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ORIGINAL INVESTIGATION

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Neuroleptic-induced vacuous chewing movements in rodents: incidence and effects of long-term increases in haloperidol dose

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Abstract Rats treated chronically with neuroleptics develop vacuous chewing movements (VCMs), similar in some respects to tardive dyskinesia (TD) in man. The VCM syndrome was used as a model of TD to examine the ability of increased neuroleptic doses to produce long-term suppression of dyskinetic movements. The incidence and persistence of the VCM syndrome in individual rats were also assessed to look for affected and unaffected subgroups. Rats were initially treated for 15 weeks with haloperidol decanoate. For the next 21 weeks, half the group received a 50–150% increase in dose while the other half continued to receive the same dose. Animals were also followed during a 28-week withdrawal period. Total VCM ratings showed a skewed distribution, with some rats exhibiting few movements while others developed marked and persistent movements. Increasing doses did not suppress VCMs, nor did they exacerbate movements during the withdrawal period. To the extent that the VCM syndrome models TD, the absence of long-term suppression of the VCM syndrome suggests that, at this dosage range, increasing depot neuroleptic doses may not be a useful long-term strategy for TD suppression.

Key words Tardive dyskinesia · Rats · Haloperidol · Vacuous chewing movements

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Introduction

Tardive dyskinesia (TD) is a movement disorder affecting 20–40% of patients treated chronically with neuroleptic medications (Khot et al. 1992). Symptoms include involuntary orofacial movements such as lip smacking, tongue protrusions, and chewing, as well as abnormal truncal and limb movements. Many agents have been used to suppress TD, with only limited success. Several reviews have suggested that short-term suppression can be achieved most effectively with increased doses of neuroleptics (Jeste and Wyatt 1979 1982; Jeste et al. 1988). Studies using neuroleptics to suppress TD are limited by small sample sizes and brief durations of treatment (e.g. 8–18 weeks) (see Jeste et al. 1988, for review). Furthermore, this treatment strategy is usually avoided due to concerns that increased doses may eventually worsen TD.

Long-term neuroleptic treatment produces vacuous chewing movements (VCMs) in rats, reminiscent of the orofacial dyskinesias of TD. Although controversial, this model has been used to investigate the pharmacology and pathophysiology of TD (see Waddington 1990 for review). Several studies have examined suppression of VCMs with increased neuroleptic doses. These, however, have only looked at acute effects after a single injection. Furthermore, results have been inconsistent as one study found marked suppression (Gunne et al. 1982) while two others did not (Waddington et al. 1986a 1988). Regarding long-term consequences, higher doses (ranging from 0.07 mg/kg to 0.24 mg/kg per day of haloperidol) appear to produce higher VCM scores (Johansson et al. 1986). These studies suggest that increased doses may be effective for short-term suppression of VCMs but could result in long-term exacerbation.

It is unclear how closely the VCM syndrome resembles TD. A subgroup of patients treated with neuroleptics develop TD. Symptoms can persist during

extended withdrawal periods. A second group of patients consistently show few if any movements, while a third have intermittent dyskinesias (Bergen et al. 1989). VCMs have been reported to develop in many (Gunne and Haggstrom 1983; Waddington et al. 1983; Tamminga et al. 1990) if not all (Mithani et al. 1987) rats treated chronically with neuroleptics. Regarding persistence after neuroleptic withdrawal, previous studies are conflicting (see Waddington1990 for review). Demonstration that a only a subgroup is affected with persistent movements, while others remain unaffected would support the use of the VCM syndrome as a model for TD.

The purpose of this study was threefold. The first was to test the ability of haloperidol to produce long-term suppression of VCMs with increased doses. The severity of the VCM syndrome was compared in groups treated chronically with different doses of haloperidol and then withdrawn for 28 weeks. Second, the existence of subgroups that did or did not develop VCMs was explored. Finally, the persistence of the VCM syndrome was examined during a 6-month withdrawal period. These features of the VCM syndrome are compared with previously published data from human studies to assess similarities with TD.

