Hypothalamic-Pituitary-Adrenal Axis Hypersensitivity to Naloxone in Opioid Dependence: A Case of Naloxone-Induced Withdrawal

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A case of opioid withdrawal precipitated in an opioid-dependent person by low plasma levels of naloxone is presented. In this patient, changes were observed in the hypothalamic-pituitary-adrenal (HPA) axis that preceded the clinical symptoms and adrenergic signs of withdrawal. Plasma naloxone levels were strongly correlated with plasma cortisol levels ($P < .0001$, $R^2 = .73$, $r = .85$). In addition, these neuroendocrine changes persisted after adrenergic changes and clinical symptoms had been ameliorated by administration of a short-acting opioid agonist. It is suggested that the HPA axis is a more sensitive indicator of opioid withdrawal than the adrenergic system.

OPIOID WITHDRAWAL is a complex set of physiologic events that occur reproducibly in man or animals when either becomes tolerant to and physically dependent on opioid agonists. In the acute setting, spontaneous withdrawal in humans is characterized by yawning, lacrimation, rhinorrhea, perspiration, mydriasis, tremor, gooseflesh, restlessness, myalgia, anorexia, nausea, vomiting, abdominal cramps, diarrhea, fever, hyperpnea, hypertension, and, if prolonged, weight loss.[1] Depending on the dose used, withdrawal precipitated by opioid antagonists produces a syndrome that is qualitatively similar but may be more rapid in onset and severe in intensity.[2,3] In addition, the magnitude of the withdrawal syndrome depends on the dosage of opioids taken and the duration of opioid dependence.[4] Supersensitivity to naloxone with symptoms of opioid withdrawal is evident after administration of a single dose of opioid antagonist in drug-free former addicts.[5]

Related to this, it has been suggested in animal models and human case reports that there is an inverse relationship between the degree of tolerance and physical dependence that develops and the amount of specific opioid antagonist, such as naloxone, required to precipitate opioid withdrawal.[6,7] When low doses of naloxone (<5 mg intravenously [IV]) are administered to normal volunteers, no signs or symptoms of any type appear, although the endogenous opioids are transiently displaced from their receptors. However, when moderate to large doses (>10 mg) of IV naloxone are given to normal subjects, changes in neuroendocrine function are observed, including transient increases in corticotropin (ACTH), β-endorphin, and cortisol.[8-10] In opiate-naive humans, only the endogenous opioids are present at receptor sites for displacement.

Many of the acute manifestations of opioid withdrawal described are mediated by the loss of opioid feedback inhibition to the locus ceruleus.[11] This disinhibition leads to noradrenergic hyperactivity. Thus, the α_2-adrenergic agonist clonidine ameliorates some early overt symptoms of opioid withdrawal and the α_2-antagonist yohimbine can elicit some signs and symptoms of withdrawal. There is no evidence that the adrenergic system in humans is significantly perturbed during the cycle of addiction to short-acting opioid agonists or after achievement of the drug-free state. However, there is evidence that opioid addiction and withdrawal perturb the hypothalamic-pituitary-adrenal axis (HPA) more significantly than they affect the adrenergic system. Addiction to short-acting opioid agonists such as heroin or morphine is characterized by cycles of drug administration followed by acute abstinence. The HPA axis is suppressed in these patients (Table 1). Opioid withdrawal is associated with an increased activity of the HPA axis characterized by above-normal plasma levels of ACTH, β-endorphin, and cortisol.[12-14] In patients receiving the long-acting opioid methadone, baseline levels of these hormones are normal.

Most reports of activation of the HPA axis during acute opioid withdrawal in physically tolerant and dependent persons have understandably implied that this activation is secondary to the stress of the other signs and symptoms of withdrawal. However, we have hypothesized that activation of the HPA axis may be a central process involved in withdrawal of opioids in tolerant and dependent persons, and that this activation may contribute to rather than result from the signs and symptoms of the acute and protracted abstinence syndrome.[15-17] This case report supports this hypothesis.

CASE REPORT

The patient was a 60-year-old woman who had been paraplegic for 13 years. She was participating in a study evaluating the efficacy of oral naloxone for the treatment of opioid-induced constipation (the findings of this study have been reported elsewhere[18]). Unlike IV naloxone, orally administered naloxone has limited systemic bioavailability. The patient was taking oxycodone 5 mg/acetaminophen 325 mg in combination (Percocet; Dupont Pharmaceuticals, Manah, Puerto Rico), two tablets every 4 hours, and methadone 10 mg orally three times daily for relief of chronic low-back pain. She had been taking these medications for approximately 13 years under physician supervision.

