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BRIEF COMMUNICATION

A Long-Acting Buprenorphine Delivery System

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PONTANI, R B AND A L MISRA *A long-acting buprenorphine delivery system* PHARMACOL BIOCHEM BEHAV 18(3) 471–474, 1983 —A subcutaneously implantable buprenorphine delivery system utilizing cholesterol-glyceryltristearate matrix for prolonged release of drug is described Implantable cylindrical pellets of buprenorphine (cholesterol 36 mg, glyceryltristearate 4 mg, buprenorphine hydrochloride 10 mg), diameter 3 mm, length 6 mm blocked the antinociceptive action (hot plate, 55°C) of 10 mg kg^{-1} SC challenge dose of morphine in rats for 12 weeks or more (longer periods not evaluated) The cumulative percent release of buprenorphine from the test devices 2, 4, 6, 10 and 12 weeks after implantation was 27 4, 35 9, 37 6, 39 9 and 43 1, respectively The release of buprenorphine from 10 mg pellets approximated first-order kinetics with half-lives of 0 85 and 50 24 weeks, for α and β phases, respectively The test devices possess the desirable characteristics of simplicity, biocompatibility, nontoxicity, ease of sterilization with ethylene oxide, small size for ease of insertion and removal, minimal encapsulation by surrounding tissue and an extended period of drug release unaffected by body metabolism No side effects were seen in implanted rats which fed well and gained weight during entire treatment Neither deterioration of implant nor any gross anatomic changes at implant site were apparent 12 weeks after pellet implantation

Buprenorphine hydrochloride Long-acting delivery system Subcutaneous cylindrical implant
In vivo release in rats Response latency on hot plate

BUPRENORPHINE, an oripavine derivative is a potent opiate partial agonist/antagonist with a long-lasting analgesic action and little clinically significant physical dependence liability or serious toxicity [2, 3, 4, 8, 9, 20] It is 25 to 40 times more potent than morphine in mouse writhing or rat tail pressure test after subcutaneous or intraperitoneal injections [3] The systemic bioavailability of buprenorphine in rats after single 0 2 mg kg^{-1} doses by intraarterial, intravenous, intrarectal, intrahepatoportal, sublingual or intraduodenal routes of administration have been shown to be 100, 98, 54, 49, 13 and 9 7%, respectively (1) Buprenorphine is self-administered by primates [12] and may be more effective than methadone in suppressing heroin self-administration in the rhesus monkey [13] In human subjects, the analgesic potency of buprenorphine is 25 to 30 and 15 5 times that of morphine after intramuscular and sublingual administration, respectively, and duration of action equivalent to that of morphine, about 6 hr [7, 8, 10, 19] Chronically administered in a single daily dose of 8 mg, buprenorphine produces morphine-like subjective effects and euphoria equivalent to that produced by 30 mg of morphine administered subcutaneously four times daily or a single daily oral dose of methadone in the range of 40 to 60 mg [8] Buprenorphine in 8 mg daily doses significantly suppressed heroin intake (21 to 40 5 mg per day intravenously) over 10 days by heroin addicts [11] in comparison to placebo controls It is also an effective antagonist for high doses of morphine in rodents [5] and in man 8 mg daily doses blocked the subjective and miotic effects of high doses of morphine (60–120 mg/day) for up to 29 5 hrs [8] It is equivalent to naltrexone in potency and duration of opiate blockade [8] Because of these properties, low abuse potential and minimal possibility of overdose, buprenorphine possesses distinct advantages over methadone or naltrexone as a safe and highly effective pharmacotherapeutic agent for the treatment of opiate dependence

It is felt that a long-acting buprenorphine delivery system will have greater potential for clinical usefulness and prevention of relapse to opiate-seeking behavior In addition such a system will eliminate the needs for clinic visits in opiate-dependent individuals without reducing the protection against self-administered opiates and reduce the emphasis on medication and refocus it on rehabilitation aspects

Utilizing methods developed in our laboratory for a long-acting naltrexone delivery system [14–16], we report here the development of a subcutaneously implantable buprenorphine