Materials and methods

Animals and neuroleptic drug treatment

Fifty-three male Sprague-Dawley rats initially weighing 140–160 g were housed in groups of two with free access to food and water, a 12-h light-dark cycle (with lights on at 7 a.m. and off at 7 p.m.), and constant temperature (25°C). Animals were initially divided into two groups. The control group (n = 13) was treated with vehicle (provided by McNeil Pharmaceuticals) while the haloperidol group (n = 40) was treated every 3 weeks with intramuscular haloperidol decanoate 28.5 mg/kg (McNeil Pharmaceuticals), the equivalent of 1.0 mg/kg per day of unconjugated haloperidol. After five injections (*first period,* 15 weeks), the haloperidol group was divided into two groups; one received the equivalent of haloperidol 1.5 mg/kg per day (high dose group, n = 20) while the other (low dose group, n = 20) continued to receive the equivalent of 1.0 mg/kg per day. Injections were given every 3 weeks for the next 21 weeks (*second period*). The high dose group received a final seventh injection (week 21 of the second period) of 2.5 mg/kg per day, while the low dose group was again given 1.0 mg/kg per day. These doses were chosen based on results from previous studies. Similar increases in dose, on a mg/kg basis, have been reported to acutely suppress TD in humans (e.g Frangos and Christodoulides 1975: Gerlach and Casey 1983) and VCMs in rats (Gunne et al. 1982). Animals were followed for the next 28 weeks *(third period)* with no further injections, permitting additional comparisons at (presumably) lower brain haloperidol levels. Ratings for one session were not available for analysis (week 25 of the third period). The study was approved by the NIMH Animal Care and Use Committee.

Behavioral measures

Rating sessions were held from 10 a.m. to 12 noon in the same room in which animals were housed. Animals were rated in random order every 3 weeks, 1 day before injections were given. They were transferred from their home cages to uncovered 20 × 30 × 40 cm plastic cages. A mirror was placed behind these cages allowing raters to observe mouth movements at all times. Habituation periods were not employed.

All ratings were performed by two raters blind to treatment and previous ratings. Interrater reliability, using the intraclass correlation coefficient (ICC) (Bartko and Carpenter 1976), based on 32 joint ratings (n = 3–4 per rating period for ten rating periods), was highly significant (F = 12.1, df = 31,32, ICC = 0.85, $P < 0.0001$). Vacuous chewing movements were counted during a 2-min observation period. As previously noted, two types of jaw movements were observed (Gunne 1982). Intermittent chewing movements which occurred in isolation and were unrelated to grooming, gnawing or mouthing food were each counted as one movement. A second type of movement were bursts of chewing, often associated with jaw tremors. Each chewing movement was counted as one occurrence. Jaw tremors were counted as two VCMs. This scoring system has been used previously (e.g. Gunne et al. 1982; Tamminga et al. 1990), but is somewhat arbitrary since the two types of movements could be functionally and neurochemically distinct. Scores were combined in this study to assess overall severity of the entire syndrome, as is done with TD (Egan et al. 1992). This method of assessment does not permit a separate analysis of subcomponents of the VCM syndrome to changes in dose. Tongue protrusions were also observed but not counted. We did not use Plexiglas tubes for restraint, since these ratings appear to be different than those in an open field (Levy et al. 1987; See and Ellison 1990). While additional studies are needed to compare different methods, results using human observers and VCM counts of rats in small cages appear to be relatively consistent (Waddington 1990).

Haloperidol levels

Haloperidol levels were obtained in a subset of animals. Following the final rating session, animals were anesthetized with 1.0 mg/kg pentobarbital IP followed by cardiac perfusion with 4C phosphate buffered saline. Brains were quickly removed, the cerebellum detached, frozen in isopentane, and stored at −70C until further processing. The cerebellum was subsequently thawed, weighed, and homogenized in 1.0 ml of deionized water, 1.5 ml of a sodium bicarbonate buffer (pH 10.5), and an internal standard. Resulting samples were concentrated using an alkaline buffered 5 ml extraction column containing diatomaceous earth, eluted with hexane/isoamyl alcohol, and back extracted into 0.01 N sulfuric acid. Subsequent analysis was performed by high pressure liquid chromatography using a cyanopropyl column in a reverse phase chromatographic mode with UV detection at 254 nm. Detection level was 1 ng/ml. Between-run coefficient of variation was 7.3%.

