CLINICAL OBSERVATIONS ON THE USE OF AMIDONES FOR ANALGESIA * †

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SINCE the first of this century when it became evident that opium or its most active ingredient, morphine, produced undesirable effects, mainly addiction, in man upon repeated administration for the control of pain, numerous studies have been made to find a substitute for morphine which produced the desired effects of morphine without at the same time having addiction liabilities.

The most extensive of these studies were those supported by the National Research Council extending from 1928–1941 with Dr. Small as the chemist, Dr. Eddy as the pharmacologist, and Dr. Himmelsbach as the clinical investigator. Their excellent studies reported in four books of some 3000 pages produced metapon, from morphine, which is superior to morphine in relation to addiction liabilities (1).

In 1939 Eislaub and Schaumann prepared isonipecaine (demerol) in their attempts to develop new substances with actions like atropine (2, 3). This substance on careful pharmacologic studies and clinical investigation has proved to be a fair substitute for morphine with secondary atropine-like properties, but it also possesses addiction liabilities (4).

At the end of the recent war a team of investigators of the Technical Industrial Intelligence Committee found that German chemists had prepared a series of new organic chemicals during the war and that some of these were of great interest as theraputic agents (5). One of these, amidone (dolophine, 10820) was later prepared in this country and has been under investigation at several places during the past two years (6, 7, 8). Recently the name methadon has been accepted by the Council of Pharmacy and Chemistry of the American Medical Association for this substance known chemically as 6-dimethyl-amino-4, 4-diphenyl-3-heptanone (9). In addition to amidone some of its isomers have been prepared and studied for their analgesic and toxic properties (10, 11).

Several reports of laboratory investigations as well as a few preliminary reports of clinical studies using d-l amidone have been made

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† The data on l-Isoamidone have been added since the paper was presented.

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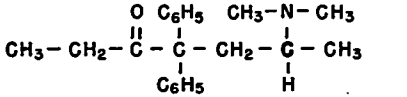
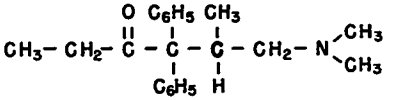
recently (6, 7, 8). The reaction of the animal or man following the administration of this new drug is in the main quite similar to that following morphine (6, 7, 8).

During the past eighteen months we have been carrying out a clinical investigation of d,l-amidone, l-amidone, d,l-isoamidone and l-isoamidone for preanesthetic and postanesthetic analgesic medication in order to obtain an estimation of their possible place as substitutes for morphine.

From a chemical point of view the amidones are an entirely different type of substance than either morphine or isonipecaine. The structural formulas of amidone and isoamidone are given in figure 1.



METHADON (AMIDONE, DOLOPHINE, I0820)



ISOAMIDONE

FIG. 1. Structural formulae of amidone and isoamidone.

With carbon-6 being asymmetric one has three possible types of amidone—d,l- or racemic, l- and d-. Likewise, with carbon-5 being asymmetric one has three possible types of isoamidone. The d-amidones have very weak analgesic properties. The analgesic activity of the d,l-amidone (methadon) and d,l-isoamidone is due almost wholly to the levo components (10, 11).

In our studies the hydrochloride salt of the racemic and levo forms of the two isomers was used to prepare the solutions. As a rule the d,l-compounds were made to a 1 per cent concentration and the l-compound to a 0.5 per cent concentration. All the drugs used were prepared by the Mallinckrodt Chemical Works and sent directly to us, except for some two hundred 1 cc. ampules of 1 per cent amidone that were put up by the S. E. Massengill Company, using the drug prepared by Mallinckrodt Chemical Works.

The drugs were given by subcutaneous or intramuscular injection in all instances.

The results of this investigation can be shown best in tabular form. Tables 1–4 summarize data on d,l-amidone. Tables 5–8 summarize data on l-amidone. Tables 9–12 summarize data on d,l-isoamidone. Tables 13–16 summarize data on l-isoamidone.

