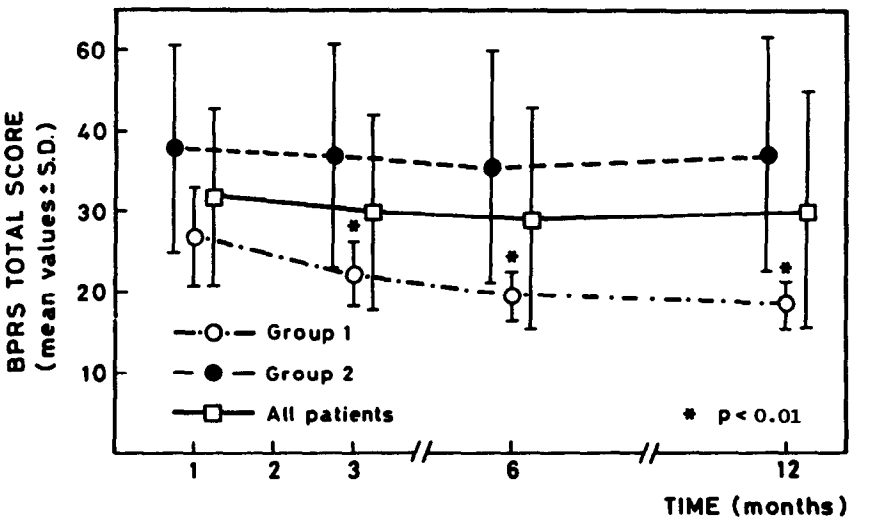

Fig 1. Patterns of total BPRS scores (mean values) recorded during the course of the study for Group 1, Group 2 and all patients, indicating no significant fluctuations in BPRS for all patients and Group 2. Only for Group 1 there was a significant decrease (*p <0.01 vs month 1) in BPRS score.

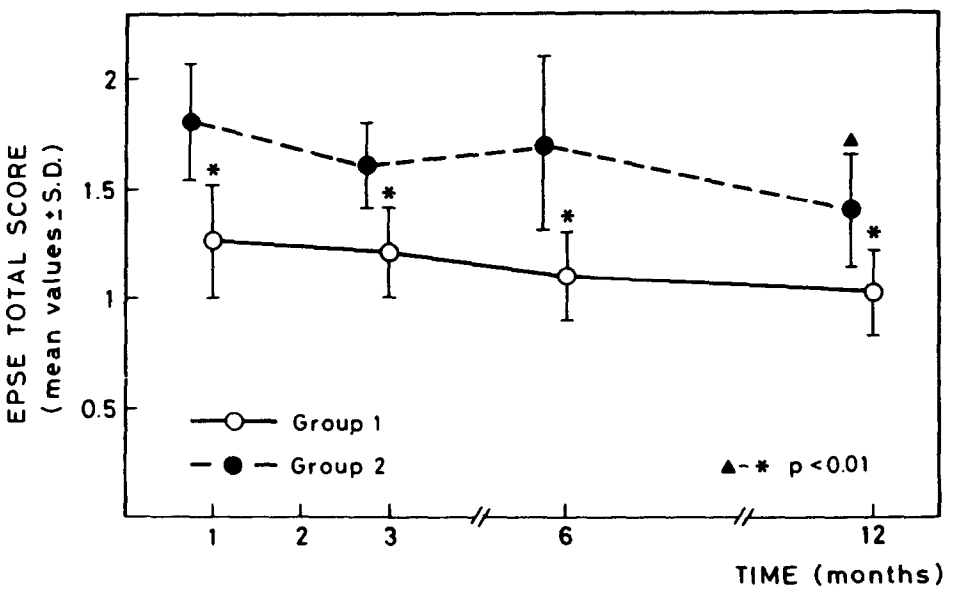

Fig 2. Patterns of total EPSE scores (mean values) recorded during the course of the study for Group 1 and Group 2, indicating a significant difference (*p <0.01) between them. Only for Group 2 there was a significant decrease (▲p <0.01 vs month 1) in the EPSE score at the end of the study.

lacking in Group 2 which also showed a higher inter-individual variability in BPRS scores compared to Group 1 (Fig 1).

EPSE total scores did not show significant changes during the monitored period.Patients from Group 2 showed significant higher EPSE total scores compared to those of Group 1 ($p < 0.01$)(Table 2, Fig 2) and a significant EPSE amelioration at 12 month ($p < 0.01$ vs month 1)(Fig 2).

For all patients,a highly significant correlation was found between BPRS and EPSE total scores at month 1 ($r = 0.55$, $p < 0.01$), and at month 12 ($r = 0.74$, $p < 0.01$).

ii) Pharmacokinetic Data

HL plasma levels ranged from 1.5 to 8.2 ng/ml (mean 4.31 ± 1.004 SD) (Table 1).

