CIRCULATION VI

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TITLE: IN VITRO MYOCARDIAL EFFECTS OF BENZODIAZEPINE AGONISTS AND ANTAGONISTS

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Introduction. We limited in vitro data available suggest that the benzodiazepine (BD) midazolam in a more potent direct myocardial depressant than diazepam. Although vasodilation associated with midazolam administration in vivo compensates for direct cardiac depression resulting in no decrease in cardiac output, it has been suggested that midazolam be used with caution in patients with impaired cardiac function. To study this further, we utilized a rabbit papillary muscle preparation to evaluate (1) the direct myocardial depressant effects of midazolam, diazepam, and the potent peripheral BD agonist RO 5-4864, and (2) the ability of the central BD antagonist PK 11195 and the peripheral BD antagonist FK 1195 to reverse the cardiac depression produced by the BD agonists.

Methods. Male rabbits, 1.5-2.5 kg, were deeply anesthetized with triethanolamine (2-5) mg/kg intravenously in a closed chamber followed by tracheotomy and rapid cardiac occlusion. The hearts were maintained in 22°C saline while suitable right ventricular papillary muscles were excised. The muscles were then placed in the muscle bath containing Krebs-Henseleit buffer at 38°C bubbled with 95% O2, 5% CO2, pH 7.40. The muscles were stimulated at a frequency of 0.3 Hz and allowed to equilibrate for at least 30 min. Each muscle was stretched until maximal isotropic tension developed and was then equilibrated for 60 min prior to baseline measurements. Incremental additions of the BD agonists were then made: the response to RO 5-4864 (n=4) was studied over the range of 10⁻⁴ M to 10⁻⁵ M and the responses to diazepam (n=4) and midazolam (n=4) were studied over the range of 10⁻⁵ M to 10⁻⁶ M. Following the final dose of the agonist, the central BD antagonist PK 11195 (10⁻⁴ M) was added to the bath followed by additions of the peripheral BD antagonist FK 1195 (10⁻⁴ M and 10⁻⁵ M). Finally, the bath was rapidly drained and replaced with fresh buffer (Washout). Following each intervention, responses were measured after the muscle had equilibrated (15-30 min). Responses to the agonists were converted to percent of baseline and analyzed using a two-way ANOVA with repeated measures followed by one-way ANOVA and Student's t-test to identify group differences at the various doses. The responses to the antagonists were converted to percent of agonist values and analyzed in the same fashion. Results. Peak tension was depressed in a dose-dependent manner by all three BD agonists (Figure 1). At 10⁻⁴ M, the depression of peak tension was significantly different (p<0.05) among the three groups (RO 5-4864 > diazepam > midazolam). At 3×10⁻⁵ M, the depression produced by diazepam was still greater than that produced by midazolam but the difference was not significant. Peak rate of tension development (dP/dtmax) was similarly depressed (RO 5-4864 > diazepam > midazolam) although the differences between the midazolam and diazepam groups were not significant at any single dose. The addition to the bath of the central and peripheral BD antagonists was associated with a small amount of additional depression (5-10%) that was similar in all three groups; there was no appreciable reversal of the BD agonist-induced depression (Figure 2). Following washout, there was an increase in function in the diazepam and midazolam groups.

Discussion. Our data indicate that midazolam is associated with less direct cardiac depression than diazepam. These data suggest that midazolam should be better tolerated than diazepam in patients with depressed cardiac function, particularly since midazolam is a more potent anesthetic. The disparity between our results and those of a previous in vitro study, in which midazolam was associated with more cardiac depression than diazepam, may be attributed to the difference in the doses studied. In the earlier study, the effects of midazolam and diazepam were similar at their lowest dose (14-15 μg/ml) and the midazolam dose-response curve was steeper, suggesting that midazolam could be less depressant than diazepam in the dosage range that we studied (3 μg/ml - 10 μg/ml). Considering that plasma levels following anesthetic induction with midazolam are 3.5-10 μg/ml (1.5-3×10⁻⁵ M), our findings may be more clinically relevant. The depression associated with addition of PK 1195 was unexpected since PK 1195 has been reported to antagonize the cardiac depression produced by BD agonists using much larger ratios similar to those that we studied. However, this antagonism has only been demonstrated in studies in which PK 1195 is administered prior to the BD agonist. In contrast, our data indicate that both BD antagonists may possess intrinsic myocardial depressant properties.