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Effects of raclopride treatment on plasma and CSF HVA: relationships with clinical improvement in male schizophrenics

John G. Csernansky[1], John W. Newcomer[1], Karen Jackson[2], Leon Lombrozo[2], Kym F. Faull[3], Robert Zipursky[2,3*], Adolf Pfefferbaum[2,3], William O. Faustman[2,3]**

[1] Department of Psychiatry, Washington University School of Medicine, St. Louis, MO 63110, USA
[2] Palo Alto DVA Medical Center, Palo Alto, CA 94304, USA
[3] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA 94305, USA

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Abstract. Thirty-two acutely psychotic, male schizophrenic patients received raclopride, at 2, 6, or 12 mg/day, or haloperidol, 15 mg/day for 4 weeks after randomized, double-blind assignment. Twenty-six patients, including 19 who had been assigned one of the three doses of raclopride, completed the study. Raclopride, particularly at 12 mg/day, increased CSF homovanillic acid (HVA) at 4 weeks, and plasma HVA at 2 days, of treatment. The clinical response to raclopride was significantly correlated with plasma raclopride concentrations and baseline plasma HVA concentrations. Although raclopride is a substituted benzamide with atypical properties in animals, these results suggest that the doses of raclopride required for clinical efficacy and elevation of clinical indices of brain dopamine turnover are similar.

Key words: Schizophrenia – Antipsychotics – Dopamine – Raclopride

Substituted benzamides, such as raclopride, have an atypical profile in rodent models of antipsychotic drug action. In particular, they block apomorphine-induced hyperlocomotion at doses below those required for the blockade of apomorphine-induced stereotypy or for the production of catalepsy (Ogren et al. 1986; Hall et al. 1989). Blockade of apormorphine-induced hyperlocomotion has been widely used to predict an antipsychotic drug's beneficial effects, while anti-stereotypic and cataleptogenic effects have been linked to the production of extrapyramidal side-effects, particularly pseudoparkinsonism (see Seeman 1980 for review). In addition, Magnusson et al. (1986) have reported that several benzamides, including raclopride, block apomorphine-induced hyperlocomotion at doses also below those required to increase indices of dopamine turnover in homogenates of rat striatum and nucleus accumbens.

These animal studies suggest that raclopride should be clinically effective at doses below those that produce extrapyramidal side-effects, particularly pseudoparkinsonism, or that increase indices of dopamine turnover in plasma or cerebrospinal fluid [e.g. homovanillic acid (HVA) concentrations]. In support of this hypothesis, two open trials demonstrated that raclopride had antipsychotic efficacy, while producing little pseudoparkinsonism, in doses of 6–12 mg/day (Farde et al. 1988a; Cookson et al. 1989). These doses produce 65–72% subcortical dopamine D_2 receptor occupancy, as assessed by positron emission tomography in schizophrenic patients (Farde et al. 1988b, 1989). Farde et al. (1988a) have also reported that after 4 weeks of treatment with raclopride, 8 mg/day, only modest decreases in plasma HVA (pHVA) were found when the plasma was sampled one hour after the last raclopride dose. Studies of pHVA during the first few days of treatment, when increases relative to baseline might be best observed (Davidson et al. 1987a, b; Davila et al. 1988), and studies of cerebrospinal fluid HVA (cHVA) have not yet been done. Such studies would have importance in helping to find neurochemical predictors of antipsychotic efficacy and in testing the validity of the rodent behavioral models discussed above.

The current study was undertaken as part of a larger multi-center, double-blind, dose-finding trial of raclopride versus haloperidol in acutely psychotic schizophrenic inpatients. In addition to assessments of clinical efficacy and side-effects, plasma and CSF were sampled before and during the trial for the measurement of HVA concentrations. CSF methoxyhydroxyphenylacetic acid (cMHPG) and 5-hydroxyindoleacetic acid (c5-HIAA) were also assessed. Our primary aims were to 1) determine the dose of raclopride required to alter pHVA and cHVA (if any in the range tested), and 2) determine whether clinical efficacy was related or unrelated to changes in these clinical indices of brain dopamine turnover.

