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Urapidil Versus Clonidine
Acute Haemodynamic Effects During Control of Intraoperative Hypertensive Episodes

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Acute arterial hypertension is a haemodynamic complication that develops in more than 30% of patients undergoing coronary artery bypass surgery (Kaplan et al. 1976; Tobias 1981). The intraoperative episodes occur after sternotomy, especially during pericardial traction and manipulation of the aortic root; postoperatively, the emergence from anaesthesia is often accompanied by arterial hypertension.

In patients with coronary artery disease, arterial hypertension can provoke myocardial ischaemia if myocardial oxygen requirements exceed oxygen supply. Therefore, rapid control of the arterial hypertension by antihypertensive therapy is necessary and important.

The purpose of this study was to evaluate the efficacy of urapidil and clonidine in the management of intraoperative hypertensive episodes. Both drugs are approved antihypertensives and can be administered intravenously. Their pharmacodynamic profiles are, however, quite different: urapidil possesses peripheral α_1-adrenergic antagonistic activity and centrally acting effects on serotoninergic receptors, whereas clonidine has α-adrenoceptor agonist activities in the brain and the peripheral adrenergic nerves.

1. Patients and Methods

30 patients with good left ventricular function scheduled for elective coronary artery bypass surgery were studied. This study fulfilled Human Investigation Committee guidelines of the institution.

The patients were premedicated with oral flunitrazepam. All necessary catheters were placed using local anaesthesia, and general anaesthesia was induced using flunitrazepam (0.01 to 0.015 mg/kg), fentanyl (0.01 mg/kg) and pancuronium bromide

Table I. Changes in haemodynamic parameters in the first 9 minutes after intravenous bolus injection of urapidil or clonidine

	Minutes after drug administration						
	0.5	1	2	3	5	7	9
Urapidil (0.45 mg/kg; n = 15)							
MAP (mm Hg)	−32*	−25*	−19*	−21	−22	−23	−26
HR (beats/min)	7	7	8*	8*	10	10	11
TPR (dyn · sec · cm^{-5})		−806*		−700	−658	−716	−730
CO (L/min)		0.5		0.4	0.3	0.4	0.3
Clonidine (1.36 μg/kg; n = 15)							
MAP (mm Hg)	10	5	2	−12	−17	−24	−29
HR (beats/min)	8	−7	−8	−8	−5	−6	−5
TPR (dyn · sec · cm^{-5})		−27		−230	−248	−504	−645
CO (L/min)		0.2		−0.2	−0.3	−0.3	−0.3

Abbreviations: MAP = mean arterial pressure; HR = heart rate; TPR = total peripheral resistance; CO = cardiac output.
* = Statistically significant difference between urapidil and clonidine ($p < 0.05$).

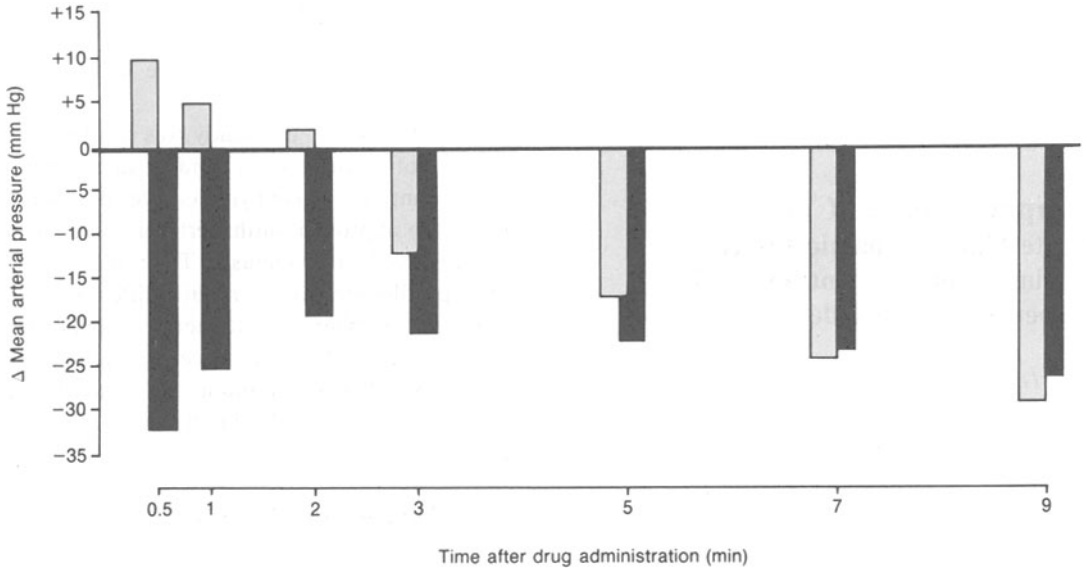

Fig. 1. Changes in mean arterial pressure during the first 9 minutes after intravenous bolus administration of urapidil (■; n = 15) or clonidine (▨; n = 15).

