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# BRIEF COMMUNICATION

## Preparation and Evaluation of a Sustained Morphine Delivery System in Rats[1]

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MCGINITY, J. W. AND C. S. MEHTA. *Preparation and evaluation of a sustained morphine delivery system in rats.* PHARMAC. BIOCHEM. BEHAV. 9(5) 705–708, 1978.—A new drug delivery system to induce physical dependence to morphine in rats is described. The device consists of a silicone polymer containing a water soluble "carrier" material, sodium alginate, which swells on contact with moisture to release the drug. The silicone or silastic® pellets formulated to contain morphine sulfate are very easily prepared and the advantages over existing methods to induce physical dependence to morphine are discussed. In addition, a comparison of the percent of drug released and withdrawal intensities in rats was made with a silastic-morphine sulfate pellet, silastic-morphine base pellet and a microcrystalline cellulose-morphine base pellet.

Morphine Silicone polymer Physical dependence Drug delivery system

CHRONIC administration of morphine during pharmacological studies in small animals poses many problems. The relatively short half-life of morphine necessitates frequent injections to maintain the desired levels. To avoid this tedious routine, several different methodological attempts to deliver morphine at a constant rate to an animal over a period of days, have been reported. Collier *et al.* [3] used a single injection of 150 mg/10 ml/kg of a sustained-release preparation of morphine in rats and reported that the animals became dependent within 24 hr. Other workers have employed intraventricular injection [6], systemic injection [15], IV self-administration [9], and ventricular perfusion by an osmotic minipump [18]. Stolerman and Kumar [13,19] self-administered morphine orally to the animal by adding the drug to the drinking water. Morphine sulfate has been absorbed into molecular sieves to induce dependence in rats [11]. Goode [10] induced physical dependence in rats using an implanted reservoir of morphine solution. The reservoir consisted of a silicone tubing with a cellophane membrane at one end to allow the morphine hydrochloride to diffuse out slowly. Other workers have employed implanted tableted pellets which slowly release their content of morphine [8, 14, 20].

The most useful method to date has been the tablet pellet implant technique reported several years ago by Gibson and Tingstad [8]. The tablets essentially consist of a 1:1 mixture of morphine base and microcrystalline cellulose plus miniscule quantities of lubricant to aid in the compression of the pellet.

The suitability of silicone polymers to provide prolonged "continuous infusion" of drug has been studied for several medicinals including steroids [5], barbiturates [7] and cancer chemotherapeutic agents [4]. Pellets have been successfully formulated to release the various drugs at predictable rates for up to several months. Recent studies by the authors have confirmed the general impression that water soluble drugs are released exceedingly slowly from the silicone matrix. However, the rate of release of morphine sulfate from the pellet was greatly increased by the addition of water soluble carrier materials to the matrix [16]. Of those carriers tested, sodium alginate was found to exert the greatest influence on drug release. Silastic rubber implants containing morphine

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free base or its sulfate salt were formulated and their ability to induce physical dependence to morphine was compared to the currently accepted microcrystalline cellulose pellets.

## METHOD

### *Animals*

At the time of experimentation, male Sprague-Dawley rats were approximately 8 weeks old and weighed 175–200 g. Animals were given food and water ad lib during the entire period of the study, and following pellet implantation, they were housed in separate cages.

### *Materials*

The chemicals and their suppliers were as follows: morphine sulfate, Mallinckrodt, Inc. (St. Louis, MO); sodium alginate (Kelcosol®), Kelco Company (Clark, NJ); polydimethylsiloxane (Silastic 382®), silicone oil (360 Medical Fluid) and stannous octoate (Catalyst M), Dow Corning Corp. (Midland, MI); Microcrystalline cellulose (Avicel®), FMC Corp. (Marcus Hook, PA).

### *Pellet Formulations and Preparation*

Three pellet formulations were prepared to contain the equivalent of 75 mg morphine base. The microcrystalline cellulose pellets were manufactured according to the specifications of Gibson and Tingstad [8]. The 2 silicone rubber implants were formulated to contain morphine sulfate (or base) 40%, sodium alginate 10%, polydimethylsiloxane 25% and 360 medical fluid 25%. Twenty microliters of catalyst (stannous octoate) were used per gram of pellet formulation. The pellet materials were mixed by spatulation on a glass slab. The powders were mixed with the oil and the polymer until a homogenous mass was produced. Then, the hardening catalyst was added, and it was quickly and uniformly dispersed throughout the mixture. Cylindrical pellets were prepared by adding the mixture to a plastic mold of the desired dimensions (No. 3 Hand Triturate Mold, Arthur Colton Co., Detroit, Michigan). The rubber pellets were hardened at room temperature for 12 hr and then removed from the mold and weighed. The morphine sulfate pellets weighed 250 ± 5 mg and measured 0.8×0.74 cm.