**Present address:* Department of Psychiatry, University of Toronto, Toronto, Canada

***Present address:* Department of Psychiatry, University of California, Los Angeles, CA, USA

Materials and methods

Subject selection and treatment design. As part of a multi-center clinical trial (Casey 1991), 32 male patients, who met DSM-IIIR (American Psychiatric Association 1987) criteria for schizophrenia, and who had no history of alcohol dependence (DSM-IIIR) within 3 months prior to participation, or serious medical illnesses that would have made their participation unsafe, were recruited from among the inpatient admissions to the Palo Alto Department of Veterans Affairs Medical Center. Psychiatric diagnoses were determined by the consensus of a research psychiatrist who employed a semi-structured interview and a specially-trained research assistant who employed SCID (Spitzer et al. 1989). The research assistant also obtained a treatment history from all patients, and patients were excluded who had been consistently refractory to neuroleptics. All patients gave informed consent prior to their participation in the study.

Prior to entry into the treatment phase of the study, and after 1 week of single-blind placebo administration, the patients were required to have a total Brief Psychiatric Rating Scale (BPRS; Overall 1974a) score of at least 36 (BPRS items anchored at 0), and a minimum score of 4 (moderate severity) on at least two of the following four items, conceptual disorganization, suspiciousness, hallucinatory behavior and unusual thought content. Treatment then consisted of 4 weeks of double-blind administration of raclopride – 2 mg/day (RAC-2), raclopride – 6 mg/day (RAC-6), raclopride – 12 mg/day (RAC-12), or haloperidol – 15 mg/day (HAL) after random assignment. All medication with the exception of raclopride, 2 mg/day, was given in divided doses twice daily. During the first week of double-blind treatment, patients assigned to the RAC-6, RAC-12 and HAL groups achieved their final doses by daily dose increments. Treatment with benztropine mesylate was allowed after the appearance of clinically significant extra-pyramidal side-effects. The administration of chloral hydrate (500–1000 mg doses) was permitted for sleep and for control of agitation throughout the medication-free period, the placebo-treatment period, and the drug treatment period.

By the last day of placebo treatment, all patients had been discontinued from neuroleptic treatment for at least 20 days. Five patients had been drug-naive prior to study entry, and for one patient the exact length of his neuroleptic-free period beyond 20 days could not be determined. Of the remaining 26 patients, the median length of their neuroleptic-free period was 36 days (range 20–763 days).

All patients were rated at study entry, at the end of the 1 week placebo treatment period, and weekly thereafter using the following instruments, in addition to the BPRS: the Clinical Global Impression scale (CGI), the Neurological Rating Scale (NRS; Department of Health and Human Services, modified by Simpson); the Barnes Akathesia Scale (BAS; Barnes 1989), and the Abnormal Involuntary Movement Scale (AIMS). Interrater reliability for the BPRS was routinely monitored, and concurrent interrater reliability estimates (Spearman rho) for the BPRS total score, thinking disturbance (TD), hostility suspiciousness (HS), and withdrawal retardation (WR) scores (Overall 1974a) were 0.81, 0.94, 0.76, and 0.66, respectively.

Of the 32 patients assigned to double-blind treatment, 26 completed all 4 weeks of treatment. Of the six patients who dropped out, four did so for administrative reasons (the patients withdrew consent or eloped from the hospital without an explanation), and two were withdrawn because routine urine toxicology screens were positive for cocaine. No patient dropped out primarily because of a clinically significant worsening of symptoms, or because of intolerable side-effects. Of the patients who dropped out, two had been assigned to the RAC-2 group, one had been assigned to the RAC-6 group, two had been assigned to the RAC-12 group, and one had been assigned to the HAL group.

