A CONTROLLED CLINICAL EVALUATION OF TWO NEW ANALGESICS, PHENAZOCINE AND PHENAMPROMID

THOMAS J. DEKORNFELD, M.D. and LOUIS LASAGNA, M.D.

PHENAMPROMID * (N-(1-methyl-2-piperidinoethyl)-propionanilide hydrochloride) is one of a series of synthetic alkylene diamine compounds found to have pharmacodynamic effects qualitatively similar to the narcotic class of analgesic drugs (morphine, codeine, meperidine and methadon). Animal studies at the Lederle Laboratories [1] suggested that phenampromid was inferior, on a weight basis, to morphine in analgesic potency, but similar to meperidine and codeine in its effects on the D'Amour-Smith rat tail, radiant heat technique. The formula of this drug is shown in figure 1.

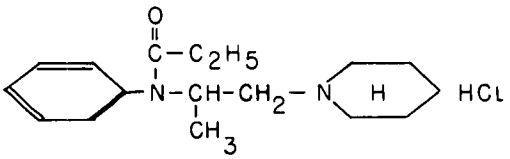

FIG. 1. Phenampromid—N-(1-methyl-2-piperidinoethyl)-propionanilide hydrochloride.

Phenazocine † is one of a series of drugs in the benzomorphan series synthesized by May and his colleagues.[2, 3] Its chemical formula is *dl*-2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide, and its structure is depicted in figure 2. Unpublished data [4] suggested that the drug was a more potent analgesic drug than morphine in animals.

Both drugs, accordingly, were compared with a standard drug, morphine, in regard to efficacy in relieving clinical postoperative pain.

Presented at the Annual Meeting of the American Society of Anesthesiologists, Inc., Miami Beach, Florida, October 8, 1960, and accepted for publication November 25, 1959. The authors are in the Department of Anesthesiology, Baltimore City Hospitals, and Departments of Medicine (Division of Clinical Pharmacology) and Pharmacology and Experimental Therapeutics, Johns Hopkins University School of Medicine, Baltimore, Maryland.

* Lederle-CL-20,977, supplied by American Cyanamid Co.

† SKF 657-4-C, supplied by Smith, Kline & French.

METHODS

Patients were selected from the surgical wards of the Baltimore City Hospitals by one of the authors (T.J.D.), who wrote orders for pain relief, prescribing alternate doses of intramuscular medication, identified only by code letters. The period of observation was the first 48 hours after surgery. In each experiment, 10 mg. of morphine were alternated with a dose of one of the new agents. These doses were 25 and 50 mg. of phenampromid and 0.5, 2.0, and 3.0 mg. of phenazocine.‡

In approximately half of the patients in any group the standard (morphine) was administered first, and in the other half of the patients, one of the experimental drugs was given first. Neither patients nor interviewing technicians were aware of the nature of the medications. Medication was administered only on request of the patient for pain relief, and no medication could be given less than 2 hours after the preceding medication. Patients were interviewed prior to injection, and at intervals of ½, 1, 2, 3 and 4 hours after injection. At these interviews, patients were awakened if necessary and asked to categorize their pain as absent, slight, moderate, severe or very

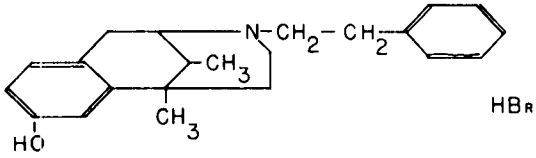

FIG. 2. Phenazocine—*dl*-2′-hydroxy-5,9-dimethyl-2-phenethyl-6,7-benzomorphan hydrobromide.

severe. A decrease in pain from predrug level to the next level was counted as a score of + 1, a drop of two levels as + 2, etc. If no change occurred a score of zero was given and if pain increased over the predrug level (a relatively

‡ Weights of drugs refer to the salts of the three compounds, i.e. morphine sulfate, phenampromid hydrochloride, and phenazocine hydrobromide.

