Antihypertensive Effect Of Urapidil

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Summary:

Urapidil, an antihypertensive alpha receptor blocking drug, was given to 12 out-door patients for six weeks. Mean systolic pressure decreased from 180.8± 6.7 mmHg to 139.5 ±4.9 mmHg(P=<0.001). Mean diastolic pressure fell from 111.2± 3.9 mmHg to 85.5±1.8 mmHg (P=<0.001). Mean pulse rate dropped from 96.2 ±3.8/ min to 88.5±30/min (P=<0.05). No serious side effects were observed. No significant differences in laboratory tests were observed at the end of treatment.

Introduction:

The availability of several new antihypertensive agents enable the physicians to select a specific antihypertensive therapy for every different hypertensive patient in relation to the haemodynamic characteristics of the patient and the long term haemodynamic effect of each drug[1].

Urapidil a derivative of Uracil type (monosubstance), with single salt, is a new antihypertensive drug. In animal models and human trials it has shown significant reduction in mean arterial pressure by reducing total peripheral resistance[1,2,10,11,12,19].

Urapidil is a postsynaptic alpha 1 adrenoceptor antagonist[18-22,16,17] with mild alpha 2 adrenergic receptor agonist[16,17,22] property. It has central hypotensive effect by an action on brain stem[1,11,16,17,21]. Intracisternal administration of Urapidil in dogs has manifested a central hypotensive effect and suppression of reflex induced tachycardia[21]. It has also weak beta 1 adrenocepter blocking activity[17]. It is less potent as alpha receptor blocker than Prazosin[1]. It is found as effective as Sodium Nitroprusside in lowering blood pressure following coronary artery surgery[13].

Urapidil does not cause increase in heart rate[1,2,5,12,15,21,22] as shown in animal and human studies. However, reflex tachycardia in rats[2] and in humans[10] has been observed. Slight change in heart rate was also noticed by K. ZECH[3], cardiac output is either maintained[2,12] or is increased[11]. On echocardiography ejection fraction was not effected significantly[10].

Urapidil is metabolised to a major extent in the liver. It can be used safely in cirrhosis of the liver though with delayed metabolism[6]. Plasma renin activity, catecholamine activity, electrolytes and water balance are uneffected by Urapidil[15].

It mainly causes vasodilitation[1]. It is also active as renal vasodilator[20]. In conscious Goldblatt hypertensive rats and dogs it has caused renal arterial dilitation also[1]. It is eliminated through renal route[3]. It does not effect GFR,PAH and insulin clearance in the patients with chronic renal failure[8,9]. In end stage renal failure it can be used safely[7]. Urapidil is found highly effective in elderly patients[4].

Pregnancy induced hypertension (Pre-eclempsia, eclempsia) is associated with increase in total peripheral resistance (TPR)[14]. If TPR is increased, fetal circulation may be decreased. Urapidil is found better than Hydralazine in such cases[14]. Urapidil does not increase the intracranial pressure like Hydralazine or Diazoxide which may lead to intracranial haemorrhage[4]. No kind of untoward effect was observed in infants, neonates and mothers after the use of Urapidil[14].

The goal of this trial was to obtain diastolic blood pressure less than or equal to 90 mmHg in supine position and to observe untoward effects.

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Patients and Methods:

The study comprised 12 male and female out patients with essential hypertension. Patients were either taking antihypertensive treatment on which they were not controlled or were diagnosed recently. All treatments were stopped at least 72 hours before starting therapy with Urapidil.

TABLE NO. 1

SITTING BLOOD PRESSURE

	Before Treatment	After Treatment
Systolic Pressure	180.08±06.7mmHg	139.05±4.9*mmHg
Diastolic Pressure	111.02±03.9mmHg	85.05±1.8*mmHg
Mean Arterial Pressure	134.44 mmHg	103.55± mmHg
Mean Pulse Rate	096.02±03.8/min	88.05±3.0**/min

* p = <.001
**p=<.05

Exclusion criteria were:-

Marked renal or hepatic impairment.
Heavy smoking.
Pregnancy and lactation.
Severe left ventricular failure.
Patient under the age of 18 years.
Hypertensive patients responding to previous treatment.
Newly diagnosed patients with BP less than 95 mmHg.
Patients with coronary heart disease.

