Changes in Sensitivity to the Rate-Decreasing Effects of Opioids in Pigeons Treated Acutely or Chronically with l-α-Acetylmethadol

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Accepted for publication January 31, 1997

ABSTRACT
The purpose of this study was to examine the effects of acute and chronic treatment with l-α-acetylmethadol (LAAM), a long-acting mu opioid agonist that is used to treat opioid dependence. In pigeons responding under an FR20 schedule of food presentation, LAAM decreased responding in a dose- and time-dependent manner, with the largest decrease occurring 4 hr after the administration of 5.6 mg/kg. Acute (1.0–5.6 mg/kg) or chronic (1.0–5.6 mg/kg/day) treatment with LAAM decreased sensitivity to morphine and increased sensitivity to naltrexone, although for both drugs changes in sensitivity were 3- to 10-fold greater during chronic treatment. Chronic LAAM treatment (5.6 mg/kg/day) also decreased sensitivity to fentanyl and etonitazene by 3-fold and increased sensitivity to nalorphine and nalbuphine by 30- and 6-fold, respectively; sensitivity to endoline and ketamine increased only 2- to 3-fold. When LAAM treatment was temporarily suspended for 1 day, response rates decreased to 33% of control; this disruption was reversed by acute administration of morphine or etonitazene. Increased sensitivity to naltrexone and disruptions in responding when LAAM treatment was temporarily suspended indicate that dependence developed to LAAM. Tolerance and cross-tolerance to agonists as well as increased sensitivity to antagonists can be similar during chronic treatment with morphine or LAAM; however, increased sensitivity to nalbuphine during LAAM treatment is not typically observed during morphine treatment, suggesting that dependence on LAAM might not be identical to dependence on morphine. Finally, changes in sensitivity to other drugs might predict altered sensitivities to opioids and nonopioids in humans receiving LAAM.

Opioid abuse continues to be a worldwide problem despite the availability of several different treatment options. One approach that often reduces the intake of illicit opioids involves the administration of a compound that is pharmacologically similar to the abused drug. For example, the mu opioid agonist methadone and its derivative LAAM have been used to treat heroin abuse (Kosten, 1990; Ling et al., 1994; Tennant et al., 1986), and when administered chronically, they prevent the emergence of opioid withdrawal, reduce heroin intake, increase employment and decrease the number of arrests (Fraser and Isbell, 1952; Jaffe et al., 1970, 1972; Jaffe and Senay, 1971). One disadvantage of methadone is that daily visits to the clinic are required for adequate treatment (i.e., suppression of withdrawal), and some patients are unable or unwilling to comply with this clinical schedule. Although some patients have the privilege of taking home additional quantities of methadone for administration on subsequent days, these doses are occasionally sold illegally or are accidentally ingested by others, sometimes with serious consequences (Ling et al., 1994). A drug with a longer duration of action than methadone might require less frequent clinical visits, thereby increasing patient compliance, while eliminating the need to provide additional doses for use away from the clinic.

LAAM has a longer duration of action than methadone and can be administered as infrequently as three times per week while maintaining the desired therapeutic effects (Tennant et al., 1986). Thus, LAAM might provide advantages over methadone by decreasing the required number of clinical visits. To successfully treat opioid abuse, LAAM must be administered chronically for long periods of time; however, chronic treatment with opioids often results in the development of tolerance, cross-tolerance and dependence. Because ethical and safety concerns sometimes preclude the use of human subjects in drug studies, other species (e.g., pigeons) are often used to examine the effects of chronic drug treatment. Many of the consequences of drug treatment (tolerance, cross-tolerance and dependence) that are evident in humans are also

ABBREVIATIONS: LAAM, l-α-acetylmethadol hydrochloride; FR, fixed ratio; p.o., oral.

Received for publication August 16, 1996

1 This work was supported by United States Public Health Service Grant DA05018. C.P.F. is the recipient of a Research Scientist Development Award (DA00211), and L.R.G. is the recipient of a National Research Service Award (DA05579). Portions of these results were presented at annual meetings of the College on Problems on Drug Dependence, Scottsdale, AZ, 1995 (Gerak and France, in press).
evident in nonhumans, including pigeons (Craft et al., 1989; France and Woods, 1985, 1990; Picker and Yarbrough, 1991). Furthermore, the effects of opioid antagonists are exacerbated in both humans and pigeons treated chronically with an opioid agonist. Thus, results obtained in pigeons can be used to predict the effects of opioids in humans.

Schedule-controlled behavior has been used to examine tolerance, cross-tolerance and dependence in pigeons and, in particular, to characterize the effects of chronic treatment with the prototypic mu opioid agonist morphine (e.g., Craft et al., 1989; France and Woods, 1985; Picker and Yarbrough, 1991). Tolerance and cross-tolerance can develop during chronic morphine treatment as demonstrated by a decreased sensitivity to morphine and other mu opioid agonists and no change in sensitivity to kappa agonists or nonopioids (Craft et al., 1989; France and Woods, 1985; Picker and Yarbrough, 1991). Dependence on morphine is evident by the emergence of a withdrawal syndrome after termination of morphine treatment or after the administration of an opioid antagonist, and one manifestation of opioid withdrawal is a disruption of lever-pressing in animals responding for food (Holtzman and Villarreal, 1973). Moreover, dependence also confers an increased sensitivity to the rate-decreasing effects of opioid antagonists (France and Woods, 1985; Oliveto et al., 1991; Picker et al., 1991; Picker and Yarbrough, 1991). The development of tolerance, cross-tolerance and dependence can be systematically evaluated by examining the changes in sensitivity that develop to opioid agonists and antagonists during chronic treatment with an opioid agonist. For example, in pigeons treated daily with LAAM and responding for food, the development of tolerance has been demonstrated by a decreased sensitivity to LAAM; acute administration of 10.0 mg/kg LAAM (p.o.) decreased response rates to <50% of control rates, whereas during chronic treatment with 10.0 mg/kg/day, the same dose of LAAM did not decrease response rates. Other drugs were not studied in these LAAM-treated pigeons, thereby precluding an assessment of the possible development of cross-tolerance or dependence (McGivney and McMillan, 1981).

