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REVIEW

Urapidil, a Dual-Acting Antihypertensive Agent: Current Usage Considerations

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ABSTRACT

Despite the availability of a wide range of effective blood pressure (BP)-lowering agents, a substantial proportion of patients with hypertension fail to achieve target BP levels. The majority of patients with hypertension need a combination of two or more drugs to achieve BP targets and choice of second-line or subsequent-line therapy is an important consideration in hypertension management. Alpha-1-adrenoreceptor antagonists (alpha-blockers) have a BP-lowering effect broadly similar to the other antihypertensive drug classes and are effective as add-on therapy in patients with inadequately controlled hypertension. Alpha-blockers may also have therapeutic benefits that go beyond BP control, including improvements in lipid profile and glucose metabolism, as well as reducing the symptoms of benign prostatic hyperplasia. Urapidil has an alpha-blocking effect but, unlike other alpha-blockers, also has a central sympatholytic effect mediated via stimulation of serotonin $5HT_{1A}$ receptors in the central nervous system. Several studies have suggested that oral urapidil is effective and well tolerated when used as second-line therapy in patients with BP inadequately controlled with other agents. Urapidil has also been shown to improve glucose and lipid metabolism in hypertensive patients with concomitant diabetes and/or hyperlipidemia. Intravenous urapidil is effective in the treatment of hypertensive crises, perioperative hypertension, and pre-eclampsia and may have a potential role in the management of acute stroke. In this review, the use of alpha-blockers in hypertension is discussed, with particular focus on urapidil for the lowering of BP in a variety of clinical settings.

Keywords: alpha-1-adrenoreceptor antagonists; blood pressure; hypertension

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INTRODUCTION

Hypertension is a well-recognized cardiovascular risk factor and a leading cause of mortality. In the World Health Organization Global Burden of Disease study, nonoptimal blood pressure (BP) was identified as the main cause of mortality and morbidity in both

developed and developing countries.[1] A wide range of effective pharmacologic treatments are now available to treat high BP. Despite this, hypertension control is often inadequate and the numbers of people with uncontrolled BP is increasing.[2]

Studies have shown that a substantial proportion of patients with hypertension are either not treated or, if treated, fail to achieve BP targets. In one analysis of hypertension surveys across several countries, less than one-third of patients in Europe with a BP of ≥140/90 mmHg received antihypertensive therapy, with only 23% to 38% having their BP controlled to below 160/95 mmHg and less than 10% to below 140/90 mmHg.[3] Similarly, a recent international survey of patients with arterial hypertension reported that only about one-third had controlled BP.[4] Other studies have also reported similarly low rates of effective BP management.[5,6] Inadequate BP control continues to be a problem across all hypertensive populations, but is a particular concern in high-risk patients, such as those with type 2 diabetes or chronic kidney disease.[2]

Evidence from randomized trials of antihypertensive therapy has shown that the main benefits of treatment are due to BP lowering per se, regardless of which drug is used to achieve this.[7] In a meta-analysis of 147 randomized trials, the five major classes of BP-lowering drugs (thiazides, beta-blockers, angiotensin-converting-enzyme [ACE] inhibitors, angiotensin II receptor blockers [ARBs], and calcium channel blockers) had similar effects in reducing coronary heart disease and stroke for a given reduction in BP, with the exception of a minor additional protective effect of calcium channel blockers against stroke.[8] However, the various antihypertensive classes all have different properties and particular agents may be more appropriate in certain groups of patients. In particular, patients with hypertension typically have multiple concomitant risk factors (eg, diabetes, hyperlipidemia), which may influence choice of therapy.[9]

THE USE OF ALPHA-BLOCKERS IN HYPERTENSION

The majority of patients with hypertension need a combination of two or more drugs to achieve target BP levels.[7] Choice of second-line or third-line therapy is an important consideration in hypertension management and a wide range of drug combinations have been shown to be effective and well tolerated.[7]

Alpha-1-adrenoreceptor antagonists (alpha-blockers) have been shown to have a BP-lowering effect broadly similar to the other antihypertensive drug classes.[10] Several studies have indicated that alpha-blocker add-on therapy is effective in reducing BP in patients with inadequately controlled hypertension.[11] Alpha-blockers may also have therapeutic benefits that go beyond BP control, including improvements in lipid profile and glucose metabolism, as well as reducing the symptoms of benign prostatic hyperplasia (BPH).[11] These additional beneficial effects of alpha-blockers may be an important consideration in many patients, particularly older people.