Statistics

Behavioral ratings were used to assess five issues: 1) the effects of haloperidol treatment compared to vehicle, 2) the incidence of the VCM syndrome and its persistence in a subset of animals, 3) the effects of different doses on VCM scores, 4) the effects of neuroleptic withdrawal on VCM scores, and 5) the relationship between cerebellar haloperidol levels, dose, and VCMs. All statistics were performed using Super ANOVA (Abacus Concepts, Berkeley, Calif.). The multivariate analysis of variance method was employed for all-repeated measures analysis of variance (rmANOVA).

Effects of haloperidol treatment were examined using an rmANOVA with one between group (drug treatment) and one within group (time) factor. To assess the incidence and persistence of the VCM syndrome, rats were categorically identified as having (+VCM) or not having (−VCM) the VCM syndrome in each of the three treatment periods. The VCM syndrome was defined as

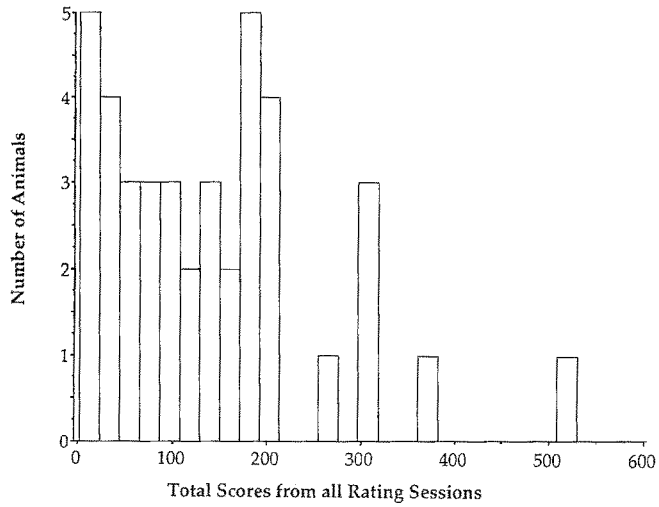

Fig. 1 Distribution of total VCM scores from all rating periods in animals treated with haloperidol decanoate. Two peaks are seen, one with ratings from 0 to 20, the second with total ratings from 170 to 190. Ratings are markedly skewed (skewness = 1.18)

present when elevated scores were seen in at least two of the last five rating sessions of each period. Elevated scores were taken as seven or more, which was two standard deviations above the mean of all ratings for the vehicle group. Subsequent analyses examined different aspects of severity or persistence.

a) Does the +VCM assignment persist in a subgroup of animals over all three rating periods? This analysis focuses on persistence in individual animals, similar to patients with TD. The observed distribution of assignment as + or −VCM in all three periods was compared to the expected random distribution (2^3 = 8 possible outcomes, see Table 3).

b) Do rats with persistent movements fall at one end of a normally distributed curve, or are VCM ratings, as with TD, skewed? Distribution and skewness of total VCM scores for all rating periods was assessed. Similar analyses were performed on the number of rating sessions with scores of 7 or more (two standard deviations above the mean of the vehicle-treated group) as an additional test of this issue.

The effect of dose was examined using an rmANOVA. Neuroleptic suppression of VCMs following dose increase was also explored using paired *t*-tests and the Mann-Whitney *U* test. Ratings of animals in the high dose group before the two dose increases were compared with subsequent ratings after the increases using paired *t*-tests. Identical comparisons were performed only on ratings from the +VCM group (as assessed in the first rating period) treated with the higher dose. Differences between the high (n = 9) and low (n = 8) dose +VCM (first period) groups were tested with the Mann-Whitney *U*-test (due to unequal variances between groups). For these multiple comparisons, P = 0.01 was accepted as significant.

Effects of neuroleptic withdrawal were examined several ways. To compare scores during treatment versus those during withdrawal, an rmANOVA was performed with one between (treatment) and two within factors (rating session and treatment period). For the latter, treatment period included two cells: 1) rating sessions from the second period, and 2) rating sessions from the withdrawal (third) period. Second, to examine whether withdrawal dyskinesias developed and were worse in the high dose group, interactions between dose and time were examined using an rmANOVA with scores from the third (withdrawal) period alone. Finally, to explore the possibility that withdrawal dyskinesias developed transiently in the +VCM, −VCM, high dose, or low dose groups, or the entire haloperidol treated group, ratings immediately before withdrawal were compared with subsequent ratings after withdrawal using paired *t*-tests.

