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REDUCED HALOPERIDOL/HALOPERIDOL RATIOS AFTER ORAL HALOPERIDOL AND DECANOATE ADMINISTRATION IN SCHIZOPHRENICS

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Abstract

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1. Haloperidol and reduced haloperidol plasma concentrations were measured in thirteen stable schizophrenic patients that received both oral haloperidol and haloperidol decanoate.
2. Significant correlations between reduced haloperidol/haloperidol ratios from oral haloperidol and haloperidol decanoate occurred at week two and week 16, respectively.
3. The formation of RH was consistent during haloperidol decanoate treatment.

Keywords: haloperidol, plasma concentrations, reduced haloperidol, RH/HL ratios.

Abbreviations: haloperidol (HL), haloperidol decanoate (HLD), reduced halopridol (RH), plasma concentrations (Cps)

Introduction

Haloperidol (HL) is a widely used antipsychotic agent used in the treatment of various psychiatric disorders. HL can be administered to patients via different routes that include intravenous, intramuscular and oral dosage formulations. As with other antipsychotic agents, HL is also available in a long-action injectable decanoate formulation (HLD). HLD is synthesized by the reaction of HL and decanoyl chloride and then dissolved in sesame oil (Reyntijens et al 1982). Typically, HL is

administered orally to patients and based upon its elimination half-life that ranges between 14.1 hours to 24.1 hours, the time to reach its steady-state plasma concentrations would be approximately 5-6 days (Froemming et al 1989). The time to achieve steady-state plasma concentrations for HL has been reported to be 3-4 months when HLD was administered on a monthly basis (Reyntijens et al 1982, Jann et al 1985).

HL metabolism involves several different pathways that includes reduction to form a reduced metabolite - reduced haloperidol (RH) (Inaba and Kovacs 1989). Although RH was reported to be an inactive metabolite (Kirch et al 1985), RH has been demonstrated to be converted back to HL in schizophrenic patients (Jann et al 1990, Tyndale et al 1991). The role of RH in determining clinical response to HL therapy remains to be elucidated (Froemming et al 1989). RH plasma concentrations (Cps) have not been investigated in HLD treated patients. This study will examine HL and RH Cps from HLD and oral HL treatment in schizophrenic patients.

Methods

Subjects

Thirteen chronic stable schizophrenic patients (9 males and 4 females) diagnosed according to DSM-III criteria participated in the study. Their mean age and weight were 37.2 years $\pm$ 8.8 and 81.3 kg $\pm$ 10.0, respectively. Patients were treated at the Chingyang Psychiatric Hospital (mean 9.0 years $\pm$ 7.0). Each patient was free of depot neuroleptics for at least six months and oral neuroleptics for four weeks prior to study entrance. Informed consent was obtained from each patient for participation in the study. Clinical assessments such as the Brief Psychiatric Rating Scale were not performed.

Drugs

All patients received HL orally and HLD (Janssen Pharmaceuticals, Beerse, Belgium). Only trihexyphenidyl 4 mg/day and nitrazepam 5 mg at bedtime were allowed during the study.

Study Design

HLD 100 mg was administered every four weeks over five months to all patients. Blood samples for HL and RH were obtained every four weeks from HLD administration prior to the next decanoate injection. After a three month washout period, each patient was placed on oral HL 5 mg BID (9am and 9pm). Samples from oral HL at steady-state conditions were obtained weekly at weeks 1 and 2. HL and RH Cps were assayed by high-performance liquid chromatography with electrochemical detection (Chang et al 1989). The lower limit of sensitivity was 0.2 ng.ml with intra and interassay coefficients of variation of less than 10% at HL and RH Cp 2-10 ng/ml.

Data Analysis

The Pearson's regression analysis and paired Student's t-test were used to compare HL and RH Cps and RH/HL ratios from oral HL and HLD therapy.

Results

The HL and RH Cps from decanoate and oral HL therapy are shown in Table 1. HL and RH Cps after oral HL were higher than after HLD. HL Cps from HLD appeared to plateau after the third injection. HL and RH steady-state Cps for both oral HL and HLD were attained by week 2 and 12, respectively. In comparison to oral HL treatment at week 2 to HLD week 16, HL Cps were three times higher ($t= 4.05$, $d.f. = 12$, $p<0.0005$). RH Cps were also lower in HLD but maintained stable concentrations after the first injection. RH/HL ratios observed after oral HL were generally lower than RH/HL ratios after HLD except for week 16.

Table 2 shows the correlation coefficients in comparison between the decanoate weeks 4 to 20 to oral therapy at week 2. The optimal correlation was determined to be at week 16. However, one patient had a RH/HL ratio of 0.05 at week 16 while the remainder of the RH/HL ratios ranged between 0.25 - 0.33 (mean 0.27 ± 0.03). When the mean value of 0.27 was substituted, the correlation values slightly improved to $r=0.686$, $r^2 = 0.470$, $F=9.764$, $p=0.0097$. Values in comparing HLD to oral HL at week 1 in Table 3 were not as consistent as week 2 with only one analysis showing statistical significance.