Under some experimental conditions, acute treatment with an opioid agonist is sufficient to enhance sensitivity to the behavioral effects of opioid antagonists. For example, acute administration of morphine can dramatically increase sensitivity to the response rate-decreasing effects of antagonists such as naltrexone or naloxone (France and Woods, 1988; White-Ghadebo and Holtzman, 1994; Young, 1986); this phenomenon is often referred to as acute dependence. The enhanced sensitivity to antagonists that occurs after a single injection of morphine is related to the dose of morphine administered (Adams and Holtzman, 1990; France and Woods, 1988; Jacob et al., 1974) and the time between the administration of morphine and the administration of an antagonist (Jacob et al., 1974; Young, 1986). Furthermore, acute dependence is also evident after brief treatment with other mu agonists (Adams and Holtzman, 1990). After acute administration of morphine, changes in sensitivity to morphine can vary dramatically; under some conditions, sensitivity to morphine decreases (i.e., acute tolerance; Yano and Takemori, 1977), and under other conditions, sensitivity to morphine does not change (White-Ghadebo and Holtzman, 1994; Young, 1986). Under still other conditions, sensitivity to morphine increases (France and Woods, 1988). Despite possible differences in the changes in sensitivity to mu agonists that occur after either acute or chronic treatment with a mu agonist, increased sensitivity to opioid antagonists that occurs after either acute or chronic treatment with a mu agonist is similar, suggesting that acute dependence might be predictive of the dependence that develops during chronic treatment. Although the effects obtained under chronic dosing conditions often are related to the effects obtained under acute dosing conditions, there are situations in which effects under one set of conditions do not accurately predict effects under another. Thus, to fully characterize tolerance, cross-tolerance and dependence that develop during chronic LAAM treatment, changes in the potency of agonists (cross-tolerance) and antagonists (dependence) must also be assessed after acute LAAM treatment.

The purpose of the present study was to examine the possible development of tolerance, cross-tolerance and dependence during LAAM treatment in pigeons. Initially, changes in sensitivity to morphine, naltrexone and the nonopioid ketamine were determined after the acute administration of LAAM; the dosing conditions for a second study, on chronic LAAM treatment, were based on the results of these acute studies. Changes in sensitivity to opioid agonists, antagonists and ketamine also were determined during daily administration of LAAM; these changes in sensitivity were compared with the changes that were observed after acute administration of LAAM.

**Methods**

**Animals.** Seven adult white Carneaux pigeons had free access to water and grit and were housed individually on a 12-hr light/dark schedule. Subjects were maintained at 80% of their free-feeding weight by food (Purina Pigeon Checkers) received during experimental sessions and, when necessary, supplemental feeding with mixed grain in the home cage. Four of the seven pigeons (pigeons 459, 129, 41 and 85) participated in studies in which LAAM was administered acutely or chronically (see below); these pigeons had a history of responding under an FR20 schedule of food presentation and had received opioids and nonopioids in other studies (Gerak and France, 1996b). The other three pigeons (pigeons 39, 491 and 482) did not participate in the study in which LAAM was administered acutely (see below). One of these pigeons (pigeon 38) had responded under a progressive ratio schedule of food presentation and had received opioids in other studies; however, it had not received drug for 4.5 months before the beginning of this study. Two pigeons (pigeons 491 and 482) were experimentally naive at the beginning of the current study. Animals used in these studies were maintained in accordance with the Animal Care and Use Committee, Louisiana State University Medical Center, New Orleans, and guidelines of the Committee on Care and Use of Laboratory Animal Resources, National Research Council (Department of Health, Education and Welfare, Publication No. NIH 85–23, revised 1983).

**Apparatus.** During experimental sessions, pigeons were placed in experimental chambers (BRS/LVE, Laurel, MD) that were equipped with three response keys that could be transilluminated, a food hopper and a light that could illuminate the food hopper; in the current study, the left and right response keys were not transilluminated and were inactive. Experimental conditions were controlled and data were recorded by microprocessors that were connected to the chambers by a commercially available interface (MedAssociates, Inc., St. Albans, VT).

**Procedure.** Animals responded under an FR20 schedule of food presentation during experimental sessions comprising two to eight discrete, 15-min cycles. Cycles began with 10-min timeout periods...
during which the chamber was dark and responses had no programmed consequence. Timeout periods were followed by response periods that had a maximum duration of 5 min. During the response period, the center key was transilluminated red and 20 responses on the center key resulted in access to food (2-sec access for 2 pigeons and 4-sec access for 5 pigeons); responses on either the left or right nonilluminated response key had no programmed consequence. Stimulus lights were extinguished after 5 min or the delivery of 10 reinforcers, whichever occurred first, signaling the end of the response period. The subsequent cycle did not begin until 15 min had elapsed since the beginning of a cycle, and any time remaining between the end of the response period and the beginning of the next cycle was a timeout period.

Injections were administered intramuscularly during the first minute of cycles; for some training sessions, saline was administered during each cycle, and for other training sessions, pigeons were handled but did not receive injections (“sham”). The only difference between training sessions and test sessions was the administration of drug before and during test sessions. To determine the duration of action of LAAM, a single dose of drug was administered at various times before a session comprising eight sham cycles. For other test sessions, increasing doses of drug were administered during the first minute of each cycle. Generally, doses ranged from a small dose, which had no effect on response rates, to a dose that decreased rates to <10% of control.

Acute studies. The rate-decreasing effects of LAAM were determined in four pigeons by administering a single dose of LAAM (1.0–5.6 mg/kg) at various times before experimental sessions consisting of eight sham cycles; during a single experimental session, the rate-decreasing effects of LAAM were examined every 15 min for 2 hr. To examine the duration of action of LAAM, each dose was administered at least twice to all four animals: once during the first cycle of the experimental session and once 2 hr before the session, so that each dose of LAAM was studied for a total of 4 hr. For some doses of LAAM, response rates remained decreased 4 hr after LAAM administration, and for those doses, the interval between LAAM administration and the session was increased in 2-hr increments until response rates after LAAM administration were similar to control rates. At least 6 days separated LAAM injections during the acute studies.

Once the time course for LAAM was determined, acute interactions between LAAM and other compounds were examined in the same four pigeons. Dose-effect curves for naltrexone, morphine and ketamine were determined in the absence of LAAM. On separate occasions, a dose of LAAM (1.0 mg/kg) that had no effect on response rates was administered 1 hr, 4 hr or 2 days before increasing doses of naltrexone. The naltrexone dose-effect curve determined 2 days after the administration of 1.0 mg/kg LAAM was not different from the control curve, and longer intervals were not studied. A larger dose of LAAM (5.6 mg/kg), which decreased response rates to <20% of control, was studied in combination with naltrexone, morphine or ketamine. On separate occasions, LAAM was administered: 1 hr, 4 hr, 1 day, 2 days, 4 days and 7 days before increasing doses of naltrexone; 1 hr, 1 day and 7 days before increasing doses of morphine; and 1 hr and 1 day before increasing doses of ketamine. Because there was only a small change in sensitivity to ketamine 1 day after LAAM administration, longer intervals were not studied. Consecutive injections of LAAM were separated by ≥6 days.

