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Tolerance Development to Butorphanol: Comparison With Morphine

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FENG, Y. Z., Y. T. TSENG, S. P. JAW, B. HOSKINS AND I. K. HO. *Tolerance development to butorphanol: Comparison with morphine.* PHARMACOL BIOCHEM BEHAV **49**(3) 649-655, 1994.—In order to evaluate and to compare the time course, dose response, and the degree of tolerance development to butorphanol and morphine, rats were continuously intracerebroventricularly (ICV) infused with saline vehicle (1 μl/h), butorphanol (6.5, 13, 26, and 52 nmol/μl/h), or morphine (1.6, 6.5, and 26 nmol/μl/h) through osmotic minipumps for 1 to 3 days. The tail-flick responses were determined pre-, during, and postinfusion. Tolerance to morphine developed faster than that to butorphanol. The antinociceptive response to the ICV challenge dose (6 h after the termination of drug infusion) of butorphanol or morphine was decreased significantly and there was a negative correlation between the dose of the drug infused and the observed antinociceptive response. In terms of butorphanol and morphine tolerance, a parallel rightward shift in the dose-response curve was produced with the degree of shift proportional to the log of the infusion dose. In tail-flick tests, the shifts of the dose-response curves for butorphanol and morphine in tolerant animals were 11.8- and 46.3-fold, respectively. However, in the acetic acid writhing test, the shifts of the dose-response curves for butorphanol and morphine in tolerant animals were 11.3- and 11.7-fold, respectively. These results suggest that there is a greater degree of tolerance to morphine than there is to butorphanol, but the degree of butorphanol tolerance is still substantial. In addition, two pain assays (tail flick vs. writhing) yielded different estimations of tolerance in a comparison of morphine and butorphanol.

Butorphanol Morphine Tolerance Antinociception Intracerebroventricular infusion Osmotic minipump

BUTORPHANOL tartrate is a potent mixed agonist/antagonist opioid analgesic that belongs to the group of opioids known as morphinans (8,20,25). Very little information is available regarding its tolerance, especially in direct comparison with morphine. Although it is believed to have a low abuse potential, a few cases of butorphanol abuse have been reported since its introduction in 1978 (13). Pircio et al. (25) reported that the degree of tolerance developed to butorphanol and morphine was similar in writhing tests in mice. Using the same test, Horan et al. (9) reported that tolerance developed to the antinociceptive effects of butorphanol in butorphanol-infused rats as evidenced by its significantly increased ED_{50} value, as compared to that of saline-treated animals. Because of its abuse potential and capability of producing severe physical dependence when used in excess dosages and or for long durations (2,5,14,27), the assessment of tolerance development to butorphanol is of great value. The present study focused on time course and dose-response experiments to demonstrate the development of tolerance to butorphanol. The degree of tolerance development to butorphanol was also assessed and compared with that of morphine.

METHOD

Animals and Chemicals

Seven- to eight-week-old male Sprague-Dawley rats (Charles River, Wilmington, MA), weighing 225-250 g, were used. Animals were kept in a room with an ambient temperature of 21 ± 2°C and 12 L : 12 D cycle with free access to food and water, for a week prior to the experiment. Butorphanol was a generous gift of the Bristol-Myers Corporation (Syracuse, NY). Morphine was purchased from Mallinckrodt Chemical Works (St. Louis, MO). All other chemicals were purchased from Sigma Chemical Company (St. Louis, MO) unless otherwise specified.

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Surgical Procedures

Rats were anesthetized with Equithensin (4.25 g chloral hydrate, 2.23 g $MgSO_4 \cdot 7H_2O$, 0.972 g sodium pentobarbital, 44.4 ml propylene glycol, 10 ml 95% ethanol, and distilled water to make the final volume of 100 ml), 3 ml/kg (IP), and placed in a stereotaxic instrument. An indwelling stainless steel guide cannula (26 gauge, 10 mm long) was implanted into the right cerebral lateral ventricle (AP: −0.5 mm, LAT: +1.3 mm, and DV: −4.5 mm) with the bregma chosen as the stereotaxic reference point (22). Dental acrylic cement (Lang Dental MFG. Co., Wheeling, IL) was applied to the surface of the skull and a protective cap was placed around the cannula. After the acrylic became hardened, the animal was removed from the stereotaxic frame. A stylet (32 gauge stainless steel tubing) was placed into the guide cannula to allow the cannula to remain patent. The presence of cerebrospinal fluid (CSF) in the guide cannula was examined to assure proper placement. After surgery, rats were given 150,000 units of procaine penicillin G (Pfizerpen-AS, Pfizer Corp., NY), SC, to prevent infection. One week of recovery was allowed before beginning the infusion of drugs.

