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HALOPERIDOL AND REDUCED HALOPERIDOL PLASMA CONCENTRATIONS AFTER A LOADING DOSE REGIMEN WITH HALOPERIDOL DECANOATE

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Abstract

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1. Haloperidol and reduced haloperidol plasma levels were measured in schizophrenic patients who received both oral (10 mg, N=16 and 20 mg, N=4)and depot haloperidol treatment.
2. Patients were of Asian ethnicity and were safely and effectively converted from oral to depot therapy using a loading dose regimen using a 100 mg weekly injection interval for 4 weeks, biweekly for one month and then monthly.
3. Significant correlations were found for plasma haloperidol and reduced haloperidol levels and reduced haloperidol/haloperidol ratios between oral and depot therapy in these non-smoking patients.
4. A loading dose regimen is needed due to the long elimination half-life of decanoate of 26 days otherwise steady-state condition will not occur until 3-4 months of therapy.
5. Patients were maintained on monthly depot treatment for 40 weeks after the loading dose regimen and only one patient relapsed during treatment despite dosage increases.
6. The formation of reduced haloperidol remained consistent for oral and depot haloperidol treatment.

Keywords: haloperidol, halopderidol decanoate, plasma concentrations, reduced haloperidol, reduced haloperidol/haloperidol ratios.

Introduction

Haloperidol, a butyrophenone, is one of the most widely prescribed agent used to treat a variety psychiatric disorders. Haloperidol can be administered to patients intravenously, intramuscularly and orally for acute psychotic episodes (Froemming et al, 1989). A depot preparation of haloperidol has been developed to treat chronic schizophrenic patients who are noncompliant with oral medications and require prolonged antipsychotic therapy (Johnson 1984, Beresford and Ward 1987). Haloperidol decanoate was shown to be clinically effective in the maintainence of schizophrenic patients (Chouinard et al 1984, Vasavan et al 1986). The transition from oral to depot haloperidol therapy was originally based upon multiplying the total daily oral dose by a factor of 20 and the depot injection administered on a monthly basis (Deberdt et al 1980). A bioavailability study compared the depot to the oral formulation in schizophrenic patients (Nayak et al 1987). When the data was normalized by a factor of 21.4, no significant differences in pharmacokinetic parameters were found between the oral and depot administration. Kane (1986) suggested that the initial monthly dose of haloperidol decanoate of 10-15 times the total oral haloperidol daily dose.

However, when patients are transitioned from oral to depot treatment, the achievement of steady-state conditions with depot therapy does not occur until 3-4 months later (Reyntijens et al 1982, Jann et al 1985). This prolonged time to reach steady-state is due to the pharmacokinetics of the depot agents and a function of the drug's slow absorption rate from the injection site. When this monthly dosage administration has been used in the clinical environment, several clinicians have reported that some patients experienced acute excerbations of psychotic symptoms during those initial months that required oral neuroleptic supplementation to control their behavior (Gelders et al 1982, Fernando et al 1984).

This problem led to the possibility of increased dosages or a loading dose method for haloperidol decanoate. An early method recommemded that a 200 mg loading dose be initially given followed by monthly injections of 100 mg (DeCuyper et al 1986). Plasma haloperidol concentrations were measured after the first injection with a peak level noted at day 7 post-administration. Subsequent monthly injections and plasma concentrations remained stable. The clinical status of two-thirds of the patients were reported to be either unchanged or improved. Two retrospective studies were reported with haloperidol decanoate that recommended a loading dose of 20 times the total oral daily dose given every 3-7 days (Ereshefsky et al 1990, Ereshefsky et al 1993). Patients were reported to tolerate the transition without excerbation of acute psychotic symptoms. Initial plasma haloperidol concentrations from the decanoate injections were reported to be lower than the oral administration, however, by the third week comparable plasma level were observed between the two administration routes.

The metabolism of haloperidol consists of several different pathways that includes reduction to form a reduced metabolite - reduced haloperidol (Froemming et al 1989). Although inactive, reduced haloperidol has been suggested to potentially influence the clinical response to haloperidol in psychiatric patients (Chang 1993a). Reduced haloperidol has been also shown to be converted back to haloperidol in guinea pigs and man (Chang et al 1991, Jann et al 1990).

