Reports

Drug Synergism (Potentiation) in Pain Relief in Man: Papaverine and Morphine

For the clinical evaluation of analgesics two general methods are in use: (i) One group receiving one drug is compared with a different group medicated with another drug. (ii) The patient is used as his own control, receiving both drugs on different occasions. Comments on these methods have been made by Beecher (*1*). He pointed out that method i suffers from inconsistency among patients and requires a larger series, whereas in method ii, which is employed in this laboratory, the possibility of drug interaction is present.

In recent experiments in this laboratory, papaverine was tested as an antipruritic and was compared with morphine in experimental and pathologic pruritus in man. Since both morphine and papaverine appeared to relieve pathological pruritus, and since there is reason to believe that itch and pain are mediated by the same apparatus (*2*), papaverine was compared with morphine in pathological pain. Here, unexpectedly, an example of drug interaction was observed.

In a "double-blind" experiment 69 patients with abdominal, thoracic, and major orthopedic operations were studied postoperatively to determine relief of steady wound pain, according to methods previously described (*1*). The pain was rated as "severe" or "moderate" before medication was given. Forty-five patients received morphine, 10 mg, alternating with papaverine, 50 mg, and 24 patients received morphine, 10 mg, alternating with papaverine, 100 mg. These weights refer to the salts and were contained in 1 ml of solution. The drugs were injected subcutaneously, per 70 kg of body weight. After a drug was given, the patients were visited by technicians at 45, 90, 150, 210, 270, and 330 minutes after medication.

The pain was recorded as "unchanged," "less than half gone," "more than half gone," or "disappeared." The relief reported by the patient was then rated as 0, 1, 2, and 3, respectively. Only "paired" data were evaluated—that is, data for doses of morphine and papaverine given to the same patient for the same degree of pain. The effects of the drugs on "moderate pain" and "severe pain" were examined separately.

The data were analyzed as previously described by Gravenstein and Beecher (*3*). When the pain level is controlled and correlated data are used, papaverine, 50 mg, and 100 mg, is consistently less effective than morphine, 10 mg. An analysis of variance of these data shows a significant difference in pain relief between morphine and papaverine at all times with either dose. The relief with papaverine in the 50-mg dose is that expected from a placebo (25 percent versus 30 percent). Papaverine, 100 mg, relieved 14 percent of the patients in pain. The difference in analgesic power between papaverine, 100 mg, and morphine, 10 mg, is consistently greater than the difference between papaverine, 50 mg, and morphine, 10 mg. This curious "antianalgesic" effect of the larger dose of papaverine is similar to the effect of the dextrorotatory form of iso-methadone, on which Denton and Beecher commented (*4*).

Data from all patients who received morphine or papaverine as their very first and second postoperative medication for the given pain level are presented in Table 1. In this group morphine, 10 mg, was found to be more effective when given as the second drug following papaverine than when given as the first drug—that is, preceding papaverine. For the statistical analysis of this difference, the only data used were those which were obtained from 18 patients medicated for one pain level, moderate pain. Pain relief was significantly better for all checks 45, 90, and 150 minutes after medication ($p < 0.01$ in all three checks) when morphine was given as the second drug postoperatively, following papaverine, as compared with the identical dose of morphine given as the first postoperative medication. In the group of patients with severe pain the numbers are too small for statistical analysis; however, the results corroborate the findings for moderate pain.

Papaverine has no analgesic power. The significance of this fact in view of its antipruritic effectiveness is interesting and is discussed elsewhere (*5*). Great interest attaches to the finding that in this study where the patients serve as their own control, morphine given as the very first drug postoperatively was much less effective than the identical dose of morphine given after papaverine. This cannot be explained as an effect of waning postoperative pain, since the pain level was controlled and since it has been shown (*3*) that the pain levels identified by the patients are sufficiently reliable as measurements of intensity of pain. It is conceivable that the very first pain report by a patient is different from the second. This possibility can be examined in the data of Gravenstein and Beecher (*3*). These data therefore were reevaluated, and the pain relief afforded by the first dose of morphine was compared with that afforded by a second and identical dose in the same patient given for the same degree of pain. In 24 patients there is no difference in pain relief between doses one and two. These data are presented in Table 2. The conclusion that less pain relief is obtained from morphine not preceded by papaverine therefore gains significance.