Fig 3 shows the kinetic curves obtained in the first month of treatment in two subjects (21 and 6): peak plasma concentrations were observed at the third day from injections.

All patients achieved HL steady-state plasma levels between the third and sixth month of treatment. Patients from Group 2 showed a higher interindividual variability in plasma levels and reached the steady-state more slowly than those from Group 1, as also shown by the patterns of L/D ratios (Fig 4). Patients from Group 2 showed a lower total L/D ratio compared to Group 1 (Table 2).

A positive correlation was found between the administered dose and HL plasma levels (at month 6, $r = 0.71$ $p < 0.01$ and at month 12, $r = 0.86$ $p < 0.01$). No correlation between BPRS or EPSE and plasma levels was observed.

Discussion

i) Clinical Data

The patient population proved relatively stable in clinical terms. BPRS, in fact did not show significant fluctuations during the follow-up period, although interindividual variability was higher in patients with longer duration of illness.

Our study already shows that duration of illness can influence the clinical outcome, since the longer the disease, the fewer improvement recorded in the patients during the follow-up period. This could be due to the clinical course of the disease itself (mostly characterized by negative symptoms) and/or to the influence of duration of the illness on the pharmacokinetics of HL, as discussed later.

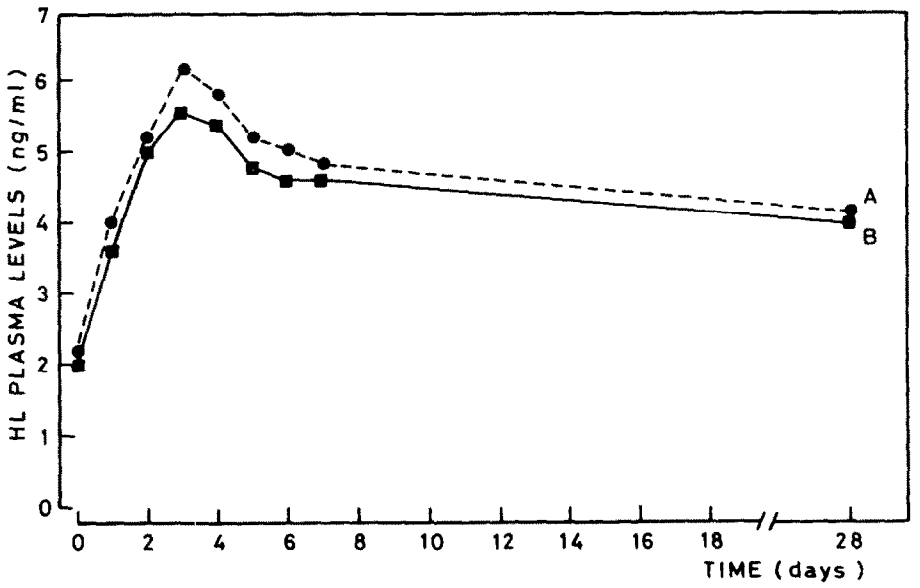

Fig 3. The kinetic profiles of HL-D after the first injection, for two patients (A = PT 21, B = PT 6).

Table 2

The Variables Characterizing the Two Groups of Patients

	GROUP 1 Mean ± SD	GROUP 2 Mean ± SD	P value
Patients (N)	10	12	
Age (yrs)	29.2 ± 8.86	49.5 ± 7.07	< 0.001
Duration of illness	5.3 ± 3.71	20.2 ± 5.39	< 0.001
Dose (mg/kg)	2.03 ± 0.61	2.42 ± 0.97	N.S.
BPRS	22.4 ± 5.22	37.2 ± 13.19	< 0.001
EPSE	1.18 ± 0.15	1.64 ± 0.21	< 0.001
Plasma levels (ng/ml)	4.44 ± 0.68	4.19 ± 1.22	N.S.
L/D ratio	2.43 ± 0.53	1.88 ± 0.47	< 0.03

The higher extrapyramidal symptoms scores in Group 2 could be linked to the previous treatments (neuroleptic combinations) and differences in age. This means that HL-D monotherapy produced fewer side-effects compared to neuroleptic combination therapies (Youssef 1983). The positive correlation between BPRS and EPSE total scores could be

