Effect of Naltrexone Upon Self-Injurious Behavior, Learning and Activity: A Case Study

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TAYLOR, D. V., W. P. HETRICK, C. L. NERI, P. TOUCHETTE, J. L. BARRON AND C. A. SANDMAN. *Effect of naltrexone upon self-injurious behavior, learning and activity: A case study.* PHARMACOL BIOCHEM BEHAV **40**(1) 79–82, 1991.— Naltrexone significantly attenuated self-injurious behavior in a 20-year-old mildly retarded autistic male patient. The patient was videotaped daily and behavior was evaluated with a time-sampling procedure. Behavioral ratings of SIB frequency, SIB severity, and activity were collected automatically with a computerized system. Learning and memory were tested on a weekly basis with a modification of a paired associate learning test (PALT). Treatment with naltrexone resulted in (a) attenuation of SIB in the unstructured setting and (b) improvements in learning and memory without influencing activity levels.

SELF-INJURIOUS behavior (SIB) is a treatment-resistant behavior with no clear pathogenesis. Several studies indicate that opioid receptor blockers attenuate SIB (3, 5, 6, 17, 22, 31, 33, 34). Two biological hypotheses have been proposed to explain the involvement of the endogenous opioid system in SIB (10, 12, 31). The addiction hypothesis maintains that SIB supplies a "fix" for tolerant, down-regulated opioid receptors and is supported by evidence that β-endorphin (BE) is released in response to aversive stimulation (27) and that BE administration results in tolerance and physical dependence (36). The pain hypothesis suggests that the SIB patient may have an opioid-induced elevated sensory threshold obviating the experience of pain. Elevated levels of opioids found in CSF (16) and plasma (30) of SIB patients, and the lowering of sensory thresholds after naloxone (2) supports this possibility. Thus treatment with naltrexone would restore normal pain thresholds making SIB more aversive.

Another possibility is that naltrexone does not reduce SIB specifically, but sedates the patient and reduces all activities. Research has indicated that naltrexone is stimulating at low doses and sedating at high doses (6). Moreover, low doses of opiate blockers enhance both learning and retention in animals (13) probably by removing inhibition of adrenergic and dopaminergic neurons involved in central amygdaloid processing (1, 14, 15, 21, 28). In contrast, opiate agonists impair learning and retention in animals (7). Research on the effectiveness of opiate blockers or agonists in modulating the learning process in developmentally impaired SIB patients is unknown, although some positive effects were observed in a female SIB patient of normal intelligence (32). The present study was undertaken to evaluate the effectiveness of treating SIB with naltrexone and determine its effects on cognition and sedation.

METHOD

The patient was a 20-year-old male with the clinical diagnosis of autism, mild mental retardation, and microcephaly who had been transferred for clinical evaluation to Fairview Developmental Center from the community, where he resides in a home with his adoptive mother. The patient was assessed to have a Leiter Mental age of 7–4, an IQ of 56, and a Visual-Motor Integration (VMI) age equivalent of 6–10. His Peabody Individual Achievement Test (PIAT) scores indicated mid-kindergarten skills in letter/word recognition and spelling with lower abilities in mathematics and general information. His hearing and vision were normal, and a score of 113 in the fine and gross motor domains of the Vineland social adaptation test is representative of high average physical aptitude.

During the course of the study the patient was continued on 13.75 mg/day Haldol, and 4.0 mg/day Cogentin which were previously prescribed. Screening with a fifteen item modification of the DISCO revealed no signs of tardive dyskinesia. However, the patient did show stereotypy.

Three doses of naltrexone (0.5, 1.0, 2.0 mg/kg administered orally) were compared with placebo in a partially blinded clinical evaluation design. Each dose and placebo was evaluated for 1 week. The drug doses were given in ascending order on consecutive weeks following two weeks of placebo. However, drugs and matching placebo were given only on Monday and Wednesday at 8:00 a.m. Thus the patient received two exposures to each treatment.

The patient was videotaped four days per week for six five-minute intervals throughout the day in his unstructured environment. At least 15 minutes separated the intervals. Three were in

the morning and the other three were in the afternoon. No alteration in the patient's schedule was imposed except for the learning measures (structured environment) described below.

After one week of accommodation to the procedures, systematic behavioral measures were made from the videotape. Data were recorded with the operation of an observational data acquisition program (18). A single observer blind to order of drug administration scored the videotape. The observer scored frequency of SIB by depressing keys on a computer terminal customized to the patient's behavior. In addition, for each five-minute interval, the observer was prompted to rate severity of self injury on a six-point scale and patient's activity on a seven-point scale (33). The patient's SIB repertoire included biting arms, head banging, pounding hands or wrist against hard objects, kicking himself, slapping himself, and hitting his head with a clenched fist. Data were collapsed across a one-week interval, and SIB measurements were integrated to hourly frequency.