The formation of reduced haloperidol in schizophrenics from a single dose of haloperidol decanoate injection was reported to occur rapidly and peak in the first week (Chang et al, 1995). Previous studies examining a loading dose method for haloperidol decanoate did not measure reduced haloperidol plasma concentrations.

The purpose of this study is to prospectively examine plasma concentrations of haloperidol and reduced haloperidol in schizophrenic patients upon conversion from oral administration to decanoate therapy utilizing a loading dose regimen with haloperidol decanoate.

Methods

Subjects

Twenty-one schizophrenic patients diagnosed according to DSM-III-R criteria (12 males and 9 females) participated in this study. Patients were hospitalized at the Hung-Chi Psychiatric Hospital throughout the study. The facility's Institutional Review Board approved this study and informed consent was obtained from each patient. The population's demographics included age (mean 39.3 ± 6.3 years), and weight (mean 58.3 ± 11.4 kg). Each patient had a physical examination, complete medical history and biochemical and hematological tests(SMA-12, complete blood count, and urinalysis) prior to the study's initiation. All the results for each patient were unremarkable. Patients were non-smokers and not taking any known enzyme inducers or inhibitors known to influence plasma haloperidol concentrations (Froemming et al, 1989).

Drug Administration

Each patient remained on a stable oral haloperidol dose either 10 mg or 20 mg per day for a minimum of six weeks to ensure steady-state conditions. Patients were discontinued from their oral medication and decanoate administration was immediately initiated. No overlapping oral supplemental haloperidol was ordered. Oral or intramuscular lorazepam 2 mg was ordered as needed for agitation. Trihexyphenidyl 4 mg per day was used prophylactically during the oral and decanoate treatments and shown previously reported not to influence plasma haloperidol and reduced haloperidol concentrations.

A loading dose of haloperidol 100 mg was selected based upon our previous work examining the disposition of haloperidol decanoate (Chang et al,1995). The decanoate administration schedule was weekly for the first four weeks, then the injection interval was increased to every two weeks for the second month and only every four weeks afterwards. There were no changes in the decanoate dosage.

Assessments

Venous blood samples (10 ml) were collected during oral haloperidol therapy during the last three weeks prior to the decanoate injections. Samples were obtained 10-12 hours after the evening dose and prior to the morning dose. Blood samples collected during the decanoate treatment were prior to the next injection. Blood samples were obtained at weeks 2,3,4,6,8,12,16,20 and every 4 weeks to week 52 during decanoate administration. All blood samples were drawn into powdered edetic acid tubes and immediately centrifuged. The separated plasma was frozen at -20°C until assay. Plasma haloperidol and reduced haloperidol were assayed by high-performance liquid chromatography (HPLC) with electrochemical detection

(Chang et al, 1989). The intraassay and interassay coefficients of variation were 4.0 - 12% at 2-10 ng/ml. The lower limit of detection for haloperidol and reduced haloperidol was 0.4 ng/ml.

Patients were not formally assessed with any standardized ratings scales such as the Brief Psychiatric Rating Scales (BPRS), but monitored closely by the nursing and hospital staff for any changes in their clinical status or adverse side effects. Each patient was interviewed by the psychiatrists prior to the next decanoate injection and remained blinded to the results of the plasma haloperidol and reduced haloperidol concentrations. Reduced haloperidol/haloperidol ratios were calculated for each blood sample.

Data Analysis

Statistical analysis included the analysis of variance with repeated measures (ANOVA) to determine significany differences between oral and decanoate plasma haloperidol, reduced haloperidol concentrations and reduced haloperidol/haloperidol ratios. Pearson Product Correlation Coefficient was used to compare oral versus decanoate haloperidol and reduced haloperidol plasma concentrations and reduced haloperidol/haloperidol ratios. Statistical significance was defined as $p < 0.05$.

Results

Plasma Haloperidol and Reduced Haloperidol Concentrations

The haloperidol and reduced haloperidol plasma concentrations from oral and decanoate therapy are presented in Table 1. Plasma haloperidol and reduced haloperidol concentrations in the 20 mg oral dose group were approximately twice the amount of the 10 mg oral dose group. Upon initiating decanoate treatment, plasma haloperidol concentrations decreased. With subsequent weekly decanoate injections, plasma haloperidol levels slowly increased to their maximum concentrations at weeks 4 or 6. Visual inspection of the data revealed that plasma haloperidol and reduced haloperidol concentrations did not greatly differ between the two oral dose groups during decanoate administration.

