$GABA_A$ actions of ABP-700 and its Carboxylic Acid Metabolite CPM-Acid: Implications for Toxicological Studies and Clinical Development

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Background: ABP-700 (also known as cyclopropyl-methoxycarbonyl metomidate) is a soft analog of etomidate. It acts as a positive allosteric modulator of the γ-aminobutyric acid type A ($GABA_A$) receptor and is rapidly metabolized by non-specific esterases to CPM-acid (CPM-A). In toxicological studies using beagle dogs, convulsive seizures were observed during the final 5 minutes of the ABP-700 infusion or in the minutes to hours afterward. The late timing of the seizures suggests that they were caused by the metabolite, CPM-A. In order to better understand the mechanism of such seizures, the $GABA_A$ receptor pharmacology of ABP-700 and CPM-acid were characterized.

Materials and methods: The concentration-dependent actions of ABP-700 and CPM-acid were defined in oocyte-expressed $\alpha_1\beta_3\gamma_{2L}$ $GABA_A$ receptors using voltage clamp electrophysiology. Potentiation of GABA-mediated currents was characterized by adding increasing concentrations of ABP-700 or CPM-A to an EC_5 GABA concentration (6 μM). Inhibition of GABA-mediated currents was characterized by adding drug to a receptor-saturating GABA concentration (1000 μM). The effect of CPM-A on the GABA concentration-response curve was similarly defined using electrophysiological techniques.

Results: The concentration-response curves defining the impact of ABP-700 and CPM-acid on $GABA_A$ receptor-mediated currents evoked by 6 μM GABA was biphasic, potentiating currents at low (clinically-relevant) concentrations while inhibiting them at very high (toxic) concentrations. The EC_{50} for current potentiation was 2.3 μM for ABP-700 (95% CI, 1.623 to 3.309) and 347 μM for CPM-A (95% CI, 123.9 to 971.7; p=0.0025). The IC_{50}s for current inhibition determined using 1000 μM GABA were 752 μM for ABP-700 (95% CI, 657.7 to 859.3) and 1530 μM for CPM-A (95% CI, 1308 to 1718; p<0.0001). CPM-A (1500 μM) reduced the peak current amplitude produced by high GABA concentrations from 104% to 64% (p<0.0001) without altering the GABA EC_{50} (44 μM versus 45 μM in the absence and presence of CPM-A, respectively; p = 0.9146).

Conclusion: Inhibition of $GABA_A$ receptors is a well-established mechanism for seizure production. Our studies show that CPM-acid non-competitively inhibits $GABA_A$ receptors at the blood concentrations achieved in beagle dogs that received prolonged high dose infusions of ABP-700. This provides a mechanistic explanation for seizures observed in beagle dogs, a dog breed known to have a relatively low seizure threshold. This concentration is ~100x

higher than that reached in human clinical studies of ABP-700, suggesting that this action is not clinically relevant.