TABLE 1

AGE AND SEX DISTRIBUTION OF PATIENTS RECEIVING D,L-AMIDONE

Age, years	No.	Male	Female
11–20	7	3	4
21–30	43	8	35
31–40	67	9	58
41–50	76	17	59
51–60	44	14	30
61–70	24	11	13
71–80	10	5	5
81+	3	2	1
Total	274	69	205

TABLE 2

NUMBER AND SIZE OF DOSES OF D,L-AMIDONE

Size, mg.	5.0	7.5	10.0	15.0	20.0
Number	530	611	134	54	103

Total doses = 1432

TABLE 3

D,L-AMIDONE FOR PREANESTHETIC MEDICATION

	Anesthetic Technic			
	Pentothal + N_2O Patients	N_2O + Ether Patients	Spinal or Local Patients	Total
Amidone 7.5 Mg.+Atropine	40	56	3	99
Amidone 5. Mg.+Atropine	19	36	19	74
Total	59	92	22	173

TABLE 4

SUMMARY OF PATIENTS RECEIVING D,L-AMIDONE ACCORDING TO TYPES OF DISEASE

Disease	Cases
Vascular system	10
Skeletal system and extremities	20
Face and neck	5
Breast	9
Abdominal wall or abdominal viscera	51
Thoracic cage or contents	24
Kidney and urinary tract	14
Female genital organs and tract	125
Miscellaneous	16
Total	274

TABLE 5

AGE AND SEX DISTRIBUTION OF PATIENTS RECEIVING l-AMIDONE

Age, years	No.	Male	Female
11–20	3		3
21–30	18	1	17
31–40	24	1	23
41–50	25	2	23
51–60	16	2	14
61–70	12	2	10
71–80	5	1	4
Total	103	9	94

TABLE 6

NUMBER AND SIZE OF DOSES OF l-AMIDONE

Size, mg.	2.5	3.7	5.0	7.5	10.0
Number	101	141	31	42	35

Total doses = 350

TABLE 7

l-AMIDONE FOR PREANESTHETIC MEDICATION

	Anesthetic Technic		
	Pentothal + N_2O Patients	Ether Patients	Total
l-Amidone 5.0 Mg.+atropine	3	8	11
l-Amidone 3.7 mg.+atropine	9	16	25
l-Amidone 2.5 mg.+atropine	9	11	20
Total	21	35	56

TABLE 8

SUMMARY OF PATIENTS RECEIVING l-AMIDONE ACCORDING TO TYPES OF DISEASE

Disease	Cases
Vascular system	2
Skeletal system and extremities	4
Face and neck	3
Breast	3
Abdominal wall or abdominal viscera	16
Thoracic cage or contents	11
Urinary tract	1
Female genital organs and tract	63
Miscellaneous	2
Total	105

TABLE 9

AGE AND SEX DISTRIBUTION OF PATIENTS RECEIVING D,L-ISOAMIDONE

Age, years	No.	Male	Female
11–20	3		3
21–30	18	3	15
31–40	33	6	27
41–50	25	3	22
51–60	21	5	16
61–70	7	1	6
71–80	3	3	
Total	110	21	89

TABLE 10

NUMBER AND SIZE OF DOSES OF D,L-ISOAMIDONE

Size, mg.	5.0	7.5	10.0	15.0
Number	42	37	269	18

Total doses = 366

TABLE 11

D,L-ISOAMIDONE FOR PREANESTHETIC MEDICATION

	Anesthetic Technic		
	Pentothal + N_2O Patients	Ether Patients	Total
d,l-Isoamidone 15.0 mg.+atropine		3	3
d,l-Isoamidone 10.0 mg.+atropine	14	41	55
d,l-Isoamidone 7.5 mg.+atropine	1	5	6
Total	15	49	64

TABLE 12

SUMMARY OF PATIENTS RECEIVING D,L-ISOAMIDONE ACCORDING TO TYPES OF DISEASE

Disease	Cases
Vascular system	2
Skeletal system and extremities	7
Breast	2
Abdominal wall or abdominal viscera	15
Thoracic cage or contents	6
Urinary tract	7
Female genital organs and tract	60
Miscellaneous	11
Total	110