Due to the small number of subjects (N=4) in the 20 mg dose group, statistical analysis was conducted only in the 10 mg oral dose group. For the 10 mg oral dose group, no significant differences were found in plasma haloperiol levels during the oral treatment phase (d.f.= 15,32, $F = 0.464$, p = n.s.). A similiar finding occurred with the reduced halopridol plasma concentrations (d.f.= 15,32, $F = 0.324$, p = n.s.). Fig. 1 displays the plasma level time course of haloperidol and reduced haloperidol plasma concentrations during oral and decanoate treatment for patients in the 10 mg oral dose group. Plasma haloperidol levels significantly dropped during the conversion from oral to decanoate treatment (d.f.= 15,56, $F = 4.112$, $p < 0.05$). However, with weekly injections for the first four weeks, plasma haloperidol levels increased to concentrations similiar to that of the oral treatment phase. Although plasma haloperidol concentrations were lower at week 3 during decanoate therapy versus the oral concentrations, this finding was not significant (d.f.= 15,32, $F = 0.769$, p = n.s.). Comparing weeks 4 and 6 during decanoate administrations to oral treatment, no significant differences in plasma haloperidol concentrations were found (d.f.= 15, 56, $F = 0.173$, p = n.s.; d.f.= 15,56, $F = 0.063$, p = n.s., respectively). Plasma haloperidol concentrations decreased from week 6

Table 1

Summary (mean ± SEM) of Haloperidol and Reduced Haloperidol Plasma Concentrations (ng/ml) in Schizophrenic Patients.

Oral Dose Group	Time (weeks)																		
	Oral			Decanoate															
	4	5	6(1)	2	3	4	6	8	12	16	20	24	28	32	36	40	44	48	52
10 mg HL (N=17)	8.06	7.54	7.91	3.59	5.52	7.56	7.70	6.52	3.95	3.65	2.45	2.51	2.46	2.47	2.99	2.53	2.88	2.45	2.94
±	1.04	0.96	1.16	0.93	1.22	1.21	1.62	1.07	0.80	0.76	0.26	0.22	0.28	0.22	0.34	0.28	0.32	0.20	0.33
RH	3.39	3.23	3.22	1.89	3.02	3.03	3.70	3.09	2.27	2.30	0.65	0.63	0.65	0.68	0.63	0.67	0.76	0.60	0.64
±	0.96	0.72	0.79	0.90	1.48	1.45	1.81	1.52	1.47	1.52	0.09	0.09	0.09	0.10	0.09	0.13	0.17	0.11	0.12
RH/HL	0.38	0.38	0.37	0.41	0.38	0.29	0.35	0.35	0.33	0.34	0.26	0.26	0.26	0.27	0.23	0.29	0.25	0.23	0.21
±	0.05	0.04	0.05	0.06	0.07	0.06	0.07	0.07	0.08	0.09	0.03	0.03	0.03	0.03	0.03	0.05	0.04	0.04	0.03
20 mg HL (N=4)	17.43	14.53	15.07	3.37	3.86	5.86	6.63	5.58	3.72	3.37	2.59	2.59	2.44	2.31	2.51	2.06	2.56	2.77	3.17
±	1.48	2.32	3.21	0.72	0.61	1.02	0.53	0.81	0.78	0.35	0.17	0.14	0.24	0.12	0.16	0.12	0.56	0.37	0.43
RH	7.75	7.66	7.18	1.37	1.18	1.22	1.68	1.53	0.93	0.77	0.62	0.58	0.62	0.56	0.51	0.27	0.46	0.54	0.56
±	2.65	2.34	2.54	0.39	0.33	0.29	0.22	0.45	0.29	0.17	0.17	0.13	0.11	0.14	0.19	0.03	0.05	0.14	0.11
RH/HL	0.43	0.50	0.44	0.38	0.28	0.20	0.25	0.25	0.20	0.22	0.23	0.22	0.27	0.23	0.19	0.13	0.21	0.22	0.19
±	0.14	0.12	0.10	0.09	0.07	0.04	0.03	0.06	0.05	0.05	0.06	0.05	0.07	0.06	0.07	0.02	0.06	0.08	0.05