Under ether anesthesia, animals were implanted SC with osmotic minipumps (Alzet 2001, Alza Corp., Palo Alto, CA) between the scapulae. A 4-cm piece of tygon tubing (0.38 mm inner diameter, Cole-Palmer, Chicago, IL) was applied to connect the minipump to a piece of L-shaped stainless steel injector tubing (32 gauge with 30 mm in length) with one end having the same length as the guide cannula. Drug solution and vehicle were filtered through a 0.2 μm Acrodisk syringe filter (Gelmen Sciences, Ann Arbor, MI) before being introduced into the minipumps. All the delivery apparata were assembled under sterile condition. Minipumps were primed overnight at room temperature in normal saline so that the optimal flow rate (1 μl/h) was obtained.

Administration Schedule and Induction of Tolerance

To induce tolerance to butorphanol or morphine, rats were infused ICV with different doses of butorphanol (6.5, 13, 26, and 53 nmol/μl/h), or morphine (1.6, 6.5, 13, and 26 nmol/μl/h) for 3 days. The duration and dosing regimens were determined to be optimal in previous experiments (15). Drugs were dissolved in sterile physiological saline. All drug doses, calculated as the free base, were expressed in nmol/μl/h for the infusion or nmol/5 μl/rat for the assessment of dose-response curves for analgesia after 3 days of infusion. Antinociceptive responses were measured and assessments of tolerance were performed in each rat twice a day during the 3-day period of drug infusion and after drug infusion. To minimize the interference of infused compound on the endpoint, a 6-h period was allotted prior to analgesic tests. An ICV challenge of butorphanol (26 nmol/5 μl/rat), or morphine (1.6 nmol/5 μl/rat) was given to the butorphanol- and morphine-infused animals, respectively. Saline-infused control groups also received the same dose of respective drug. Tail-flick latencies were determined in each rat every 15 min for up to 150 min.

To assess the effect of the duration of drug infusion on the development of tolerance to butorphanol, rats were infused ICV with butorphanol, 26 nmol/μl/h, for 24, 48, or 72 h. Six hours after termination of infusion, a challenge dose of butorphanol, 26 nmol/5 μl/rat, ICV, was given. Antinociceptive responses were then measured in each rat every 15 min for up to 150 min.

For assessment of the degree of tolerance development to butorphanol in comparsion with morphine, rats were infused ICV continuously with saline (1 μl/h), butorphanol, or morphine (26 nmol/μl/h) for 3 days. Six hours after termination of infusion, different groups of saline-infused rats received an ICV injection of butorphanol (8.7, 13, 26, or 52 nmol/5 μl/rat), or morphine (0.53, 1.06, 1.6, or 2.6 nmol/5 μl/rat). The butorphanol-infused rats received an ICV injection of butorphanol 65, 130, 260, 520 nmol/5 μl/rat and morphine-infused rats were administered morphine 13, 26, 65, or 130 nmol/5 μl/rat. Tail-flick latencies were measured 15 min after the injection. The ED_{50}s and 95% confidence intervals were determined via the method of Litchfield and Wilcoxon (18). Antinociception tests involving thermal noxious stimuli (tail-flick lantency test) is thought to be mediated by μ and δ opioid receptors, while μ, δ and κ opioid receptors appear to be involved in tests which involve visceral-chemical stimuli (such as the writhing test) (26,29). To assess tolerance development to butorphanol or morphine by the acetic acid writhing assay, 6 h after termination of infusion, saline-infused rats received an ICV injection of butorphanol (2.17, 6.5, 26, or 65 nmol/5 μl/rat) or morphine (0.18, 0.54, or 2.17 nmol/5 μl/rat). The butorphanol-infused rats received an ICV injection of butorphanol 65, 130, or 260 nmol/5 μl/rat and the morphine-infused rats were administered morphine 6.5, 13, 26, or 65

