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A New Subcutaneously-Implantable Reservoir for Sustained Release of Nicotine in the Rat[1]

CARLTON K. ERICKSON,[2] SALOMON A. STAVCHANSKY, KATHE I. KOCH AND JAMES W. McGINITY

Drug Dynamics Institute, College of Pharmacy, The University of Texas, Austin, TX 78712

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ERICKSON, C. K., S. A. STAVCHANSKY, K. I. KOCH AND J. W. McGINITY. *A new subcutaneously-implantable reservoir for sustained release of nicotine in the rat.* PHARMAC. BIOCHEM. BEHAV. 17(2) 183–185, 1982.—A subcutaneously-implantable reservoir for the sustained release of nicotine is described. The device, dubbed INR for Implantable Nicotine Reservoir, is a small glass cup sealed with Silastic® polymer. It releases 3.4 mg of nicotine per 24 hours. When implanted into moderately-sized female Sprague-Dawley rats it produces blood nicotine levels of 400–500 ng/ml which remain relatively stable over at least 18 days. INRs are nontoxic, reproducible, inexpensive, and adaptable for pharmacological and toxicological studies in rats and other small animals.

Nicotine Sustained release Rats Body temperature Blood levels Implant

NICOTINE, the predominant alkaloid in tobacco, has become a widely studied drug for its pharmacological and toxicological effects. It may induce or exacerbate several cardiovascular, respiratory, and neoplastic states in both humans and laboratory animals [7, 8, 10].

In humans, nicotine is normally administered by inhalation of cigarette smoke or buccally, through the lining of the mouth by absorption of solubilized nicotine from chewing tobacco. Blood nicotine levels often remain high as the result of chain-smoking or the continual chewing of tobacco. In animals, forced-administration methods for nicotine include parenteral injection [13–16], administration by inhalation of cigarette smoke [3], solubilization in drinking water [14] and injection in single doses [2] or chronically via Alzet minipump [1] into the ventricles of the brain. Nicotine has also been self-administered intravenously [17]. The most common route of forced administration in animals is by parenteral injection. Oftentimes, up to 6 daily doses are given, the duration of each dose being 15–120 minutes, depending upon the size of the dose [9, 13].

Previous animal studies involving tolerance to nicotine or to the toxicological effects of continual exposure to nicotine have been hampered by the inability of investigators to administer nicotine conveniently over long periods of time. We felt that a sustained-release form of nicotine would be useful, in much the same manner as sustained release forms for morphine [11], ethanol [5,6], and amphetamine [4] have been useful for studying chronic toxicity and dependence in animals. This paper reports the successful development of a glass implant with a Silastic® cap through which nicotine is slowly released.

METHOD

Materials

The drug and chemical sources were as follows: nicotine alkaloid, Sigma Chemical Co. (St. Louis, MO); Silastic® elastomer, 382 Medical Grade Elastomer mixed with catalyst, Catalyst M Stannous Octoate, Dow Corning Co. (Midland, MI); N-ethylnornicotine, a gift from Dr. P. Jacobs, University of California at San Francisco.

Animals

Sixteen female SD/ARC rats (derived from Sprague Dawley stock originally obtained from Charles River and bred at The University of Texas) were used in the experiments. They were housed in groups of 3–4 in wire bottomed stainless steel cages on a 12/12 light/dark cycle at 25°. Food (Lab Blox, Purina) and water were available ad lib. The rats weighed 200–250 g at the start of the experiment.

Implant Manufacture

Preliminary (unpublished) results in our laboratory indicated that the solid nicotine bitartrate did not release easily from a silastic matrix such as the one used for morphine [11]. Therefore, we chose the liquid nicotine alkaloid for our release studies. In further tests we found that the release of

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[2]Send reprint requests to: Carlton K. Erickson, College of Pharmacy, The University of Texas, Austin, TX 78712.