Urapidil (Ebrantil®, Nycomed, Zurich, Switzerland) has an alpha-blocking effect but, unlike other alpha-blockers, also has a central hypotensive action.[12] Urapidil is available as an oral sustained release capsule for the treatment of mild to moderate hypertension and as an intravenous injection for the treatment of hypertensive crises, severe or treatment-resistant hypertension, perioperative or postoperative hypertension and pre-eclampsia. The pharmacodynamics, pharmacokinetics, and therapeutic efficacy of urapidil compared

with other antihypertensive agents have previously been reviewed.[13] Here, we focus on the potential role of urapidil as an add-on agent in combination therapy, in patients with concomitant disease and for the treatment of hypertensive crises, settings in which the use of urapidil may be most appropriate.

Urapidil in Combination Therapy

There is considerable evidence that urapidil effectively lowers BP in patients with hypertension.[13] However, fewer studies have investigated its role as add-on therapy in patients whose BP is not adequately controlled with other agents, although this is its most likely use in the antihypertensive therapeutic arsenal today. Studies that have been reported are summarized in Table 1.

In the largest study of urapidil as add-on therapy, 273 patients with BP inadequately controlled with nifedipine monotherapy were randomized to open-label treatment with either urapidil 60-120 mg/day or metoprolol 100-200 mg/day as add-on therapy for 3 months.[14] Both combinations produced significant reductions in BP, 16.6/13.6 mmHg with nifedipine plus urapidil (P<0.001) and 15.1/14.0 mmHg with nifedipine plus metoprolol (P<0.001) (Figure 1). There was no significant difference between the two treatment groups overall, although significantly greater reductions in BP with urapidil were observed in a post hoc analysis of patients aged ≥60 years (n=51). The authors suggested that this might be attributable to an age-related decrease in beta-adrenoceptor sensitivity, although prospective studies in older people are needed to confirm this. After 3 months, 234 responders to combination treatment with nifidepine plus urapidil or nifedipine plus metoprolol were treated with nifidepine plus urapidil for a further 3-month period. Systolic BP (SBP) decreased by 2% and diastolic BP (DBP) by 4% (P<0.001 versus baseline and versus end of third month).

Similarly, in a small study of 12 patients with BP not controlled with nifedipine 40 mg/day alone, 12 weeks of treatment with urapidil 60 mg/day plus nifedipine 40 mg/day significantly reduced SBP (from 166.2±10.3 to 146.4±16.2 mmHg; P<0.001) and DBP (from 96.2±7.1 to 85.8±8.9 mmHg; P<0.001).[15]

Urapidil has also been shown to be effective when used as add-on therapy in patients who do not respond adequately to thiazide diuretics. In 17 patients with BP not controlled after 8 weeks of monotherapy with hydrochlorothiazide 25 mg/day, the addition of urapidil 120 mg/day resulted in significant reductions in supine BP (from 153±9.4/101±4.8 to 144.3±13.7/92.6±8.4 mmHg) and standing BP after 4 weeks (from 146.5±10.7/101.5±4.7 to 139.6±14.7/92.8±8.1 mmHg).[16]

In a double-blind comparative study in outpatients with mild to moderate essential hypertension, urapidil 30-120 mg/day (n=99) or prazosin 1.5-6 mg/day (n=91) in combination with a thiazide diuretic resulted in similar reductions in BP.[17] After 12 weeks, SBP and DBP significantly decreased in both the urapidil group and the prazosin group (P<0.001 versus baseline, no between group differences). Approximately two-thirds of patients in both groups responded (–20/–10 mmHg or ≤150/90 mmHg) to treatment (67% in the urapidil group and 65% in the prazosin group).