HL = Haloperidol, RH = Reduced Haloperidol, RH/HL = Reduced Haloperidol/Haloperidol ratio

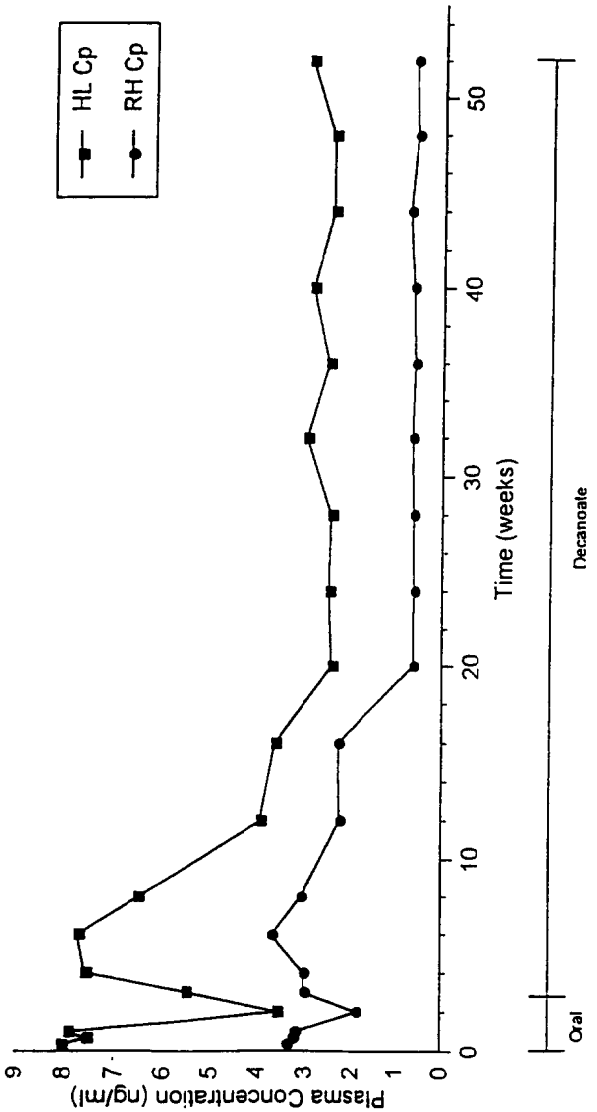

Fig 1. Mean Plasma Levels of Haloperidol and Reduced Haloperidol in Schizophrenic Patients that Received Oral and Decanoate Treatment.

but remained stable after week 20 through week 52. The decreased plasma haloperidol levels are due to the increase in the injection intervals from every two weeks to every four weeks.

Plasma reduced haloperidol levels paralleled the plasma haloperidol levels also shown in Fig.1 with amounts decreasing as the injection intervals increased over time. No significant differences were found in reduced haloperidol concentrations during the oral phase (d.f.= 15,32, F = 2.104, p = 0.09). Although reduced haloperidol levels slightly dropped upon initiation of decanoate therapy at week 2, this finding was not significant (d.f.= 15, 32, F= 0.583, p = n.s.). Reduced haloperidol levels increased during the first four weeks of decanoate treatment. At weeks 3 and 4 during decanoate treatment, reduced haloperidol levels were not significantly different from oral therapy (d.f.= 15,56, F = 0.004, p = n.s.; d.f.= 15,56, F = 0.037, p = n.s.; respectively). After week 6, reduced haloperidol plasma levels continued to decrease but also remained stable from week 20 through week 52.

Ratios of Reduced Haloperidol/Haloperidol

Reduced haloperidol/haloperidol ratios remained consistent throughtout the study for both the oral and decanoate treatment periods (Table 1). Only at week 4 in the decanoate phase that the ratio was slightly lower. After week 20, reduced haloperidol/haloperidol ratios dropped but remained consistent to week 52. No significant differences were found between the oral and decanoate reduced haloperidol/haloperidol ratios at weeks 2,3,4, and 6 (analysis for week 6 only d.f.= 15,32, F = 0.030, p = n.s.).