Chronic studies. The four pigeons used in the acute studies as well as three additional pigeons (see Animals) were treated chronically with LAAM. Before chronic treatment, control dose-effect curves were determined for the mu agonists etonitazene, fentanyl, morphine and nalbuphine, the opioid antagonists naltrexone and nalorephine, the kappa agonist endanolone and the nonopioid ketamine. Initially, a dose of 1.0 mg/kg/day LAAM was administered 4 hr before experimental sessions, and treatment with this dose continued for 5 weeks. On day 4 of each of the first 4 weeks, LAAM treatment was temporarily suspended, and saline was administered 4 hr before a session during which a morphine dose-effect curve was determined. LAAM treatment was temporarily suspended to avoid a potential toxic interaction between the two mu agonists. On day 7 of each of the first 4 weeks, a naltrexone dose-effect curve was determined in the presence of the daily dose of LAAM (i.e., LAAM treatment was not temporarily suspended). There were no further shifts in either the morphine or the naltrexone dose-effect curves during the fourth week of treatment compared with the third week of treatment; during the fifth week of treatment with 1.0 mg/kg/day LAAM, morphine was studied in the presence of the daily dose of LAAM (i.e., saline was not substituted for LAAM 4 hr before the session) and naltrexone was studied in the absence of LAAM (i.e., saline was substituted for LAAM 4 hr before the session). The dose of LAAM was increased to 3.2 mg/kg/day during week 6 and to 5.6 mg/kg/day during week 11. For the first 5 weeks of treatment with each dose of LAAM, morphine and naltrexone dose-effect curves were determined as described above for 1.0 mg/kg/day LAAM. The dose of LAAM was not increased further, and pigeons continued to receive 5.6 mg/kg/day LAAM for a total of 32 (n = 2) or 34 (n = 5) weeks.

To determine whether changes in sensitivity to morphine or naltrexone were reversed by longer periods of LAAM deprivation, LAAM treatment was discontinued for 2, 4, or 7 days with saline administered 4 hr before daily sessions. Initially, LAAM treatment was temporarily suspended for 2 days, and a naltrexone dose-effect curve was determined during the experimental session of the second day. LAAM treatment resumed the morning after the naltrexone dose-effect curve and continued for 7 days during which time no tests were conducted. Subsequently, saline was substituted for LAAM for 4 days, and a naltrexone dose-effect curve was determined during the session conducted on the fourth day. Pigeons were then treated with LAAM for 8 days; during the session conducted on the eighth day, a naltrexone dose-effect curve was determined in the presence of LAAM to verify that this period of LAAM treatment was sufficiently long for the recovery of sensitivity to naltrexone (i.e., to control values, as observed before the temporary suspension of LAAM treatment). A naltrexone dose-effect curve was determined 7 days after the last administration of LAAM followed by an 8-day period of LAAM treatment with the naltrexone dose-effect curve studied in the presence of LAAM on the last day. Changes in sensitivity to morphine were examined in a manner similar to that described above for naltrexone, except that morphine dose-effect curves were determined 8 days after LAAM treatment was resumed. Thus, LAAM treatment was temporarily suspended on six occasions.

LAAM tolerance and dependence were further characterized by determining dose-effect curves for several other drugs in pigeons treated chronically with 5.6 mg/kg/day LAAM. The drugs included the opioids nalorephine, etonitazene, fentanyl, nalbuphine and endanolone and the nonopioid ketamine. On separate occasions, each drug was studied in the presence and absence of the daily dose of LAAM; no more than two test sessions were conducted per week.

To determine the duration of changes in sensitivity to naltrexone or morphine that occurred during chronic LAAM treatment, dose-effect curves for naltrexone or morphine were generated at various times after termination of LAAM treatment. Saline was substituted for the daily LAAM injection, and for each of the next 4 weeks, a morphine dose-effect curve was determined on day 4 and a naltrexone dose-effect curve was determined on day 7. Subsequently, the interval between determinations of morphine and naltrexone dose-effect curves was increased to 2 weeks. By the eighth week after termination of LAAM treatment, sensitivity to morphine was similar to the sensitivity observed before chronic LAAM treatment, and additional morphine dose-effect curves were not determined until the last week of the study (see below); however, naltrexone dose-effect curves continued to be generated every 2 weeks for an additional 6 weeks. Fourteen weeks after termination of LAAM treatment, a final naltrexone dose-effect curve was determined. A
morphine dose-effect was determined 3 days after the last naltrexone dose-effect curve to confirm that sensitivity to morphine was unchanged over the last 6 weeks of testing with naltrexone.

**Drugs.** The drugs used in these studies were enadoline hydrochloride (Warner-Lambert/Parke-Davis, Ann Arbor, MI); etonitazene hydrochloride, fentanyl hydrochloride, LAAM, morphine sulfate, nalorphine hydrochloride and naltrexone hydrochloride (Research Technology Branch, National Institute on Drug Abuse, Rockville, MD); ketamine hydrochloride (Fort Dodge Laboratories, Fort Dodge, IA) and nalbuphine hydrochloride (Mallinckrodt, St. Louis, MO). With the exception of ketamine, which was purchased as a commercially prepared solution, drugs were dissolved in sterile water. To improve the clarity of presentation of time course data, for each pigeon response rates determined during the first four cycles (i.e., first hour) of each session were averaged. These mean response rates were then averaged among pigeons. For time course and dose-effect curve determinations, rates were expressed as a percentage of control rates and plotted as a function of dose or time.

Linear regression was used to estimate the dose required to decrease response rates to 50% of control (ED$_{50}$) when three data points were available; otherwise, ED$_{50}$ values were estimated by interpolation. The ED$_{50}$ values for morphine and naltrexone determined during the first 15 weeks of chronic LAAM treatment were plotted as a function of week of treatment. Because for some tests response rates did not always reach 50% of control rates, ED$_{50}$ values for some animals could not be determined for some treatment conditions; consequently, some of the mean ED$_{50}$ values shown in fig. 5, bottom, represent data from fewer than seven pigeons.

