Title: DROPERIDOL ABOLISHES ACUTE THROMBUS FORMATION IN STENOSED DOG CORONARY ARTERIES

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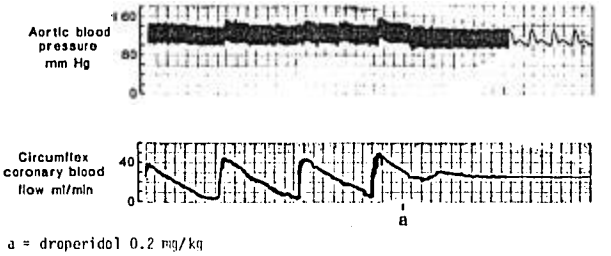
Introduction. In patients with coronary artery disease, formation of platelet thrombi in areas of coronary atherosclerotic plaques is thought to be responsible for both unstable angina and acute myocardial infarction. Drugs such as aspirin that inhibit platelet aggregation may be therapeutic in these conditions. We have previously used an open-chested dog model with a mechanical coronary stenosis to demonstrate the formation of occlusive platelet thrombi and the cyclical blood flow reductions (CFR) that these thrombi cause.[1] We have also shown that epinephrine exacerbates the formation of platelet aggregates and CFR. This model provides a useful in vivo assessment of platelet function. We have previously shown that chlorpromazine attenuates platelet aggregation and associated CFR.[2] Chlorpromazine is of limited usefulness as an adjunct to anesthesia, however, droperidol, a related drug, can be a component to anesthesia. The purpose of this study was to determine whether or not intravenous droperidol would inhibit spontaneous and epinephrine induced platelet aggregation and associated coronary flow reductions.

Methods. Five adult dogs (23-26 kg) were anesthetized with sodium pentobarbital (20 mg/kg), intubated and ventilated with oxygen. Thoracotomy was performed, an electromagnetic flow probe placed around the proximal left circumflex coronary artery and a rigid 3 mm long encircling plastic cylinder placed around the artery distal to the flow probe. A critical 60-80% stenosis was induced and produced spontaneous CFR.[1] ECG was recorded from an epicardial electrode placed in the distribution of the circumflex coronary artery. Aortic blood pressure (ABP) was measured. After monitoring CFR for 30 minutes, droperidol (0.2 mg/kg) was administered as an IV bolus and the effects on CFR, ABP, and ECG were measured. Thirty minutes later, IV epinephrine infusion was started at 10 µg/min for 15 minutes and all parameters continuously recorded (0.1 mm/sec). In 2 of 5 animals, an additional 0.8 mg/kg droperidol was given as IV bolus and epinephrine repeated.

Results. The stenosis produced CFR in all five dogs. Reductions in flow lasted 4-7 minutes before platelet thrombi were mechanically dislodged and coronary flow restored (Fig.1). Ischemic ECG changes were observed during low coronary flow levels as were slight decreases in aortic arch pressure. Droperidol (0.2 mg/kg) IV produced complete abolition of CFR within 2 minutes in all five animals (Fig. 1 at a). Mean aortic blood pressure was reduced 8 ± 2 mmHg ($p < 0.05$). CFR remained absent during the 30 min observation period. During epinephrine infusion CFR recurred in all five animals. Figure 2 shows return of CFR following epinephrine infusion despite the presence of droperidol. However, following additional doses of droperidol at points labelled "c" (total dose 0.8 mg/kg) the CFR were abolished and remained absent desite the epinephrine infusion. In all cases droperidol administration produced reversal of established CFR or spontaneous restoration of flow in vessels occluded with platelet thrombi.

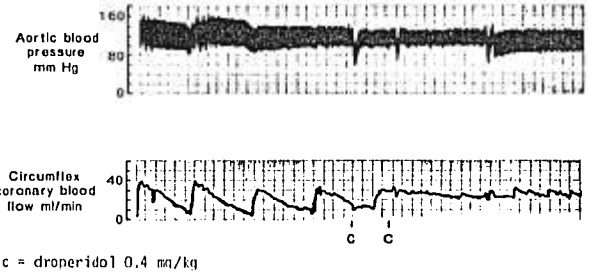
Discussion. These results show a prompt antithrombotic effect of low dose droperidol in stenosed coronary arteries of pentobarbital anesthetized dogs. The mechanism may involve antagonism of platelet alpha or 5-HT receptors by droperidol or membrane stabilizing effects of droperidol on the platelet membrane. The effects of droperidol in vessel wall-platelet interactions and platelet aggregation in man are unknown, however, this data suggests droperidol may have a beneficial antithrombotic effect. In addition, it may offer protection even in the presence of high catecholamine levels.

Figure 1



a = droperidol 0.2 mg/kg

Figure 2



c = droperidol 0.4 mg/kg

References.
1. Folts JD: Experimental platelet thrombosis, platelet inhibitors, and their possible clinical relevance. Cardiovasc Rev Rep 3:370-382, 1982
2. Bertha BG, Folts JD: Protection against epinephrine exacerbated acute platelet thrombus formation in stenosed dog coronary arteries with chlorpromazine and mesoridazine. Fed Proc 41:1236, 1982.