Beneficial Effects of Nalmefene Augmentation in Neuroleptic-Stabilized Schizophrenic Patients

Mark Hyman Rapaport, M.D., Owen Wolkowitz, M.D., John R. Kelsoe, M.D., Carlos Pato, M.D., P. Eric Konicki, and David Pickar, M.D.

It was postulated that chronic blockade of the opioid system in neuroleptic-stabilized schizophrenic patients would have a beneficial behavioral effect. Eleven neuroleptic-stabilized psychotic inpatients received augmentation with nalmefene for an average of 36.7 days in a double-blind placebo-controlled study. The patients exhibited significant reductions in Bunney–Hamburg psychosis ratings and the Brief Psychiatric Rating Scale thinking disturbance subscale during the augmentation period. This study presents preliminary data supporting the hypothesis that chronic augmentation of neuroleptic-stabilized schizophrenic patients with opiate antagonists is beneficial. ***[Neuropsychopharmacology 9:111–115, 1993]***

KEY WORDS: *Schizophrenia; Opiates; Neuroleptics; Opiate antagonists; Psychotropic treatment*

The role of the endogenous opioid system in the etiology and pathogenesis of schizophrenia has been extensively investigated but remains controversial (Pickar et al. 1981a, Davis et al. 1986; Wolkowitz et al. 1986). Initial impetus for these investigations came from animal studies of the behavioral effects of endogenous opioids (Bloom et al. 1976; Segal et al. 1977; Bissette et al. 1986). Early human studies found increased levels of endogenous opioid-like substances in cerebrospinal fluid and in postmortem brains of schizophrenic subjects (Terenius et al. 1976; Lindstrom et al. 1976, 1986; Pickar et al. 1982b; Davis et al. 1986; Wiegant et al. 1988); however, other studies using more specific techniques did not replicate these findings (for review see, Bissette et al. 1986; Pickar et al. 1989).

Human pharmacologic investigations also suggested that there is an association between the endogenous opioid system and psychotic illness. Clinical trials found that the administration of exogenous opiates (β-endorphin and cyclazocine) produces auditory hallucinations, elation, disorientation, and conceptual disorganization, and that naloxone, a short-acting opiate antagonist, can block the emergence of these symptoms (Jasinski et al. 1967, 1968; Pickar et al. 1984). The results of treatment studies using naloxone have been inconclusive (see Bissette et al. 1986; Pickar et al. 1989). Opiate antagonists were ineffective when used as the sole treatment for schizophrenia; however, when used as an adjuvant; brief trials of naloxone decreased positive symptoms of psychosis (Bissette et al. 1986; Pickar et al. 1981a, 1981b, 1982c). Unfortunately, the World Health Organization (WHO) international collaborative repeated-dose naloxone augmentation trial could not confirm the results of these single-dose studies (Pickar et al. 1989). In an attempt to resolve this controversy about the efficacy of opiate antagonists as adjuvants in

From the Department of Psychiatry, University of California, San Diego and the Psychiatric Service of the San Diego VAMC (MHR, JRK); Department of Psychiatry, University of California (OW), San Francisco, California; Department of Psychiatry, Brown University (CP), Providence, Rhode Island; Department of Psychiatry, Case Western Reserve (PEK), Cleveland, Ohio; and Experimental Therapeutics Branch, National Institute of Mental Health (DP), Bethesda, Maryland.

Address correspondence to: Mark Rapaport M.D., Department of Psychiatry (0655), UCSD School of Medicine, La Jolla, CA 92093.

Received June 28, 1991; revised December 23, 1991, September 4, 1992, December 10, 1992, January 22, 1993; accepted March 19, 1993.

