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THE LOCAL ANESTHETIC PROPERTIES OF AMIDONE (DOLOPHINE)* †

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SEVERAL recent reports indicate that the new synthetic compound 6-dimethylamino-4, 4-diphenyl-3 heptanone called amidone (Dolophine-Lilly)‡ promises to be the first of a new series of effective analgesic agents (1). While most of the pharmacological and clinical studies of

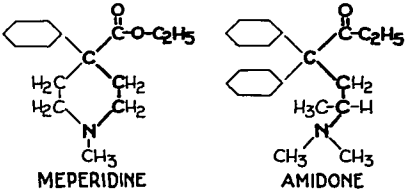

FIGURE 1.

amidone have been done in this country, the drug was discovered during World War II (2) by the same group of German workers who introduced meperidine (isonipecaine or demerol) (3). Amidone and several of its analogues now being investigated represent a further chemical development of the meperidine series. Structurally, as shown in figure 1, amidone differs from meperidine in that the nitrogen is at-

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tached to an aliphatic chain instead of being incorporated in a ring, and that the central carbon atom is linked to two benzene rings instead of to one. Considerable structural similarity between the two compounds is retained, however, since in both, the methylated nitrogen is separated from the central carbon atom by two carbon atoms, and the ketone structure of amidone is similar to the ester linkage of meperidine. On this basis, it would be expected that these compounds would have similar pharmacological properties. This has been demonstrated with respect to analgesia, spasmolysis on isolated intestines and certain parasympathomimetic actions (4, 5). In view of Way's (6) recent report of the local anesthetic properties of meperidine, we were interested in finding out whether or not amidone possessed a similar action.

METHODS

Cocaine, meperidine and amidone were compared by the two methods considered most satisfactory for the testing of local anesthetic agents (7). These are (a) anesthetic effect on the rabbit's cornea, and (b) the human intradermal wheal method.

a. Anesthesia of the Rabbit Cornea.—One, two and four per cent solutions of the hydrochloride salts dissolved in physiological saline were used. Rider's (8) modification of the Schmitz and Loevenhart (9) technic with minor alterations was used. In place of a blunt probe, a fine von Frey hair pressing with a maximal strength of 0.1 Gm. before bending served for stimulating the cornea. The lateral part of the cornea was tested since it responded quicker and more regularly. Pupil size and corneal appearance were noted. Following observation of the corneal reaction by gentle pricking or pressure with the von Frey hair, the drug was instilled into the conjunctival sac. The instillation was carried out with the head of the rabbit turned so that its ears pointed to the left of the operator and the left eye was in a horizontal position. The lids of the left eye were then opened and held apart while an assistant instilled sufficient solution to flood the conjunctival sac. After fifteen seconds, the lids were shut and rapidly reopened and the conjunctival sac refilled; this procedure was repeated so that four such instillations were made within one minute. The lids were then allowed to close and the eye was gently wiped from the outside so as to expel any surplus solution. The response to gentle pressure with the von Frey hair was then tested every minute and continued until the wink reflex returned. This period was considered as the duration of complete anesthesia.

A large number of rabbits was used in this experiment and intervals of at least forty-eight hours elapsed between studies on the same rabbit to permit adequate recovery and avoid tolerance to the drug effects.

b. Human Intradermal Wheal Anesthesia.—While 1 per cent concentrations of the three drugs were first tested, the anesthesia produced was too prolonged to allow suitable measurement and comparison. Besides, the solutions of meperidine and amidone were extremely irritating. Consequently, 0.25 per cent solutions of the hydrochlorides of meperidine, cocaine and amidone were used. The intradermal injections were made into the shaved skin of the forearm with a ¼ cc. graduated tuberculin syringe and a one-half inch 28 gauge needle. The wheal was then tested for duration of anesthesia at one minute intervals with a

von Frey hair displacing 0.1 Gm. Any response to this stimulus, after a period of anesthesia, was considered as the end of complete anesthesia. Intervals of forty-eight hours or longer were allowed between consecutive tests on the same individual.

Since anesthesia of both the cornea and of the skin wheal occurred almost immediately following drug administration, the speed of onset of anesthesia was not measured.

RESULTS

Table 1 shows the comparative results obtained with cocaine, meperidine and amidone for rabbit corneal anesthesia. Each of the three strengths of solutions of amidone caused corneal anesthesia of approximately the same duration as that produced by similar strength

TABLE 1

THE DURATION OF LOCAL ANESTHESIA OF THE RABBIT CORNEA BY COCAINE, MEPERIDINE AND AMIDONE

Drug	No. of Experiments	Mean Duration Anesthesia	Standard Error	1% Cocaine		Same Strength Cocaine	
				+ or (−)	P^1	+ or (−)	P^2
		mins.					
1% Cocaine HCl	27	23.9	1.26				
2% Cocaine HCl	17	30.5	2.27	+	<0.01		
4% Cocaine HCl	5	41.6	0.81	+	<0.05		
1% Amidone HCl	28	21.1	1.44	(−)	>0.10		
2% Amidone HCl	15	27.7	2.85	(−)	>0.05	(−)	>0.4
4% Amidone HCl	6	32.8	1.35	+	<0.02	+	<0.01
1% Meperidine HCl	27	0.81	0.42	+	<0.01	+	<0.01
2% Meperidine HCl	14	0.93	0.51	+	<0.01	+	<0.01
4% Meperidine HCl	6	7.3	1.02	+	<0.01	+	<0.01

The calculated P (probability) considered significant if P = 0.05 or less. From "Statistical Methods for Research Workers," by R. A. Fisher, Oliver and Boyd, London, 1930.

P^1 = the probability that results are significantly different from those obtained for 1% solutions of cocaine.

