Comparison of Analgesic and Side Effects of Parenteral d-Propoxyphene and Meperidine

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THE present study was undertaken to evaluate the analgesic potency of parenteral *d*-propoxyphene as compared to meperidine. The patients used in this study were those who had undergone surgery or who had organic pain from other causes. All of the patients selected had evidences of disease sufficient to warrant persistent pain and the use of morphine. In addition they were expected to be able to give reliable information as to relief of pain and not be jeopardized by the use of any of the drugs to be administered. Willingness to participate and the absence of language or intelligence barriers were also mandatory.

The study was conducted as a blind experiment. The medications were supplied and coded by a research laboratory. A sealed copy of the code was held by the observers during the study. It was returned unopened to the statistician at the completion of the project. All medications were available in rubber stoppered ampuls containing 10 ml. each. The dose of each preparation was 1 ml. intramuscularly. The nine medications utilized in this study were as follows:

Code Number	Medication
11	Blank, injection sodium chloride, U.S.P.
12	Blank, injection sodium chloride, U.S.P.
13	Blank, injection sodium chloride, U.S.P.
21	Meperidine hydrochloride, 50 mg.
22	Meperidine hydrochloride, 100 mg.
23	Meperidine hydrochloride, 25 mg.
31	*d*-Propoxyphene hydrochloride, 50 mg.
32	*d*-Propoxyphene hydrochloride, 100 mg.
33	*d*-Propoxyphene hydrochloride, 25 mg.

The medications were given once daily intramuscularly to different groups of patients (not cross-over). The number of patients in each group is presented in table 1. Medications were administered between 8 A.M. and 2 P.M. daily. To minimize any carry-over, a lapse of six hours was required following previous pain therapy. Special report forms were used for gathering the data (table 2). The data were obtained and recorded by one observer (R. S.) according to scores arbitrarily assigned to the empirical scales presented in table 3. Respiratory rate was determined in counts per minute. Pupil size was measured in millimeters by comparison with black dots on a white card. Side effects were recorded as spontaneously expressed. The patients were not questioned about untoward symptoms.

The data were obtained at the following time intervals after administration of the medications: 0, ½, 1, 1½, 2, 3, and 4 hours. If the patients reported moderate (a lot) or severe (terrible) pain at the end of one hour or later, the study was discontinued and other medications given. Therefore, some of the patients completed only one hour and others longer periods (up to four hours). An assumption was made, for purposes of analysis, that the clinical picture as present when the study was discontinued persisted until the end of the four hour time period. The statistical methods used in this study (correlation, variance, and co-variance) appear in various standard textbooks.[1, 2]

Results

Different groups of patients were given each of the medications. Therefore, patients with more intense pain might, by chance, have been assigned to the same therapy. However, examination of the reports of the intensity of the initial pain indicated that no significant differences in the groups of patients

Accepted for publication August 16, 1961. Dr. Stoelting is in the Department of Anesthesiology, and Mr. Stoelting is a Medical Student, Indiana University School of Medicine, Indianapolis, Indiana. Dr. Gruber is in the Lilly Laboratory for Clinical Research, Marion County General Hospital, Indianapolis, Indiana.

TABLE 1. Total Intensity of Initial Pain Per Number of Patients

Medication	Dose of Medication in Milligrams		
	25	50	100
Blank	87/29	93/31	93/31
Meperidine Hydrochloride	89/28	100/32	101/33
d-Proproxyphene Hydrochloride	87/28	97/32	97/32

were present. The total pain intensity scores before medication were obtained by adding the initial pain intensity scores together. These and the number of patients in each group may be seen in table 1.

Analgesia may be determined either from estimates of pain intensity (by determining the change in intensity) or from estimates of pain relief. The frequencies of occurrence of reports with respect to these parameters are presented in table 4. The correlation coefficient for these data was 0.88. It appears

