CASE REPORT

Influence of Naloxone on Brain and Behavior of a Self-Injurious Woman

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Introduction

Self-injurious behavior (SIB), a dramatic behavioral aberration, occurs in 40% of institutionalized psychotic children (Green 1967; Shodell and Reiter, 1968) and 7%–19% of mentally retarded individuals (Smeets 1971; McKay et al. 1974; Maisto and Baumeister 1978; Schroeder et al. 1978). This behavior remains resistant to most interventions (Romanczyk and Goren 1975). Although diseases with components of self-abuse, such as the Lesch-Nyhan syndrome, have genetic or physiological correlates (Cataldo and Harris 1982), the more common disorder has no known biological substrate.

Recently, the endogenous opiate system, specifically β-endorphin, has been proposed as a possible mediating factor in SIB. Gillberg et al. (1985) reported elevated β-endorphin levels in the CSF of autistic patients who were self-injurious compared with autistic patients who were not. Recently, we (Sandman et al. 1986) found elevated β-endorphin in plasma of developmentally disabled patients with SIB. However, the strongest evidence linking SIB with the opiate system is its reduction by treatment with the opiate antagonist naloxone. Four separate reports (Davidson et al. 1983; Richardson and Zaleski 1983; Sandman et al. 1983; Sandyk 1985) have indicated that naloxone greatly attenuated or completely eliminated SIB in retarded patients. These effects have lasted from 1 hr (Sandman et al. 1983; Sandyk 1985) to 2 days (Richardson and Zaleski 1983). The present case study evaluated the influence of naloxone in a 21-year-old girl of normal intelligence with a history of self-injurious acts.

Methods

Patient History

K. was a short, stocky (59-inch; 116-pound), 21-year-old woman of normal intelligence who was alert and quick to respond. K. behaved in a child-like, highly demanding,

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Received September 15, 1986; revised December 5, 1986.

0006-3223/87/$03.50

manipulative, and negativistic manner. Her mood was labile; she became precipitously and uncontrollably angry if frustrated in her demands. She reported hearing voices that told her to hurt or kill herself. These auditory hallucinations were precipitated by boredom, or being alone, frustrated, and upset. The voice was described as a "heavy loud voice, like that of a man." The voices said: "If you don't want to suffer, kill yourself;" "You are dying;" "Cut yourself real deep;" "Stab yourself and your throat." She had a history of multiple types of self-injurious behavior (e.g., head-banging, biting self, picking sores, swallowing metal, glass, and other dangerous substances, and slashing self); highly manipulative attention-seeking behavior (e.g., expressions of asymptomatic illness); and insomnia. She had several 3–4-inch scars on the volar aspects of both arms. K. was first institutionalized at the age of 13 because of her increasingly self-destructive behavior.

Personal History

K. was the product of a normal gestation, labor, and delivery and showed normal development until the age of 7, when she contracted viral encephalitis. She was in status epilepticus and comatose for 9 days with profound respiratory difficulties leading to a tracheostomy. The acute phase of her illness lasted nearly 1 month, but the resultant physical sequellae included complex motor and absence-petit mal seizures. She evidenced no obvious cognitive or intellectual impairments. However, following her hospitalization, she showed marked personality change, with extreme hyperactivity, decreased attention span, and auditory hallucinations.

Eventually, because of maladaptive behavior, she was made a ward of the court and admitted to a state hospital. She entered the hospital with a fracture of the left humerus and right radius, following a jump from a 25-foot tree. She claimed that "voices" told her to jump. She was agitated, minimally communicative, and her self-injurious behavior required a posey belt and soft tie restraints. K. has resided in state hospitals for a total of 5 of the past 8 years, during which she was placed in 27 less-restrictive residential treatment facilities. All placements proved unsuccessful due to her self-injurious and aggressive behavior. Her longest stay in any community placement was 55 days, and her shortest was 7 days.

K., had two identified medical conditions: grand mal seizures and dysmenorrhea. Her seizures occurred approximately 4 times per month and she reported a subjective sensation (aura), involving her feet becoming hot before her seizures. Electroencephalograms (EEGs) repeatedly indicated diffuse slowing and bilaterally symmetrical, paroxysmal slower activity. A recent CAT scan was normal.

Psychological Test Results

Recent psychological testing with the Wechsler Adult Intelligence Scale (WAIS) revealed that K. was functioning within the normal range of intelligence (full scale IQ 92). Her scores indicated above-average skills in abstract and logical thinking and perception of fine visual details. Bender-Gestalt performance was at the 9-year-old level; however, her memory for figures was excellent. Projective testing indicated concern over sexual development and family relationships. Mild deficits in social independence were noted, most probably related to her institutional living situation.

