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BRIEF COMMUNICATION

Technique for the Continuous Infusion of High Doses of Cocaine by Osmotic Minipump

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JOYNER, C. M., G. KING, T. H. LEE, AND E. H. ELLINWOOD, JR. *Technique for the continuous infusion of high doses of cocaine by osmotic minipump.* PHARMACOL BIOCHEM BEHAV **44**(4) 971-973, 1993.—The present article describes a procedure for modifying osmotic minipumps to avoid the local, toxic, necrotic effects of high concentrations of drug at the exit portal during the chronic, continuous infusion of cocaine. The present procedure eliminates the occurrence of necrotic skin lesions otherwise produced by SC administration of cocaine and/or other vasoconstrictive agents. The method of administration will therefore be useful for administration of other chronic drug regimens.

Continuous cocaine Intermittent cocaine Rats Minipump

THE route of administration and temporal dynamics are critical determinants of drug effects. Such factors are especially important for the analysis of human cocaine abuse. Human cocaine abusers can be separated into two groups, the intermittent recreational user and the chronic continuous "binging" abuser (1,2). A binge is characterized by readministration of the drug approximately every half hour or less. In typical recreational users, a binge typically lasts 12 h or less, whereas in high-dose users it frequently lasts days (1,2,5).

The pharmacokinetics of cocaine depend upon the route of administration. With the intranasal ("snorting") route of administration, peak plasma cocaine levels are obtained in approximately 30 min (3) and the half-life is approximately 40–60 min. (4). In contrast, IV use of cocaine results in a reported "rush" after 1–2 min (5), and users report a willingness to take another dose after approximately 30–40 min (3); the half-life with this route is approximately 40–60 min (4). The smoking of cocaine base ("crack") has a kinetic profile similar to intravenous use: a rapid onset due to respiratory absorption, short effect, and half-life of approximately 40–60 min (5).

This analysis of cocaine use (recreational vs. binge) and the pharmacokinetics of cocaine would indicate that during a binge although the plasma cocaine levels will fluctuate as a function of an oscillating pattern of self-administration the abuser nonetheless is maintaining a reasonably sustained plasma cocaine level, not infrequently over prolonged periods. Because this aspect of cocaine abuse is not represented by daily, intermittent cocaine injections, we decided to develop a continuous-infusion paradigm to model the binge-like consumption pattern of high-dose cocaine abusers.

One major obstacle to the development of a continuous cocaine administration procedure is the development of severe necrotic lesions resulting from the potent vasoconstrictive properties of cocaine (8). For example, we found that in the course of several pilot studies the area around the portal delivery end of the minipump often developed lesions and at times the delivery portal would penetrate through the skin. To overcome these problems, we developed a method for modifying Alzet minipumps for the continuous infusion of large doses of cocaine without the development of necrotic skin lesions. The procedure utilizes a microdialysis filament attached to the output delivery end of the minipump to spread the drug over a greater surface area. The following describes the specific procedures for the modifications.

TECHNIQUES

Materials

Alzet minipumps were purchased from Alza Corp. (Palo Alto, CA). The Spectra Por RC hollow fiber bundles (Spectrum, Inc., Los Angeles, CA) were obtained from Krakeler Scientific. Duro brand epoxy was purchased locally. RTV surgical silicon elastomer was purchased from Southern Prothesis Supply. Surgical autoclips were purchased from Clay Adams.

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Minipump Modification

A 6- to 8-mm long piece of microdialysis fiber was cut from a single strand in the bundle (a bundle consists of 176 150-μm strands). The piece of fiber was slipped into the portal delivery tube of the modulator tip (A) of the minipump and epoxyed (B) into place. Surgical silicon elastomer was then coated around the tip to secure it in place (C). Figure 1 illustrates the procedure. After air drying for 24 h, the flow of the modified modulator and the microfiber was checked by injecting saline (0.9%) through the portal delivery tube of the moderator and out through the microdialysis fiber using a 1-cc syringe.

Minipump Preparation

Prior to surgical implantation, the minipumps were filled with cocaine dissolved in 0.9% saline. Before surgery, the minipumps were primed in a water bath at 20°C for 4 h.