TABLE 1

ANALGESIC EFFICACY OF MORPHINE AND PHENAMPROMID IN POSTOPERATIVE PATIENTS

(Mean Pain Relief Scores, All Doses)

Drug	Hours after Medication				
	½	1	2	3	4
Morphine, 10 mg. (N-24 doses)	1.00	1.78	2.19	2.38	2.05
Phenampromid, 25 mg. (N-17 doses)	0.67	1.53	1.84	1.78	1.06
Morphine, 10 mg. (N-33 doses)	0.88	1.39	2.00	1.83	1.79
Phenampromid, 50 mg. (N-34 doses)	0.78	1.34	1.41	1.41	1.41

rare phenomenon) a negative score was given. If a medication was administered less than 4 hours after a previous medication, scores of zero were automatically counted for whatever interviews were thus ruled out for the earlier drug.

RESULTS

The data are presented in a variety of ways:

Mean Pain Relief Scores For All Doses Administered. Here each dose contributes equally to the score, but some patients contribute considerably more than others, since the number of doses administered to a given patient varied from 1 to 9.

TABLE 2

ANALGESIC EFFICACY OF MORPHINE AND PHENAMPROMID IN POSTOPERATIVE PATIENTS

(Mean "Individual" Pain Relief Scores)

Drug	Hours after Medication				
	½	1	2	3	4
Morphine, 10 mg. (N-12 pts.)	1.05	1.75	1.99	2.54	2.13
Phenampromid, 25 mg. (N-12 pts.)	0.67	1.36	1.85	1.85	1.11
Morphine 10 mg. (N-17 pts.)	0.84	1.32	1.78	1.80	1.61
Phenampromid, 50 mg. (N-18 pts.)	0.79	1.36	1.53	1.61	1.67

TABLE 3

ANALGESIC EFFICACY OF MORPHINE AND PHENAMPROMID IN POSTOPERATIVE PATIENTS

(Percentage of Patients Reporting Complete Relief, All Doses)

Drug	Hours after Medication				
	½	1	2	3	4
Morphine, 10 mg.	8.3	17.4	28.6	33.5	23.8
Phenampromid, 25 mg.	0	11.8	18.8	27.8	5.9
Morphine, 10 mg.	6.1	12.1	29.6	23.3	28.6
Phenampromid, 50 mg.	9.4	12.5	12.5	18.8	18.8

Mean "Individual" Pain Relief Scores. Here each patient contributes equally to the total score, since a mean score is computed at each interview point for each drug for each patient (regardless of how many times drug was given) and then a mean of these average scores is calculated.

Incidence of Complete Pain Relief (All Doses). The percentage of doses providing complete relief at the various time intervals is shown.

Phenampromid. (Table 1, 2, 3.) It will be seen that the results with 25 and 50 mgm.

TABLE 4

ANALGESIC EFFICACY OF MORPHINE AND PHENAZOCINE IN POSTOPERATIVE PATIENTS

(Mean Pain Relief Scores, All Doses)

Drug	Hours after Medication				
	½	1	2	3	4
Morphine, 10 mg. (N-44 doses)	1.07	1.74	2.33	2.40	2.42
Phenazocine, 0.5 mg. (N-36 doses)	0.61	1.06	1.22	1.26	1.14
Morphine, 10 mg. (N-48 doses)	1.39	2.47	2.31	2.00	1.39
Phenazocine, 2 mg. (N-48 doses)	0.87	1.40	1.53	1.32	0.97
Morphine, 10 mg. (N-36 doses)	0.82	1.59	1.69	1.85	1.57
Phenazocine, 3 mg. (N-34 doses)	1.42	1.72	1.97	1.88	1.58

TABLE 5

ANALGESIC EFFICACY OF MORPHINE AND PHENAZOCINE IN POSTOPERATIVE PATIENTS

(Mean "Individual" Pain Relief Scores)

