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RAPID COMMUNICATION

Tolerance to the Effects of Buprenorphine on Schedule-Controlled Behavior and Analgesia in Rats[1]

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BERTHOLD, C. W., III AND J. M. MOERSCHBAECHER. *Tolerance to the effects of buprenorphine on schedule-controlled behavior and analgesia in rats.* PHARMACOL BIOCHEM BEHAV **29**(2) 393–396, 1988.—Responding in rats was maintained under a fixed-ratio 30 schedule of food presentation. When administered acutely buprenorphine (0.018–0.56 mg/kg) produced dose-related decreases in overall rate of responding. In addition to schedule-controlled behavior, the analgesic effects of buprenorphine were evaluated during chronic administration using the tail-flick method. Tolerance developed to the effects of buprenorphine on both measures. In general dose-effect curves for the rate-decreasing effects of buprenorphine were shifted to the right by approximately 2 log units. In one subject, however, tolerance did not develop to the rate-decreasing effects of 10 mg/kg, suggesting that behavioral tolerance to buprenorphine is dose limited. Finally, the data also suggested that tolerance may develop more slowly, yet more completely, to the analgesic than to the rate-decreasing effects of buprenorphine.

Tolerance Buprenorphine Schedule-controlled behavior Analgesia

WHEN administered acutely buprenorphine has consistently been shown to disrupt food-maintained responding in squirrel monkeys [8,10] and rats [2,17]. For example, in rats responding under a fixed-ratio discrimination procedure buprenorphine decreased response rate and increased errors in a dose-related manner similar to that of morphine [17]. Studies concerning the acute effects of buprenorphine on schedule-controlled behavior in old world primates have yielded somewhat conflicting results. For example, in several studies buprenorphine was found to have little or no effect on overall rate of responding [13, 14, 17, 18] while others have reported that buprenorphine produces dose-related decreases in response rate [12, 15, 22]. It should be noted, however, that rate-decreasing effects generally obtain only at very high doses (3.2 mg/kg and above).

When administered chronically tolerance has been reported to develop to the analgesic effects of buprenorphine in a variety of assays including the phenylquinone-writhing test [5], rat tail-flick [1] and shock titration procedure [11]. There have, however, been few studies concerning the chronic effects of buprenorphine on schedule controlled behavior. In one study Dykstra [10] investigated the effects of chronic buprenorphine in squirrel monkeys responding under a multiple fixed-ratio, fixed-interval schedule of food presentation. In that study tolerance failed to develop to the rate-decreasing effects of buprenorphine when administered daily. The results of another such study suggest, however, that tolerance develops to the rate-decreasing effects of buprenorphine in macaque monkeys when responding is maintained by food presentation under a second-order schedule [15]. The present study was therefore designed to widen this narrow data base by determining whether tolerance would develop to the effects of buprenorphine on schedule-controlled behavior and analgesia in the rat. Drug effects on schedule controlled behavior were evaluated under a fixed-ratio schedule of food presentation, while analgesia was measured by the tail-flick method [6,9].

METHOD

Subjects

Three naive adult male Long-Evans hooded rats were maintained at approximately 80% of their free-feeding weight by food presented during the sessions and by post-session

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supplemental feeding (Purina Rat Chow). Water was continuously available in the individual home cages.

Apparatus

The experimental operant chamber measured 23.5× 30×26.5 cm. A lever was mounted on the side wall 5 cm above the grid floor. A downward force of 0.25 N was required to activate the lever and record a response. Three pilot lamps located 5 cm above the lever were illuminated during the session and a pellet trough was located 6 cm to the right of the lever. Solid-state equipment controlled the experiment and the data recorded on counters, running-time meters and a cumulative recorder.

The tail-flick apparatus was similar to those previously described [9] and consisted of a bulb fitted with a reflector with which radiant heat could be focused on the tip of a rat's tail. Response latencies to this stumulus were automatically determined by an electronic timer.

