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Relative Analgesic Potencies of Morphine and Hydromorphone in Postoperative Pain

Donald L. Mahler, M.D.,* and William H. Forrest, Jr., M.D.†

Because of discrepancies in the estimates of the relative analgesic potencies of hydromorphone and morphine, the drugs were compared in two four-point, double-blind bioassays. In the first study, hydromorphone, 1 and 2 mg, was compared with morphine, 5 and 10 mg, in 31 postoperative patients; in the second, hydromorphone, 0.5 and 1 mg, was compared with morphine, 5 and 10 mg, in 112 postoperative patients. Subjective responses to nurse–observer questions were used to quantitate analgesia for postoperative pain. Hydromorphone is more potent than commonly believed: approximately 0.9 to 1.2 mg is equianalgesic with 10 mg of morphine, with a similar incidence of side effects. (Key words: Analgesics, narcotic, hydromorphone; Analgesics, narcotic, dihydromorphinone; Analgesics, narcotic, morphine; Pain, postoperative.)

DESPITE THE USE of hydromorphone (Dilaudid) for the past 48 years, there exists little general agreement over its analgesic potency relative to morphine, the literature showing ranges from two to 12 times as potent. In 1926, the first report on the clinical use of hydromorphone[1] showed that 2 to 4 mg produced analgesia equivalent to that produced by 10 mg of morphine. Later, Seevers and Pfeiffer[2] found that approximately 1 mg of hydromorphone was equianalgesic with 10 mg of morphine in an experimental pain model. In 1957, Eddy *et al.*,[3] in an extensive review of the literature under the auspices of the World Health Organization, concluded that 2.5–5 mg of hydromorphone were equianalgesic with 10 mg of morphine and that the duration of effect was three to four hours, a little shorter than that of morphine. In 1962, Hanna *et al.*,[4] studying postoperative pain, found that 1.5 mg hydromorphone were equivalent to 10 mg morphine in onset, potency, and duration of action. In the first edition of *The Pharmacological Basis of Therapeutics* (1941),[5] Goodman and Gilman described hydromorphone as ten times as potent as morphine; in the second edition (1955),[6] as five to ten times; by the third edition (1965),[7] the potency was described as five times that of morphine; in the fourth edition (1970),[8] it was again described as ten times that of morphine. In 1969, Houde (personal communication), in double-blind studies of patients with cancer pain, found a relative potency, compared with morphine, of 8, but a shorter duration of action for hydromorphone.

Because of the continuing clinical use of hydromorphone, such discrepant findings prompted us to compare these drugs, using the methodology developed in the Veterans Administration Cooperative Analgesic Study (VACAS)[9]; this methodology, *vide infra*, is a modification of the technique of Houde *et al.*[10] The study design was a four-point, double-blind bioassay in which each patient received two doses of hydromorphone and two doses of morphine. Estimating the equianalgesic doses from the literature and clearly biased by recent practice, we decided to compare 1 and 2 mg of hydromorphone with 5 and 10 mg of morphine. However, the chosen doses of hydromorphone proved to be more effective than 5 and 10 mg of morphine,

* Chief of Anesthesiology, Boston Veterans Administration Hospital; Professor of Anesthesiology, Tufts University School of Medicine.

† Anesthesiologist, Palo Alto Veterans Administration Hospital; Associate Professor of Anesthesiology, Stanford University School of Medicine.

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Address reprint requests to Dr. Forrest, Veterans Administration Hospital, 151 G, 3801 Miranda Avenue, Palo Alto, California 94304.

TABLE 1. Mean* Response Scores, SPID and TOTPAR, Study 1

	Complete Rounds					Incomplete Rounds (First Dose Only)				
		SPID		TOTPAR			SPID		TOTPAR	
Medication	N†	Mean	SE‡	Mean	SE	N	Mean	SE	Mean	SE
Morphine, 5 mg	18	2.57	0.57	4.89	0.76	3	1.75	0.75	5.58	1.81
Morphine, 10 mg	18	3.79	0.57	7.74	0.76	3	2.25	0.75	5.92	1.81
Hydromorphone, 1 mg	18	4.28	0.57	7.33	0.76	3	0.42	0.75	1.50	1.81
Hydromorphone, 2 mg	18	5.50	0.57	10.36	0.76	4	6.94	0.65	12.94	1.57

* Means are weighted for length of observation period.
† N = number of treatments given.
‡ SE = pooled standard error.