TABLE 2. Parenteral Analgesics—Report Form

Column	Row	Item	Column	Row	Item
1	—	Study number	41	—	1½ hour—Pain intensity
2	—	Study number	42	—	1½ hour—Dysphoria-Euphoria
3	—	Anesthesia number	43	—	1½ hour—Nausea-Retching
4	—	Anesthesia number	44	—	1½ hour—Hiccough
5	—	Anesthesia number	45	—	1½ hour—Bronchospasm
6	—	Anesthesia number	46	—	1½ hour—Respirations per minute
7	—	Anesthesia number	47	—	1½ hour—Respirations per minute
8	—	Anesthesia number	48	—	1½ hour—CNS response
9	—	Medication × Dose	49	—	1½ hour—Pupil size
10	—	Medication × Dose	50	—	1½ hour—Pain relief
11	—	Medication × Dose	51	—	2 hour—Pain intensity
12	—	0 hour—Pain intensity	52	—	2 hour—Dysphoria-Euphoria
13	—	0 hour—Dysphoria-Euphoria	53	—	2 hour—Nausea-Retching
14	—	0 hour—Nausea-Retching	54	—	2 hour—Hiccough
15	—	0 hour—Hiccough	55	—	2 hour—Bronchospasm
16	—	0 hour—Bronchospasm	56	—	2 hour—Respirations per minute
17	—	0 hour—Respirations per minute	57	—	2 hour—Respirations per minute
18	—	0 hour—Respirations per minute	58	—	2 hour—CNS response
19	—	0 hour—CNS response	59	—	2 hour—Pupil size
20	—	0 hour—Pupil size	60	—	2 hour—Pain relief
21	—	¼ hour—Pain intensity	61	—	3 hour—Pain intensity
22	—	¼ hour—Dysphoria-Euphoria	62	—	3 hour—Dysphoria-Euphoria
23	—	¼ hour—Nausea-Retching	63	—	3 hour—Nausea-Retching
24	—	¼ hour—Hiccough	64	—	3 hour—Hiccough
25	—	¼ hour—Bronchospasm	65	—	3 hour—Bronchospasm
26	—	¼ hour—Respirations per minute	66	—	3 hour—Respirations per minute
27	—	¼ hour—Respirations per minute	67	—	3 hour—Respirations per minute
28	—	¼ hour—CNS response	68	—	3 hour—CNS response
29	—	¼ hour—Pupil size	69	—	3 hour—Pupil size
30	—	¼ hour—Pain relief	70	—	3 hour—Pain relief
31	—	1 hour—Pain intensity	71	—	4 hour—Pain intensity
32	—	1 hour—Dysphoria-Euphoria	72	—	4 hour—Dysphoria-Euphoria
33	—	1 hour—Nausea-Retching	73	—	4 hour—Nausea-Retching
34	—	1 hour—Hiccough	74	—	4 hour—Hiccough
35	—	1 hour—Bronchospasm	75	—	4 hour—Bronchospasm
36	—	1 hour—Respirations per minute	76	—	4 hour—Respirations per minute
37	—	1 hour—Respirations per minute	77	—	4 hour—Respirations per minute
38	—	1 hour—CNS response	78	—	4 hour—CNS response
39	—	1 hour—Pupil size	79	—	4 hour—Pupil size
40	—	1 hour—Pain relief	80	—	4 hour—Pain relief

TABLE 3. Scores Arbitrarily Assigned to the Empirical Scales Used in Reporting Data

Pain Intensity

0 = none
1 = a little
2 = some
3 = a lot
4 = terrible

Pain Relief

0 = none
1 = a little
2 = some
3 = almost complete
4 = complete

CNS Response (Sleepiness)

0 = none
1 = a little
2 = some
3 = a lot
4 = complete

Dysphoria-Euphoria

0 = very unhappy; crying, whining
1 = unhappy with occasional tears
2 = statement of unhappiness, no tears
3 = a little unhappy
4 = normal state of mind
5 = a little happy
6 = definitely happy
7 = happy with occasional laughter
8 = laughing uncontrollably

Nausea-Retching

0 = none
1 = a little nausea
2 = some
3 = a lot of nausea
4 = a little retching
5 = some retching
6 = a lot of retching
7 = constant retching

that in this situation either parameter may be used as a measure of analgesia. A similar technique in postpartum patients produced an opposite result.[3]

The means of the pain relief scores reported by the patients are presented graphically in figure 1. Variance analysis (table 5) indicates the existence of significant differences among hours, drugs, and doses. Maximum or almost maximum relief was apparently present one-half hour after administration. The degree of relief declined rapidly after the first hour and at about the same rate for all medications, including the blank.

The responses to *d*-propoxyphene and meperidine were significantly different in mean intensity. Both drugs provided greater pain relief than did the blank. Meperidine provided significantly greater pain relief at 100 mg. than did the same dose of *d*-propoxyphene. At the 50 mg. dose, no significant differences were demonstrated between the two analgesics. The effects with the 25 mg. doses were not statistically significant in comparison with the blank.

An association might be expected to exist between the pain relief observed by the patients and their feeling of well being. The correlation coefficient for these data is 0.62. This suggests, as would be expected, that the patients were happier when their pain was relieved, and vice versa. In evaluating the feeling of well being, therefore, adjustment for pain relief was accomplished by use of analysis of co-variance. This analysis is presented in table 6. When this correction for pain relief was made, the evaluation of the reports of feeling well being was as follows: First, no significant difference was apparent between meperidine and *d*-propoxyphene; second, the blank was associated with significantly more unhappiness than were the analgesics; and third, a significant dose response was obtained.

