

During the first 10 days of withdrawal Himmelsbach scores indicated the presence of mild abstinence (Fig. 18). The abstinence syndrome was below the level of clinical significance for morphine withdrawal. Comparison of the peak and total area scores for the first 10 days of withdrawal from buprenorphine is less than observed with other drugs which have produced mild abstinence syndromes in direct addiction tests (Table 10).

In the 2 subjects who withdrew, a test dose of 30 mg of morphine was administered on the 11th day of withdrawal and a placebo was administered on the 13th day of withdrawal to determine if buprenorphine was still present in significant amounts to block the effects of morphine. The lack of a clear abstinence syndrome suggested the possibility that buprenorphine was still present in large amounts. The responses to morphine were comparable to those obtained in the pre-drug control period. These 2 subjects reported increased withdrawal symptoms following these tests (14th - 17th day of withdrawal).

The other 3 subjects who were withdrawn double blind continued on observations and continued to show Himmelsbach scores in the range of approximately 10 points through the 13th day of withdrawal. On the 14th day of withdrawal, there was a marked increase in withdrawal signs and Himmelsbach scores increasing from a mean of 9 points on the 13th day to a mean of 23 points on the 14th day. Subjects reported feeling bad, were depressed and demanded relief of their symptoms with morphine. Nausea, vomiting, restlessness, insomnia and diarrhea were present for the first time indicating more severe withdrawal.

These and other studies indicate that buprenorphine 1) is a morphine-like agent in man which may be a partial agonist, 2) is relatively non-toxic in chronic administration; 3) has an extremely long duration of action, and 4) effectively blocks the effects of large doses of morphine during chronic administration.

These findings suggest that buprenorphine may have utility as a maintenance drug in the treatment of narcotic addicts. Buprenorphine has the duration of methadone, is an effective blocker of narcotics, has a lesser abuse potential than methadone, and is less toxic than methadone or d-propoxyphene.

Comparative Metabolism of *d*-Propoxyphene HCl and *d*-Propoxyphene Napsylate in Man

Five of eleven subjects participating in a double blind crossover experiment to evaluate the morphine-like effects of propoxyphene¹ agreed to participate simultaneously in this study to explore possible pharmacokinetic differences between propoxyphene HCl and propoxyphene napsylate.