Published by Elsevier Science Publishing Co., Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/93/$6.00

neuroleptic-stabilized patients, we performed a double-blind placebo-controlled study in which typical neuroleptic treatment was augmented with nalmefene. Nalmefene (6-desoxy-6-methylene naltrexone) has a half-life of approximately 12 hours, blocks κ-, δ-, and μ-opiate receptors and is 50 times more potent than naloxone (Gal et al. 1986; Dixon et al. 1987; Hahn et al. 1975). We hypothesized that nalmefene would decrease positive symptoms of schizophrenia, while causing an increase in serum cortisol levels. We further postulated that nalmefene would cause a transient increase followed by a slow decrease in serum homovanillic acid (HVA) and prolactin levels, but would not change serum growth hormone or 3-methoxy-4-hydroxyphenylglycol (MHPG) levels.

METHODS

Ten inpatients who met both DSM-III-R criteria and Research Diagnostic Criteria for schizophrenia and one inpatient who met criteria for atypical psychosis (a presumptive diagnosis of schizophrenia changed during Schedule for Affective Disorders and Schizophrenia re-consensus) were studied after granting informed written consent (Table 1). All patients were medically healthy, maintained on a low monoamine diet, and had been stabilized on either fluphenazine (n = 10; mean dose 28 mg/day) or thioridazine (n = 1; 300 mg/day) prior to the administration of nalmefene. The mean age of the eight male and three female patients was 26 years old (range 18 to 36 years). All of the patients received benztropine mesylate, and two patients also received concomitant amantadine hydrochloride. Patients were treated with nalmefene for an average of 36.7 days (range 32 to 50 days) at a mean dose of 79 mg/day (range 70 to 80 mg/day). Nalmefene was administered orally in a double-blind crossover fashion. During the first 5 days of augmentation, an optimal dose was established for each patient based on their tolerance of the nausea and orthostasis sometimes associated with nalmefene. Nalmefene was discontinued after a minimum of 3 weeks on a stabilized optimal dose, with the nalmefene tapered over a 48-hour period.

Psychiatrists blind to the patients' medication status rated the subjects on a weekly basis using the modified Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1961; Lukoff et al. 1986), the Bunney-Hamburg Global Rating Scales (Bunney and Hamburg 1963), and the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982). Nurses blind to the patients' medication status rated patients with the Bunney-Hamburg Global Rating Scales. Blood samples and behavioral ratings were analyzed from three discrete 2-week time periods: the 2 weeks immediately prior to nalmefene augmentation, the last 2 weeks stabilized on the optimal dosage of nalmefene, and the first 2 weeks after discontinuation of nalmefene.

Weekly blood samples for cortisol, growth hormone, prolactin, and MHPG were analyzed. Blood samples were collected three times per week for determination of HVA and the sum of the samples was used to derive a weekly mean value for each patient. Samples used for the HVA and MHPG assays were collected on ice in ethylenediaminetetraacetic acid-containing tubes and were centrifuged at 3000 rpm for 10 minutes. The plasma was frozen at −20°C until assayed by high-performance liquid chromatography with electrochemical detection (Chang et al. 1983; Scheinin et al. 1983). The serum used in the cortisol, growth hormone, and prolactin assays was stored in a similar fashion until assayed by Hazelton Laboratories, using radioimmunoassays. The inter- and intraassay reliabilities for HVA samples were 6.2% and 2.4% respectively, and for MHPG they were 8.6% and 7.5% respectively. The inter- and intraassay reliabilities were 6.5% and 6.0% for cortisol, 4.8% and 1.0% for growth hormone, and 5.4% and 13.6% for prolactin (Orth 1979; Abraham et al. 1972).

The patients' behavioral ratings, hormone, and metabolite values were used to generate a data set that consisted of each of the 6 weeks as time points. A preliminary analysis of variance (ANOVA) identified significant differences; however, because the power was limited and no statistical differences were found between the 2 weeks of each treatment condition, the data set was collapsed so that mean values were generated for the pretreatment, nalmefene, and posttreatment periods. These data were again analyzed with a repeated-measures ANOVA and any differences between specific time points were determined using an additional ANOVA with specific contrasts. (There were no major differences in the results of the two analyses. Data from the second, collapsed, analysis are presented in this paper.)

