Effects of Haloperidol Decanoate on Plasma Homovanillic Acid in Chronic Schizophrenic Patients

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The effects of acute and chronic oral antipsychotic treatment on plasma homovanillic acid (pHVA) have been extensively studied over the past several years. However, the pHVA response to depot preparations remains unknown. This study reports an elevation in pHVA after haloperidol decanoate (HLD) administration in chronic schizophrenic patients.

Thirteen stable chronic schizophrenic patients diagnosed by DSM-III-R criteria participated in this study. Informed consent was obtained from each patient. The study consisted of nine men and four women with a mean age of 37.2 ± 6.9 years and weight of 61.3 ± 10.0 kg. These patients had been institutionalized at Chingyang Psychiatric Hospital for 9.0 ± 7.0 years and had been free of oral neuroleptics for at least 4 weeks and free of depot neuroleptics for at least 6 months prior to beginning the study. All subjects were placed on a low-monoamine diet and received noncaffeinated and nonalcoholic beverages for 4 weeks prior to and during the study.

Intramuscular injections of HLD (Haldol decanoas) 100 mg were given every 4 weeks. After five injections, HLD was discontinued. The only concurrent medications were trihexyphenidyl (4 mg/day) and nitrazepam (5 mg/day), which do not influence haloperidol (HL) plasma concentrations (Cps) (Froemming et al 1989) and has not been reported to change pHVA levels. Venous blood was sampled on days 0 (baseline), 2 and 4, and the end of weeks 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 19, 20, 21, 23, 25, 27, and 29. Blood samples were collected into ethylenediaminetetraacetic acid (ETDA) tubes, and plasma was separated by a centrifuge at 3,000 RPM for 15 min. All specimens were kept at −50° C until assayed. Cps of HVA and HL were determined with high performance liquid chromatography (HPLC) using electrochemical detection (Chang et al 1983, 1989b).

As shown in Figure 1, the initial level of pHVA prior to HLD injection was 6.1 ± 1.8 ng/ml. A gradual increase in pHVA levels was noticed after the first three injections. A repeated-measures analysis of variance (ANOVA) indicated a highly significant effect of 20 weeks HLD treatment on pHVA [$F(19,228) = 2.49$, $p < 0.001$]. The 6-week (2 weeks after the second injection; 8.4 ± 3.0 ng/ml, $t = 2.392$, $p = 0.034$) through 15-week (3 weeks after the fourth injection; 8.8 ng/ml, $t = 2.388$, $p = 0.034$) pHVA levels were significantly higher than the initial level before treatment ($p < 0.05$ or less). The peak value at the 11-week point (3 weeks after the third injection) was 9.7 ± 2.9 ng/ml (versus baseline value, $t = 3.393$, $p = 0.005$). Thereafter, the pHVA levels were gradually decreased and returned close to pretreatment level at the 19-week point (3 weeks after the fifth injection; 6.6 ± 2.0 ng/ml versus 6.1 ± 1.8 ng/ml, $t = 0.265$, NS). These results suggest that depot HL administration can produce an increase in pHVA and tolerance of pHVA response can develop after repeated injections. Furthermore, a recurrent elevation in pHVA levels was found at weeks 21–25, 5–9 weeks after HLD discontinuation. The peak value of 10.5 ± 4.0 ng/ml was noticed 7 weeks after the last injection (versus baseline value, $t = 3.521$, $p = 0.004$). The elevation in pHVA levels was in parallel with HL Cps after the first three injections. The increment of pHVA from the baseline level, however, was not correlated with the steady state HL Cps ($r = 0.1004$, NS). The pharmacokinetic parameters of HLD in these patients have been described in detail elsewhere (Chang et al 1993 a,b).

Based on clinical investigation, no improvement or exacerbation in psychiatric symptoms was found during 20 weeks of HLD treatment.

The pHVA response to oral HL administrations in schizophrenic patients has been extensively studied by a number of investigators. Both increased and decreased pHVA levels after neuroleptic treatment have been reported. Some of the studies have indicated that elevated pHVA response to neuroleptics is associated with a poorer clinical response (Chang et al 1990; Mazure et al 1991). Whereas the pHVA levels have been found

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to decrease during neuroleptic treatment among responders (Pickar et al 1984, 1986; Chang et al 1990; Davila et al 1988; Mazure et al 1991). Indeed, the present study demonstrates that the administration of HLD produced an increase in pHVA in a group of stable chronic schizophrenic patients who had been institutionalized at a sanitorium for years and did not respond to the previous and present neuroleptic treatments.