Table 1.

Summary of Haloperidol and Reduced Haloperidol Plasma Concentrations From Oral and Decanoate Administration (mean ± s.d.).

Time Periods	HL CP (ng/ml)	RH Cp (ng/ml)	RH/HL (ng/ml)
		Decanoate	
Week 4	1.2 ± 0.5	0.4 ± 0.2	0.41 ± 0.28
Week 8	1.6 ± 0.7	0.5 ± 0.2	0.33 ± 0.18
Week 12	2.2 ± 1.1	0.5 ± 0.2	0.31 ± 0.21
Week 16	2.5 ± 1.0	0.5 ± 0.3	0.21 ± 0.11
Week 20	2.3 ± 0.9	0.6 ± 0.4	0.30 ± 0.17
		Oral HL	
Week 1	5.8 ± 3.5	1.5 ± 1.0	0.27 ± 0.10
Week 2	7.5 ± 4.4	1.8 ± 1.3	0.25 ± 0.09

Table 2.

Correlation Coefficient Values Between Week 2 Oral HL and Decanoate RH/HL Ratios.

Injection time Weeks	r	r^2	F	p
4	0.543	0.295	4.596	0.0552
8	0.564	0.318	5.119	0.0449
12	0.361	0.130	1.645	0.2261
16*	0.600	0.360	6.194	0.0301
20	0.566	0.321	3.891	0.0694

*Adjusted values: $r = 0.686$, $r^2 = 0.470$, $F = 9.764$, $p = 0.0097$.

Table 3.

Correlation Coefficients Between Week One Oral HL and Decanoate RH/HL Ratios

Injection time (Weeks)	r	r^2	F	p
4	0.499	0.249	3.653	0.0824
8	0.492	0.242	3.506	0.0879
12	0.768	0.590	15.834	0.0022
16	0.482	0.232	3.320	0.0957
20	0.058	0.003	0.030	0.8663

Results

Only one patient relapsed during the three month time period after HLD discontinuation and prior to oral HL treatment. Data from that one

patient was excluded from the analysis. Only two patients required trihexyphenidyl during oral HL therapy.

Discussion

These results suggests that stable chronic schizophrenic patients treated with HLD can be maintained on minimal therapeutic HL plasma concentrations. The proposed therapeutic range for HL Cps is suggested to range between 2-30 ng/ml (Froemming et al 1989). Although HL Cps in HLD were significantly lower than oral Hl Cps (week 20 - 2.3 ng/ml v.s week 2 - 7.5 ng/ml), clinical relapse in our patients were not observed during treatment. Unfortunately, we did not systematically assess our patients with standardized rating scales during this study. The lower HL Cps attained with HLD compared to that with oral HL was also reported by other investigators (Nayak et al 1987). Further, the consistent HL Cps observed from our HLD treated patients has been previously reported by others (Reyntijens et al 1982, Nayak et al 1987).

The suggested conversion from oral HL treatment to HLD is recommended to range from 10-20 times the total HL oral daily dose to be administered every four weeks (Deberdt et al 1980, Kane 1986). Based upon our data utilizing HL Cps, our conversion factor for HLD with 10 times the total HL daily dose is within those previously suggested parameters.

Based upon HL pharmacokinetics, the time to reach steady-state HL Cp for oral HL has been reported to be achieved at one week of therapy and in HLD 3-4 months (Froemming et al 1989, Jann et al 1990). The formation of RH from HLD appears to occur at a constant rate despite increasing HL plasma concentrations. This is one of the first reports concerning RH Cps from HLD administration. The conversion from RH to HL cannot be

determined as administration of RH decanoate is required.

Due to the reduction/oxidation metabolic pathway of HL and RH, this pattern could also provide additional information when steady-state conditions are attained. At these low HL Cps, reversible metabolism RH and HL could still occur (Jann et al 1990). The most significant correlation between RH/HL ratios for oral HL and HLD occurred at week 2 and week 16, respectively ($r = 0.600$). However, when RH/HL ratios were adjusted for one patient, the correlation slightly improved. Although a significant correlation was found between oral HL at week one versus HLD week 12, the overall correlations versus the other weeks were not significant. After administration HLD, consistent HL Cp are observed after the third injection. Steady-state HL Cp from HLD are reached after the third injection at week 12 and our data is comparable to that of Reyntijens et al 1982. Data from Table 1 shows consistent RH/HL ratios for both oral HL and HLD would lend further support for achievement of steady-state conditions. Stable RH/HL ratios would also support the attainment of equilibrium in the interconversion process between RH and HL.

Conclusion

In conclusion, stable schizophrenic patients can be maintained on minimal therapeutic plasma concentrations of HL treated with HLD. RH/HL ratios can assist in the determination when steady-state conditions are reached when comparing oral HL and HLD. The formation of RH appear to be consistent during HLD treatment.

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