Tolerance to morphine respiratory depression: Reversal by ethanol

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Fatal heroin overdoses are often reported to have an inverse correlation of heroin to ethanol blood content following post-mortem analysis (1); with overdoses often occurring after typically non-lethal heroin doses in experienced users (2). Ethanol has been reported to reverse morphine antinociceptive tolerance in vivo in mice (3) and so the present investigation examined the potential role of ethanol in reversing tolerance to morphine respiratory depression in mice.

Respiration in freely moving male mice (CD-1) was monitored using whole body plethysmography whilst animals were breathing 95% air/5% CO₂ (none-humidified) to increase respiration and prevent sleep. Tolerance to morphine was induced by the subcutaneous implantation of a single 75 mg morphine pellet on the dorsal flank for 6 days. All challenge drugs to both naïve (un-implanted) and implanted mice were given intraperitoneally. All drugs were dissolved in sterile saline. Mice were injected with either saline, morphine (10 mg/kg), ethanol (0.3 g/kg), or morphine (10 mg/kg) plus ethanol (0.3 g/kg). Minute volume was 165.2 mL/min ± 17 s.d. (n=34). Data were normalised and area under the curve (AUC) calculated for post drug period of 30 minutes.

![Figure 1: Effect of ethanol on tolerance to morphine respiratory depression. * indicates significance from saline/ethanol control. $\$\$\$\$\$$\$ indicates significance from implanted morphine challenged control. $$ P<0.01. $$$/** P<0.001.

Ethanol (0.3 g/kg) injected into naïve mice caused no significant depression of respiration relative to saline control whereas morphine (10 mg/kg) caused significant depression (P<0.001). Morphine (10 mg/kg) injected into morphine pellet implanted mice after 6 days caused less depression of respiration relative to naïve mice receiving the same dose. Morphine (10 mg/kg) and ethanol (0.3 g/kg) injected simultaneously in morphine pellet implanted mice produced a significant depression of respiration (P<0.01) compared to pellet implanted morphine. A one-way ANOVA with Bonferroni’s post-test was used to compare groups.

These data provide good evidence that ethanol modulates tolerance to morphine respiratory depression in a manner similar to that observed previously with tolerance to morphine antinociceptive tolerance.