P^2 = the probability that the results obtained are significantly different from those obtained for a solution of cocaine of the same percentage.

+ = Plus. (−) = Minus.

solutions of cocaine. On the other hand, with the 1 per cent and 2 per cent solutions of meperidine only incomplete anesthesia was observed, while the 4 per cent solution showed a mean duration of anesthesia of 7.3 minutes, compared to the mean of 41.6 minutes for the 4 per cent solution of cocaine and 32.8 minutes for amidone.

In about half the number of rabbits the three strengths of cocaine solutions caused some pitting and wrinkling of the corneal layer, which disappeared after twenty-four hours. Conjunctival injection was only rarely observed with cocaine instillation. While neither the hydro-

chloride salt of amidone nor meperidine appeared to cause more than slight irregularity and roughness of the corneal surface, conjunctival irritation was seen in almost all animals treated with these drugs. The 4 per cent concentrations of amidone and meperidine appeared quite irritating, meperidine being more marked in this respect. In some of the animals mild sedation and hypnosis followed the instillation of the 4 per cent solutions of meperidine and amidone. Some degree of mydriasis was noted following instillation of amidone, which appeared greater than that produced by cocaine. Only slight mydriasis was observed for meperidine.

With the human intradermal wheal method, it was found that both cocaine and amidone showed approximately the same duration of complete anesthesia for each of the concentrations used (table 2). With

TABLE 2

DURATION OF ANESTHESIA OF THE HUMAN INTRADERMAL WHEAL FOR COCAINE, AMIDONE AND MEPERIDINE

Drug	No. of Experiments	Duration Anesthesia (mean)	Standard Error	Calculated P^a
		mins.		
1% Cocaine HCl	3	57	*	
0.25% Cocaine HCl	12	17.3	1.41	—
0.25% Meperidine HCl	11	10.6	0.88	<0.01
0.25% Amidone HCl	11	18.5	1.23	<0.5
0.85% Saline	4	0	0	

P^a = significant if P equals 0.05 or less. From "Statistical Methods for Research Workers," by R. A. Fisher, Oliver and Boyd, London, 1930.

* = No standard error was computed for Cocaine HCL 1% because of the small number of experiments performed with this strength of solution. The three data were sixty-four, fifty-nine and fifty-one minutes.

the 0.25 per cent solution of cocaine the mean duration of anesthesia was 17.3 minutes while with the same strength of amidone, it was 18.5 minutes. The mean duration of anesthesia for meperidine was considerably shorter. Cocaine solutions did not cause irritation or burning on injection, but both meperidine and amidone appeared somewhat irritating, the meperidine solutions more so than amidone. Both drugs produced pseudopod-like projections extending from the center of injection with occasionally a fine red macular eruption of about two inches in diameter. Itching and hyperaesthesia of this area after the period of anesthesia was complained of in most instances by those who received meperidine or amidone; again this appeared more severe after meperidine. It was noted that when the tests were done in warm weather a somewhat shorter period of anesthesia resulted, possibly due to the increased cutaneous circulation.

DISCUSSION

Our results show that amidone, in comparison with cocaine possesses a strong local anesthetic effect. Meperidine, however, while having some local anesthetic action, was considerably weaker than either cocaine or amidone. Our findings for meperidine do not agree with those of Way (6) who found that 1 per cent isonipecaine was about 6/10 as active as the same concentration of cocaine for duration of rabbit corneal anesthesia. We found that the 1 and 2 per cent solutions of meperidine (isonipecaine) produced incomplete anesthesia. These differences are more significant when it is realized that the technic we used for drug instillation assured application of large amounts of the solution. Even when we followed the method specified by Way, it was impossible to produce complete corneal anesthesia in most instances. We feel that the use of a blunt pencil or a probe covered with wax is a less accurate method for testing corneal sensation than the fine von Frey hair which provides a stimulus of very small intensity. Krop (10) has recently described a similar method of stimulation using a nylon bristle which displaces 3 Gm. when bent. It is our opinion that this is too stiff a bristle which may displace the entire eye-ball and therefore stimulate deeper nervous structures.

When the intradermal wheal was used for comparing the anesthetic effects of these drugs, approximately the same duration of anesthesia was observed for both cocaine and amidone with the 0.25 per cent solutions, while that caused by meperidine was significantly shorter. Way found that 1 per cent solutions of meperidine produced 7/10 the duration of anesthesia noted for 1 per cent cocaine. We were unable to use this strength solution of meperidine in more than a few patients because of the intense irritation produced.

Recently Copen (11) reported on the injection of mixtures of monocaine and meperidine in an attempt to obtain both local anesthesia and central analgesia in surgery of the oral cavity. The use of such a mixture containing a local anesthetic apparently offsets the local irritation caused by meperidine and, through a synergistic effect, allows the use of weaker concentrations of both drugs. In spite of its potent local anesthetic action, the practical use of amidone for either topical or subcutaneous infiltration anesthesia is precluded at present because of its irritant properties. It may be possible, however, that further development of compounds of this type will produce synthetic agents which will be less irritant and retain local anesthetic properties combined with effective analgesia.

SUMMARY

1. The local anesthetic action of amidone (Dolophine) in comparison with cocaine and meperidine (isonipecaine) was investigated by testing for the duration of anesthesia produced in the rabbit's cornea and on the human intradermal wheal.

2. Amidone was found to possess strong local anesthetic effects in the concentrations we used. It produced a duration of anesthesia for the rabbit's cornea approximately equal to that with cocaine, while that for the human intradermal wheal was slightly longer with amidone.

3. Meperidine, in comparison with cocaine and amidone, produced incomplete anesthesia of the rabbit cornea and a much shorter duration of anesthesia for human skin.

4. The irritant properties of both amidone and meperidine preclude their practical use at present as local anesthetics.

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