TABLE 2. Mean* Response Scores, SPID and TOTPAR, Study 2

	Complete Rounds					Incomplete Rounds (First Dose Only)				
		SPID		TOTPAR			SPID		TOTPAR	
Medication	N†	Mean	SE‡	Mean	SE	N	Mean	SE	Mean	SE
Morphine, 5 mg	52	2.39	0.27	5.26	0.44	12	2.88	0.75	6.08	1.32
Morphine, 10 mg	52	3.19	0.27	7.00	0.44	18	2.65	0.61	7.64	1.08
Hydromorphone, 0.5 mg	52	2.25	0.27	4.27	0.44	11	2.39	0.78	4.39	1.38
Hydromorphone, 1 mg	52	3.50	0.27	6.98	0.44	19	2.34	0.60	7.01	1.05

* Means are weighted for length of observation period.
† N = number of treatments given.
‡ SE = pooled standard error.

so a second study comparing 0.5 and 1 mg of hydromorphone with 5 and 10 mg of morphine was done. Both studies were done in the same participating hospital (Boston).

Method

Patient Selection

The principal investigator and nurse-observers specially trained in subjective-response techniques reviewed the charts of patients scheduled for surgery to find candidates suitable for the study. Those selected were interviewed preoperatively by the nurse-observer, who explained the goals and protocol of the study; candidates were considered suitable if they could communicate with the nurse-observer, could tolerate morphine, 10 mg, and had no medical or other contraindication. If the patient volunteered to participate, he was asked to sign an informed consent. He was told that the nurse-observer would care for his postoperative pain needs during the study hours, that is, 8 AM to 10 PM. The patient was free to drop out of the study at any time.

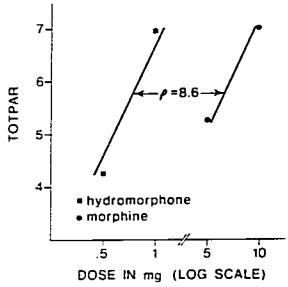

FIG. 1. Relative potency for TOTPAR (completers), Study 2.

TREATMENTS

Treatments were packaged identically and each patient was assigned all four treatments in random order. For the first study the treatments were 1 and 2 mg of hydromorphone and 5 and 10 mg of morphine. For the second study the treatments were 0.5 and 1 mg of hydromorphone and 5 and 10 mg of morphine. Although it was hoped that all patients would receive all four treatments for relief of their postoperative pain, many did not because they no longer needed parenteral analgesia. No patient dropped out because of adverse effects of the analgesics.

DATA COLLECTION

If the postoperative patient requested medication for his pain, the ward nurse informed the nurse–observer, who again interviewed the patient, establishing his analgesic needs and determining his baseline pain intensity. She then administered the randomly assigned treatment. The patient was observed and interviewed 30 minutes later and again at five 45-minute intervals for a possible total of six postmedication visits (30, 75, 120, 165, 210, and 255 minutes after medication), a time span of 4¼ hours. On the basis of each patient's report, pain intensity was scored as follows: 0 (no pain), 1 (slight pain), 2 (moderate pain), or 3 (severe pain). A pain-intensity difference (PID) for each visit was calculated by subtracting the pain intensity at that time from the intensity of pain before the analgesic was administered. One of our two measures of analgesia, the sum of the pain-intensity differences (SPID), was obtained by adding the PID's for all visits for each patient.

During each interview, the patient was also asked to describe his pain relief, which was scored as follows: 4 (complete), 3 (good), 2 (moderate), 1 (slight), or 0 (no relief). Pain-relief scores were then totaled for all postmedication visits to provide the other measure of analgesia, the total pain-relief score (TOTPAR). At any time after two hours,

TABLE 3. Analysis of Variance for TOTPAR Completers, Study 2

Source	Degrees of Freedom	Sum of Squares	Mean Square	f	P
Patients	51	1,927.8	37.8	3.81	<0.0005
Treatments	3	282.9	94.3	9.50	<0.005
Medication	1	13.3	13.3	1.34	<0.25
Slope	1	257.4	257.4	25.95	<0.0005
Nonparallelism	1	12.2	12.2	1.23	<0.50
Error	153	1,518.1	9.9		

TABLE 4. Relative Potencies for SPID and TOTPAR, Study 1, Study 2, and Pooled (Completers)

	SPID			TOTPAR		
	Relative Potency	Lower Limit*	Upper Limit	Relative Potency	Lower Limit	Upper Limit
Study 1	13.2	6.5	∞	9.1	6.2	20.6
Study 2	10.6	7.1	16.5	8.6	6.1	11.2
Pooled	10.8	6.9	16.9	8.7	6.3	11.8

* 95 per cent confidence limits.