Neurochemical and drug level assays. Blood was obtained on the last day of placebo treatment, as well as 24 and 48 h after the first dose of active drug, for the measurement of pHVA concentrations. Thereafter, pHVA concentrations were determined at the end of each treatment week. Blood was almost always collected between 7:00 and 8:00 a.m., and during treatment, just before the next drug dose. The patients generally fasted overnight and engaged in no strenuous physical activity before blood collection. No attempt was made to change the patients' smoking habits. However, previous studies have shown that mild physical activity and tobacco use do not seriously confound the interpretation of pHVA measurements (Davidson et al. 1987b). After the separation of plasma, it was stored at −20° C until the time of assay. The reverse phase high pressure liquid chromatography (HPLC) method of Chang et al. (1983) was modified for the determination of pHVA concentrations (interassay CV=4.4%), as reported elsewhere (Petrie et al 1990). Blood samples obtained at the end of treatment weeks 1, 2 and 4 were also used to determine plasma concentrations of raclopride and haloperidol. Both raclopride (Briem 1990) and haloperidol (Nilsson 1988) were assayed using reverse phase HPLC techniques. The interassay CV for raclopride ranged from 6.5 to 25% depending upon drug level, and the interassay CV for haloperidol ranged from 1.0 to 3.7% depending drug level. The plasma drug concentrations from all three time points were averaged and mean values were used in all data analyses.

In 13 patients, lumbar punctures were performed to obtain 25 ml CSF on the day prior to beginning placebo treatment, and on the day following the last drug dose. Informed consent for lumbar punctures was separately obtained. Three patients in each of the raclopride-treated groups and four patients in the haloperidol-treated group underwent the two lumbar punctures. The lumbar punctures were performed at approximately 8:00 a.m., after an overnight fast, and almost always in the lateral decubitus position. In a few cases when CSF could not be successfully obtained in the former position, the patient was briefly raised to a sitting position. An aliquot of CSF corresponding to ml. 2–6 was collected, mixed with 4 μmol ascorbic acid and stored at −80° C until the time of assay. cHVA, c5-HIAA and cMHPG concentrations were determined using selected ion monitoring following gas chromatography/mass spectrometry, as reported previously (Faull et al. 1984).

Data analysis. Clinical change was assessed by calculating weighted change scores for BPRS-total, BPRS-TD, BPRS-HS, and BPRS-WR; that is, the scores at the end of the placebo week (baseline) were divided by two, and subtracted from the scores obtained at the end of each week of treatment. In this way, weekly BPRS scores were adjusted for baseline values and the degree of clinical improvement usually expected (50%) in antipsychotic drug trials (Overall 1974b; Overall and Ashby 1991). Only the data from the 26 patients who had completed all 4 weeks of treatment were analyzed. Change in any neurochemical variable was calculated as a simple difference. Weighted change scores, and other measures, were then compared across the four treatment groups using a repeated measures ANOVA, followed by appropriate post-hoc procedures. The $P < 0.05$ level of statistical significance was maintained for all analyses.

Results

Changes in clinical variables

Table 1 summarizes selected baseline demographic, clinical, and neurochemical features of the entire sample and of the 26 patients who completed the study. There were no apparent differences between the two groups on any of these measures. Although this study was not primarily a study of drug efficacy, we assessed the degree of clinical change during treatment to determine the most appropriate clinical change variable for use in the planned

Table 1. Description of patient population

	Completed treatment (n=26)	Drop-outs (n=6)
Age (years)	40.5 (7.7)[a]	35.0 (6.3)
Age at onset (years)	26.4 (8.2)	25.0 (6.0)
Baseline psychopathology		
BPRS-total	49.1 (6.4)	48.2 (7.4)
BPRS-TD	11.5 (2.9)	10.2 (3.3)
BPRS-H5	8.8 (2.8)	10.8 (3.9)
BPRS-WR	8.3 (2.9)	8.5 (2.0)
Baseline total AIMS Score	8.0 (11.7)	5.8 (7.8)
Baseline pHVA (ng/ml)	11.3 (3.6)[b]	9.0 (3.8)
Baseline CSF variables (ng/ml)		
HVA	32.6 (13.8)[++]	–
5-HIAA	22.3 (8.0)[++]	–
MHPG	10.5 (3.7)[++]	–