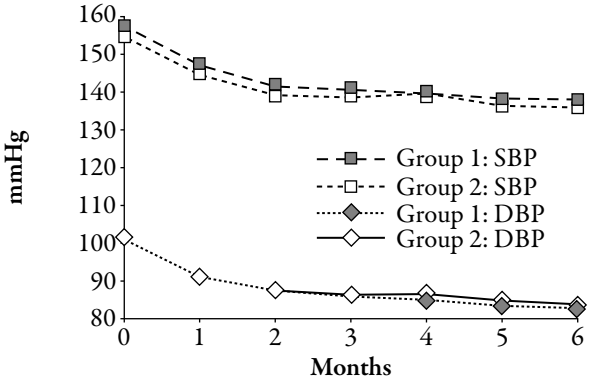
In another study in 34 outpatients with DBP >105 mmHg after 4 weeks of treatment with a thiazide or loop diuretic in combination with either a sympatholytic or a beta-blocker, addition of urapidil 15-60 mg/day for 8 weeks resulted in mean BP being reduced by ≥13 mmHg in 74% of patients and DBP being reduced by ≥10 mmHg in 68% of patients.[18] The same

Table 1. Urapidil in combination with other antihypertensive agents.

Study	Patients	Design	Results
Zanchetti (1995)[14]	Hypertensive patients nonresponsive to 2 weeks of treatment with nifedipine.	Randomized, open label. Nifedipine 40 mg/day + urapidil 60-120 mg/day (n=144) or nifedipine 40 mg/day + metoprolol 100-200 mg/day (n=129) for 3 months. After 3 months, patients (n=247) were treated with nifedipine plus urapidil irrespective of previous treatment for a further 3 months.	BP reduction of 16.6/13.6 mmHg with urapidil vs. 15.1/14 mmHg with metoprolol (both P<0.001 vs. baseline). Total cholesterol and LDL cholesterol reduced (−3.8 and −3.9 mg/dL, respectively; both P<0.001) after the addition of urapidil but increased with metoprolol (9.9 mg/dL and 8.1 mg/dL, respectively; both P=0.001); P<0.01 between groups. Serum TGs did not change with urapidil but significantly increased with metoprolol (8.4 mg/dL; P<0.001); the between-group difference was not statistically significant. Plasma glucose did not change after the addition of urapidil but increased (2.9 mg/dL; P<0.001) in the metoprolol-added group (P<0.05 between groups).
Mizuno and Fukuchi (1991)[15]	Patients with essential hypertension noncontrolled after nifedipine alone for 12 weeks.	Nonrandomized, noncontrolled. Nifedipine 40 mg/day + urapidil 60 mg/day (n=12).	SBP reduced from 166.2±10.3 to 146.4±16.2 mmHg (P<0.001), DBP reduced from 96.2±7.1 to 85.8±8.9 mmHg (P<0.001).
Fariello (1990)[16]	Patients with BP noncontrolled after hydrochlorothiazide alone after 8 weeks.	Nonrandomized, noncontrolled. Hydrochlorothiazide 50 mg/day + urapidil 120 mg/day (n=17).	Significant reductions in supine BP (from 153±9.4/101±4.8 to 144.3±13.7/92.6±8.4 mmHg) and standing BP after 4 weeks (from 146.5±10.7/101.5±4.7 to 139.6±14.7/92.8±8.1 mmHg).
Kaneko (1988)[17]	Patients with essential hypertension treated with urapidil or prazosin alone or in combination with a thiazide diuretic.	Randomized, double blind. Urapidil 30-120 mg/day (n=99) or prazosin 1.5-6 mg/day (n=91) in combination with a thiazide diuretic.	After 12 weeks, SBP decreased by 21.5±1.5 mmHg in the urapidil group and 21.7±1.5 mmHg in the prazosin group. DBP decreased by 12.9±0.8 mmHg in the urapidil group and 11.2±0.8 mmHg in the prazosin group (all decreases P<0.001 versus baseline, no between group differences). Response rates (−20/−10 mmHg or ≤150/90 mmHg) were similar in both groups (67% with thiazide plus urapidil and 65% with thiazide plus prazosin).
Takeda (1998)[18]	Patients with DBP >105 mmHg after a thiazide or loop diuretic in combination with either a sympatholytic or a beta-blocker for 4 weeks.	Nonrandomized, noncontrolled. Thiazide or loop diuretic in combination with either a sympatholytic or a beta-blocker + urapidil 15-60 mg/day (n=34).	SBP reduced from 180±2.4 to 157±2.9 mmHg (P<0.001) and DBP reduced from 115±1.2 to 98±2.0 mmHg (P<0.001) after 8 weeks. Response rates of 73.5% (mean BP reduced by ≥13 mmHg) or 67.6% (DBP reduced by ≥10 mmHg).