Drug	Hours after Medication				
	½	1	2	3	4
Morphine, 10 mg. (N-17 pts.)	1.15	1.87	2.47	2.51	2.62
Phenazocine, 0.5 mg. (N-16 pts.)	0.63	1.10	1.36	1.44	1.37
Morphine, 10 mg. (N-19 pts.)	1.38	2.03	2.25	2.04	1.62
Phenazocine, 2 mg. (N-20 pts.)	0.78	1.31	1.40	1.31	1.08
Morphine, 10 mg. (N-22 pts.)	0.72	1.53	1.62	1.81	1.57
Phenazocine, 3 mg. (N-23 pts.)	1.29	1.64	1.92	1.97	1.78

of this agent approach but do not seem to equal or surpass the performance of 10 mgm. of morphine.

Phenazocine. (Table 4, 5, 6.) The results with this agent were definitely inferior to those achieved with morphine when 0.5 or 2.0 mg. of phenazocine were employed. At the 3.0 mg. level, however the efficacy of phenazocine is essentially undistinguishable from that of the standard dose of morphine.

TABLE 6

ANALGESIC EFFICACY OF MORPHINE AND PHENAZOCINE IN POSTOPERATIVE PATIENTS

(Percentage of Patients Reporting Complete Relief, All Doses)

Drug	Hours after Medication				
	½	1	2	3	4
Morphine, 10 mg.	2.3	11.6	32.5	45.2	57.8
Phenazocine, 0.5 mg.	2.8	5.6	16.7	17.1	25.7
Morphine, 10 mg.	16.7	34.7	43.1	35.5	27.9
Phenazocine, 2 mg.	10.9	20.0	22.0	18.9	15.4
Morphine, 10 mg.	14.7	35.2	43.7	48.1	36.6
Phenazocine, 3 mg.	27.7	30.5	41.1	45.4	41.6

Side Effects. No obvious unpleasant side-effects attributable to the drugs were seen except for one report of slight nausea after a dose of morphine and two instances of nausea and vomiting after the 3 mg. dose of phenazocine. In the case of this latter dose of phenazocine, which appears as effective as 10 mg. or morphine, there was less sedation observed as gauged by the number of post-drug interviews at which patients had to be awakened (42.4 per cent for phenazocine and 55.6 per cent for morphine).

DISCUSSION

Our data on phenampromid are in some ways reminiscent of results seen with codeine in postoperative pain studies by Lasagna and Beecher [5] in that the reasonably good performance of the lower dose was not substantially increased by doubling the dose. Only further studies with higher doses of phenampromid, however, could define this point with assurance. The definite inferiority of this drug to morphine on a weight basis is in accord with the animal data.

In regard to phenazocine also, our findings are in agreement with the work indicating a superiority of this drug to morphine on a weight basis. Unlike Eckenhoff, however,[6] whose data suggested that phenazocine was 7 to 10 times as potent as morphine, our experience would indicate that the ratio is closer to 3 or 4 to 1. This agent is also known to be a potent euphoriant and a more potent suppressor of morphine abstinence than morphine.[7] On the basis of our observations there is little reason at present for suspecting that phenazocine represents a major advance in the dissociation of analgesic potency and addiction liability. Our study sheds little light on the relative ability of morphine and phenazocine to cause unpleasant side effects, but nausea and vomiting were observed after the 3 mg. dose of phenazocine.

SUMMARY

In the treatment of postoperative pain, phenampromid in doses of 25 mg. and 50 mg. approaches but does not equal or surpass the performance of 10 mg. of morphine.

Phenazocine was inferior to 10 mg. of morphine at the 0.5 mg. and 2.0 mg. dose levels,

but essentially similar to this dose of morphine when given in doses of 3.0 mg. Phenazocine seemed to be somewhat less sedative than morphine in equieffective doses.