**Results**

Control response rates for individual pigeons, as well as the group mean rates, determined before, during and after chronic LAAM treatment are shown in table 1. For the four pigeons that contributed to the acute studies, the rates reported before chronic LAAM treatment occurred during the acute studies. For individual pigeons, response rates were significantly increased under at least some treatment conditions, although the particular conditions under which the increase occurred varied among animals. For example, the largest increase in rates for pigeon 459 was observed near the end of treatment with 5.6 mg/kg/day LAAM, whereas for pigeon 492, the largest increase occurred during treatment with 3.2 mg/kg/day. For some pigeons (e.g., pigeon 85), response rates were significantly decreased under some treatment conditions and significantly increased under other conditions. The group mean response rate for each treatment condition was not significantly different from that of control. During treatment with 5.6 mg/kg/day LAAM, there was no significant difference in response rates across cycles within experimental sessions for six of the seven pigeons; for pigeon 38, rates determined during the first cycle were significantly lower than rates determined during the third cycle and there was no significant difference among the other cycles (data not shown).

**Acute studies.** Acute administration of LAAM decreased response rates in a dose- and time-dependent manner (fig. 1). A dose of 1.0 mg/kg LAAM had no effect on rates up to 4 hr after administration, whereas 3.2 mg/kg LAAM decreased the mean rate to <80% of control 2 and 4 hr after adminis-

### Table 1

**Mean response rates for 10 control sessions during which only saline was administered**

The control sessions occurred before LAAM treatment, during the first 5 weeks of treatment with 1.0, 3.2 or 5.6 (EARLY) mg/kg/day of LAAM, during the sixth month treatment with 5.6 mg/kg/day began (LATE) or 2 to 6 weeks after termination of LAAM treatment.

<table>
<thead>
<tr>
<th>BIRD</th>
<th>Before LAAM</th>
<th>LAAM dose (mg/kg/day)</th>
<th>After LAAM</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1.0</td>
<td>3.2</td>
</tr>
<tr>
<td>459</td>
<td>2.10 ± 0.02$^a$</td>
<td>2.62 ± 0.06$^b$</td>
<td>2.78 ± 0.07$^b$</td>
</tr>
<tr>
<td>129</td>
<td>1.84 ± 0.05</td>
<td>1.93 ± 0.05$^b$</td>
<td>1.73 ± 0.04$^a$</td>
</tr>
<tr>
<td>38</td>
<td>1.03 ± 0.02</td>
<td>1.29 ± 0.06$^b$</td>
<td>1.33 ± 0.05$^a$</td>
</tr>
<tr>
<td>41</td>
<td>1.47 ± 0.03</td>
<td>1.69 ± 0.03$^b$</td>
<td>1.78 ± 0.02$^a$</td>
</tr>
<tr>
<td>185</td>
<td>2.99 ± 0.07</td>
<td>2.74 ± 0.06$^b$</td>
<td>2.57 ± 0.03$^a$</td>
</tr>
<tr>
<td>491</td>
<td>1.84 ± 0.02</td>
<td>1.88 ± 0.03</td>
<td>3.42 ± 0.12$^b$</td>
</tr>
<tr>
<td>482</td>
<td>2.22 ± 0.07</td>
<td>2.53 ± 0.14$^b$</td>
<td>3.10 ± 0.13$^a$</td>
</tr>
<tr>
<td>Mean</td>
<td>1.93 ± 0.23</td>
<td>2.10 ± 0.21</td>
<td>2.39 ± 0.30</td>
</tr>
</tbody>
</table>

$^a$ Each value is the response rate averaged for 10 control sessions (±1 S.E.M.).

$^b$ Significantly different from averaged rate determined before LAAM treatment.
The decrease in rates was no longer evident 5 hr after administration of 3.2 mg/kg LAAM. The maximum rate-decreasing effect of the largest dose (5.6 mg/kg) of LAAM occurred 4 hr after LAAM administration when rates were reduced, on average, to 17% of control. Response rates recovered within 14 hr of administration of 5.6 mg/kg LAAM, and response rates were similar to control rates 24 hr after administration of each dose of LAAM.

Naltrexone dose-dependently decreased response rates, with a cumulative dose of 56.0 mg/kg eliminating responding (fig. 2, ●). The administration of 1.0 mg/kg LAAM 1 or 4 hr before experimental sessions slightly increased response rates and shifted the naltrexone dose-effect curve to the left of the control curve (fig. 2, ▽ and ◊); under these conditions, the dose of naltrexone (32.0 mg/kg) that eliminated responding was 2-fold smaller than the dose that eliminated responding in the absence of LAAM. The naltrexone dose-effect curve was similar to the control curve 2 days after administration of 1.0 mg/kg LAAM.

Acute treatment with a larger dose of LAAM resulted in larger shifts to the left in the naltrexone dose-effect curve (fig. 3, left), and this increased sensitivity to naltrexone persisted for at least 2 days. A dose of 5.6 mg/kg LAAM, administered either 1 or 4 hr before experimental sessions, decreased response rates to 64% or 58% of control, respectively (fig. 3, left, ▽ and ◊), and this decrease was reversed by a small dose of naltrexone (fig. 3, left, 0.032 mg/kg); a dose of 5.6 mg/kg LAAM did not decrease response rates when it was administered 1 or 2 days before experimental sessions (fig. 3, left, △ and □). When 5.6 mg/kg LAAM was administered 1 hr before determination of a naltrexone dose-effect curve, the dose of naltrexone that eliminated responding in three of the four pigeons was 0.32 mg/kg; the fourth pigeon continued to respond up to a dose of 10.0 mg/kg naltrexone (fig. 3, left, ▽). Similar results were obtained when 5.6 mg/kg LAAM was administered 4 hr, 1 day or 2 days before determination of a naltrexone dose-effect curve. Under these conditions, doses of 0.32 or 1.0 mg/kg naltrexone eliminated responding in three pigeons, whereas a larger dose of naltrexone (3.2–32.0 mg/kg) was required to eliminate responding in a fourth pigeon (fig. 3, left, ◊, △ and □). This increased sensitivity to naltrexone was no longer evident 7 days after administration of 5.6 mg/kg LAAM (fig. 3, left, ○).

In contrast to the increased sensitivity to naltrexone that persisted for at least 2 days after LAAM administration, sensitivity to morphine was either increased or decreased depending on the interval between the administration of LAAM and determination of the morphine dose-effect curve. In the absence of LAAM, a dose of 32.0 mg/kg morphine decreased response rates to <10% of control in all animals (fig. 3, right, ●). A dose of 5.6 mg/kg LAAM, administered 1 day before determination of the morphine dose-effect curve, increased sensitivity to morphine; this increased sensitivity to morphine was no longer evident 7 days after administration of 5.6 mg/kg LAAM (fig. 3, right, □).
hr before an experimental session, decreased response rates to 72% of control and shifted the morphine dose-effect curve to the left of the control curve so that in the presence of LAAM, a dose of 1.0 mg/kg morphine decreased rates to <10% of control (fig. 3, right, △). In contrast, sensitivity to morphine was decreased 24 hr after acute administration of 5.6 mg/kg LAAM; under this condition, the dose of morphine (100.0 mg/kg) that eliminated responding was 3-fold larger than the dose of morphine required to decrease rates to <10% of control in the absence of LAAM (fig. 3, right, ◊). Seven days after an acute administration of 5.6 mg/kg LAAM, the morphine dose-effect curve was still shifted 2-fold to the right of the control dose-effect curve (fig. 3, right, ◊).

