Pergamon

Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 1995. Vol. 19. pp. 1119-1135
1995 Elsevier Science Inc.
Printed in Great Britain.
0278 - 5846/95 $29.00

0278-5846(95)00230-8

PHARMACOCLINICAL CORRELATIONS IN SCHIZOPHRENIC PATIENTS TREATED WITH HALOPERIDOL DECANOATE: CLINICAL EVALUATIONS, CONCENTRATIONS OF PLASMA AND RED BLOOD CELL HALOPERIDOL AND ITS REDUCED METABOLITE, AND PLASMA HOMOVANILLIC ACID

NICOLE AYMARD[1-2], ANNIE VIALA[3], ISABELLE STEIN[1] and FRANCOIS CAROLI[3]

[1]Unité de Pharmacologie, Laboratoire Central, Centre Hospitalier Sainte-Anne, Paris, France
[2]Laboratoire de Pharmacologie, Université René-Descartes, Paris, France.
[3] Unité Médico-Psychologique du XIVème arrondissement Ouest,
Centre Hospitalier Sainte-Anne, Paris, France.

(Final form, June 1995)

Abstract

Aymard Nicole, Annie Viala, Isabelle Stein and François Caroli : Pharmacoclinical correlations in schizophrenic patients treated with haloperidol decanoate: Clinical evaluations, concentrations of plasma and red blood cell haloperidol and its reduced metabolite, and plasma homovanillic acid. Prog. Neuro. Psychopharmacol. & Biol. Psychiat. 1995, 19(7): 1119-1135.

1. The aim of this open study was to determine whether a more rational therapeutic approach could be devised for psychotic patients (n = 11) treated for long periods with long-acting (LA) haloperidol. The mean multiplication factor for the transition from the oral formulation to the long-acting one was 12.8 (10.4, standard deviation), lower than the theoretically recommended factor of 20.
2. The best dose (mg/kg)-concentration correlations were found for haloperidol (HAL) and reduced HAL (RHAL) in the red blood cells (RBC) (representative of the free drug fraction) rather than in the plasma of patients that had attained the steady state (at the third cycle and afterwards)
3. Pharmacokinetic analyses were conducted at the same time as clinical evaluations, grading using the BPRS and determinations of plasma levels of total, free and conjugated homovanillic acid (HVA), a marker of central dopaminergic activity.
4. A between groups comparison at the steady state (patients (n = 20) with oral administration and the above patients (n = 11) with long-acting form of HAL), showed that the plasma and RBC RHAL/HAL ratios of long-acting HAL decreased significantly ($p < 0,005$) in comparison with oral administration, at least by half.
5. Plasma HVA values complete the information provided by plasma and more especially RBC HAL and RHAL levels. All these results taken together, as substantiated by the clinical assessment scales (BPRS), assure a better pharmacoclinical surveillance and can be predictive of a patient's response.

Keywords: clinical correlations , schizophrenia, haloperidol decanoate, plasma, red blood cells, haloperidol, reduced metabolite, plasma free, conjugated, total homovanillic acid, predictive value.

Abbreviations: Brief Psychiatric Rating Scale (BPRS), conjugated (c), Diagnostic Statistical Manual third edition revised (DSMIIIR), free (f), haloperidol (HAL), haloperidol decanoate (HALD), high pressure liquid chromatography (HPLC), homovanillic acid (HVA), long-acting (LA), plasma (P), red blood cells (RBC), reduced haloperidol (RHAL), total (t).

Introduction

Many studies have investigated the pharmacokinetics of orally administered haloperidol (HAL). Various authors notably Chang et al. (1989), Forsman and Larson (1978), Korpi et al. (1985), found that the principal active metabolite was reduced haloperidol (RHAL). However, for Altamura et al. (1988), Ereshefsky et al.

(1984) and Ko et al. (1989), a high level of RHAL reflects a poor therapeutic response. Only a few studies (Altamura et al., 1990, Chang et al.,1993a, Ereshefsky et al., 1990; Gelders et al., 1982; McKane et al., 1987;) have been conducted in schizophrenic patients treated with haloperidol decanoate (HALD). In particular, Chang et al. (1993a) noted pharmacokinetic differences between oral HAL and HALD in their study that also included measurements of RHAL. Since, to the best of our knowledge, no study has evaluated the drug concentrations in the red blood cells (RBC) of patients given HALD, the authors thought it would be useful to determine whether pharmacokinetic correlations exist between the RBC levels of HAL and RHAL and those of homovanillic acid (HVA), a marker of central dopaminergic activity.

Material and Methods

Subjects :

The study has been performed in an open, setting and has included 11 patients, 3 women and 8 men, with age ranging from 23 to 52 years (mean age 35.5 ± 8.5 SD) , with a weight from 53 to 81.5 kg (mean weight 66 ± 9 SD), with mean duration of illness of 1 to 17 years (mean duration, 7.6 ± 5.9 SD) and were followed up in this study for 4 to 30 months (mean duration 12.2 ± 9.05 SD). (Table 1)

All of them were schizophrenic patients, who met DSMIII-R criteria for paranoïd schizophrenia. They were aware of the aim of the study. Patients suffering from organic disorders, drug addiction were not included in the study. None of them presented tardive dyskinesia.

Table 1

Patient Charactéristics

Patient	Sexe	Age (years)	Weight (Kg)	Duration of illness (years)	HALD Followed up for (months)	Stabilized Oral HAL Dose mg - mg/kg	BPRS before HALD
1	M	45	74	3	22	4 - 0,054	54
2	M	52	55	17	24	4,5 - 0,082	53
3	M	32	59	15	6	15- 0,25	63
4	F	32	78	7	30	20 - 0,256	62
5	M	43	65	15	18	30 - 0,46	55
6	M	29	68	6	7	15 - 0,22	52
7	M	33	81	13	9	15 - 0,184	46
8	M	41	73	2	4	40 - 0,55	45
9	F	29	53	1	4	25 - 0,47	70
10	M	23	67	1	4	40 - 0,59	55
11	F	27	53	3	6	28 - 0,53	65
Mean ± SD	(8M)	35,5	66	7,6	12,2	21,5 0,33	56
	(3F)	± 8,5	± 9	±5,9	±9,05	±11,8 ± 0,184	±8

Drug Administration

Patients had been admitted in acute state in our hospitalization unit. The first phase of treatment consisted of the administration of HAL, either initially injectable and then oral, or directly oral. When they were clinically stabilized on oral HAL treatment (from 4 to 40 mg/day with means ± SD of : 21.5 ± 11.8 mg/day and 0.33 ± 0,18 mg/kg/day), the second phase began and consisted of an intramusculary administration of HALD (2 to 6 ampules, that is 100 to 300 mg per injection) every 4 weeks with a dose ranging from 1.28 to 4.61 mg/kg (mean dose of 2.71 ± 1.08 SD) to maintain clinical efficacy without increased adverse reactions. All of them left the hospitalization unit and came regularly at our out-patient consultation.