Procedure

The rats were trained to respond under a fixed ratio (FR) 30 schedule of food presentation. Under this schedule 30 responses were required to produce a food pellet (Bio-Serv, Product No. 0021, 45 mg). Each daily session lasted 30 minutes. Drug testing began when responding under the FR schedule stabilized and no systematic change was evident from session to session. Tail-flick latency was recorded before each session and then again five minutes after completion of each session. Stimulus intensity was determined for each subject such that the control latency was 2 to 5 seconds. A cut-off time of 10 seconds was used to avoid tissue damage from the heat source.

During the acute phase of the study, sessions were conducted five days a week. Drug testing was generally conducted on Tuesdays and Fridays with saline control sessions on Thursdays. During the chronic phase sessions were conducted daily.

Drugs

Buprenorphine HCl (supplied by the National Institute on Drug Abuse, Rockville, MD) was dissolved in sterile water. Injections were given IP with the volume of injection being 2 cc/kg b.wt. Buprenorphine was administered IP 15 minute presession.

Data Analysis

Response rate was determined by dividing the total number of responses by the session time. Tolerance to the effects of buprenorphine on response rate was generally defined as a return to the saline control range for two consecutive sessions. After tolerance developed to the effects of a given dose on response rate, the chronic dose was increased 1/4 log unit (e.g., 0.18 to 0.32 mg/kg). Each dose was generally administered for at least three days even if response rates were unaffected.

Tail flick data were expressed as percent maximum possible effect (% MPE) [9] where:

$$\% \text{ MPE} = \frac{\text{post-drug latency} - \text{predrug latency}}{\text{cut off time (10 sec)} - \text{predrug latency}} \times 100$$

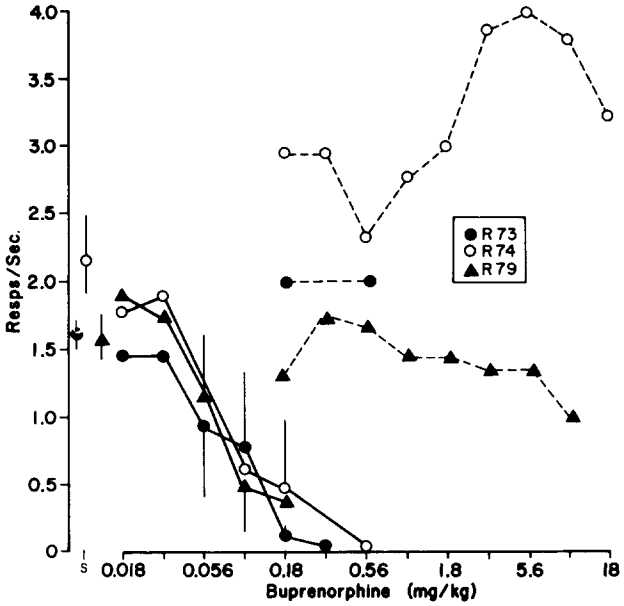

FIG. 1. Effects of varying doses of buprenorphine on overall response rate under the fixed-ratio (FR) schedule in each subject. Points connected by the solid lines were determined prior to the chronic drug administration. The points with vertical lines in these dose-response curves indicate the mean and the range for at least two determinations. The points without vertical lines indicate either a single determination or an instance in which the range is encompassed by the point. Each point connected by the dashed lines was collected following the chronic administration of that dose. The points and vertical lines above S indicate the mean and the range for at least twelve saline doses for each subject.

Tolerance to the analgesic effects of buprenorphine was generally defined as 10% MPE or less for two consecutive sessions.

RESULTS

The acute effects of varying doses (0.018–0.56 mg/kg) of buprenorphine on responding under the FR schedule are shown in Fig. 1. Buprenorphine produced dose-related decreases in overall response rate in each of the rats tested. On the basis of these data a dose of 0.18 mg/kg was chosen as the initial chronic dosage. This dose was chosen for chronic administration because it was the lowest dose which reliably decreased response rate by at least 50% in each of the subjects.

Also shown in Fig. 1 are the effects of various doses of buprenorphine on response rate following the chronic administration of that dose (dashed lines). Tolerance clearly developed to the rate-decreasing effects of buprenorphine in each subject. For example, in R79 at the end of the chronic administration the magnitude of the rate-decreasing effect produced by buprenorphine, 10 mg/kg, was comparable to that produced by a dose of approximately 0.056 mg/kg in this same subject on an acute basis. By extrapolation these data would indicate a $2^1/_2$ log unit shift to the right in the buprenorphine dose-effect curve as a result of chronic drug administration.

