Title: REDUCTION OF ANESTHETIC REQUIREMENT AND CARDIOVASCULAR EFFECTS OF BHT 920, A SELECTIVE ALPHA-2 ADRENERGIC AGONIST.

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Introduction: Acutely administered clonidine, a centrally acting alpha-adrenergic agonist has been shown to reduce halothane requirement by 48%. The potential clinical advantages of attenuating the hemodynamic responses to noxious stimuli while reducing anesthetic requirement with clonidine have been demonstrated in coronary artery bypass surgery. However, clonidine as an adjunct to anesthesia is limited by a "ceiling" to the anesthetic sparing effect and its lack of availability as a parenteral preparation. We studied BHT 920 (Boehringer Ingelheim), an azepline derivative, which is a more selective alpha-adrenergic agonist, and report its potentialization of isoflurane (ISO) anesthesia and the associated cardiovascular effects.

Methods: ISO was administered by mask to unpremedicated mongrel dogs to produce deep anesthesia. The dogs were intubated and then allowed to breathe spontaneously, 2% ISO in oxygen, during the period of sham preparation. All drugs and fluids were administered through a catheter in the femoral vein. Heart rate (HR), arterial (MAP), central venous, pulmonary arterial and left ventricular pressures (LVEDP and dP/dt) were recorded continuously on a direct writing polygraph. Cardiac outputs (CO) were determined in triplicate by thermodilution. End-tidal ISO and CO2 concentrations were measured. Core temperature was maintained at 38 ± 1°C. Following a stabilization period of one hour, breathing 1.5% end-tidal ISO, the minimum alveolar concentration (MAC) of ISO was determined as published.1

BHT 920 was administered by bolus injection in successive doses of 0.1 mg/kg and 0.3 mg/kg and MAC determined after each dose. The inspired ISO was then increased and after 15 minutes yohimbine, an alpha-adrenergic antagonist, (0.3 mg/kg), was given. MAC was determined for the final time. A second group of dogs were studied in exactly the same manner but following glycopyrrolate (GLYCO), 100 µg/kg, at the start of the protocol and 20 µg/kg every 60 mins thereafter. Cardiovascular parameters and serum catecholamines were measured prior to each MAC determination.

Results: BHT 920 reduced the ISO anesthetic requirement by 86% at 0.1 mg/kg and 93% at 0.3 mg/kg. Yohimbine partially reversed this reduction. HR and CO were significantly reduced by BHT 920 in a dose dependent manner; 46% and 47% respectively at (0.1 mg/kg) and 54% and 68% at the higher dose (Fig. 1). The LVEDP and systemic vascular resistance were significantly increased whereas the MAP and dP/dt were unchanged (Fig. 2). All the cardiovascular parameters returned to control levels following yohimbine. Serum catecholamine concentrations declined progressively following BHT 920. In GLYCO treated dogs, the reduction in HR was attenuated but not in CO.

Discussion: BHT 920 caused a profound reduction in anesthetic requirement so that ISO was discontinued. Indeed, its peak effect was limited by the washout of ISO and it is likely to be a complete anesthetic. However, this effect was accomplished by undesirable hemodynamic changes, namely reduced HR and CO and increased SVR and LVEDP. The reduction of CO was not attenuated by GLYCO. The mode of administration was designed to maximize the hemodynamic effects and these may be attenuated by a slower rate of infusion. In contrast to the cardiovascular changes the potentiation of anesthesia was only partially reversed by yohimbine. Certainly, increasing alpha-adrenergic agonist selectivity appears to be associated with greater anesthetic potentiation.

REFERENCES