Medication

Pharmacological history included unsuccessful drug trials with a number of medications, including stimulants, sedatives, and neuroleptics. Currently, she was maintained on 100 mg/day phenobarbital and 200 mg/day carbamazapine for seizure control. Interestingly, K. had a history of paradoxical response to phenobarbital, a finding that may be diagnostically useful in SIB patients (Barron and Sandman, 1983, 1985).

Procedure

The patient voluntarily agreed to participate in this program. She and her guardian were presented with the details of the nature and purpose of the trial, its potential benefit, and the risks/discomforts. Several weeks before the naloxone trial she was gradually weaned (without her knowledge) from medications, using placebo replacement, with no apparent change in behavior or in seizure activity.

These 3 im doses of naloxone (0.4, 0.8, and 1.2 mg) were compared with a volume-matched saline injection in a double-blind procedure. At least 3 days intervened between naloxone treatments. Test sessions began at 9:00 AM each day and never exceeded 90 min, which is consistent with the half-life of naloxone. Injections were not given until K. was completely prepared for the EEG procedure, including attachment of the electrodes. Ten minutes after the injection, the EEG procedure was initiated. This procedure, including removal of electrodes, took 25 min. Within 1–2 min after the EEG procedure, K. was tested with an item recognition test under computer control, which took 15 min. The anxiety inventory was given last and was completed within 5 min. The Conners Scale was administered to the ward staff after K. returned to her residential unit. As such, the Conners reflected measures of behavior that extended beyond the physiological half-life of naloxone. Several objective measurements were made: computer averaged event-related potentials of the brain, memory for items, trait and state anxiety, and behavioral ratings.

Event-Related Potential of the Brain

All testing was conducted in an electrically shielded, sound-attenuating chamber. K. reclined in a comfortable chair as transducers were applied to the scalp. Binaural headphones were placed over the ears, and white noise, supplied by floor speakers, saturated the cubicle to mask extraneous noise. K. was presented with sequences of tones; one tone was frequent (common) and one was infrequent (rare). The sequences were presented in two conditions, one with a fixed or predictable distribution of common-to-rare stimuli, and a second condition in which the occurrence of the stimuli was probablistically determined (i.e., random). In both conditions, a ratio of 1:4 rare (target) to common stimuli was generated. K. was exposed to both the fixed and random conditions in the same test session. In both sequences, she was asked to close her eyes and press a hand-held button when she heard the target stimulus. A pretesting session determined K.'s ability to discriminate the common and rare stimuli. ERPs were collected by sampling the EEG at 200 Hz for 1280 msec. Trials contaminated by movement artifacts were rejected automatically.

Apparatus

Physiological recordings were made with a Grass polygraph, Model 79, equipped with 7P511 amplifiers (Grass Instrument Co., Quincy, MA). Data collection and formatting were accomplished with a MINC 11/74 computer (Digital Equipment Corp., Marlboro, MA). Stimulus was initiated by the same computer system, via a Grass Click-Tone Control Module (Model S10CTCMA). Grass silver cup electrodes were placed according to the international 10–20 system at C3, C4, Fz, and Pz and were referenced to linked mastoids in monopolar arrays. The electrodes were filled with Grass Ed-2 creme and affixed to the scalp. Electrode placements were matched for impedance (no greater than 1000-ohm differences), and pairs of electrodes with impedance of greater than 10K ohms were replaced. The EEG signals were amplified with 1/2-amplitude settings at 60 Hz (high) and 0.30 Hz (low), the latter being equivalent to a 1.1. sec tc.

Event-Related Potential Analysis

Forty ERPs to the common and target tones in both conditions were averaged. A digital filter, with an absolute roll-off at 50 Hz, collapsed the ERPs by averaging four temporally adjacent points. The fidelity of ERP components up to 25 Hz was thus preserved.

Item Recognition Task

The Sternberg Item Recognition Task required K. to memorize a target set composed of one, two, or four digits. First, the target set appeared on a computer screen for 0.8–1.2 sec, depending on size of the target set. Second, a warning signal appeared, followed by a single test digit embedded in a background of letters (distracting stimuli). The subject depressed one electronic switch if the test digit was a member of the memorized set, and a second switch if it was not. One half of the test digits were members of the set and half were not. Ideally, reaction time (RT) is a linearly increasing function of the size of the memory set. Current models (Sternberg 1969) posit that RT consists of (A) time needed to encode the test digit; (B) time needed to compare the test digit with the target set; and (C) time needed to select the response. Attentional processes are reflected in (A) and (C) and appear as changes in the intercept. Memory is reflected in (B) and appears as changes in slope.

Spielberger State-Trait Anxiety Inventory (STAI)

The STAI is a self-administered inventory measuring state (SA) and trait (TA) anxiety (Spielberger et al. 1970). The SA scale, which consists of 20 statements that evaluate how one feels "right now, at this moment" on a 4-point scale was completed each day.