Cognitive ability was measured using a modification of a paired associate learning test (PALT) (35). The test required the patient to make a spatial association with three-dimensional objects as opposed to making a verbal association with pictures. The test was performed at the same time in the same room on Wednesday of each week (structured environment). The patient was given a sweet reinforcer upon entering the session and again upon completing the task. The learning session was initiated by seating the patient at a table in front of two identical trays and presenting him with an object and instructing him to place it in the designated tray. The patient was given verbal and gestural prompts on the first trials. When the patient could place the object correctly without prompts, he was given another object and another corresponding tray location. The number of objects and trays were incremented until a maximum of 4 trays were in use. The number of objects was unlimited. Objects were presented in a randomized order. Each session was fifteen minutes long unless terminated by the patient expressing inattention or unwillingness to continue through failure three times to respond to verbal request or prompts on a single trial, or communicative gestures such as moving away from the table or pushing away the trays. Behaviors during the test and ten minutes posttest were filmed and scored (structured environment). Data were collected for duration, number of trials completed, number of correct placements, and number of prompts used per session. An initial test was given one week before the baseline test in order to allow the patient familiarity with the task. Data from this test were excluded. Attention, learning rate, and short-term memory were assessed.

RESULTS

The patient displayed six different types of self injury (Fig. 1) throughout the course of the study. Three behaviors, pounding hands against objects, hitting head with fist, and biting arms, were seen during the baseline period. On the 0.5 mg/kg dose, pounding objects and hitting head were eliminated while arm biting was reduced. During the 1.0 mg/kg dose there was a resurgence of object pounding, a reduced amount of arm biting, while hitting head was eliminated. All of the initially observed behaviors were reduced by 2.0 mg/kg though there was an emergence of three new behaviors on day three. No acute withdrawal effects were seen. On one day immediately after the second 1.0 mg/kg dose the rate of behavior was higher than the day of drug administration.

The data in structured and unstructured environments are presented in Fig. 2. All doses of naltrexone decreased the rate
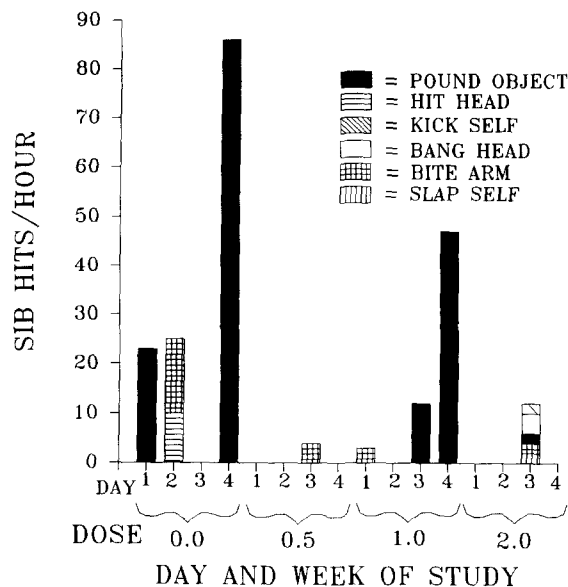

FIG. 1. Frequency of SIB for each behavior for each day of each week (week 1 = placebo, 2 = 0.5 mg/kg, 3 = 1.0 mg/kg, and 4 = 2.0 mg/kg) of the study expressed in hits per hour. Drug doses were given at 8:00 a.m. on days 1 and 3 and observations were made on days 1–4 or Monday–Thursday of each week.

of self-injurious behavior in the unstructured, normal residential environment. It appears that 0.5 and 2.0 mg/kg doses were the most effective for attenuating SIB. SIB was not evident in the structured environment during placebo and a slight increase in SIB was seen during the treatment period.

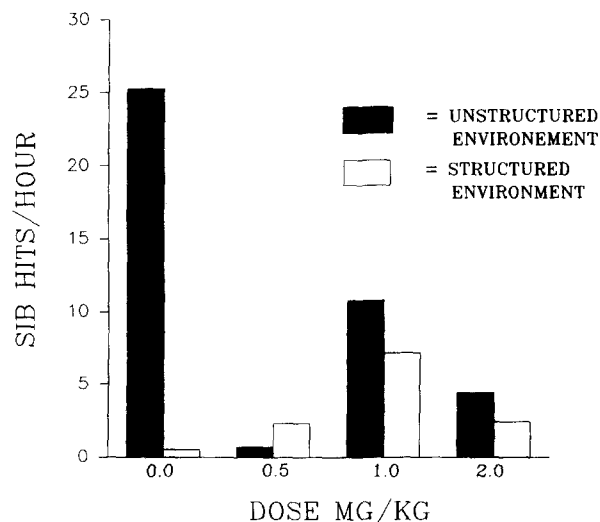Activity level was rated 3.29 ± 1.36 S.D. during placebo base-