[a] (SD)
[b] n = 25, [++]n = 13

correlational analyses between clinical change and neurochemical variables. The antipsychotic efficacy of raclopride relative to haloperidol in this trial has been reported elsewhere (Casey 1991). Table 2 summarizes BPRS baseline scores and weekly weighted change scores for each group. A series of two-way repeated measures ANOVAs for each set of BPRS total and subscale weighted change scores across all treatments indicated a significant duration of treatment effect for BPRS-TD scores only [F (3,22) = 3.08, P = 0.034]. A series of one-way endpoint (week 4) ANOVAs for each set of BPRS total and subscale scores across all treatments indicated a trend for BPRS-HS scores only [F = (3,22) 2.81, P = 0.063]. Therefore, BPRS-TD and BPRS-HS weighted changes scores were selected for use in subsequent correlational analyses.

In general, both raclopride and haloperidol were well tolerated by the patients in the doses administered. A series of two-way repeated measures ANOVAs revealed no significant drug treatment or time of treatment effects for any extrapyramidal side-effect variable (i.e. parkinsonism, akathisia, or dystonia). In raclopride-treated patients, extrapyramidal side-effects were especially mild. During week 4 of treatment, only two of six RAC-12 patients and one of seven RAC-6 patient had akathisia beyond a questionable level of severity (rated 2 or more on the BAS). Also, the maximum NRS score recorded in raclopride-treated patients during week 4 was 12 (possible NRS range 8–40). Dystonia was recorded in only one RAC-6 patient (during week 1), and only four raclopride-treated patients required anticholinergic medications, all in the final week of treatment.

Changes in pharmacokinetic and neurochemical variables

In raclopride-treated patients who completed all 4 weeks of treatment (n = 19), larger raclopride doses were associated with greater plasma raclopride concentrations. A one-way ANOVA, comparing mean plasma raclopride concentrations across the RAC-2 group [mean (SD) = 12.9 (5.4) nmol/l), the RAC-6 group [mean (SD) = 21.1 (11.8) nmol/l) and the RAC-12 group [mean (SD) = 42.7 (17.8) nmol/l) indicated a statistically significant difference [F(2,16) = 11.9, P = 0.0007]. In addition, plasma raclopride concentrations were significantly correlated with endpoint BPRS-HS weighted change scores (Pearson r = −0.588, P < 0 .01), but not with endpoint BPRS-TD weighted change scores (Pearson r = −0.325, P NS). In haloperidol-treated patients who completed all four weeks of treatment (n = 7), haloperidol plasma concentrations were 16.8 (5.0) nmol/l [mean (SD)].

