RELATIVE RESPIRATORY DEPRESSANT EFFECTS OF OXYMORPHONE (NUMORPHAN) AND MORPHINE

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CLINICAL evaluations of oxymorphone (*l*,14-hydroxydihydromorphinone hydrochloride, Numorphan) have suggested that the incidence of side effects was less than with morphine. In particular it was stated that the dose could be increased for the treatment of pain without serious respiratory depression.[1] If this were true this agent would have a significant advantage over potent analgesics, such as morphine, which are known to produce respiratory depression.

To test the validity of this premise a double-blind cross-over, controlled experiment was set up to evaluate the respiratory effects of morphine and oxymorphone in seven healthy volunteers. The shift in the alveolar ventilation-alveolar P_{CO_2} curve was taken as an index of respiratory depression.[2] These alveolar ventilation-alveolar P_{CO_2} response curves were obtained by a modification of the method of Eckenhoff, Helrich and Hege [3] and were plotted automatically by an analog computer while the subject rebreathed in the closed circuit system.[4, 5] The respiratory depressant potency of oxymorphone relative to morphine was calculated from the shifts of the post-drug response curves from the average of the control curves.

METHOD

Seven volunteer men, who were carefully examined and found to be free of respiratory and cardiovascular disease, served as subjects for this study. We have described the basic method in previous reports.[4, 6] After two control runs each subject received an intramuscular injection of morphine sulfate (5 or 10 mg.) or oxymorphone (0.5 or 1 mg.). Response curves were then determined at one and two hours after injection. The drugs were administered in a random fashion under double-blind conditions. To avoid cumulative effects at least three days and usually one week elapsed between test sessions in any subject. All subjects completed the round of medications so that they received each compound at two-dose levels and thus served as their own controls. Respiratory depression was defined in terms of parallel displacement of the respiratory response curve measured at an alveolar ventilation of 20 liters/min. The displacement was expressed in mm. Hg P_{CO_2} (table 1). Positive values indicate a shift to the right (respiratory depression) and negative values, a shift to the left (respiratory stimulation) of the control curve.

TABLE 1

DISPLACEMENT OF RESPONSE CURVE IN MM. HG P_{CO_2}

Subject	Morphine				Oxymorphone			
	5 mg.		10 mg.		0.5 mg.		1 mg.	
	1 hr.	2 hr.	1 hr.	2 hr.	1 hr.	2 hr.	1 hr.	2 hr.
1	0.8	3.0	4.4	5.5	5.3	7.6	4.0	4.8
2	0	.8	6.9	7.6	−0.5	1.0	3.9	0.5
3	1.5	3.8	7.5	9.4	2.7	3.0	8.6	11.6
4	0	1.1	5.6	4.1	4.4	1.7	9.0	9.0
5	0.4	3.4	3.0	1.1	4.8	4.4	6.0	7.5
6	4.2	1.1	3.6	1.7	3.8	5.3	6.3	3.6
7	−2.2	0.4	−0.8	1.1	−2.2	0.4	0	9.5

RESULTS

The parallel displacement of the after-drug response curves from the average of the two control curves were calculated for the one and two-hour post drug determinations and entered in a table with four entries for medication and seven entries for subject (table 1). An analysis of variance was carried out on the

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TABLE 2

ANALYSIS OF VARIANCE
(Mean of 1 and 2-hour data)

Source of Variance	Degrees of Freedom	Sum of Squares	Mean Square	F Ratio
Total	27	234.75		
Subject	6	67.09	11.18	2.40
Treatment	3	83.97	27.99	6.02*
Error	18	83.69	4.65	

* $P_{0.05}$, F = 3.16; $P_{0.01}$, F = 5.09.

mean of the one and two-hour determinations (table 2). The variance due to treatment was significant ($P < 0.01$) while that due to subject was not. Orthogonal treatment comparisons were made to determine the significance of slope, difference in drug effect and deviations from slope (table 3). The slope was significant ($P < 0.01$) indicating a difference in effect between the upper and lower doses of morphine and oxymorphone. Morphine and oxymorphone were evaluated at slightly different effect levels. However, this was not statistically significant. The deviation from slope was not significant indicating no appreciable difference between the common slope and the dose effect slopes for morphine or oxymorphone.