In the presence of LAAM, sensitivity to ketamine increased, although this change in sensitivity to ketamine was different from changes observed for naltrexone or morphine. In the absence of other treatment, a dose of 32.0 mg/kg ketamine decreased rates to <10% of control (fig. 4, □). At 1 hr after the administration of 5.6 mg/kg LAAM, a 10-fold smaller dose of ketamine (3.2 mg/kg) decreased response rates to <10% of control (fig. 4, ▼). When LAAM was administered 24 hr before the experimental session, sensitivity to ketamine was still slightly increased, with a dose of 10.0 mg/kg ketamine decreasing rates to <10% of control (fig. 4, △).

**Chronic studies.** Chronic LAAM treatment began after completion of the acute studies; seven pigeons, including the four used in the acute studies described above, were treated daily with LAAM. Doses of LAAM that decreased response rates when administered acutely also decreased response rates when administered chronically, although tolerance developed to this effect of LAAM during chronic treatment. A dose of 1.0 mg/kg/day LAAM had no effect on response rates after either acute (fig. 1, ◊) or chronic (fig. 5, top, weeks 1–5, ◊) treatment, and rates did not decrease when chronic treatment with this dose of LAAM was temporarily suspended for 1 day (fig. 5, top, weeks 1–5, △). When the dose of LAAM was increased to 3.2 mg/kg/day in week 6 and then to 5.6 mg/kg/day in week 11, rates were initially decreased (fig. 5, top, ◊).

![Graph](image1.png)

**Fig. 4.** Changes in sensitivity to ketamine after acute administration of 5.6 mg/kg LAAM. Ketamine dose-effect curves were determined in the absence of LAAM as well as 1 and 24 hr (1 day) after an acute injection of 5.6 mg/kg LAAM (n = 4). Abscissa, dose of ketamine in mg/kg/b.wt. Points above L represent the effects of LAAM on response rates. Ordinate, average rate expressed as a percentage of control response rate ± 1 S.E.M.

although the decreases were not as large as the decreases observed after acute treatment with each of these doses of LAAM (compare figs. 1 and 5). During subsequent weeks of daily treatment with 3.2 or 5.6 mg/kg LAAM (weeks 7–10 and 12–15, respectively), response rates recovered to control rates. When treatment with 3.2 or 5.6 mg/kg/day LAAM was temporarily suspended (1 day), response rates decreased (fig. 5, top, △), and this effect was either maintained (3.2 mg/kg/day) or increased (5.6 mg/kg/day) as the dose or duration of treatment increased. This decrease in rates that occurred after the temporary suspension of LAAM treatment was no longer evident 1 week after termination of LAAM treatment with rates remaining similar to control for 14 weeks after termination of LAAM treatment.

![Graph](image2.png)

**Fig. 5.** Changes in sensitivity to LAAM, morphine and naltrexone in pigeons treated chronically with LAAM. Top, response rates determined in the presence (◊) or absence (△) of the daily injection of LAAM. For seven LAAM-treated pigeons, LAAM was administered 4 hr before experimental sessions; response rates shown in the top (◊) were determined during the first cycle of sessions conducted on day 4 or day 7 of each week. On subsequent cycles, either a morphine (day 4 of weeks 5, 10 and 15) or naltrexone (day 7 of weeks 1–4, 6–9 and 11–14) dose-effect curve was determined. For LAAM-deprived animals, saline was substituted for the daily dose of LAAM 4 hr before the session (i.e., LAAM had been administered 28 hr before the session); response rates shown in the top (△) were determined during the first cycle of sessions conducted on day 4 or day 7 of each week. On subsequent cycles, either a morphine (day 4 of weeks 1–4, 6–9 and 11–14) or naltrexone (day 7 of weeks 5, 10 and 15) dose-effect curve was determined. Bottom, EDSO values were calculated from the naltrexone dose-effect curves (▼) determined in the presence of LAAM (weeks 1–4, 6–9 and 11–14) and morphine dose-effect curves (□) determined in animals acutely deprived of LAAM (weeks 1–4, 6–9 and 11–14). Abscissa, consecutive weeks. Points above C represent effects determined before chronic treatment. Ordinate, top, average rate expressed as a percentage of control response rate ± 1 S.E.M.; bottom, drug of choice (either naltrexone or morphine) required to decrease response rates to 50% of control rates (EDSO) in mg/kg ± 1 S.E.M. Each data point represents the mean EDSO value of four to seven pigeons; in some cases, 50% effect was not obtained in all animals. Error bars that are not visible are contained within the symbol. The top dashed line in the bottom panel indicates 1 S.E.M. above the mean EDSO value for morphine under control conditions, and the bottom dashed line indicates 1 S.E.M. below the mean EDSO value for naltrexone under control conditions. Note that between the 15th week of treatment with 5.6 mg/kg/day LAAM and the termination of LAAM treatment (i.e., week 0 above 0 mg/kg LAAM) was a 27- or 29-week period during which animals were treated daily with 5.6 mg/kg LAAM and dose-effect curves were determined for other drugs.
Changes in sensitivity to naltrexone and morphine that occurred during chronic LAAM treatment were qualitatively similar to the changes in sensitivity that occurred 24 hr after acute administration of LAAM. Chronic LAAM treatment increased sensitivity to naltrexone and decreased sensitivity to morphine, as evidenced by dose- and time-dependent decreases in ED\textsubscript{50} values for naltrexone (fig. 5, bottom, △) and increases in ED\textsubscript{50} values for morphine (fig. 5, bottom, □). For both drugs, the maximum changes in potency occurred during treatment with 5.6 mg/kg/day LAAM, resulting in a 1000-fold decrease in the ED\textsubscript{50} value for naltrexone and a 4-fold increase in the ED\textsubscript{50} value for morphine compared with ED\textsubscript{50} values determined before LAAM treatment (fig. 5, bottom, points above C). Although acute administration of 5.6 mg/kg LAAM also produced the largest changes in sensitivity to naltrexone and morphine in the acute study, daily administration of 5.6 mg/kg LAAM resulted in 2- to 10-fold greater changes in sensitivity to naltrexone and morphine compared with results obtained in the acute study (see fig. 3). Termination of LAAM treatment reversed the changes in sensitivity to naltrexone and to morphine that were evident during treatment with 5.6 mg/kg/day LAAM. Within 6 weeks of the last injection of LAAM, the ED\textsubscript{50} value for morphine was not different from the ED\textsubscript{50} value determined before chronic LAAM treatment (fig. 5, bottom right, □ above Week 6). The ED\textsubscript{50} value for naltrexone determined after the termination of LAAM treatment was 300-fold larger than the ED\textsubscript{50} value determined during treatment with 5.6 mg/kg/day LAAM; the naltrexone ED\textsubscript{50} value determined after the termination of LAAM treatment remained 3-fold smaller than the ED\textsubscript{50} value determined before LAAM treatment until 14 weeks after the last LAAM administration.