C=cholesterol; DBP=diastolic blood pressure; LDL=low-density lipoprotein; SBP=systolic blood pressure; TGs=triglycerides.

Figure 1. Blood pressure during treatment with nifedipine plus urapidil versus nifedipine plus metoprolol in patients with blood pressure (BP) noncontrolled with nifedipine monotherapy. Reproduced with permission from Zanchetti A. Addition of urapidil or metoprolol to the treatment of hypertensive non-responders to nifedipine monotherapy: efficacy and metabolic effects. Italian Urapidil Study Group. Blood Press Suppl. 1995;3:38-46.[14]



group also reported that reductions in BP with urapidil in combination with a thiazide diuretic were maintained for 1 year in 47 patients with essential hypertension.[18]

Effect of Urapidil in Patients with Type 2 Diabetes and Hyperlipidemia

Patients with hypertension frequently have multiple comorbid metabolic disturbances, including diabetes and hyperlipidemia. Concomitant diabetes substantially increases the risk of developing renal and other organ damage, leading to increased incidence of cardiovascular morbidity and mortality. Owing to this, tighter control of BP (<130/80 mmHg) is recommended in patients with diabetes, and there is an even greater need for multiple drug therapy.[7] However, certain antihypertensive agents are known to have a diabetogenic effect. In particular, both beta-blockers and thiazide diuretics worsen insulin resistance and have been reported to increase the incidence of new onset diabetes compared with other antihypertensive drug classes.[19,20] Beta-blockers and diuretics also tend to have a detrimental effect on plasma lipid profiles, and as such their use as first-line agents is not recommended in patients with diabetes, hyperlipidemia or related metabolic abnormalities (eg, metabolic syndrome).[7] Calcium channel blockers, ACE inhibitors, and ARBs are generally considered to have little or no metabolic effects. However, alpha-blockers may have a beneficial effect on both glucose and lipid metabolism.[11]

A small number of studies with urapidil have been reported in patients with type 2 diabetes and/or hyperlipidemia (Table 2). In a large randomized study of urapidil, 309 patients with type 2 diabetes and mild to moderate hypertension were treated with urapidil at a dose of either 60 mg/day (n=157) or 120 mg/day (n=152) for 4 weeks.[21] BP was significantly reduced (P<0.01) in both treatment groups at 4 and 16 weeks. Fasting blood glucose and glycated hemoglobin (HbA_{1c}) decreased significantly (P<0.01) during treatment with both urapidil 60 mg and 120 mg/day (Figure 2). No further changes were seen with the addition of thiazide. Treatment with urapidil was also associated with a significant decrease in total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides, and a significant increase in high-density lipoprotein (HDL) cholesterol. This lipid-lowering effect was dose related, with the reduction in triglycerides significantly greater in patients treated with the higher dose. When thiazide was added to nonresponders to urapidil, there was a significant increase in total cholesterol and a significant decrease in HDL cholesterol.