The study was conducted as an open uncontrolled study. All patients were followed weekly, their BP and pulse were recorded both in supine and standing position by the same observer. The point of disappearance of 5th Korotkoff sounds was taken as diastolic blood pressure Mercury sphygmomanometer was used to measure B.P.

Blood and urine samples were taken on the 1st and last visit of the trial. All patients were advised to come empty stomach between 8.00 a.m. to 11.00 a.m. All patients visited the clinic weekly except one patient who failed to report during his last visit.

Eight patients with diastolic pressure >=105mmHg were given B.D. dose. Only in 2 patients dose was increased to 60mg B.D. but due to untoward effects dose was decreased to 30mg B.D. with the addition of Calcium Channel blocker. 4 patients with diastolic pressure ≤104 mmHg were given 1 O.D. dose. Only in one patient the dose was increased to 1 B.D.

Statistical Analysis:

Twelve patients were included in this study (3 males and 9 females). Mean weight was 61.2±3.9 Kg (range 45-95Kg.) Mean height was 143.8±2.4 cm (range 140-170 cm). Mean duration of hypertension was 3.4±0.93 years (range newly diagnosed to 9 years). All patients except one were taking medicines but blood pressure was not controlled with these medicines.

Four patients were receiving Beta blockers, diuretics, and Aldomet combination therapy. 2 patients were taking Aldomet alone. 2 patients were taking Aldomet and diuretic combined. 2 patients were taking Beta blocker, diuretic and vasodilator. One was taking Aldomet and Beta Blocker. 9 patients were hypertensive for more than one year. One patient was diabetic whose diabetes was controlled on oral hypoglycemic agents.

TABLE NO. 2

STANDING BLOOD PRESSURE

	Before Treatment	After Treatment
Systolic Pressure	175.4±6.8	13.2±5.2*mmHg
Diastolic Pressure	114.9±4.3	90.4±2.4**mmHg
Mean Arterial Pressure	135	106 mmHg
Mean Pulse Rate	99.6±4.2	90.1±2.8 Min

* p = <.05
**p=<.02

Results:

Clinically:

Systolic and diastolic blood pressure decreased slowly during six weeks period. Mean systolic pressure on the 1st visit was 180.8±6.7 mmHg after 2 weeks it dropped to 165.8 ± 5.9 mmHg, after 4 weeks it was 148.3±5.3 and after 6 weeks it was

139.5 ± 4.9 mmHg in supine position. Mean diastolic pressure in the beginning was 111.2±3.9 mmHg, after 2 weeks it was 95.4±2.9 mmHg, after 4 weeks it was 90.75±2.60 mmHg and in the last visit mean diastolic pressure was 85.5±1.8 mmHg in supine position.

TABLE NO. 3

S. Triglycerides	189.07±16.3mg/dl	157.01±17.9mg/dl
S. Cholesterol	193.01±07.0mg/dl	187.04±7.2mg/dl
S. Creatinine	1.01±00.7mg/dl	1.02±0.07mg/dl
S. Potassium	3.07±00.1mg/dl	3.6±0.1mg/dl
S. Glucose	118.01±13.5mg/dl	112.00±9.9mg/dl
S.G.P.T.	14.04±02.8K.U/ml	17.02±2.8K.U/ml

Mean arterial pressure before starting therapy was 134.44 mmHg, after 2 weeks it was 118.8 mmHg, after 4 weeks it was reduced to 109.9 mmHg. At the end of trial the mean arterial pressure came down to 103.55 mmHg in supine position.