Some of the dose-effect curves from which the ED\textsubscript{50} values in the lower panel of figure 5 were calculated are shown in figure 6. Before chronic LAAM treatment, a dose of 100.0 mg/kg naltrexone (fig. 6, left, ○) or a dose of 56.0 mg/kg morphine (fig. 6, right, ●) eliminated responding. During chronic LAAM treatment, sensitivity to naltrexone increased in a dose-related manner. For example, during treatment with 5.6 mg/kg/day LAAM, a dose of 0.1 mg/kg naltrexone eliminated responding (fig. 6, left, ○). In contrast, sensitivity to morphine decreased in a dose-related manner. For example, during treatment with 5.6 mg/kg/day LAAM, only a dose of 178.0 mg/kg morphine eliminated responding in all pigeons (fig. 6, right, △).

When 5.6 mg/kg LAAM was administered 4 hr before the session (figs. 6 and 7, ○), the naltrexone dose-effect curve (left) was shifted 1000-fold to the left and the morphine dose-effect curve (right) was shifted 4-fold to the right of the respective dose-effect curves determined before chronic treatment. When LAAM treatment was temporarily suspended for 1 day (i.e., 28 hr since the last injection of LAAM), response rates decreased (fig. 7, left and right, △ above S); naltrexone exacerbated this decrease in rates as reflected by the observation that a 3-fold smaller dose of naltrexone (0.032 mg/kg) decreased response rates to <10% of control rates in the absence of LAAM (fig. 7, left, △) compared with the dose of naltrexone required in the presence of LAAM (fig. 7, left, ○). Small doses of morphine reversed the decrease in rates produced by a 1-day suspension of LAAM treatment and larger doses eliminated responding (fig. 7, right, △). When LAAM treatment was temporarily suspended for longer periods (fig. 7, left: 2 days, □; 4 days, △; 7 days, ○), naltrexone dose-effect curves shifted progressively rightward of the curve determined when pigeons received 5.6 mg/kg/day LAAM (fig. 7, left, ○); however, 7 days after the last injection of LAAM, the naltrexone dose-effect curve remained shifted 3-fold to the left of the curve determined before chronic LAAM treatment (fig. 7, left, compare ○ and △). Similarly, when LAAM treatment was temporarily suspended, the morphine dose-effect curve shifted progressively leftward of the

![Fig. 6. Sensitivity to naltrexone and morphine determined in pigeons receiving LAAM daily. These dose-effect curves represent only some of the dose-effect curves that were used to calculate the ED\textsubscript{50} values shown in figure 5. Morphine dose-effect curves were determined on day 4 of weeks 5, 10 and 15, and naltrexone dose-effect curves were determined on day 7 of weeks 4, 9 and 14 (n = 7); all dose-effect curves in the figure were determined 4 hr after administration of the daily dose of LAAM. Abscissa, dose in mg/kg b.wt. Points above S represent the effects of the daily dose of LAAM administered 4 hr before the session. Ordinate, average rate expressed as a percentage of control response rate ± 1 S.E.M.](Image)

![Fig. 7. Sensitivity to naltrexone and morphine after a temporary suspension of daily LAAM treatment. The interval between the daily administration of 5.6 mg/kg LAAM and determination of either a naltrexone or morphine dose-effect curve was progressively increased resulting in a partial recovery of sensitivity to both drugs (n = 7). Abscissa, dose in mg/kg b.wt. Points above S represent the effects obtained when LAAM treatment was temporarily suspended. Ordinate, average rate expressed as a percentage of control response rate ± 1 S.E.M.](Image)
curve determined in the presence of LAAM (fig. 7, right, ◊) and remained shifted 3-fold to the right of the curve determined before LAAM treatment (fig. 7, right, compare ● and ○).

During treatment with 5.6 mg/kg/day LAAM, the nalorphine dose-effect curve was shifted 30-fold and the nalbuphine dose-effect curve was shifted 6-fold to the right of the respective curves determined before LAAM treatment (fig. 8, compare ● and ◊). The decrease in response rates that occurred when LAAM treatment was temporarily suspended (fig. 8, △ above S) was not reversed by either nalorphine or nalbuphine, with the same dose of each drug decreasing rates to <10% of control either in the presence or absence of LAAM (fig. 8, compare △ and ○).

In contrast to results obtained with nalorphine and nalbuphine, during treatment with 5.6 mg/kg/day LAAM, the etonitazene and fentanyl dose-effect curves were shifted 3- to 6-fold to the right of the respective dose-effect curves determined before LAAM treatment (fig. 9, compare ● and ◊). In most pigeons, etonitazene and fentanyl reversed the disruptions in response rates that occurred when LAAM treatment was temporarily suspended (fig. 9, △).

During chronic treatment with 5.6 mg/kg/day, dose-effect curves for enadoline and ketamine were shifted ≤3-fold to the left of the curves determined before LAAM treatment (fig. 10, compare ● and ◊). The doses that decreased rates to <10% of control before and during chronic LAAM treatment were 1.0 and 0.32 mg/kg, respectively, for enadoline and 32.0 and 10.0 mg/kg, respectively, for ketamine. These compounds did not reverse the disruptions in response rates that occurred when LAAM treatment was temporarily suspended (fig. 10, △), and for each drug, the same dose (e.g., 0.32 mg/kg enadoline) decreased rates to <10% of control in the presence or absence of LAAM (fig. 10, compare △ and ○).