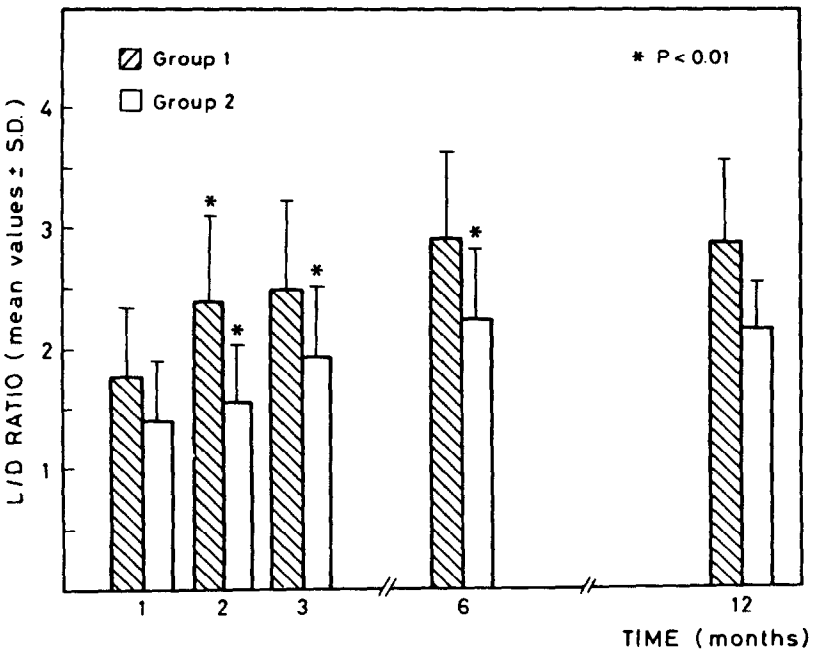

Fig 4. The pattern of the L/D ratios (mean values) recorded in the course of the study for Group 1 and Group 2 indicating a significant increase (*$p < 0.01$ vs each previous value) until the second month for Group 1 and the sixth month for Group 2.

ascribed to the influence of extrapyramidal side-effects on psychopathological features, particularly depressive ones, as known for conventional neuroleptic drugs as well (Altamura et al 1989). In other words, prevention and treatment of unwanted extrapyramidal side-effects could possibly contribute to a better clinical response in schizophrenia, avoiding the so-called "akinetic depression (Van Putten et al 1984) due to neuroleptics mediated extrapyramidal symptoms.

ii) Pharmacokinetic data

Plasma levels were significantly related to the administered dose, as reported by others (De Buck et al 1981, De Cuyper et al 1986, Parent et al 1981, Reyntjens et al 1982). This indicates reduced interindividual variability in drug bioavailability due to the lack of "first pass effect". The steady-state was reached after about three months' treatment, and during this period the L/D ratio was lower than during the following months of treatment. This finding could provide grounds justifying a higher relapse rate during the early phase of the therapy with HL-D in subjects shifting from conventional to

long-acting preparations, particularly in patients with a long lasting duration of illness. In accordance to this finding higher doses of HL-D should be administered during the early phase of treatment with the long-acting drug as reported by De Cuyper et al (1986).

The duration of the illness seems to be a factor capable of influencing HL-D kinetics. In fact, subjects with longer duration of the illness needed higher doses to achieve plasma levels comparable to those of patients with a shorter clinical history and showed a higher interindividual variability in plasma levels and in the time required to achieve steady-state plasma concentrations. This could be attributed to the age phenomenon and probably reflect a more unpredictability in drug metabolism (Cheng et al 1987).

Effective maintenance HL plasma levels in our sample were lower than those reported for acute psychotic relapses (from 5 to 15 ng/ml)(Mavroidis et al 1983, Potkin et al 1985, Smith et al 1985, Van Putten et al 1988). Moreover the poorer therapeutic response and higher variability in BPRS scores reported in Group 2 could be at least partly due to the higher variability in HL plasma levels.

All these findings about the differences between the two groups could be partially attributable to the aging process even if there are reports of no influence of age on HL pharmacokinetics (Forsman & Ohman 1976) and overall older patients showed lower L/D ratios in our study.

Conclusions

In conclusion also considering the limitation of a "naturalistic" approach we can summarize that the duration of illness must be taken into account when administering HL-D since it seems to influence both the clinical outcome and pharmacokinetic features.

Moreover, the pharmacokinetic approach seems desirable in the early phases of the treatment in order to adjust the dose and avoid relapses as suggested for other antipsychotics (Altamura et al 1985).

References

ABERNETHY, D.R., GREENBLATT, D.J. and OCHS, H.R. (1984) Haloperidol determination in serum and cerebrospinal fluid using gas-liquid gaschromatograph with nitrogen/phosphorus detection, application to pharmacokinetic studies. J Chromatogr 307:194-199.

ALTAMURA, A.C., CURRY, S.H., MONTGOMERY, S. and WILES, D.H. (1985) Early unwanted effects of fluphenazine esters related to plasma fluphenazine concentrations in schizophrenic patients. Psychopharmacology 87: 30-33.

