Continuous evaluation of drug withdrawal in the rat using telemetry: Effects of morphine and chlordiazepoxide.


Abstract

INTRODUCTION:
The procedures used to assess withdrawal must be sensitive and widely applicable, i.e. not specific to any particular drug class. Furthermore, the measurements should not be affected by repeat testing.

METHODS:
We have used implanted telemetry devices to continuously follow body temperature, locomotor activity (LMA), heart rate (HR) and mean arterial blood pressure (mean ABP) in addition to food intake and body weight gain over 20 days of treatment and 8 days of withdrawal. The effects of morphine (32 and 64 mg/kg p.o., b.i.d.) and chlordiazepoxide (16, 32 and 64 mg/kg p.o., b.i.d.) were studied in rats.

RESULTS:
The results show that during the treatment phase chronic morphine reduced food intake and body weight gain, increased body temperature, HR, mean ABP and LMA. These effects continued over the 20 days of treatment. In contrast, chlordiazepoxide slightly increased food intake and body weight gain throughout the treatment period. It also decreased body temperature and LMA but increased HR and mean ABP after the first few administrations but these effects disappeared over the 20 days of treatment. Following discontinuation, both morphine- and chlordiazepoxide-treated rats showed a dose-related decrease in food intake and loss of weight on days 2 and 3 of discontinuation. Morphine discontinuation also induced a nocturnal hypothermia and a diurnal hypertension (i.e. during the light phase) which lasted for 4-5 days and also moderate diurnal increases in locomotor activity and heart rate over the first 3 days of discontinuation. Chlordiazepoxide discontinuation induced small increases in telemetry parameters some of which, such as the effect on locomotor activity, lasted for more than 5 days. The intensity and duration of effects for both substances were broadly dose-related.

DISCUSSION:
These data show that telemetry can increase the sensitivity of withdrawal experiments to changes that might otherwise be missed and allows a better definition of the time-course of withdrawal effects. This technique is therefore useful as part of safety pharmacology abuse liability evaluation of novel test substances across a broad range of pharmacological and therapeutic classes.