Comparison Between Oral and Decanoate Haloperidol Plasma Levels

Table 2 shows the correlation coefficients comparing plasma haloperidol concentrations from oral therapy at week 6 versus decanoate treatment at weeks 2 to 8. A strong trend in significance was found at week 4 and significance was determined at weeks 6 and 8. Fig. 2 shows that correlation between plasma haloperidol levels comparing oral therapy at week 6 to decanoate administration at week 4. With the exception of only six patients, most of the plasma haloperidol levels were within the 90% confidence interval.

Clinical Status of the Patients

Only one patient relapsed during the study (patient #16) at week 40. The patient's plasma haloperidol level was 2.41 ng/ml. The decanoate dose was increased to 200 mg per month without any further problems. Due to the prophylactic use of trihexiphenidyl, extrapyramidal side effects were not observed or reported during the study. Lorazepam was also not used during the study.

Discussion

Transition from Oral to Decanoate Administration

These results suggests that schizophrenic patients can transition safely from oral haloperidol therapy to depot treatment without any diminished clinical efficacy using this loading dose strategy. Plasma haloperidol and reduced haloperidol concentrations shown in Table 1 remained stable during oral treatment indicating steady-state conditions prior to decanoate administration. Upon discontinuation of oral therapy and immediately initiating decanoate

Table 2.

Correlation Coefficients of Haloperidol Plasma Concentrations Between Oral Treatment at Week 6 and Decanoate Administration at Weeks 2,3,4,6,and 8 for the 10 mg Oral Dose Group.

Time Period (weeks)	r	r^2	F	p
2	0.428	0.184	3.147	0.097
3	0.321	0.103	1.612	0.224
4	0.453	0.206	3.883	0.067
6	0.605	0.366	7.509	0.017
8	0.536	0.288	6.054	0.026

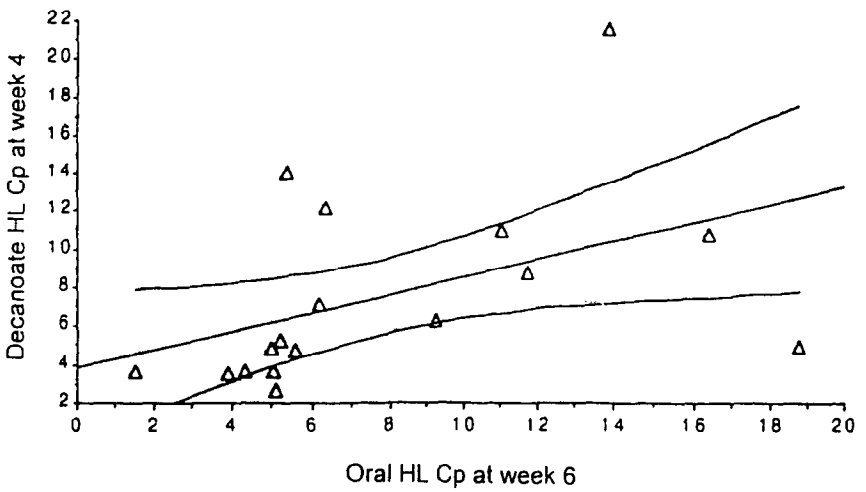

Fig 2. Correlation (with 90% Confidence Intervals) of Plasma Haloperidol Levels and Oral Treatment at Week 6 and Decanoate at Week 4. HL = Haloperidol; Cp = Plasma Concentration (ng/ml).

treatment, plasma haloperidol levels decreased during the first three weeks of depot therapy. In the 10 mg oral dose group, plasma haloperidol concentrations were comparable to oral treatment at the fourth week of decanoate therapy.

Haloperidol Decanoate Kinetics

The increasing plasma haloperidol concentrations during the first four weeks of decanoate treatment indicates the accumulation of drug with subsequent injections. This accumulation phase has been previously described as the "flip-flop" pharmacokinetics of the decanoate agents where the time to reach steady-state conditions are dependent upon the slow release or absorption rate of the drug from the injection site and not upon the elimination rate (Jann et al 1985). It remains unknown whether or not plasma haloperidol levels would continue to increase with subsequent weekly decanoate injections.

