The Effect of Intravenous Lidoflazine on Serotonin-Induced Cerebral Vascular Contraction — An In Vivo Study

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SUMMARY Lidoflazine, a piperazine derivative with known selectivity for vascular smooth muscle, was evaluated as a possible agent for prophylaxis of cerebral vascular contraction induced by subarachnoid perfusion with serotonin. The animals treated with serotonin (5 x 10^-6 M) had a 60% reduction in the diameter of basilar artery but when pretreated with Lidoflazine (1 mg/kg) intravenously, only had a 20% reduction in diameter (p < 0.01). Lidoflazine, when administered intravenously at a slow rate will not adversely lower systemic blood pressure and can prevent the contraction of cerebral vessels when the stimulus for contraction is in the subarachnoid space.

CEREBRAL VASOSPASM after subarachnoid hemorrhage is a major cause of morbidity and mortality in this patient population. Much interest has evolved in the use of calcium antagonists in the prophylaxis and reversal of cerebral vasospasm. Many drugs evaluated experimentally in the prophylaxis of vasospasm have either been applied topically to a vessel or have been shown to have no effect when given intravenously because of poor lipid solubility or instability in solution. Lidoflazine, a piperazine derivative and calcium antagonist, is a potent coronary artery dilator which has been used in Europe for the treatment of exertional and vasospastic angina. The purpose of this study was to determine the efficacy of this drug when administered intravenously to prophylax against basilar artery contraction produced by subarachnoid perfusion with serotonin.

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Methods

Experiments were carried out in Sprague-Dawley rats weighing approximately 350 grams. The animals were initially anesthetized with 1.5% Halothane, nitrous oxide, and oxygen. After completion of tracheostomy, pancuronium bromide 0.05 mg/kg was administered intravenously for skeletal paralysis and ventilation was controlled. Cannulae were placed in the femoral artery for determination of blood gases and measurement of blood pressure, the femoral vein for administration of fluids and drugs, and the internal jugular vein for measurement of central venous pressure. Anesthesia was then maintained with Fentanyl 20 mcg/kg and oxygen, a technique to minimize cerebral vascular reactivity and alterations in cerebral blood flow. The arterial blood pressure and central venous pressure were maintained in a physiologic range. The partial oxygen pressure was kept at 100-150 mm Hg and the partial carbon dioxide pressure was maintained at 38-42 mm Hg. Clivectomy was then performed and the dura was opened. The basilar artery and its branches, as well as pial circulation were readily identified. The arachnoid was opened and the subarachnoid space was perfused in the following manner:
Two 27 gauge catheters were placed in the subarachnoid space; one for irrigation and the other for suction. In this manner, slow continuous delivery of the perfusate was delivered. Thirty minutes was allowed for equilibration before any measurements were taken. After that time period, the four groups were divided as follows: (Group 1) Five animals were perfused with 0.9% saline at 37°C and adjusted to a pH of 7.40; (Group 2) Five animals were perfused with serotonin $5 \times 10^{-6}$ M; (Group 3) Five animals were pre-treated with Lidoflazine 1 mg/kg intravenously and then perfused with the serotonin solution; (Group 4) Five animals were perfused with saline, as previously described, and then given Lidoflazine 1 mg/kg intravenously. Color slide photographs (Ektachrome 400 daylight film) were made of the basilar arteries through a Zeiss dissecting microscope at a magnification of 40 x. A micrometer scale was photographed using the same magnification. The image of the micrometer scale was projected on a digitizing table connected to an Apple II pulse computer for calibration of length measurements. The diameters of the basilar arteries were determined by projecting the images of the vessel on the digitizing table and tracing out their dimensions over a distance of at least 2 mm. The mean diameter of each vessel was then calculated.

**Results**

The results of the four groups are listed in table 1. In group 1, there were no significant changes in vessel diameter over a sixty minute period. There were also no significant changes in blood pressure or CVP. Group 2 had a 60% reduction in vessel caliber when serotonin was added to the subarachnoid space perfusate. A 10–15% rise occurred in blood pressure and CVP. Group 3 had only a 20% reduction in vessel diameter and no significant fluctuations in blood pressure or CVP. Group 4 had no significant changes in vessel diameter, blood pressure, or CVP. Using an analysis of variance, the diameter changes were analyzed indicating that the reduction in vessel diameter after intravenously administered Lidoflazine was significantly less in those treated with serotonin alone ($p < 0.01$).

**Discussion**

In that Lidoflazine is a drug relatively unknown in North America, a brief description of its cardiac and cerebrovascular pharmacology is in order.

In numerous animal studies the drug has been shown to improve the function of the failing or ischemic myocardium. It has been shown to reduce arterial impedance and splanchnic tone, decrease heart rate, augment coronary perfusion and antagonize the response of coronary vascular smooth muscle to vasoconstrictive stimuli which may be involved in the genesis of coronary vasospasm. Evidence has shown that cardiac output decreased significantly less in the Lidoflazine group as compared to other calcium antagonists. Arterial blood pressure and heart rate remain more stable with Lidoflazine as compared to other agents with a similar site of action.

The protective effect of Lidoflazine on ischemic and reperfused cardiac muscle has been demonstrated in several studies. Evidence of protection was provided by maintenance of near normal tissue stores of ATP, creatine phosphate and the maintenance of the oxidative phosphorylating and ATP generating capacity of the mitochondria. Studies have also demonstrated similar actions and protective effects in the brain after circulatory arrest.

Although studies have focused on the cerebral protective effects of Lidoflazine, little attention has been focused on the cerebrovascular reactivity to this drug. The first step in evaluating this drug for potential use in the treatment of vasospasm after subarachnoid hemorrhage was to determine whether this agent has any effect on cerebral vascular contraction and relaxation.

These results of this study demonstrate:

1) Intravenous Lidoflazine can prevent the contraction of cerebral vessels when the stimulus for contraction is in the subarachnoid space, a situation analogous to subarachnoid hemorrhage.

2) Lidoflazine, when administered intravenously at a slow rate, will not adversely lower systemic blood pressure, an important consideration in a patient with impaired cerebral perfusion perhaps secondary to cerebral vasospasm after subarachnoid hemorrhage.

The potential theoretical advantages of Lidoflazine include:...
in the prophylaxis and treatment of cerebral vasospasm are several. First, it has a known specificity for small vessels and no significant effects on the myocardium, both important considerations in maximizing cerebral blood flow. Second, it has excellent lipid solubility, a prime consideration in crossing the blood-brain barrier. Third, it reduces in vitro collagen and thrombin induced platelet aggregation and ADP induced platelet aggregation, as well as inhibiting 14C-5-hydroxy-tryptamine release, all postulated contributors to the ischemic syndrome of subarachnoid hemorrhage.

Although it is realized that serotonin alone is not the cause of clinical cerebral vasospasm, this study demonstrates that intravenous Lidoflazine can prophylactically prevent basilar artery contraction induced by a vasogenic compound in the subarachnoid space, a situation analogous to that seen in patients who develop vasospasm after rupture of an intracranial aneurysm. More in vivo studies using this drug to prevent chronic vasospasm are needed before its true efficacy can be determined.

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