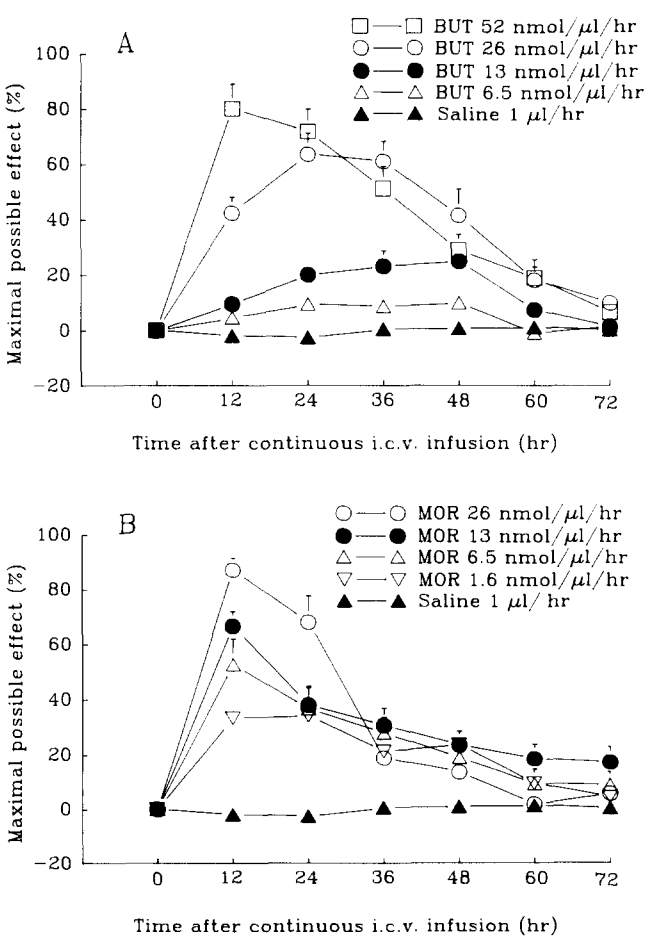

FIG. 1. Time course of development of tolerance to butorphanol or morphine in the tail-flick test by continuous ICV infusion of different doses of butorphanol and morphine for 72 h. Data are means ± SEM of six to eight animals in each group.

nmol/5 μl/rat. Fifteen minutes later the rats were given 0.6% acetic acid, 10 ml/kg, IP. Ten minutes following the administration of acetic acid, the rats were individually sequestered and observed for the presence of a writhe (defined as a characteristic stretching of the hind limbs and/or constriction of the abdominal musculature) for a 10-min period. The ED_{50}s and 95% confidence intervals were determined by the method of Litchfield and Wilcoxon (18).

Analgesic Tests

Antinociceptive responses were measured by a modified (1) tail-flick test (4) and the acetic acid writhing test (7). In the tail-flick test, the pretreatment tail-flick latencies of each rat were determined three times at 5-min intervals, and the mean was designated as the baseline latency (BL). Lamp voltage was adjusted to obtain mean BL values of approximately 3.6–4.3 s (mean BL and SD were 3.9 ± 0.14 s) and held constant throughout the experiments. A cutoff point of 10 s was chosen to minimize thermal damage to the tail. Any animals having a BL of tail-flick greater than 4.5 s or less than 3.5 s were excluded from the study to eliminate any false positive antinociceptive scores. Data were expressed as the percent of maximal possible effect (%MPE) using the equation: %MPE = [(posttest latency − BL)/(cutoff latency − BL)] × 100. Area under the time course curve (AUC) was calculated by a trapezoidal approximation of the MPE curve and expressed as percent maximum AUC (100% or no tolerance) when all animals in a group reached the cutoff point of 10 s. In the acetic acid writhing tests, rats that did not writhe were considered to have an analgesic response, and were called responders. The percent response (number of responders/number in dosing group) was evaluated at each dose.

Statistics

For statistical comparisons, the overall antinociceptive responses of each animal were converted to AUC by the trapezoidal rule (28). Group AUC values were compared across time and across treatments using two-way analysis of variance (ANOVA) followed by the *t*-test or Dunnett's test. Linear regression was used to generate the MPE AUC vs. ICV infusion dose curve. The dose-response curves represent computer-assisted regression equations. The degree of tolerance development was defined as the ED_{50} of morphine- or butorphanol-