An association between depression of the

TABLE 4. Frequencies of Occurrence of Combinations of Reports

		Estimates of Pain Relief				
		0	1	2	3	4
Change in estimates of pain intensity	−2					
	−1	9				
	0	206	87	19		5
	1	20	49	106	59	
	2		5	17	207	6
	3				28	191
	4					13

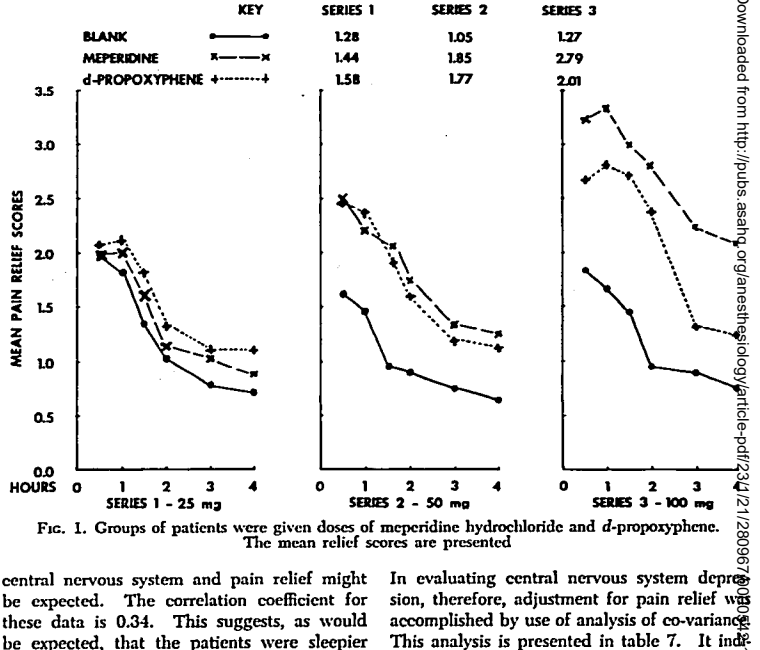

FIG. 1. Groups of patients were given doses of meperidine hydrochloride and *d*-propoxyphene. The mean relief scores are presented

central nervous system and pain relief might be expected. The correlation coefficient for these data is 0.34. This suggests, as would be expected, that the patients were sleepier when their pain was relieved and vice versa.

In evaluating central nervous system depression, therefore, adjustment for pain relief was accomplished by use of analysis of co-variance. This analysis is presented in table 7. It indicates that significantly more central nervous

TABLE 5. Variance Analysis of the Pain Relief Scores

Main Effects	Sum of Squares	Degrees of Freedom	Mean Square	*F* Value	*P* Less Than
Hours	344	5	68.8	23.56	0.001
Medications	414	8	41.8	14.31	0.001
Drugs	215	2	107.5	36.81	0.001
Blank vs. *d*-propoxyphene	99.1	1	99.1	33.93	0.001
Doses	111	2	55.5	19.01	0.001
Slope	98.5	1	98.5	33.73	0.001
Curvature	10.8	1	10.8	3.70	
Drug × Dose Interaction	88	4	22.0	7.53	
Blank vs. *d*-propoxyphene at 25 mg.	8.1	1	8.1	2.99	
Meperidine vs. *d*-propoxyphene at 100 mg.	58.2	1	58.2	20.31	0.001
Interaction of Hours × Medications (error term) for main effects	117	40	2.9	1.55	
Hours × Drugs	6	10	0.6		
Hours × Doses	4	10	0.4		
Remainder (error term for interactions)	3,017	1,602	1.9		
Total	3,892	1,655			

TABLE 6. Co-Variance Analysis of the Reports Concerning Feeling of Well Being (*Y*) in Which Pain Relief (*X*) is the Concomitant Variable

Source of Variance	Sum of Squares and Products			Corrected (*Y*)	*df*	*ms*	*F*	*P*
	(*X*)	(*XY*)	(*Y*)					
Medication	214.8	22.3	5.0	18.8	2	9.4	19.58	0.001
d-Propoxyphene vs. meperidine	18.8	8.7	4.1	0.2	(1)	0.2		
Blank vs. analgesic	195.6	13.5	0.9	18.6	(1)	18.6	38.75	0.001
Dose	111.4	48.2	34.4	13.9	2	6.9	14.38	0.001
Slope	98.5	42.3	31.0	13.1	(1)	13.1	27.29	0.001
Curvature	10.8	5.8	3.7	0.9	(1)	0.9	1.88	
Error	3,560.1	1,345.8	1,303.9	795.2	1,651	0.48		
Total	3,892.3	1,416.3	1,343.3					

system depression was noted when meperidine was administered than when *d*-propoxyphene was given.

