Dosage/Side-Effect Relationships of Morphine and Meperidine

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KNOWLEDGE of dose/response relationships would be the ideal basis for comparison of the efficacy of drugs, but such data are not available for most, especially for those whose principal effects are subjective and therefore difficult to quantify. Even where an effect can be measured, the sheer volume of work required before an accurate dose/response curve can be constructed is often in itself daunting.

Morphine and meperidine are among the most commonly used strong analgesic agents in current medical practice. Over the past 10 years, both these drugs have been included as standards in the long-continuing assessment of preanesthetic medication conducted in this department.[1] It was thought worthwhile to reanalyze the data from this large number of administrations to see what dose/response relationships might emerge. The side actions for which such data were available included the incidence of nausea and/or vomiting, dizziness, the degree of hypnotic activity, and relief of preoperative anxiety.

METHOD

The methodology of the preoperative assessment and postoperative followup in this program has been described elsewhere[2-4] and will be summarized here only briefly. The drug being assessed was administered intramuscularly, as preanesthetic medication, to healthy patients scheduled for minor gynecologic surgery under a standard methohexital-nitrous oxide-oxygen anesthesia. Numbers of administrations were balanced, so that half the patients had cervical dilation in addition to uterine curettage. Following premedication, the patient was left undisturbed except for visits by the observer at 20, 40, 60, and 90 minutes after injection. Observations recorded, by double-blind technic, included drowsiness, apprehensiveness, restlessness, dizziness, and nausea and/or vomiting. The incidence of nausea in the first 6 postoperative hours was also recorded.

This technic, critically reviewed after more than 10,000 patients had been included in the series, was found to have a high degree of reproducibility.[1] Therefore records of all patients in the series who had received either morphine or meperidine in standard, nonweight-related dosage were retrieved and reanalyzed on a dose/body weight basis. The dose range was found to be 0.051 to 0.5 mg./kg. for morphine and 0.4 to 3.3 mg./kg. for meperidine. Initially, within these ranges

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there was inequality of distribution, the numbers of patients at some dose levels being too small for analysis. It was also necessary to "even up" the numbers in each group having cervical dilation as well as curettage, because of the influence of dilation on postoperative emesis.[1]

For these reasons, a further 232 patients were studied with morphine given at the required dose level. The double-blind methodology was maintained by doing this concurrently with other, unrelated drugs, a colleague allocating the drug and dose so that the observer would be unaware of what had been given. The meperidine figures had already been completed for the previous study.[1] Data from a saline control series have been included for comparison. The final analysis was based on 608 patients having morphine, 872 meperidine, and 200 saline controls.

RESULTS

Emetic Sequelae.—The proportions of patients who had nausea and/or vomiting of any degree in the 8 hours following premedication are shown in tables 1 and 2, and the total incidence of emesis is illustrated in

TABLE 1
Percentage Incidence of Nausea (N) and Vomiting (V) in Patients Premedicated with Meperidine

Dose range, mg./kg.	0.4	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.2
Number of subjects (872)	58	68	42	64	36	82	98	92	114	62	58	36	34	28
Preoperative														
N	5	7	10	13	17	16	21	24	14	24	31	17	41	21
V	0	0	0	0	17	7	9	12	6	15	14	3	12	11
Early postoperative														
N	14	3	7	6	8	11	7	10	8	8	10	8	9	7
V	7	10	10	17	22	21	17	13	16	16	12	0	12	4
Late postoperative														
N	7	3	7	3	6	17	12	15	20	15	26	8	15	7
V	3	3	0	6	19	22	26	16	23	31	21	19	29	14
Total														
N	21	12	21	16	19	17	19	23	29	29	33	17	26	21
V	9	12	10	19	39	28	39	29	29	42	33	22	41	25
N and V	30	24	31	35	58	45	58	52	58	71	66	39	67	46

TABLE 2
Percentage Incidence of Nausea (N) and Vomiting (V) in Patients Premedicated with Morphine or Saline Solution