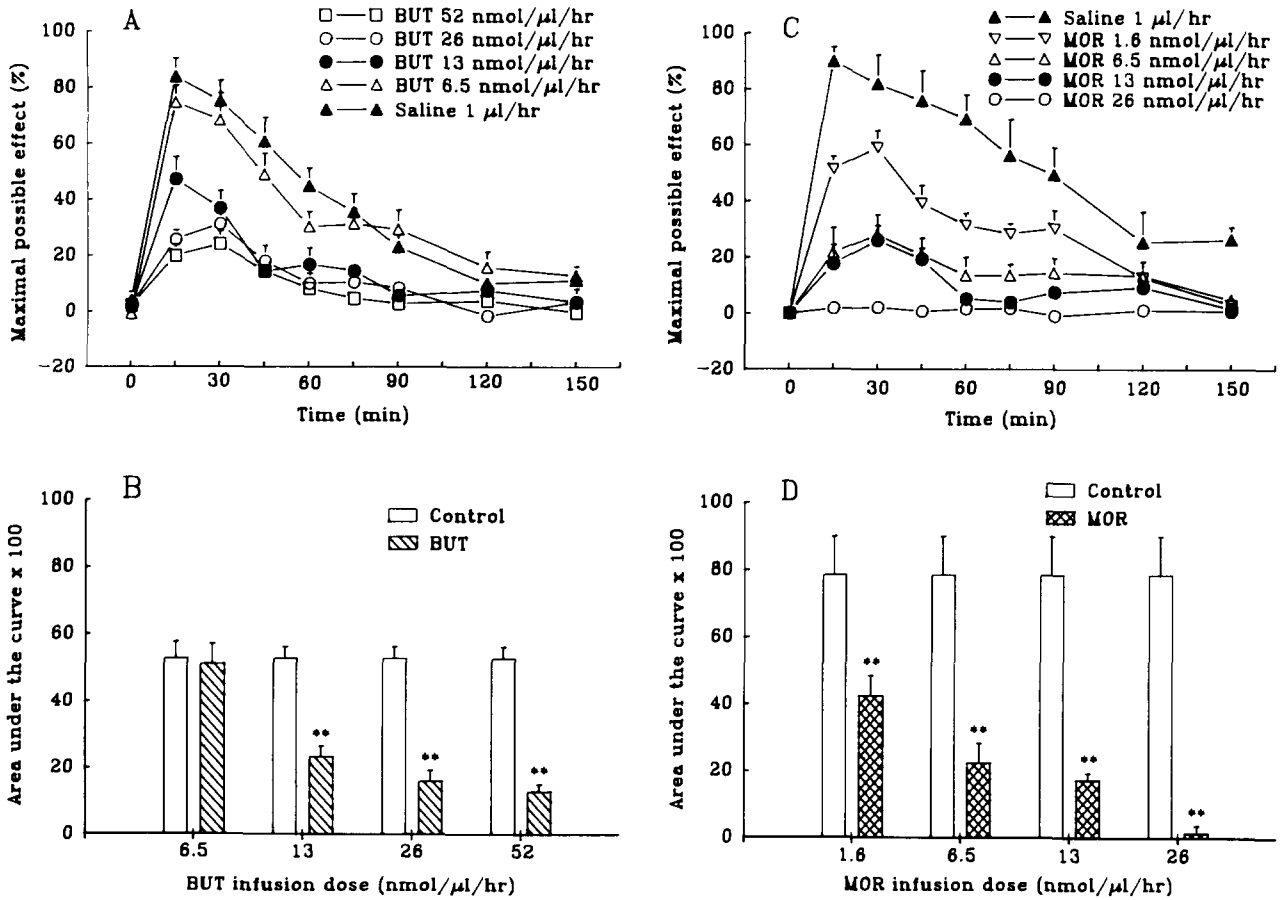

FIG. 2. Assessment of tolerance to butorphanol and morphine. Tolerance was induced by continuous ICV infusion of different doses of butorphanol or morphine for 72 h. Six hours after the termination of infusion, rats were injected with one dose of butorphanol (26 nmol/5 μl/rat) or morphine (1.6 nmol/5 μl/rat). Panels A and B represent butorphanol groups and panels C and D represent morphine groups. The tail-flick test was performed at 15-min intervals. Areas under the curve calculated from the maximal possible effect (MPE)-time curves, are shown in B (butorphanol groups) and D (morphine groups). Data are mean ± SEM of six to eight animals in each group. **Differs from saline vehicle group, $p < 0.01$.

infused animals divided by the ED_{50} of saline-infused animals. Differences were considered significant if $p < 0.05$.