As a study participant, naloxone was administered orally to this patient once daily in a titration design. She received 0.5, 1.0, 2.0, 4.0, 8.0, 16.0, 10.0, 14.0, and 12.0 mg naloxone orally once daily at 10 AM. In a second part of the study, she received two doses of 12 mg oral naloxone 3 hours apart on 1 day. Each patient in the study was carefully monitored for signs and symptoms of opioid withdrawal. This was quantified using a modified Himmelsbach Scale.[1,18] Subjects were rated daily with respect to yawning, lacrimation, rhinorrhea, perspiration,

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Table 1. HPA Axis Response to Opioids and Their Antagonists

Condition	Drug-Free Formerly Addicted	Chronic Use of Heroin	MMTP	Opioid-Naive	Chronic Naltrexone Treatment
Baseline					
Cortisol	Normal	↓	Normal	↑	↑↑
BEP	Normal	↓	Normal	↑	↑↑
Metyrapone test					
ACTH	> Normal ↑	< Normal ↑	Normal ↑	NR	NR
BEP*	> Normal ↑	< Normal ↑	Normal ↑	NR	NR

Abbreviations: MMTP, methadone-maintenance treatment program; BEP, β endorphin; NR, not reported in the literature.

*Normal BEP increase after methyrapone is 2 to 4 times baseline.

tremor, mydriasis, piloerection, and restlessness. The signs were quantified on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe).

This patient noted no symptoms of withdrawal when doses of 0.5, 1.0, 2.0, and 4.0 mg of oral naloxone were administered on separate days. After 8 mg oral naloxone, the patient complained of chills that quickly resolved. After 16 mg oral naloxone, the patient complained of chills, shivering, and feeling depressed. No subjective symptoms were noted after 10 mg oral naloxone. After 12 mg orally, the patient noted abdominal cramps but no other symptoms. After 14 mg, she complained of mild shakiness and her pupillary size was noted to be increased; in addition, she had the abdominal cramping of pending laxation. When the patient was given two 12-mg doses of oral naloxone separated by 3 hours, she was subjectively and objectively noted to be in opioid withdrawal. She had chills and increased yawning 30 minutes after the second dose. One hour after the second dose, she complained of total body pain and depression. She was noted to be restless and shivering, and she had rhinorrhea. Her blood pressure increased to 150 mm Hg systolic pressure from a 6:00 AM baseline of 100/70 mm Hg. Because of the severity and persistence of these symptoms, she was treated with one tablet of Percocet and 2 mg of intramuscular morphine 10 and 20 minutes, respectively, after the onset of the symptoms. By 2 hours after the second dose of oral naloxone and 70 minutes after the intramuscular dose of morphine, all signs and symptoms of opioid withdrawal had subsided.

MATERIALS AND METHODS

Plasma levels of naloxone were measured by a radioimmunoassay procedure developed by our group, previously reported elsewhere (performed in collaboration with Dr C.E. Inturrisi, Cornell University Medical College).[18,19] Blood samples were drawn from indwelling catheters, placed in heparinized tubes, and centrifuged at 4°C. The plasma was separated and frozen at −20°C until analysis. Tritiated naloxone (specific activity, 48 Ci/mmol) was obtained from New England Nuclear (Boston, MA). Standards were prepared by serial dilution in 0.1% bovine serum albumen in saline. The antiserum was developed by Hahn et al.[19] This antibody has significant cross-reactivity with naloxone glucuronide, previously determined by our laboratory to be approximately 4%, thus necessitating extraction.[19] The antibody also has significant cross-reactivity with naltrexone and its metabolites, but not with any of the commonly used opioid analgesics.[20,21] The naloxone samples were treated with 100 μL bovine serum albumin and/or 100 μL control plasma, and 100 μL of a sodium carbonate–sodium bicarbonate buffer (pH 9.0, 1 mol/L). They were then extracted with 2.5 mL of a 7:3 toluene:butanol mixture. The antiserum was diluted with a phosphate (pH 7.2, 0.01 mol/L) saline gelatin (0.1%) buffer (PSG) so that 100 μL would produce a final assay dilution of 1:2,400. A 0.05-mL aliquot of a sample or a standard, 30,000 dpm of [^{3}H]naloxone, and PSG to a final volume of 0.3 mL were incubated at room temperature (20°C) for 1 hour. The assay tubes were then transferred to an ice-water bath for 10 minutes. Separation of antibody bound from free ligand was accomplished by addition of a 0.2-mL aliquot of a suspension of 0.10% dextran and 1.0% charcoal in PSG. After 12 minutes in the ice bath, the assay tubes were centrifuged for 15 minutes at 1,500 × g. The clear supernatant was decanted into a 7-mL polyethylene vial containing 3 mL Liquiscint (National Diagnostics, Sommerville, NJ) and counted for at least 5 minutes in a Beckman LS3100 liquid scintillation counter (Beckman Instruments, Fullerton, CA). The mean interassay coefficient of variation for replicate analyses using this radioimmunoassay procedure following extraction of plasma containing free naloxone was 6.4% from this laboratory. Plasma levels of cortisol were measured by a standard radioimmunoassay technique (Diagnostic Products, Los Angeles, CA).

