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Effect of Etoxadrol on Coronary Blood Flow and Cardiac Dynamics[1] (37743)

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With the introduction of ketamine (Ketalar, Ketaject) in February of 1970, an era of new anesthetic drugs began. This type of agent has been termed dissociative anesthesia (1). Etoxadrol (also known as CL-1848 C or [(+)-2-(2-ethyl-2-phenyl-1,3-dioxylan-4-yl) piperidine HCl] is a drug of a chemically different nature but possessing pharmacologically similar activity to ketamine in terms of the alterations in cardiovascular and respiratory status they produce (2–4). Concerning the cardiovascular system, a prominent tachycardia occurs which results in an elevation of cardiac output and systemic arterial pressure. These factors increase the work of the heart with a resultant increased myocardial oxygen demand and consumption. For this reason we considered it important to know the effects of etoxadrol on the coronary circulation, reasoning that if the drug produced a coronary vasoconstricting action in concomitance with the increased oxygen demands of the heart that it would have serious limitations in certain categories of patients. Conversely, if the drug dilated the coronary system, adverse effects on a stimulated heart would be of less concern. This study was designed to answer this question.

Methods. This study was performed on 10 healthy mongrel dogs of either sex, ranging in weight from 22 to 25 kg. The animals were anesthetized with 30 mg/kg of intravenous pentobarbital. No additional anesthesia was administered during the experiment. The animals' tracheas were intubated and they were allowed to breath spontaneously until later in the protocol. They were placed on a water-flow thermal blanket so as to maintain body temperature in the range of 37.5–38.5°. This variable was recorded with a rectal probe thermister and a Yellow Springs telethermometer. A midline incision was made in the neck so as to expose the right carotid artery. Two femoral cutdowns were also made. Through the femoral vein a polyethylene catheter was placed in the right atrium for recording of the central venous pressure (CVP) and injections of drugs. A Teflon cardiac catheter was positioned in the left ventricle via retrograde cannulation of the femoral artery. Arterial blood pressure was monitored from the opposite femoral artery.

The animals were positioned on their right side and positive pressure ventilation with a Bird Mark VIII respirator and 100% oxygen was instituted. A left thoracotomy was performed parallel to the ribs in either the third or the fourth interspace so as to expose the left lateral aspect of the heart. The left main coronary artery, as it emerged from the aorta, was freed by careful dissection and two loose ligatures were positioned around it. The animals were heparinized with 300 units/kg of sodium heparin. An external loop primed with the animals' own blood was then established between the previously isolated right carotid artery and the left main coronary artery. The cannulation of the latter was accomplished by a retrograde approach through the subclavian artery. This loop contained a Carolina Series 300 cannulating-type flow probe, ¼ in. in diameter. Distal to the flow probe (and

[1] A preliminary report of this work was presented: Annu. Meet. Amer. Soc. Clin. Pharmacol. Ther., 73rd, Houston, TX, 1972.

proximal to the coronary artery) was a side arm for measuring pressure. This was a modification of a technique originally described by Eckenhoff, Hafkenschiel and Landnesser (5). With the flow probe and side arm in the loop, coronary flow (CF) and pressure (CP), respectively, were monitored.

Left ventricular end diastolic pressure (LVEDP) and the maximum derivative of the left ventricular pressure (*dP/dt*) were measured with the left ventricular catheter. CP, LVEDP and the CVP were monitored with Statham P23Db transducers. CF was measured with a Carolina Model 321 square wave electromagnetic flowmeter. Recordings of all variables were made on an Electronics for Medicine DR 12 photographic oscilloscope recorder equipped with an electronic differentiator channel for obtaining the *dP/dt*. Heart rate was monitored from the R–R interval of the standard lead II EKG. Coronary vascular resistance was calculated as the mean coronary artery pressure minus the mean CVP divided by the mean CF. So as to eliminate the influence of extravascular factors (*i.e.*, myocardial compression of intramural coronary vessels) this was done with readings obtained in late diastole, the so-called late diastolic coronary vascular resistance (LCVR).