### *Morphine Assays*

To determine the content of morphine in the pellets, the pellet was weighed, cut into small pieces and extracted for 48 hr into 20 ml of 0.01 N hydrochloric acid. The absorbance of the filtered solution was determined spectrophotometrically at 286 nm and compared to a standard curve to determine drug content. Content uniformity studies showed that the pellets contained within ±3% of theoretical values.

### *Measurement of Morphine Withdrawal Intensity*

Light ether anesthesia was used to implant the morphine pellets subcutaneously in rats along the midline in the dorsal neck region posterior to the ears. Control rats received similar pellets in which lactose was substituted for morphine. Quantitation of the morphine withdrawal was carried out by observing the number of episodes of wet dog shakes for 10 min immediately following the administration of naloxone hydrochloride (4.0 mg/kg, IP). The wet dog shake phenomenon may be defined as brief episodes of rapid, repetitive shaking of the entire trunk which resembles a dog shaking water from its back. Wei [21] also used 10 min observation periods to count wet dog shakes and obtained good quantifications of morphine withdrawal. Other investigators have employed 30 min [12] and 120 min [2] to count the number of shakes. Other signs of morphine withdrawal such as diarrhea, lacrimation, teeth chattering, piloerection, and gnawing were observed in all morphine dependent animals. The weight lost by each rat following naloxone challenge was also monitored by weighing the rats before and 30 min after the naloxone injection. Statistical comparisons were made using the Student's *t* test.

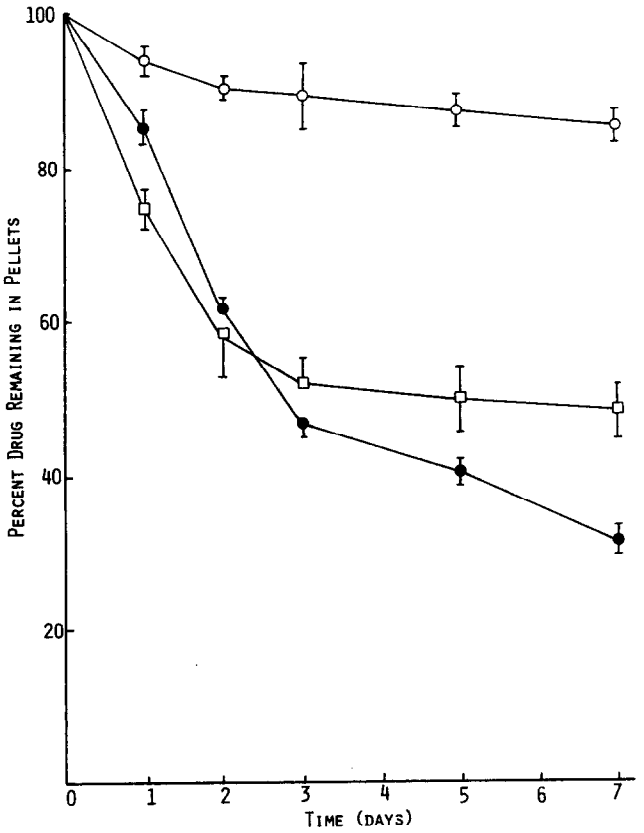


FIG. 1. Determination of in vivo release of morphine from pellets containing the equivalent of 75 mg morphine base in Sprague-Dawley rats. Key: ○, silastic/morphine base; ●, silastic/morphine sulfate; □, cellulose/morphine base. Vertical bars equal S.E. n=4.

## RESULTS

The in vivo release of morphine from the three pellet formulations implanted subcutaneously in rats is shown in Fig. 1. The implants were removed from the animals at various times, and the residual amount of drug left in the pellet was determined. As shown in Fig. 1, drug was released very slowly from the morphine base-silastic pellet, and after 7 days, less than 20% of the drug had diffused from the pellet. It is important to note that, after one day, the release from the microcrystalline cellulose pellet "appears" to be more rapid than that from the morphine sulfate-silastic pellet. However, visual qualitative estimations of drug action or behavior at frequent time intervals during this period

TABLE 1

MEASUREMENT OF INTENSITY OF NALOXONE INDUCED MORPHINE WITHDRAWAL

| Days of Implant | Wet Dog Shakes†Following Naloxone‡ Morphine Sulfate* Silastic | Morphine Base Silastic | Morphine Base Microcrystalline Cellulose |
|---|---|---|---|
| 1 | 10 ± 2 | 7 ± 2 | 7 ± 2 |
| 2 | 16 ± 4 | 6 ± 3 | 12 ± 3 |
| 3 | 21 ± 4 | 9 ± 2 | 16 ± 5 |
| 5 | 13 ± 3 | 7 ± 2 | 10 ± 2 |
| 7 | 11 ± 4 | 7 ± 4 | 7 ± 2 |

*Each pellet contained the equivalent of 75 mg morphine base.
†Mean number of shaking episodes ± SEM (n=4) within a 10 min period.
‡4 mg/kg IP.