Table 2. Clinical change during drug treatment

Group	n	Baseline	W1 WT Δ[*]	W2 WT Δ	W3 WT Δ	W4 WT Δ
BPRS total scores						
RAC-2	6	47.3 (5.2)[b]	21.0 (6.6)	20.8 (11.4)	20.7 (6.3)	21.8 (11.6)
RAC-6	7	48.7 (5.7)	19.8 (2.4)	18.8 (9.2)	15.5 (4.6)	19.4 (6.4)
RAC-12	6	54.0 (5.9)	18.7 (9.9)	17.8 (7.6)	15.8 (10.7)	13.5 (9.5)
HAL	7	46.9 (7.1)	18.1 (7.3)	15.3 (6.2)	16.0 (7.3)	13.6 (6.0)
BPRS-HS scores						
RAC-2	6	8.5 (3.7)	4.2 (1.9)	5.2 (3.2)	4.6 (2.8)	5.1 (2.8)
RAC-6	7	8.0 (2.9)	3.5 (0.6)	3.3 (2.9)	3.0 (2.1)	4.1 (1.8)
RAC-12	6	10.2 (2.8)	2.2 (2.9)	2.4 (2.4)	2.1 (1.9)	1.8 (2.8)
HAL	7	8.9 (2.1)	2.9 (2.1)	2.7 (2.1)	2.4 (2.3)	2.0 (2.3)
BPRS-TD scores						
RAC-2	6	10.8 (4.1)	5.1 (1.4)	4.1 (2.7)	3.9 (3.4)	4.6 (3.1)
RAC-6	7	12.4 (3.6)	4.8 (1.8)	3.8 (2.1)	2.9 (1.2)	3.8 (1.8)
RAC-12	6	12.2 (1.7)	4.4 (1.6)	3.9 (2.7)	3.4 (3.4)	2.8 (3.3)
HAL	7	10.4 (1.5)	3.5 (2.5)	2.5 (3.3)	2.9 (3.2)	1.6 (3.3)
BPRS-WR scores						
RAC-2	6	8.7 (3.3)	3.5 (0.8)	3.3 (1.4)	4.8 (1.3)	4.0 (1.9)
RAC-6	7	7.9 (3.1)	3.4 (2.2)	4.2 (1.7)	2.9 (1.7)	4.1 (2.3)
RAC-12	6	8.2 (1.5)	3.8 (1.6)	2.8 (0.9)	3.8 (2.3)	2.1 (2.3)
HAL	7	8.4 (3.9)	4.2 (1.8)	3.5 (2.2)	4.4 (1.9)	3.4 (1.9)

[a] Week 1 (W1), week 2 (W2), week 3 (W3), and week 4 (W4) weighted (WT) change (Δ) scores
[b] (SD)

Table 3. Plasma HVA (ng/ml) changes during drug treatment

Group	*n*	Baseline	Day 2Δ[a]	W1Δ	W2Δ	W3Δ	W4Δ
RAC-2	5	8.8 (2.5)	0.2 (1.5)	−0.5 (2.7)	1.8 (3.5)	0.4 (3.7)	4.3 (5.6)
RAC-6	7	9.7 (2.1)	0.5 (4.7)	4.2 (2.5)	1.3 (1.9)	3.7 (2.3)	1.4 (1.6)
RAC-12	5	13.6 (3.7)	3.1 (1.2)	2.2 (6.6)	−1.3 (5.1)	−2.8 (4.3)	1.7 (3.2)
HAL	5	13.1 (4.2)	3.3 (3.2)	0.1 (2.4)	1.0 (4.9)	0.4 (5.0)	0.6 (4.5)

[a] Change scores (Δ) at day 2, week 1 (W1), week 2 (W2), week 3 (W3), and week 4 (W4) are presented

pHVA concentrations at baseline and change scores during each week of treatment are summarized in Table 3 for all patients who completed treatment. A two-way repeated measures ANOVA of weekly change scores in raclopride-treated patients revealed a significant drug treatment × duration of treatment effect [F (2,14)=3.6, P = 0.002]. When pHVA change scores from each raclopride treatment group were analyzed separately using one-way repeated measures ANOVA across the weeks of treatment, only the RAC-12 group demonstrated a statistically significant difference [F (4,20) = 4.8, P = 0.01]; pHVA concentrations on treatment day 2 were elevated to the greatest extent. The largest pHVA change scores were also observed in haloperidol-treated patients on treatment day 2, although one-way repeated measures ANOVA across the weeks of treatment was not statistically significant [F (4,20) = 0.6, P NS].

Table 4 summarizes baseline and week 4 CSF monoamine metabolite concentrations and week 4 change scores in all patients who completed treatment and underwent two lumbar punctures. Across the three groups of patients treated with raclopride (n = 9), there was a significant difference in baseline cHVA concentrations [F (2,6) = 5.9, P = 0.04]. In these patients, a two-way repeated measures ANOVA (using baseline and week 4 values) revealed a significant duration of treatment effect [F (1,6) = 11.9, P = 0.01], but no significant treatment group effect [F (2,6) = 2.5, P = 0.17] for cHVA concentrations. A one-way ANOVA comparing the cHVA change scores across the three RAC treatment groups was also not significant [F (2,6) = 2.2, P = 0.20]. Raclopride treatment appeared to have no significant effects on c5-HIAA or cMHPG concentrations. In the few haloperidol-treated patients who underwent two lumbar punctures, cHVA concentrations also increased during treatment, although this change was not significant by Students t-test (t = 1.2, P = 0.309).