The authors are indebted to Mrs. Diane Keyes and M. Richard Schillaci for their assistance in gathering the data and to the surgical staff of Baltimore City Hospitals for the opportunity to study their patients.

This investigation was supported in part by a grant (D59-4) awarded by the Committee on Drug Addiction and Narcotics, National Academy of Science, National Research Council, from funds contributed by a group of interested pharmaceutical manufacturers, and by a grant (B365-C3) from the National Institutes of Health.

REFERENCES

1. American Cyanamid Co., Research Division Progress report, December, 1957 (unpublished data).
2. Eddy, N. B., Murphy, J. G., and May, E. L.: Structures related to morphine; extension of Grewe morphinan synthesis in benzomorphan series and pharmacology of some benzomorphans, J. Org. Chem. 22: 1370, 1957.
3. May, E. L., and Fry, E. M.: Structures related to morphine; further synthesis in benzomorphan series, J. Org. Chem. 22: 1366, 1957.
4. Eddy, N. B.: Personal communication.
5. Lasagna, L., and Beecher, H. K.: Analgesic effectiveness of codeine and meperidine (Demerol), J. Pharmacol. & Exper. Therap. 112: 306, 1954.
6. Eckenhoff, J. E.: Phenazocine, new benzomorphan narcotic analgesic, ANESTHESIOLOGY 20: 355, 1959.
7. Fraser, H. F., and Isbell, H.: Addiction liabilities of *dl*-2′-hydroxy-5,9-dimethyl-2-(2 phenethyl)-6,7 benzmorphan HBr (NIH-7519) and *l*-3-hydroxy-N-phenacylmorphinan methane sulfonate (NIH-7525), Addendum to Minutes of the Twentieth Meeting of the Committee on Drug Addiction and Narcotics of the National Research Council.

ACUTE BARBITURATE INTOXICATION Phenobarbital 60-200 mg. kg. was administered intravenously to nephrectomized dogs. States of alkalosis or acidosis, either respiratory or metabolic were then induced experimentally and the concentration of barbiturate determined in arterial blood. An increase in *p*H was followed by an increase in the concentration of the barbiturate in the plasma, while a decrease in *p*H produced a decrease in concentration. Increase in *p*H of blood increased the ionization of the barbiturate; the ionized form of the drug was unable to pass through the cellular membrane, which explained the increase in concentration in the blood during alkalosis; a decrease in *p*H had the opposite effect upon the ionization, the penetration of the drug through the cell membrane and its concentration in the blood. Alkalosis interfered with the passage of the drug into the cellular compartment, while acidosis favored this passage into the cell. This fact was useful during treatment of barbiturate intoxication. (*Mollaret, P., and others: I. Effects of Changes in Acid-Base Equilibrium upon Distribution of Phenobarbital in Nephrectomized Dog, Rev. franç étud. clin. et biol. 4: 575 (June) 1959.*)

ACUTE BARBITURATE INTOXICATION The renal excretion of phenobarbital is investigated in dogs in whom the urine is made alkaline by the intravenous injection of either acetazolamide (Diamox) or of an hypertonic solution of bicarbonate or both. The ventilation in these dogs is maintained at a constant volume. An increase in renal excretion of phenobarbital occurs when urine is made alkaline by bicarbonate than by acetazolamide. This increase in renal excretion is due to a decrease in tubular reabsorption of the drug. That the amount of phenobarbital excreted after bicarbonate is larger than after acetazolamide is explained by the fact that the metabolic alkalosis induced by bicarbonate increases the concentration of barbiturate in the plasma, therefore increasing it in the glomerular filtrate. On the other hand, acetazolamide produces a metabolic acidosis which decreases the amount of barbiturate circulating in the blood; the glomerular filtration is also less than after bicarbonate. (*Mollaret, P., and others: Effect of Urinary Alkalosis on the Renal Excretion of Phenobarbital in Dog, Rev. franç. étud. clin et biol. 4: 661 (Sept.) 1959.*)