A number of analgesic drugs affect the respiratory rate and pupil size. In this study no significant changes were associated with drugs, doses, or time. Other side effects were reported so infrequently that analysis was not undertaken.

Discussion

Pain is a composite phenomenon that must involve the stimulation of the receptors, the transmission of this stimulation to the central nervous system and the integration of these impulses with the other impulses to produce a response. Thus, there are several places at which treatment may interfere with the pain experience, *e.g.*, stimulation of the receptors, arousal of an impulse at the receptor, the transmission of this impulse to the central nervous system, and the integration of impulses in the central nervous system.

Pain is affected by past experience and motivation. Anticipation of pain is also an important factor and may cause disruption of behavior. Thus, the analysis of the action of analgesic drugs is complicated and difficult.

Most patients, if properly selected, are capable of observing changes in pain intensity after the administration of analgesic drugs. For close observation of these changes, frequent bedside visits are necessary. Records obtained without close observation may not demonstrate analgesic effectiveness and the duration of pain relief. However, data obtained in this manner will give evidence of untoward reactions.

In this study, there was no significant difference in pain intensity in any of the groups of patients at the time the analgesics were administered. Maximum or almost maximum

TABLE 7. Co-Variance Analysis of the Reports Concerning Central Nervous System Response (*Y*) in Which Pain Relief (*X*) is the Concomitant Variable

	Sum of Squares and Products			Corrected (*Y*)	*df*	*ms*	*F*	*P*
	(*X*)	(*XY*)	(*Y*)					
Medication	214.8	98.7	73.1	37.6	2	18.8	8.62	0.001
d-Propoxyphene vs. meperidine	18.8	31.5	52.9	38.5	(1)	38.5	17.66	0.001
Blank vs. analgesic	195.6	67.0	20.2	−0.9	(1)	−0.9		
Dose	111.4	35.1	8.9	−1.6	2	−0.8		
Slope	98.5	25.7	7.3	0.6	(1)	0.6		
Curvature	10.8	9.4	1.2	−2.7	(1)	−2.7		
Error	3,560.1	874.8	3,810.2	3,595.3	1,651	2.18		
Total	2,893.3	1,008.6	3,892.2					

relief of pain was present one-half hour after the administration of drugs. The responses to *d*-propoxyphene and meperidine were significantly different in mean pain intensity and dose response. A significant reduction of pain occurred when the analgesics were substituted for the blank. Meperidine gave greater pain relief at 100 mg. than did the same dose of *d*-propoxyphene. No significant differences in the analgesic properties could be demonstrated at lower dose ranges.

Patients when relieved of pain were more cooperative and happy. When the correction for pain relief was made, no significant difference in the patients' feeling of well being was noted between *d*-propoxyphene and meperidine. A significant amount of unhappiness was noted in the patients receiving the blank.

Patients were sleepier when their pain was relieved. A significant increase in central nervous system depression was noted when meperidine was given but not when *d*-propoxyphene was administered.

Other side effects were not of significance.

Conclusions and Summary

In patients reporting "a lot" of pain before administration of analgesic drugs, close correlation was obtained between estimates of relief of pain and change in estimates of pain intensity. Significantly more pain relief was reported by patients receiving 25, 50, or 100 mg. of *d*-propoxyphene or meperidine parenterally than those receiving blank. Significantly more pain was reported by patients given 100 mg. of meperidine than those administered 100 mg. of *d*-propoxyphene. No difference in analgesic effectiveness was found when these drugs were used in 25 or 50 mg. doses.

Relief of pain increased the patients' feeling of well being and sleepiness or vice versa. Even after correction for pain relief, more unhappiness was noted when blank was given than when either analgesic was administered. Significantly more sleepiness was noted with meperidine, after correction for pain relief, than with *d*-propoxyphene or blank. No difference in frequency of occurrence of other undesirable effects from the medications was observed.

References

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HYALINE-MEMBRANE FORMATION Observations of the level of plasminogen activator in the lungs of newborn infants confirm the occurrence of a deficiency of this activity in the majority of infants with hyaline-membrane disease. This enzymatic derangement is shown to be due to the presence of a potent inhibitor of the plasminogen activator. The postulated mechanism for hyaline-membrane formation in newborn infants states that placental infarction associated with premature labor and diabetes mellitus releases the inhibitor of plasminogen activator by the blood stream so that fibrinolysis is inhibited in the lungs of the newborn baby. The presence of this inhibitor prevents the dissolution of intra-alveolar fibrin, resulting in its retention and subsequent formation of hyaline membranes. (*Lieberman, J.: Nature of Fibrinolytic-Enzyme Defect in Hyaline-Membrane Disease, New Engl. J. Med. 265: 363 (Aug. 24) 1961.*)