RESULTS

Patients had significant reductions in the BPRS thinking disturbance subscale (Guy 1976) (F = 4.49; df 2,20; p = .025) and the nurse-rated Bunney-Hamburg psychosis scale (F = 4.18; df 2,20; p = .031). There was also a trend toward a significant decrease in physicians' Bunney-Hamburg psychosis scale (F = 3.32; df 2,20; p = .057) (Table 1). Post-hoc analysis employing a second ANOVA with contrasts for the pre-nalmefene, nalmefene, and post-nalmefene treatment periods established that the significant differences identified were due to decreases in ratings between the pre-nalmefene and nalmefene periods. In particular, the BPRS thinking disturbance subscale decreased from 10.1 ± 0.9 to 9.0 ± 0.8 (SEM) (F = 11.21; df 1,10; p = .007). The nurses' ratings with the Bunney-Hamburg psychosis scale also

Table 1. Demographic Characteristics and Selected BPRS and Bunney-Hamburg Ratings

SS#	Current Diagnosis	Sex	Age (yrs)	Age of Onset	No. of Hospital	Mos. in Hospital	Days on Neuroleptics
1	Schizophrenia	F	18	17	1	3.0	83
2	Schizophrenia	M	24	9	1	10.0	48
3	Schizophrenia	F	31	20	2	1.0	63
4	Atypical psychosis	M	25	16	3	8.0	42*
5	Schizophrenia	M	26	17	1	2.0	70
6	Schizophrenia	M	22	15	0	0.0	45
7	Schizophrenia	F	26	17	2	2.0	29
8	Schizophrenia	M	36	13	5	14.0	76
9	Schizophrenia	M	30	17	3	50.0	173
10	Schizophrenia	M	23	20	4	2.5	174
11	Schizophrenia	M	29	21	4	4.0	47

	BPRSTD[1]			BPRSTOT		
SS#	Pre	Nal	Post	Pre	Nal	Post
1	7.5	7.5	8.5	41.6	47	50
2	12.0	11.0	10.5	75.2	74	82
3	10.0	10.0	11.0	69	75	70
4	12.0	10.5	13.0	80	75	85
5	11.5	11.5	10.5	66	68	80
6	8.0	6.5	7.0	48	43	45
7	6.5	6.5	7.5	60	58	55
8	7.0	5.5	6.5	46	41	49
9	10.5	8.5	8.0	78	74	73
10	8.0	7.5	6.5	52	44	46
11	17.0	15.0	16.0	95	83	86
Mean	10.1 (3.0)	9.1 (2.8)	9.5 (3.0)	64.3 (16.9)	61.9 (15.8)	65.3 (16.7)

	B-H Psych[3] (Physicians)			B-H Psych[2] (Nurses)		
SS#	Pre	Nal	Post	Pre	Nal	Post
1	6.5	4.0	4.0	6.0	5.4	5.5
2	9.0	7.5	7.0	7.8	7.0	6.9
3	6.0	7.0	6.0	7.1	7.0	6.3
4	7.5	8.0	9.0	8.4	8.8	9.0
5	6.0	7.5	7.0	6.4	7.3	5.9
6	6.5	5.0	5.0	7.0	5.6	5.7
7	5.5	5.0	5.0	5.8	5.2	5.6
8	5.5	4.5	5.0	6.2	4.9	5.6
9	6.5	6.0	5.0	5.7	5.7	5.5
10	7.0	4.5	4.5	6.7	4.9	5.2
11	9.5	9.0	9.0	9.7	9.1	9.9
Mean	6.9 (11.3)	6.1 (1.8)	6.0 (1.7)	7.0 (1.2)	6.4 (1.5)	6.5 (1.6)