The daily effects of chronic buprenorphine on overall response rate and analgesia are shown for subject 74 in Fig. 2. Tolerance rapidly developed to both the rate-decreasing and analgesic effects of the initial chronic dose of 0.18 mg/kg.

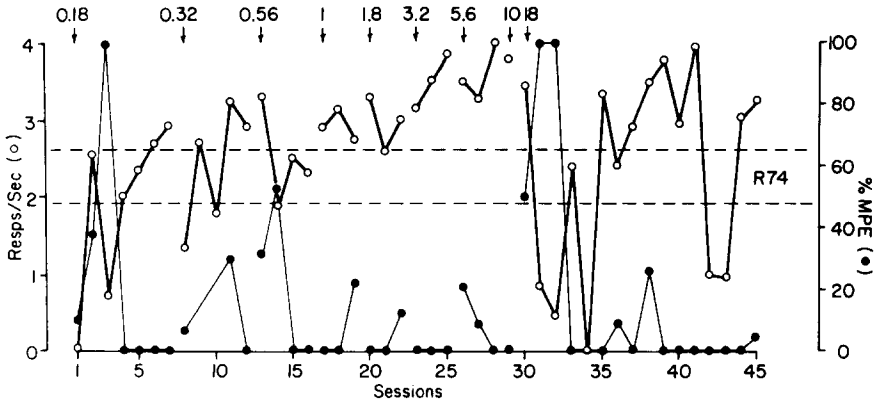

FIG. 2. Effects of chronic buprenorphine on overall response rate (Resp/Sec) under the FR schedule and on analgesia (%MPE) as measured by the tail-flick method for subject R74. The horizontal dashed lines indicate the control range for 15 sessions which were preceeded by saline injections. The chronic daily dose (mg/kg) is indicated by the numbers at the top of the figure. Occasionally (e.g., session 10) no data point is plotted for %MPE due to apparatus failure on that day.

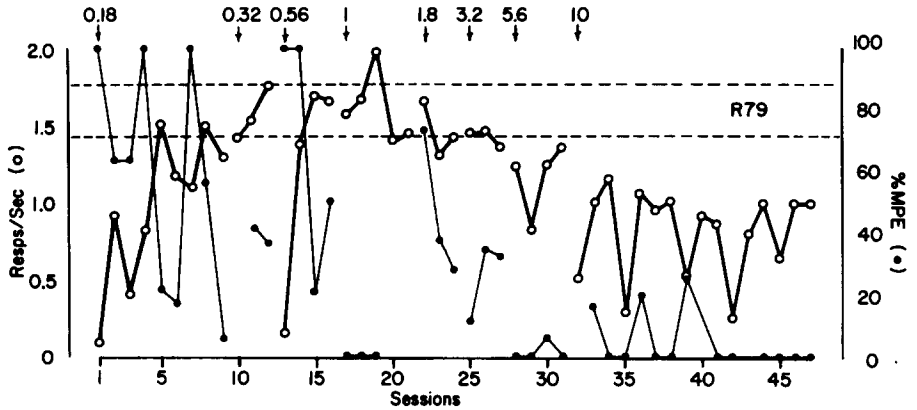

FIG. 3. Effects of chronic buprenorphine on overall response rate (resps/sec) under the FR schedule and on analgesia (%MPE) as measured by the tail-flick method for subject R79. The horizontal dashed lines indicate the control range for 12 sessions which were preceeded by saline injections. Otherwise the details are the same as in Fig. 2.

Over the next 29 sessions the dose was increased to 10 mg/kg. Tolerance to the rate-decreasing effects of buprenorphine was evident. Increasing the dose of buprenorphine did not decrease response rate. Rather, a trend towards increases in response rate above the control rate can be seen in the data across this dose range. Similarly, with a few perturbations, tolerance also developed to the analgesic effect of buprenorphine. Unlike the data for response rate, however, increasing the dose of buprenorphine often resulted in an initial increase in analgesic activity followed by the development of tolerance (e.g., 0.32, 0.56 and 5.6 mg/kg). These data are similar to those observed at the lower chronic dose in subject R73 (data not shown). Thus, in both subjects limited analgesic activity could be detected at doses at which tolerance was clearly evident in terms of the rate-decreasing effects of buprenorphine. On session 30 the chronic dose of buprenorphine was increased to 18 mg/kg. Over the next few sessions (30–34) response rate decreased and the analgesic effects increased. With continued administration of this dose, however, tolerance developed to buprenorphine's effect on both measures.

