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Addiction Potentialities of 1, 1-Diphenyl-1-(β-Dimethylaminopropyl)-Butanone-2 Hydrochloride (Amidone) in the Monkey.*

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1,1-Diphenyl-1 - (β-dimethylaminopropyl)-butanone-2 hydrochloride (amidone, 10820, dolophine) has recently become the subject of intensive pharmacological studies as a result of its analgetic action. Information concerning this compound has been published by the U. S. Department of Commerce.[1] More recently reports have been published describing in greater detail the pharmacological actions of this derivative and its analgetic potency.[2,3] It is the purpose of this paper to present experimental data concerning the addiction potentialities of amidone in rhesus monkeys.[4] This animal is well suited for this type of study since the course of addiction and the signs of abstinence are similar to those observed in man.[5]

Chronically morphinized monkeys were used as a basis for comparison. Two rhesus monkeys were given morphine sulfate subcutaneously daily for 86 to 95 days, increased from 7.5 to 100 mg/kg in 50 days and maintained at this level. Four monkeys received amidone subcutaneously daily for 75 to 96 days, the initial dose of 5 mg/kg being increased to a maximum dose (13 mg/kg in the most resistant animals) in 24 to 26 days. The animals were maintained during the rest of the period on the maximum tolerated dose as determined by the severity of acute depression and weight loss. Pertinent data are summarized in Table I.

The chronically morphinized monkeys exhibited characteristic abstinence signs[5] after withdrawal of the drug. No characteristic signs of abstinence or evidence of increased irritability was observed in the monkeys receiving amidone. They returned to normal activity in a few days, appetite and weight loss were regained, and the response was entirely different from the morphinized animals.

Both morphine and amidone, when chronically administered, produce anorexia and weight loss (see Table I) to about the same extent. In addition, however, amidone causes considerable irritation and fibrosis at the site of injection resulting in marked aversion to daily administration.

Amidone, administered subcutaneously to the monkey, produces an acute depression which is maximum in 90 minutes and lasts 4 to 5 hours as an average response. Mydriasis, salivation, lacrimation, profound muscular weakness, and severe respiratory depression are characteristic signs, as with morphine. In the monkey the lethal dose of amidone lies between 10 and 20 mg/kg, death resulting from respiratory failure. Shortage of animals, which prevailed at the time of this study, prevented the establishment of a more accurate toxicity value.

With amidone, repeated administration does not confer tolerance to the lethal dose nor to other manifestations of depression. In fact, increased susceptibility is the rule as evidenced by the fact that profound depression required a reduction in dosage below that previously tolerated.

In order to determine if any crossed tolerance from amidone to morphine had devel-

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1 Kleiderer, E. C., Rice, J. B., Conquest, V., and Williams, J. H., Report No. 981, Office of the Publication Board, Department of Commerce, Washington, D.C.

2 Scott, C. C., and Chen, K. K., *Fed. Proc.*, 1946, **5**, 201; *J. Pharm. Exp. Therap.*, 1946, **87**, 63.

3 Scott, C. C., Robbins, E. B., and Chen, K. K., *Science*, 1946, **104**, 587.

4 Woods, L. A., Wyngaarden, J. B., and Seevers, M. H., *Fed. Proc.*, 1947, **6**, in press.

5 Seevers, M. H., *J. Pharm. Exp. Therap.*, 1936, **56**, 147.

TABLE I.
Dosage and Weight Data of Chronically Poisoned Monkeys.

Monkey No.	Sex	Initial wt (kg)	Loss in wt (%)	Drug	Days of injection	Max. dose tolerated mg/kg
40	M	4.8	10.4	M.S.	95	—
45	F	5.5	19.1	"	86	—
27	F	4.3	30.2	Amid.	96	13
28	M	5.0	18.0	"	96	13
42	M	5.0	10.2	"	75	11
46	M	5.6	7.0	"	75	12

oped, the 4 amidone monkeys (on the 73rd day for monkeys No. 27 and No. 28 and 53rd day for monkeys No. 42 and No. 46) and 4 normal monkeys were injected with morphine sulfate 20 mg/kg at approximately the same time and careful observations and comparisons noted. The depth and duration of depression, and the degree of lacrimation, mydriasis, and salivation and other signs were not significantly different for the 2 series of animals, indicating that chronic poisoning with amidone does not confer tolerance to morphine.

Observations on the chronically morphinized monkeys, however, did indicate some, but not marked, crossed tolerance to amidone. Monkeys No. 40 and No. 45 were each given 15 mg/kg of amidone at 2 different times separated by a week's interval. Each of these 4 injections produced only a mild to moderate depression. Injection of monkey No. 40 with 18 mg/kg of amidone produced a moderately severe depression. During these injections of amidone, although 48 hours elapsed between morphine sulfate administration, no withdrawal signs appeared. Five normal control monkeys were injected with 15 mg/kg of amidone and the effects were more pronounced than those seen in the morphinized animals since: one monkey died in spite of artificial respiration; one monkey was very severely depressed but the animal survived after artificial respiration and administration of metrazol; 2 monkeys were very depressed with very slow respiratory rate and Cheyne-Stokes breathing. Only one of this group of 5 exhibited mild to moderate depression, comparable to that produced by a similar quantity of amidone in the chronically morphinized animal.

Summary. It may be stated that chronic administration of amidone in the monkey does not lead to a condition of physical dependence on this drug such as is noted with morphine. Tolerance to this drug does not develop, but on the contrary an increased susceptibility to its depressant effect occurs. Crossed tolerance from amidone to morphine does not occur but chronically morphinized monkeys do exhibit some crossed tolerance to amidone. The later is only minimal and not comparable in degree to that which occurs from one morphine derivative to another. Amidone produces an acute depression which is maximum in 90 minutes and is of 4 to 5 hours' duration in this animal. The lethal dose in the monkey lies between 10 and 20 mg/kg and death occurs from respiratory failure.