Dose range, mg./kg.	0.075	0.125	0.175	0.225	0.275	0.325	0.375	0.425	0.5	Saline
Number of subjects (608)	40	60	170	96	80	40	42	40	40	200
Preoperative										
N	13	10	9	11	10	5	24	10	15	5
V	0	7	1	2	4	8	12	5	3	1
Early postoperative										
N	10	15	12	14	13	18	7	8	10	5
V	23	20	17	16	30	20	36	28	48	7
Late postoperative										
N	18	12	17	12	12	5	8	10	10	4
V	8	34	33	42	68	60	79	65	70	6
Total										
N	25	17	20	15	10	5	10	10	8	10
V	28	42	37	43	68	63	84	68	78	12
N and V	53	59	57	58	78	68	94	78	86	22

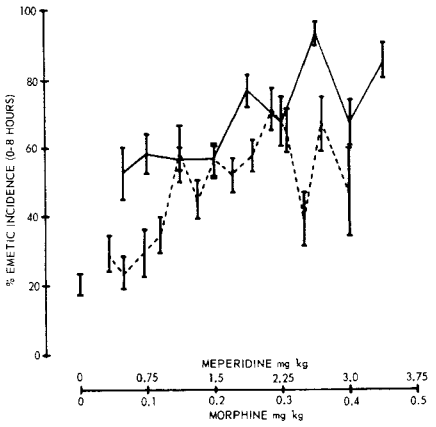

FIG. 1. Percentage incidence of emesis (0-8 hours) in patients premedicated with meperidine (---), morphine (—), or saline (0 dose data). Vertical lines indicate standard error of proportion.

figure 1. In the case of morphine, there was a consistent tendency for the incidence to rise with increasing dosage. After meperidine, the incidence remained relatively low until 0.75 mg./kg. was exceeded, after which it rose abruptly, to reach a maximum at 2.25 mg./kg., thereafter falling off. Over the normal therapeutic range (0.1 to 0.2 mg./kg.), morphine was followed by a relatively constant incidence of emesis (57 percent), while meperidine gave somewhat less consistent results, rising from 31 to 58 percent.

Drowsiness.—The proportion of patients exhibiting notable (marked or moderate) drowsiness increased from 12.5 percent for morphine to a maximum incidence of 85 percent. The equivalent figures for meperidine were 20 percent and 86 percent (tables 3 and 4). The increase in the proportion of patients displaying notable drowsiness rises steeply in the lower range of dosage, but tends to a plateau for dosages in excess of 0.275 mg./kg. of morphine or 2 mg./kg. of meperidine (fig. 2).

Preoperative Anxiety (tables 3 and 4).—Morphine was associated with two peak levels of apprehension at extremes of dosage,

TABLE 3

Percentage Incidence of Drowsiness, Dizziness, Apprehension, and Tachycardia in Patients Given Meperidine

Dose range, mg./kg.	0.4	0.6	0.8	1.0	1.2	1.4	1.6	1.8	2.0	2.2	2.4	2.6	2.8	3.2
Drowsiness														
Marked	3	3	10	11	8	29	33	32	33	45	47	44	68	57
Moderate	16	25	26	39	44	27	41	39	48	42	38	42	18	36
Slight	45	43	48	23	36	33	20	20	16	10	12	8	15	7
Dizziness	9	13	12	17	28	32	48	58	57	47	59	53	62	68
Apprehension														
Notable	4	2	3	8	9	5	6	5	6	5	7	6	12	4
Total	33	29	33	38	50	44	37	41	33	26	26	28	33	18
Tachycardia	4	12	19	10	17	22	26	13	20	28	28	22	27	18

TABLE 4

Percentage Incidence of Drowsiness, Dizziness, Apprehension and Tachycardia in Patients Given Morphine or Saline Solution

Dose range, mg./kg.	0.075	0.125	0.175	0.225	0.275	0.325	0.375	0.425	0.5	Saline
Drowsiness										
Marked	3	13	31	39	47	43	33	50	45	13
Moderate	10	33	37	35	33	43	48	35	38	14
Slight	70	43	23	24	16	13	19	15	18	29
Dizziness	15	18	28	34	32	50	41	58	48	11
Apprehension										
Notable	10	5	6	5	10	15	14	5	8	8
Total	63	40	26	26	35	33	45	35	53	38
Tachycardia	10	13	10	16	24	18	29	10	5	10

