

Bon Secours Richmond
Pharmacy & Therapeutics Committee
Propoxyphene

Dear Professional Staff,

Propoxyphene and combination products containing propxoxyphene are not recommended for use in pain management due to limited potency and accumulation of toxic metabolites (norpropoxyphene $T_{1/2}$ 39 hours, seizures, cardiac toxicity). Propoxyphene and norpropoxyphene have potent local anesthetic properties. Propoxyphene has a low therapeutic index and deaths have been reported with its use. Propoxyphene appears to display non-linear kinetics; steady state serum levels are 5-7 higher than those obtained after the first dose. Propoxyphene and norpropoxyphene are not removed by dialysis and naloxone is ineffective in treating cardiac toxicity. Alkalinization of the urine decreases propoxyphene excretion by 95%.

Toxicity

Hum Toxicol. 1984 Aug;3 Suppl:175S-185S. Related Articles,
Dextropropoxyphene deaths: coroner's report.
Whittington RM.

Dextropropoxyphene has been increasingly prescribed as an analgesic in the UK, chiefly in the form of Distalgesic (dextropropoxyphene hydrochloride 32.5 mg and paracetamol 325 mg per tablet). After reports of sudden deaths from the misuse of this combination, prescribing is declining. Distalgesic remains the most common cause of fatal drug overdose in the West Midlands, UK. The 1983 Birmingham inquests are compared with those from the year 1976 to 1979. In comparison with other drug fatalities, death characteristically occurs rapidly, as little as 1 h after ingestion and usually before hospital treatment can be initiated. Toxicity is increased by alcohol which is also extensively abused. The fatal dose may be as small as 15 tablets or possibly less. Many victims are young and some never intended to take their life. Convulsions and respiratory failure precede death. The elderly and respiratory cripples may be more vulnerable to accidental death. Evidence suggests a liability to dependence or even addiction with dextropropoxyphene.

South Med J. 1977 Aug;70(8):938-42. Related Articles, Links
Fatal poisoning with propxoxyphene: report from 100 consecutive cases.
Hudson P, Barringer M, McBay AJ.

The first 100 deaths caused by propoxyphene and recorded by the Chief Medical Examiner of North Carolina were studied. Victims ranged evenly in age from the second to the seventh decade. Over 65% were suicides with a female to male ratio of 2:1. Blood propoxyphene concentrations of 0.2 mg/dl were fatal, representing rapid ingestion of approximately ten capsules. In North Carolina, deaths due to propoxyphene have increased from five in 1969 to 49 in 1975. Raising physician-awareness of propoxyphene's toxicity and placing the drug in Schedule II are two of the author's recommendations for reducing the number of propoxyphene deaths.

Clin Pharmacol Ther. 1982 Feb;31(2):157-67. Related Articles,
Propoxyphene and norpropoxyphene kinetics after single and repeated doses of propoxyphene.
Inturrisi CE, Colburn WA, Verebey K, Dayton HE, Woody GE, O'Brien CP.

Plasma concentrations of propoxyphene (P) and its pharmacologically active metabolite norpropoxyphene (NP) were determined in normal subjects after single 130-mg oral doses and during and after 13 consecutive oral doses of 130 mg P, and in former heroin addicts who were maintained on 900 to 1200 mg of P per day. The data were analyzed using a first-pass elimination pharmacokinetic model. Both P and NP cumulated during repeated dosing to levels 5 to 7 times those after the first dose. In contrast, "maintenance" patients exhibited steady-state trough plasma NP cumulation that exceeded that of P by a factor of 13. Several changes in P and NP kinetics occurred during repeated dosing with P to the normal subjects: P clearance decreased from 994 to 508 ml/min, NP clearance decreased from 454 to 2210 ml/min, P half-life ($t_{1/2}$) increased from 3.3 to 11.8 hr, NP $t_{1/2}$ increased from 6.1 to 39.2 hr, and area under the concentration time curves for P and NP were doubled. These changes in kinetics during repeated dosing resulted in more extensive accumulation of P and NP than would be predicted from the single-dose kinetic profile. Changes in the extent of first-pass elimination of P result in variability in plasma P and NP that may contribute to P-induced toxicity.

Clin Pharmacol Ther. 1980 Apr;27(4):508-14. Related Articles,
Effect of hemodialysis on propoxyphene and norpropoxyphene concentrations in blood of anephric patients.
Giacomini KM, Gibson TP, Levy G.

Our purpose was to determine whole-blood hemodialysis clearances and the effect of hemodialysis on blood propoxyphene concentrations and of its major metabolite, norpropoxyphene, in anephric patients under apparent steady-state conditions with respect to propoxyphene. Propoxyphene hydrochloride 130 mg was given orally every 8 hr for 7 doses to 4 patients. Blood propoxyphene and norpropoxyphene levels were determined repeatedly during the sixth dosing interval (before hemodialysis) and during the seventh dosing interval (during hemodialysis). There were no statistically significant differences in the areas under the blood level/time curves of propoxyphene and norpropoxyphene during the sixth and seventh dosing intervals, indicating that hemodialysis contributes negligibly to their total clearance from the body. The low hemodialysis clearances of propoxyphene and norpropoxyphene were confirmed by direct *in vivo* determination of their hemodialyzer extraction ratios. Propoxyphene produces much higher propoxyphene plasma levels and higher as well as more persistent norpropoxyphene plasma levels in anephric patients than in normal subjects. In view of their substantive cumulation during repeated propoxyphene administration, their central nervous system and cardiac toxicity at high concentrations, their low hemodialysis clearance, and the apparent sensitivity of patients with renal failure to narcotics, propoxyphene should be used cautiously in anephric patients.

J Pharmacol Exp Ther. 1977 Jan;200(1):245-53. Related Articles,
Propoxyphene and norpropoxyphene: pharmacologic and toxic effects in animals.
Nickander R, Smits SE, Steinberg MI.

alpha-d-Propoxyphene and its principle metabolite, alpha-d-norpropoxyphene, were compared pharmacologically to establish their relative opioid profiles as defined by naloxone reversal. Propoxyphene exhibited opioid activity in the following tests: mouse abdominal constriction and rat tail heat analgesic tests, inhibition of the twitch of the guinea-pig ileum and acute lethality in rodents. Norpropoxyphene also showed opioid activity in the rat tail heat and guinea-pig ileum tests, but exhibited nonopioid activity in the mouse abdominal constriction and acute toxicity studies. Jumping in mice, precipitated by naloxone, suggests the following order for liability to produce physical dependence after repeated administration: morphine greater than codeine greater than propoxyphene greater than norpropoxyphene approximately saline. Propoxyphene and norpropoxyphene depressed axonal conduction in isolated peripheral nerve and were comparable in potency to standard local anesthetic agents. The nonopioid actions of norpropoxyphene might be due in part to its local anesthetic properties.

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