Pharmacology Biochemistry & Behavior, Vol. 9, pp. 265–267. Printed in the U.S.A.

BRIEF COMMUNICATION

Effects of Repeated Injections of Naltrexone on Antagonism of Rate Decreases by Morphine in the Pigeon[1]

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(Received 1 June 1978)

SMITH, J. B. *Effects of repeated injections of naltrexone on antagonism of rate decreases by morphine in the pigeon.* PHARMAC. BIOCHEM. BEHAV. 9(2) 265–267, 1978.—Responding of three pigeons was maintained under a multiple schedule of food presentation in which key-pecks produced access to grain under a fixed-interval schedule in the presence of one stimulus and a fixed-ratio schedule in the presence of another stimulus. Repeated daily injections of 1 mg/kg naltrexone had no systematic effect on overall response rate during either schedule component, and the naltrexone continued to antagonize rate decreases of periodic single injections of 10 mg/kg morphine for seven weeks. Tolerance did not occur to the antagonistic effects of naltrexone on rate decreases generally produced by morphine.

Naltrexone Morphine Tolerance Schedule-controlled responding Pigeon

THOUGH naltrexone has been widely used in clinical trials for treatment of narcotic addicts [5, 7, 10], there is little systematic information on the effects of its long-term repeated administration. In treatment programs, for example, too few patients have continued to rely exclusively on naltrexone in their effort to forego narcotic self-administration, and for those who continue treatment for long periods, success is often attributed more to ongoing counseling than to occasional doses of naltrexone [2, 6, 7, 8, 10]. Consequently, the extent of tolerance development to the effects of naltrexone is not well studied, although there are indications that tolerance does occur for many of its direct undesirable effects. In squirrel monkeys, for example, weight loss, rhinitus, and colitus do not occur after 12 mg/kg naltrexone when that dose is reached in gradual increments, but do occur when animals initially receive 12 mg/kg naltrexone [1]. Similarly in humans, nausea and abdominal pains that occur after initial administration of 20–40 mg/kg naltrexone disappear after repeated administration [4]. It is not known, however, if tolerance also occurs for the antagonistic effects of naltrexone. The purpose of the present experiment was to study tolerance development for the antagonism by naltrexone of the rate-decreasing effects of morphine on schedule-controlled responding of the pigeon.

METHOD

Animals

Three male White Carneaux pigeons (P-294, P-8071, and P-3917) were housed individually and maintained at approximately 80% of free-feeding weights. Water and grit were always available in living cages. Animals had previously responded under a variety of schedules of food presentation and had previously received a variety of drugs, including morphine.

Apparatus

The general features of the experimental chamber have been described elsewhere [3]. The chamber was a modified picnic ice chest which included a standard response key (No. G6315; Ralph Gerbrands Co., Arlington, Mass.) mounted on a false wall. The key was transilluminated by either a red or a blue light and could be operated with a minimum force of about 15 g. Access to mixed grain could be provided through an opening located beneath the response key. Programming and recording equipment were located in an adjacent room.

Procedure

Key-pecking was maintained under a multiple schedule. Responding in the presence of a red keylight was maintained under a 10-min fixed-interval schedule (FI), and responding in the presence of a blue keylight was maintained under a 30 response fixed-ratio schedule (FR). Schedule components alternated, and daily experimental sessions consisted of 6 presentations of each component. Food was available for 10 sec upon completion of each component. Experimental sessions were conducted Monday–Friday.

After responding was stable under control conditions, saline (0.5 ml/kg) was injected intramuscularly just prior to 5

[1]Research supported by Grants MH-18421 and DA-01015 from the U.S. Public Health Service. I thank J. W. McKearney for comments of an earlier form of the manuscript and A. Oldham for technical assistance.