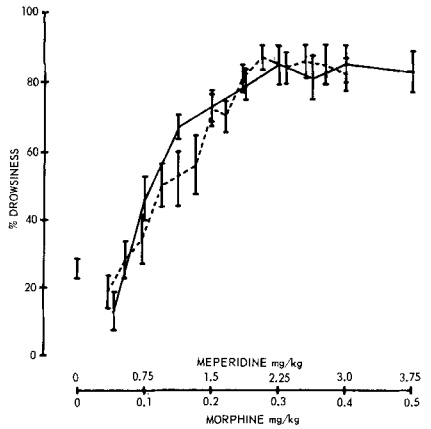

FIG. 2. Percentage incidence of drowsiness (marked and moderate degrees) in patients premedicated with meperidine (---), morphine (—), or saline (0 dose data). Vertical lines indicate standard error of proportion.

while the minimum incidence occurred within the therapeutic range. Meperidine showed a maximal incidence of apprehension within its therapeutic range (fig. 3).

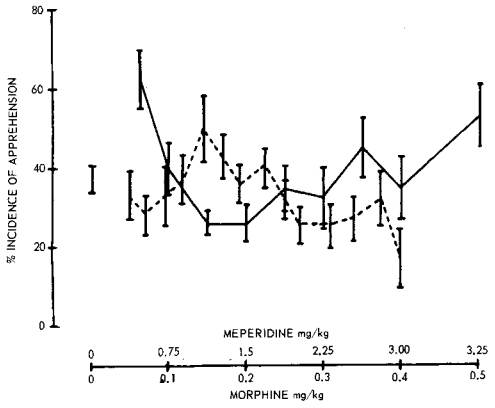

FIG. 3. Percentage incidence of preoperative apprehension in patients premedicated with meperidine (---), morphine (—), or saline (0 dose data). Vertical lines indicate standard error of proportion.

Dizziness.—With each drug, the frequency of dizziness rose more or less linearly with increasing dosage (fig. 4).

Tachycardia. — There was no consistent relationship between the dose of either drug and the occurrence of tachycardia (tables 3 and 4).

DISCUSSION

The purpose of this survey was not to compare the properties of meperidine and morphine—comparisons based on some of the data reanalyzed herein have appeared elsewhere[5]—but rather to define the nature of the dose/response relationship, if such existed, for several aspects of the drug activity for which there were data. In graphing the dose/response curves, we have equated 75 mg. of meperidine with 10 mg. of morphine, on the assumption that these are equianalgesic doses.[6]

As mentioned above, there is relatively little knowledge of the relationship between

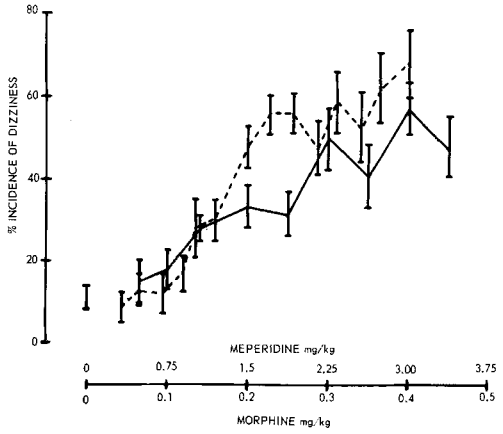

FIG. 4. Percentage incidence of dizziness in patients premedicated with meperidine (---), morphine (—), or saline (0 dose data). Vertical lines indicate standard error of proportion.