From week 4 to week 8, plasma haloperidol levels remained consistent as the injection interval increased from weekly to every two weeks. The plasma haloperidol levels decreased at week 12 and continued to drop until week 20. After week 20, plasma haloperidol concentrations remained stable. The injection interval was lengthened from every 2 weeks to every 4 weeks at week 8 and remained unchanged through week 52. The decrease in plasma haloperidol concentrations noted at week 6 is reflected by the increased injection interval from the preceeding two weeks. The delay in observing the decrease in plasma haloperidol concentrations could be due to the continued release of drug from the injection site. This occurrence is observed again when the injection interval was increased at week 8, however, plasma haloperidol levels did not stabilize until week 20. This 12 week difference can be explained by the pharmacokinetic properties of depot neuroleptics (Jann et al 1985). The elimination half-life of haloperidol decanoate was reported to be approximately 21 days (Reyntjens et al 1982, Beresford and Ward 1987). For drugs that are constantly infused like the depot agents, multiplying the elimination half-life by a factor of four (Gibaldi 1991) provides the estimated time within 90% to steady-state conditions. With haloperidol decanoate, this would be approximately 84 days. This calculation closely resembles the observed data in Table 1 and Fig. 1.

Although only four patients received 20 mg per day of oral haloperidol, plasma concentrations were approximately twice the amounts observed with the 10 mg dose group. Upon conversion to depot therapy, using the identical 100 mg dose, plasma haloperidol concentrations resembled the 10 mg dose group shown in Table 1. The pattern of declining plasma haloperidol concentrations with increasing injection intervals also followed the 10 mg dose group.

Plasma haloperidol concentrations for both groups remained stable from week 20 to week 52 with a few exceptions where a slight increase occurred. These slight increased plasma concentrations could be due to several sources: the back conversion from reduced haloperidol to haloperidol; redistribution of haloperidol from the various body tissues; or enterohepatic recycling of haloperidol (Froemming et al 1989).

Reduced Haloperidol Plasma Concentrations

Reduced haloperidol plasma concentrations closely paralleled plasma haloperidol levels. This finding is expected since reduced haloperidol plasma levels are dependent upon its conversion from haloperidol (Froemming et al 1989). Reduced haloperidol plasma concentrations were observed to be rapidly formed from a single injection of intramuscular hydrochloride or decanoate preparations (Jann et al 1994, Chang et al 1995). The reduced haloperidol plasma levels in the 20 mg dose group was approximately twice the amount compared to the 10 mg dose group during only the oral treatment phase. From week 2 to week 8, plasma reduced haloperidol levels in the 20 mg dose group were lower than the 10 mg dose group. The reasons for this finding are not apparent and the small number of patients in this group does not permit any speculation.

Reduced Haloperidol/Haloperidol Ratios

Reduced haloperidol/haloperidol ratios shown in Table 1 remained consistent during oral haloperidol treatment. The reduced haloperidol/haloperidol ratios decreased during the decanoate loading dose treatment in the 10 mg oral dose group. When the injection interval was increased to every two weeks, the ratios stabilzed at week 6 to week 8 and remained unaltered until week 20. Again, after week 20 through week 52, the ratios remained stable. The decreased ratio during the loading dose phase can be explained by the accumulation of increasing haloperidol plasma concentrations and the relative stability of reduced haloperidol plasma levels. An exception should be noted for week 2 as reduced haloperidol plasma levels are at the lowest concentration upon decanoate initiation. The ratios dropped at week 20. Since patients had received decanoate on an every four week schedule from week 8, this delay can be explained by the pharmacokinetic properties of the depot agents. Like the plasma haloperidol levels mentioned earlier, mutliplying the 21 day elimination half-life of haloperidol decanoate times four results in a calculation of 84 days. This time period matches the stabilization of reduced haloperidol/haloperidol ratios after week 20. When the ratios are consistent for both the oral and decanoate (after week 20) time periods, this condition would tend to support the achievement of steady-state conditions. Stable ratios could also account for the attainment of equilibrium for the interconversion process between reduced haloperidol and haloperidol (Chang et al 1993b).

Correlation Between Oral and Decanoate Haloperidol Adminstration

The correlation coefficients comparing haloperidol plasma levels from oral treatment at week 6 to depot therapy are shown in Table 2. A strong trend was observed at week 4 with statistical significant seen afterwards. Figure 2 shows the actual data comapring the oral versus decanoate plasma haloperidol concentrations. The majority of the patient's had decanoate haloperidol plasma levels within the 90% confidence intervals. Three patients had higher than expected plasma haloperidol concentrations. This indicates that plasma haloperidol levels are higher in these patients when given by the decanoate route compared to oral administration. A possible explanation for this occurrence is an impaired drug absorption from the gastrointestinal tract

and intramuscular administration would be the preferred route of therapy in these patients. The lack of statistical significance for the initial decanoate injections at weeks 2 and 3 are due to the drug's continued accumulation in the body.