Table 1 Incidence of +VCM classification in haloperidol treated rats[a]

Period	1	2	3
+VCMs	17	21	24
−VCMs	23	19	16
Total	40	40	40

[a]No vehicle-treated rats met criteria for inclusion in the +VCM group during any period.

Results

Effects of haloperidol treatment

Haloperidol increased VCM ratings compared with vehicle treatment when ratings from all three periods are examined using rmANOVA (treatment effect, F = 8.6, df = 1, P = 0.006; time effect, F = 2.52, df = 21, P = 0.0002; group by time interaction, F = 0.82, df = 20, P = 0.69) (Fig. 2).

Incidence of the VCM syndrome

Assignment of rats to +VCM and −VCM groups are described in Table 1. The persistence of +VCM and −VCM assignment is shown in Table 2. Distribution of + and −VCM diagnosis over all periods for haloperidol-treated rats was markedly different from a random distribution (χ^2 = 28.2, df = 3, $P < 0.00001$) (Table 3). VCM ratings for haloperidol treated rats categorized as VCM during all three periods (mean ±SD = 1.4 ± 1.0) were no different than ratings for the vehicle group (rmANOVA F = 0.396, df = 1,14, P = 0.54) but were markedly different from all other haloperidol-treated rats (mean = 8.74 ± 4.95; F = 15.64, df = 1,29, P = 0.0005). This demonstrates that assignment to + and −VCM groups is markedly different from a random distribution. It also suggests the existence of a subgroup with persistent VCMs, and a second group that is relatively free of VCMs.

Total VCM scores from all rating sessions of haloperidol treated animals showed a markedly skewed distribution (Fig. 1). A similar skewed distribution was seen in total number of rating sessions with scores of 7 or more. While the demonstration of a bimodal distribution of scores would support the existence of subgroups, analysis for a mixture distribution (Gibbons 1984) was not performed due to the low number of subjects. These analyses suggest that VCM scores, like TD ratings, are not simply at one end of a normally distributed continuum of hyperkinetic movements but are markedly skewed.

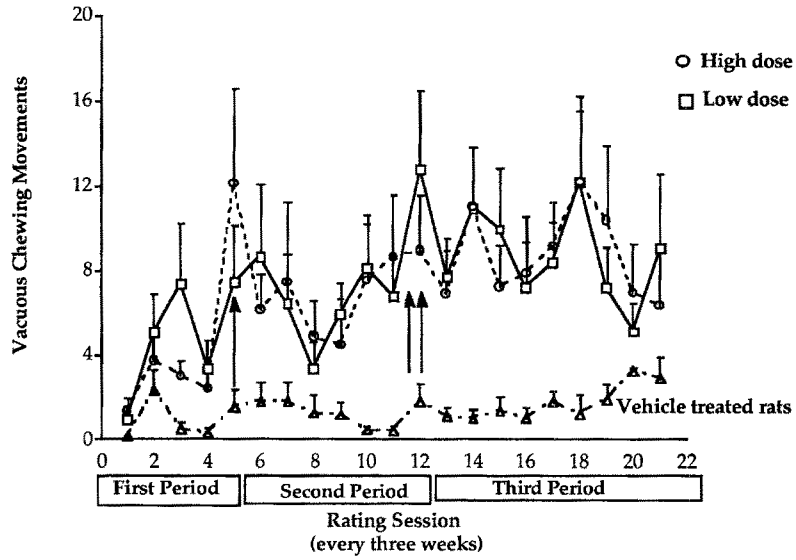

Fig. 2 Effects of haloperidol dose on VCM scores (±SD): After 15 weeks (*single arrow, first period*), animals treated with haloperidol (1.0 mg/kg per day) were given high (1.5 mg/kg per day, $n = 20$) or low doses (1.0 mg/kg per day, $n = 20$) during the second period. After the final injection (*double arrow*) (high dose group = 2.5 mg/kg per day, low dose group = 1.0 mg/kg per day) animals were rated during the third period. There was no Dose effect during any period, or time effect in the withdrawal (third) period. Between and within group comparisons were not significant. o high dose, □ low dose