Pigeons were maintained on 5.6 mg/kg/day LAAM for either 32 (n = 2) or 34 (n = 5) weeks. After termination of LAAM treatment, morphine and naltrexone dose-effect curves were determined periodically to examine whether sensitivity to either drug recovered. Sensitivity to naltrexone recovered partially 1 week after the last administration of LAAM (fig. 7, left, ◊) and recovered completely 14 weeks after termination of LAAM treatment (fig. 5 and fig. 11, left, △). The naltrexone dose-effect curve determined 14 weeks after the termination of LAAM treatment was steeper than the dose-effect curve determined before LAAM treatment, and a smaller dose of naltrexone (56.0 mg/kg) eliminated responding in all pigeons compared with the dose (100.0 mg/kg) that was required to eliminate responding before chronic LAAM treatment. In contrast, sensitivity to morphine recovered partially 1 week after the last injection of LAAM (fig. 7, right, ◊) and recovered completely within 6 weeks of the termination of LAAM treatment (fig. 5 and fig. 11, right, △). In fact, the dose of morphine that eliminated curves were determined periodically to examine whether sensitivity to either drug recovered. Sensitivity to naltrexone recovered partially 1 week after the last administration of LAAM (fig. 7, left, ◊) and recovered completely 14 weeks after termination of LAAM treatment (fig. 5 and fig. 11, left, △).
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**Discussion**

LAAM is a mu opioid agonist with a slow onset and a long duration of action (Fraser and Isbell, 1952; Holtzman, 1979), and it has been used successfully to treat heroin abuse (Tennant et al., 1986). Because LAAM and the prototypic opioid morphine have similar mechanisms of action, it might be predicted that treatment with LAAM, either acutely or chronically, would produce qualitatively similar effects to those produced by morphine. The current study demonstrates that tolerance, cross-tolerance and dependence develop during LAAM treatment in pigeons; however, the changes in sensitivity that were obtained with some drugs appear to be different during LAAM treatment compared with results from studies in which pigeons were treated with morphine, suggesting that chronic treatment with LAAM is not identical to chronic treatment with morphine.

In pigeons, as well as in other species, chronic treatment with morphine can decrease sensitivity to morphine; this change in sensitivity can be demonstrated either by the reduced effectiveness of a single dose of morphine or by shifts to the right in a morphine dose-effect curve (Craft et al., 1989; France and Woods, 1985; Picker and Yarbrough, 1991; Smith, 1979). In the current study, decreases in response rates that were evident after acute administration of 5.6 mg/kg LAAM diminished in a time-related manner during chronic treatment with 5.6 mg/kg/day LAAM. Similarly, under control conditions, rate-decreasing effects are observed with a dose of 10.0 mg/kg LAAM (p.o.); during chronic LAAM treatment, this dose has no effect on response rates (McGivney and McMillan, 1981). The development of tolerance to the rate-decreasing effects of LAAM has also been demonstrated in rats; during treatment with 5.6 mg/kg/day LAAM, the LAAM dose-effect curve is shifted 3-fold to the right of the curve determined before chronic treatment (McMillan and Brocco, 1984). Thus, tolerance develops during chronic LAAM treatment, and this tolerance does not appear to be qualitatively different from the tolerance that develops to other mu agonists.

In general, the development of tolerance to a mu agonist is accompanied by the development of cross-tolerance to other mu agonists. For example, during chronic LAAM treatment, sensitivity decreases not only to LAAM but also to morphine, etonitazene and fentanyl, demonstrating cross-tolerance between LAAM and each of these mu agonists (France and Woods, 1990; Picker and Dykstra, 1989). The development of cross-tolerance to these drugs indicates that mu receptors mediate the rate-decreasing effects of LAAM and each of the other agonists and further suggests that the cross-tolerance conferred by LAAM is pharmacologically selective. The decreased sensitivity to morphine that is evident during chronic LAAM treatment is similar in magnitude to the decreased sensitivity to morphine that is evident during chronic morphine treatment (Craft et al., 1989; France and Woods, 1985; Picker and Yarbrough, 1991). For example, morphine dose-effect curves are shifted 6- to 10-fold to the right during chronic morphine treatment and 4-fold to the right during chronic LAAM treatment compared with morphine dose-effect curves determined before chronic treatment. Decreased sensitivity to morphine is evident whether 5.6 mg/kg LAAM is administered acutely or chronically, although the magnitude of cross-tolerance to morphine is 2-fold greater when LAAM is administered chronically; the slight decrease in sensitivity to morphine that was observed 24 hr after an acute administration of LAAM is not always evident after acute administration of morphine (France and Woods, 1988; White-Ghadeo and Holtzman, 1994; Yano and Take-mori, 1977; Young, 1986). One qualitative difference between acute and chronic administration of LAAM is the change in sensitivity to morphine that occurs shortly after LAAM is administered. At 1 hr after the acute administration of 5.6 mg/kg LAAM, sensitivity to morphine appears to be dramatically increased, perhaps because the rate-decreasing effects of LAAM and morphine are additive. During chronic treatment, sensitivity to morphine is decreased regardless of whether saline or the daily dose of LAAM was administered 4 hr before the session (i.e., the effects of LAAM are no longer additive with morphine). Thus, the temporal proximity of the LAAM and morphine injections appears to influence the effects of these mu agonists when LAAM is administered acutely and not when it is administered chronically. If this difference between acute and chronic administration of LAAM is also evident in humans that are receiving LAAM, then the combination of heroin and LAAM might not increase toxicity.

Increased sensitivity to opioid antagonists can be indicative of the development of dependence. For example, during chronic treatment with 5.6 mg/kg/day LAAM, the naltrexone dose-effect curve was shifted 1000-fold to the left of the curve determined before chronic treatment. In pigeons treated daily with 100.0 mg/kg morphine, there is a quantitatively similar change in sensitivity to naltrexone (France and Woods, 1985). These data are consistent with results from...
another study, in which precipitated withdrawal, but not abstinence-induced withdrawal, was equivalent between LAAM and morphine (Young et al., 1979). In the current study, acute dependence also appeared to develop to LAAM insofar as sensitivity to naltrexone increased in pigeons treated acutely with LAAM; however, increased sensitivity to naltrexone during chronic treatment was 10-fold greater than increased sensitivity to naltrexone after acute administration of LAAM. In pigeons, acute dependence also develops to morphine, and the magnitude of the change in sensitivity to naltrexone after acute administration of 100.0 mg/kg morphine (France and Woods, 1988) is equivalent to the 100-fold change in sensitivity observed after acute administration of 5.6 mg/kg LAAM. Thus, sensitivity to naltrexone increases after either acute or chronic treatment with LAAM, and these increases are similar in magnitude to the increased sensitivity that is evident after either acute or chronic treatment with morphine.