Assessment

Blood samples were drawn approximatively 12 hours post bed time and prior to the morning dose when the patients received oral HAL. When they received HALD injection, we used only the blood samples on days 7 and 28 from the third cycle and afterwards because when administered every four weeks, pharmacokinetic studies of HALD in schizophrenics reported that steady state haloperidol plasma concentrations are achieved in 3-4 months (Vasavan-Nair et al, 1986). But with haloperidol decanoate, the plasma concentration time profile demonstrated that in each cycle peak levels of HAL occured one week after decanoate injection, then the levels declined rapidly until the next injection ; but at the steady state the profile was constant ; and we chose to analyse samples, on days 7 and 28 (Table 3) because they were found to correspond respectively to the maximal and residual product concentration (Furet et al 1991). Both blood samples were drawn in the morning. At day 28, blood sample was drawn before the injection, patients came more regularly at day 28, which was the day of the next injection, than at day 7 : that explains why we have more results corresponding to day 28 than to day 7. During the study , for 3 patients HALD doses were modified, in response to each patient's condition (patients n° 1-3-4). But with some patients it was possible to draw blood samples on days 7, 14, 21 and 28 of the cycles.

The treatment was prescribed as a neuroleptic monotherapy. Only antiparkinsonian drugs were commonly associated, none were on enzyme inducing agents nor inhibiting drugs. The only concurrent medications allowed did not influence haloperidol plasma concentrations.

At the time of each sampling, a pharmacoclinical evaluation was performed, including a Brief Psychiatric Rating Scale (BPRS) grade, and determinations of plasma levels of total (t), free (f) and conjugated HVA (cHVA) (dopaminergic marker). In this study, the authors also followed the evaluation of plasma and RBC HAL and RHAL levels over a period of at least 4 months ; some patients were monitored for longer times, sometimes several years, and thus the evolution of these values over the short and long term could be compared. It explains that at days 7 and 28 we could have collected respectively 27 and 45 pharmacoclinical observations. Vital signs, biochemical and haematological laboratory tests were measured prior and during the study.

The authors made a between groups pharmacokinetic study under steady state condition, comparing oral and long-acting parenteral formulations ; the reference patient population (n = 20) for oral administration (Aymard et al - 1990) was comparable to the above study group, with schizophrenia diagnosed according to DSM III criteria, with age ranging from 26 to 51 years (mean age 34.7 ± 8.6 SD), with weight from 55 to 90 kg (mean weight 64.7 ± 11.4 SD). Their daily medication doses ranged from 4.5 to 30 mg/day (mean 21.7 ± 11.8 SD) and from 0,075 to 0,68 mg/kg/day (mean 0.31 ± 0.16 SD).

Analytical Methods

HAL and HVA plasma levels were determined by high-pressure liquid chromatography (HPLC).

HAL and RHAL (Aymard et al 1990).The method used was a modified version of the one described by Jatlow et al. (1982), using chlorohaloperidol as internal standard.

Reagents and Chemicals The reference compounds were : haloperidol, reduced haloperidol and chlorohaloperidol from Janssen Pharmaceuticals (Beerse, Belgium), acetonitrile and n-hexan, RS - plus for HPLC from Carlo Erba (Milano Italy), potassium dihydrogenphosphate from Merk (Darmstadt Germany).

Apparatus Liquid chromatography was carried out using a pump (LC - 6 A Shimadzu), a 150 mm x 4.6mm ID collumn packed with μ Bondapak C 18 size 5μm (Waters) and an ultra-violet detector (SPD - 6 AV Shimadzu).

Sample Preparation Blood samples were collected into sodium heparin vacutainers, plasma and RBC were separated within 30 minutes and stored at -20°C until assayed. Drug and metabolite levels were determined in plasma and RBC after lysis, with the latter representing the free fraction. The compounds were extracted with n-hexan. HAL and RHAL, released by 0.1 N HCl, passed from the organic into the aqueous phase, which was then injected by means of a Rheodyne model 7125 and its 100 µl sample loop into the reverse-phase HPLC system . The column was balanced with a mobile phase composed of acetonitrile/0,05 M phosphate buffer (pH = 3.8), 40/60 (v/v) reagent. The flow rate was 1.0 ml/min. The wave length was 195 nm.

Characteristics of the Method A linear relationship between peak-heigh ratios (HAL or RHAL to internal standard) and concentrations of HAL and RHAL (ng/ml) was observed between 2 and 100 ng/ml with a correlation coefficient r of 0.9995. For the two compounds the detection limit was estimated at 0.7×10^{-12} moles (0.5×10^{-9}g). The day to day reproducibility obtained for ten determinations for HAL and RHAL concentrations corresponding for each one to 5 ng/ml led to a coefficient of variation (CV) of 7 % . The within-day reproducibility obtained from twenty determinations for two, HAL dans RHAL concentrations (2 and 20 ng/ml) gave a CV of 8 %.

Total (t), Free (f) and Conjugated (c) HVA (Aymard et al 1992) . A modified version of the method of Garcia et al. (1989) was used; homovanillyl alcohol served as internal standard.

Reagents and Chemicals The reference compounds were : homovanillic acid, homovanillyl alcohol and EDTA (ethylene diamine tetraacetic acid), from Sigma (St Louis, MO. USA) ; Pic B.7 (1- heptane sulfonic acid) from Waters Assoc. (Milford, MA, USA) ; potassium dihydrogenphosphate from Merck (Darmstadt, Germany) ; methanol from FSA Laboratory (Loughborough, UK).

Apparatus Liquid chromatography was carried out using a pump (Beckman Gold system), a 150 mm x 4.6 mm ID column packed with µ Bondapack C_{18} size 5 µm (Waters) and an electrochemical amperometric detector (Bioanalytical System LC - 4C).

Sample Preparation Blood samples were drawn into sodium heparin and the plasma was separated within 30 minutes and then stored at -80 °C until tested. HVA exists in at least two forms : free and sulfoconjugated. Protein were precipitated with perchloric acid (0.4 N final). Plasma free HVA was assayed by injection of 50 µl of deproteinized plasma directly into the reverse-phase HPLC system coupled with electrochmicael detection . Hydrolysis of HVA conjugates was performed by acid hydrolysis (127.5 µl of $H_2 S0_4$ 1M containing H COOH. 0.03 M added to 372.5 µl of deproteinized plasma - then incubated for 12 min in a 95°C water bath). The hydrolysed sample (50 µl) was then injected into the HPLC system in order to determine the amount of plasma total HVA. The cHVA value was calculated as the difference between tHVA and fHVA levels. The column was balanced with a mobile phase composed of 10 % methanol, 0.1 M phosphate buffer, 0.1 mM EDTA and 0.005 M Pic B7 reagent, in deionized water. The pH was adjusted to 3.5. The flow rate was 1.0 ml/min. The detection potential was set to 0.8 V.