FIG. 2. Frequency of SIB interpolated to hits/hour in the unstructured and structured environment after open treatment with placebo and 3 doses (0.5, 1.0 or 2.0 mg/kg) of naltrexone given orally at 8:00 a.m. on Monday and Wednesday.
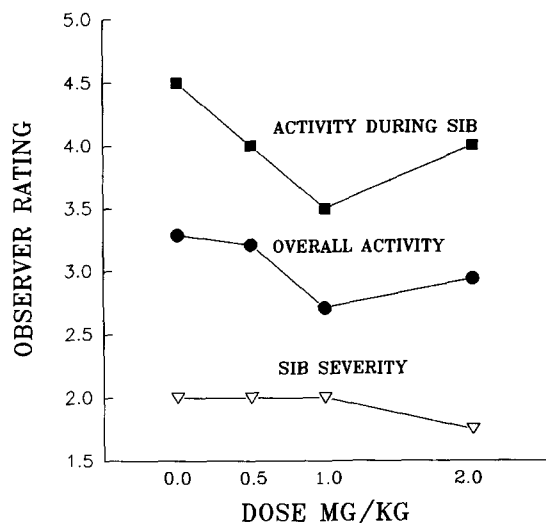
FIG. 3. Rating of patient activity level on a seven-point scale (0 was completely inactive and 7 was uncontrolled hyperactivity) both during SIB and overall and rating of SIB severity for sessions in which SIB occurred on a six-point scale (0: did not occur to 6: eminently life threatening) during treatment with placebo and naltrexone.
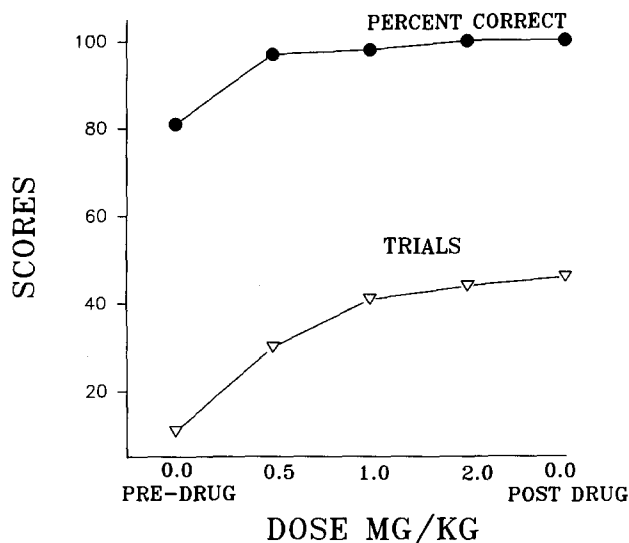
FIG. 4. Improvement in accuracy (percent correct responses) and number of trials completed per session during learning task after naltrexone. All tests given on day three of week four hours after 8:00 a.m. drug administration.

line and was slightly lower at all drug doses (Fig. 3). Over the course of drug administration the patient's activity level corresponded with the patient remaining awake and sitting quietly (average activity = 3.01 ± 1.20). There was a slight drop in activity during the 1 mg/kg dose. Severity of self injury was constant between placebo and the first two doses but dropped slightly at the highest dose.

The patient was able to perform the learning task independent of prompting except for one prompt needed during the postdrug session. Learning accuracy and attention to task increased during administration of naltrexone at all doses. Figure 4 shows that the patient completed more trials per session and improved in accuracy as the dosage increased. During baseline the patient was able to remain on task for three minutes. Time on task increased to fourteen minutes for all subsequent tests. The learning test was repeated one week after medication had been withdrawn. Learning performance was maintained and did not improve but there was a marked decrease in compliance and an increase in maladaptive behavior including SIB.

DISCUSSION

All doses of naltrexone abruptly and dramatically attenuated SIB in the unstructured, residential setting without causing sedation of the patient. This result is consistent with studies suggesting that opiate blockers may be effective in treating SIB (3, 5, 6, 17, 22, 31, 33). Further, the effect of naltrexone was only observed when SIB was most frequent (unstructured setting) and the effect was most apparent in reducing the most frequent behavior. This is consistent with other reports that naltrexone was more effective with severe patients (33,17). The difference between structured environment and unstructured environment may reflect the patient's response external demands being placed upon him (11). Naltrexone may be more effective in reducing behavior that is primarily biologically and not environmentally contingent.

Behavior was reduced during the four-day observation period even though drug was administered on days one and three of each week. Single doses of naltrexone in the dose range used have been shown to block opiate receptors for a 24-hour period (27) and one study has shown a significant holdover effect (3). Opiate blockers have been shown to precipitate withdrawal in opiate-addicted individuals (27), so the absence of withdrawal symptoms is the only evidence against an addiction hypothesis of SIB. However, while withdrawal effects indicate that physical dependence existed, physical addiction can occur independent of physical dependence (9). Validity of the alternate pain hypothesis cannot be assessed because no data was collected to indicate sensory thresholds after naltrexone administration.

Improvement on the learning task was associated with naltrexone administration. The effects were not dose dependent because all doses had an equal effect upon learning. Learning performance was maintained two weeks after withdrawal of naltrexone, even though increased maladaptive behavior was seen during testing. Maintenance of test performance may reflect naltrexone's property of improving retention (13,26) in contrast to drugs which elicit state-dependent learning (35).

Although these findings are preliminary, other studies of discrimination learning in mice have shown that injections of opiate blockers before learning enhanced the retention of learning one week after testing (28). It is possible that BE not only "drives" and/or maintains SIB, but also actively interferes with information processing (7, 19, 20, 23, 28). Future studies will determine if naltrexone reliably improves adaptive functioning such as learning and memory among autistic and SIB patients.

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