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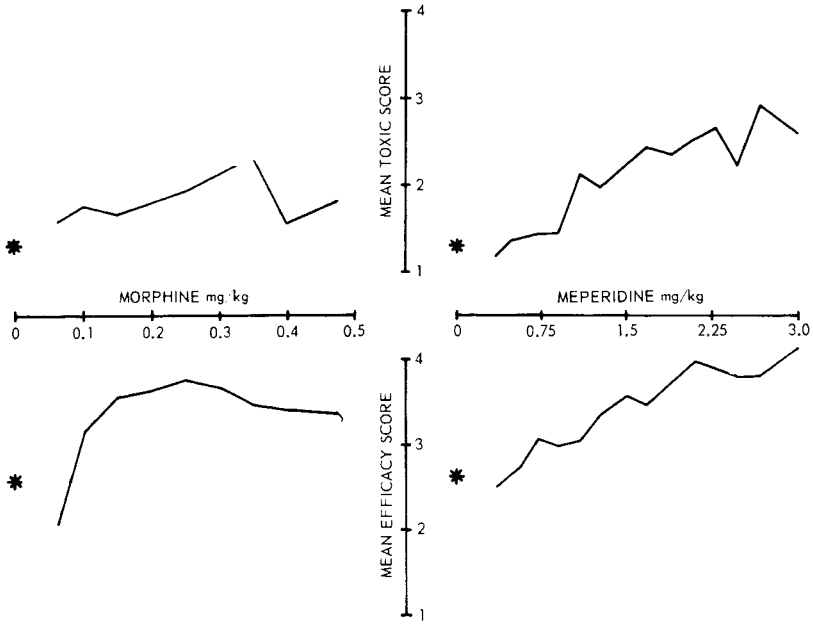

FIG. 5. Mean toxic and efficacy scores for meperidine and morphine. This incidence for saline is included.

dosage and the effect for many of the activities of the opiates. However, Denton and Beecher[7] suggested that the dose/response curve for analgesia from morphine became flattened at a dose level of 9 mg., higher doses not producing any increase in analgesia. Keats and associates[8] presented further evidence to suggest that doses in excess of 10 mg. did not improve the analgesic response, although Lasagna and Beecher[9] presented some further work, in which 15 mg. of morphine gave satisfactory pain relief in a higher proportion of patients than did 10 mg. Using experimental pain, Gaensler[10] found that the threshold was not further raised by doses in excess of 16 mg.

The data analyzed herein are not related to analgesia but to side effects of these two drugs. Nonetheless, it is interesting that in regard to nausea and drowsiness the same general pattern emerged, that is, a more-or-less linear increase in incidence up to a dosage of 0.2 mg./kg. of morphine or 1.5 mg./kg. of meperidine, followed by a flattened response. This was most obvious with respect to drowsiness but rather less so for nausea. In contrast, the relief of apprehension showed a different relationship. As dosage was increased, there was an initial increase in sedative effect which, however, diminished as dosage was further increased. For meperidine, the response was initially poor but improved consistently through the higher dose ranges.

Thus, it would appear that with both these opiates, the dose/response relationship is not the same for each aspect of the drug's action, showing that the rational clinical use of any drug demands knowledge not only of this relationship for its primary action but also for any significant side effects that may limit its usefulness. These dose/response curves may not be parallel.

In the evaluation of analgesic agents, or indeed of any drug whose desired primary effect is wholly subjective, it has been suggested from time to time that a reasonable approach is to measure some objective parameter of its activity and to extrapolate from this to the subjective response, less readily quantitated accurately. For example, in the case of opiate analgesic agents, respiratory depression has been presented as a useful measure of probable analgesic potency.[11,12] Until it has been shown that the analgesic and respiratory-depression dose/response curves are parallel, this would seem to rely on a possibly erroneous assumption to the contrary.

Certainly in respect of some of the side effects of morphine and meperidine, the

present survey has shown that the relationship with dosage for varying actions of individual drugs may be quite different. It also shows that the dose/response curve differs with respect to the desired and side effects of these commonly used drugs.

SUMMARY

The incidence of side effects over a wide dose range of morphine and meperidine were studied when these were given as sole premedication before a standard operation. A total of 608 patients received 0.05 to 0.5 mg./kg. of morphine, 872 were given 0.2 to 3.2 mg./kg. of meperidine, and 200 controls received saline solution.

The incidence of drowsiness and dizziness were both related to dosage. With the former, there is an exponential relationship, while with the latter this is linear. However, even at low doses there was a high incidence of nausea after morphine, and this rose linearly throughout the range. In contrast, nausea following meperidine was initially much less and reached a plateau in mid-range. The ability of both drugs to relieve anxiety was less at the extremes of dosage.

This study clearly shows that the nature of the dose/response curve varies for different actions of the drug, differs for the desired and side effects, and that drugs having the same therapeutic effect can behave differently with respect to side effects.

ACKNOWLEDGMENT

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Generic and Trade Name of Drug
Meperidine—Demerol

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A fellow who is always declaring he's no fool usually has his suspicions.

—*Wilson Mizner*