In this 9 week crossover study each subject received 3 oral doses of *d*-propoxyphene HCl (210, 420 and 600 mg), 3 oral doses of *d*-propoxyphene napsylate (310, 620 and 700 mg), 2 subcutaneous doses of morphine, and a placebo in random order at weekly intervals. Blood samples of 5 or 10 ml were drawn by venipuncture into heparinized tubes 1/2 hour before drug administration and after drug at 1/2 hour, 1, 2, 3, 5, 12 and 24 hours. Plasma was immediately separated and frozen until analyzed. Plasma samples were also collected from one subject approximately every other day (at 2 hours post oral drug) during substitution of propoxyphene napsylate, 300 mg p.o. q.i.d., for morphine, 15 mg subcutaneously q.i.d. The substitution period was 21 days followed by 10 days of abrupt withdrawal (under blind conditions).

Samples were analyzed for plasma concentrations of propoxyphene, norpropoxyphene and cyclic dinorpropoxyphene by the gas chromatographic method of Nash *et al.*[18] who assisted in setting up the procedure.

Mean plasma propoxyphene concentrations are shown in Fig. 19. There was a significant positive correlation of these values (and also mean norpropoxyphene levels) with mean decrease in pupillary diameter, with correlation coefficient equal to 0.85. Propoxyphene HCl was somewhat more rapidly absorbed than propoxyphene napsylate, giving significantly greater propoxyphene concentrations in the first 2 hours after drug administration and showing peak mean levels at 2 hours compared to 3 hours for the napsylate. Peak mean plasma propoxyphene levels were slightly greater for the HCl than the napsylate in the low and middle pairs of doses, which were approximately equimoler in propoxyphene for the 2 preparations. However, in the high doses mean propoxyphene levels were approximately equal for the 2 salts, even though the napsylate dose was lower than the HCl dose in this pair. Propoxyphene napsylate showed a linear dose response relationship in peak mean propoxyphene levels. However, propoxyphene hydrochloride also showed a significant quadratic relationship with peak mean propoxyphene levels approximately the same for the middle and high doses. After 2 hours post-drug only a linear dose response relationship was seen in mean propoxyphene levels. This could indicate a dose-related difference in absorption of propoxyphene hydrochloride or, with a small n of 5, it could be a random statistical anomaly. Mean plasma propoxyphene values found after the largest propoxyphene doses of both salts were in the range of 400-500 ng/ml, which may represent near maximum non-toxic plasma levels in non-tolerant subjects.

Peak norpropoxyphene levels were 10 to 75% greater than propoxyphene levels and occurred 2 to 6 hours later. The dose response relationships were not as clearly defined as for the propoxyphene levels. Norpropoxyphene values in the order of 50 ng/ml were seen consistently 7 days after