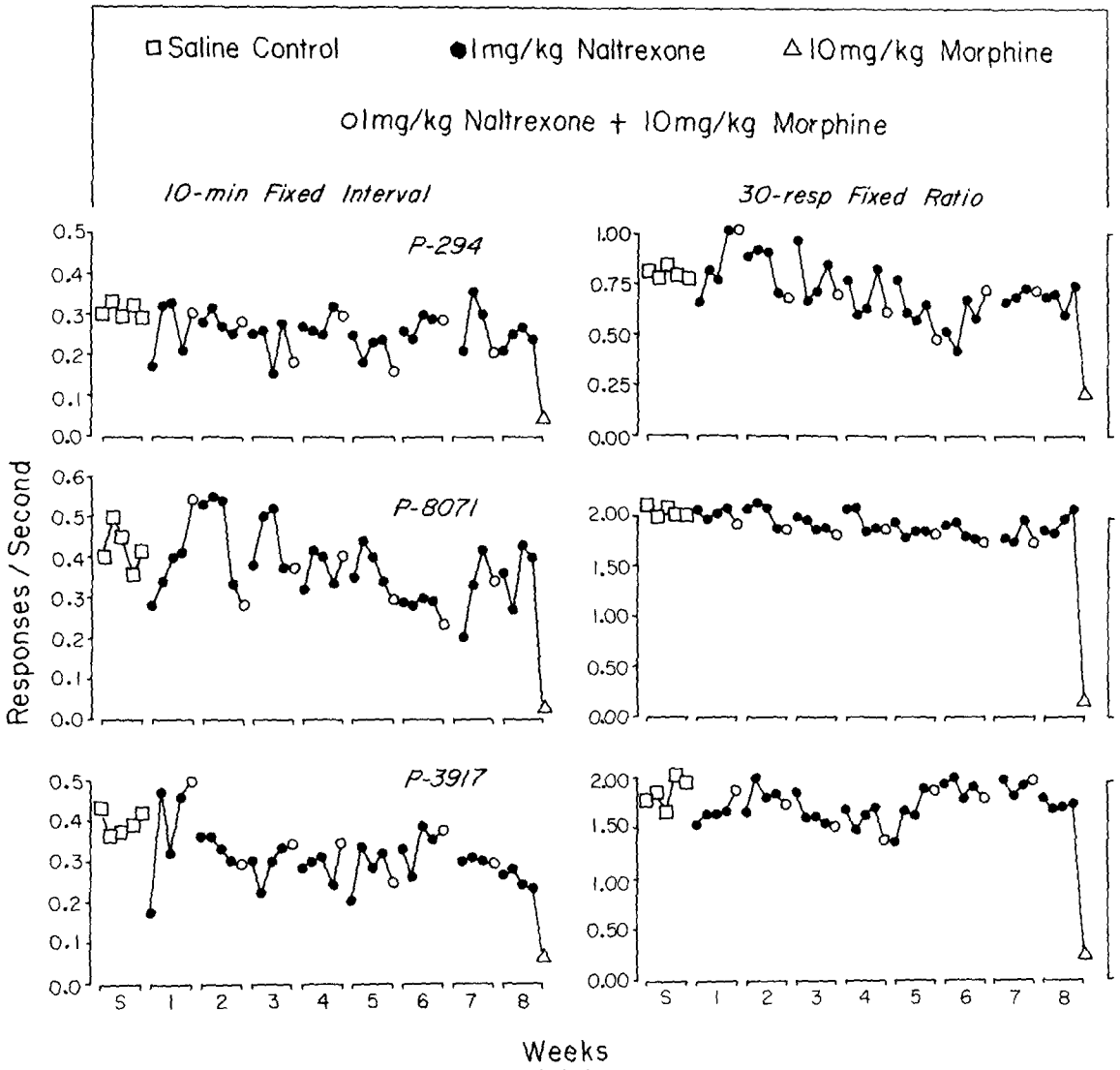

FIG. 1. Effects of repeated administration of 1 mg/kg naltrexone on the rate-decreasing effects of 10 mg/kg morphine. Left-fixed interval; right-fixed ratio. Effects in each row are for a different animal. Open squares: saline; closed circles: 1 mg/kg naltrexone; open circles: 1 mg/kg naltrexone plus 10 mg/kg morphine; open triangles: 10 mg/kg morphine. Ordinate: Response rate in responses per sec. Abscissa: Consecutive sessions for 8 weeks.

daily experimental sessions. Then, for the next 7 weeks, 1 mg/kg naltrexone (courtesy of Endo Laboratories) was injected intramuscularly just prior to daily sessions on Monday–Thursday, and 1 mg/kg naltrexone plus 10 mg/kg morphine were injected just prior to sessions on Friday. This dose of morphine is one that typically decreases response rate under these schedules approximately 80–90%. Naltrexone was also injected on Saturdays and Sundays when sessions were not conducted. During the eighth week, 1 mg/kg naltrexone was injected just prior to daily sessions Monday–Thursday, and 10 mg/kg morphine alone was injected just prior to the session on Friday.

After the eighth week of repeated daily injections, animals were given no further injections for eight more weeks. Experimental sessions were conducted as usual during this additional time. Then, during the ninth week, 10 mg/kg morphine alone was once again injected.

RESULTS AND DISCUSSION

Saline had no systematic effect on responding under either schedule (Fig. 1, open squares; FI-left, FR-right). Naltrexone alone disrupted responding initially, but had no systematic effects thereafter (Fig. 1, closed circles). Similarly, when naltrexone and morphine were injected together, responding was not systematically affected under either schedule component (Fig. 1, open circles). If tolerance had occurred to the antagonism by naltrexone to the rate-decreasing effects of morphine, responding would have been progressively decreased during successive sessions when morphine was administered. Consequently, tolerance did not occur to the antagonistic effects of naltrexone within 7 weeks, and there was no indication that tolerance would have developed over a longer time period.

When morphine was administered alone prior to the last session of the eighth week of repeated daily injections, re-

sponding was substantially decreased during both schedule components (Fig. 1, open triangles). Consequently, tolerance had not developed to the acute effects of morphine during its repeated weekly administration in combination with naltrexone, and previous naltrexone had not accumulated enough to antagonize rate decreases of morphine alone when the morphine was administered 24 hr after the last naltrexone dose. Therefore, the absence of rate decreases after morphine on preceding Friday sessions was most likely due to the repeated antagonism by individual doses of naltrexone.

When morphine (10 mg/kg) was administered alone after 8 drug-free weeks, responding was again substantially decreased during both schedule components. These effects are not shown in Fig. 1, but responses/sec for each animal during the fixed-interval and fixed-ratio schedules respectively were: P-294 0.13, 0.46; P-8071 0.03, 0.23; P-3917 0.09, 0.26. Additionally, morphine (10 mg/kg) comparably decreased responding in P-294 and P-8071 under similar schedule conditions prior to repeated injections of naltrexone [9]. Consequently, morphine had similar acute effects whether administered prior to repeated daily injections of naltrexone, just after the repeated naltrexone, or 8 drug-free weeks after the repeated naltrexone. Daily injections of 1 mg/kg naltrexone did not alter the effects of 10 mg/kg morphine alone.

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