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Technical Report: The Subcutaneous Administration of Cocaine in the Rat

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DURAZZO, T. C., D. V. GAUVIN, K. L. GOULDEN, R. J. BRISCOE AND F. A. HOLLOWAY. *Technical report: The subcutaneous administration of cocaine in the rat.* PHARMACOL BIOCHEM BEHAV 49(4) 1007–1010, 1994.—Eight male Sprague–Dawley rats were treated with 32 mg/kg cocaine, twice daily, for 2 weeks using a SC route of administration. Using a cocaine stock solution of 1.2–1.6 mg of cocaine hydrochloride per ml of sterile saline, we demonstrate, for the first time, the relative safety of subcutaneously administered cocaine in the rat. There was absolutely no evidence for focal dermal necrosis, in any rat, after the 2-week chronic period.

Cocaine Rats Subcutaneous administration

THIS laboratory has recently concluded a study designed to assess the relative interoceptive hedonic valence associated with both intraperitoneally (IP) and subcutaneously (SC)-administered cocaine using a conditioned place learning assay [cf., (2)]. The use of the SC delivery of cocaine in animal subjects has met with a surprising level of resistance, in spite of the limited experimental data generated using this specific route of administration.

In a number of recent studies focussing on the teratogenic and/or the behavioral effects of prenatal cocaine exposure, in which IP cocaine could not be utilized, the SC route of cocaine administration was used. The SC delivery of cocaine to rats has been reported to produce plasma and brain cocaine and benzoylecognine levels equivalent to those described in human cocaine abusers (12).

Physiologically, the absorption of cocaine in the IP cavity results from uptake by the vasculature of the g.i. tract and passage through the splanchnic circulation before entry into the general circulation. During IP cocaine dosing procedures, the drug may be metabolized in the liver in a first pass effect, thus limiting the functional dose in the CNS. El-Maghrabi, Calligaro, and Eldefrawi (3) have previously shown high stereospecific affinity to selected liver sites, and that cocaine is a potent hepatotoxin in mice. Severe depression of a variety of hepatic enzymes, fatty infiltration, and both midzonal and periportal liver necrosis have been reported with IP cocaine delivery (6,11). Nayak, Misra, and Mule (8) have previously reported that the SC route of administration of cocaine results in an effective half-life of 1.8 to 2 h, compared to the intravenous and IP half lives of 0.3 h and 0.25 h [cf., (4)], respectively. Petit et al. (9) and Pan et al. (9)have recently reported the neurochemical changes resulting from acute and chronic SC cocaine. They have demonstrated: a) repeat SC cocaine injections did not reveal a buildup in adipose tissue and, more importantly, b) chronic SC cocaine resulted in statistically significant increases in both brain and plasma concentrations of cocaine and extracellular concentrations of dopamine in the nucleus accumbens following an acute IP cocaine challenge injection. These authors concluded that a physiological change occurred in the periphery as a result of the chronic SC cocaine administration, which altered the absorption process of a later IP injection.

The principle argument usually presented against the use of SC cocaine administration in the rat is based on the focal dermal necrosis, most often reported anectdotely, at the injection sites (but see (1)]. For example, Lau, Imam, Mau, and Falk (7) have reported that, "subcutaneous injection of a single dose of cocaine solution produced a large patch of dermal

