

*Propoxyphene vs. placebo:* In addition to the studies cited in my 1966 review, several additional controlled analgesic studies have confirmed that that 65 mg dose of propoxyphene hydrochloride or the equivalent 100 mg dose of propoxyphene napsylate is statistically significantly superior to placebo in relieving post-operative and trauma pain [Sunshine *et al.*, 1970; Sunshine *et al.*, 1971; Young, 1978], postpartum uterine cramping [Baptisti *et al.*, 1971; Gruber *et al.*, 1971], postpartum episiotomy pain [Berry *et al.*, 1975], pain subsequent to oral surgery in outpatients [Winter *et al.*, 1973] and chronic pain of mixed etiology [Wang, 1974].

A couple of studies have also succeeded in demonstrating a statistically significant difference between placebo and either 32 mg propoxyphene hydrochloride [Sunshine and Kantor, 1966] or the equivalent 50 mg dose of propoxyphene napsylate [Sunshine *et al.*, 1971] but these obviously represent threshold or marginally effective doses of propoxyphene, the analgesic effect of which doses can only very rarely be measured in even the most sensitive analgesic assays.

*Propoxyphene dose-response curve:* Several additional studies have also confirmed the existence of a significant positive slope for the dose-response curve of propoxyphene using various graded doses of the hydrochloride salt from 32 to 200 mg and/or the equivalent doses of the napsylate salt of 50 to 300 mg [Sunshine *et al.*, 1970; Sunshine *et al.*, 1971; Sunshine *et al.*, 1978; Baptisti *et al.*, 1971; Gruber *et al.*, 1971].

In my opinion, the above cited studies, alone and in conjunction with those I have previously reviewed [Beaver, 1966], prove beyond any doubt that propoxyphene hydrochloride in doses of 65 mg and higher or propoxyphene napsylate in doses of 100 mg and higher have some analgesic activity in patients with pain of a wide variety of etiologies. Indeed, since propoxyphene produces narcotic-like responses in all pharmacologic tests with which I am familiar, can produce drug dependence of the classic narcotic type and produces an overdose syndrome characteristic of narcotics, I would find it impossible to explain how the drug could possibly *not* be an effective analgesic at some dose level.

Yet, several double-blind studies which ostensibly meet the minimum criteria for a controlled clinical trial of analgesic efficacy have not demonstrated a statistically significant difference between the analgesic effect of 65 mg of propoxyphene hydrochloride and a placebo treatment. There are a number of possible explanations for this state of affairs, and most of them hinge on an understanding of the concept of assay sensitivity as it applies to clinical trials of analgesics. Because of the multiplicity of known and unknown variables which affect the course of a patient's pain and its response to analgesics, and because there is no satisfactory measure of a patient's pain other than the patient's own subjective reports of this experience, analgesic clinical trials vary greatly in their ability to demonstrate the efficacy of even known effective analgesics: i.e., they vary widely in their assay sensitivity. Therefore, unless an analgesic clinical trial contains an internal measure of assay sensitivity that demonstrates that the trial is capable of measuring an analgesic effect of the magnitude anticipated to result from administration of the test drug (e.g., propoxyphene), a negative finding concerning the efficacy of the test drug has no meaning [Modell and Houde, 1958; Houde *et al.* 1965, 1966]. Most of the clinical trials which did not distinguish propoxyphene from placebo either did not contain a measure of assay sensitivity or were clearly insensitive in that they also could not distinguish known analgesics (e.g., codeine or aspirin) from placebo. Furthermore, since single doses of propoxyphene 65 mg are almost certainly less effective than the usually used doses of the mild analgesic standards, codeine 65 mg, aspirin 650 mg, acetaminophen 650 mg or 2 APC tablets, an oral mild analgesic study may have adequate assay sensitivity to demonstrate a statistically significant difference between one or more of these standards and the placebo, while still not being able to identify the less substantial analgesic effect of propoxyphene 68 mg as statistically significant [Moertle *et al.*, 1972].

Other confounding factors in the interpretation of mild analgesic clinical trials include the fact that some types of pain may respond much more dramatically to peripherally-acting analgesics (e.g., aspirin and acetaminophen) than to centrally-acting narcotics (e.g., codeine and propoxyphene) [Cooper and Beaver, 1976; Bloomfield *et al.*, 1976] and the fact that patients who have received narcotics develop tolerance to these drugs and will subsequently experience more pain relief from aspirin or acetaminophen relative to codeine or propoxyphene than narcotic-naïve subjects [Houde *et al.*, 1965, 1966].