Analgetic Activity of Optical Isomers of 3-hydroxy-N-methylmorphinan* and 6-dimethylamino-4,4-diphenyl-3-heptanone.†‡ (20702)

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Although many potent analgetics have resulted from investigation of this class of pharmacologic agents, their mechanism(s) of action has not been elucidated. It is generally accepted that the morphine-type analgetics possess a similar mechanism of action, although no direct evidence in support of this concept is available. Several investigators(1-7) have demonstrated that the *l*-isomers of optically active analgetics possess all or most of the analgetic activity of the racemic form of the compound. Slomka and Gross(4) demonstrated that dextrorphan tartrate inhibited the analgetic activity of levorphan tartrate and of morphine sulfate. This indicated that these structurally very similar compounds possessed a similar mechanism of action. It was of interest to extend this study to a structurally somewhat dissimilar analgetic agent in order to test the accepted but unproven contention that the mechanism of action of the morphine-type analgetics is the same.

Methods. The effects of drug treatments were determined on 6 trained normal human subjects using a warm wire analgesiometer patterned after that of Lee, Williams, and Pfeiffer(8). Pain thresholds were determined on the finger nail bed at 30-minute intervals. The subjects were allowed freedom of movement during the experimental period. The minimal intensity increment that the subjects were required to distinguish was equivalent to approximately a 4% rise in threshold, and this represents the maximal variability of the apparatus. The drugs in physiologic saline, were administered subcutaneously. The treatments tested were: 1) 2.0 mg levorphan tartrate; 2) 3.2 mg levorphan tartrate; 3) 3.2 mg dextrorphan tartrate; 4) 3.2 mg levorphan tartrate and 3.2 mg dextrorphan tartrate; 5) 3.2 mg levorphan tartrate and 5.0 mg *d*-Methadone Hydrochloride; 6) 5.0 mg *l*-Methadone Hydrochloride; 7) 5.0 mg *d*-Methadone Hydrochloride; 8) 5.0 mg *l*-Methadone Hydrochloride and 5.0 mg *d*-Methadone Hydrochloride; 9) 5.0 mg *l*-Methadone Hydrochloride and 3.2 mg dextrorphan tartrate; 10) 1.6 mg levorphan tartrate and 2.5 mg *l*-Methadone Hydrochloride; 11) saline placebo; 12) 60 ml 95% ethyl alcohol; 13) 60 ml 95% ethyl alcohol and 3.2 mg dextrorphan tartrate; 14) 60 ml 95% ethyl alcohol and 5.0 mg *d*-Methadone Hydrochloride. The ethyl alcohol was always given orally to the fasting subjects. Drug treatments were randomized in 2 groups, namely, 1-11 and 12-14, and neither the operator nor the subjects knew what drug combinations were employed.

Results. The results of this investigation are summarized in Table I. If visual inspection was insufficient to determine the significance of desired comparisons between drug treatments, the Null Hypothesis and Student's "t" Test(9) were applied. The statistical analysis is summarized in Table II.

A comparison of treatments 1 and 2 indicates that on this type of experimental pain, 3.2 mg levorphan tartrate possesses about one and a half times the analgetic potency of 2.0 mg. A comparison of treatments 2 and 6 indicates that the doses of the *l*-isomers,

* The levo form of 3-hydroxy-N-methylmorphinan (generic designation levorphan) and its dextro form (generic designation dextrorphan) used as tartrates and supplied by Hoffmann-LaRoche, Inc., Nutley, N. J.

† The levo and dextro forms of 6-dimethylamino-4,4-diphenyl-3-heptanone were made available by Eli Lilly and Co., Indianapolis, Ind., as *d*- and *l*-Methadone Hydrochlorides.

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TABLE I. Summary of Data.

Treatment	levorphan tartrate	" "	dextrorphan "	levorphan " & dextrorphan "	levorphan " & *d*-Methadone hydrochloride	*l*-Methadone hydrochloride	*d* " "	*l* " " & *d* " "	*l* " " & dextrorphan tartrate	levorphan tartrate & *l*-Methadone hydrochloride	saline placebo	95% ethyl alcohol (orally)	*idem.* & 3.2 mg dextrorphan tartrate	*idem.* & 5.0 mg *d*-Methadone hydrochloride
mg	(1) 2.0	(2) 3.2	(3) 3.2	(4) 3.2 3.2	(5) 3.2 5.0	(6) 5.0	(7) 5.0	(8) 5.0 5.0	(9) 5.0 3.2	(10) 1.6 2.5	(11)	(12) 60 ml	(13) 60 ml	(14) 60 ml
$\bar{x}$	7.4	11.5	.7	5.0	5.1	13.6	1.7	5.1	4.2	11.6	.7	8.3	3.2	2.4
n	10	13	6	6	5	6	6	6	6	6	7	6	6	6
$v_{\bar{x}}$	1.08	.34	.52	.01	.04	1.16	1.11	.02	.73	1.39	.40	1.15	1.05	1.15
$s_{\bar{x}}$	1.04	.58	.72	.1	.2	1.08	1.05	.14	.85	1.18	.63	1.07	1.03	1.07

$\bar{x}$ = Mean % increase in pain threshold produced by drugs and drug combinations.
n = No. of observations. $v_{\bar{x}}$ = variance of mean. $s_{\bar{x}}$ = Stand. dev.

levorphan tartrate (3.2 mg) and *l*-Methadone Hydrochloride (5.0 mg), possess equal analgetic potency.

