THE EFFECT OF ANALGESICS ON RADIANT HEAT THRESHOLDS IN MAN

HUGH H. KEASLING, PH.D., AND E. G. GROSS, M.D., PH.D.

THE experiment reported herein was designed to combine an estimation of the effectiveness of 3 analgesic drugs with a partial evaluation of the reliability of the Wolff-Hardy-Goodel technique for assessing this analgesic activity in man. The drugs compared in this study were 1-methyl-3-allyl-4-phenyl-4-propionoxy-piperidine hydrochloride (RO 2-7113), alphaprodine (Nisentil®), and meperidine hydrochloride (fig. 1). The pharmacology of RO 2-7113 has been described by Benson *et al.* (1).

EXPERIMENTAL

The apparatus and procedure are essentially that of the Wolff-Hardy-Goodel technique as previously utilized in this laboratory (2). Radiant heat thresholds were determined in normal, healthy, adult males * before drug administration and at 30-minute intervals for 150 minutes after drug administration. In the determination of thresholds, individual stimuli were delivered at one-minute intervals to a blackened spot on the subject's forehead. The subject moved his head from the apparatus between stimuli. Approximately five minutes are required to determine an individual threshold, thus limiting the experiment to 6 subjects per run. In order to minimize side effects, the subjects remained in bed between threshold determinations. The experimental runs occurred at weekly intervals, in the morning. The subjects did not eat breakfast prior to the experiment. The thresholds were determined in a separate quiet room with only the operators present. The subjects were trained on 3 successive weeks prior to the start of the experiment to recognize threshold stimuli and become acquainted with the procedure of the experiment. During this training period each subject received a dose of 7.5 mg. of morphine sulfate intramuscularly, and exhibited rises in threshold consistent with those previously reported from this laboratory. These data are not included in this report, however, since the operators were aware of this procedure. The subjects were told only that in the experimental runs they would follow the above described procedure and receive analgetic

* The subjects were 2 graduate students in pharmacology, 2 premedical students who have done technical work in the laboratory, and 2 general technicians. The remuneration involved formed a part of the subject interest in this study.

Accepted for publication July 31, 1956. The authors are in the Department of Pharmacology, College of Medicine, State University of Iowa, Iowa City, Iowa. This study was supported by a grant from Hoffmann-LaRoche, Inc.

drugs and placebo in random order. They were assured that the drugs would not be given in excessive dosage.

The experimental runs reported herein were carried out by the following "double blind" technique. Preliminary discussions were held during which the drugs, route of administration and dosages were decided as shown in table 3. Ten code letters were then chosen, one to be assigned to each of the 10 experimental treatments. Six random orders of drug administration were chosen by drawing lettered slips of paper from a box, and the 6 subjects were randomly assigned to the treatment orders in a similar manner. These subject-treatment orders were then given to the physician who administered all drugs. Furthermore, the actual assignment of treatments to code letters was not carried out in this laboratory. The treatment code information was transmitted only to the hospital pharmacist who prepared the drugs. The drugs were delivered to the physician in charge of administration labeled only with code letter and route of administration. The oral doses were in identical capsules with a dose of one capsule in each case.

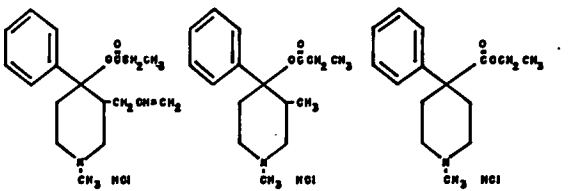

FIG. 1. Chemical structures of analgesic compounds tested.

The hypodermic solutions were in identical containers and all contained water-clear solutions with a dose of 1 ml. in each case. The drugs were administered in a separate room so that the operators of the experiment had no knowledge of what treatment or route of administration was administered to any of the subjects on any day until the completion of all 10 runs.

RESULTS AND DISCUSSION

The control threshold data, one item obtained for each subject in each run, were subjected to an analysis of variance as shown in table 1.

