

3. Physicians in general are very sensitive to the issue of the dependence liability of narcotic drugs. In many situations, this concern has been far in excess of what was warranted by any realistic evaluation of the likelihood of producing iatrogenic narcotic dependence. This anxiety extended to codeine, which in fact has extremely low abuse liability when used in any medically responsible way. Propoxyphene was probably originally perceived by physicians as a non-narcotic substitute for codeine and propoxyphene-containing combinations were marketed which correspond to all of the existing codeine-containing combinations. Until the beginning of 1977, propoxyphene was an unscheduled drug, which implied that it was safer than codeine and its combinations in terms of dependence liability and also made for more convenient prescribing and dispensing.

4. Although the most appropriate and, in fact, most popular use of both propoxyphene and codeine is in combination with the antipyretic-analgesics, there are occasional pain problems in which the physician can quite legitimately want to prescribe either propoxyphene or codeine alone. These include situations where there is an allergy or contraindication to the use of aspirin and acetaminophen. It would also include situations in which the practitioner wished to use a mild analgesic with no associated antipyretic effect.

5. There is, in fact, good evidence that combinations of narcotics with antipyretic-analgesics produce more analgesia than the antipyretic-analgesic given alone, and this increment of analgesic effect may often make the difference between unsatisfactory and satisfactory pain relief for particular patients. This increment of analgesia is often associated with very little increase in adverse effects and therefore constitutes a very real benefit for the patient. To my way of thinking, this constitutes the major acceptable rationale for the use of propoxyphene. It should be noted that this rationale does not apply if the prescribed dose of a combination contains substantially less than the usual full therapeutic dose of the antipyretic-analgesic constituent.

6. Controlled clinical trials of analgesics invariably compare the average responses of groups of patients to the various treatments. While the average relative performance of various analgesics is the best predictor of how the generality of patients with pain will respond, individual patients may, for reasons which we simply do not currently understand, derive a better analgesic effect from a drug which on the average is less effective than another. Controlled clinical trials of analgesics are not currently designed to explore this phenomenon, and the determination of the optimal analgesic regimen for any given patient must ultimately be based on the empirical observation of the effect of various analgesics in that patient. It is therefore in the patient's interest to have as wide a variety of effective analgesics available as possible, even though some of these may on the average be less efficacious than others.

7. Virtually all controlled clinical trials of analgesics, including propoxyphene, have involved comparison of single administrations of various analgesics; however, in the practice of medicine, most patients receive not a single dose but repetitive doses of analgesic drugs for the control of their pain. While up to this time, the results of single administration studies have seemed to constitute reasonably accurate predictors of the relative performance of analgesics when administered repetitively (if one keeps in mind the impact of the development of tolerance to narcotics), it is conceivable that repeated administration of some analgesics results in a higher level of efficacy than would be predicted on the basis of single-dose administration. Propoxyphene has a substantially longer half-life in the blood than other mild analgesics such as codeine, acetaminophen or aspirin. When administered every four to six hours, as mild analgesics usually are, there will be a significantly greater cumulation of propoxyphene levels than with alternative mild analgesics [Waife et al., 1975]. We do not currently understand the relationship between the blood level of an analgesic and the analgesic effect experienced by the patient, but a plausible argument can be made on the basis of blood level data that one might expect greater analgesia after a few repeated doses of propoxyphene relative to alternative mild analgesics than is, in fact, seen in single administration studies. Unfortunately, few analgesic studies of repeated dosing have been done to examine this hypothesis, and those that have been done are difficult to interpret [Gruber, 1977; Young, 1978]. It is, therefore possible that practitioners empirically find that propoxyphene products are more effective in regular clinical use (i.e., when administered in repeated doses) than would be predicted on the basis of the controlled clinical trials which involve single administrations of test medication.