There was considerable overlap in the effect of these two compounds so that it was possible to calculate the relative potency without extrapolation. The relative potency, ϕ, of oxymorphone relative to morphine was calculated from the formula,

$$\log \phi = \frac{\beta w - \bar{Z}_2}{2\beta}$$

where ϕ is the relative potency, β is the common slope, w is the log ratio of the doses of

TABLE 3

ORTHOGONAL COMPARISONS
(MEAN OF 1 AND 2-HOUR DATA)

	Mean Z	Morphine		Oxymorphone		Mean Square	F Ratio
		5 mg.	10 mg.	0.5 mg.	1 mg.		
Sum		9.3	30.4	21.1	42.3		
Slope (Z_1)	6.0	−	+	−	+	64.2	13.8*
Difference in effect (Z_2)	3.4	−	−	+	+	20.2	4.3
Deviation from slope (Z_3)	.01	+	−	−	+	0.01	

* $P_{0.05}$, F = 4.41; $P_{0.01}$, F = 8.28.

test medications administered, and $\bar{Z}_2$ is the mean difference in effect; ϕ was found to be 14.8 with the upper and lower 95 per cent confidence limits of 32 and 10, respectively.**[7,8]

DISCUSSION

These results indicate that oxymorphone is 14.8 times as potent as morphine in terms of their respiratory depressant effects or that 0.68 mg. of oxymorphone is equivalent to 10 mg. of morphine. The relative analgesic potency of these drugs in patients with chronic pain, ϕ, was found to be 8.95 with the upper and lower 95 per cent confidence limits of 10.8 and 7.9, respectively.[9] Thus, in terms of analgesic effects, 1.12 mg. is considered to be equivalent to 10 mg. of morphine. In another independent study Eddy and Lee[10] determined 1.02 mg. of oxymorphone to be equivalent to 10 mg. of morphine. Our estimate of the relative potency based on the mean one and two-hour respiratory effects is significantly higher than the analgesic potency estimates[11] ($P < 0.01$) even though the lower limit (10.0) of the respiratory assay does overlap the upper (10.8) limit of the analgesic assay. This implies that oxymorphone at comparable analgesic dose causes more respiratory depression than an equivalent analgesic dose of morphine. This would confirm the clinical observation of Eddy and Lee who stated that a higher incidence of respiratory depression was seen with oxymorphone than with morphine.[10]

Though our estimate of the relative respiratory depressant actions of these drugs is based

** The 95 per cent confidence limits were calculated from the formula

$$\alpha_L = \frac{w + K_u \log 4}{2} \quad \text{and} \quad \alpha_u = \frac{w + K_L \log 4}{2}$$

where α_L, α_u equal the lower and upper limits, respectively; w is the log ratio of the test drugs and K_u and K_L are calculated from the formula

$$K = \frac{-B \pm \sqrt{B^2 - 4AC}}{2A}$$

where $A = \bar{Z}_1^2 - t^2_{0.05}\, se_z^2$, $B = 2\bar{Z}_1\bar{Z}_2$ and $C = \bar{Z}_2^2 - t^2_{0.05}\, se_z^2$. The standard error squared, se_z^2, was calculated from the mean square of the error term from the analysis of variance by multiplying it by T/N where T is the number of treatments (four) and N the number of subjects[7,8,12] (seven). If the upper and lower limits are calculated according to the method described by Irwin[13,14] they are 29.1 and 11.0 respectively.

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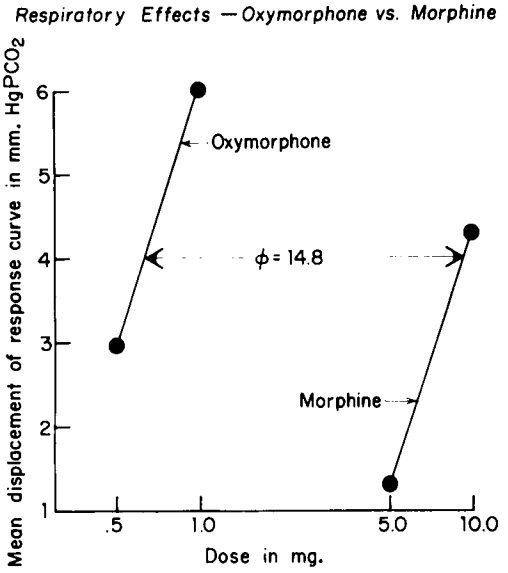

FIG. 1. Dose-effect curves for oxymorphone and morphine. The mean of the one and two-hour displacements of the respiratory response curve obtained in the seven subjects is plotted against the dose (log scale) for oxymorphone and morphine. The common slope, β, is drawn through these points; ϕ, the distance between these regression lines on the log scale, represents the relative potency of oxymorphone compared to morphine.

on measures of effect which in most patients would probably escape detection clinically, the doses of oxymorphone and morphine tested are within the range of those often employed in the treatment of pain. In clinical use, it is true that alarming respiratory depression would probably be encountered only rarely with such doses of these drugs but this should not lead to a false sense of security. Respiratory depression to a degree sufficient to be obvious by clinical signs alone is always profound and serious. It is neither necessary nor justifiable to use this as an end point in drug assays. Respiratory depression induced by the narcotic drugs is not an "all or none" effect. It has long been known that graded degrees of depression of alveolar ventilation can be produced in animals and man by graded doses of these drugs. Since the dose-effect curves for oxymorphone and morphine were reasonably parallel in this study, we have every reason to believe that the same relative potency would be obtained at doses capable of producing more profound respiratory depression.