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TABLE 1

RESPONSE LATENCIES* ASSESSED ON HOT-PLATE OF RATS IMPLANTED SUBCUTANEOUSLY WITH 10 mg BUPRENORPHINE AND PLACEBO PELLETS FOR VARIOUS PERIODS BEFORE AND AFTER THE CHALLENGE DOSE (10 mg kg,$^{-1}$ SC) OF MORPHINE

Treatment and Test Conditions	Weeks	(hr) Before	Reaction times after morphine injection 0.5	1	2	4
Buprenorphine-pelleted animals	2	3.7 ± 0.5	5.1 ± 0.5‡	6.3 ± 0.6‡	4.2 ± 0.1	4.3 ± 0.3
	6	4.3 ± 0.4	5.2 ± 0.9	4.0 ± 0.5	5.2 ± 0.8	4.6 ± 0.4
	9	3.1 ± 0.1	4.8 ± 0.9	5.0 ± 0.5‡	4.9 ± 0.6‡	3.7 ± 0.4
	12	6.3 ± 1.6	6.8 ± 1.2	5.6 ± 0.4	4.8 ± 1.1	4.5 ± 0.9
7 days after 12 wk pellet removal‡		4.2	14.0	15.8	10.8	6.0
Placebo-pelleted animals	2	3.7 ± 0.3	18.4 ± 4.9‡	23.2 ± 4.9‡	24.5 ± 5.6‡	5.9 ± 1.2
	6	4.5 ± 0.6	16.6 ± 2.9‡	16.5 ± 2.0‡	13.5 ± 2.0‡	5.0 ± 0.7

*Results are expressed as mean ± SEM (sec) from 5 rats in each time group. The temperature of the hot plate was 55°C and the criterion of the reaction of the rat was licking of one paw or intensive jerking with lifting off or jumping of hind legs. The test was terminated if response latency exceeded 30 sec (cut-off time).

†Values represent mean of response latencies for 2 animals only; other animals were sacrificed for the analysis of drug in brain.

‡Denotes significant difference at $p < 0.05$ from that before morphine injection.

delivery system which can block the antinociceptive effects of challenge doses of morphine in rats for 12 weeks or more.

METHOD

Buprenorphine hydrochloride was provided by Norwich-Eaton Pharmaceutical Company, Norwich, NY, through the kind courtesy of Dr. Kenneth Anderson. Cholesterol m.p. 146–149°C (J. T. Baker Chemical Company, Philipsburgh, NJ) and glyceryl tristearate m.p. 65–67°C (K & K Laboratory Inc., Plainview, NY) were commercial samples.

Preparation of Buprenorphine Pellets

Cholesterol (360 mg), glyceryl tristearate (40 mg) and buprenorphine hydrochloride (100 mg) were dissolved in 50 ml chloroform and 15 ml absolute ethanol and the clear solution evaporated to dryness *in vacuo* in a Rota Vapor and the residue further dried *in vacuo* overnight. The thoroughly mixed powder (50 mg) was compressed [14] to a cylindrical pellet, diameter 3 mm, length 6 mm, surface area 56.5 mm^2, volume 42.4 mm^3 in a Carver Laboratory Press (Fred Carver Inc., Summit, NJ). The individual weights of pellets were within the limits of 95% and 105% of the average 50 mg weight. Placebo pellets were similarly prepared using cholesterol and glyceryl tristearate.

Animal Experiments

Cylindrical pellets containing 10 mg buprenorphine hydrochloride and placebo pellets were implanted subcutaneously in the dorsal area behind the right hind limb of naive male Wistar rats (150–200 g), pushed away from incision and the incision sutured. The response latencies of animals in the 2 groups were measured by an earlier procedure [6] on a hot plate (55°C) with a cut-off time of 30 sec before morphine injection and 0.5, 1, 2, 4 hr after a 10 mg kg^{-1} SC injection of morphine. The observations were made manually using a stopwatch. The criterion of the reaction of the rat was licking of one paw or jumping on hind legs. The usual range of response latencies observed with our naive male Wistar rats using the hot-plate technique was 3.0 to 4.5 sec. The duration of effective antagonism of analgesia due to challenge doses of morphine was tested at 2, 6, 9, 12 weeks after implantation of a single 10 mg buprenorphine pellet (n=5 in each time group). After being in place for 12 weeks, the buprenorphine pellets were removed from the selected group of rats and the responses of animals to challenge doses of morphine given 7 days after pellet removal compared with the placebo group.