* Thioridazine + 19 days on fluphenazine.
[1] $p < .02$ (pre-treatment vs nalmefene treatment periods).
[2] $p < .03$ (pre-treatment vs nalmefene treatment periods).
[3] $p < .075$ (pre-treatment vs nalmefene treatment periods).

decreased from 7.0 ± 0.4 to 6.4 ± 0.5 (SEM) ($F = 4.86$; df 1,10; $p = .05$), and there was a trend toward a significant decrease in the physicians' ratings with the Bunney-Hamburg psychosis scale from 6.9 ± 0.4 to 6.1 ± 0.5 ($F = 3.52$; df 1,10; $p = .09$). In fact, 5 of 11 (45%) subjects had a decrease in Bunney-Hamburg psychosis ratings of at least 17%, and two subjects had a greater than 35% decrease in physician assessments of psychosis. The Bunney-Hamburg psychosis ratings done by the research nurses demonstrated a similar pattern, 9 of 11 subjects had decreases in their psychosis ratings during the nalmefene augmentation period (Table 1).

The other BPRS subscales, the SANS, the Bunney-Hamburg ratings for depression, mania, and anxi-

Table 2. The Effect of Nalmefene on Biologic Variables

	Pre-Nalmefene	Nalmefene	Post-Nalmefene	*p*
H.V.A.	56.05 pm/ml (25.82)	50.88 pm/ml (23.73)	49.07 pm/ml (18.57)	NS
MHPG	15.19 pm/ml (3.72)	14.68 pm/ml (4.95)	15.82 pm/ml (6.54)	NS
Cortisol	23.00 mg/dl (2.14)	20.39 mg/dl (3.12)	18.82 mg/dl (3.78)	NS
Prolactin	38.36 ng/ml (16.14)	41.29 ng/ml (16.5)	41.77 ng/ml (24.97)	NS
Growth hormone	<0.5 ng/ml	<0.5 ng/ml	<0.5 ng/ml	NS

ety (Table 2), and the biological variables measured did not vary significantly with nalmefene treatment (see Table 2).

DISCUSSION

These decreases in Bunney–Hamburg psychosis ratings and the BPRS thinking disturbance score extend the previous findings of Pickar and colleagues that short-term opioid system blockade decreases positive symptoms of psychosis (Pickar et al. 1981a, 1981b, 1982c). What is particularly impressive about this data set is that two separate groups of blind raters independently found decreases in psychotic behavior with nalmefene treatment. This type of consensus in psychosis ratings is intriguing evidence that further implicates the opioid system in the modulation of positive psychotic symptoms (Pickar et al. 1981a; Bissette et al. 1986). In fact, 5 of 11 patients had a 17% or greater decrease in the physician rated Bunney–Hamburg psychosis scale (Table 1). These data compare favorably with the initial efficacy trials of clozapine in the treatment of refractory schizophrenia (Kane et al. 1988).

Our findings differ from the conclusions of the WHO collaborative study in which repeated naloxone infusions did not decrease positive psychotic symptoms (Pickar et al. 1989). We believe that this discordance is due to differences in the half-lives and the potencies of nalmefene and naloxone. Nalmefene has a much longer half-life and is approximately 50 times more potent than naloxone (Gal et al. 1986; Dixon et al. 1982; Hahn et al. 1975). In the WHO collaborative report, Pickar and colleagues speculated that their failure to extend the results of the single-dose trials might have been an artifact caused by the inability of repeated naloxone infusions to produce prolonged opioid receptor blockade; our data would support this supposition (Pickar et al. 1989).

Another important observation from this study is presented in Table 1: decreases in positive symptom ratings observed during nalmefene augmentation drift back toward preaugmentation baselines after discontinuation of nalmefene. This implies that the behavioral changes observed are due to nalmefene rather than being an artifact caused by the continuing resolution of positive symptoms by typical neuroleptic treatment over time.