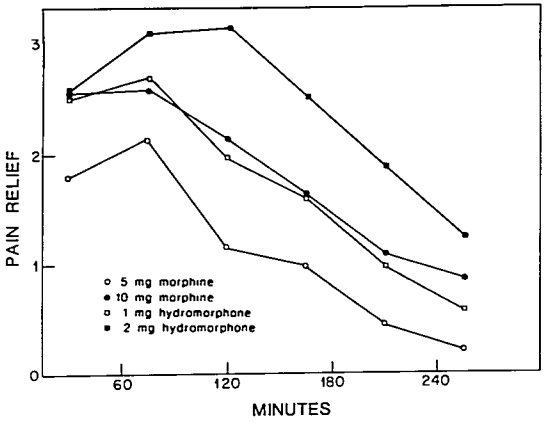

FIG. 2. Time-effect curves for pain relief (completers), Study 1.

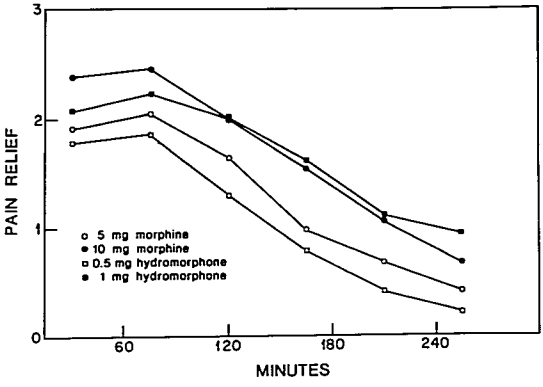

FIG. 3. Time-effect curves for pain relief (completers), Study 2.

if the patient's pain returned to his baseline intensity, he could receive the next study medication, or a non-study medication if the nurse–observer was going off duty.

For purposes of analysis, a "completer" was defined as a patient who received all four treatments, *i.e.*, both doses of morphine and both of hydromorphone; an "incompleter" was one who did not receive all four treatments. For simplicity, only the first treatment of an incompleter was analyzed.

Side effects recorded were those either volunteered by the patients or observed by the nurse–observer. Once an effect was recorded, its presence was determined on all subsequent visits.

Thirty-one patients participated in Study 1, and 18 received all four treatments; 112 patients participated in Study 2, and 52 received all four treatments.

Results

Mean Responses

In Study 1, 1 and 2 mg of hydromorphone were compared with 5 and 10 mg of morphine. For completers, there were steep dose-response curves for both drugs for both

TABLE 5. Incidences of Side Effects, Completers and Incompleters (Both Studies)

	Morphine		Hydromorphone*		
	5 mg (85 Patients) (Per Cent)	10 mg (91 Patients) (Per Cent)	0.5 mg (63 Patients) (Per Cent)	1.0 mg (92 Patients) (Per Cent)	2.0 mg (22 Patients) (Per Cent)
Sleepiness	28	28	27	36	59
Headache	2	1	3	0	0
Vertigo	1	2	2	4	4
Nausea	1	4	3	1	0
Sweating	0	1	3	2	4
Itchiness	0	1	0	1	4
Vomiting	1	1	2	0	0
Visual	0	0	0	2	0

* These side effects were reported once with the following medication: hydromorphone, 1.0 mg, sensory changes, numbness.

SPID and TOTPAR (table 1). However, the analgesic effects of hydromorphone were much greater than those of morphine, suggesting that the doses chosen for hydromorphone were too high to obtain a satisfactory comparison of the two drugs. Comparison of lower doses of hydromorphone with morphine showed that hydromorphone, 0.5 and 1 mg, was equianalgesic to 5 and 10 mg of morphine (table 2). Although mean drug effects were similar for first-treatment incompleters for both SPID and TOTPAR, steep dose-response curves were obtained for TOTPAR only.