Effects of haloperidol dose on VCMs

There was little evidence of suppression of VCMs with higher haloperidol doses during active treatment or during the withdrawal period (Figs 2 and 3). Using scores from all haloperidol-treated animals ($F = 0.0001$, $df = 1$, $P = 0.98$) or only those from the +VCM groups (as assessed in the first period) ($F = 0.002$, $df = 1$, $P = 0.96$), no dose effect was observed. In +VCM rats treated with high doses, ratings from only the seventh session of the second period (Fig. 3) were reduced compared with those prior to the dose increase (last session of first period) (paired $t = 3.5$, $P = 0.008$). Other comparisons failed to show significantly reduced VCM scores with higher doses. High and low dose groups had similar numbers of rats with + and VCMs in the second ($\chi^2 = 0.10$, $P = 0.75$) and third ($\chi^2 = 0.018$, $P = 0.84$) treatment periods. Both analyses suggest that there is no increase in +VCM incidence or severity with the higher dose regimen.

There was no evidence that the higher haloperidol dose, compared with the lower dose, worsened movements in −VCM animals. Of 11 animals in the high dose group with −VCMs in the first period, 4 developed persistent VCMs in the next two periods. In the low dose group, 3 out of 12 −VCM rats (as assessed in the first period) developed persistent VCMs in both subsequent periods. These differences were not significant using a chi square ($\chi^2 = 0.35$, $P = 0.55$). Comparing VCM ratings for these two groups using rmANOVA, no differences were seen for VCM scores from the second and third (withdrawal) treatment periods ($F = 0.001$, $df = 1$, $P = 0.98$).

Table 2 Persistence of VCM classification in haloperidol treated rats

Period	1	2	3
+VCMs	17	14	12
VCMs	23	16	13
Total	40	30	25

Effects of haloperidol withdrawal

During the 6-month withdrawal (third) period, VCM ratings remained elevated in haloperidol-treated rats (Figs 2 and 3). Ratings during the withdrawal period were no different than those in the second treatment period ($F = 1.07$, $df = 1$, $P = 0.31$). A separate rmANOVA using ratings from the withdrawal period alone showed a significant effect of drug treatment ($F = 8.88$, $df = 1$, $P < 0.005$) but not time ($F = 0.326$, $df = 8$, $P = 0.96$) or treatment by time interaction ($F = 0.641$, $df = 8$, $P = 0.74$). Animals in the +VCM group in both the first and second period had markedly elevated ratings compared with the vehicle group during withdrawal (treatment effect $F = 16.7$, $df = 1$, $P = 0.0009$, time effect $F = 0.70$, $df = 8$, $P = 0.69$, interaction effect $F = 1.08$, $df = 8$, $P = 0.38$), including higher mean ratings (11.1 ± 12.5 versus 2.8 ± 2.9, respectively) at the final rating session (one-tail unpaired t-test, $P = 0.04$). Using paired t-tests, VCM scores were not elevated in any group compared with ratings immediately before withdrawal in any of the haloperidol-treated groups. These analyses suggest that in the subgroup with persistent VCMs during haloperidol treatment, movements persist during extended withdrawal periods, but that withdrawal exacerbation of VCMs does not occur.

Table 3 Expected versus observed distribution of VCM classifications across all three treatment periods in haloperidol treated rats

1st/2nd/3rd Period	Expected N	Observed N
+VCM/+VCM/+VCM	5	12
+VCM/+VCM/−VCM	5	2
+VCM/−VCM/+VCM	5	2
−VCM/+VCM/+VCM	5	7
+VCM/−VCM/−VCM	5	1
−VCM/−VCM/+VCM	5	3
−VCM/+VCM/−VCM	5	0
−VCM/−VCM/−VCM	5	13
	40	40