None of the biological measures evaluated varied significantly during any phase of this preliminary study (Table 2). This is surprising because acute naloxone infusions increase cortisol levels; however, these increases may be an acute effect that normalizes with chronic blockade. (Pickar et al. 1982b; Wolkowitz et al. 1986). Further studies are needed to clarify the prolonged effects of opiate blockade on neuroendocrine function.

In conclusion, this small study finds that augmentation with nalmefene, a potent long-lasting opiate antagonist, successfully decreases positive symptoms of psychosis in neuroleptic-stabilized patients with residual positive symptoms. These findings support initial studies in which opiate antagonists were acutely given to neuroleptic-stabilized patients, but differ from studies where repeated naloxone infusions were used in an attempt to achieve long-term opioid system blockade. Such results may encourage further research into the role of the opioid system in the pathophysiology of psychosis and also suggest that adjuvant treatment with long-acting opiate antagonists may be useful for patients with residual positive symptoms. In light of the recent longitudinal follow-up data indicating that treatment response is the best predictor of long-term prognosis, techniques like neuroleptic augmentation, which optimize short-term outcome, may become increasingly important in the treatment of schizophrenia (Breier et al. 1991).

REFERENCES

Abraham GE, Buster JE, Teller RC (1972): Radioimmunoassay of plasma cortisol. Anal Lett 5:757–766

Andreasen NC (1982): Negative symptoms in schizophrenia: Definition and reliability. Arch Gen Psychiatry 39:748–788

Bissette G, Nemeroff CB, Mackay AV (1986): Neuropeptides and schizophrenia. Prog Brain Res 66:161–174

Bloom F, Segal D, Ling N, Guillemin R (1976): Endorphins: Profound behavioral effects in rats suggest new aetiological factors in mental illness. Science 194:630–632

Breier A, Schreiber JL, Dyer J, Pickar D (1991): National Institute of Mental Health Longitudinal Study of Chronic

Schizophrenia: Prognosis and predictors of outcome. Arch Gen Psychiatry 48:239–246

Bunney WE, Hamburg DA (1963): Methods for reliable longitudinal observation of behavior. Arch Gen Psychiatry 9:280–294

Chang WH, Scheinin M, Burns RS, Linnoila M (1983): Rapid and simple determination of homovallinic acid in plasma using high performance liquid chromatography with electrochemical detection. Acta Pharmacol Toxicol 53:275–279

Davis TP, Culling-Berglund AJ, Shoemaker H (1986): Specific regional differences of in vitro β-endorphin metabolism in schizophrenics. Life Sci 39:2601–2609

Dixon R, Gentile J, Hsu HB, Hsiao J, Howes J, Gary D, Weidler D (1987): Nalmefene: Safety and kinetics after single and multiple oral doses of a new opioid antagonist. J Clin Pharmacol 27:233–239

Gal TJ, DiFazio CA, Dixon R (1986): Prolonged blockade of opioid effect with oral nalmefene. Clin Pharmacol Ther 40:537–542.

Guy W (ed) (1976): ECDEU Assessment Manual for Psychopharmacology. DHEW Publication No. (ADM), Washington DC 76–338

Hahn EF, Fishman J, Heilman RD (1975): Narcotic antagonists. 4. Carbon-6 derivatives of N-substituted noroxymorphones as narcotic antagonists. J Med Chem 18: 259–262

Jasinski DR, Martin WR, Haertzen CA (1967): The human pharmacology and abuse potential of N-allyl-noroxymorphone (naloxone). J Pharmacol Exp Ther 157:420–426

Jasinski DR, Martin WR, Sapira JD (1968): Antagonism of the subjective behavioral, pupillary, and respiratory depressant effects of cyclazocine by naloxone. Clin Pharmacol Ther 9:215–222

Kane J, Honigfeld G, Singer J, Meltzer H, and the Clozaril Collaborative Study Group (1988): Clozapine for the treatment-resistant schizophrenic: A double-blind comparison with chlorpromazine. Arch Gen Psychiatry 45: 789–796

