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Title : I.V. MINOXIDIL: A POTENTIAL DRUG FOR AFTERLOAD REDUCTION

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Introduction. Minoxidil (Loniten) is a potent antihypertensive agent used in patients who do not respond to routine antihypertensive treatment. Oral minoxidil is reported not to cause blood pressure reduction below normotension (80 diastolic), however, preliminary studies in our laboratory demonstrated significant afterload reducing properties in dog when minoxidil is administered via the intravenous route. The present study was carried out to measure the afterload reducing properties of minoxidil, the associated hemodynamic changes and the sympatho-adrenal response to pressure reduction by intravenous minoxidil for the purpose of determining the potential use of this drug for control of blood pressure.

Methods. A total of 25 adult male beagle dogs were used, weighing 11-15 kg. Following anesthetic induction using sodium pentothal, the dogs were intubated and mechanically ventilated. Maintenance anesthesia consisted of N_2O (1L), O_2 (2L), and enflurane (1.5-2.0%). A butterfly IV was placed in the forelimb for the administration of fluids and drugs. A Cordis introducer was placed in the right external jugular vein, thru which a 7-French thermal dilution Swan-Ganz catheter was placed to the wedge position for hemodynamic measurements. Cardiac output was triply measured by thermal dilution. In addition, a percutaneous intra-arterial catheter was placed in the femoral artery for blood pressure and blood gas measurements. Continuous heart rate was monitored via Lead 2 electrocardiogram. A femoral vein catheter was positioned 2 cm cephalad to the adrenal gland outflow for catecholamine sampling. Urine output was monitored using a balloon tipped catheter. Body temperature was kept at 36-37°C using a heating blanket. Afterload reducing properties, hemodynamic measurements and adrenal epinephrine and norepinephrine release was determined in anesthetized dogs at 30-minute intervals before and after administration of intravenous minoxidil over the range of 0.01 to 5.0 mg/kg. For comparison, minoxidil's afterload reducing properties were studied in non-anesthetized dogs.

Results. In the enflurane anesthetized dog, minoxidil was found to have significant afterload reducing properties over the range of IV doses from 0.1 to 3.0 mg/kg (18-70%↓XBP). Analysis of the data by linear regression provided a highly significant correlation, of 0.969 ($p<.0001$). Selected minoxidil doses administered in the unanesthetized dog produced reductions in mean blood pressure as predicted from the dose response curve of the anesthetized dogs. Hemodynamic results demonstrated the expected dose related fall in total vascular resistance accompanying the decline in blood pressure. Cardiac output, on the other hand, increased in proportion to the drop in blood pressure. Surprisingly, heart rate changed little even when mean blood pressure was reduced by more than 40%. The sympatho-adrenal responses to afterload reduction by minoxidil were minimal to 30%↓or greater from control when significant increases in adrenal epinephrine and norepinephrine occurred ($p<.05$). Doses between 0.01 and 0.10 mg/kg provided erratic and unpredictable results. At these lower doses blood pressure did not lower except for an occasional dog. However, heart rate and total vascular resistance increased significantly with a decline in cardiac output. Adrenal epinephrine and norepinephrine release increased significantly ($p<.05$) 114 and 80 percent, respectively with minoxidil doses of <0.1 mg/kg.

Discussion. The demonstrated ability of minoxidil to lower blood pressure in dogs during anesthesia in a dose-related fashion suggests its potential value for afterload reduction. IV or oral minoxidil has a similar slow 30-60-minute onset of action which prevents dose titration to the desired pressure, i.e. nitroprusside and nitroglycerin. On the other hand, the long 24-48 hour duration of pressure reduction, which was found to be very stable, may offer an advantage over nitroprusside infusion with its risk of cyanide toxicity. In several experiments, we attempted reversal of minoxidil's hypotensive action using a variety of agents and found phenylephrine infusion to provide adequate reversal of the hypotension. Mean pressure reductions of less than 10 percent from baseline were judged unsatisfactory by ou results. Based upon these first results on the afterload reducing properties of minoxidil, we feel that further studies are warranted on its use as a hypotensive agent.