RESULTS

Plasma cortisol levels increased in a dose-dependent fashion on each study day when signs of withdrawal were present (Fig 1). Serum cortisol levels increased in response to plasma naloxone levels less than 4.00 ng/mL with a strong correlation ($P < .0001$, $R^2 = .73$, $r = .85$, third-order polynomial regression; Fig 2). Also, cortisol increases preceded the signs and symptoms of withdrawal (Fig 3). Despite resolution of the patient's subjective complaints of withdrawal after acute administration of a short-acting opioid agonist, her cortisol levels were still elevated 15 minutes later (Fig 2).

DISCUSSION

The release of pro-opiomelanocortin (POMC) peptides, ACTH and β-endorphin, and probably corticotropin-releasing factor is prevented by feedback inhibition by cortisol acting at anterior pituitary and hypothalamic sites, respectively. There is also increasing evidence that POMC peptide release from the anterior pituitary in humans is tonically inhibited by endogenous opioids. Volavka et al[8] first showed that 10 mg IV naloxone causes an increase in serum cortisol and ACTH levels in normal men without a history of opioid addiction. Kreek et al[22] have shown that this effect, including the increase of β-endorphin, is easily observed after 10 mg IV and consistently evoked by 30 mg IV naloxone.[22] A similar dose-response of serum cortisol to high-dose naloxone was observed by Cohen et al,[9] who used doses up to 4 mg/kg (~280 mg) IV. Therefore, a decrease in feedback inhibition by either cortisol or β-endorphin may result in the increased release of POMC peptides.

Orally administered naloxone results in much lower plasma levels of active, nonbiotransformed naloxone than the same dose administered IV. This occurs because naloxone is extensively glucuronidated on first pass through the liver. Albeck et al[20] reported peak plasma levels of naloxone greater than 100 ng/mL after IV administration of 30 mg naloxone, as opposed to less than 4 ng/mL noted after oral administration of 30 mg naloxone, using a specific high-performance liquid chromatographic method for measuring levels of unmetabolized naloxone.

In this study, we have shown that displacement of opioid agonists by low plasma levels of the opioid antagonist naloxone, following oral administration in an opioid-dependent person, produces an elevation of serum cortisol that precedes the onset of the acute opioid withdrawal syndrome. Also, the

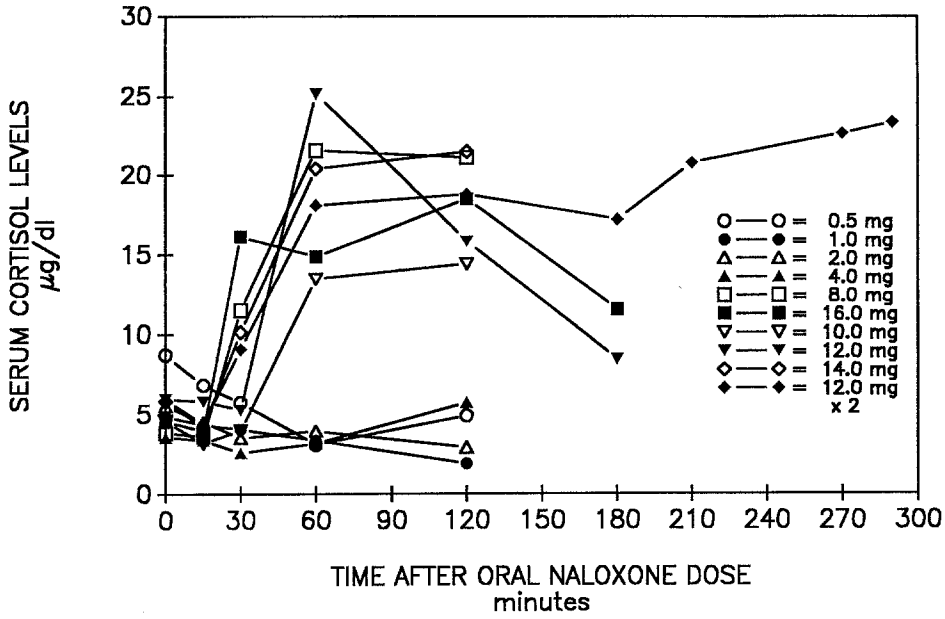

Fig 1. Change in serum cortisol after increasing doses of oral naloxone.