Characteristics of the Method. A linear relationship between peak-heigh ratios (HVA to internal standard) and concentrations of HVA (ng/ml) was observed between 2 and 100 ng/ml with a correlation coefficient r of 0.9994. The detection limit was estimated to be 1×10^{-12} mole ($0,5 \times 10^{-9}$g). The day to day reproducibility obtained for ten determinations for a HVA concentration corresponding to 5 ng led to a coefficient of variation (CV) of 4 % . The within-day reproducibility obtained from twenty determinations for two HVA concentrations (2 and 20 ng) gave a CV of 7 %.

Data Analysis.

Mean and standard deviation (M ± SD) was determined for all variables. Pearson correlations coefficients were calculated ; oral and long-acting parenteral administrations were compared, between two groups of patients, by one - way analysis of variance (ANOVA).Significance levels of $p<0.05$ were considered statistically significant (Student's t-test).

Results

1) Transition from the Oral to the Parenteral Long-Acting Formulation.

To obtain equivalent blood concentrations with the oral and long-acting formulations, in a number of early studies initial dose of haloperidol was determined by a theoretical conversion methodology based on a formula utilizing the estimated bioavailability of oral haloperidol and the 4 weeks dosing interval for the depot form : Deberdt et al. (1980) and Schulz et al. (1989) recommended multiplying the daily oral dose (t.i.d.) by a factor of 20 to determine the dose to be given in a single monthly injection. However, Levron and Ropert (1987) and Vasavan-Nair et al. (1986) observed clinical stabilization during this transition from the oral form to the long-acting one, despite lower plasma concentrations obtained with a smaller multiplication factor (from 9.4 to 20). French therapists prescribe between 10 and 80 mg daily of oral haloperidol (Deniker 1987, Miquet 1991) ; these prescriptions seem to be higher than those commonly used by other therapists and could explain a lower multiplication factor than that theoretically proposed during the transition to the long-acting formulation (3 to 7 ampules, i.e. 150 to 350 mg). For the 11 patients included in this study, the multiplication factor ranged between 5 and 25, with a mean of 12.8 ± 10.4 and a greater frequency in the zone betwen 5 and 15 (Table 2).

Table 2

Repartition of the Subjects According to the Parenteral/Oral Ratio of their Doses (mg/kg)

Ratios	2.5 to 5	5 to 7.5	7.5 to 10	10 to 12.5	12.5 to 15	15 to 17.5	17.5 to 20	20 to 22.5
Number of subjects	2	6	4	0	3	0	0	3

N.B. : During the course of treatment, the neuroleptic doses were modified, several times, for 3 patients which explains why the number of data exeeds 11.

In the study, the doses of haloperidol decanoate were based both on the patient's psychiatric history and on his maintenance dose of oral haloperidol.

2) Pharmacokinetic of the Long-Acting Formulation

Blood Sample Analysis. The patients'samples studied were those drawn at the third cycle and afterwards when it was possible, that is to say, once the steady state had been reached. During the cycles, samples on days 7 and 28 were analysed. Table 3 shows the mean pharmaco-clinical parameters.

Dose-Plasma Concentration Correlations and Contribution of RBC Determinations. Statistical analysis showed that highly significant correlations existed, between the dose in mg/kg and the plasma concentration of HAL but not of RHAL (Table 4).

Table 3

Summary of the Different Parameters Evaluated on Days 7 and 28 of the Cycle Once the Steady State had been Attained for all the Patients given a Monthly Injection of Long-Acting Haloperidol Decanoate. (Mean ± SD [range])

Parameter	Day 7 (n = 27)	Day 28 (n = 45)
P Concentrations (ng/ml)		
HAL	11.5 ± 7.2 [1 - 30]	6.50 ± 5.2 [0,5 - 24]
RHAL	4.8 ± 4.3 [0.5 - 17]	2.8 ± 2.5 [0.5 - 12.4]
RBC Concentrations (ng/ml)		
HAL	8.4 ± 6.8 [0,5 - 22,5]	6.5 ± 7,9 [0,5 - 45]
RHAL	8.1 ± 8,6 [0,5 - 34]	5.4 ± 9.2 [0,5 - 56]
Concentration ratios		
HAL RBC/P	0.87 ± 0.34 [0.32 - 1.42]	0,98 ± 0.64 [0.33 - 2.07]
RHAL RBC/P	1.91 ± 1.3 [0.3 - 6]	1.82 ± 1,09 [0.11 - 5.3]
P RHAL/HAL	0.55 ± 0.68 [0.13 - 2.9]	0.64 ± 0.63 [0.11 - 2.8]
RBC RHAL/HAL	0.96 ± 0.80 [0.20 - 3.5]	0.95 ± 0.7 [0.16 - 4]
P HVA concentrations (ng/ml)		
Total	16.2 ± 6.1 [9.2 - 32.2]	15.1 ± 4.3 [6.1 - 23.7]
Free	8 ± 3 [4.3 - 15]	7.6 ± 2.3 [3.6 - 13.4]
Conjugated	8.2 ± 3.7 [3.1 - 17.6]	7.5 ± 3.2 [1.8 - 13.9]
BPRS	49 ± 13 [30 - 77]	45 + 12 [26 - 78]

Abbreviations: P: Plasma; HAL: haloperidol; RHAL: reduced haloperidol; RBC: red blood cell; HVA: homovanillic acid; BPRS : brief psychiatric rating scale.

Mean Dose (mg/kg) of HALD : 2.71 ± 1.08 [1.28 - 4.61].

Table 4

Pearson Correlation Coefficients (r) and Significance Levels (p) Between the Dose (mg/kg) and the Plasma Concentration on Days 7 and 28, of the cycle, Once the Steady State had been Attained.

Day	Number samples	Haloperidol r	Haloperidol p	Reduced Haloperidol r	Reduced Haloperidol p
7	27	0.533	<0.005	0.273	<0.25
28	45	0.49	<0.005	0.353	<0.25

$p < 0.05$ was considered significant.

However, since it is known (Aymard et al., 1993) that plasma level, especially of psychotrops, do not accurately reflect therapeutic activity, the authors also determined product levels in RBC which have also been used as predictors of clinical response and have been correlated with clinical efficacy (Ko et al., 1989; Neborsky et al., 1982, Vatassery et al., 1990;). First , the authors established correlations between plasma and RBC HAL and RHAL concentrations, thereby demonstrating that the RBC contents are indeed in equilibrium with the plasma free fractions and may give a better indication than the plasma total concentrations, of the therapeutic efficacy and the diverse clinical manifestations, including side effects (Table 5).

Table 5

Pearson Correlation Coefficients (r) and Significance Levels (p) Between Plasma and RBC Concentrations on Days 7 and 28 of the cycle, Once the Steady State had been Attained.

Day	Number sample	Haloperidol r	Haloperidol p	Reduced Haloperidol r	Reduced Haloperidol p
7	27	0.838	<0.0001	0.612	<0.005
28	45	0.821	<0.0001	0.825	<0.0001

$p < 0.05$ was considered significant.

Then it was verified that the dose in mg/kg and the RBC concentrations not only of HAL but also RHAL were significantly correlated (Table 6). These correlations were equally valid for the entire population taken together (as above) and for individuals when their doses were modified.