The question can be raised whether this is due to some specific effect of papaverine or whether the same phenomenon could be observed with other drugs. Data from a study of identical design as the papaverine experiment just described, in which dihydrocodeine, 30 mg, was compared with morphine, 5 mg, and

Table 1. Mean pain relief scores for 18 patients with moderate pain. Patients were given morphine, 10 mg, preceding or following papaverine, 50 mg, as the first postoperative medication.

Injection	Score		
	45 min	90 min	150 min
Morphine following papaverine	2.44	2.67	2.56
Morphine preceding papaverine	1.11	1.67	1.67
Difference	+ 1.33	+ 1.00	+ 0.89

All technical papers are published in this section. Manuscripts should be typed double-spaced and be submitted in duplicate. In length, they should be limited to the equivalent of 1200 words; this includes the space occupied by illustrative or tabular material, references and notes, and the author(s)' name(s) and affiliation(s). Illustrative material should be limited to one table *or* one figure. All explanatory notes, including acknowledgments and authorization for publication, and literature references are to be numbered consecutively, keyed into the text proper, and placed at the end of the article under the heading "References and Notes." For fuller details see "Suggestions to Contributors" in *Science* 125, 16 (4 Jan. 1957).

Table 2. Mean pain relief scores for 24 patients given two 10-mg doses of morphine.

Dose	Severe pain		Moderate pain	
	45 min	90 min	45 min	90 min
1	1.93	2.07	2.44	2.44
2	1.93	2.27	2.22	2.44
Difference	0.00	+0.20	−0.22	0.00

again with morphine, 10 mg, suggested that morphine following dihydrocodeine would be more effective than when given alone. Data on these studies are limited to few patients, not justifying statistical analysis, and can serve only as suggestive support.

So far as we have found, the material presented here is the first occasion where synergism in the relief of pathological pain in man has been clearly demonstrated with analgesic drugs. Attention must be called, however, to the related work of Macht (*6*). Macht worked on himself and two colleagues with experimental pain produced by the Martin method. He failed to use essential controls and arrived at the erroneous conclusion that papaverine is a powerful analgesic. He did report, among other things, that the analgesic effect of morphine is increased when it is combined with narcotine, a drug chemically related to papaverine.

In animals (*7*), evidence suggesting a synergism between morphine and drugs pharmacologically related to papaverine has been published. However, the literature contains no report on the interaction between morphine and papaverine in pathological pain, and no suggestion about the possible mode of interaction in this situation. Veldstra (*8*) has discussed synergism in general and has attempted to formulate possible explanations.

On the basis of our data, interaction among drugs in the experimental situation described does occur. No clue about the nature of this interaction is available.

In every experiment which utilizes patients who have received medication before being studied as to their response to an experimental drug, there is the possibility of drug interactions. While investigators using patients with chronic pain have certain advantages, since their experimental design is not limited by waning pain, they are nevertheless confronted by this interaction problem. Patients with chronic pain usually receive pain-relieving opiates and frequently in relatively large dosages while they are not under investigation (*10*). Thus the use of patients with chronic pain creates difficulties in evaluating the "priming" effect of a drug given for the very first time. On the other hand, when patients with postoperative pain are used, the effect of preceding anesthetics cannot be easily evaluated. The same influence can conceivably affect data on respiratory and other side effects when patients with chronic pain are used. It is not suggested that such possible drug interaction completely invalidates the results, but it is emphasized that data obtained under such conditions can be representative only of the conditions under which they were obtained. A complete assessment of the clinical characteristics of a drug therefore is possible only after the drug has been studied under various conditions with different methods (*10*).