A comparison of treatments 2, 3, and 4 and of 6, 7, and 8, respectively, shows that the analgetic activity of 3-hydroxy-N-methylmorphinan and of 6-dimethylamino-4,4-diphenyl-3-heptanone resides in the levo isomers of these compounds and that the analgetically inactive dextro isomers are able to inhibit the analgetic activity of their stereo-isomers. Comparison of treatments 2, 4, and 5 and of 6, 8, and 9, respectively, indicates that the analgetic activity of levorphan tartrate and *l*-Methadone Hydrochloride is inhibited by the inactive dextro isomer of the other compound to the same degree as by its own inactive stereo-isomer. A comparison of treatments 2, 6, and 10 shows that the effects of a combination of half the dose of each levo isomer are additive in nature.

The inhibition of analgesia of levorphan tartrate and of Methadone Hydrochloride by the dextro isomers of either compound and the additive effect of a combination of the levo isomers suggest that the mechanism of action of these agents is the same. It would be plausible to assume that the inhibition of morphine analgesia effected by dextrorphan tartrate(4) would also be effected by *d*-Methadone Hydrochloride.

It was of interest to determine the effects of dextrorphan tartrate and *d*-Methadone Hydrochloride on the analgesia produced by ethyl alcohol. A comparison of treatments 12, 13, and 14 indicates that both compounds were equally effective in inhibiting the analgesia produced by ethyl alcohol. This inhibition suggests that some aspect of alcohol analgesia involves a mechanism similar to that of the morphine-type analgetics or that some aspect of the mechanism of alcohol analgesia may be mediated through their site of action.

Nausea and dizziness were reported occasionally by 5 subjects, with emesis following in 3 after they had received 3.2 mg levorphan tartrate. The same 3 subjects reported nausea and dizziness after they had been given 5.0 mg *l*-Methadone Hydrochloride with emesis following in one. No side effects were reported after the administration of 2.0 mg levorphan tartrate. Emesis was produced in one subject by the combination of 1.6 mg levorphan tartrate and 2.5 mg *l*-Methadone Hydrochloride. In the preliminary training period one individual—a 7th subject—was eliminated since he showed a drug sensitivity characterized by an extensive rash to levor-

TABLE II. Statistical Analysis.

Between treatments	1 vs 2	2 vs 6	2 vs 10	3 vs 4	3 vs 5	3 vs 7	4 vs 5
d	4.1	2.1	.1	4.3	4.4	1.0	.1
V_d	1.42	1.50	1.73	.53	.56	1.63	.05
s_d	1.19	1.23	1.32	.73	.75	1.28	.22
"t"	3.45	1.71	0.008	5.90	5.87	.78	.46
N	21	17	17	10	9	10	9
P	.01–.001	.30–.20	>.90	<.001	<.001	.50–.30	.70–.50

Between treatments	6 vs 10	7 vs 8	7 vs 9	7 vs 11	8 vs 9	9 vs 11	2, 6, and 10 vs 4, 5, 8, and 9
d	2.0	3.4	2.5	1.0	.90	3.5	7.2
V_d	2.55	1.13	1.84	1.51	.75	1.13	.77
s_d	1.60	1.06	1.36	1.23	.87	1.06	.88
"t"	1.25	3.21	1.84	.77	1.03	3.30	8.18
N	10	10	10	11	10	11	46
P	.30–.20	.01–.001	.10–.05	.50–.30	.30–.20	.01–.001	<.001

Between treatments	11 vs 13	11 vs 14	12 vs 13	12 vs 14	13 vs 14	11 vs 13 and 14	12 vs 13 and 14
d	2.5	1.7	5.1	5.9	.8	2.1	5.5
V_d	1.45	1.55	2.20	2.30	2.20	.92	1.67
s_d	1.21	1.25	1.48	1.52	1.48	.96	1.29
"t"	2.07	1.36	3.44	3.81	.54	2.19	4.26
N	11	11	10	10	10	17	16
P	.10–.05	.30–.20	.01–.001	.01–.001	.70–.50	.05–.02	<.001

d = Difference between means. V_d = Variance. s_d = Stand. dev. N = No. of degrees of freedom. P = Probability.

phan tartrate, as proven by a positive response to the intracutaneous injection of 0.16 mg levorphan tartrate; this sensitivity did not extend to *l*-Methadone Hydrochloride.

Summary and conclusions. 1. The relative analgetic potencies of the tartrates of the optical isomers of 3-hydroxy-N-methylmorphinan and of the hydrochlorides of Methadone were determined in normal human subjects on finger nail bed pain. 2. An inhibitory effect of the dextro isomers on the analgetic activity of the levo isomers and an additive effect of a combination of the levo isomers were demonstrated. 3. An inhibitory effect of the dextro isomers on ethyl alcohol analgesia was observed. 4. The results of this investigation suggest that the mechanism of action of the morphine-type analgetics studied is the same.

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