Conners Parent–Teacher Questionnaire

The Conners Rating Scale (Conners 1969) consists of 10 behavioral items. Behavior was rated by staff who indicated whether each item applied "not at all," "just a little," "pretty much," or "very much." Scores of 0, 1, 2, or 3 were assigned to the four response classes of the questionnaire, respectively. Totals were calculated for each day of rating.

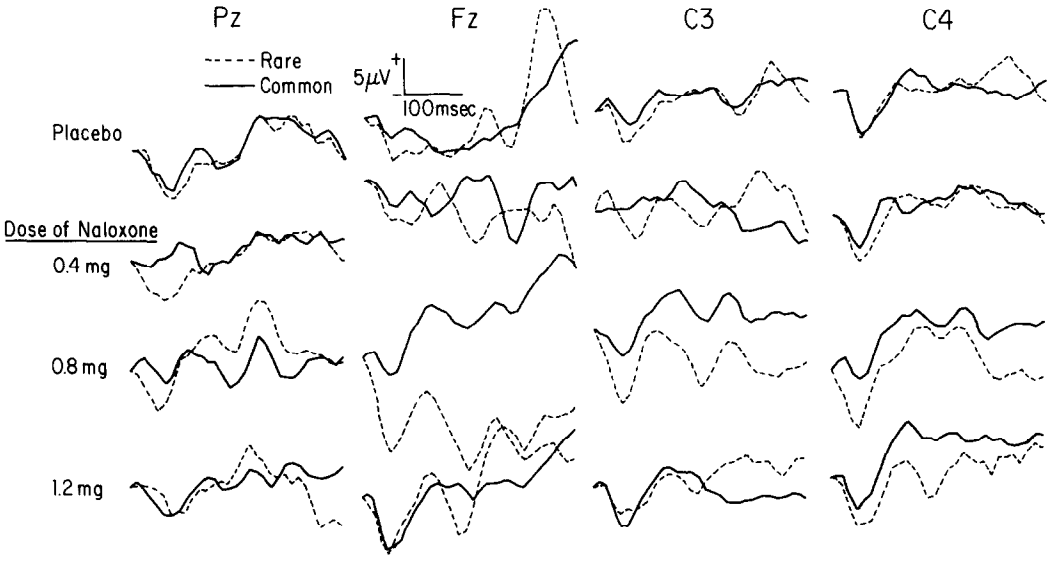
Results

The effects of naloxone on the ERP are presented in Figure 1. The measurement during placebo indicated that the average waveform was somewhat disorganized (especially over Fz), with no evidence of the commonly observed discrimination between the rare and common tone. Treatment with 0.8 and 1.2 mg of naloxone resulted in a robust P3 (at roughly 450 msec) to rare stimuli at all placements, though it was most consistent at P2. The amplitude of P3 is 7–8 μV at Pz and 14 μV at Fz with the 1.2 mg dose. Compared to 22 age-matched controls tested with this procedure, these values are within 1 standard deviation at Pz (7–6 μV ± 4.3), and within 2 standard deviations at Fz (7–1 μV ± 4.7) (Sandman and Donnelly 1983). Furthermore, with the highest dose (1.2 mg), a robust N1 to both rare and common stimuli was apparent at all placements.

Figure 2 presents the results of the item recognition test. The slope of reaction time as a function of set size (memory load) with placebo treatment (333 msec/item) was 4 standard deviations ($p < 0.01$) greater than controls. For a sample of 84 control subjects, aged 20–29, RT slope was 102 ± 61 msec/item. The influence 0.8 and 1.2 mg of naloxone greatly reduced RT slope (135 msec/item) due mostly to faster RT for the largest memory load (the results of 0.4 mg were not available). This slope is within 1 standard deviation of the control sample. Thus, RT slope (reflecting memory scanning) was normalized by treatment with naloxone. The intercept (stimulus encoding and response selection) was not influenced by treatment.

K.'s scores (SA, 61 and 70) were significantly elevated (age-matched controls, 35 ± 13) during placebo (Figure 3). Naloxone attenuated anxiety, with the lowest anxiety score reported after the 0.4-mg dose of naloxone (SA, 52). On the Connors Scale (Figure 3),

Figure 1. Event-related potential averaged from the EEG measured over the posterior (Pz), frontal (Fz), midline left (C3), and right (C4) cerebral cortex. The ERP was collected after treatment with 4 doses (0.0, 0.4, 0.8, and 1.2 mg) of naloxone.