In view of the lack of significant variation among subjects on a given day and the significant variation from day to day, the mean threshold for a given day was utilized in the subsequent handling of the data. Our results in this regard are in contrast to those of Wolff, Hardy, and Goodel, who have reported that while subjects may vary

in control threshold one from the other, the day to day responses are constant for a given subject. This discrepancy may, in part, be due to the fact that we have not utilized daily radiometer checks of stimulus intensity.

The error term in the analysis of variance of thresholds provided an estimate of the error involved in control threshold determinations and we have used this estimate to compute the 99 per cent confidence interval for mean control thresholds for each day. Only readings which lie outside the 99 per cent confidence interval for control threshold determinations have been utilized in evaluating drug effects. Readings of thresholds are obtained in increments of 5 millicalories, therefore, the lowest reading exceeding the 99 per cent confidence interval of the mean control threshold for a given day was recorded as 5, and higher readings computed from this value. This procedure retains the discontinuity of the original data, and at the same time utilizes only those values which can be adjudged as significantly higher (or lower) than control thresholds.

TABLE 1

ANALYSIS OF VARIANCE OF CONTROL THRESHOLDS (− 230)

Item	*d.F.*	S.S.	M.S.	*F*
Subjects	5	65.420	13.084	1.424
Days	9	341.202	37.911	4.125*
Error	45	413.614	9.191	
Total	59	820.236		

* *F* 99 per cent = 3.17.

d.F. = degrees of freedom, S.S. = sums of squares, M.S. = mean square (S.S. ÷ *d.F.*), and *F* is the variance ratio (item M.S. ÷ error M.S.).

The post-drug administration threshold data, following subtraction of the control threshold as described above, were subjected to an analysis of variance. The results of this analysis are shown in table 3.

In view of the lack of significance of the *Treatments* × *Times* and *Times* × *Subjects* interactions, these may be combined with error to yield a new mean square for error with 230 *dF*, M.S. = 23.83.

This error term yields 1.26 as the standard error for the difference between any two treatment means. These means are listed in table 3. Inspection of table 3 reveals that for oral or intramuscular administrations the drugs are clearly significantly more effective than placebo, while for subcutaneous administration, this experiment does not appear to discriminate between drugs and placebo.

Examination of the primary data reveals that in 6 out of 18 trials the 6 subjects responded to placebo with increases in threshold greater than the mean of the drug trials. One subject showed no placebo responses, 4 showed one, and one showed 2 placebo responses. Such

TABLE 2

ANALYSIS OF VARIANCE OF TREATMENT THRESHOLDS

Item	*d.F.*	S.S.	M.S.	*F*
Treatment (Tr)	9	2,906.7	322.97	13.55†
Subjects (S)	5	1,508.0	301.6	12.66†
Times (T)	4	2,444.0	611.0	25.64†
Tr × S	45	10,135.4	225.23	9.45†
Tr × T	36	786.8	21.86	0.881
T × S	20	378.0	19.9	0.762
Tr × T × S	174*	4,316.1	24.805	
Total	293	22,475.		

* One subject was administered RO 2-7113 two times orally instead of once orally and once subcutaneously. The values for the subcutaneous administration for the analysis of variance were supplied by the means for that treatment of the other 5 subjects and the degrees of freedom reduced by 6.

† *F* Significant at the 99.9% level.

d.F. = degrees of freedom, S.S. = sums of squares, M.S. = mean square (S.S. ÷ *d.F.*), and *F* is the variance ratio (item M.D. ÷ error M.S.).

placebo responses occurred following all routes of administration, the mean value for subcutaneous administration being much larger, since 4 subjects responded to this procedure.

The 33 per cent placebo response which we have noted is of interest in the light of Beecher's discussion of this point (3). Our results might indicate that placebo responses occur about one-third of the time in all subjects rather than always in one-third of the subjects. If this is true, then the practice of rejecting placebo responders in assessing analgetic activity may not truly increase the precision of the estimates of effectiveness but might actually reduce them by eliminating a portion of the population from the experiment. In view of the limited data in this report, it is to be hoped that clinical experiments designed to test this hypothesis will be forthcoming. In any event, our data support the contention that the "placebo response"

TABLE 3

TREATMENT MEANS*

Drug	Dose (mg.)	Route			
		Oral	Subcutaneous	Intramuscular	Mean
Nisentil® HCl	15	8	10.3	11.83	10.04
Meperidine HCl	50	12.67	—	12.17	12.42
RO 2-7113	1.5	11.17	7.33	—	9.25
Placebo	—	3.83	9.0	3.67	5.50

* These treatment means arise as a result of the particular way in which these data were treated and essentially only have meaning with respect to their relations to each other and the standard error of 1.26.

is a factor which must be seriously considered with respect to the evaluation of analgetic drugs in man.