The buprenorphine pellets were removed 2, 4, 6, 10 and 12 weeks after implantation from another group of rats (270–300 g) and the amount of drug remaining in the removed pellets was determined by shaking the pellets in ether and repeated extraction of the ether solution by 0.5 M HCl. The absorbance of the acid extract was measured UV spectrophotometrically at 285 nm against a corresponding reference standard prepared from the placebo pellet removed from the rat at the same time as the experimental pellet.

RESULTS

Data on the reaction times of placebo and buprenorphine-pelleted animals challenged with a 10 mg kg^{-1} SC dose of morphine appear in Table 1. The response latencies to hot-plate thermal stimulus in the 2, 6, 9 weeks buprenorphine-pelleted animals and in the placebo-pelleted group before morphine injection are within the normal range for our naive animals (3.0–4.5 sec). The corresponding mean response latency and standard error in the 12 weeks group before morphine injection although somewhat higher, was not significantly different from the values in other groups.

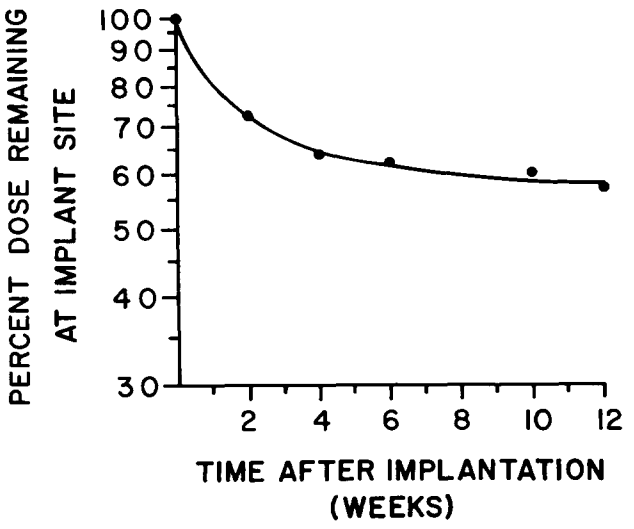

FIG 1 Semi-logarithmic plot of percent dose remaining in 10 mg cylindrical buprenorphine pellets at various times after SC implantation in rats Data represent mean values (n=2) at each time from animals each implanted SC with a single 10 mg pellet

The response latencies in 6 and 12 weeks buprenorphine-pelleted animals at 0 5 to 4 hr were not significantly different from the reaction time before morphine injection by correlated t-test Seven days after the removal of buprenorphine pellets, the reaction times observed between 0 5 to 4 hr after the morphine dose were not significantly different from those in 6 weeks placebo-pelleted animals The results showed that the delivery system produced effective blockade of analgesia of the challenge doses of morphine in test animals for 12 weeks or more (longer periods were not tested in this study)

Analyses of buprenorphine pellets removed 2, 4, 6, 10 and 12 weeks after implantation showed that the cumulative percent release of drug from the test devices was 27 4, 35 9, 37 6, 39 9, 43 1%, respectively during these periods (Fig 1) The release of drug from pellets approximated first-order kinetics with $t^1/_2$ values of 0 85 and 50 24 weeks for α and β phase, respectively The data could be fitted to the equation 2 303 log (Y)=4 218-0 0138 X where ordinate Y=100−% drug released) The rate constant for drug release from pellets was 1 37% week^{-1} for the β-phase corresponding to approximately 3–4 μg kg^{-1} hr^{-1} between 2 to 12 weeks Hence the 10 mg pellet gave a satisfactory release of buprenorphine for an extended period of time and the release was unaffected by body metabolism