RESULTS

Time Course of the Development of Tolerance to Butorphanol or Morphine

A dose-dependent analgesic effect was evident in animals that received continuous infusions of butorphanol or morphine (Fig. 1A and B). Maximal analgesia was reached 12 h after morphine infusion. The MPEs for morphine groups were 87.2, 66.7, 52.7, and 33.4% for 26, 13, 6.5, and 1.6 nmol/μl/h groups, respectively. However, in butorphanol-infused animals, maximal analgesia were reached at 12, 24, and 48 h for the 52-, 26-, and 13-nmol/μl/h infused groups, respectively. The MPEs for butorphanol groups were: 80.2, 63.7, and 28.9% for the groups receiving 52-, 26-, and 13-nmol/μl/h, respectively. The antinociceptive response to morphine was more evident than that to butorphanol, as compared to corresponding 26 ($t = 2.478$, $p < 0.05$) and 13 ($t = 6.427$, $p < 0.01$) nmol/μl/h dosing groups, via continuous ICV infusion. Tolerance to morphine (26, 13, 6.5 nmol/μl/h groups) was developed 24 h of its infusion, as evidenced by the return of BL control values to between 36 and 48 h during the infusion. Tolerance to butorphanol developed by 36 h (52 nmol/μl/h group), 48 h (26 nmol/μl/h group), of infusion of butorphanol, as the BL returned gradually to the control values between 60 and 72 h of the infusion.

Compared to morphine, higher doses of butorphanol (13, 26, and 52 nmol/μl/h) were required to induce substantial degrees of tolerance, as assessed by the antinociceptive responses to a challenge dose of butorphanol, 26 nmol/5 μl/rat (Fig. 2A and B). On the other hand, smaller doses of morphine (1.6, 6.5, 13, and 26 nmol/μl/h) induced significant tolerance to morphine (Fig. 2C and D). It was also evident that the development of tolerance to butorphanol or morphine was dose dependent (Fig. 3).

In separate experiments, the effects of the duration of infusion on the development of tolerance to butorphanol was also investigated. Different groups of animals were infused ICV with 26 nmol/μl/h for 24, 48, and 72 h. Six hours after the termination of drug infusion, these animals were challenged with butorphanol, 26 nmol/5 μl/rat and the tail-flick tests were performed every 15 min for up to 150 min. As noted on Fig. 4A and B, tolerance to butorphanol was only evident in animals that had been infused with butorphanol for 48 h or longer.

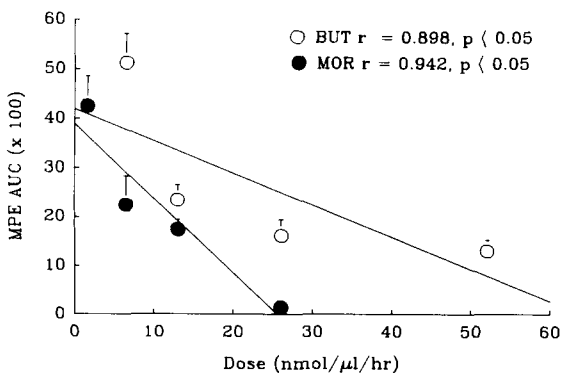

FIG. 3. Dose-response curves for butorphanol and morphine after development of tolerance. Figures are plotted from areas under the curve vs. doses shown in Figs. 2B and D. Each point represents the mean ± SEM of determinations in six to seven rats.