Sensitivity to the effects of other opioid antagonists can also increase during treatment with a mu agonist. In the current study, nalorphine and nalbuphine dose-effect curves determined during chronic LAAM treatment were shifted 30- and 6-fold, respectively, to the left of curves determined before chronic treatment. Increased sensitivity to nalorphine during chronic LAAM treatment was similar in magnitude to the increased sensitivity that occurs during chronic morphine treatment; however, in pigeons, increased sensitivity to nalbuphine is not evident during chronic treatment with 56.0 mg/kg/day morphine (Picker and Yarbrough, 1991). Nalbuphine can produce mu agonist or mu antagonist effects, depending on the experimental conditions. Nalbuphine substitutes for fentanyl in pigeons discriminating fentanyl from vehicle (Picker and Dykstra, 1989), suggesting that nalbuphine has mu agonist effects. In contrast, nalbuphine does not substitute for morphine and partially substitutes for naltrexone in pigeons treated chronically with morphine and discriminating among naltrexone, morphine and saline (France and Woods, 1990), suggesting that, under these conditions, nalbuphine has mu antagonist effects. Qualitative differences in the effects of nalbuphine in animals treated chronically with either LAAM or morphine might be due both to the pharmacological profile of nalbuphine and to the magnitude of dependence that develops to each agonist. For example, in animals treated once daily with morphine, nalbuphine might have sufficient efficacy so as not to precipitate withdrawal (i.e., it has morphine-like effects). However, in animals treated with the longer-acting LAAM, a greater dependence might develop, and consequently, nalbuphine might not have sufficient efficacy to avoid the precipitation of withdrawal (i.e., it has naltrexone-like effects). Thus, the low efficacy of nalbuphine results in antagonist actions in LAAM-treated animals; under these conditions, nalbuphine precipitates withdrawal as demonstrated by the shift to the left in the nalbuphine dose-effect curve. During chronic LAAM treatment, drugs with more efficacy than nalbuphine would prevent the emergence of withdrawal, whereas drugs with less efficacy than nalbuphine would precipitate withdrawal. Differences in sensitivity to nalbuphine in LAAM- or morphine-treated pigeons indicate that dependence on LAAM is not identical to dependence on morphine.

The development of dependence can be demonstrated by the emergence of a withdrawal syndrome either on discontinuation of drug treatment or on administration of a pharmacological antagonist, and one sensitive indicator of withdrawal can be disruptions in food-maintained responding (Holtzman and Villarreal, 1973). When chronic LAAM treatment was temporarily suspended in pigeons, responding decreased in a dose- and time-dependent manner. In contrast, when chronic morphine treatment is temporarily suspended, food-maintained responding is disrupted in some (monkeys; Holtzman and Villarreal, 1973) but not in all (pigeons; France and Woods, 1985; Picker and Yarbrough, 1991) animals, and when these decreases in response rates occur, they are reversed by the administration of a mu agonist (Holtzman and Villarreal, 1973). In the current study, decreases in response rates that occurred when LAAM treatment was temporarily suspended were reversed by the mu agonists morphine and etonitazene, further demonstrating the pharmacological selectivity of the dependence that develops to LAAM. Furthermore, in pigeons, disruptions in responding occur when LAAM treatment is temporarily suspended and not when morphine treatment is temporarily suspended, providing further evidence that dependence on LAAM is not identical to dependence on morphine.

If the tolerance and dependence that develop during chronic LAAM treatment are due to interactions exclusively at mu receptors, then chronic LAAM treatment should not change the sensitivity of animals to drugs that act primarily at receptors other than mu receptors. During treatment with 5.6 mg/kg/day LAAM, sensitivity to enadoline (kappa agonist) and ketamine (nonopioid) increased slightly, although the magnitude of these changes was considerably less than the magnitude of increases to the rate-decreasing effects of opioid antagonists. Furthermore, these non-mu compounds neither reversed nor exacerbated the disruption in responding that occurred when LAAM treatment was temporarily suspended. Collectively, these data provide further evidence for the pharmacological selectivity of the tolerance and dependence that develop to LAAM.

One difference between LAAM and other mu agonists, that might account for differences observed during chronic treatment, is the slower onset and longer duration of action of LAAM. Like other mu agonists, LAAM decreases response rates in a dose- and time-related manner; however, other mu agonists have more rapid onsets than LAAM. Acute injection of morphine, methadone or fentanyl decreases response rates when drug is administered either immediately or 30 min before experimental sessions (McMillan et al., 1970; Picker and Dykstra, 1989), whereas the rate-decreasing effects of LAAM are not evident until 2 hr after drug administration (fig. 1), with the largest decrease in response rates occurring 4 hr after administration of 5.6 mg/kg LAAM. One factor that apparently alters the onset of action of LAAM is the route by which it is administered. For example, in the current study, rate-decreasing effects of 5.6 mg/kg LAAM were not evident until 2 hr after intramuscular administration; however, response rates are decreased to <40% of control immediately after p.o. administration of 10.0 mg/kg LAAM (McGivney and McMillan, 1981). In addition to a slower onset of action, LAAM has a longer duration of action than methadone. In the current study, the rate-decreasing effects of 5.6 mg/kg LAAM (intramuscular) were evident for 13 hr; after p.o. administration, the rate-decreasing effects of LAAM are evident for ≈6 hr. In contrast, the rate-decreasing effects of
methadone are markedly diminished 3 h after p.o. administration and are no longer evident 6 h after p.o. administration (McGivney and McMillan, 1981). The slow onset and long duration of action of the rate-decreasing effects of LAAM have also been demonstrated after intraperitoneal administration in rats (Aigner et al., 1978; McGivney and McMillan, 1979; McMillan and Brocco, 1984). Although the onset of action of LAAM appears to vary among different routes of administration, LAAM decreases response rates and has a long duration of action regardless of the route by which it is administered.

Although one presumed clinical advantage of LAAM is its long duration of action, which can reduce the frequency with which patients must attend clinic to receive drug, the long duration of action of LAAM might also have some clinical liability. For example, the current study shows that the effects of some drugs that are pharmacologically unrelated to LAAM are enhanced during either acute or chronic LAAM treatment, suggesting that the toxic effects of some drugs might be exacerbated in patients receiving LAAM. Furthermore, in pigeons, withdrawal (i.e., disruption in responding) is maximal 24 h after the last dose of LAAM, and the largest dose of LAAM administered in the current study (5.6 mg/kg/day) is only 6-fold smaller than the lethal dose (McGivney and McMillan, 1981). If the same relationship between therapeutic dose and toxic dose is evident in humans, then the possibility of overdose with LAAM could severely limit its use for the treatment of opioid abuse.

Acknowledgments

The authors thank H. Burden, T. LaFrance, L. Landers and J. Mitchell for technical assistance.

References


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