No response to orally administered d-propoxyphene napsylate was greater than that observed with 10 mg of subcutaneous morphine (Fig. 1). For this reason, valid relative potencies could not be obtained using morphine (10 and 20 mg) as a reference drug. Potency estimates were then calculated between the d-propoxyphene napsylate and d-propoxyphene hydrochloride using the responses to the two lower doses of the d-propoxyphene hydrochloride as a standard. A valid relative potency estimate on pupils of 1.5 was obtained which would be expected for the two salts on the basis of equal base content. A tendency for the salt of the napsylate to be less potent was indicated by the various scale scores (Fig. 1); however, because of the wide confidence limits, these differences in potencies were not statistically significant.

The data was further analyzed to determine if there is any difference in the onset of action between d-propoxyphene napsylate and the hydrochloride since plasma concentration studies in dogs administered large toxic doses of d-propoxyphene indicate delayed absorption of the napsylate salt.[12] Time action curves for d-propoxyphene napsylate, 620 mg, and d-propoxyphene hydrochloride, 420 mg, (containing equal amounts of base) were compared and also to the response to d-propoxyphene napsylate, 700 mg orally, and placebo (Fig. 2). The napsylate, at these dose levels, appears to have a longer latency to onset.

The second group of experiments was conducted using subjects dependent upon 60 mg of morphine administered subcutaneously (15 mg q.i.d.). This level of dependence has been shown to be associated with a discomforting abstinence syndrome upon abrupt withdrawal[13] and with sufficient dependence to conduct substitution and precipitation tests. The first series of experiments were 24 hour substitution tests,[14] each subject being given, in place of regular doses of morphine, the following drugs: placebo (oral capsule plus subcutaneous injection); morphine 3 and 6 mg subcutaneously, d-propoxyphene hydrochloride 110 and 220 mg orally, and d-propoxyphene napsylate 165 and 330 mg orally. Each of these doses was administered double blind at weekly intervals 3 times for 3 consecutive 15 mg maintenance doses of morphine. Double blind conditions were maintained by administration of appropriate blank medications so that subjects received an oral capsule and an injection each time. From the 14th through the 24th hour after the last stabilization dose of morphine observations were made hourly for withdrawal sickness as 0 = not sick; 1 = slightly sick; 2 = moderately sick; 3 = severely sick.