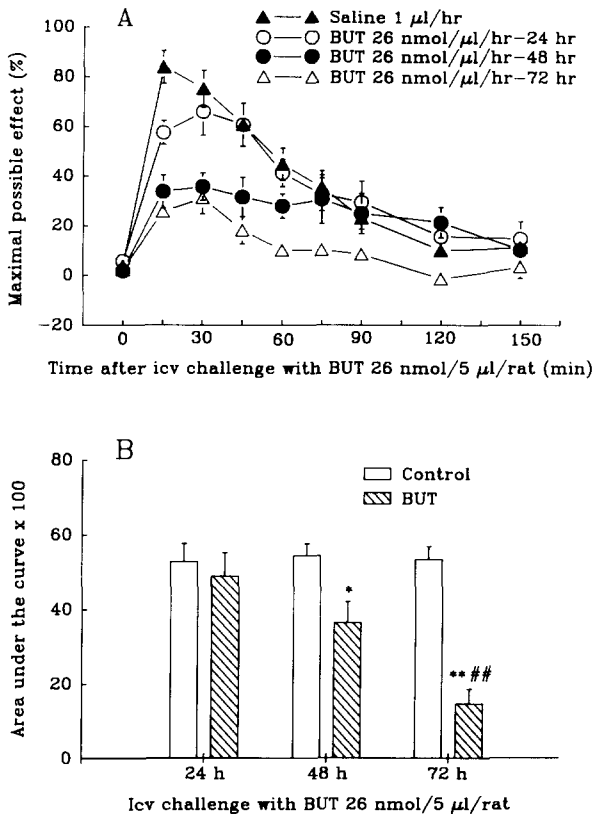

FIG. 4. Effects of the duration of butorphanol ICV infusion on the development of tolerance to butorphanol. Animals were ICV infused with butorphanol, 26 nmol/μl/h, for 24, 48, or 72 h. Six hours after the termination of infusion, rats were injected ICV with one dose of butorphanol, 26 nmol/5 μl/rat. (A) The tail-flick assay was performed on each rat at 15-min intervals. No differences were found among 24, 48, and 72 h saline-infused groups (data not shown). (B) Areas under the curve calculated from the maximal possible effect (MPE)-time curves. Data are mean ± SEM of six to seven animals in each group. *Differs from saline vehicle group, $p < 0.05$. **Differs from saline vehicle group, $p < 0.01$. ##Differs from 24 h-infusion group, $p < 0.01$.

Degree of Tolerance Development to Butorphanol or Morphine

The degrees of tolerance development to butorphanol or morphine as assessed by the tail-flick test after 3 days of ICV infusion of butorphanol (26 nmol/μl/h) or morphine (26 nmol/μl/h) are shown in Fig. 5. Injection of the ICV challenge doses of butorphanol in butorphanol-tolerant rats revealed a significant, rightward shift as compared with the saline-infused groups. The tolerance ratio was 11.8, as compared to saline controls (Table 1). Injection of the ICV challenge doses of morphine in morphine-tolerant rats showed an even more marked, rightward shift as compared with the saline-infused animals. The tolerance ratio was 46.3, as compared to saline controls (Table 1).

The degrees of tolerance development to butorphanol or morphine as assessed by the acetic acid writhing test after 3

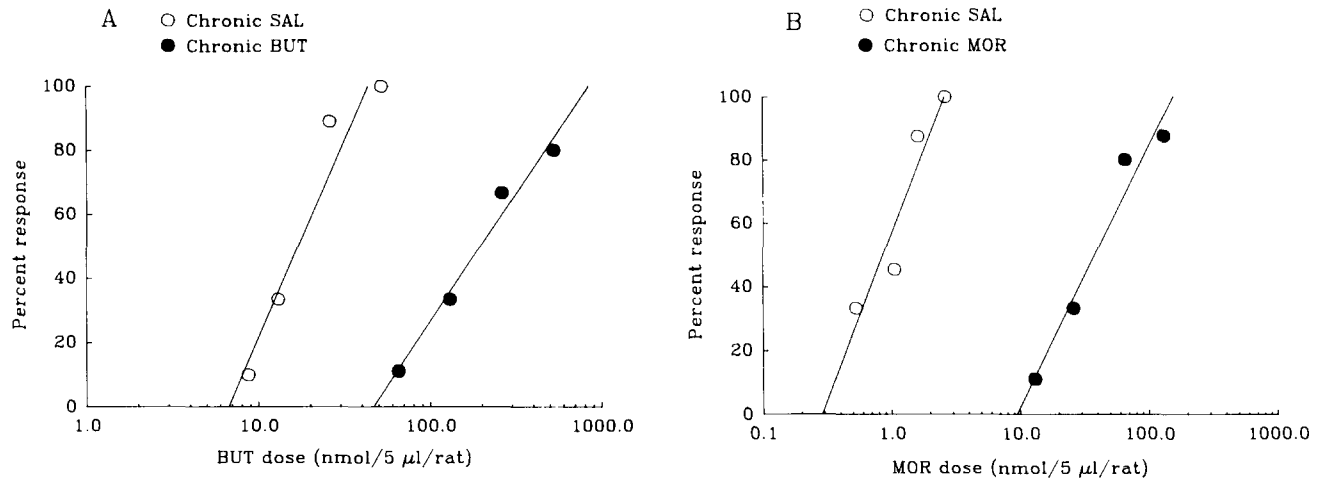

FIG. 5. Degree of tolerance development to butorphanol or morphine using the tail-flick test. Rats were infused ICV continuously for 72 h with saline (1 μl/h) or butorphanol (26 nmol/μl/h), and with saline (1 μl/h) or morphine (26 nmol/μl/h). Six hours after the termination of infusion, rats were challenged ICV with butorphanol (A) or with morphine (B). Each group consisted of 9–10 animals. See Table 1 for tail-flick test ED_{50} values.