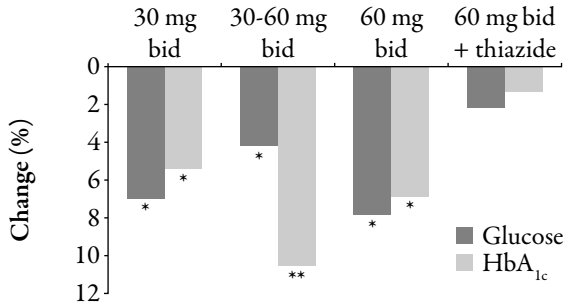
In another study, 33 patients with type 2 diabetes and DBP of 95-115 mmHg were treated with either 60 or 120 mg/day of urapidil, with a gradual increment up to a maximum of 180 mg/day in order to reduce DBP to

Table 2. Urapidil in patients with type 2 diabetes or hyperlipidemia.

Study	Patients	Design	Results
Type 2 diabetes			
Fariello et al (1992)[21]	Patients with mild to moderate essential hypertension and type 2 diabetes.	Randomized. Urapidil 60 mg/day (*n*=157) or urapidil 120 mg/day (*n*=152) for 4 weeks. The dose was doubled in nonresponders (DBP >90 mmHg or DBP decrease <10% of baseline) to urapidil 60 mg/day, while thiazide was added to nonresponders in the urapidil 120 mg/day group for another 12 weeks.	In the 60 mg/day group, 69% of patients were responders after 4 weeks, compared with 60% in the 120 mg/day group. After 16 weeks, response rate was 90% in both groups. Fasting blood glucose and HbA_{1c} decreased significantly (P<0.01) during treatment with both urapidil 60 mg/day and 120 mg/day. No further changes were seen with the addition of thiazide. Treatment with urapidil was also associated with a significant decrease in total cholesterol, LDL cholesterol and TGs, and a significant increase in HDL cholesterol.
Oren et al (1996)[22]	Patients with type 2 diabetes and DBP of 95-115 mmHg.	Nonrandomized, noncontrolled. Urapidil 60 mg/day or urapidil 120 mg/day for 12 weeks (*n*=33), with a gradual increment up to a maximum of 180 mg/day in order to reduce DBP to <90 mmHg or by at least 10% in the sitting position.	Significant reductions (P<0.0001) in sitting and standing SBP and DBP were achieved after 12 weeks of treatment, whereas heart rate did not increase. HbA_{1c} levels were unchanged with urapidil (from 10.4±2% to 10.4±3%; P=NS). The insulin:glucose ratio was significantly lower after treatment with urapidil (from 0.14±0.19 to 0.08±0.09; P=0.047). No significant changes in total cholesterol (232±53 to 237±53 mg/dL), HDL cholesterol (46±13 to 48±14 mg/dL) or TGs (222±145 to 206±107 mg/dL).
Hyperlipidemia			
Goto (1992)[23]	Patients with hypertension and hypercholesterolemia.	Nonrandomized, noncontrolled. Urapidil 30-90 mg/day for 12 weeks (*n*=28).	Urapidil was associated with significant improvements in total cholesterol (from 240±8 to 226±9 mg/dL; P<0.05) and apolipoprotein-B (125±5 to 113±6 mg/day; P<0.001) in patients with hypertension and hyperlipidemia.
Ferrara et al (1994)[24]	Patients with hypertension and mild to moderately severe hypercholesterolemia.	Randomized, double blind and placebo controlled. Urapidil 60-120 mg/day (*n*=26) or placebo (*n*=23) for 6 months.	Significant decreases in BP with urapidil (from 159/99±13/2 to 152/90±23/8 mmHg) but not placebo (P<0.05 between groups). Total cholesterol decreased from 265±42 to 260±36 mg/dL (P=NS) in the urapidil group but increased from 256±29 to 260±36 mg/dL in the placebo group. LDL cholesterol and apolipoprotein-B100 also showed a slight decrease with urapidil and slight increase with placebo. None of these changes were statistically significant. HDL cholesterol was unchanged in both groups.
Pattinier and Von Heusinger (1992)[25]	Retrospective analysis of six clinical trials in which patients were treated with urapidil 120 mg/day for 3 months. Individual studies not specified.	*n*=1482	Significant reductions in total cholesterol (*n*=427, −5.9%; P<0.0001) and TGs (*n*=64, −18.2%; P<0.0001). LDL cholesterol decreased (*n*=21, -13.9%) and HDL cholesterol increased (*n*=52, 12.3%), although these changes were not significant.