The fourth column of table 3 is the average effect of the 3 drugs and placebo taken from all routes of administration. This averaging of effect would appear to be justifiable in the light of the nonsignificance of the *Treatments* × *Times* interaction in the analysis of variance, thus suggesting that route of administration had no influence on the time action curves obtained in this experiment. If conclusions are drawn based upon the mean effects of treatments, disregarding route of administration, the method gives clear cut evidence of drug effect over placebo ($p < 0.001$). In addition, it would appear the alphaprodine at 15 mg. and RO 2-7113 at 1.5 mg. are not significantly different ($0.4 > p > 0.3$), while meperidine at 50 mg. is slightly superior to these agents ($p < 0.01$).

The design of the experiment and the doses of analgesics utilized were chosen to minimize side effects, since we felt that the presence of significant side effects might bias our results. We did not question the experimental subjects in detail, but rather recorded side effects as they were offered by the subjects or observed. The incidence of side effects is recorded in table 4.

TABLE 4

RECORDED SIDE EFFECTS*

Drug	Side Effects
Nisentil®	2 sleepy 2 dizzy 5 numb 1 woozy
RO 2-7113	1 sleepy
Demerol	2 sleepy 1 droopy 1 numb
Placebo	1 headache

* All subjects are included in the above table and each side effect listing means that it was reported once by one subject for one time period only. In general, these effects all occurred in the first ninety minutes following drug administration.

SUMMARY AND CONCLUSIONS

The Wolff-Hardy-Goodel technique for measuring analgesia has been utilized in a "double blind" experiment to compare the effectiveness of alphaprodine, meperidine and RO 2-7113 (1-methyl-3-allyl-4-phenyl-4-propionoxy-piperidine hydrochloride) in adult males.

Alphaprodine (15 mg.) and RO 2-7113 (1.5 mg.) are of equal effectiveness, while meperidine (50 mg.) was slightly more active in this procedure.

It is concluded that the Wolff-Hardy-Goodel technique as utilized herein provides satisfactory correlation with clinical assessment of analgetic activity.

The occurrence of placebo responses in this study suggests that such responses may occur approximately one-third of the time in all individuals rather than always in one-third of the individuals.

ACKNOWLEDGMENT

The authors wish to thank Dr. Jack Stone of the Division of Anesthesiology, Department of Surgery, College of Medicine, State University of Iowa, who administered all drugs, Dr. M. J. Schiffrin of Hoffmann-LaRoche, Inc., who provided the RO2-7113 used in this study and carried out the coding of drugs, and Mr. William Tester, Hospital Pharmacist, State University of Iowa, Iowa City, Iowa, who prepared the drugs for administration.

We also wish to thank Dr. Robert Hogg, Department of Mathematics, College of Liberal Arts, State University of Iowa, Iowa City, Iowa, for his consultation in connection with the statistical analyses utilized in this report.

REFERENCES

1. Benson, W. M., Cunningham, D. J., Hane, D. L., and Van Winkle, S.: Analgesic Activity and Toxicity of RO 2-7113, Fed. Proc. 15: 400 (March) 1956.
2. Slomka, M. B., and Gross, E. G.: Evaluation of Analgetic Activity of Dromoran Isomers, Proc. Soc. Exper. Biol. 81: 548 (Nov.) 1952.
3. Beecher, H. K.: Powerful Placebo, J. A. M. A. 159: 1602 (Dec.) 1955.

SIXTH MEXICAN CONGRESS OF ANESTHESIOLOGY

The Sixth Mexican Congress of Anesthesiology will be held in the historic Hospital Juarez, Mexico City, from November 11 to November 17.

The Post-Congress Course in Anesthesiology will also take place in the Hospital Juarez from November 19 to November 21.