TABLE 2

WEIGHT LOSS* (G) IN RATS AFTER NALOXONE CHALLENGE

| Days of Implant | Morphine Sulfate† Silastic | Morphine Base Silastic | Morphine Base Microcrystalline Cellulose |
|---|---|---|---|
| 1 | 3.75 ± 0.8 | 2.0 ± 1.1 | 2.75 ± 1.3 |
| 2 | 4.75 ± 0.9 | 3.5 ± 1.5 | 3.50 ± 1.0 |
| 3 | 5.50 ± 1.1 | 3.5 ± 0.8 | 4.75 ± 0.8 |
| 5 | 5.25 ± 0.8 | 3.0 ± 1.3 | 3.25 ± 0.9 |
| 7 | 5.30 ± 0.6‡ | 3.0 ± 1.3 | 2.50 ± 0.8 |

*N=4 and the mean weight loss for all blanks was ≤1.0. Expressed as mean ± SEM.
†Each pellet contained the equivalent of 75 mg morphine base.
‡Significantly different from morphine base-cellulose pellet, $p<0.05$.

suggested that the reverse would occur, i.e. animals implanted with the silastic pellet (morphine sulfate) during the first 12 hr were very drowsy and sedate.

As shown in Tables 1 and 2, the intensity of naloxone induced morphine withdrawal in rats implanted with the cellulose pellet containing morphine base reached a peak level on the third day. Thereafter, the intensity gradually diminished such that on the seventh day the intensity was similar to that observed on Day 1. Weight loss and numbers of wet dog shakes following naloxone challenge in rats implanted with the morphine sulfate-silastic pellet also peaked after 3 days. Silastic pellets containing morphine base produced a uniform low degree of naloxone induced morphine withdrawal. A comparison of the morphine sulfate-silastic pellet and the morphine base cellulose pellet in Table 1 shows that the number of wet dog shakes following naloxone challenge after 7 days of implantation were not significantly different.

The weight loss in rats following naloxone challenge is seen in Table 2. A comparison of the data from the morphine sulfate-silastic pellet and the morphine base-cellulose pellet shows no significant difference for the first 5 days. The difference after 7 days is significant ($p<0.05$) and is probably due to the fact that the silastic pellet continues to release the soluble morphine salt after 3 days (as seen in Fig. 1).

No wet dog shakes were seen in placebo implanted rats and the mean weight loss for these animals was less than 1 g.

## DISCUSSION

The presence of the sodium alginate in the silastic pellet causes the pellet to swell when it comes in contact with moisture. As the pellet increases in size, it is probable that channels were developed through which the drug diffuses. Some swelling occurred with the other "carriers" studied (gelatin, sodium lauryl sulfate and lactose) but to a much lesser extent compared to the sodium alginate. The slow release of morphine base from the silastic pellet is probably due to the poor solubility of the base at physiological pH.

The cellulose pellet suffers disadvantages as a suitable drug delivery system for morphine. However, it still remains the most popular method for inducing morphine dependence. One of the disadvantages has been that drug release in the animal ceases after 3 days with only half the drug being released from the pellet for absorption. The pellet also tends to become encapsulated by membraneous tissue which could account for the diminished bioavailability of its contents [1, 17, 20, 21]. Since the pellet contains approximately 50% microcrystalline cellulose, a tablet disintegrant, the pellet

quickly becomes soft and mushy, and complete removal of the implanted pellet is difficult. Failure to remove all of the implanted pellet from the animal would give erroneously high values for the percent of morphine absorbed. The specifications for the pellets, with regard to tablet weight, thickness, diameter and hardness, were reported by Gibson and Tingstad [8]. It is obvious that the preparation of such tablets requires the services of an individual skilled in tablet technology, as well as the ready availability of the necessary machinery.

The advantages of the silastic-morphine sulfate pellet system are many and overcome many of the previously discussed problems. Compared to other pellet formulations which require heavy tablet presses to manufacture the drug delivery system, the silastic pellet can be readily prepared in any laboratory. The pellets were easy to insert in the animal, and since they do not disintegrate, they were easily removed. In addition, negligible tissue encapsulation or irritation was observed even after 7 days of implantation. Once the pellet is removed from the animal, the drug remaining in the implant can be readily extracted so that the quantity delivered to the rat can be accurately determined. The silastic pellets containing morphine sulfate and the alginate, should also be very convenient for chronic morphine studies. This new drug delivery system is currently being investigated with other drugs, and preliminary data with sodium pentobarbital and amphetamine sulfate suggest that silastic pellets containing sodium alginate can be successfully formulated to slowly deliver the implanted drug over a desired time period.

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