The daily effects of chronic buprenorphine on overall response rate and analgesia are shown for subject R79 in Fig. 3. As in the other subjects tested, 0.18 mg/kg decreased response rate and produced a marked analgesic effect. Tolerance developed to both of these effects at this and subsequent doses up to 5.6 mg/kg. As was seen in the other subjects, instances occurred where tolerance was complete in terms of the rate-decreasing effects of buprenorphine but not in terms of its analgesic effects. This differential tolerance was apparent at several doses (e.g.; 0.32, 0.56 and 3.2 mg/kg). On session 32 the chronic dose was increased to 10 mg/kg. While tolerance subsequently developed to the analgesic effects, complete tolerance did not develop to the rate-decreasing effects of buprenorphine at this dose.

DISCUSSION

On an acute basis buprenorphine decreased overall response rate at doses ranging from 0.056 to 0.56 mg/kg. These data are in good agreement with those previously reported in rats responding under both a fixed-ratio and fixed-

consecutive number discrimination procedures [2,17]. Despite some individual differences in the data, upon chronic administration tolerance clearly developed to buprenorphine in terms of both schedule-controlled behavior and analgesia. In addition, there was good accord among the subjects in terms of the degree of tolerance which developed.

Dykstra [11] has pointed out that in each study in which tolerance has been reported to the effects of buprenorphine, the dose was one which produced an analgesic effect. Such was also the case in the present study. This observation is, however, also critically related to the species under study. It should be noted that in old world monkeys and rats analgesia is produced at doses of buprenorphine less than or equal to those required to affect schedule controlled behavior [3–5, 17, 18]. In squirrel monkeys, however, this same relationship does not hold. Rather, buprenorphine appears to produce analgesic effects only at doses greater than those required to affect schedule-controlled behavior [10,11]. Thus, relative to other species the squirrel monkey appears to be inordinately sensitive to the effects of buprenorphine on schedule-controlled behavior.

In squirrel monkeys responding under a multiple fixed-ratio fixed-interval schedule some tolerance develops to the rate-decreasing effects of buprenorphine after weekly administration but not to the effects of daily administration at a dose of 0.01 mg/kg [10]. In the present study, however, tolerance developed to the rate-decreasing effects of buprenorphine during daily administration. It is generally acknowledged that tolerance will develop in those situations where the action of the drug is such that it results in a decrease in the rate of reinforcement [7,19]. While this criterion was met in both the present and previous study [10], tolerance following daily administration developed in only the present study. These seemingly discrepant findings may be related, in part, to the chronic dose administered. It is a general finding that the development of behavioral tolerance is dose limited [16, 20, 21]. That tolerance did not develop following the daily administration of 0.01 mg/kg in the previous study [10], may simply represent a dose-limitation in terms of the development of tolerance to the rate-decreasing effects of buprenorphine in the squirrel monkey. That, in the present study, tolerance developed to the analgesic but not to the rate-decreasing effects of 10 mg/kg in subject R79 (see Fig. 3) would further support the conclusion that behavioral tolerance to the rate-decreasing effects of buprenorphine is dose limited.

Finally, the present data are also consistent with previous reports that tolerance develops to the analgesic effects of buprenorphine in a variety of assays and species [1, 5, 11]. While in general tolerance to the rate-decreasing and analgesic effects of buprenorphine developed in a parallel fashion, there were periodic exceptions to this finding. For example, in each subject, on several days complete tolerance was apparent to the rate-decreasing but not to the analgesic effects of buprenorphine. This was true at several doses and might suggest that, in the rat, tolerance develops somewhat more slowly yet more completely to the analgesic than to the rate-decreasing effects of buprenorphine.

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