Diastolic pressure in 10 patients after 6 weeks was 90 mmHg. Only in 2 patients it was 100 mmHg. Systolic pressure in 9 patients was less than or equal to 150 mmHg. In three patients it was 160 mmHg after 6 weeks.

Mean pulse rate/min in the beginning was 96.2±3.8/min, after 2 weeks it was 93.0 ± 3.03/min, after 4 weeks it was 92.0±3.1/min, after 6 weeks mean pulse rate dropped to 88.55±3.00/min in supine position.

Laboratory Results:

Mean S. Triglycerides level before starting treatment was 189.7±16.3mg/dl after 6 weeks it reduced to 157.1±17.9mg/dl. Mean Serum Cholesterol level in the beginning was 193.1±7.0 mg/dl after 6 weeks it reduced to 187.4±7.2 mg/dl. Mean serum creatinine level initially was 1.1±0.07 mg/dl at the end of 6 weeks it was raised to 1.2±0.07 mg/dl. Mean serum potassium level was 3.79±0.19 meq/L. in the beginning while after 6 weeks it was reduced to 3.66±0.12 meq/L. Mean glucose level was 118.18±13.55 mg/dl in the beginning, after six weeks it was reduced to 112.00±9.97 mg/dl. Mean S.G.P.T. level was 14.45±2.80 K.U/ml initially, after 6 weeks it was raised insignificantly to 17.2±2.8 K.U/ml.

No statistically significant difference was observed in other laboratory tests like Hb., TLC, DLC, ESR and urine complete examination.

Side Effects:

Side effects were evaluated at weekly visit from both spontaneous complaints and direct questioning by the attending physician to the patient.

No serious side effect leading to withdrawal of treatment was observed. All the patients had complaint of transient burning sensation in the chest for 30 to 60 minutes after taking medicine. This complaint disappeared spontaneously within 2 to 3 weeks.

Five patients did not have any other complaint. One patient had transient skin rash, three patients had mild nausea and dizziness in early morning. Dry mouth, uneasiness, abdominal pain, palpitation and loose motion were reported only once. No active treatment was given for these complaints.

In two patients, one male and one female, Urapidil 60mg B.D. was given. Dose was reduced to 30 mg B.D. to overcome the complaint of enuresis.

Discussion:

The purpose of our study was, to observe the efficacy of Urapidil in lowering blood pressure both in supine and standing position, to see the acceptability by the patient, to observe the side effects and to see postural hypotension.

TABLE NO. 4

Spontaneous Complaints	Number
Nausea, Vomiting	03
Dry Mouth	01
Uneasiness	01
Pain Abdomen	01
Loose Motion	01
Palpitation	01
Morning Dizziness	03
Skin Rash	01
Enuresis	02
Burning Chest	12
Total	26

In 10 patients, having mild to moderate hypertension blood pressure, was controlled with 1 B.D. dose. To 2 patients having severe blood pressure, addition of a Calcium Channel blocker gave a good response.

Both mean systolic and mean diastolic pressure fell significantly (P<0.001), mean arterial pressure decreased from 134.44 mmHg to 103.55 mmHg.

It has not produced any reflex tachycardia or bradycardia except decrease in heart rate (see Tab. No. 4). It has reduced the blood pressure gently and was used safely in patients with diabetes mellitus. Decrease in heart rate was significant (P<0.05).

No serious side effect except enuresis with 60mg B.D. dose was observed, which disappeared with reducing the dose to 30mg B.D. The B.P. of these patients was controlled with the addition of Calcium Channel blocker. All complaints were transient in nature and disappeared spontaneously within 2-3 weeks.

Conclusion:

In conclusion Urapidil, an alpha receptor blocker with central effect was effective in controlling mild to moderate hypertension, i.e., diastolic pressure <115 mmHg or in severe hypertension in combination with other drugs. The number of patients treated was small (12) and the incidence of side effects was high but these were mild and disappeared upon reducing the dose or spontaneously. Side effects did not necessitate withdrawal of the drug in any patient. No significant abnormality in laboratory tests was detected.

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