TABLE 1

ED_{50} VALUES OF MOR OR BUT IN MOR OR BUT NONTOLERANT AND TOLERANT RATS*

Drugs	Dose† nmol/μl/h	Challenge‡ nmol/5 μl/Rat	ED_{50} (95% Confidence Intervals) nmol/5 μl/Rat	Degree of Tolerant Development
SAL	–	MOR	0.82 (0.56–1.20)	–
MOR	26	MOR	37.99 (21.15–68.24)§	46.3
SAL	–	BUT	15.42 (10.30–23.11)	–
BUT	26	BUT	181.54 (106.02–310.85)§	11.8

*Antinociception assessed by the tail-flick method.
†MOR or BUT, 26 nmol/μl/h, ICV infused for 72 h.
‡Six hours after the termination of infusion.
§Significant shift of the dose-response curve as compared to saline-infused control group ($p < 0.01$).

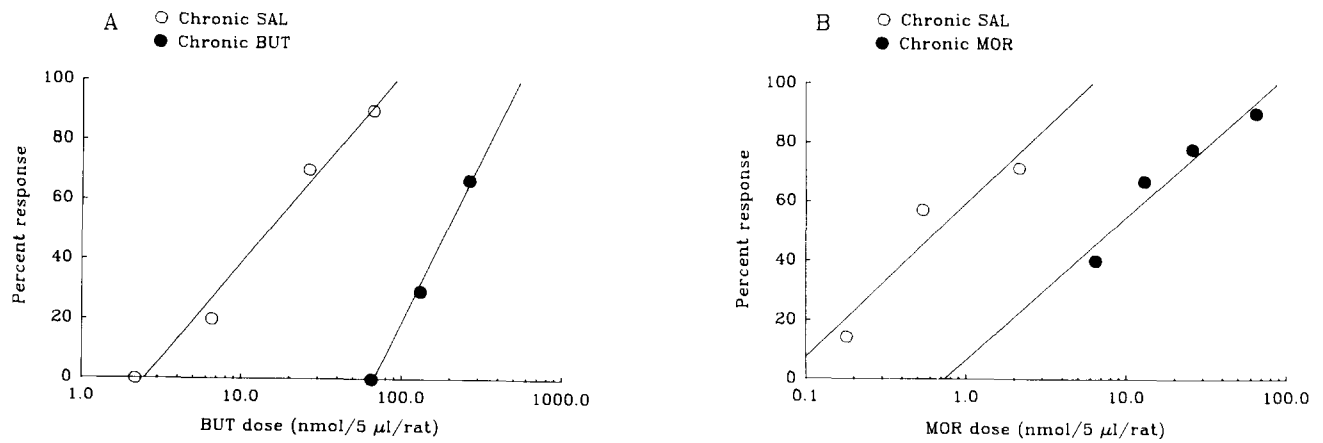

FIG. 6. Degree of tolerance development to butorphanol or morphine in the acetic acid writhing test. Rats were infused ICV continuously for 72 h with saline (1 μl/h) or butorphanol (26 nmol/μl/h) and challenged ICV with butorphanol (A); and saline (1 μl/h) or morphine (26 nmol/μl/h) and challenged with ICV MOR (B). Each group consisted of 9–10 animals. See Table 2 for acetic acid writhing test ED_{50} values.