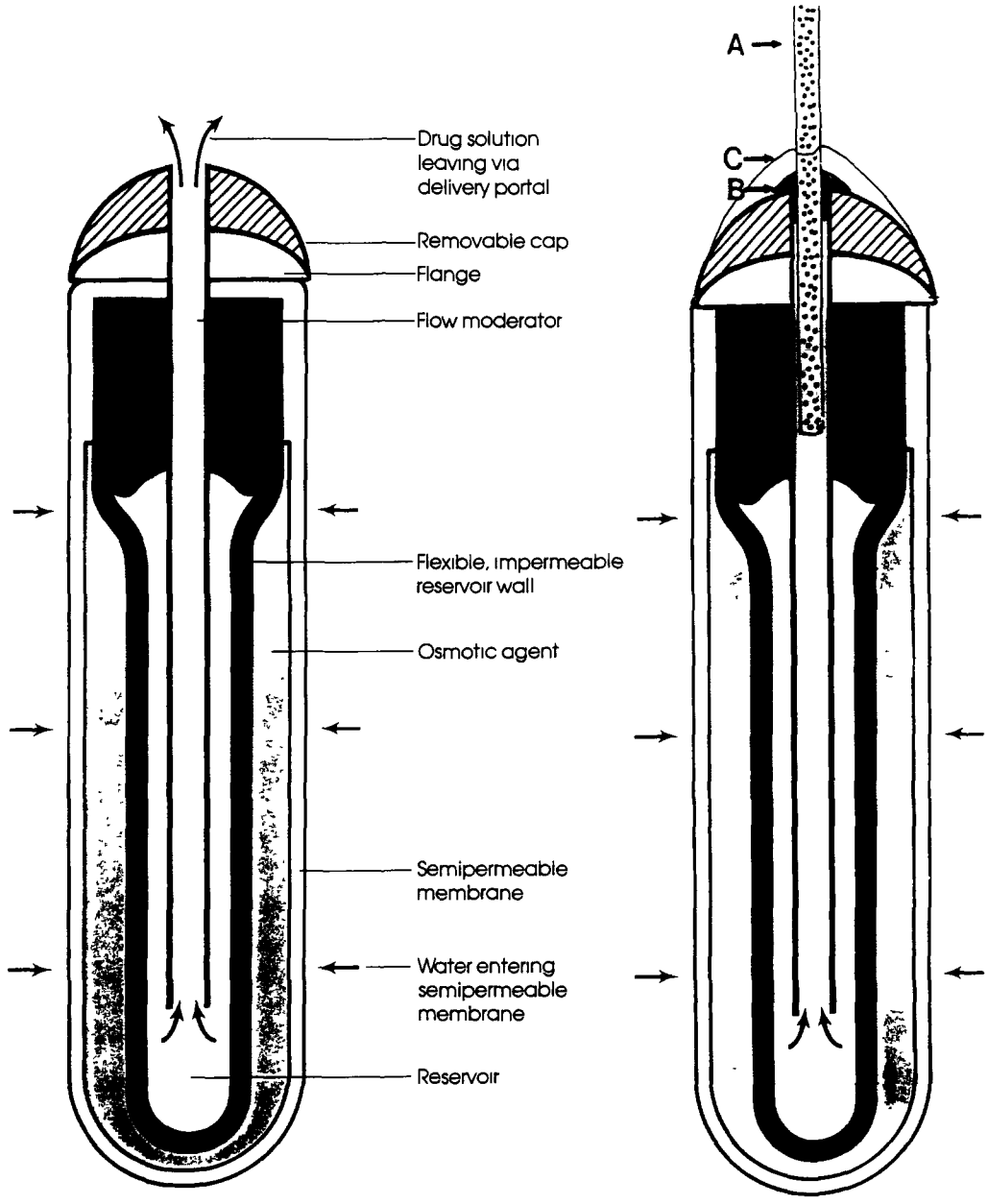
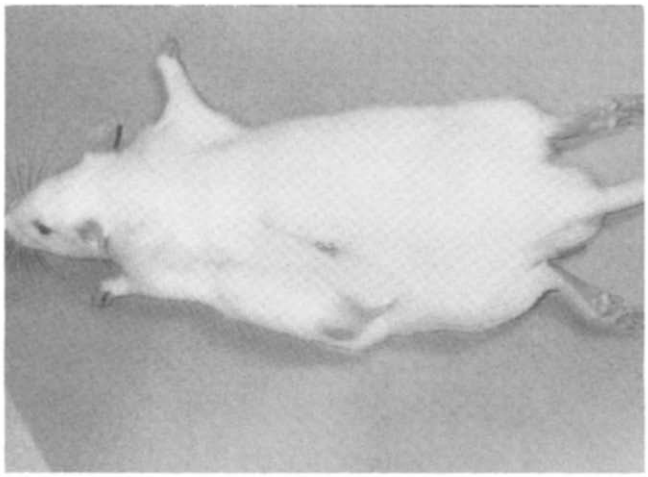
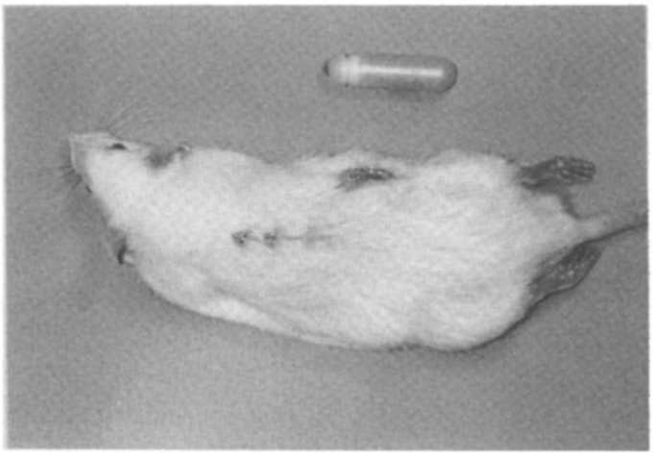