Table 6

Pearson Correlation Coefficients (r) and Significance Levels (p) Between the Dose (mg/kg) and the RBC Concentrations on Days 7 and 28 of the Cycle, Once the Steady State had been Attained.

Day	Number sample	Haloperidol r	p	Reduced Haloperidol r	p
7	27	0.463	<0.025	0.632	<0.005
28	45	0.415	<0.01	0.432	<0.005

$p < 0.05$ was considered significant.

Pharmacokinetic Study Comparing, under Steady State Conditions, Oral and Long-Acting Parenteral Formulations

When changing from the oral to the long-acting (LA) parenteral formulation, the RHAL/HAL ratios in plasma and RBC decreased significantly by half (Table 7), however, the RBC extraction coefficients for HAL and RHAL (HAL $\frac{RBC}{P}$, RHAL $\frac{RBC}{P}$) remained unchanged. (Fig 1)

Table 7

Between Group Comparisons of Concentrations Ratios, at theSteady State, in Patients Receiving Oral or Long-Acting (LA) Haloperidol

	P $\frac{RHAL}{HAL}$	RBC $\frac{RHAL}{HAL}$	HAL $\frac{RBC}{P}$	RHAL $\frac{RBC}{P}$
- ORAL HAL				
20 Patients	1,037± 0,55 a	2,79 ± 1,6 d	0,81 ± 0,27 g	2,14 ± 0,64 j
- L A HAL				
11 patients				
. **Day 7**	0,55 ± 0,68 b**	0,96 ± 0,8 e ***	0,87 ± 0,34 h	1,91 ± 1,3 k
. **Day 28**	0,64± 0,63 c***	0,95 ± 0,7 f***	0,98 ± 0,64 i	1,84 ± 1,09 l

Abbrevations : HAL : Haloperidol ; LA : Long-Acting ; P : Plasma ; RBC : Red Blood Cell ; RHAL : Reduced haloperidol

All variables are mean and standart deviation : M ± SD.
Asterisks show statistically significant differences : a vs b, a vs c, d vs e, d vs f, g vs h, g vs i, j vs k, j vs l
* $p < 0,05$ - ** $p < 0,01$ - *** $p < 0,001$ (Student's t - test)

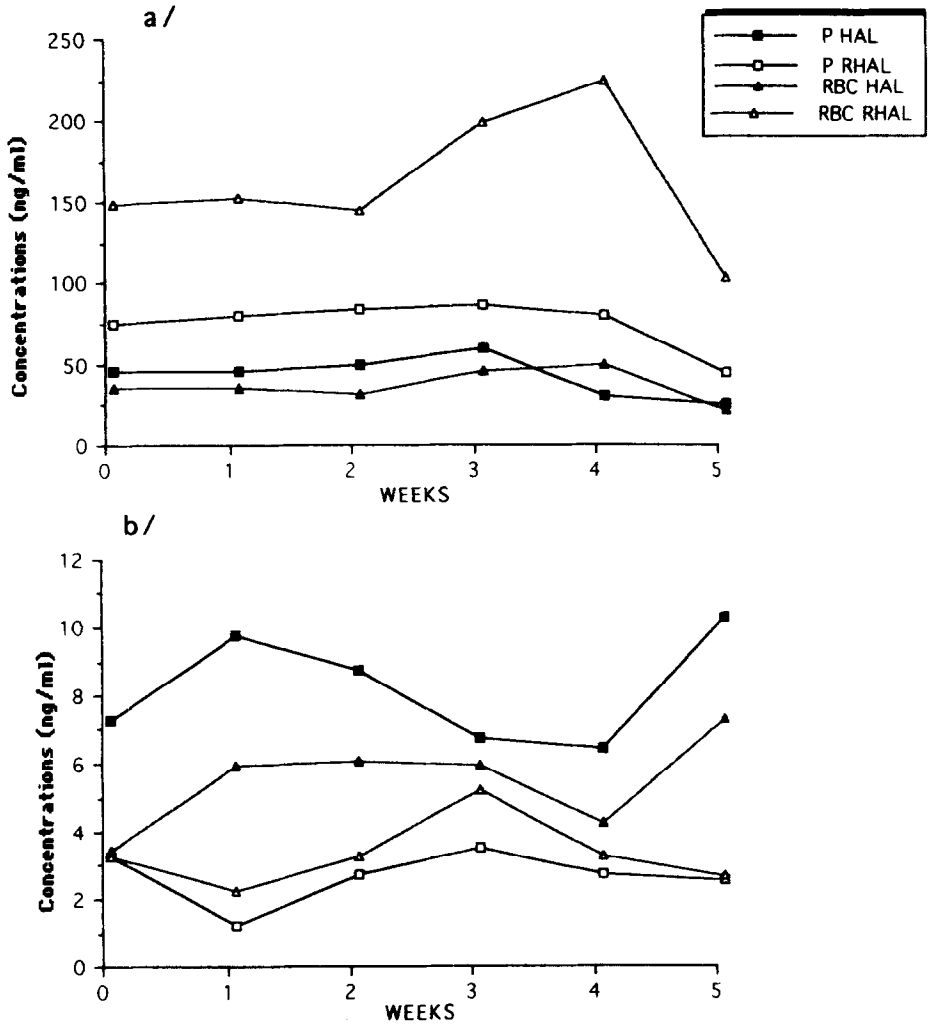

Fig 1 : Representative profiles in one patient that illustrate the modification of the RHAL / HAL ratio in Plasma (P) and RBC for the oral (a) and long-acting parenteral formulations (b) (patient 9)

3) Pharmacoclinical Correlations

Determination of Total, Free and Conjugated HVA Complementary to the Analysis of HAL Kinetics.

HVA remains one of the best markers of central dopaminergic activity (Bacopoulos et al., 1979). Although less than 20 percent originates in the brain, plasma HVA has been found to reflect levels of psychopathology better than HVA in urine or CSF. Only the free unconjugated form of HVA has been studied by most investigators, but HVA also exists in a sulfoconjugated form (generated by phenolsulfo-transferase). Garcia et al (1989) suggested that there is an imbalance between plasma free and conjugated HVA in schizophrenic patients when compared with controls.

BPRS Evaluation as a Complement to Kinetic Study of HAL and HVA.

The BPRS is the most commonly used score to monitor the clinical evolution of psychotic patients. It is composed of 18 items that enable equally good assessment of clinical improvement and relapse. In this analysis of the overall scores, the authors did not distinguish between positive or negative factors.

Observations on the Evolution of HVA Concentrations

The authors in earlier studies (Aymard et al 1992, Galinowski et al 1992) have investigated free, conjugated and total HVA plasma levels in healthy volunteers (n = 17), in drug free schizophrenic patients (n=17) and in chronic schizophrenic patients (n = 13) treated with oral haloperidol (stable daily doses : between 6 and 45 mg). The mean plasma HVA levels of these three populations and of the patients treated with haloperidol decanoate are given on Table 8. No statistical significative difference was observed for free HVA or any other HVA value.