The elevation in pHVA in response to oral neuroleptics has been reported to appear within 2 weeks in psychiatric patients (Chang et al 1990; Davila et al 1988). The pHVA increment in the present study, however, was observed after 6 weeks HLD treatment. The delayed pHVA response might be explained by the fact that HL is slowly released from the depot formulation. The significantly higher pHVA levels were observed during a period of the following 9 weeks (from weeks 6–15). The tolerated pHVA response did not develop until week 12. These results suggest that the tolerance of pHVA to depot HL appears much later than that to oral HL (less than 2 weeks) (Chang et al 1990; Davila et al 1988). The properties of depot HL in these pharmacodynamic results, in combination with those in pharmacokinetic data (more stable Cps), might be one of the reasons why some patients respond better on decanoate than they do on oral treatment (Beresford and Ward 1987).

Some studies using rats have found that the brain HVA concentrations were reduced to below control value following withdrawal from chronic HL administration (Chang et al 1989a). In clinical studies, however, increased pHVA levels after withdrawal from long-term oral neuroleptic treatment in schizophrenic patients have been noticed (Pickar et al 1986; Davidson et al 1991). In consistent with these clinical findings, the increase in pHVA after the discontinuation of repeated HLD injections might be explained as a rebound to drug withdrawal. Another possibility is that the second pHVA peak in January–February is related to the seasonal factor, as elevated HVA in cerebrospinal fluid and postmortem brain in the winter has been reported by some investigators (Losonczy et al 1984; Karson et al 1984).

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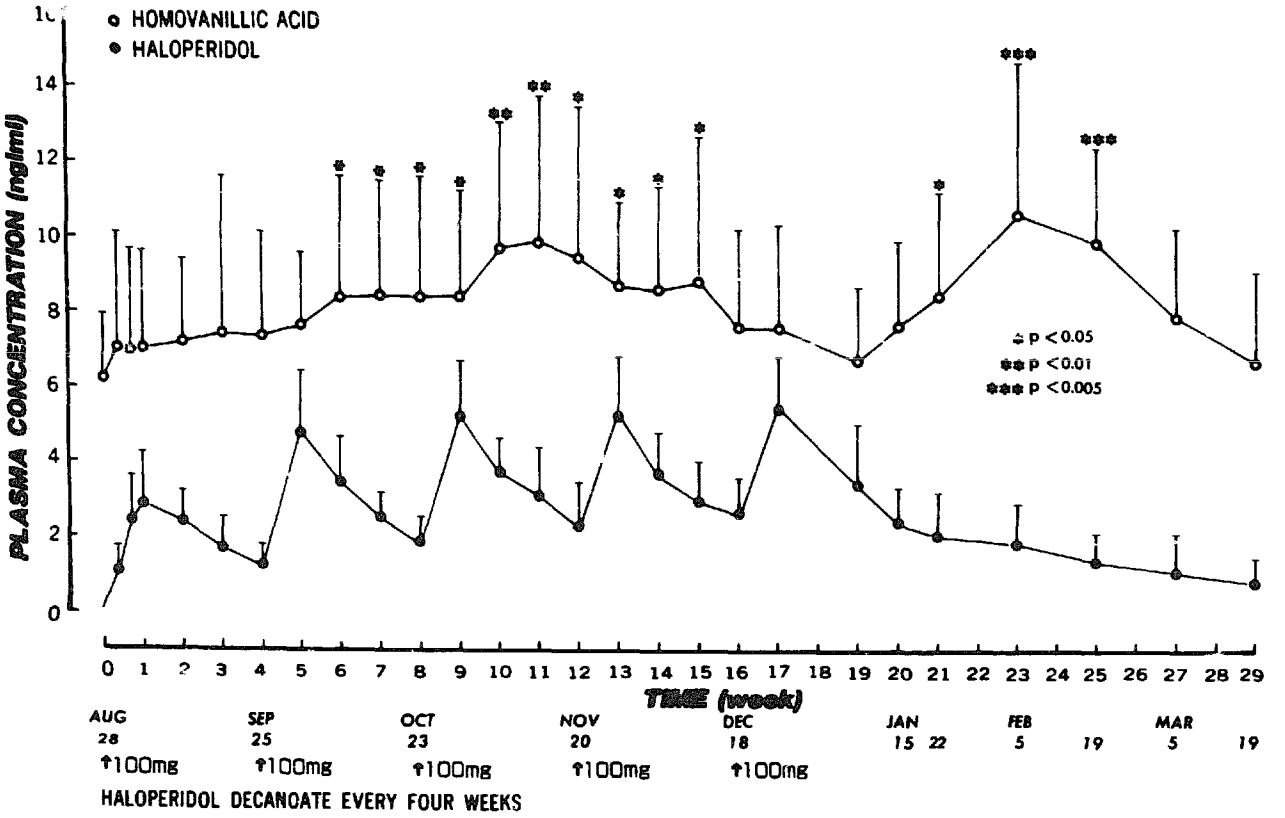

Figure 1. Plasma homovanillic acid and haloperidol concentrations prior to, during, and after withdrawal from haloperidol decanoate 100 mg/4 weeks in 15 chronic schizophrenic patients.

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