After all monitoring equipment was positioned, control readings of all variables were taken. Injections of either normal saline or the experimental drug were made via a 25 gauge needle inserted into the external perfusion loop distal to the flow probe. Thus these injections were made directly into the coronary blood stream. A 20 mg/ml solution of etoxadrol in normal saline was prepared fresh for each animal. By appropriate dilution with distilled water, the dosages described below were administered such that each injection consisted of only a 0.2 ml volume. Each animal served as its own control according to the following sequence of events. Control readings were taken after which a 0.2 ml injection of saline was made and any responses were recorded. Following this, another control was taken and a dose of the experimental drug was administered with similar recording of any changes in the variables. Sufficient time was allowed for all variables to return to the control level or stabilize and the sequence was repeated with a different dose. The dosages employed ranged from 0.125 to 4.0 mg and were increased in an arithmetic progression, *i.e.*, 0.125, 0.25, 0.5, 1.0, 2.0 and 4.0 mg to test for a dose response. In each dog a different sequence of the doses was followed so as to randomize the sequence of administration. Data comparisons were made between the presaline control (SC) and the postsaline changes (SC vs S), between the predrug control (DC), and postdrug changes (DC vs D). In addition, the changes for SC vs S were compared to the changes for DC vs D. Data were analysed using a Student's *t* test for paired data, with the 95% confidence limit (*i.e.*, $P < 0.05$) being considered statistically significant.

Results. Establishing the experimental set-up required an average of 90 min. The actual protocol required an additional 60 min, including time allowed between dosages. During the experimental period the changes in heart rate, central venous pressure, arterial pressure, $Pa\bar{O}_2$ and body temperature did not change significantly, remaining between 137–151 beats/min, −2.3 to −2.7, 85–98, 300–400 mm Hg and 37.7–38.0°, respectively. For this reason these variables are not presented graphically.

Figures 1 and 2 illustrate the observed mean changes for the other variables (see figure descriptions for complete details of figures). For all of the variables, as expected, there were no significant changes from control when saline was injected (solid bars). When etoxadrol was injected (stippled bars), there was a significant increase in mean coronary flow (MCF) and a significant decrease in late coronary vascular resistance (LCVR) for all dosages employed when compared to the predrug control values. A significant decrease in mean coronary pressure (MCP) was seen with all doses except for 0.125 and 0.5 mg. A small but significant depression of the ventricular *dP/dt* was seen only with the three larger doses, 1, 2 and 4 mg. The left ventricular end diastolic pressure (LVEDP) increased significantly only with the 4 mg dose. Dose–response curves for the changes

