Anamnestic Response to an Opioid

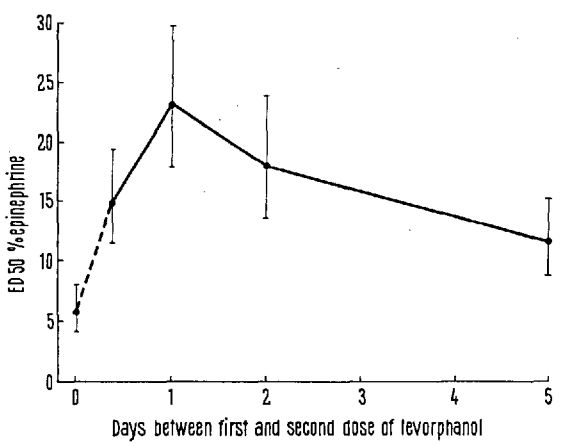
Transient opacities develop in the lenses of mice soon after parenteral injection of a large dose of an opioid[1]. Tolerance to this effect can be detected even after a single dose[2]. The degree of tolerance produced is related to the size of the initial dose and can be determined[3] sensitively by potentiating the opioid dose with instilled L-epinephrine to obtain a 50% incidence of cataract formation. The palpebral fissure widens after insillation of strong solutions of L-epinephrine. This increases the incidence of opacification since the area of corneal exposure affects the rate of evaporation of the transudate from the anterior chamber of the mouse eye. Loss of this water diminishes hydration of the lens and reduces its clarity. By itself, instilled L-epinephrine in concentrations up to 30% has no cataractogenic effect.

The purpose of the present study was to determine whether an initial dose of the opioid levorphanol, sensitized the mouse to develop greater tolerance to the second dose of opioid than would be expected from only an additive effect. The rationale for this experiment arose from the finding[3] that inhibitors of protein synthesis blocked lenticular tolerance. If the development of cataractogenic tolerance to levorphanol is related to new protein synthesis then this tolerance process might show recall as occurs in the immune state.

In control experiments, 3 groups of 20 Swiss-Webster female mice, weighing 20–25 g, were injected i.p. with a levorphanol tartrate solution (0.2 ml) in a single dose of 25 μmoles/kg. 48 h later, levorphanol was given i.p. in a test dose of 75 μmoles/kg. The latter dose normally produces about 20% incidence of opacity in naive mice. 3 h before the test dose of levorphanol, phenoxybenzamine, 10 mg/kg, was given i.p. in order to block the potentiating action of circulating L-epinephrine absorbed from the eye. 30 min before the test dose of levorphanol, strong solutions of L-epinephrine were instilled in the conjunctival sac.

The concentration of 5.9% L-epinephrine potentiated the test dose of levorphanol and produced opacities in the lenses of half of the mice made tolerant with a single previous dose (25 μmoles/kg) of levorphanol (Figure). The ED50 was calculated using the graphic method of LITCHFIELD and WILCOXON[4]. In the next experiment, 3 groups of mice were made tolerant to fractional doses of levorphanol; initially 15 μmoles/kg was injected and 8 h later an additional dose was given of 10 μmoles/kg. 36 h after the last dose of levorphanol, the mice were tested as before. The tolerance produced by this schedule increased the ED50 of L-epinephrine to 15%. When the interval between the first levorphanol dose (15 μmoles/kg) and the second dose (10 μmoles/kg) was increased to 24 h, the ED50 concentration of L-epinephrine rose to 23%. However, when 2 days separated dosing, the L-epinephrine ED50 fell to 18%. When the interval was extended to 5 days the ED50 of L-epinephrine dropped to 13%. To ascertain whether the difference between the experimental values and control resulted solely from the increased experimental period, mice were injected with levorphanol in a dose of 25 μmoles/kg, but not tested until 6 days after the injection. These mice showed an L-epinephrine ED50 of 8.6%, slightly higher than for mice tested only 2 days after the initial levorphanol injection. This value was still significantly different ($p < 0.05$) from the ED50 of each experimental value.

The possibility exists that tolerance sensitization produced by the first opioid dose may in fact represent an adaptive enzyme process. However, in a recent review[5] of the mechanisms responsible for opioid tolerance, Cochin concluded that tolerance did not result from altered drug metabolism. Indeed, the activity of the inducible microsomal enzyme, N-demethyltransferase, is actually reduced[6] in livers of animals made tolerant to the analgesic effects of opioids. In the present study, the greatly increased tolerance which developed after the second opioid dose given days later strongly suggests an anamnestic effect and is in accord with the postulated[7] existence of an immune-like mechanism for opioid tolerance[8].



Effects of single or fractional doses of levorphanol tartrate on the development of tolerance to the cataractogenic effect of a test dose (75 μmoles/kg) of levorphanol. Mice were pretreated with a single dose of 25 μmoles/kg or the dose was fractionated as follows: 15 μmoles/kg was injected first and then 10 μmoles/kg was given 8 h to 5 days later. The degree of tolerance was estimated from concentrations of instilled L-epinephrine which enabled half of the mice to develop cataracts (ED50). Horizontal bars indicate 95% confidence limits.

Zusammenfassung. In Mäusen entsteht eine Toleranz gegen den kataraktogenen Effekt einer Einzeldosis von Opioid. Werden fraktionierte Dosen gegeben, so entwickelt sich jedoch eine weitaus grössere Toleranz, wofür eine Sensibilisierung als Ursache angenommen wird.

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