Table 8

Values of Plasma HVA Levels (Mean ± SD - ng/ml)

	Free HVA	Conjugated HVA	Total HVA
- HealthyVolunteers n = 17	9,6 ± 3,1	8,5 ± 2,6	18,2 ± 5,1
- Drug Free Schizophrenics n = 17	9,4 ± 2,9	6,4 ± 3,9	15,9 ± 4,7
- Chronic Schizophrenics with HAL per Os			
at Day 28 n = 13	9,1 ± 1,8	6,1 ± 1,4	15,4 ± 1,7
- Chronic Schizophrenics with HALD			
at Day 7	8,1 ± 3,1	8,2 ± 3,7	16,2 ± 6,1
at Day 28	7,6 ± 3,1	7,5 ± 3,2	15,1 ± 4,3

The chronic Schizophrenics, with HAL per os and with parenteral HALD were at the Steady State.

The authors did not confirm the findings of Garcia et al (1989) which, suggested a modification of phenol sulfotransferase activity in schizophrenic patients leading to a lack of correlation between tHVA and cHVA.. In this HALD study, significant correlations were found between fHVA and cHVA ($r = 0.615$; $p < 0.005$), between fHVA and tHVA ($r = 0.872$: $p < 0.0001$) and between cHVA and tHVA ($r = 0,879$; $p < 0,0001$). The curves of fHVA, cHVA and tHVA for one patient (patient 1) receiving HALD illustrated these correlations. (Fig 2)

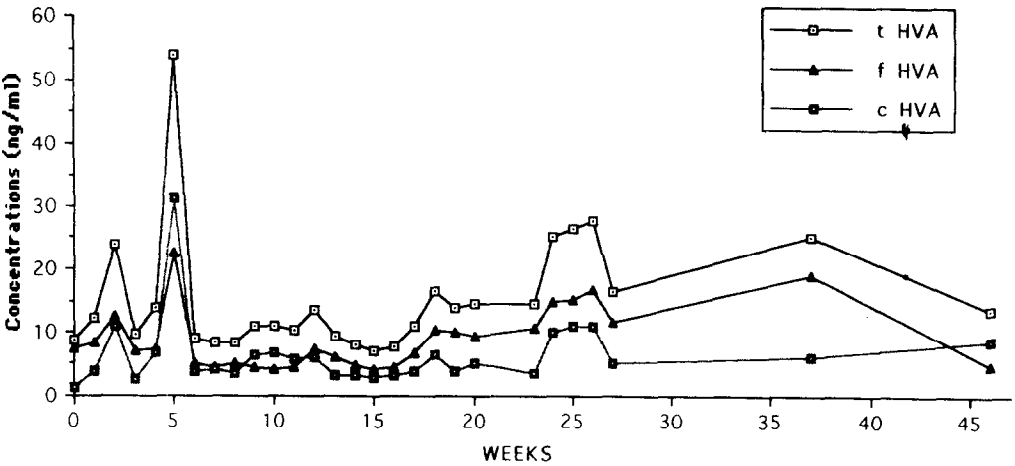

Fig 2. An example of the relationships between total (t). free (f) and conjugated (c) HVA in one patient during the course of treatment with haloperidol decanoate (patient 1).

Observations on the Evolution of the Clinical Characteristics

Patients were notably stabilized on oral haloperidol, with total BPRS values ranging from 70 to 44 (mean BPRS, 56 ± 8 SD), before being switched to the decanoate form, beginning by emotional withdrawal, suspiciousness and hallucinatory behaviour. The target symptoms improved then progressively and haloperidol decanoate is at least comparable to oral haloperidol in managing psychotic symptoms. During the time of our study, BPRS targets were improving regularly but more slowly than during the oral phase or during the 3 first months of decanoate phase - (ranging from 78 to 26 - Mean value 47 ± 13 SD).

Three out of the 11 Patients are Discussed in the Following Case Reports

Case n° 1 : Patient 6 is a man, 29 years old ; schizophrenia was diagnosed at the age of 25. He was hospitalized in May 1990, treated with oral haloperidol (15 mg per day) and BPRS total score improved from 60 to 52. He was then switched to the decanoate form (200 mg per injection) and BPRS total score improved from 52 to 49 during the 3 first months and then progressively from 49 to 37 during the two following years. During the time of the study, as shown on Fig 3, BPRS was almost stable. Correlations were found between the plasma HVA levels and RBC.HAL concentrations (between RBC Haldol and tHVA concentrations, $r = 0,621$ with $p < 0,025$ - between RBC Haldol and fHVA concentrations, $r = 0,796$ with $p < 0,005$). As it was described by Chang et al (1993b), in the first three cycles, depot HAL administration produced an increase in HVA levels with a peak value at J7. After repeated injections the HVA levels decreased and were correlated with the slowly decrease of the BPRS ($r = 0,512$, $p < 0,05$). Case n° 1 is for the authors the illustration of a stabilized patient.

Case n°2 : Patient 7 is a man 33 years old, treated for schizophrenia for 10 years. During the time of the study, as shown on Fig 3, BPRS scores decreased from 46 to 31 and then with accidental fluctuations increased up to 50. The evolutions of the plasma HVA and of the RBC HAL concentrations were not correlated as they were by the Case n°1. These fluctuations illustrated acute anxious states which led the patient to take alcohol (week 14 - week 29), which seemed to induce an increasing of the plasma and RBC HAL concentrations (alcohol as enzymatic inhibitor).

Case n°3 : Patient 3 is a man, 31 years old, treated for schizophrenia for 5 years. During the time of the study, a slowed psychomotor activity led the authors to the reduction in the dose of HALD which in turn aggravated the patient's psychotic state. It should be noted, as shown on Fig 3 that plasma and RBC HAL levels were

decreasing, when HVA was increasing, just before BPRS increasing. The authors think retrospectively that the patient was having a relapse and needed an increase of his treatment rather than a diminution. This case illustrates, for the authors, the predictive value of such biological sampling to adjust the initial dose based on the patient's symptomatology and previous medication history.

Discussion

Two sets of data were obtained in the course of this investigation in schizophrenic patients treated with haloperidol decanoate. First there are pharmacokinetic results and then the presentation of pharmacoclinical correlations.