C=cholesterol; DBP=diastolic blood pressure; HbA_{1c}=glycated hemoglobin; LDL=low-density lipoprotein; HDL=high-density lipoprotein; NS=not significant; SBP=systolic blood pressure; TGs=triglycerides.

Figure 2. Changes in plasma glucose and glycated hemoglobin (HbA_{1c}) after treatment with urapidil 30-60 mg. Urapidil 30-60 mg twice daily group=30 mg twice daily for weeks 1-4, then dose escalation to 60 mg twice daily for weeks 5-16. *P<0.05, **P<0.01 vs. baseline. *Reproduced from Fariello R, et al. Influence of a new multifactorial antihypertensive on blood pressure and metabolic profile in essential hypertension associated with non-insulin-dependent diabetes mellitus. Eur Heart J. 1992;13(suppl. A):65-69, with permission of Oxford University Press, Oxford, UK.*[21]



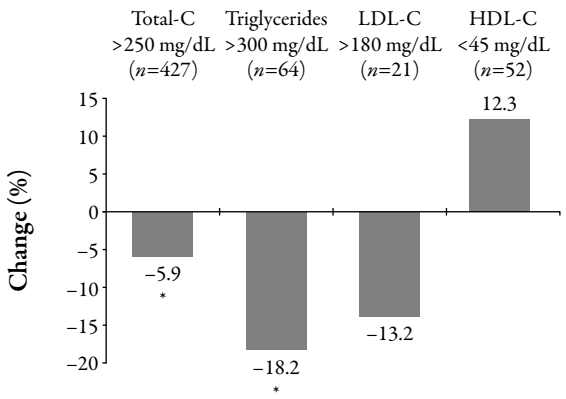
<90 mmHg or by at least 10% in the sitting position.[22] Significant reductions (P<0.0001) in sitting and standing SBP and DBP were achieved after 12 weeks of treatment, whereas heart rate did not increase. Unlike in the study by Fariello et al,[21] HbA_{1c} levels were not improved with urapidil. Fasting insulin levels before a standard oral glucose tolerance test were similar at baseline and after 12 weeks of treatment, but peak concentration at 90 minutes after glucose loading was higher at study end. The ratio of insulin to glucose (used as an indirect marker of insulin resistance) was significantly lower after treatment with urapidil 60-180 mg. This suggests that urapidil increased insulin sensitivity, since patients treated with urapidil needed less endogenous insulin in order to maintain similar blood glucose levels.

Urapidil also has a beneficial effect on lipid profile in patients with concomitant hyperlipidemia. In one study of 28 patients with hypertension and hyperlipidemia, treatment with urapidil 30-90 mg/day for 12 weeks was associated with significant improvements in total cholesterol, LDL cholesterol and apolipoprotein-B.[23] In another study, there was a trend towards reduced total and LDL cholesterol with urapidil compared with slight increases with placebo in 49 hypertensive patients with hypercholesterolemia.[24]

In a retrospective analysis of six clinical trials, treatment with urapidil 120 mg/day for 3 months significantly reduced total cholesterol (n=427, –5.9%; P<0.0001) and triglycerides (n=64, –18.2%; P<0.0001).[25] LDL cholesterol was also reduced (n=21, –13.9%) while HDL cholesterol increased (n=52, 12.3%), although these changes were not significant (Figure 3).