(0.01 mg/kg). Patients were normoventilated with a gas mixture of 50% oxygen and 50% nitrous oxide. Before skin incision and sternotomy, additional doses of fentanyl 0.005 mg/kg were given. During surgery, anaesthesia was supplemented with isoflurane 0.5 vol. %.

When mean arterial pressure increased to 110mm Hg, as a result of sternal spread or surgical manipulation of the aorta, patients were given antihypertensive treatment. The 30 patients were randomised in a double-blind manner to receive urapidil (0.45 mg/kg) or clonidine (1.36 μg/kg). In the following 9 minutes haemodynamic measurements, including cardiac output, heart rate, mean arterial pressure, mean pulmonary arterial pressure, pulmonary capillary wedge pressure, and right arterial pressure, were performed. Total peripheral resistance was calculated from a standard formula.

Data are presented as the means of the absolute changes from the initial values of the haemodynamic parameters in response to each drug.

2. Results

The changes in haemodynamic variables observed during treatment are summarised in table I. Clonidine treatment resulted in a further increase in elevated arterial pressure in 14 of 15 patients. After 3 minutes, mean arterial pressure fell below 110mm Hg (the value at which antihypertensive therapy was initiated). The mean arterial pressure of all 15 patients decreased immediately in response to urapidil, with an initial pronounced drop during the first minute (fig. 1). After 5 minutes, there was no apparent difference between urapidil and clonidine in the blood pressure decrease (fig. 1). There was a slight increase in heart rate with urapidil and a slight decrease with clonidine. Urapidil produced an immediate and distinct decrease in total peripheral resistance, whereas clonidine induced a minor vasodilatation, commencing at the third minute or later. Cardiac output was increased with urapidil but was lowered with clonidine.

3. Discussion

Several reports demonstrate that acute intra- and postoperative hypertension in patients with coronary artery disease is partially attributable to sympathetic stimulation (Roberts et al. 1977; Wallach et al. 1980). The rationale for controlling these episodes is that the more specifically a pathophysiological change is treated, the less the control of cardiovascular regulation is impaired. Consequently, in this type of hypertension, peripherally or centrally acting antiadrenergic drugs should be used. Urapidil and clonidine both interfere with sympathetic nerve activity but at different sites of the vasomotor control axis.

When intravenous clonidine is used, its peripheral α-adrenoceptor agonist activity causes an initial increase in blood pressure for 2 to 3 minutes. Later, the agonistic effect of clonidine at presynaptic α_2-adrenoceptors in the brainstem predominates and arterial vasodilatation occurs. Control of blood pressure with clonidine is accompanied by a decrease in heart rate and cardiac output resulting from inhibition of sympathetic outflow and stimulation of the baroreflex mechanism (Haensler 1975; Houston 1981). In contrast to clonidine, urapidil is a fast-acting vasodilator; it exerts a specific α_1-adrenergic blocking effect and as it does not suppress the presynaptic α_2-receptor activity at the sympathetic nerve endings, the physiological feedback of noradrenaline (norepinephrine) release is not compromised. Urapidil also causes a reduction in central sympathetic outflow by an interaction with serotonin$_{1A}$ receptors (Ramage 1986). These specific central and peripheral effects of urapidil prevent pronounced reflex tachycardia during vasodilatation. This is confirmed by our clinical study, in which only a small increase in heart rate could be observed in spite of a marked decrease in peripheral resistance. The increase in cardiac output with urapidil is partially the result of lowered aortic impedance.

Urapidil seems to be more suitable than clonidine for the control of acute arterial hypertensive episodes, because it produces an immediate effect and causes a more favourable haemodynamic profile.

References

Haensler G. Cardiovascular regulation by central adrenergic mechanisms and its alteration by hypotensive drugs. Circulation Research 36 (Suppl. 1): 223-232, 1975

Houston MC. Clonidine hydrochloride: review of pharmacologic and clinical aspects. Progress in Cardiovascular Diseases 23: 337-350, 1981

Kaplan JA, Dunbar RW, Jones EL. Nitroglycerin infusion during coronary-artery surgery. Anesthesiology 45: 14-21, 1976

Ramage AG. A comparison of the effects of doxazosin and alfuzosin with those of urapidil on preganglionic sympathetic nerve activity in anaesthetised cats. European Journal of Pharmacology 129: 307-314, 1986

Roberts AJ, Niarchos AP, Subramanian VA, Abel RM, Herman SD, et al. Systemic hypertension associated with coronary artery bypass surgery. Journal of Thoracic and Cardiovascular Surgery 74: 846-857, 1977

Tobias MA. Comparison of nitroprusside and nitroglycerin for controlling hypertension during coronary artery surgery. British Journal of Anaesthesia 53: 891-897, 1981

Wallach R, Karps RB, Reves JG. Pathogenesis of paroxysmal hypertension developing during and after coronary bypass surgery: a study of hemodynamic and humoral factors. American Journal of Cardiology 46: 559-565, 1980

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