Table 4. CSF neurochemistry changes during drug treatment

Group	*n*	Baseline	Week 4	Δ
CSF HVA				
RAC-2	3	29.9 (7.0)[a]	34.7 (3.1)	4.9 (9.9)
RAC-6	3	47.8 (11.1)	62.8 (20.6)	15.0 (10.3)
RAC-12	3	25.6 (6.3)	54.2 (25.5)	28.5 (19.6)
HAL	4	28.4 (17.5)	42.3 (32.2)	13.9 (22.8)
CSF 5-HIAA				
RAC-2	3	19.9 (6.1)	23.3 (15.8)	3.4 (15.2)
RAC-6	3	30.1 (10.1)	29.8 (10.7)	−0.2 (2.9)
RAC-12	3	18.8 (5.4)	28.3 (18.5)	9.5 (13.8)
HAL	4	20.9 (8.0)	21.4 (9.1)	0.6 (3.2)
CSF MHPG				
RAC-2	3	12.1 (5.1)	10.2 (2.9)	−2.0 (2.8)
RAC-6	3	9.3 (0.7)	10.2 (1.6)	0.9 (1.6)
RAC-12	3	9.8 (3.0)	12.5 (4.4)	2.7 (4.2)
HAL	4	10.8 (5.0)	10.4 (3.9)	−0.4 (1.5)

[a] (SD)

Neurochemical variables as correlates of clinical change

Table 5 summarizes the relationships between several pHVA variables and the two selected measures of clinical change (i.e. BPRS-TD and BPRS-HS weighted change scores). Only baseline pHVA was a significant predictor of clinical change. In addition, mean raclopride concentations were directly correlated with increases in pHVA concentrations on treatment day 2.

Although the number of available subjects was small for a correlational analysis (n = 9), we also determined, at least preliminarily, whether baseline cHVA concentrations or cHVA change scores were strong correlates of clinical change. Neither of these CSF variables was correlated with BPRS-TD or BPRS-HS change scores. However, cHVA change scores were significantly correlated with mean plasma raclopride concentrations (r = 0.713, P < 0.05). cHVA change scores were also correlated at the trend level (r = 0.608, P < 0.10) with pHVA change scores at day 2; however, this is not surprising given the relationship between pHVA increases at day 2 and mean plasma raclopride concentrations (see above).

Discussion

These data show that raclopride, particularly at the 12 mg/day dose, increases the concentrations of both pHVA and cHVA in schizophrenic patients. Raclopride-induced increases in pHVA concentrations on day 2 of treatment were equivalent, if not larger, in magnitude to the effects of haloperidol, 15 mg/day. Likewise, raclopride, at doses of both 6 and 12 mg/day, produced increases in cHVA that were equivalent to the effect of haloperidol, 15 mg/day. Neither Raclopride nor haloperidol significantly altered c5-HIAA or cMHPG at any dose. In addition to showing that the effects of raclopride on both pHVA and cHVA concentrations were dose-related, the data also indicated significant correlations between mean plasma raclopride concentrations and increases in both pHVA (day 2) and CSF HVA (week 4).

