HUMAN PHARMACOLOGY

After the administration of a single dose of propoxyphene in man, plasma propoxyphene concentrations reach peak levels around 2 hours and decrease thereafter, with a half-life of 6 to 12 hours. Peak plasma concentrations of norpropoxyphene are noted within a half to one hour following peak propoxyphene concentrations. The half-life of norpropoxyphene is 30 to 36 hours.

In human subjects given a loading dose of propoxyphene (300 mg napsylate [N] or 195 mg hydrochloride [HCl]) followed by 100 mg N or 65 mg HCl at four-hour intervals for 31 doses (5 days), peak plasma concentrations of norpropoxyphene between 1.0 and 1.2 micrograms/ml (with the hydrochloride) and between 0.75 and 1.0 micrograms/ml (with the napsylate) were noted at about 120 hours.

Single daily doses of 125 mg norpropoxyphene administered to humans for 7 days resulted in peak plasma concentrations of norpropoxyphene of 0.25 to 0.55 micrograms/ml and did not elicit any overt adverse effect.

ANIMAL PHARMACOLOGY AND TOXICOLOGY

In acute toxicity studies the oral LD_{50} values for propoxyphene HCl in mouse, rat, and dog are 282, 230, and 100 mg/kg, respectively, and are approximately equivalent to 35, 29, and 12 times the maximum recommended dose of 8 mg/kg/day for humans. Propoxyphene napsylate in acute doses is about one-half as toxic as the hydrochloride salt, especially in dogs, due to the more gradual absorption of the napsylate salt. Animals given lethal doses of propoxyphene die following clonic and tonic convulsions.

Acute toxicity studies in rodents reveal that the LD_{50} for propoxyphene is lower than that for norpropoxyphene, and in the rat this difference is of the order 4 to 5 times (on a molecular basis). The acute lethality of norpropoxyphene in mice is not reduced by naloxone.

Dogs tolerated large daily oral doses of either the hydrochloride or napsylate salt of propoxyphene (equivalent to 35–70 times the maximal human dose) for as long as two years. In a few dogs some fatty change, usually of slight degree, was noted in the liver.

The oral administration in dogs of increasing doses of propoxyphene, beginning with 20 mg/kg/day and increasing to 60 mg/kg/day in 5 to 15 mg/kg increments at intervals of three to four days over a period of 17 days, resulted in maximal plasma norpropoxyphene concentrations of 16–20 micrograms/ml, at which time propoxyphene concentrations were 2 to 3 micrograms/ml. (It should be recalled that the starting dose of 20 mg/kg/day is 2½ times the recommended human dose.) The dogs remained ambulatory on this enormous dosage regimen, free of any evidence of circulatory impairment, although they lost weight due to anorexia and occasional emesis, noted usually only after the first incremental dose, along with sedation and tremor. Tissue analyses for propoxyphene and norpropoxyphene indicated higher concentrations in plasma than in the following tissues: brain, heart, kidney, liver, lung. Highest concentrations of both compounds were observed in the liver. Slightly increased serum glutamate pyruvate transaminase and alkaline phosphatase values were observed, but glucose, bilirubin, creatinine, or BUN remained unchanged.

Animal studies indicate that norpropoxyphene has little analgesic ("opioid") property (½ to 1/40 that of propoxyphene, depending on the assay method utilized), while its local anesthetic properties are two to three times that of the parent compound. Opiate effects are antagonized by naloxone, nalorphine, and levallorphan, whereas local anesthetic effects are not.

The toxicological effects of propoxyphene relate to its analgesic (opioid) properties, which are shared to a much lesser degree by norpropoxyphene, and are readily reversed by antagonists such as naloxone. The local anesthetic properties, shared by both propoxyphene and norpropoxyphene, but to a greater extent by norpropoxyphene, lack specific antagonists. Since (1) both propoxyphene and norpropoxyphene possess local anesthetic effects not reversible by specific antagonists and (2) in view of the higher plasma and tissue concentrations of norpropoxyphene attained during chronic propoxyphene administration, as well as (3) the relatively long half-life of norpropoxyphene, the possible role of the local anesthetic properties of the parent compound and its principal metabolite in propoxyphene-induced toxicity merits further study.

The local anesthetic effects of norpropoxyphene have been compared with standard local anesthetic agents ,such as dibucaine, cocaine, and lidocaine, by