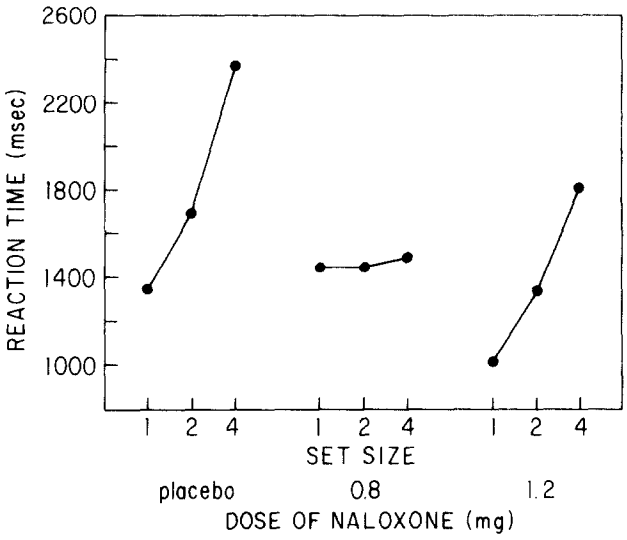


Figure 2. Reaction time (RT) as a function of memory load (set size) and dose of naloxone. Faster RTs are evident after naloxone, especially for the condition with greatest demand on memory (set 4).

improvement was apparent after 0.8 mg of naloxone, but the other two doses were inconsequential. There were no incidences of SIB during the trial with naloxone after a history of 2–6 incidents a week before treatment. K. reported during interviews that the voices had completely disappeared.

Discussion

These clinical findings add support to the contention that opiate antagonists may be effective in treating SIB. The results of the present study are particularly interesting because of the opportunity to evaluate brain and behavioral correlates of naloxone treat-

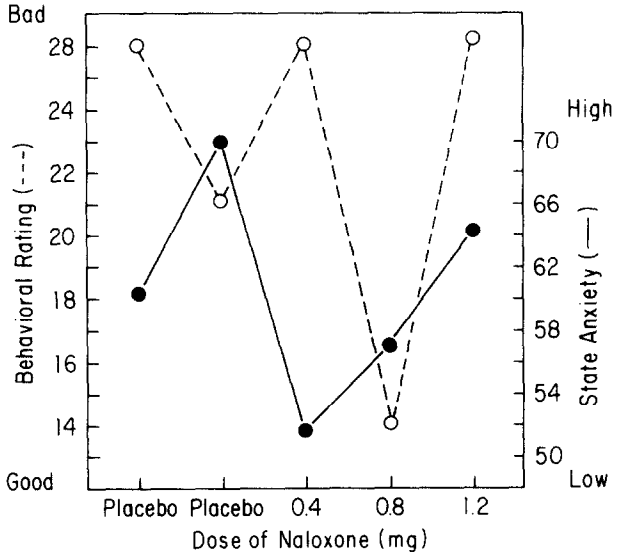


Figure 3. Effects of naloxone compared with two placebo days on anxiety and behavioral ratings. All doses of naloxone decreased anxiety, but only the 0.8-mg dose of naloxone improved behavioral ratings.

ment in an SIB patient. The previously reported studies (Davidson et al. 1983; Richardson and Zaleski 1983; Sandman et al. 1983; Sandyk 1985) of the influence of naloxone on SIB have included subjects unable to submit to the assessment procedures described here. The present data indicated that treatment with naloxone resulted in "normalization" of brain response to external stimulation, increased cognitive capacity, and decreased anxiety. In addition, self-injurious episodes and reported auditory hallucinations that initiated the SIB were eliminated.

Two hypotheses involving the opiate system have been suggested to account for SIB (Richardson and Zaleski 1983; Sandman et al. 1983; Barron and Sandman 1983, 1985). One hypothesis posits that self-injurious individuals may become addicted to their own opiate system and resort to SIB to produce increased levels of β-endorphin. As addiction proceeds and receptors become tolerant, extreme SIB may be required to release β-endorphin and prevent withdrawal. The second hypothesis proposes that SIB is an extreme form of self-stimulation that is required for an underaroused and dampened nervous system. The improvement in cognitive functioning and in the integration of the ERP after treatment with naloxone is consistent with the latter possibility.

The results of this single case are consistent with several other reports. First, augmentation by naloxone of late components of the ERP has been reported in healthy volunteers (Arnsten et al. 1983). Second, improvement in learning and memory have been reported in rats following administration of naloxone (Izquierdo and Gaudenz 1980; Gallagher 1982; Gallagher et al. 1983). Third, Gunne et al. (1977) have suggested, in a somewhat controversial report, that naloxone reduced auditory hallucinations in schizophrenics. Improved interpretation and response to the environment in a self-abusive woman treated with naloxone supports the hypothesis that a type of SIB may be caused and maintained by the endogenous opiate system. Release of the tonic opiate inhibition by naloxone resulted in robust ERPs, improved item recognition, decreased anxiety, and at the 0.8-mg dose, more tractable behavior.

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