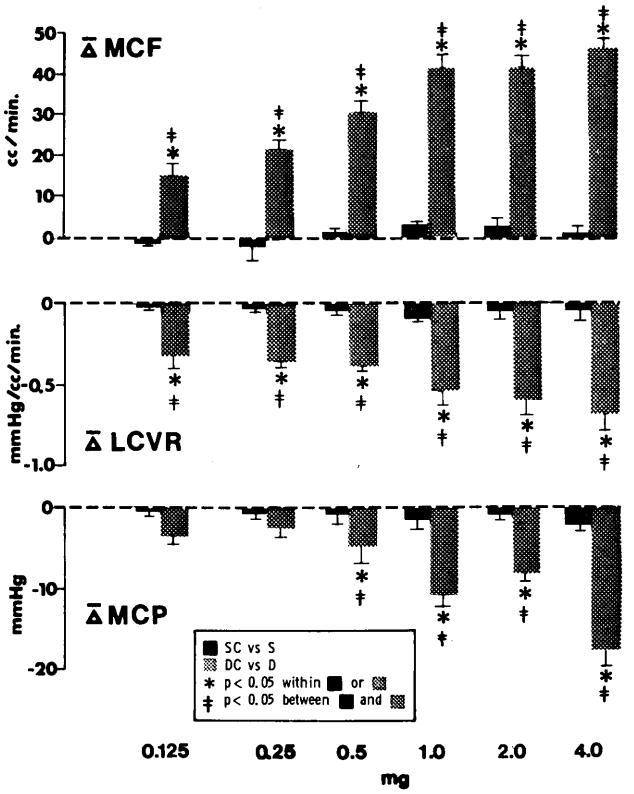

FIG. 1. The changes in mean coronary flow (MCF), late diastolic coronary vascular resistance (LCVR) and mean coronary pressure (MCP). Data are expressed on the ordinate as mean changes from the control values ± SEM for each of the dosages indicated. Control values were: 79–94 ml/min for MCF, 1.14–1.33 mm Hg/ml/min for LCVR and 88–98 mm Hg for MCP. Solid bars represent the changes observed when the saline injection (S) was compared to the presaline control (SC). Stippled bars represent the changes observed when the drug injection (D) was compared to the predrug control (DC). (*) Statistically significant changes after either the saline injection or the drug injection. † Significant differences between the saline response (solid bars) and the drug response (stippled bars).

in MCF, LCVR and MCP are shown in Fig. 3.

Discussion. To be sure that the observed changes were in fact due to etoxadrol, it was necessary to rule out certain other factors that could cause similar changes. All of the animals were ventilated with 100% oxygen and thus arterial hypoxia, a potent dilator of the coronary system, was not a factor. Since the drug injections were made directly into the coronary arteries, other cardiovascular changes that can augment coronary flow reflexly did not occur, *i.e.*, changes in blood pressure and heart rate. Cerebral hypoxia and carbon dioxide accumulation are two other factors that would augment sympathetic activity and thereby increase cardiac oxygen consumption and thus coronary flow. The former was eliminated by the high inspiratory oxygen concentration (F_1O_2) of the gas mixture. The latter was not felt to be a factor because of the continuous mechanical ventilation. Another factor to consider is pH changes from the drug injection itself. The pH of the stock solution of drug was 5.0. When 0.2 cc of this solution was mixed with 75 cc of arterial blood *in vitro,* the pH change was virtually nil. In light of this, it is felt that the observed changes could not have been due to pH alterations. The increased coronary flow was not due to changes in mechanical factors of the heart; *i.e.*, increased contrac-

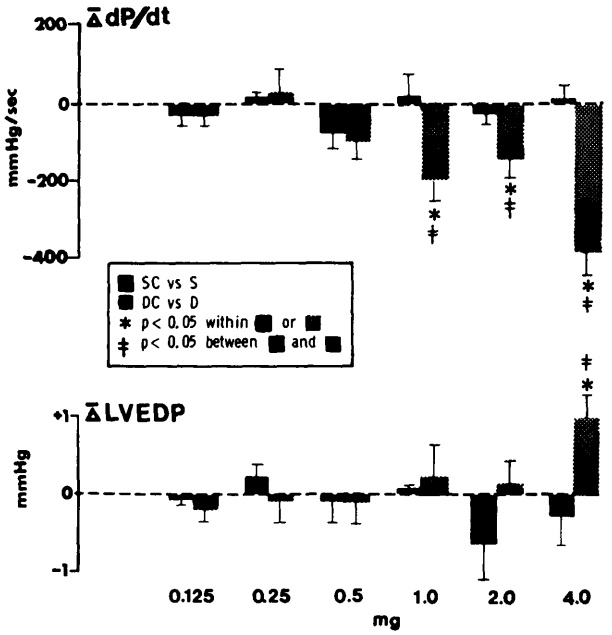

FIG. 2. The changes in left ventricular maximum *dP/dt* and left ventricular end diastolic pressure (LVEDP). Data are expressed on the ordinate as mean changes from the control values ± SEM for each of the dosages indicated. Control values were 1739 to 2262 mm Hg/sec for *dP/dt* and +2.7 to +4.6 mm Hg for LVEDP. Solid bars represent the changes observed when the saline injection (S) was compared to the presaline control (SC). Stippled bars represent the changes observed when the drug injection (D) was compared to the predrug control (DC). (*) Statistically significant changes after either the saline injection or the drug injection. † Significant differences between the saline response (solid bars) and the drug response (stippled bars).

tility as the *dP/dt* either did not change or decreased with the larger doses. A decrease in contractile force would be expected to decrease coronary flow (6). The LVEDP was significantly increased only with the 4 mg dose. With the lower doses the *dP/dt* and LVEDP did not change but coronary resistance and flow were still decreased and increased, respectively.

