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Article in European Journal of Pharmacology · February 2006

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Hemodynamic effects of bupropion in anesthetized dogs

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Abstract

Bupropion is a non-nicotinic drug used in smoking cessation therapy. However, its acute effects remain unclear. In this study, we investigated the effects of bupropion on hemodynamic parameters in pentobarbital-anesthetized mongrel dogs. Bupropion administered either in bolus injections (3 or 6 mg/kg, i.v.) or in cumulative doses of 0.01, 0.1, 1, 3 and 10 mg/kg showed, in both studies, a significant increase of mean pulmonary arterial pressure and pulmonary vascular resistance index. These results show that bupropion can elevate the pulmonary pressure. Further investigations should be done to test this effect in smokers with chronic obstructive pulmonary disease.

Keywords: Nicotine; Smoking cessation; Pulmonary hypertension

1. Introduction

Bupropion, which has been prescribed as an antidepressant (Cicardo et al., 1986), is the first non-nicotinic drug to be used therapeutically for smoking cessation. The usefulness of bupropion in smoking cessation is related to the fact that, in contrast to most antidepressants that selectively inhibit serotonin reuptake or monoamine oxidase activity, bupropion inhibits the reuptake of dopamine and noradrenaline (Ascher et al., 1995). Bupropion has less potent effects on cardiac function than tricyclic antidepressants and, compared to the latter, has no anticholinergic or sympathomimetic effects (Soroko and Maxwell, 1983).

The effectiveness and safety of bupropion have been demonstrated in many studies (Roose et al., 1991; Holt et al., 2005). However, its pharmacological profile, dosage and administration, clinical effectiveness, safety and tolerability are still a matter of discussion, particularly when the drug is administered to cardiopathic smokers (Thomson and Rigotti, 2003) or individuals with chronic obstructive pulmonary disease (Tonstad and Johnston, 2004). Some of the cardiovascular side effects of bupropion include orthostatic hypotension and the exacerbation of hypertension (Roose et al., 1991), chest pain (de Graaf and Diemont, 2003) and even myocardial infarction (Patterson and Herity, 2002).

Although there is considerable information on the effectiveness and safety of bupropion, very little is known about its cardiovascular effects mainly on the pulmonary circulation. As obvious ethical issues restrict invasive investigations in humans, we performed this study in anesthetized dogs.

2. Materials and methods

2.1. General procedures

All procedures were approved by the institutional animal care committee at UNICAMP and the experiments were done in accordance with the guidelines for animal care and use published by the National Institutes of Health and the European Community guidelines for the use of experimental animals. Thirty-four mongrel dogs (15±1 kg) of either sex were...
anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and the level of anesthesia was maintained with an infusion of pentobarbital (6–10 mg/kg/h). The dogs were intubated for mechanical ventilation with room air using a volume-cycled respirator (tidal volume=15 ml/kg) (Harvard Apparatus, Boston, MA, USA). Fluid-filled catheters were placed in the left femoral artery and right femoral vein to measure mean arterial pressure via a pressure transducer (AS-3 Datex-Engstrom, Helsinki, Finland) and for fluid administration, respectively. A 7F balloon-tipped Swan-Ganz thermodilution catheter was placed in the pulmonary artery via the left femoral vein and its correct location was confirmed by detection of the typical pressure wave of this artery. The catheter was connected to a pressure transducer (AS-3 Datex-Engstrom, Helsinki, Finland) to allow monitoring of the mean pulmonary arterial pressure, central venous pressure, and pulmonary capillary wedge pressure. The transducers were zeroed at the level of the right heart and recalibrated before each set of measurements. Cardiac output was determined in triplicate by injecting 5 ml of saline, and the results were recorded and stored on a computerized system. The index cardiac, systemic vascular resistance index and pulmonary vascular resistance index were calculated by using standard formulas. Heart rate was measured using a surface electrocardiogram (lead I). After at least 20 min of stabilization, a baseline hemodynamic evaluation was done. For the experiments, the dogs were randomly assigned to one of five groups in two studies, as described below.

2.2. Study 1—hemodynamic effects of single doses of bupropion (3 or 6 mg/kg)

Dogs in Group A (n=6) and Group B (n=6) received a bolus injection (10 ml) of 3 mg/kg or 6 mg/kg of bupropion (Laboratory Mag, Italy), respectively, whereas the control group (n=6) received the same volume of saline alone. Hemodynamic variables were measured 1, 10 and 20 min after the administration of saline or bupropion.

2.3. Study 2—hemodynamic effects of cumulative doses of bupropion

Dogs in Group C (n=8) received cumulative bolus injections of 0.01, 0.1, 1, 3 and 10 mg of bupropion/kg in 10 ml of saline, whereas dogs in the control group (n=8) received the same volume of saline alone. The hemodynamic variables were measured after the administration of each dose of bupropion or saline.