FIG. 1. Cross section of a functioning osmotic minipump (left panel). Cross section of a modified functioning osmotic minipump (right panel). Part A is the modulator tip. Part B is the epoxy. Part C is the surgical silicon elastomer.



(A)



(B)

FIG. 2. Photographs of a rat (A) immediately after surgery and (B) at the end of a 14-day treatment period.

Surgery

Rats were anesthetized with Metofane (methoxyflurane) by inhalation and given local SC injections of 1% lidocaine in the area of the incision. A 3-mm incision was made along the dorsal midline and a large SC pocket formed with surgical scissors. A large SC pocket is necessary to increase the area of drug delivery. This increased area allows the drug to infuse along a 2-to 3-in. area as opposed to all seeping out in one small area. Delivery of cocaine to a small, restricted area promotes the development of necrotic lesions. At the time of implantation, the modified modulator was put on the minipump and inserted into the SC pocket with the microfiber delivery end toward the head. Surgical autoclips (9 mm) were used to suture the opening.

Figure 2 presents photographs of a rat after 14 days of treatment using the present procedures. The rat was infused with 40 mg/kg/day cocaine. On day 14 after implantation, the minipumps were surgically removed in the same manner. Figure 2 indicates that there are no apparent necrosis after the 14-day treatment.

DISCUSSION

The present article presents a technique for the continuous administration of high doses of cocaine that eliminates the production of necrotic skin lesions associated with SC administration of cocaine. We have used this paradigm in several series of experiments (6,7). The results of such studies indicate that the continuous infusion of cocaine results in subsequent tolerance to its locomotor-stimulating,and stereotypy-inducing properties. Further, the continuous infusion of cocaine results in profound 5-hydroxytryptamine$_{1A}$ (5-HT$_{1A}$) receptor subsensitivity. These results indicate that the continuous infusion of cocaine produces effects that are opposite to those found with the more typical procedure of daily intermittent injections of cocaine. Hence, the present continuous-infusion procedure will be useful not only for an examination of the effects of chronic cocaine administration but may also be useful for the examination of other chronic drug regimens.

ACKNOWLEDGEMENTS

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