Haloperidol Decanoate Loading Dose Recommendations

Previous reports recommending a loading dose administration regimen of 3-7 days during the first month showed a mean total monthly dose of 410.0 ± 68.0 mg (Ereshefsky et al 1993). This method of a weekly 100 mg injection is a comparable technique. The second monthly dose of 200 mg in this method is lower than the 287.0 ± 50 mg. Administration of the 100 mg dose was chosen to its availability in this specific dosage formulation. A weekly administration schedule was selected based upon the absorption profile of plasma haloperidol levels with decanoate injection where peak plasma concentrations are achieved 7 days post injection (Meco et al 1983, Chang et al 1995). If the decanoate is given in a shorter time interval, this could result in the continued accumulation of drug without achievement of maximal peak plasma levels. From a practical issue, a weekly injection schedule would be easier to follow and minimize any potential errors.

The majority of the patients in this study received oral haloperidol 10 mg per day and only a few patients treated with 20 mg per day. Application of this loading dose method should be interpreted cautiously for other patients who are treated with different doses. Interestingly, with this technique, plasma haloperidol levels of 6-7 ng/ml are reached from the 100 mg dose at weeks 3-4. The suggested therapeutic range for plasma haloperidol concentrations was 5-12 ng/ml (Van Putten 1992, Palao et al 1994). Therefore, therapeutic concentrations are rapidly achieved with this loading dose regimen. After week 20 of decanoate treatment, minimal plasma haloperidol concentrations of 2-3 ng/ml were observed. Only one patient relapsed during this study which occurred at week 40 and the plasma haloperidol level was measured at 2.41 ng/ml. The decanoate dose was increased to 200 mg per month without any further problems in this patient. An explanation for the maintainence of the other patients on minimal plasma haloperidol levels could be also related to the pharmacokinetic properties of the depot preparation. The minimal plasma haloperidol concentrations after week 20 reflect the trough sampling time period as the sample was obtained prior to the next injection. Previous studies have reported peak plasma haloperidol levels of 5-6 ng/ml one week after a monthly decanoate injection schedule (Chang et al 1993c). Therefore, minimal therapeutic plasma haloperidol levels are observed during a monthly administration schedule.

Unfortunately, a standardized clinical rating assessment was not used in this study. The lack of extrapyramidal side effects in these patients was probably due to the prophylactic use of trihexiphenidyl. Further research is needed with haloperidol decanoate and its conversion from oral to decanoate therapy using plasma haloperidol and reduced haloperidol plasma concentrations.

Conclusions

Schizophrenic patients can be safely and effectively transitioned from oral to depot haloperidol therap based upon depot pharmacokinetic principles. Utilization of plasma haloperidol and reduced haloperidol levels can assist the clinician in the therapeutic monitoring of depot treated patients. Patients can be maintained on minimal therapeutic plasma levels of haloperidol with decanoate treatment. The formation of reduced haloperidol appears to be consistent. Reduced haloperidol/haloperidol ratios can assist in the determination of steady-state conditions.

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References

BERESFORD, R. and WARD, A. (1987) Haloperidol decanoate. Drugs, 33, 31-49.

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

CHANG, W.H., LIN, S.K., and JANN, M.W. (1991) Interconversions between haloperidol and reduced haloperidol in schizophrenic patients and guinea pigs: a steady-state study. J. Clin. Psychopharmacol., 11, 99-105.

CHANG, W.H. (1993a) Reduced haloperidol: A factor in determining the therapeutic benefit of haloperidol treatment? Psychopharmacol., 106, 289-296.

CHANG, W.H., LIN, S.K., JUANG, D.J., CHEN L.C., YANG, C.H., HU, W.H., CHIEN, C.P., LAM, Y.W.F., and JANN, M.W. (1993b) Reduced haloperidol/haloperidol ratios after oral haloperidol and decanoate administration in schizophrenics. Prog. Neuropsychopharmacol.Biol. Psychiat., 17, 105-112.