Analysis of Variance

For TOTPAR completers in Study 2, patient and treatment effects were highly significant ($P < 0.0005$ and $P < 0.005$, respectively, as shown in table 3). Three measures for validity of this bioassay (orthogonal contrasts) indicate that the assumption of nonparallelism is satisfied ($P < 0.5$), there is measurable increase in effect with increase in dose (slope is significant, $P < 0.0005$), and the drugs were studied in their equieffective ranges (medication effect nonsignificant, $P < 0.25$). Results obtained from the analysis of variance for SPID completers (not shown) were quite similar and also indicated a valid bioassay.

Analgesic Relative Potency

For the most efficient bioassay—Study 2, TOTPAR completers—a relative potency of 8.6 with good limits was obtained (see figure 1 and table 4). Relative potencies for the other assays ranged from 9.1 to 13.2 and had reasonable confidence limits. Using the method of Bennett,[11] which weighs for assay efficiency, we pooled relative potencies across studies to obtain a single estimate for each analgesic measure (see table 4). Estimates of 10.8 and 8.7 (with reasonable limits) for SPID and TOTPAR, respectively, were obtained, indicating that for analgesia lasting as long as 4¼ hours, hydromorphone, 0.9–1.2 mg, was equivalent to 10 mg of morphine in our population of patients.

Peak Effects

Having established relative potencies of hydromorphone and morphine for analgesia lasting as long as 4¼ hours, we then determined their peak analgesic relative potencies. Assuming that hydromorphone is ten times more potent than morphine for analgesia lasting 4¼ hours, we can make a direct comparison between 10 mg of morphine and 1 mg of hydromorphone on the pain relief time-effect curves for each study (figs. 2 and 3). In both figures these time-effect curves practically overlap, suggesting not only similar peak effects but also similar time courses of action. Analysis of peak effects by bioassay confirmed these similarities, showing a relative potency of 10.3 for hydromorphone.

Side Effects, Both Studies

Sleepiness was the most common side effect, and was dose-related for hydromor-

phone (table 5). Sleepiness was volunteered approximately a third of the time for both doses of morphine and the two lower doses of hydromorphone, and almost two thirds of the time for the higher (2 mg) dose of hydromorphone. The low incidences of the remaining side effects—headache, vertigo, nausea, sweating, itchiness, vomiting, and visual disturbances—precluded comparisons between the drugs but are consistent with our previous work and reports in the literature.

Discussion

This study strongly suggests that the doses of hydromorphone usually recommended for the treatment of pain are too high. The drug description for Dilaudid in the *Physicians' Desk Reference* (the same information appears on the package insert) states: "The usual parenteral dose for pain relief is 2 mg administered subcutaneously or intramuscularly every 4 to 6 hours as necessary."[12] Dilaudid is packaged in such a way that larger doses are encouraged (in ampules of 1, 2, 3, and 4 mg per ml). Hanna's careful work, and Goodman and Gilman's change from 2 to 1 mg, have had no influence on the manufacturer's suggested dosage regimen. As long ago as 1942, Seevers said of hydromorphone "It is thus possible to obtain pain relief with this compound with quantities of the drug below that ordinarily recommended and by so doing reduce the amount of lethargy which would accompany the administration of larger amounts."[13] That the drug has remained in use for such an extended period prescribed at higher doses is probably a testimonial to its relative safety. Our side-effect data would support the notion of safety of doses as large as 2 mg, although we have no comparative data for 20 mg of morphine (approximately equal to 2 mg hydromorphone) in our VACAS studies.

Hydromorphone seems to cause sleepiness at about the same frequency or perhaps a little oftener than morphine in the equieffective range. The manufacturer's claim that Dilaudid "seldom produces drowsiness"[12] seems unjustified on the basis of our data, particularly since we demonstrated a dose-response relationship for this side effect and found that 59 per cent of patients had sleepiness with 2 mg.

This work was done within the framework of the Veterans Administration Cooperative Analgesic Study, in which the principal investigators at the time of the study (1969) were Drs. E. G. Beer, B. Ciliberti, W.H. Forrest, Jr., D.L. Mahler, and P.F. Shroff.

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