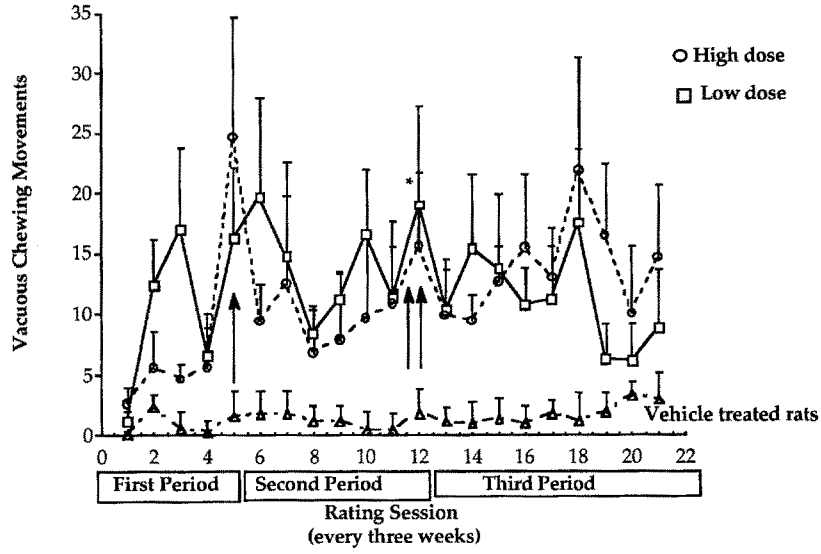

Fig. 3 Effects of haloperidol dose on VCM scores (±SD) in +VCM rats, as assessed in the first period: There was no Dose effect dur ing any period. Between group comparisons (high vs low dose; $n = 9$ and $n = 8$, respectiv ely) were not significant. Comparing ratings just before dose increases in the high dose group with all subsequent ratings in that period, only one (*) was significant ($t = 3.5$, $P = 0.008$). o high dose, □ low dose

Haloperidol levels

The mean (± standard deviation) cerebellar haloperidol level was 60.8 ± 22.0 ng/g brain tissue ($n = 23$). There was no difference between +VCM and VCM rats (meeting these criteria for all three periods) ($n = 12$ and 10, respectively, two tailed unpaired $t = 0.68$, $P = 0.50$). Rats treated with the higher doses did have significantly higher levels (72.7 ± 21.0 ng/g, $n = 10$) compared with rats treated with lower doses (51.6 ± 18.7 ng/g, $n = 12$) (two tailed unpaired t-test, $t = 2.55$, $P = 0.02$).

Discussion

The results of this study demonstrate four features of the VCM syndrome. First, one subgroup of rats treated chronically with haloperidol develops the VCM syndrome, while another group consistently has few movements. Second, increasing doses of depot haloperidol from 1.0 mg/kg per day to 1.5–2.5 mg/kg per day does not suppress VCMs, despite higher cerebellar haloperidol levels. Third, increased doses above 1.0 mg/kg do not exacerbate movements over the long-term. Finally, rats that do develop the syndrome have persistent movements for more than 6 months following cessation of treatment, although haloperidol is still detectable in the cerebellum.

Incidence of the VCM syndrome

The VCM syndrome appears to affect a subgroup of rats, while leaving a second group relatively unaffected. This is supported by the observations that assignment of rats to the + or −VCM groups showed consistency over time (Table 2) and that distribution of ratings are skewed. In contrast, rats treated acutely with dopamine agonists show hyperactivity or stereotypies that are normally distributed (e.g. Piazza et al. 1989).

Four previous studies of the VCM syndrome have reported incidence rates. Tamminga et al. (1990) found that 38% of rats never expressed VCMs during chronic oral haloperidol treatment while vigorous movements were seen in 41%. Other studies have reported incidences of 18–53%, depending on the neuroleptic (Waddington et al. 1983), few or no movements in up to 33% of rats (Gunne and Haggstrom 1983), or VCMs in all neuroleptic-treated animals (Mithani et al. 1987). None of these studies described whether individual animals consistently demonstrated movements. Overall, these reports are consistent with findings from the current study regarding the existence of subgroups.

Effects of haloperidol treatment and dose

As most previous studies have shown (Waddington et al. 1983; Johansson et al. 1986; Mithani et al. 1987; Tamminga et al. 1990; Waddington 1990), haloperidol treatment produced a marked increase in VCMs compared with vehicle treatment. Increasing haloperidol doses, however, did not appear to affect VCM severity, despite markedly increased cerebellar levels. In particular,there was little evidence that either the first or second dose increases suppressed VCMs in the short term nor worsened them in the long run.