Pharmacokinetic of the Long-Acting Formulation

The clinical stabilization that the authors observed with these lower doses confirmed the hypothesis put forth by Levron and Ropert (1987) and Vasavan-Nair et al. (1986) of a difference in the action of the oral and that of the parenteral long-acting form. In light of the fact that these are chronic patients receiving long-acting therapy, it was impossible to envisage, from an ethical point of view, for them, a comparative study between daily oral and parenteral administrations. Nonetheless, it must be kept in mind that the long-acting form bypasses several degradation mechanisms: the first-pass liver effect and partial metabolism in the intestinal mucosa. Ereshefsky et al (1984), Forsman and Ohman (1977a), Forsman et al. (1977b), Korpi et al. (1984, 1985) studied the principal metabolic pathways of HAL: first, reductive to RHAL and second oxidative returning to HAL. All the patients of this study were Caucasians and the present results confirmed, for the oral form (Table 7), these of Jann et al (1992) who reported and compared HAL and RHAL plasma concentrations in different ethnic groups, chinese, caucasian, hispanic and black people. The present results also confirmed those of Chang et al. (1993a) concerning the decrease of the RHAL/HAL ratio after administration of HALD (Fig.1 Table 7). However, it remains to be established whether this diminution of the RHAL/HAL ratio operates for the benefit of the oxidative pathway and/or at the expense of the reductive one. And the authors showed significant correlations between the dose in mg/kg of haloperidol decanoate and the RBC concentrations of not only HAL but also RHAL. As free fractions of the drugs, the RBC levels, better than the plasma concentrations could be utilized as therapeutic index of psychotrops. We could remember the first studies of Ahtee and Paasonen (1966), Freeman and Spirstes (1963) and Garver et al (1977) about possible correlations between the RBC concentrations of phenothiazines and, firstly their therapeutic activity and secondly the appearance of dystonies.

Pharmacoclinical Correlations

According to the determination of HVA, Aymard et al. (1992), Bowers et al (1989), Chang et al. (1990, 1993 b, c), Davidson et al. (1987), Davidson and Davis (1988) and Davila et al. (1988), noticed that, HVA increases during the first 24 hours following oral administration, then decreases before the end of the first week of treatment. These authors concluded that this initial enhancement reflected dopamine turnover attributabie to the blockade of postsynaptic receptors, whereas the secondary diminution mirrored the later blockade of the presynaptic receptors. Chang et al. (1990) differentiated between "responding" patients, who had higher HVA levels (as compared to a control population) that decreased under treatment, and "non-responders", whose concentrations were lower and remained unaffected by therapy. Davila et al. (1988) also reported that an increase in the plasma concentration of HVA during the first 4 days of treatment was predictive of clinical improvement during the next 28 days. But only the free unconjugated form of HVA has been studied by most investigators, nevertheless HVA exists in two forms : free and sulfo-conjugated. Few studies have sought to clarify the significance in man of fHVA, cHVA ant tHVA. For dopamine in humans there are three major catabolic pathways, : deamination by monoamine oxidase, 0 - methylation by catechol 0 - methyltransferase and conjugation mainly by phenol sulfotransferase. Conjugation by phenosulfotransferase is a major catabolic pathway for dopamine in both the central nervous system and the periphery. In the human brain the phenosulfotransferase contributes to 15 % of the total dopamine catabolism. In addition glucuronide conjugates, but not sulfates, are usually stable under acid hydrolysis, so it appears that the conjugated HVA we detected is probably mainly sulfate HVA.Plasma free HVA has been reported to be mainly of central origin according to studies in humans with debrisoquin. Garcia et al. (1989) noted that a positive linear correlation existed between cHVA and tHVA in healthy volunteers, but that this correlation was no longer present in

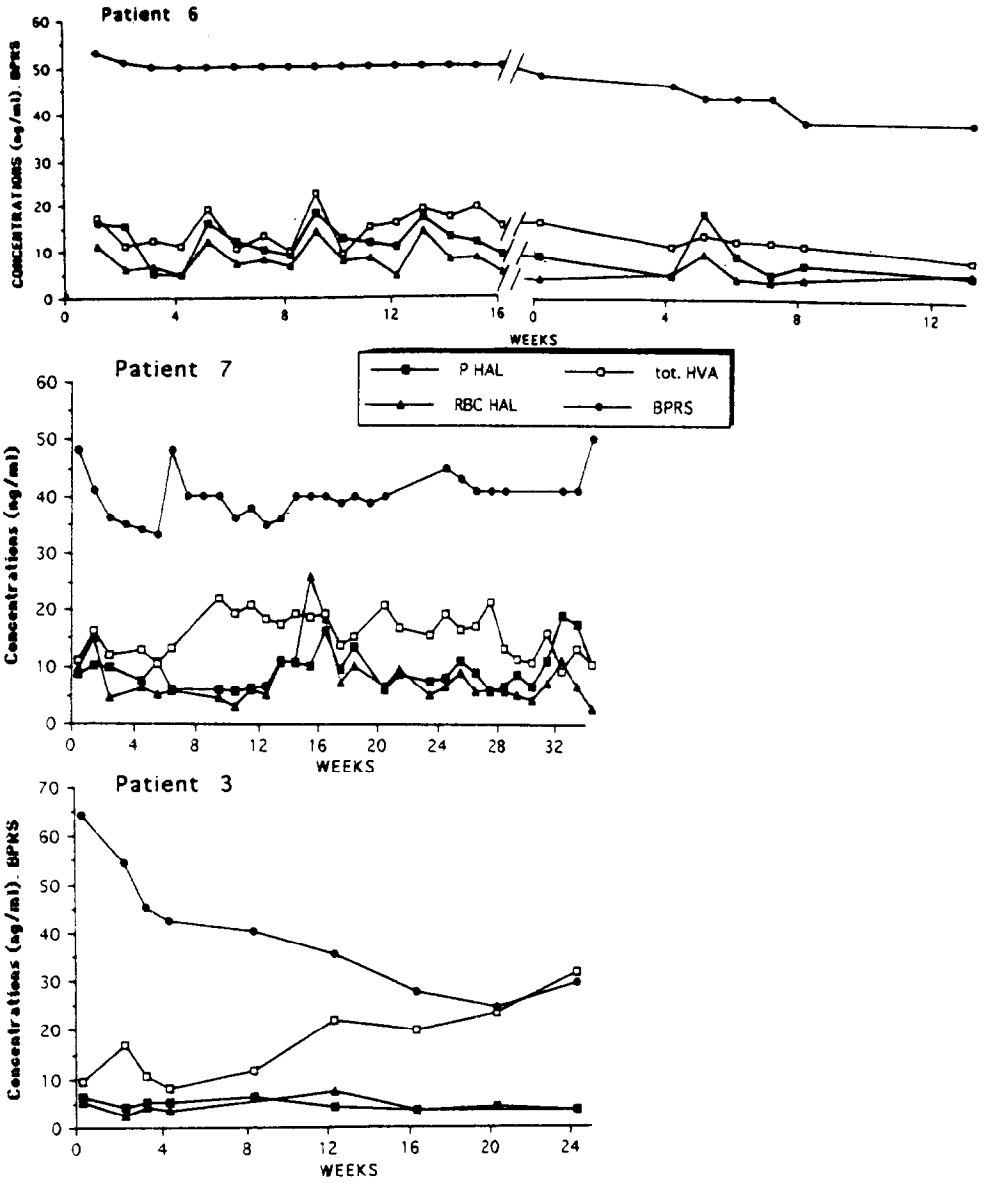

Fig 3 Curves illustrating the evolution of various parameters in 3 patients treated with haloperidol decanoate. (patient 6 - patient 7 - patient 3)

psychotic patients ;The high plasma free HVA level in schizophrenic patients is usually explained by the hyperactivity of the central dopaminergic system and the decrease of plasma conjugated HVA by a peripheral catabolic disturbance but there is no reason to reject the hypothesis of a modification of central enzymatic activities. In another study, Galinowsky et al. (1990) did not observe this difference between healthy control and drug free psychotic populations. There is no longitudinal study of free and conjugated plasma HVA in schizophrenic patients treated with neuroleptic drugs. To the best of our knowledge, only Chang et al (1993b) have studied HVA (fHVA) in patients treated with HALD : parallel increases were seen in plasma HVA and HAL concentrations up to the 9 th week on the average (range, 6 th to 15 th week), followed by secondary stabilization. Concerning HVA, in their longitudinal study, the authors did not find modifications of phenol sulfotransferase activity by these schizophrenic patients treated with HALD, total and conjugated HVA were correlated ; the patients were chronic stabilized schizophrenics with durable neuroleptic treatments and that could perhaps explain the absence of free/conjugated HVA imbalance.