elevation in plasma cortisol persists after the signs and symptoms of the acute withdrawal syndrome have been treated successfully with a short-acting opioid agonist. This increase in plasma cortisol induced by naloxone administered orally is dose-dependent and correlates significantly ($r = .85, P < .0001$) with the low plasma levels of naloxone achieved with this poorly bioavailable route of drug administration (Fig 2).

There is other evidence that opioid addiction and withdrawal is characterized by specific changes in the HPA axis. Individuals who are on changing doses or irregular dosing intervals of opioids, such as active heroin abusers, chronic-pain patients, and patients early in methadone maintenance, have depressed baseline levels of β-endorphin.[23-25] Humans addicted to short-acting opioid agonists also have blunted plasma β-endorphin and ACTH responses to metyrapone stimulation, thermal stress, and psychological stress.[26,27] Metyrapone abruptly inhibits cortisol synthesis by blocking 11β-hydroxylation of the precursor. Decreased levels of serum cortisol should stimulate POMC peptide release by disinhibition at hypothalamic sites. However, we hypothesize that the excess levels of exogenous opioids may override the disinhibition produced by the sharp decrease in cortisol levels resulting from metyrapone. Conversely, an abrupt reduction in levels of exogenous opioids may effect disinhibition and thus release of POMC peptides. This is the situation that pertains in opioid withdrawal.

Drug-free former opioid addicts have normal baseline cortisol and β-endorphin plasma levels.[14-17] However, their cortisol and β-endorphin response to metyrapone is exaggerated and

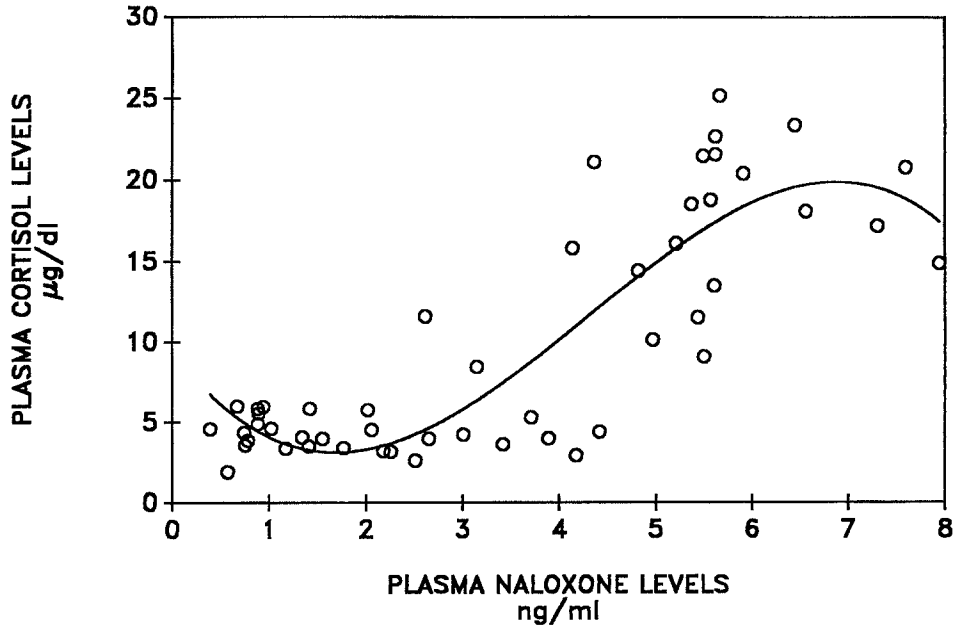

Fig 2. Correlation of plasma cortisol levels with plasma levels of naloxone.

