

effect of a narcotic and an antipyretic-analgesic given together is often significantly greater than the analgesia achieved by doubling the dose of either drug administered alone.

Furthermore, antipyretic-analgesics probably exhibit a ceiling of analgesic effect at about the usually used doses—650 to 1,000 milligrams—and the usefulness of higher doses may also be limited by increased incidence of adverse effects and serious cumulative toxicity.

Increasing doses of codeine, propoxyphene and other narcotics are associated with a progressively increasing incidence and severity of gastrointestinal and central nervous system side effects and increased risk of drug dependence.

The problem of providing adequate pain relief in the face of the above noted limitations of currently available analgesics may sometimes be circumvented by combining an optimal dose of an antipyretic-analgesic with an orally effective narcotic in a modest dose which is reasonably safe and well-tolerated.

Older relevant studies for both codeine and propoxyphene combinations are cited in my 1966 review. There are a few more recent studies which appear to demonstrate a significant increase in analgesic effect produced by the addition of propoxyphene to acetaminophen.

Dr. Moertel and his associates showed a small increase in the effect of aspirin 650 milligrams produced by the addition of propoxyphene napsylate 100 milligrams, but the difference was not statistically significant.

Now I would like to briefly touch on the adverse effects of propoxyphene. There are really three types and it is important to think clearly about this issue, to keep these types of adverse effects separate in one's mind, because they have different implications in relation to drug abuse.

These three types are adverse effects seen at recommended therapeutic doses; adverse effects seen in overdose and the issue of drug dependence on propoxyphene.

In relation to adverse effects of propoxyphene at therapeutic dose levels or recommended dose levels, which is propoxyphene hydrochloride 65 milligrams or propoxyphene napsylate 100 milligrams, propoxyphene produces an extremely low level of adverse effects.

As a matter of fact, most studies are unable to demonstrate a significantly higher incidence of adverse effects with these doses of propoxyphene than with a placebo.

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.

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.

Now, concerning the toxicity of propoxyphene in overdose: As noted above and as is amply attested to by numerous individual case reports and several epidemiologic studies; propoxyphene, like any