The authors observed that, by the patients, when they were stabilized under long-acting haloperidol therapy, the BPRS scores were improving regularly and slowly, without fluctuations ; the concentrations of the plasma HVA and RBC HAL were correlated during the 4 weeks between two injections, with peak values 7 days after the dose injection. But accidental fluctuations of the BPRS or/and of plasma HVA could be indicators of acute states or of relapses ; it seemed that the increase of HVA concentrations would precede the increase of the BPRS scores. These results lead the authors to suggest that evaluations of BPRS scores and determinations of plasma HVA, plasma and RBC HAL concentrations are not only good means of monitoring the prescribed drug, but also represent a predictive analysis of the patient's clinical evolution under long-acting haloperidol therapy. The limitations of this naturalistic study are evident, the data were gathered by only 11 patients, it was not easy, during long period, to follow up schizophrenic patients which were no more hospitalized and must come as regularly as possible at the out-patient consultation.

Conclusion

The authors chose to undertake a naturalistic study reflecting clinical practise; in light of the unusually long duration of this investigation (from 6 months to 2,5 years), it was not possible to impose a monotherapeutic regimen.

Not only was the dose administered reflected in the plasma concentration, it was even more significantly correlated with the RBC concentration (correlations found for both HAL and RHAL).

In addition, determination of the concentration of plasma HVA, a marker of central dopaminergic activity, further completes the profile of haloperidol's therapeutic activity.

Monitoring of all these compounds, as indicated by the clinical evaluation grades, would ensure better pharmacoclinical surveillance based on their predictive value.

Références

AHTEE, L. and PAASONEN, M.K. (1966) Distribution of some phenothiazines in red blood cells and platelets. J. Pharm. Pharmac. 18: 126-128

ALTAMURA, C.A., MAURI, M., CAVALLARO, R., COLACURCIO, F., GORNI, A. and BAREGGI, S. (1988) Reduced haloperidol/haloperidol ratio and clinical outcome in schizophrenia: Preliminary evidences. Prog. in Neuro-Psychopharmacol. & Biol. Psychiat., 12: 689-694.

ALTAMURA, C. A., COLACURCIO, F., MAURI, M., MORO, A. and DE NOVELLIS, F. (1990) Haloperidol decanoate in chronic schizophrenia: A study of 12 months with plasma levels. Prog. in Neuro-Psychopharmacol. & Biol. Psychiat., 14: 25-35.

AYMARD, N., LEYRIS, A., TOFFIS, V., VIALA, A., EPINETTE, C,. and DELTEIL, P. (1990) Haloperidol and reduced haloperidol concentrations in plasma from chronic schizophrenic patients. XI Congress of Pharmacology, Amsterdam. Eur. J. of Pharmacol., 183/6: 2301-2302.

AYMARD, N., MIQUET, S., CARBUCCIA, I,. and LEYRIS, A. (1992) Efficacité thérapeutique et concentrations plasmatiques de l'halopéridol et de l'acide homovanillique dans deux populations de schizophrènes. 8ème Colloque International de Biologie prospective Metz Sept 1992. Annales de Biologie Clinique, 6 465.

AYMARD, N., RENOUARD, C., LEYRIS A., and CARBUCCIA, I. (1993) Intérêt de la détermination des concentrations intra-érythrocytaires des antidépresseurs tricycliques, tétracycliques et de leurs dérivés déméthylés. Biologie Prospective. Compte-rendu du 8ème Colloque de Pont à Mousson. John Libbey Eurotext, Paris, 191-194.

BACOPOULOS, W. G., HATTOX, S. E., and ROTH, R. H. (1979) 3-4-dihydroxyphenylacetic acid and homovanillic acid in rat plasma: possible indicators of central dopaminergic activity. Eur. J. Pharmacol., 56: 225-236.

BOWERS, M. B., SWIGAR, M. E., JALTOW, P. I., and HOFFMAN, F. J. (1989)Plasma catecholamine metabolites and treatment response at neuroleptic steady state. Biol. Psychiatry 25: 734-738.

CHANG, W. H., LIN, S. K., JANN, M. W., LAM, V. W. F., CHEN, T. Y, CHEN, T. C., HU, W. H., and YEH, E. K.(1989) Pharmacodynamics and pharmacokinetics of haloperidol and reduced haloperidol in schizophrenic patients. Biol. Psychiatry 26: 239-249.

CHANG, W. H., CHEN, T. Y., LIN, S. K., LUNG, F. W., LIN, W. L., HU, W. H., and YEH, E. K. (1990) Plasma catecholamine metabolites in schizophrenics: evidence for the two subtype concept. Biol. Psychiatry, 27: 510-518.

CHANG, W. H., LIN, S. K., JUANG, D. J., CHEN, L. C., YANG, C. H., HU, W. H., CHIEN, C. P., LAM, F., and JANN, M. W. (1993a) Prolonged haloperidol and reduced haloperidol plasma concentrations after decanoate withdrawal. Schizophrenia Research, 9: 35-40.

CHANG, W. H., LIN, S. K., JUANG, D. J., CHEN, L. C., YANG, C. H., LANE, H. Y., and JANN, M. W. (1993b) Effects of haloperidol decanoate on plasma homovanillic acid in chronic schizophrenic patients. Biol. Psychiatry, 33 557-559.

CHANG, W. H., HWU, H. G., CHEN, T. Y., LIN, S. K., LUNG, F. W., CHEN, H., LIN, W. L., HU, W. H., LIN, H. N., and CHIEN, C. P (1993c) Plasma homovanillic acid and treatment response in a large group of schizophrenic patients. Schizophrenia Research, 10: 259-265.

DAVIDSON, M., LOSONCZY, M. F., MOHS, R. C., LESSER, J. C., POVCHICK, P., FREED, L. B., DAVIS, B. M., MYKYTYN, Y. V., and DAVIS, K. L. (1987) Effects of debrisoquin and haloperidol on plasma homovanillic acid concentration in schizophrenic patients. Neuropsychopharmacol., 1: 17-23.

DAVIDSON, M., and DAVIS, K. L. (1988) A comparison of plasma homovanillic acid concentrations in schizophrenic patients and normal controls. Arch. Gen. Psychiatry, 45: 561-563.