These results indicate that the effects of clinically effective doses of raclopride on both plasma and CSF indices of dopamine turnover are similar to the effects of typical neuroleptics, such as haloperidol. Typical neuroleptics increase pHVA beginning a few hours after the

Table 5. Interrelationships of pHVA concentrations with plasma raclopride concentrations and measures of clinical change

Timepoint [a]	*n*	[Raclopride][b]	BPRS-TD W4 WT Δ *	BPRS-HS W4 WTΔ
Baseline	19	–	−0.636**	−0.249
Day 2 Δ	19	0.458*	0.154	−0.018
W1 Δ	19	0.143	0.248	0.247
W2 Δ	19	−0.069	0.285	0.134
W3 Δ	19	−0.090	0.244	0.366
W4 Δ	17	−0.264	0.096	0.233

[a] Baseline and change scores (Δ) at day 2, week 1 (W1), week 2 (W2), week 3 (W3), and week 4 (W4) are presented. Weighted change scores are referred to as WT Δ

[b] Mean raclopride concentrations (in nmol/l, averaged across weeks 1, 2 and 4) in raclopride-treated patients who completed treatment

* $P < 0.05$

** $P < 0.005$

first dose (Davidson et al. 1987a; Davila et al. 1987), and a return to baseline levels or below generally occurs by the end of the first week of treatment (Pickar et al. 1986; Davidson et al. 1987c, 1991). Similarly, typical neuroleptics elevate cHVA during the first 2 weeks of treatment, followed by a gradual return toward baseline levels (Harnryd et al. 1984). In contrast, clozapine, the most studied atypical neuroleptic, has been found by one group to decrease cHVA after 4 days and 3 weeks of treatment (Gerlach et al. 1975), and by another group to have no effect on cHVA after approximately 2 weeks of treatment (Ackenheil et al. 1974). After chronic treatment, clozapine has also been found to decrease pHVA (Meltzer 1989). In our study, cHVA concentrations were determined only twice in each patient, the latter time point being during the period when increases are still present in patients treated with typical neuroleptics (Harnryd et al. 1984). Our data also suggest that higher levels of baseline pHVA predict a favorable clinical response to raclopride, a finding also in agreement with the properties of typical neuroleptics (Bowers et al. 1984, 1986, 1987). Unfortunately, our sample size was inadequate to determine with certainty whether a similar relationship might have existed between baseline cHVA concentrations and the degree of clinical response.

These results suggest that although raclopride may have antipsychotic effects at doses below those required to produce equivalent extrapyramidal symptoms (Casey 1991), the doses of raclopride required for an antipsychotic effect and those required to produce increases in clinical indices of dopamine turnover in schizophrenic patients are similar. Our findings are in general agreement with the results of a similar study of sulpiride versus chlorpromazine conducted several years ago (Alfredsson et al. 1984; Harnryd et al. 1984). In that study, sulpiride also increased CSF HVA concentrations at clinically effective doses, with maximal elevations occuring after 2 weeks of treatment. However, sulpiride differed from raclopride in producing decreases in CSF MHPG after 4 and 8 weeks of treatment.

The fact that we found a similarity between raclopride doses required for an antipsychotic effect and those required to increase pHVA and cHVA concentrations suggests that the rodent model of apomorphine-induced hyperlocomotion blockade may not be a valid predictor of antipsychotic efficacy. The results of the sulpiride study cited above also damages the validity of this model, although less so, since sulpiride demonstrates a narrower separation between the doses required to block apomorphine-induced hyperlocomotion and stereotypies in rodents (Hall et al. 1989). While the dose of sulpiride required to increase dopamine turnover in the rat nucleus accumbens is equivalent to the dose required to block apomorphine-induced hyperlocomotion, the dose of raclopride required to block apomorphine-induced hyperlocomotion in rats is far below that required to increase dopamine turnover in any brain area.

In summary, the results of this study show that raclopride increased clinical indices of dopamine turnover during the treatment of acutely psychotic male schizophrenic patients in a manner similar to that previously observed with typical neuroleptics. Baseline levels of pHVA, but not increases or decreases in pHVA during treatment, were correlated with the degree of clinical improvement. These findings do not support the use of apormorphine-induced hyperlocomotion blockade as a valid animal model of anti-psychotic efficacy in schizophrenia, but suggest that neurochemical studies of dopamine turnover in animals may be more useful in this regard.

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