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

CHANG, W.H., JUANG, D.J., LIN, S.K., HUANG, J.D., LAM, Y.W.F., JANN, M.W., and CHIEN, C.P. (1995) Disposition of haloperidol and reduced haloperidol plasma levels after single dose haloperidol decanoate administration. Hum. Psychopharmacol. , 10: 47-51.

CHOUINARD, G., ANNABLE, L., CAMPBELL, W., BOISVERT, D., and BRADWEJN, J. (1984) A double-blind controlled clinical trial of haloperidol decanoate and fluphenazine decanoate in the maintenance treatment of schizophrenia. Psychopharmacol. Bull., 20, 108-109.

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

DECUYPER, H., BOLLEN, J., VANPRAAG, H.M., and VERSTRAETEN, D., (1986) Pharmacokinetics and therapeutic efficacy of haloperidol decanoate after loading dose adminstration. Br. J. Psychiat.,148, 560-566.

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

ERESHEFSKY, L., TONEY, G., SAKLAD, S.R., ANDERSON, C., and SEIDEL, D. (1993) A loading dose strategy for converting from oral to depost haloperidol. Hosp. Comm. Psychiat., 44, 1155-1161.

FERNANDO, J., KRISHNA, R.R., JONES, G.G., and STANLEY, R.O. (1984) The use of depot neuroleptic haloperidol decanoate. Acta Psychiatr. Scand. , 69:, 175-176.

FROEMMING, J.H., LAM, Y.W.F., JANN, M.W., and DAVIS, C.M. (1989) Pharmacokinetics of haloperidol. Clin. Pharmacokinet., 17, 396-421.

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

GIBALDI, M. (1991) Clearance Concepts. In: Biopharmaceutics and Clinical Pharmacokinetics, p. 22, 4th ed., Lea and Febiger, Phildelphia.

JANN, M.W., ERESHEFSKY, L., and SAKLAD, S.R. (1985) Clinical pharmacokinetics of the depot antipsychotics. Clin. Pharmacokinet.,10, 315-333.

JANN, M.W., LAM, Y.W.F., and CHANG, W.H. (1990) Reversible metabolism of haloperidol and reduced haloperidol in Chinese schizophrenic patients. Psychopharmacol., 101, 107-111.

JANN M.W., HUANG, H.F., LIN, S.K., JUANG, D.J., LAM, Y.W.F, and CHANG, W.H. (1994) Formation of reduced haloperidol after intramuscular haloperidol administration in schizophrenic patients. Drug Invest., 7, 13-20.

JOHNSON DAW (1984) Observations on the use of long-acting depot neuroleptic injections in the maintenance therapy of schizophrenia. J. Clin. Psychiat., 45, 13-21.

KANE JM (1986) Dosage strategies with long-acting injectable neuroleptics, including haloperidol decanoate. J. Clin. Psychopharmacol., 6, 20S-23S.

MECO, G., CASACCHIA, M., ATTENNI, M., IAFRATE, A., CASTELLANA, F., and ECARI, U. (1983) Haloperidol decanoate in schizophreniform disorders. Acta Psychiat. Belg, 83, 57-68.

NAYAK, R.K., DOOSE, D.R., and NAIR N.P.V. (1987) The bioavailability and pharmacokinetics of oral and depot intramuscular haloperidol in schlophrenic patients. J. Clin. Pharmacol. 27, 144-150.

PALAO, D.J., ARAUXO, A., BRUNET, M., BERNANDO, M., HARO, J.M., FERRIER, J., GONZALEZ-MONCLUS, E. (1994) Haloperidol: therapeutic window in schizophrenia. J. Clin. Psychopharmacol., 14, 303-310.

REYNTJENS, A.J.M., HEYKENATS, J.J.P., WOESTENBORGHS, R.J.H., GELDERS, Y.G., and AERTS, T.J.L. (1982) Pharmacokinetics of haloperidol decanoate. Inter. Pharmacopsychiat.,17, 238-246.

VAN PUTTEN, T., MARDER, S.R., MINTZ, J., and POLAND, R.E. (1992) Haloperidol plasma levels and clinical response: a therapeutic window relationship. Am. J. Psychiat., 149, 500-505.

VASAVAN NAIR, N.P., SURANYI-CADOTTE, B., SCHWARTZ, 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, dosage equivalence. J. Clin. Psychopharmacol., 6, 30S-37S.

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