DOES RO15-4513 ACT SPECIFICALLY, OR FUNCTIONALLY, TO INCREASE THE ANESTHETIC REQUIREMENT?

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INTRODUCTION: Ro15-4513 is a specific inverse agonist at benzodiazepine (BDZ) receptors, which has been shown to increase both the ethanol (ET) (1) and general anesthetic (GA) (2) requirements. For GAs, the shift was demonstrated for a structurally heterogeneous group, and was specific for the BDZ receptor, since nanomolar concentrations of Ro15-4513 were effective and effects were prevented by the specific BDZ blocker, Ro15-1788. BDZ inverse agonists produce effects opposite those of agonist BDZs, for example, muscle rigidity, anxiety, and notably, proconvulsant actions (3). Thus, it could be argued that increases in the GA requirement may be due to generalized central stimulation, resulting in a *functional*, rather than a *specific* antagonism of depressant effects. To distinguish between these two possibilities, we tested the effects of three convulsants with known sites of action, on halothane requirement in mice. Specifically, we employed pentylenetetrazol (PTZ), which blocks the GABA receptor-activated ion channel; caffeine (CA), which acts on neurons as an agonist at central adenosine receptors; and strychnine (STR), which blocks inhibitory central glycine receptors.

METHODS: The doses of PTZ, CA and STR administered were just below those previously reported to produce generalized convulsions. The endpoint of loss-of-righting reflex (LRR) was employed in a method adapted from Ref. (4), and data analyzed by the method of Waud (5) yielding halothane median dose-response effective concentrations (EC50s) and an estimate of their standard errors. Briefly, test groups of eight mice each received blinded IP injections of 0.3 ml, containing either vehicle (normal saline) alone, or 40 mg/kg PTZ, 100 mg/kg CA, or 1 mg/kg STR. Groups were then loaded into rotating cages on a carousel; this was placed in a sealed plexiglas chamber in which temperature, and the tensions of oxygen, carbon dioxide, and halothane were held constant. Experiments with each convulsant agent were performed four times.

RESULTS: There were no significant differences between the slopes of dose-response curves for any of the groups. The halothane EC50 $\pm$ SE for the groups were: Controls = 0.71 $\pm$ 0.021 %atm; PTZ = 0.75 $\pm$ 0.019 ($p > 0.1$); CA = 0.70 $\pm$ 0.019 ($p > 0.7$). A second series revealed: Controls = 0.68 $\pm$ 0.022 %atm; STR = 0.66 $\pm$ 0.030 ($p > 0.5$).

DISCUSSION: PTZ ,CA, and STR failed to increase the requirement for halothane. Thus, Ro15-4513's ability to increase the GA requirement is not a common pharmacologic property of convulsants, and therefore probably not merely due to generalized central stimulation. Other convulsants, including quipazine, a central serotonin agonist, as well as other GAs, are now being studied to strengthen this conclusion.

REFERENCES: (1) Science 234:1243, 1986; (2) FASEB J 2:A1384, 1988; (3) Br J Pharm 93:210, 1988; (4) Anesthesiol 36:339,1972; (5) JPET 183:577, 1972.

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TITLE: ISOFLURANE IMPAIRS THE PUPILLARY LIGHT REFLEX IN HUMANS

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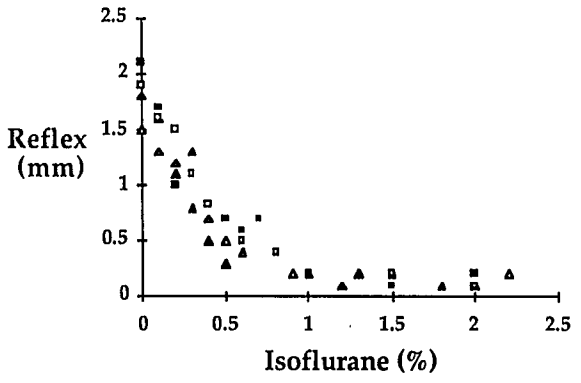
The pupillary light reflex is widely used to test cranial nerve and midbrain function, and such testing is frequently needed in the immediate postoperative period. We tested the hypothesis that isoflurane markedly impairs pupillary responses. With approval of our IRB, we anesthetized 4 volunteers with isoflurane/air for ≈ 3 h. No other medications were given. During recovery, residual end-tidal isoflurane concentrations (Datex Capnomac®) and pupillary light reflexes (electronic infrared scanner[1]) were recorded at 5 min intervals. Residual isoflurane anesthesia markedly diminished maximum constriction velocity, reflex amplitude, and maximum redilation velocity. Reflex amplitude was reduced to ≈ 0.2 mm at concentrations above 0.5 MAC (fig). The small, but consistent reflex amplitude at end-tidal isoflurane concentrations between 1 and 2% is consistent with previous reports.[2] These data indicate that pupillary constriction is significantly impaired at residual isoflurane concentrations frequently observed during the early stages of recovery from general anesthesia.



Legend: End-tidal isoflurane markedly diminished amplitude of the pupillary light reflex. The reflex was essentially absent at concentrations above 0.5 MAC.

References:

1. Radzius A, *et al*: Behavior Research Methods, Instrumentation, and Computers 21:611-618, 1989

2. Cullen DJ, *et al*: Anesthesiology 36:21-36, 1972

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