45 to 60 minutes (50 minutes for aspirin alone). Also, no practical difference was found in the median duration of pain relief that ranged between four and six hours (five hours for aspirin alone).

Except for sedation, all of the side effects for which we made specific inquiry or which the patients volunteered occurred at a frequency nearly equal for all ten drugs. The barbiturate sedative, pentobarbital, and the phenothiazine tranquilizer, promazine, produced a significant increase in sedation over the placebo (Table 2). The codeine, oxycodone, pentazocine, and propoxyphene combinations also produced increases in sedative effect when compared to placebo or aspirin alone, but these were not at a statistically significant level.

Comment

The problem of evaluating the effectiveness of analgesic combinations is made very complex by the fact that essentially all marketed products of this kind contain one or more of the analgesic-antipyretic type drugs, ie, aspirin, acetaminophen, or phenacetin. Since each of these drugs has well-established analgesic activity, the question is not whether the combinations will relieve pain; it is assumed that they will. The primary question is whether the addition of sedatives, stimulants, tranquilizers, or other analgesic agents of less well-established effectiveness really adds anything of value for the patient. Do these additives actually increase pain relief, or do they simply provide a vehicle for sales promotion and in the process subject the patient to increased cost, increased side effects, and increased risk of drug sensitization reactions?

Analgesic Combinations of No Significant Value.—As in our previous study,[1] aspirin again demonstrated a significant advantage in pain relief over placebo. The addition of the amount of caffeine equivalent to that in about one-half cup of coffee clearly added nothing to analgesic activity. A number of controlled evaluations of caffeine plus aspirin and phenacetin (APC) have also shown no superiority of this combination to aspirin alone for the relief of headache, postpartum pain, and acute and chronic pain problems of varying etiologies.[1]

Thirty-two milligrams of caffeine plus 400 mg of aspirin is the Anacin formula. Over-the-counter products such as Excedrin, Vanquish, Empirin compound, and APC compounds are mixtures of caffeine plus a lesser dose of aspirin (195 to 227 mg) with the deficit in aspirin made up by the addition of other analgesic-antipyretics such as phenacetin, acteminophen, or salicylamide. Although each of these preparations is several times as expensive as generic aspirin, there is no acceptable evidence that any provides the patient with more effective pain therapy. The widespread popularity of these preparations is clearly a tribute to the effective techniques of Madison Avenue.

The appealing presumption that allaying anxiety and apprehension will blunt pain perception has led to the marketing of a variety of combination analgesic preparations containing barbiturates or tranquilizers such as Darvo-tran, Equagesic, Fiorinal, Phenaphen, and Tranco-gesic. No evidence, however, supports this concept, and the work of Dundee and Moore[4] has seriously challenged it. In our study, the barbiturate and the tranquilizer produced the expected side effect of sedation, but they added nothing to analgesic effect. Certainly, if a patient presents a valid clinical indication for sedatives or tranquilizers, they should be employed, but for their own sake, not with the idea that they will contribute to pain relief. In view of the many potential hazards associated with indiscriminate use of barbiturates and tranquilizers, the marketing of such drugs in combination products directed primarily towards analgesia must be seriously questioned.

In our earlier study, ethoheptazine was essentially identical to placebo in analgesic effect.[1] In the present study, its combination with aspirin produces an identical analgesic effect to aspirin alone. There seems to be no valid indication for prescribing this agent either alone as Zactane, in combination with aspirin as Zactirin, or in combination with aspirin and meprobamate as Equagesic.

Propoxyphene hydrochloride used alone in our initial study showed a slight but insignificant advantage over placebo, and it was significantly inferior to aspirin.[1] Propoxyphene napsylate (Darvon-N) has been introduced as a drug that has the same analgesic effect as the hydrochloride form but allows more stable tablet formulation with aspirin. In this study, the propoxyphene napsylate combination was ranked higher than aspirin alone by all means of analysis, but in no instance was the difference statistically significant. It consistently ranked lower than codeine plus aspirin, and by all three methods of analysis, this difference was statistically significant. Thus, the therapeutic value of propoxyphene remains equivocal. The conflicting evidence in the literature regarding the effectiveness of propoxyphene, both alone and in combination, has been extensively reviewed by Beaver[5] and by Miller and associates.[6] Unquestionably, propoxyphene and its combinations are exceedingly popular prescription items, but it remains to be clearly established that this popularity reflects true analgesic effectiveness.

Effective Analgesic Combinations.—Three combinations—aspirin plus 65 mg of codeine, aspirin plus 9.76 mg of oxycodone, and aspirin plus 25 mg of pentazocine hydrochloride—showed a significant superiority in analgesic effect over simple aspirin and over all the other combinations tested. Codeine and pentazocine hydrochloride when used alone had shown a significant superiority over placebo in our earlier study.[1] The side effects of these three combinations were equally tolerable in the present single-dose study. It should be emphasized, however, that we employed only a 25-mg dose of pentazocine hydrochloride compared to the marketed form containing 50 mg. In our earlier study, we had found the 50-mg dose of pentazocine hydrochloride to produce sufficient gastrointestinal and central-nervous-system side effects to limit seriously its usefulness for the ambulatory outpatient. Oxycodone presents the very distressing hazard of increased addiction potential when compared to other available oral agents used for relief of mild to moderate pain. The serious addiction problems that may be associated with oxycodone were stressed ten years ago in the comprehensive review of Bloomquist.[7] He presented evidence that addiction liability was at least