No deterioration of the pellet implant nor any gross anatomic changes occurred at the site of implant 12 weeks after implantation Aside from some mild behavioral sedation during the initial 4 days after implantation, no side effects were seen in rats which fed well and gained weight like control rats during the entire course of implantation Minimal encapsulation by surrounding tissue was observed at the implant site

DISCUSSION

Chronic buprenorphine (0 5 mg kg^{-1}, SC twice daily) administration for 4 days in rats has been reported to antagonize morphine antinociception and higher doses (10 mg kg^{-1}, SC) injected 45 min before morphine completely blocked the antinociceptive effects of doses of morphine as high as 800 mg kg^{-1} given subcutaneously [4,5] Buprenorphine (8 mg day^{-1}, SC) blocked the subjective and miotic effects of high doses of morphine (60–120 mg day^{-1}) for up to 29 5 hr in human subjects [8] The same dose of buprenorphine (8 mg day^{-1})provided significant suppression of heroin (21–40 5 mg day^{-1}, IV) self-administration over 10 days in heroin addicts [11] Considerably higher doses of buprenorphine (0 4 to 0 8 mg kg^{-1} day^{-1}) however, were required to suppress opiate self-administration in the rhesus monkey [12,13] These buprenorphine doses in human subjects and primates roughly correspond to 4 6 and 17–34 μg kg^{-1} hr^{-1} respectively The rate of drug release from our pellets between 2 to 12 weeks corresponds to approximately 3–4 μg kg^{-1} hr^{-1} and implantation of more than one pellet could provide proportionately greater release of drug The rapid release during the first and second week of implantation amounting to approximately 54 and 24 μg kg^{-1} hr^{-1}, respectively was due to the diffusion of drug localized on the external surface of the pellet The continuous infusion of drug *in vivo* and its very slow dissociation from the receptor sites in the central nervous system possibly accounts for the prolonged blockade of anti-nociceptive effects of challenge doses of morphine

Recent *in vitro* studies [18] have shown that at physiological temperature [^{3}H] buprenorphine labeled approximately 10 times more of the high affinity binding sites in central nervous system and 2 times the total number of sites than dihydromorphine or naloxone Neither opiates (naloxone, morphine) nor endogenous opiate peptides (β-endorphin, met^5- or leu^5-enkephalin) showed high affinity for CNS receptors labeled by [^{3}H] buprenorphine [18] The binding of buprenorphine with great affinity to a larger number of opiate receptors possibly accounts for its greater analgesic potency as compared to morphine [18] The very slow rate of dissociation of buprenorphine from the opiate receptors accounts for the long duration of its action, almost twice that of methadone [3,4], and little clinically significant physical dependence [8] Because of its partial agonist properties at low dosages, the buprenorphine-pelleted animals become tolerant to buprenorphine and show cross-tolerance to morphine and other narcotics As a competitive antagonist, buprenorphine blocks the narcotic effects of morphine in buprenorphine-pelleted rats This balance of high agonist and antagonist activity of buprenorphine depending on dosages produces a biphasic bell-shaped dose-response curve for antinociception in rats [4,17] and accounts for its low physical dependence liability In our buprenorphine-pelleted animals, naloxone (5 mg kg^{-1} SC) did not precipitate any withdrawal symptoms

This study establishes the feasibility of using cholesterol-glyceryl-tristearate matrix for the slow release of buprenorphine Cholesterol provided a simple barrier effect on the diffusion of drug Because of its very low solubility (20–25 μg ml^{-1}) in M/15 phosphate buffer pH 7 4 at 37°C, buprenorphine hydrochloride (instead of its base) could be used for the preparation of pellets The SC implantable buprenorphine delivery system described here possesses the advantages of simplicity, nontoxicity, non-irritability, ease of sterilization with ethylene oxide and small size for ease of insertion and removal The factors affecting the release of drugs from similar long-acting test devices [16] were the solubility of drug, the ratio of content of cholesterol to the incorporated drug, drug loading level and surface area to unit

volume of the dosage form Larger size pellets (diameter 13 mm, length 16 mm) with a much higher drug content (650 mg) could easily be prepared for further studies in primates and these are currently being planned

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