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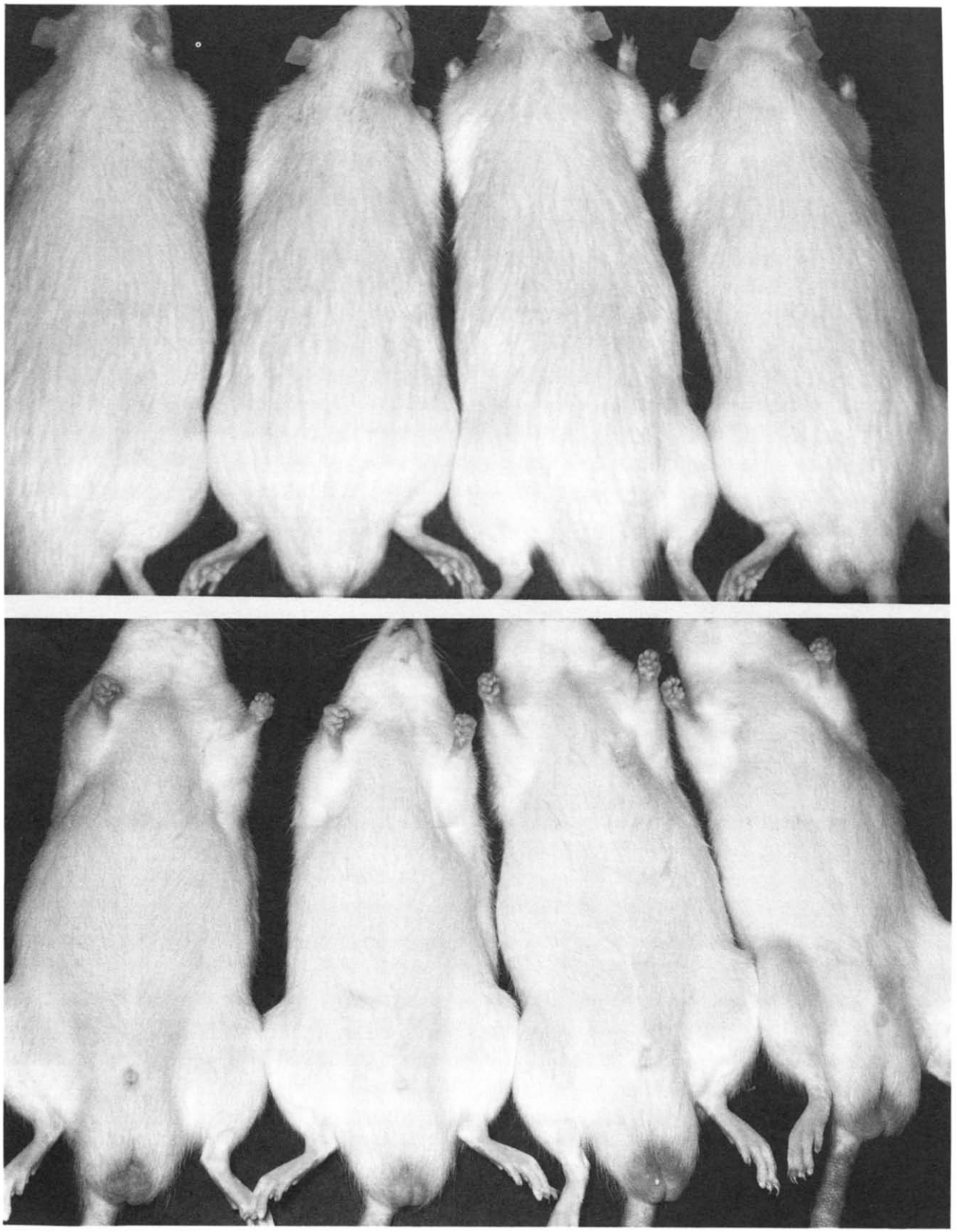

FIG. 1. Exterior photograph of eight male Sprague-Dawley rats (four dorsal views—top panel; four ventral views—bottom panel) taken on the day after a 14 day chronic cocaine treatment period. Each rat received two daily SC injections of 32 mg/kg cocaine using a standard 1.2 to 1.6 mg/ml stock solution. There is no evidence of focal dermal necrosis in any rat after chronic SC cocaine exposure.

necrosis in each case" (p. 450). These authors go on to report, "attempts to ameliorate this effect by adjusting injection volume and pH with a few pilot animals were unsuccessful" (p. 450). Although the SC route of administration was conducted in only two animals, Lau et al. report that one rat ceased to work at the test dose and the other showed a clear motor impairment along with increased work rate. The concentration of cocaine used in the Lau et al. study was 7.5 mg/ml.

