Concurrent benzodiazepines undermine the antidepressant effect of ketamine

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Background. Although predictive and modulating factors of response to ketamine are broadly studied, little is known about optimal concurrent medication protocols. Concerning gamma-aminobutyric acid neurotransmission being a shared target for both ketamine and benzodiazepines (BZD), we evaluated the influence of BZD on the antidepressant effect of single ketamine infusion in depressed patients.

Methods. Data from 47 patients (27 females) with major depression (MADRS ≥20, ≥1 prior non-response to antidepressant treatment in current episode) entered the analysis. All subjects were given infusion of subanesthetic dose of racemic ketamine (0.54 mg per kg) as an add-on medication to ongoing antidepressant treatment.

Results. Thirteen patients (28%) reached ≥50% reduction in MADRS within one week after ketamine administration. Nineteen (40%) patients took concomitant benzodiazepines on daily basis. The doses of BZDs were significantly higher in non-responders (p=0.007). ROC analysis distinguished responders from non-responders by criterion of >8mg of diazepam equivalent dose (DZ equi) with a sensitivity of 80% and a specificity of 85% (p<0.001) (Fig.1). RM-ANOVA revealed different time pattern of response to ketamine between BZD+ (>8mg of DZ equi) and BZD− (≤8mg of DZ equi) group, with significantly worse outcome in BZD+ in day 3 (p=0.04) and day 7 (p=0.02) (Fig.2).

Conclusions. BZDs may attenuate ketamine’s antidepressant effect in a dose-dependent manner. This effect was independent when adjusted to baseline anxiety and depression scores and also independent on ketamine and norketamine plasma levels during or after the infusion.

Tab.: Characteristics of high-dose BZD users (BZD+; >8mg of DE) and none-to-low-dose BZD users (BZD−; 0-8mg of DE) during the follow-up period

![Fig.1: ROC analysis distinguishing responders and non-responders (AUC=0.91, 95%CI 0.88-0.99, p 0.001)](image1)

![Fig 2: Significantly better outcome in BZD- group in day 3 (p=0.04) and day 7 (p=0.02) revealed by RM-ANOVA.](image2)

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