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Lorazepam effects on silent period and corticomotor excitability

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Background

TMS studies on the CNS effects of benzodiazepines have provided contradictory results. The objective of the study is to describe the effects of lorazepam on silent period (SP), corticomotor threshold and activated MEP recruitment curves.

Materials and methods

Twelve healthy male subjects (median age 35 years) were studied at baseline, following i.v. lorazepam administration and after reversal of the benzodiazepine effects with i.v. flumazenil. Lorazepam was given at a low-dose in one subject (0.0225 mg/kg bolus + 2 μg/kg/h infusion) and at a high-dose (0.045 mg/kg bolus + 2.6 μg/kg/h infusion) in the rest. Threshold (Thr) was measured at 1% steps. SPs were investigated with two complementary methods. First, SPs were elicited using a wide range of stimulus intensities (SIs) (from 5 to 100% maximum SI at 5% increments). At each SI, 4 SPs were obtained and the average value of SP duration was used to construct a stimulus/response (S/R) curve of SI vs. SP. The resulting S/R curves were then fitted to a Boltzman function, the best-fit values of which were statistically compared for each experimental condition (i.e., baseline vs. lorazepam vs. flumazenil). Second, a large number of SPs was elicited during the three experimental conditions using blocks of 4 stimuli with an intensity alternating between MT and 200% MT. This method was employed so as to reveal the dynamic, time-varying effects of lorazepam and flumazenil on SP duration at two stimulus intensity (SI) levels. Finally, active MEP recruitment curves were constructed and fitted to a Boltzman function the best-fit values of which were statistically compared for each experimental condition.

Results

Lorazepam at a low dose did not affect Thr, SP or the MEP recruitment curves. The high dose had also no effect on Thr (38.4 ± 7.3% vs. 39.8 ± 8.8% vs. 39.6 ± 8.9%, $p > 0.05$). In contrast, the Max value of the SP S/R curve decreased from 250.8 ± 30.3 ms at baseline to 206.8 ± 14.6 ms post-lorazepam ($p < 0.01$). V50 also decreased significantly (from 48.6 ± 3.7% to 43.1 ± 5.5%, $p < 0.01$) whereas there was no significant change regarding slope. The statistical analysis of the SP S/R curves as well as the study of SPs at two SI levels revealed that lorazepam reduced SP duration when high intensity stimuli were used (>60%). These effects of lorazepam on SP were partially reversed by flumazenil. At low SIs a small increase in SP duration was noted. Active MEP recruitment curves were not depressed by lorazepam administration.

Discussion

Enhancement of GABAergic inhibition by lorazepam results in: reduction of SP duration when high SIs are used and an increase, to a smaller degree, at the lower range of SIs. The kinetic behavior of this phenomenon as well as the possible underlying mechanisms are discussed.