TABLE 13

AGE AND SEX DISTRIBUTION OF PATIENTS RECEIVING l-ISOAMIDONE

Age, years	No.	Male	Female
11–20	2	1	1
21–30	29	1	28
31–40	28	—	28
41–50	29	1	28
51–60	27	1	26
61–70	11	2	9
71–80	1	—	1
Total	127	6	121

TABLE 14

NUMBER AND SIZE OF DOSES OF l-ISOAMIDONE

Size, mg.	5.0	7.5	10.0	15.0	20.0
Number	140	237	93	9	10

Total doses = 489

TABLE 15

l-ISOAMIDONE FOR PREANESTHETIC MEDICATION

	Anesthetic Technic		
	Pentothal + N_2O Patients	Ether Patients	Total
l-Isoamidone 7.5 mg.+atropine	22	23	45
l-Isoamidone 5.0 mg.+atropine	15	22	37
Total	37	45	82

TABLE 16

SUMMARY OF PATIENTS RECEIVING l-ISOAMIDONE ACCORDING TO TYPES OF DISEASE

Disease	Cases
Vascular system	1
Skeletal system and extremities	7
Head and neck	2
Abdominal wall or abdominal viscera	14
Thoracic cage or contents	4
Urinary tract	5
Female genital organs and tract	91
Miscellaneous	3
Total	127

TABLE 17

PATIENTS IN WHOM AMIDONES DID NOT PRODUCE SUFFICIENT POSTOPERATIVE ANALGESIA

Age, years	Sex	Operation	Postop. Sedation		Changed to:	
			Type	Amount	Type	Amount
61	F	Vaginal Hysterectomy	d,l-Amidone	7.5	Morphine	10
35	F	Abdominal Hysterectomy	d,l-Amidone	5.0	Morphine	8
83	M	Amputation of Thigh	d,l-Amidone	7.5	Morphine	8
27	F	Fracture Cast	d,l-Amidone	7.5	Morphine	8
35	M	Appendectomy	d,l-Amidone	7.5	Morphine	10
39	M	Hernia	d,l-Amidone	7.5	Morphine	10
47	M	Exploratory Laparotomy Gun Shot	d,l-Amidone	7.5	Morphine	10
47	F	Resection of Rectum	d,l-Amidone	5.0	Morphine	10
30	M	Spinal Fusion	d,l-Amidone	7.5	Morphine	10
27	M	Ventral Hernia	d,l-Amidone	7.5	Morphine	10
34	F	Hernia	l-Amidone	3.7	Dilaudid	2
75	F	Cholecystectomy	l-Amidone	3.7	Morphine	10
68	F	Resection of Rectum	l-Amidone	2.5	Morphine	8
32	F	Subcutaneous Tumor	l-Amidone	2.5	Morphine	10
51	M	Lobectomy	l-Amidone	2.5	Morphine	10
48	F	Dilatation and Curettage, radium	l-Amidone	3.7	Morphine	10
40	F	Abdominal Hysterectomy	l-Amidone	3.7	Morphine	10
44	F	Abdominal Hysterectomy	l-Amidone	2.5	Morphine	10
46	F	Abdominal Hysterectomy	l-Amidone	2.5	Morphine	10
30	M	Osteotomy Knee	d,l-Isoamidone	10.0	Morphine	10
32	M	Lumbar Disk	d,l-Isoamidone	15.0	Morphine	15
36	F	Spinal Fusion	d,l-Isoamidone	10.0	Morphine	8
38	M	Gun Shot Abdominal	d,l-Isoamidone	10.0	Morphine	10
35	F	Abdominal Hysterectomy	d,l-Isoamidone	10.0	Morphine	10
40	M	Sympathectomy	d,l-Isoamidone	7.5	Morphine	10
36	F	Spinal Fusion	d,l-Isoamidone	10.0	Morphine	10
50	F	Vaginal Hysterectomy	d,l-Isoamidone	5.0	Codeine	65
45	F	Sympathectomy	l-Isoamidone	10.0	Morphine	10
52	M	Spinal Fusion	l-Isoamidone	7.5	Morphine	15
67	M	Gastric Resection	l-Isoamidone	7.5	Morphine	10
25	M	Thoracoplasty	l-Isoamidone	10.0	Morphine	10
25	F	Vaginal Plastic	l-Isoamidone	7.5	Morphine	10
22	F	Excision Ovarian Cyst	l-Isoamidone	7.5	Morphine	10
54	F	Vaginal Hysterectomy	l-Isoamidone	5.0	Morphine	10
44	F	Abdominal Hysterectomy	l-Isoamidone	7.5	Morphine	10
34	F	Abdominal Hysterectomy	l-Isoamidone	7.5	Morphine	10