Our cocaine studies require the chronic administration of the drug. For our purposes, the SC route of administration appeared to be superior to either IP or IV routes of administration because of the longer half-life for SC administered cocaine. The current report demonstrates that cocaine can be safely administered to rats via the SC route without short- or long-term focal dermal necrosis. We report on the relative safety of administering 32 mg/kg cocaine, SC, twice daily for 2 weeks in male Sprague-Dawley rats.

METHOD

Subjects

Eight male Sprague-Dawley rats, generational cohorts to rat subjects used in our companion report (2), were purchased from Sasco, Inc. (Omaha, NE). Rats were group housed in standard Plexiglas shoebox cages in an AAALAC-accredited vivarium maintained by the Department of Animal Resources of the University of Oklahoma Health Science Center. The rats were given ad lib access to both food and water and were allowed to gain weight until the group mean body weights exceeded 350 g, at which time the experimental protocol was begun.

Dosing Protocol

Each rat received two daily injections of 32 mg/kg cocaine, subcutaneously, using a cocaine stock solution of 1.20 to 1.60 mg of cocaine hydrochloride per ml of normal sterile saline. Cocaine was weighed daily (expressed as the salt) and stored in light-attenuating bottles. A single bolus injection was administered to each rat at 2000 and 0800 h for 14 days. This specific cocaine concentration was selected because, a) it was significantly lower than the 7.5 mg/ml used in the Lau, Imam, Mau, and Falk (7) study (described above) and b) it would allow for the delivery of approximately 7.0 to 10.0 ml of fluid into the SC vault space. We have previously used this specific volume of fluid (standard Ringers solution) to successfully treat isolated cases of systemic dehydration in rats in our lab. These volumes are within the normal injection volumes typically utilized in studies using 10% w/v ethyl-alcohol for more prolonged periods of injections schedules. The 7.0 to 10.0 ml of fluid injected into the SC vault appears to be completely absorbed within 20 min of administration. After each syringe was filled to the desired volume of the cocaine stock solution, the syringe needle was immersed in sterile saline to wash off any cocaine solution residue off the needle prior to injection into the rats skin. Injections were administered as a single bolus or as two separate injections administered on alternate sides of the body. Each injection site was recorded and visually examined prior to each subsequent injection. At the end of the 2-week period, photographs were taken of the dorsal and ventral abdominal surfaces.

RESULTS

Figure 1 shows either the dorsal (top panel) or ventral (bottom panel) surfaces of eight rats treated chronically with 32 mg/kg cocaine, twice daily, for 14 days using a cocaine concentration of 1.2 to 1.6 mg/ml. There is absolutely no evidence of focal dermal necrosis in any rat throughout the dorsal or ventral locations of SC cocaine administration. Necropsy and histopathological analyses supported these visual findings and revealed no evidence of chronic inflammation or granuloma formation involving the skin, underlying skeletal muscles, or subcutis. One rat presented evidence typical of gastric ulcers; all other tissues and organs were within normal limits.

Although the drug volumes used in this study are equivalent to those used in more typical alcohol-related studies, we have conducted supplemental metabolic studies on eight no injection control rats and eight large-volume saline experimental rats 1 h after injections. Tail blood samples were drawn by snipping the distal end of the tail and collecting blood in both heparinized and nonheparinized micropipettes. Groups did not differ in blood pH or blood gases (Instrumentation Laboratories System 1301 pH/blood gas analyzer, Lexington, MA) blood lactate or glucose (YSI 2300 Stat Plus, Yellow Springs, OH), nor hematocrit (centrifuged 20 μl pipettes).

DISCUSSION

We believe that the current study clearly, and for the first time, demonstrates the relative safety of chronically administering high doses of cocaine subcutaneously in the rat. Because other laboratories have reported dermal necrosis after a single SC injection of cocaine [cf., (7)], we are confident that the current procedure would effectively protect the animals from dermal necrosis even if the chronic cocaine administration was further extended past the 2-week chronic period of this report. Recently, Joyner et al. (4) have similarly reported the relative safety of the continuous SC infusion of high doses of cocaine using osmotic minipumps. The current study and those of Joyner et al. (4) clearly demonstrate that cocaine can be safely administered subcutaneously in rats without the major focal dermal necrosis typically believed to be a result of such administration.

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