It is misleading to attempt to base any estimate of relative lack of respiratory depressant effects of oxymorphone on uncontrolled clinical observations. Single doses as high as 20 mg. have been reported to be devoid of serious consequences in some patients,[1] whereas in others, doses as low as 1.33 to 2.0 mg. have produced depression so profound as to require the administration of nalorphine.[10] Obviously, there are many factors which can influence the effects of any narcotic on respiration, and not the least of these are drug tolerance, disease and inherent patient differences. By the same token, the impressions of any investigator will be colored by how carefully his patients have been scrutinized for undesired effects and by his concepts of what is and what is not significant. The only valid way of assessing the respiratory depressant effects of the narcotic drugs is to use a method sensitive enough to detect graded effects with graded doses of drug and employ appropriate controls and standards for comparison.

SUMMARY

A cross-over double-blind controlled study of the respiratory effects of morphine and oxymorphone has been carried out in seven volunteers. Oxymorphone which is 8.95 times as potent as morphine in terms of their analgesic effects [7] was found to be 14.8 times as potent as morphine in terms of their respiratory depressant effects. The conclusion seems warranted that oxymorphone produces at least as much respiratory depression as morphine when given in comparable analgesic doses.

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REFERENCES

1. Coblentz, A. and Bierman, H. R.: The analgesic properties of numorphan (14-hydroxydihydromorphinone), New England J. Med. 255: 694, 1956.
2. Loeschcke, H. H.: Über Reiz und Erregbarkeit der Zentralen Atmungsregulation, Klin. Wschr. 27: 761, 1949.
3. Eckenhoff, J. E., Helrich, M. and Hege, M. J. D.: A method for studying respiratory func-

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tions in awake or anesthetized patients, ANESTHESIOLOGY 17: 66, 1956.
4. Bellville, J. W. and Seed, J. C.: Respiratory carbon dioxide response curve computer, Science **130**: 1079, 1959.
5. Bellville, J. W. and Seed, J. C.: The use of an analog computer for measuring respiratory depression, Trans. N. Y. Acad. Sci. **22**: 34, 1959.
6. Seed, J. C., Wallenstein, S. L., Houde, R. W. and Bellville, J. W.: A comparison of the analgesic and respiratory effects of dihydrocodeine and morphine in man, Arch. int. Pharmacodyn, **116**: 293, 1958.
7. Houde, R. W. and Wallenstein, S. L.: Clinical studies of narcotics at Memorial Center, Bull. Drug Addiction & Narcotics, App. B: 1383, 1956.
8. Mosteller, F.: Statistical problems and their solution. (Contained in Beecher's review "The measurement of pain.") Pharmacol. Rev. **9**: 103, 1957.
9. Houde, R. W. and Wallenstein, S. L.: Relative Analgesic potencies of oxymorphone and morphine, To be submitted for publication.
10. Eddy, N. B. and Lee, L. E., Jr.: The analgesic equivalence to morphine and relative side action liability of oxymorphone (14-hydroxydihydromorphinone), J. Pharm. & Exper. Therap. **125**: 116, 1959.
11. Snedecore, G. W.: Statistical Methods, p. 82, Ames, Iowa, Iowa State College Press, 1955.
12. Bross, I. D. J.: Personal Communication.
13. Irwin, J. O.: A statistical examination of the accuracy of vitamin A assays, J. Hyg. **43**: 291, 1944.
14. Gaddum, J. H.: Bioassays and mathematics, Pharmacol. Rev. **5**: 87, 1953.

TECHNIQUES OF HYPNOSIS Methods for inducing formal hypnosis are classified as direct or authoritarian, indirect or permissive, and mechanical. Preliminary tests determine a patient's susceptibility to suggestion and help to decide which method to use. The subject must understand that hypnosis is not sleep and that he will be more, not less, acutely aware. He must understand that he himself induces the hypnotic state and that the operator is only acting as a guide. This "patient-centered hypnosis" differs greatly from the outmoded and dramatic authoritarian methods of the nineteenth century. (*Kroger, W. S.: Techniques of Hypnosis, J. A. M. A. 172: 675 (Feb. 13) 1960.*)

HYPNOANESTHESIA Because of the need for a close interpersonal relationship between patient and anesthesiologist, anesthesiology must take up its abode in psychiatry. Reassurance and support, the mainstays of psychotherapy for an acute psychological crisis, are important in preparing an anxious patient for anesthesia. Since time is an important factor, such psychotherapy can be achieved rapidly by hypnosis. In its broadest sense, the perfect anesthetic should include the use of hypnosis in combination with a chemical anesthetic agent. (*Kroger, W.: Hypnoanesthesia in Surgery and Obstetrics, West. J. Surg. 68:73 (Jan.-Feb.) 1960.*)

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