Lindstrom LH, Widerlov E, Gunne LM, Wahlstrom A, Terenius L (1978): Endorphins in human cerebrospinal fluid: Clinical correlations to some psychotic states. Acta Psychiatr Scand 57:153–169

Lindstrom LH, Besev G, Gunne LM, Terenius L (1986): CSF levels of receptor-active endorphins in schizophrenic patients: Correlations with symptomatology of monoamine metabolites. Psychiatry Res 19:93–100

Lukoff D, Liberman RP, Nuechterlein KH (1986): Symptom monitoring in the rehabilitation of schizophrenic patients. Schizophr Bull 12:578–602

Orth DN (1979): Adrenocorticotropin hormone. In Jaffe BM; Behrmen HR (eds), Methods of Hormone Radioimmunoassay. New York, Academic Press

Overall JE, Gorham DE (1961): The Brief Psychiatric Rating Scale. Psychol Rep 10:799–812

Pickar D, Bunney WE Jr, Kieholtz P, Sethi BB, Vartanian M, Hippius H, Van Praag HM (1981a): Acute naloxone administration in schizophrenic patients: A World Health Organization Collaborative Study. Arch Gen Psychiatry 39:508–511

Pickar D, Bunney WE Jr, Kieholtz P, Sethi BB, Vartanian M, Hippius H, Van Praag HM (1981b): The endogenous opioid system and psychiatric illness: Effects of naloxone administration in schizophrenic and manic patients. Biol Psychiatry 16:394–397

Pickar D, Cohen MR, Naber D, Cohen RM (1982a): Clinical studies of the endogenous opioid system. Biol Psychiatry 17:1243–1276

Pickar D, Naber D, Post RM, van Kammen DP, Kaye W, Rubinow DR, Ballenger JC, Bunney WE Jr (1982b): Endorphins in the cerebrospinal fluid of psychiatric patients. Ann NY Acad Sci 399–412

Pickar D, Vartanian F, Bunney WE Jr, Maier H, Gastpar M, Prakash R, Sethi B, Lideman R, Belyaev B, Tsutsulkovskaja M, Jungkunz G, Nedopil N, Verhoeven W, van Praag H (1982c): Short-term naloxone administration in schizophrenic and manic patients: A World Health Organization Collaborative Study. Arch Gen Psychiatry 39:313–319

Pickar D, Dubois M, Cohen MR (1984): Behavioral change in a cancer patient following intrathecal β-endorphin administration. Am J Psychiatry 141:103–104

Pickar D, Bunney WE Jr, Douillet P, Sethi BB, Sharma M, Vartanian ME, Lideman RR, Naber D, Leibl K, Yamashita I, Koyama T, Verhoeven WMA, Vartanian F, Morozov PV, Ngo Khac T (1989): Repeated naloxone administration in schizophrenia: A phase II World Health Organization Study. Biol Psychiatry 25:440–448

Scheinin M, Chang WH, Jimerson DC, Linnoila M (1983): Measurement of 3-methoxy-4-hydroxyphenylglycol in human plasma with high performance liquid chromatography using elecrochemical detection. Anal Biochem 132:165–170

Segal DS, Browne RG, Bloom F, Ling N, Guillemin R (1977): β-Endorphin: Endogenous opiate or neuroleptic? Science 198:411–414

Terenius L, Wahlstrom A, Lindstrom LH, Widerlov E (1976): Increased CSF levels of endorphins in chronic psychosis. Neurosci Lett 3:157–162

Wiegant VM, Verhoef CJ, Burbach PH, de Weid D (1988): Increased concentration of alpha- and gamma-endorphin in post mortem hypothalamic tissue of schizophrenic patients. Life Sci 42:173–174

Wolkowitz OM, Doran AR, Breier A, Cohen MR, Pickar D (1986): Endogenous opioid regulation of hypothalamopituitary-adrenal axis activity in schizophrenia. Biol Psychiatry 21:366–373