Three previous studies have looked at VCM suppression with neuroleptics. One found suppression using a single intraperitoneal injection of 2.0 mg/kg in cortically lesioned rats treated previously with 1.0 mg/kg haloperidol decanoate (Gunne et al. 1982). Two others failed to find suppression (Waddington et al. 1986 a,b, 1988) using 0.75 mg/kg haloperidol subcutaneously in rats with low basal VCM scores (see

Waddington 1990 for discussion). Although we increased doses by 0.5 and 1.5 mg/kg in attempts to suppress movements, different routes of administration may account for with the Gunne et al. (1982) study. Alternatively, cortical lesions in the latter study may have affected results. Regarding long-term exacerbation of VCMs, one study reported that higher doses significantly increased VCM ratings (Johansson et al. 1986). The dosage range in that study was much lower than that used here. This suggests that doses above 1.0 mg/kg used in our study do not further increase VCM severity due to a possible "ceiling effect". The lack of detectable changes in VCMs during the withdrawal period, as brain levels presumably fell, indicates, however, that additional factors other than lower haloperidol brain levels are involved in the dose/response phenomenon reported by Johansson et al. (1986).

We might have seen a relationship between increased VCMs and higher doses if we had used a wider range of doses. VCM suppression, furthermore, may have been more impressive using lower initial doses, or using higher doses to suppress movements. We chose doses that yield plasma levels similar to therapeutic levels in humans (Tamminga et al. 1990). These doses may also produce some biochemical and behavioral effects comparable to doses used clinically. In patients on therapeutic doses, typical neuroleptics occupy 75–90% D_2 dopamine receptors (Farde et al. 1992). This is similar to the roughly 86% D_2 blockade produced in rats by flupentixol doses (0.75 mg/kg) equivalent to 1.0 mg/kg haloperidol (Hess et al. 1988). Behaviorally, at least 50–60% of patients treated with neuroleptics develop parkinsonian symptoms (Rifkin et al. 1978; Jellinek et al. 1981; Weiden et al. 1987). This is roughly similar to the 60–70% incidence of marked catalepsy seen in rats treated with 1.0 mg/kg per day of haloperidol decanoate (Hyde et al. 1995). While these similarities are suggestive of the clinical relevance of our results, additional studies with lower doses would clarify whether they are generalizable.

Effects of haloperidol withdrawal

VCMs appeared to persist in haloperidol-treated animals during the 6-month withdrawal period. No increases in VCMs were seen in any group during the withdrawal period, suggesting the absence of withdrawal dyskinesias. This could be due to a gradual reduction of haloperidol levels with depot preparations. Despite the long withdrawal period, low levels of haloperidol were detectable in the cerebellum. It is unclear whether VCMs would persist when haloperidol is completely removed from the brain.

Previous reports have been mixed on the persistence of the VCM syndrome following cessation of treatment. Comparing studies is complicated by different methods of assessing VCMs (Waddington 1990). Most reports of persistent movements assessed VCMs using human raters observing rats in either an open cage or an enclosed tube. Using these methods, two studies found persistence for 1–5 months (Waddington et al. 1983; Gunne et al. 1986) following oral administration, while two others reported disappearance within several weeks (Rupniak et al. 1985; See and Ellison 1990). Studies using depot preparations have been more consistent, with one reporting persistence for at least 2.5 months following withdrawal (Waddington et al. 1986b) and three a gradual diminution over 4–5 months (Gunne et al. 1982, 1986; Gunne and Haggstrom 1983; Mithani et al. 1987).

The persistence of haloperidol in the cerebellum was unexpected. The half-life of haloperidol decanoate in plasma is 3 weeks (Jann et al. 1985). By the final rating session following the last dose, plasma levels should have been reduced to 0.09% of steady state levels. Using a similar dosage regimen, See et al. (1989) found non-detectable haloperidol plasma levels in seven of eight animals 4 months after the final decanoate injections and 2 months after oral (drinking water) administration. The current study suggests that haloperidol could be preferentially sequestered in the brain.

