A retrospective analysis of labetalol use in management of hypertensive crisis associated with cocaine use.

Josh Leitner

A. Introduction

Hypertensive emergencies are acute, life-threatening marked elevations of systemic blood pressure associated with signs of end-organ dysfunction. While various terms are used to describe different, over-lapping clinical entities, a commonly –used approach includes categorizing hypertensive emergencies into 1) Malignant Hypertension and 2) Hypertensive Encephalopathy. Hypertensive encephalopathy, a specific subset of malignant hypertension, refers to signs of cerebral edema caused by hyperperfusion and arteriolar damage resulting from extremely elevated blood pressures that have exceeded the auto-regulatory range of the arteriolar bed and have caused disruption of vascular walls, allowing plasma constituents to enter the vascular wall. This is manifest clinically by subacute onset of headache, nausea, vomiting, and nonlocalizing neurologic symptoms including restlessness, confusion, seizures and coma.

Malignant hypertension (often termed hypertensive emergency or hypertensive crisis) can be defined as marked elevations of blood pressure with the presence of end-organ dysfunction. Typically, no specific values are used to define this syndrome, instead relying on pathophysiologic sequelae. The range of end-organ dysfunction affects a number of different organ beds. Neurologic and cerebrovascular sequelae included within malignant hypertension (in addition to signs of cerebral edema as discussed above) includes hemorrhagic or ischemic CVA. Cardiovascular manifestations can include acute left ventricular failure with pulmonary edema, acute aortic dissection, and acute MI. Renal manifestations include malignant nephrosclerosis leading to acute renal failure, hematuria, and proteinuria.

Treatment of malignant hypertension involves use of parenteral agents, often constant infusions, and close monitoring of systemic blood pressure. Oral agents, with slower onset of action and less precise control of blood pressure, are avoided in this clinical setting. Goals of drug therapy usually target a diastolic BP of 100-105 within 2-6 hours of initiation of therapy, with a maximal fall in systolic BP no greater than 25% of presenting value. More aggressive or accelerated lowering of systemic BP can lower the BP below the auto-regulatory range can be associated with ischemic events.

There are multiple agents available for the initial treatment of hypertensive emergencies. These fall generally into 2 categories of agents: 1) vasodilators (including nitroprusside, nitroglycerine, nicardipine, hydralazine, enalaplrilat, and fenoldopam) and 2) adrenergic inhibitors (including phentolamine, esmolol, and labetalol). Choice of agent typically is indicated by adverse effect profile, with little comparative studies regarding efficacy, although expert opinions cite similar efficacy among classes.

Labetalol is a combination alphia-1 and non-selective beta-receptor blocker, available in oral and parental forms, including sequential administration as well as infusion. In general, labetalol is a stronger beta blocker than it is an alpha receptor blocker with a ratio of 1:3 (PO) and 1:7 (IV) alpha: beta receptor blockade described. Labetalol is generally considered to be safe and efficacious in the management of malignant hypertension, and remains a frequently used agent. The significant clinical scenarios that would preclude the use of labetalol include asthma, severe COPD, decompensated CHF, bradycardia or 2nd or 3rd degree AV block.

Cocaine is a commonly used drug of abuse, with a 1999 survey demonstrating 3.7 million US users within the prior year and 1.5 million current users. Cocaine was associated in 30% of all drug-related ED presentations, and is the most commonly used illicit drug among patients seeking care in hospital emergency departments. Cocaine mediates its effects by blocking reuptake of norepinephrine by the preganglionic receptor, thereby altering sympathetic tone. In general, through its activity on different

adrenergic receptors, cocaine produces a host of systemic effects. Through activation of beta-1 receptors, cocaine increases heart rate, myocardial contractility, and consequently both cardiac output and myocardial oxygen demand. These cardiac parameters are also thought to be modulated via a central mechanism, as well. Through activation of alpha-1 receptors, decreased nitric oxide production, and increased endothelin production cocaine mediates increases in systemic blood pressure. Other important cardiovascular consequences of cocaine use include increased platelet activation and aggregability, and increased endothelial permeability, making cocaine use an important risk factor for ischemic and atherosclerotic heart disease.

Indeed, direct coronary vasospasm effects of cocaine were described by Lange et al in 1989. In this trial, 45 patients who were undergoing cardiac catheterization for evaluation of chest pain were randomized to receive either 2 mg/kg of intranasal cocaine (in 29 patients - doses used as topical anesthetic in ENT procedures) or intranasal saline (in 16 patients). Cocaine administration demonstrated a significant decline in coronary sinus blood flow and significant decreased in LAD diameter. These values returned to base-line values upon administration of phentolamine.

Given the hyper-adrenergic state induced by cocaine use, it appeared reasonable that adrenergic-receptor blocking agents would prove useful in management of cocaine-induced clinical syndromes. In 1990, however, Lange et al published another study in which 30 patients referred for cardiac catheterization for evaluation of chest pain were administered either intranasal cocaine or saline, and then intracoronary administration of propranolol. Again was noted increased HR and BP in the cocaine group, as well as a significant decrease in coronary artery diameter. Propranolol administration showed no change in arterial pressure or rate-pressure product, but showed a further decrease in coronary sinus blood flow and coronary vasculature resistance. The putative mechanism for these findings are that non-selective beta-blockers leave the high levels of circulating catecholamines free to bind to alpha receptor blockers, and that this "unopposed alpha" activity mediates both coronary vasoconstriction and peripheral vasoconstriction leading potentially to worsening systemic blood pressure. Doshi et al in 1984 observed a similar state induced in healthy volunteers by infusion of epinephrine. Pretreatment with propranolol resulted in increased diastolic pressure while labetalol pretreatment did not. Indeed, based on these and similar findings, the AHA guidelines for the treatment of cocaine-related ischemia or infarction list propranolol as an agent to be avoided.