TABLE 2

ED_{50} VALUES OF MOR OR BUT IN MOR OR BUT NONTOLERANT AND TOLERANT RATS*

Drugs	Dose† nmol/μl/h	Challenge‡ nmol/5 μl/Rat	ED_{50} (95% Confidence Intervals) nmol/5 μl/Rat	Degree of Tolerant Development
SAL	–	MOR	0.70 (0.28–1.80)	–
MOR	26	MOR	8.21 (4.41–15.31)§	11.7
SAL	–	BUT	17.17 (7.51–39.22)	–
BUT	26	BUT	194.18 (147.01–256.47)§	11.3

*Antinociception assessed by the acetic acid writhing method.
†MOR or BUT, 26 nmol/μl/h, ICV infused for 72 h.
‡Six h after the termination of infusion.
§Significant shift of the dose-response curve as compared to saline-infused control group ($p < 0.01$).

days of ICV infusion of butorphanol (26 nmol/μl/h) or morphine (26 nmol/μl/h) are shown in Fig. 6. The ICV injection of challenge doses of butorphanol or morphine in butorphanol- or morphine-tolerant rats revealed a similar significant, rightward shift as compared with the saline-infused groups. Tolerance ratios of butorphanol and morphine were 11.3 and 11.7, respectively, as compared to saline controls (Table 2).

DISCUSSION

The present studies are the first using ICV infusion to demonstrate the time-course development of tolerance to butorphanol, dose-dependent tolerance to butorphanol, degree of tolerance to butorphanol, and the comparison of butorphanol tolerance with that of morphine. Tolerance was evident in morphine- and butorphanol-infused rats both in the tail-flick test and in the acetic acid writhing test. Development of tolerance to butorphanol and morphine was related to the doses and the durations of ICV infusions of the drugs. The duration of tolerance development to morphine is faster than that of butorphanol, and the dose needed for tolerance development to morphine is less than that for butorphanol. The results also showed that the degree of tolerance development to morphine is more severe than that of butorphanol in tail-flick test. It is, thus, clear that the development of tolerance is significant when butorphanol is used in excessive dosage and for long duration.

In the case of the tail-flick test, antinociception is thought to be the result of a multiplicative interaction between spinal and supraspinal sites (31,32). If this is the case, then perhaps the analgesia mediated by butorphanol and morphine would be expressed at more caudal sites (i.e., spinal). As these sites would be expected to be less influenced by butorphanol due to its egress from the CSF, this could readily explain the observation that development of tolerance to butorphanol is slower than to that of morphine. Because there are μ receptors in the CNS, the effects of morphine as they pertain to both analgesia and tolerance development are greater than those of butorphanol. In the writhing test, the degree of tolerance development to butorphanol and to morphine were similar. It has been determined that butorphanol can act on μ-, δ-, and κ-opioid receptors (10). In contrast, morphine is much weaker at κ receptors. This is supported by the present results seen in the writhing test which is mediated by spinal cord κ receptors.

Pircio et al. (25) reported that using the writhing test, the analgesic ED_{50} values in butorphanol- and morphine-tolerant mice were 5.49 times and 5.31 times higher than the corresponding values in acutely treated naive mice, respectively. Horan et al. (9) reported that using the acetic acid writhing test, the ED_{50} value in butorphanol-treated animals increased by 76-fold compared to that of saline-treated animals. Similar results were obtained in the present studies.

Subcutaneous administration of butorphanol was about five times as potent as morphine in the phenylquinone writhing test in mice. In other animal test models (rat tail-flick, mouse hot place, and dog skin twitch), butorphanol, SC, was less potent (2 to 10 times) than morphine (25). When the drugs were given orally, butorphanol was about one-half as potent as morphine (25). These facts indicate that different routes of drug administration and different methods of antinociceptive measurements show different potencies of the same drug. In our study, continuous ICV infusion using the osmotic minipump was chosen to produce opioid-tolerant rats. In this model, administration of drugs requires minimal pharmacokinetic considerations such as drug metabolism and protein binding, so that the effects observed are primarily those of the parent compound. Additionally, because the majority of the effects of opioids is mediated by the CNS (19), the ICV route delivers the drug directly to the CNS and maintains constant drug levels at the site of action, thus providing a rapid development of tolerance and a more definitive nature of the endpoint of interest. Moreover, continuous ICV administration of opioids has been shown to be a more efficient means of producing tolerance than continuous systemic administration (3).

Butorphanol exhibits not only the development of tolerance, but also crosstolerance to morphine (6,24). Although butorphanol is believed to have low addictive liability at therapeutic levels (23), case reports of butorphanol abuse (2,5,27) and studies reported in the literature (25,30) and from our laboratory (11,12,15–17,21) have demonstrated that butorphanol also produces a substantial physical dependence liability after frequent, long-term administration of higher dosages. The present study substantiated and provided additional evidence in support of our earlier studies.

ACKNOWLEDGEMENT

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