

incidence of adverse effects with these doses of propoxyphene than with a placebo [Baptisti et al., 1971; Gruber et al., 1971; Gruber, 1977; Moertel et al., 1972; Moertel et al., 1974; Sunshine et al., 1971, Wang, 1974]. When large enough groups of ambulatory patients are studied to demonstrate any difference in terms of adverse effects between therapeutic doses of propoxyphene and placebo, the adverse effects consist of a very low incidence of nausea and drowsiness [Winter et al., 1973]. Considering the extraordinarily large use of propoxyphene products, there is extremely little in the entire literature which indicates that the drug in recommended therapeutic doses can produce any serious adverse effects, and even minor adverse effects seem to occur only infrequently.

Toxicity of Propoxyphene in Overdose: As noted above and as is amply attested to by numerous individual case reports and several epidemiologic studies [McBay and Hudson, 1975; Finkle et al., 1976; Sturner and Garriott, 1973] propoxyphene, like any other narcotic, can be lethal in overdose. Unlike most other narcotics, the propoxyphene overdose syndrome is complicated by a high incidence of convulsions, which complicates its treatment.

Dependence Liability of Propoxyphene: Since propoxyphene is pharmacologically a narcotic, it has some ability to produce drug dependence of the narcotic type, and this has been recognized since before the drug was marketed [Fraser, 1960]. Propoxyphene can produce the classic triad of psychic dependence, physical dependence and tolerance, and, in those patients who are able to tolerate high enough doses to result in substantial physical dependence, a narcotic-type abstinence syndrome has been observed on withdrawal. "Street abuse" of the drug clearly occurs, as does dependence secondary to therapeutic use [Chambers et al., 1971; Maletzky, 1974]. However, in my opinion, relative to the extremely wide use of propoxyphene, the demonstrated incidence of serious deliberate abuse of the drug to experience its mood effects is not great and is certainly substantially less than is the case with potent narcotics.

ADVERSE EFFECTS OF ALTERNATIVE MILD ANALGESICS

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.

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