DAVILA, R., MANERO, E., ZUMARRAGA, M., ANDIA, I., SCHWEITZER, J. W., and FRIEDHOFF, A. J. (1988) Plasma homovanillic acid as a predictor of response to neuroleptics. Arch. Gen. Psychiatry, 45: 564-567.

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

DENIKER, P. (1987) Psychopharmacologie. Les médicaments et drogues psychotropes. Ellipses. Paris.

ERESHEFSKY, L., DAVIS, C. M., HARRINGTON, C. A., JANN, M. W., BROWNING, J. L. SAKLAD, S. R., and BURCH, N. R. (1984) Haloperidol and reduced haloperidol plasma levels in selected schizophrenic patients. J. Clin. Psychopharmacol., 4: 138-142.

ERESHEFSKY, L., SAKLAD, R. St., TRAN-JOHNSON, T., TONEY, G., LYMAN, R., and DAVIS, M. C.(1990) Kinetics and clinical evaluation of haloperidol decanoate loading dose regimen. Psychopharmacol. Bulletin, 26: 108-114.

FORSMAN, A. and OHMAN, R. (1977a) Applied pharmacokinetics of haloperidol in man. Curr. Therapeut. Res., 21: 396-411.

FORSMAN, A., FÖLSCH, G., LARSSON, M., and OHMAN, R. (1977b) On the metabolism of haloperidol in man. Curr. Therapeut. Res. 21: 606-617.

FORSMAN, A. and LARSSON, M. (1978) Metabolism of haloperidol. Curr. Therapeut. Res., 24: 567-569.

FREEMAN, A.R. and SPIRSTES, M.A. (1963). Effects of chlorpromazine on biological membranes : (chlorpromazine induced changes in human erythrocytes). Biochem. Pharmacol. 12: 47-53

FURET, Y., BRETEAU, M., and ETIENNE, T. (1991) Etude des taux résiduels de neuroleptiques à action prolongée. Thérapie, 46: 119-123.

GALINOWSKY, A., AYMARD, N., POIRIER, M. F., LEYRIS, A., BEAUVERIE, P., and LOO, H. (1990) Evolution of plasma homovanillic acid in chronic schizophrenic patients treated with haloperidol. XIth International Congress of Pharmacology Amsterdam. Eur. J. Pharmacol., 183/2: 589-590.

GALINOWSKI A., AYMARD N., POIRIER M. F., LEYRIS A. and LOO H. (1992) Plasma HVA levels in drug free schizophrenic patients. 18 th Coll. Internation. Neuro Psychopharmacol. Congress, Nice - Clinical Neuropharmacology, Raven Press, 1992 - Vol 15, Supplément 1-B-251

GARCIA, A., GALINOWSKY, A., GUICHENEY, P., MIGNOT, E., LOO, H., and MEYER, P. (1989) Free and conjugated plasma homovanillic acid in schizophrenic patients. Biol. Psychiatry, 26: 87-96.

GARVER, D.L., DEKIRMENJIAN, H., DAIRS, J.M., CASPER, R. and ERIKSEN, St. (1977). Neuroleptic drug levels and therapeutic response : preliminary observations with red cell bound butaperazine. Am. J. Psychiatry 134, 3: 304-307

GELDERS, Y. G., REYNTJENS, A. J. M., ASH, C. W., and AERTS, T. J. L. (1982) 12 month study of haloperidol decanoate in chronic schizophrenic patients. Int. Pharmacopsychiatry, 17: 247-254.

JANN, M. W., CHANG, W.H., LAM, Y.W.F., HWU, H.G., LIN, H.N., CHEN, H., CHEN, T.Y., LIN, S.K., CHIEN, C.P., DAVIS, C.M., ERESHEFSKY, K., SAKLAD, S.R., RICHARDS, A.L. and SCHULTEIS W.M. (1992) Comparison of haloperidol and reduced haloperidol plasma levels in four different ethnic populations. Prog. Neuro-Psychopharmacol. & Biol. Psychiat. 16: 193-202.

JATLOW, P. I., MILLER, R., and SWRIGAR, M. (1982) Measurement of haloperidol in human plasma using reversed-phase-high-performance liquid chromatography. J. Chromatogr., 227: 233-238.

KO, G. N., KORPI, E. R., and KIRCH, D. G. (1989) Haloperidol and reduced haloperidol concentrations in plasma and red blood cells from schizophrenic patients. J. Clin. Psychopharmacol., 9: 186-190.

KORPI, E. R., KLEINMAN, J. E., COSTAKOS, D. T., LINNOILA, M., and WYATT, R.J. (1984) Reduced haloperidol in the post mortem brains of haloperidol treated patients. Psychiatry Res., 11: 259-269.

KORPI, E. R., COSTAKOS, D. T., and WYATT, R. J. (1985) Interconversions of haloperidol and reduced haloperidol in guinea pig and rat liver microsomes. Biochemical Pharmacol., 34: 2923-2927.

LEVRON, J. C.,and ROPERT, R. (1987) Pharmacocinétique clinique du décanoate d'halopéridol. L'Encéphale, XIII: 83-87.

McKANE, J. P., ROBINSON, A. D. T., WILES, D. H., McCREADIE, R. G., and STIRLING, G. S. (1987) Haloperidol decanoate versus fluphenazine decanoate as maintenance therapy in chronic schizophrenic in-patients. Br. J. Psychiat., 151: 333-336.

MIQUET, S. (1991) Suivi thérapeutique de patients schizophrènes traités par halopéridol. Thèse Université René-Descartes Paris V.

NEBORSKY, R., JANOWSKY, S., PEREL, J., and MUNSON, E. (1982) Haloperidol plasma/red blood cell ratios and clinical efficacy. Psycho-pharm. Bulletin, 18: 17-20.

SCHULZ, P., REY, M. J., DICK, P., and TISSOT, R. (1989) Guidelines for the dosage of neuroleptics. II. Changing from daily oral to long- acting injectable neuroleptics. Internat. Clin. Psychopharmacology, 4: 105-114.

VASAVAN-NAIR, N. P., SURANYL-CADOTTE, B., SCWHARTZ, G., THAVUNDAYIL, J. X., ACHIM, A., LIZONDO E, and , NAYAK, R. (1986) A clinical trial comparing intramuscular haloperidol decanoate and oral haloperidol in chronic schizophrenic patients: efficacy, safety and dosage equivalence. J. Clin. Psychopharmacol., 6: n°1 suppl, 30-37.

VATASSERY, G. T., HERZAN, L. A., and DYSKEN, M. W. (1990) Liquid chromatographic determination of reduced haloperidol and haloperidol concentrations in packed red blood cells from humans. J. Anal. Toxicol., 14:
25-27.

Inquiries and reprint requests should be addressed to :

Dr François CAROLI
Unité Médico-psychologique du XIVè arrondissement ouest
Centre Hospitalier Sainte Anne - 1, rue Cabanis 75674 PARIS Cédex 14
FRANCE
Tel : 45 65 83 09 Fax : 45 65 87 40