Concerning the changes observed in this study for *dP/dt* and LVEDP, indications of myocardial depression were only noted with the 1, 2 and 4 mg doses as previously stated. These results agree with data for intravenous administration of etoxadrol in intact animals in which 2.5 and 5 mg/kg did not alter *dP/dt* or LVEDP significantly but 10 mg/kg did cause changes in these two variables indicative of myocardial depression (3). In this study the depression of *dP/dt* was small, only averaging 150–350 mm Hg/sec, but was significant because it was a consistent response. This mild depression evidently was not severe enough with the 1 and 2 mg doses to cause any increase in the end systolic volume so as to increase end diastolic volume and LVEDP.

The dosages employed in this study were arrived at by hypothetically calculating the amount of drug that the dog heart is exposed to with a canine-anesthetizing dose of etoxadrol utilizing accepted figures for percentage cardiac output that is coronary flow and percentage of total coronary flow that travels via the left main coronary artery. Using such figures, it was calculated that with a 5 mg/kg iv dose, approximately 1.68 to 2.63 mg travels to the heart via the left coronary artery in 1 min. Thus a dosage range of etoxadrol was employed that would extend beyond both extremes of this range. The idea that etoxadrol has a direct coronary dilating action was further substantiated by intravenous injections. At the termination of each experiment an intravenous dose of etoxadrol equal

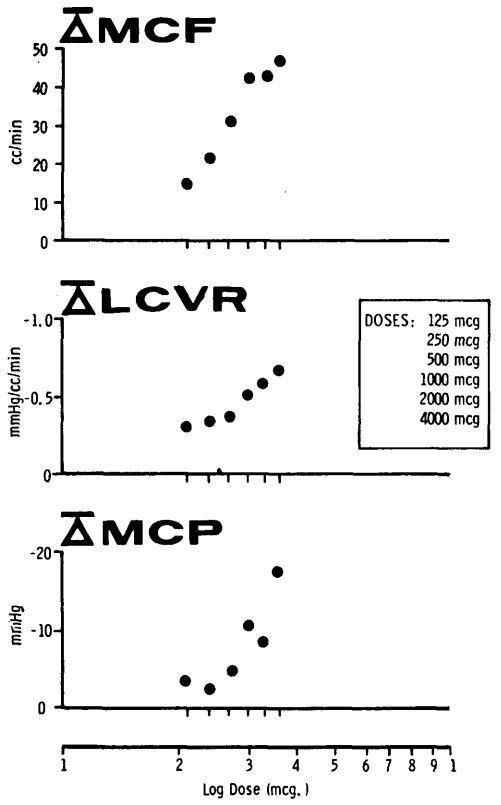

FIG. 3. The dose–response curves for mean coronary flow (MCF), late diastolic coronary vascular resistance (LCVR) and mean coronary pressure (MCP). These values are plotted as the mean changes from the control values on the ordinate against the log of the etoxadrol dose in micrograms on the abscissa.

to the sum of the six individual doses (7.875 mg) was administered. This has no significant effect on any of the variables recorded.

An important aspect of any new drug or class of drugs that have the potential for use in individuals with compromised coronary systems is consideration of what that drug does to the coronary system and cardiac dynamics. This is especially important if the drug also has properties which cause changes that increase myocardial oxygen requirements, as etoxadrol does. This study has supplied this information for etoxadrol. The results of the data presented indicate that etoxadrol, when given directly into the coronary arteries, has a vasodilating action on this vascular bed that is dose-related. This was evidenced by decreases in coronary resistance and corresponding increases in coronary artery blood flow measured electromagnetically. A mild depression of the cardiac contractile status was also noted, but only with the larger doses.

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