The use of the different size doses of d,l-amidone (table 2) does not reflect a true frequency-dose-size curve, because the 10, 15 and 20 mg. doses were given 10, 54 and 100 times respectively to one individual. This individual weighed an average of 275 pounds during his stay in the hospital. This same individual accounted for 24 and 35 doses, respectively, of the 7.5 and 10 mg. size doses of l-amidone, reported in table 6.

AMIDONES FOR PREANESTHETIC MEDICATION

d,l-Amidone, l-amidone, d,l-isoamidone or l-isoamidone was used as preanesthetic medication in place of morphine in 375 cases. In no instance was it found necessary to give a supplemental dose of morphine because of anxiety. In only one instance was there nausea with attempt at vomiting before the anesthetic was started.

In 2 individuals who received 5 mg. doses of l-amidone and one small individual who received 10 mg. of d,l-isoamidone there was a depression of respiration so that the periods of induction of anesthesia were greatly prolonged; in the remaining 217 patients who were given nitrous oxide-oxygen-ether, the induction was as rapid as would have been expected after morphine.

There is one striking point of difference in action between the amidones and morphine in patients under ether anesthesia, and that is in relation to the size of the pupil. With morphine there is a definite pattern in the change of the size of the pupil and reaction to light which is of value in estimating the plane of surgical anesthesia, whereas after administration of the amidones the pupil is usually larger than normal throughout all planes and does not react to light in the way that it does after morphine. This difference must be taken into consideration when the size of the pupil and its reaction to light are used in estimating the planes of anesthesia.

AMIDONES FOR POSTANESTHETIC ANALGESIA

In 385 cases in which amidones were ordered for postanesthetic analgesia, it was necessary to give morphine in 36 instances during the first forty-eight hours because amidones in the amounts ordered did not give sufficient relief of pain; these failures are listed in table 13. In the remaining 349 cases analgesia was satisfactory.

The infrequency of nausea and the lack of hypnotic effects of amidones were the most frequently noted differences from morphine in comments from the nurses in charge of the wards.

MISCELLANEOUS COMMENTS

Amidone was used in 5 cases of morphine, codeine or isonipecaine addiction. In each instance it was possible to change to amidone without signs or symptoms of withdrawal. Amidone satisfied the addiction. In 4 cases the amidone was gradually withdrawn over a period of seven to ten days with success. In the fifth case the drug was stopped abruptly without the onset of withdrawal signs or symptoms.

In 2 patients who received 3 to 6 doses daily for a total of 126 and 215 doses no tolerance to the drug was observed.

SUMMARY

d,l-Amidone, l-amidone, d,l-isoamidone or l-isoamidone has been given to 614 patients for a total of 2637 doses.

These drugs have been satisfactory in all instances when used for preoperative analgesia and in about 90 per cent of the cases when used for postoperative analgesia.

l-Amidone, 3.7 mg., d,l-amidone, 7.5 mg., d,l-isoamidone, 10 to 12 mg., or l-isoamidone, 7.5 mg., produces analgesia of the same degree and duration as 10 mg. morphine.

Nausea and hypnotic effects are very rarely observed following the use of the drugs in the doses listed.

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