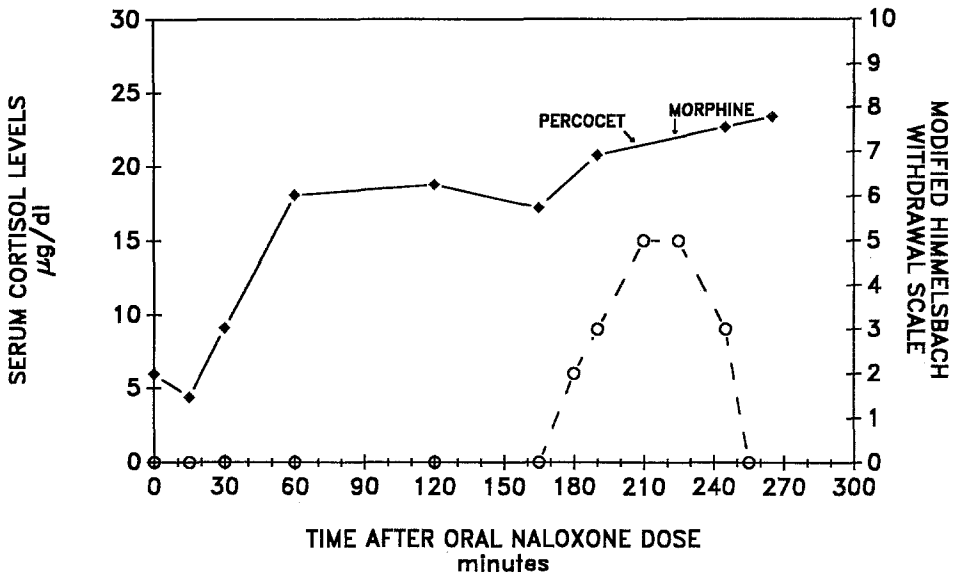

Fig 3. Change in serum cortisol and signs of opioid withdrawal after 2 12-mg doses of oral naloxone. Symbols are as in Fig 1.

may be accompanied by precipitation of signs and symptoms of withdrawal.[14,28] Long-term (>3 months) methadone-maintenance patients stabilized on moderate to high doses of methadone (40 to 100 mg) have normal baseline ACTH, β-endorphin, and cortisol plasma levels and normal circadian patterns of release for these, and they usually respond normally to the chemically induced stress of the metyrapone challenge.[13,14,24,25,28] This may be due to the steady opioid receptor occupancy by the long-acting opioid methadone, versus the "on-off" occupancy produced by short-acting opioids. All of these findings lead to an early hypothesis from this laboratory that atypical responsivity to stressors may contribute to the perpetuation of addiction, the relapse to drug use from the abstinent state, and possibly also to the development of addiction.[24,29-31]

This patient illustrates the point that changes in the HPA axis may be more sensitive indicators of opioid withdrawal than the commonly used collection of adrenergic signs and symptoms. These observations also lead one to question the efficacy of α_2-adrenergic agonists in the management of protracted abstinence. α_2-Adrenergic stabilization probably does not result in long-term HPA axis normalization such as seen with methadone maintenance. Although α_2-agonists like clonidine suppress some signs and symptoms of early withdrawal during rapid detoxification of patients from opioids, the disrupting symptoms of restlessness, irritability, poor concentration, and sleep disturbance are not improved by clonidine treatment. Also, the use of clonidine has not prevented relapse postdetoxification.[32]

Acute and prolonged treatment with the opioid antagonist naltrexone, up to 15 months, produces increases in plasma cortisol and β-endorphin similar to those found with opioid withdrawal without the signs and symptoms of acute opioid abstinence.[15,16] The prolonged HPA axis disruption associated with these therapies may be correlated with the signs and symptoms of protracted abstinence that may continue for weeks or months after cessation of shorter-acting opioid use, and thus contribute to relapse after detoxification from opioids. Therefore, stabilization of function and feedback control of these important stress-responsive hormones should be a goal of pharmacotherapy directed at stopping illicit opioid use or of pharmacotherapy for chronic pain. It is of interest that studies of metyrapone tests in methadone-maintained patients show that metyrapone can elicit signs and symptoms of opioid withdrawal. Metyrapone does not displace opioids from their receptor sites like opioid antagonists, nor does it interfere with the bioavailability of methadone. However, metyrapone does cause an increase in ACTH and β-endorphin. Tonic inhibition of the HPA axis by exogenous opioids results in a more pronounced elevation of these POMC peptides when these opioids are withdrawn. We hypothesize that the elevation of these peptides serves as an internal cue for opioid withdrawal. The signs and symptoms of withdrawal associated with metyrapone are not as severe and are of a shorter duration than the classic withdrawal syndrome produced by IV naloxone or by discontinuing opioid administration.

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