2.4. Statistical analysis

The results were expressed as the mean±S.E.M. Statistical comparisons were done using Student’s t-test for unpaired observations or analysis of variance (ANOVA) for repeated measures followed by Dunnett’s multiple comparisons test. A value of p<0.05 was considered significant. All statistical

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![Image](image-url)  
Fig. 1. Cardiac index (CI), mean pulmonary arterial pressure (MPAP), pulmonary vascular resistance index (PVRi) and systemic vascular resistance index (SVRi) at baseline (BL) and 1, 10 and 20 min after bolus injections of saline (control group) or bupropion (3 mg/kg or 6 mg/kg). Each column represents the mean±S.E.M. (n=6). *p<0.05 versus baseline. †p<0.05 versus the control group.
Calculations were done using SygmaStat for Windows (Jandel Scientific, CA, USA).

3. Results

3.1. Study 1—hemodynamic effects of single doses of bupropion

There were no significant differences in the baseline hemodynamic variables among the groups. However, in dogs that received bupropion (3 or 6 mg/kg), there were significant increases in pulmonary vascular resistance index and mean pulmonary arterial pressure (Fig. 1) when compared to the respective basal parameters and to the control group. These hemodynamic alterations returned to basal values 10 min after bupropion injection. At a dose of 3 mg/kg, bupropion significantly increased the systemic vascular resistance index within 1 min, but a similar effect was not observed with the dose of 6 mg/kg (Fig. 1). Bupropion had no significant effect on heart rate, measure mean arterial pressure, index cardiac, central venous pressure and pulmonary capillary wedge pressure when compared to the control group.

3.2. Study 2—hemodynamic effects of cumulative doses of bupropion

There were no significant differences in the baseline hemodynamic variables between the two groups. Fig. 2 shows that mean pulmonary arterial pressure and pulmonary vascular resistance index increased significantly after bupropion doses of 3 and 10 mg/kg.

Bupropion did not significantly alter further hemodynamic parameters compared to the control group.

4. Discussion

Bupropion is a structurally unique, monocyclic antidepressant with an undetermined mechanism of action that is also used as an aid in smoking cessation. Although the mechanism of action responsible for smoking cessation is unknown, there is evidence that blockade of the uptake of catecholamines and dopamine (substances responsible for the symptoms of abstinence syndrome and drug addiction) is involved (Ascher et al., 1995; Gobbi et al., 2003).

The main findings of this study were that bupropion altered the hemodynamic parameters of the pulmonary circulation and increased the mean pulmonary arterial pressure and pulmonary vascular resistance index. Our findings agree with those of Cicardo et al. (1986) who reported that the administration of bupropion (3–5 mg/kg) in anesthetized dogs did not significantly affect arterial blood pressure or heart rate. The lack of effect of bupropion on measure mean arterial pressure and heart rate seen here also indicated that the ability of this drug to block the uptake of catecholamines did not affect the hemodynamic parameters.

When cumulative doses of bupropion were administered to dogs, mean pulmonary arterial pressure increased significantly with 10 mg of bupropion/kg and pulmonary vascular resistance index after 3 and 10 mg/kg (Fig. 2), as also seen with bolus injections.

Hypoxia can cause pulmonary vasoconstriction indirectly though the release of endogenous vasoconstrictors, such as catecholamines, that can increase the pulmonary vascular resistance (Hida et al., 2002). Similarly, Cremers et al. (2003) suggested that bupropion exerted positive inotropic effects in human myocardium most probably by stimulating catecholamine release. These findings, together with the significant increase in mean pulmonary arterial pressure and pulmonary vascular resistance index seen here with doses of 3 or 6 mg/kg show that bupropion can elevate the pulmonary pressure.

According to Wagena et al. (2003) bupropion has a good safety profile and increases the abstinence rates in smokers with chronic obstructive pulmonary disease. However, little is known about the efficacy and safety of different pharmacological therapies for smoking cessation used to treat patients with...
chronic obstructive pulmonary disease who smoke. We found that bupropion doses of 3 or 6 mg/kg, which are commonly used in humans, caused pulmonary hypertension in healthy dogs. This pulmonary effect suggests that additional studies are required to assess the safety and effectiveness of bupropion in smoking cessation therapy in patients with cardiovascular diseases and chronic obstructive pulmonary disease.

Acknowledgments

The authors thank Adilson Thomaz for technical assistance and Dr. Stephen Hyslop for reviewing the English of the manuscript. This work was supported by CAPES, CNPq and Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP, Brazil).

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