Given labetalol's pharmacodynamic profile of blocking both alpha and beta receptors, it stands to reason that this combined blockade might circumvent the complications on beta-only blockade in cocaine users. Boehrer et al assessed the effects of labetalol vs. saline on coronary artery diameter and mean arterial pressure after administration of intranasal cocaine in patients undergoing cardiac catheterization for chest pain. This group found a reduction in mean arterial pressure in the labetalol group vs. the saline group, but no change in the coronary arterial area.

Other descriptions of labetalol's efficacy in the setting of elevated hemodynamic disarray and cocaine use remained on the case report level. (Labetalol treatment of cocaine toxicity; Use of Labetalol in management of cocaine crisis). Little evidence exists demonstrating that labetalol is a safe and effective agent for management of malignant hypertension in patients with positive cocaine urine toxicology screens. In clinical practice, the choice of labetalol is frequently prescribed, even in the absence of a documented drug history or urine toxicology screen. Therefore, it is not an uncommon clinical scenario for a patient to have received labetalol in the emergency department, only to find out later that the patient has a urine toxicology screen positive for cocaine, calling into question the choice of labetalol. Therefore, an analysis of the experience of these patients treated with labetalol would be valuable for guiding further management choices.

B. Hypothesis

It is hypothesized that labetalol is a safe and effective agent for the management of malignant hypertension in cocaine users.

C. Methods

a. This study will measure the efficacy and safety of labetalol in the management of malignant hypertension in patient with cocaine-positive urine toxicology screens.

b. This study will be a retrospective analysis of patients presenting to the emergency department with malignant hypertension. From this total population, those that have urine toxicology screens positive for cocaine will be studied. This study will compare those patients with malignant hypertension and positive cocaine urine toxicology screens treated with labetalol to those patients with malignant hypertension and positive cocaine toxicology screens treated with other anti-hypertensive agents. The primary outcome will be systemic blood pressure at presentation, 6 and 24 hours after medicine administration.

c. Statistical analysis will include a t-test for the primary outcome or post-treatment blood pressures among the 2 groups (labetalol and non-labetalol).

d. Sample Size / Power Analysis:

Analyzing charts over a 5-year period, it is estimated that at least 240 cases of malignant hypertension will be encountered. Of these, at least 30% are expected to have cocaine-positive urine toxicology screens, giving a total study population of 72 cases. It is further expected that 60% of these cases would be treated with labetalol, giving an N of 42 for the labetalol group and 30 for the non-labetalol group.

The primary outcome will be a comparison of the mean change in blood pressure from presentation to 24 hours post-treatment in the two treatment groups. Expected values for blood pressure measurements (220/100), coupled with a clinical goal of a 20-25% reduction in systolic blood pressure, allow the assumption of a mean of 44-55 in each treatment group. A sample size of 12 & 36 in each group would be sufficient to find this difference significant.

Assuming a standard deviation of 10 in the labetalol treatment group, a difference of 5 in the mean change of blood pressure can be detected with an alpha of 0.05, and power of 0.8.

D. Subject selection

This is a retrospective analysis that will include patients with malignant hypertension and positive cocaine urine toxicology screens. A subject of significant concern will be that the comparison groups comprise similar clinical. It is unclear at the outset what will have been some of the factors that prompted the choice of agent for BP management away from labetalol toward another class, but will likely include some of the contraindications to beta blockade (reactive airway disease, pulmonary edema, bradycardia, cardiac conduction disease) as well as physician preference.

Given that the entire study group involves a vulnerable population, the data will be made confidential to protect the identities of the patients whose data will be utilized in the study.

E. References

Grossman E, Ironi AN, Messerli FH. Comparative tolerability profile of hypertensive crisis treatments. Drug Safety. 1998 Aug 19(2) 99-122.

Lange RA, Cigarroa RG, Flores ED, McBride W, Kim AS, Wells PJ, Bedotto JB, Danziger RS, Hillis LD. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. Annals of Internal Medicine. 1990 Jun 15; 112(12): 897-903.

Lange RA, Cigarroa RG, Yancy CW, Willard JE, Popma JJ, Sills MN, McBride W, Kim AS, Hillis LD. Cocaine-induced coronary-artery vasoconstriction. N Eng J Med. 1989 Dec 7; 321(23) 1557-1562.

Lange RA and Hillis LD. Cardiovascular Complications of Cocaine Use. N Eng J Med. 2001 Aug 2; 345(5)351-358.

Boehrer JD, Moliterno DJ, Willard JE, Hillis LD, Lange RA. Influence of labetalol on cocaine-induced coronary vasoconstriction in humans. Am J Med. 1993 Jun; 94(6): 608-10.

Gay GR, Loper KA. The use of labetalol in the management of cocaine crisis. Ann Emerg Med. 1988 Mar; 17(3): 282-3.

Gay GR, Loper KA Control of cocaine-induced hypertension with labetalol. Anesth Analg. 1988 Jan; 67 (1):92.

Dusenberry SJ, Hicks MJ, Mariani PJ. Labetalol treatment of cocaine toxicity. Ann Emerg Med. 1987 Feb; 16(2) 235.

Thakur V, Godley C, Weed S, Cook ME, Hoffman E. Case reports: cocaine-associated accelerated hypertension and renal failure. Am J Med Sci. 1996 Dec; 312 (6): 295-8

Doshi BS, Kulkarni RD, Dattani KK, et al: Effects of labetalol and propranolol on responses to adrenaline infusion in healthy volunteers. J Clin Pharm Res 1984; 4:29-33.