ALTAMURA, A.C., MAURI, M.C., DE NOVELLIS, F., PERCUDANI,M. and VAMPINI, C.(1989) Residual neuroleptic induced parkinsonian symptoms in schizophrenia (a naturalistic study with orphenadrine). Pharmacopsychiatry (in press).

BERESFORD, R. and WARD, A. (1987) Haloperidol decanoate: a preliminary review of its pharmacodynamic and pharmacokinetics properties and therapeutic use in psychosis. Drugs 33: 31-49.

CHENG, Y.F., PAALZOW, L.K., BONDESSON, U., EKBLOM, B., ERIKSSON, K., ERIKSSON, S.O., LINDERBERG, A. and LINDSTROM, L. (1987) Pharmacokinetics of haloperidol in psychotic patients. Psychopharmacology 91: 410-414.

DEBERDT, R., ELENS, P., BERGHMANS, W., HEYKANTS, J., WOESTENBORGHS, R., DRIESENS, F., REYNTJENS,A.J.M.and VAN WIJNGARDEEN, I. (1980) Intramuscular haloperidol decanoate for neuroleptic maintenance therapy. Efficacy, dosage schedule and plasma levels. Acta Psychiatr. Scand. 62: 356-363.

DE BUCK, R.P., ZELASCHI, R., GILLES, C., DUROW, J. and BRAUMAN, H. (1981) Theoretical and practical importance of plasma levels of haloperidol: correlations with clinical and computerized EEG data. Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 5: 499-502.

DE CUYPER, H., BOLLEN, J., VAN PRAAG, H.M. and VERSTRAETEN, C. (1986) Pharmacokinetics and therapeutic efficacy of haloperidol decanoate after loading dose administration. Br. J. Psychiatry 148: 560-566.

FORSMAN, A. and OHMAN, R. (1976) Pharmacokinetic studies on haloperidol in man. Curr. Ther. Res. 20: 319-336.

MAVROIDIS, M.L., KANTER, D.R., HIRSCHOWITZ, J. and GARVER, D.L. (1983) Clinical response and plasma haloperidol levels in schizophrenia. Psychopharmacology 81: 354-356.

OVERALL, J. and GORHAM, D. (1962) Brief Psychiatric Rating Scale. Psychol. Rep. 10: 799-812.

PARENT, M., TOUSSAINT, C., DRIESENS, F. and GELDERS, Y (1981) Pharmacocinetique du decanoate d'haloperidol chez le psychotique. Acta Psichiat. Belg. 81: 399-405.

POTKIN, S.G., SHEN, Y., ZHON, D., PARDES, H., SHU, L., PHELPS, B. and POLAND, R. (1985) Does a therapeutic window for plasma haloperidol exist ? Preliminary chinese data. Psychopharmacol. Bull. 21(1): 59-61.

REYNTJENS, A.J.M., EYKANTS, J.J.P., WOESTENBORGHS, R.J.H., GELDERS, Y. and AERTS, T. (1982) Pharmacokinetics of haloperidol decanoate. A 2-years follow-up. Int. Pharmacopsychiat. 17: 238-246.

SAS INSTITUTE INC. (1979) User's Guide, North Carolina.

SIMPSON, R.M. and ANGUS, J.S.W. (1979) A Rating Scale for Extrapyramidal Side-effects. Acta Psychiatr. Scand. 212(S): 11-19.

SMITH, R.C., BAUMGARTNER, R., BURD, A., RAVICHANDRAN, G.K. and MAULDIN, M. (1985) Haloperidol and thioridazine drug levels and clinical response in schizophrenia: comparison of gas-liquid chromatography and radioreceptor drug level assays. Psychopharmacol. Bull. 21(1): 52-58.

VAN PUTTEN, T., MAY, P.R.A. and MARDER, S.R. (1984) Akathisia with haloperidol and thiothixene. Arch. Gen. Psychiatry 41: 1036-1039.

VAN PUTTEN, T., MARDER, S.R., MINTZ, J. and POLAND, R.E. (1988) Haloperidol plasma levels and clinical response: a therapeutic window relathionship. Psychopharmacol. Bull. 24(1): 172-175.

VIUKARI, M., SALO, H., LAMMINSIVU, V. and GORDIN, A. (1982) Tolerance and serum levels of haloperidol during parenteral and oral haloperidol treatment in geriatric patients. Acta Psychiatr. Scand. 65: 301-308.

YOUSSEF, H.A. (1983) Haloperidol decanoate in place of multiple drug therapy in chronic schizophrenic patients. Acta Therap. 9: 215-225.

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