Similarities between TD and the VCM syndrome

Clinical TD ratings of patients treated with neuroleptics share several features with VCMs ratings. First, the distributions of both are markedly skewed (e.g. see data in Owens et al. 1982). Second, subgroups can be identified with either no movements or persistent movements (Bergen et al. 1989; APA Task Force on TD 1992). These two properties support the notion that patients with TD and animals with VCMs are distinct groups that may have a unique underlying neurobiology. Their abnormal behavioral ratings are not simply at one end of a normally distributed curve. While demonstration of a bimodal distribution of TD and VCM ratings would more clearly demonstrate the existence of subgroups, such analyses have not been done due to the requisite large sample sizes (Gibbons et al. 1984). Separating affected from unaffected groups may be useful in neurochemical and neuropathological studies to identify unique changes underlying this syndrome. Studies that have not separated these two groups (Gale 1980; Gunne and Haggstrom 1983; Mithani 1987; Rupniak et al 1987) may not be able to distinguish non-specific drug effects from changes unique to the VCM syndrome.

It is unclear whether the VCM syndrome is similar to TD with respect to persistence. The VCM syndrome does appear to persist in a subgroup of animals for up to 6 months following treatment with depot neuroleptics. Human studies have shown that neuroleptic withdrawal is associated with both persistence of TD in some patients and slow improvement in others. TD may

remit in 36–55% of patients during the first 3 months of neuroleptic withdrawal (Jeste et al. 1988). Improvement may be seen for up to 5 years following withdrawal (Klawans et al. 1984). Nevertheless, persistent TD is seen in some patients who remain neuroleptic-free for many years. Data on persistence of brain neuroleptic levels in these patients is not available. Additional data on the relationship between persistent dyskinesias and brain neuroleptic levels are needed to clarify similarities between TD and the VCM syndrome.

Effects of neuroleptic dose on TD are unclear. Studies of neuroleptic dose and the incidence of TD are technically difficult and have been inconclusive (APA Task Force on TD 1992). Neuroleptics may suppress movements acutely (Doongaji et al. 1982; Jeste and Wyatt 1982; APA Task Force on TD 1992), although several studies suggest the suppressive effects are often slight and are only seen in some patients (e.g. Leiberman et al. 1988a,b). It is unclear how important dose is in these suppression studies.

Longer-term studies of neuroleptic suppression (excluding clozapine and dopamine depleters) have also been mixed (Jeste and Wyatt 1982; Jeste et al. 1988). Methodological differences confound comparisons with the current one. Most have first withdrawn patients from neuroleptics and compared subsequent changes in TD with placebo ratings (Roxburgh 1970; Singer and Cheng 1971; Kazamatsuri et al. 1972, 1973; Glazer and Hafez 1990). This may be more of a measure of ability to suppress withdrawal dyskinesias rather than persistent TD. Others have not been blinded or did not use appropriate control groups (Roxburgh 1970; Curran 1973; Jus et al. 1979; Smith and Kiloh 1979). Of three particularly well-controlled studies, two found significant suppression (Frangos and Christodoulides 1975; Gerlach and Casey 1983), while the third did not (Korsgaard et al. 1984). A fourth study using depot neuroleptics showed brief improvement (i.e. 1–2 days) along with increased blood levels immediately following drug injection in four out of six patients (Barnes and Wiles 1983). None of these studies has demonstrated a long-term reduction in TD with elevated neuroleptic doses.

VCMs have been reported by some (e.g. Rupniak et al. 1985; Steinpreis et al. 1993) but not all (e.g. Gunne et al. 1986) to develop acutely after the initiation of neuroleptic treatment. The reasons for these discrepancies are unclear (Waddington 1990), but may have to do with route of administration (See and Ellison 1990). Based on response to anticholinergic treatment, it has been proposed that *acute* VCMs may be a model for dystonia (Rupniak et al. 1985; Steinpreis et al. 1993). Further studies are needed to clarify the relationship between acute VCMs, VCMs induced by long-term treatment, and movement disorders in humans induced by neuroleptic treatment.

In conclusion, chronic neuroleptic treatment produced a delayed onset of VCMs in rats. One subgroup developed marked symptoms which persisted during a withdrawal period of more than 6 months, while a second group was relatively unaffected. There was little evidence that 50–150% increases in doses of haloperidol decanoate suppressed VCMs. Animals on chronically higher doses did not develop more severe movements during either treatment or withdrawal. To the degree that the VCM syndrome models TD, the results suggest that, at these relatively high doses of depot neuroleptics, further dose increases might not be useful in suppressing movements in patients with TD.

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