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Current Strontium-90 Level in Diet in United States

Knowledge of the concentration of strontium-90 in the diet permits calculation of the equilibrium level in the human skeleton (*1*). This report (*2*) describes measurements on approximately 100 food samples. Samples of the important calcium (and therefore strontium-90), sources—that is, milk, vegetables, cereals, and tap water—are included.

Each vegetable sample (Table 1) represents 10 packages (about 3 kg) of frozen food, which in turn represent a production run at a food plant. The cereals (Table 2) were 200-g aliquots of a dozen boxes of the most common varieties. Liquid milk samples (Table 3) came mainly from cows that had grazed on unplowed land. Meat, eggs, and fish were omitted because their con-

Table 1. Strontium-90 in common vegetables from various locations, 1956–57.

Sample	Date	SU
Maine		
Peas	8/56	21.3
Western New York State		
Beans, cut green	8/56	20.2
Beans, cut green	9/56	18.4
Beans, cut green	9/56	8.6
Beans, wax	7/57	13.6
Beans, wax	8/57	11.3
Cauliflower	10/56	**9.1**
Corn	9/56	28.4
Spinach	6/57	1.8
Av.		13.9
Eastern Pennsylvania, New Jersey, Long Island		
Asparagus	6/56	1.2
Asparagus	5/57	1.1
Beans, cut green	12/56	4.6
Beans, cut green	9/56	8.0
Beans, lima	9/56	6.6
Cauliflower	fall/56	8.1
Peas	6/57	10.0
Potatoes, sweet	?/57	13.3
Potatoes, white	?/57	6.1
Squash	fall/56	11.5
Av.		7.3
Eastern Maryland, Delaware		
Asparagus	10/56	1.7
Beans, lima	?/56	2.9
Beans, lima	9/56	8.4
Broccoli	10/56	4.7
Broccoli	10/56	6.7
Broccoli	10/56	8.5
Corn	12/56	3.6
Peas	12/56	1.3
Av.		4.7
Tennessee		
Okra	7/57	18.0
Spinach	?	6.1
Spinach	4/57	1.2
Turnip greens	5/57	21.3
Turnip greens	2/56	7.8
Av.		10.9
Minnesota		
Corn	9/56	1.6
Peas	6/56	5.8
Av.		3.7
Washington, Idaho, Oregon		
Beans, lima	9/55	6.3
Broccoli	9/56	3.7
Corn	8/57	2.1
Peas	6/57	4.8
Peas	7/56	7.8
Peas	6/56	3.0
Potatoes	?/57	8.7
Squash	9/56	3.1
Squash	10/56	3.7
Av.		4.8
California		
Asparagus	4/57	1.8
Beans, lima	5/57	4.6
Beans, lima	9/55	10.0
Beans, lima	9/56	4.3
Broccoli	4/57	4.0
Brussels sprouts	10/56	12.0
Brussels sprouts	9/56	4.3
Brussels sprouts	12/56	2.5
Brussels sprouts	11/56	1.1
Cauliflower	10/56	28.5
Cauliflower	4/57	22.5
Spinach	3/57	13.9
Spinach	3/57	9.1
Spinach	3/57	9.5
Av.		8.5
Av. for all vegetable samples		9.4
Av. for peas, beans, corn, and potatoes		8.7

Table 2. Strontium-90 in common cereals from various locations, 1956–57.

Sample and location	Date	SU
Wheat (New York)	?/56	22.8
Wheat (Washington)	55/56	9.1
Bran (Michigan)	summer/57	8.6
Flour (Illinois)	7/56	6.7
Rice (Unknown)	?/56	4.0
Wheat (Unknown)	?/56	37.5
Oatmeal (Unknown)	?/56	5.7
Av. for all cereals		13.5