

because any attempt to assess the benefit/risk ratio for propoxyphene must necessarily take into account the known adverse effects of alternative mild analgesics.

I am concerned that there is expressed or implicit in certain recent discussions of the usefulness of propoxyphene the assumption that alternative mild analgesics are more or less devoid of adverse effects and are in some general sense "safe." This is clearly not the case, and I can speak to this on the basis of having worked extensively in this field since about 1963.

Aspirin can be lethal, not only in overdose, but also at usual therapeutic dose levels in individuals who are hypersensitive to the drug or who experience massive gastrointestinal bleeding or other bleeding associated with aspirin's effects on blood coagulation.

Until recently, acetaminophen has been felt to be singularly free of adverse effects, and this is probably still true at conservative therapeutic doses. However, it is becoming increasingly apparent that overdose with acetaminophen can produce massive hepatic injury resulting in death, and in Great Britain, where the use of acetaminophen is even more widespread than in the United States, it has been estimated that acetaminophen poisoning is now a leading cause of acute hepatic failure.

Chronic use of phenacetin-containing analgesic mixtures has been associated with potentially fatal renal damage, and the Food and Drug Administration's Over-the-Counter Analgesic Review Panel has recommended removing phenacetin from the over-the-counter market for that reason.

The relative contribution of phenacetin as opposed to other mild analgesics in the development of this syndrome is a subject of debate, and it is unclear whether acetaminophen may not also produce serious renal injury when abused in combination products for prolonged periods of time.

The incidence of adverse reactions to codeine in usual therapeutic doses is low. The drug can produce a typical narcotic overdose syndrome and death, but the reported incidence of this appears low relative to codeine's extremely wide clinical use.

Codeine may be safer in this respect than equi-analgesic amounts of propoxyphene, although further study would have to be done to establish this. Codeine has narcotic-type dependence liability, although, like propoxyphene, the incidence of this problem is very low considering the wide therapeutic use of codeine-containing combinations.

Oral pentazocine is an effective mild analgesic more or less comparable to codeine in potency. Because the drug is a mixed agonist/antagonist rather than a classic narcotic, there is reason to believe that lethal overdose would be even less of a problem than with either propoxyphene or codeine. However, pentazocine seems to produce a somewhat higher incidence of unpleasant adverse effects at usual therapeutic doses than equi-effective doses of codeine, and pentazocine occasionally produces frank psychotomimetic reactions which may be very disturbing to the patient.

While pentazocine has less abuse liability than regular narcotics, deliberate self-administration of the drug for its mood effects undoubtedly occurs, and the Food and Drug Administration's Controlled