

Endothelin ETA receptor antagonist did not affect development of tolerance to glyceryl trinitrate in rat.

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Glyceryl trinitrate (GTN), extensively used for the treatment of cardiovascular disorders, is associated with rapid development of tolerance. The exact mechanism responsible for tolerance development to GTN is still not known. Recently, it has been demonstrated that GTN tolerance is associated with increased expression of endothelin (ET). This study was carried out to determine the effect of ET(A) receptor antagonist, BMS182874, on the development of tolerance to GTN in urethane-anaesthetized rats. Diastolic blood pressure (DBP), systolic blood pressure (SBP) and heart rate (HR) were continuously recorded in vehicle- and BMS182874 (3 mg kg⁻¹, i.v.)-treated rats. GTN was infused at the rate of 10 microg min⁻¹, intravenously for 4 h. Tolerance to GTN was determined using challenge doses of GTN (10, 30 and 90 microg, i.v.). GTN produced a fall in DBP, SBP and an increase in HR. In vehicle-treated rats, the fall in SBP before induction of GTN tolerance was 28 +/- 2, 43 +/- 4 and 52 +/- 4 mmHg with 10, 30 and 90 microg GTN, respectively. However, following GTN infusion (10 microg min⁻¹, i.v. for 4 h) a rapid development of tolerance was observed and the fall in SBP was 1 +/- 1, 9 +/- 4 and 15 +/- 4 mmHg with 10, 30 and 90 microg GTN, respectively. Similarly, in BMS182874-treated rats the fall in SBP in non-tolerant rats was 28 +/- 4, 42 +/- 4 and 48 +/- 5 mmHg with 10, 30 and 90 microg GTN, respectively. In BMS182874-treated rats following GTN infusion (10 microg min⁻¹, i.v. for 4 h) a rapid development of tolerance was observed and the fall in SBP was 4 +/- 3, 10 +/- 2 and 13 +/- 4 mmHg with 10, 30 and 90 microg GTN, respectively. The decrease in DBP and SBP in vehicle- and BMS182874-treated GTN-tolerant rats was statistically similar. These results suggest that ET(A) receptor antagonist BMS182874 did not affect development of tolerance to GTN in rats