In the study by Zanchetti,[14] urapidil had beneficial effects in a subgroup of 29 patients with baseline total cholesterol ≥240 mg/dL. In the nifedipine plus urapidil group, total cholesterol decreased by 8% and LDL cholesterol by 12%, whereas in the nifedipine and metoprolol group, total cholesterol increased by 7% and LDL cholesterol by 10%. In the whole study population, which included patients

Figure 3. Changes in serum lipids after treatment with urapidil 60 mg twice daily for 3 months in a retrospective analysis of six clinical trials. *P<0.0001 versus baseline. *Reproduced from Pattenier JW, von Heusinger FC. Effect of urapidil treatment on lipid metabolism in patients with hypertension. R Soc Med Int Congr Symp. 1992;196:61-67. With permission from Royal Society of Medicine Press, London, UK.*[25]



with and without hypercholesterolemia, total cholesterol and LDL cholesterol were significantly reduced ($P<0.001$) after the addition of urapidil, but increased ($P=0.001$) with the addition of metoprolol ($P<0.01$ between groups). Triglycerides did not change in the nifedipine plus urapidil group but significantly increased in the nifedipine plus metoprolol group ($P<0.001$), although the between-group difference was not significant. In addition, plasma glucose was unchanged in the nifedipine plus urapidil group, whereas it significantly ($P<0.001$) increased in the nifedipine plus metoprolol group ($P<0.05$ between groups). In patients originally randomized to the metoprolol group, the previous increases in total cholesterol, LDL cholesterol, and plasma glucose were ameliorated when switched to urapidil.

Several other studies have reported that urapidil has a neutral effect on lipid profile in patients with hypertension.[26-28] Although any improvements in lipids and glucose with urapidil are generally small and may not constitute a significant clinical benefit, the absence of negative metabolic effects compared with certain other antihypertensive drug classes is notable.

Other Effects of Urapidil

In a study in which 42 patients with hypertension were randomized to double-blind treatment with urapidil 120 mg/day or atenolol 50 mg/day, urapidil had a beneficial effect on plasma fibrinogen level, which decreased by 24% after 12 weeks with urapidil compared with a 9% decrease with atenolol 50 mg.[29] Plasminogen activator inhibitor activity decreased by 4% in the urapidil group and increased by 17% in the atenolol group, although this difference was not significant. Previous studies have suggested a correlation between plasma fibrinogen and subsequent myocardial infarction or stroke.[30,31]

Several studies have shown a dose-dependent inhibitory effect of urapidil on platelet aggregation in vitro, in volunteers and in patients with hypertension.[32-34] However, the clinical relevance of these findings is uncertain.

Urapidil has also been shown to be effective in improving symptoms in patients with BPH[35] and for voiding dysfunction in patients with neurogenic bladder.[36,37] Alpha-blockers have a specific indication in the treatment of BPH, a common comorbidity in older men with hypertension.[7] In addition, combination therapy with urapidil and a cholinergic drug appears to be more useful than monotherapy with either agent alone for the treatment of underactive detrusor.[38]

No significant changes in glomerular filtration rate have been observed in patients with normal renal function and no further deterioration of renal function occurred in a small study of patients with moderate to severe renal dysfunction.[39] Urapidil has been reported to decrease renal vascular resistance and increase renal blood flow in patients with mild hypertension and normal renal function.[40] Mild, transient increases in plasma renin, angiotensin II and aldosterone have been reported in some but not all patients after urapidil administration.[13] In a double-blind, randomized, placebo-controlled study, urapidil had no effect on renal hemodynamics or neurohormones in patients with hypertension.[41] In addition, urapidil did not affect the sodium excretory capacity of the kidney after a hypertonic saline infusion.

Antihypertensive Effect During Long-Term Treatment

Long-term treatment with urapidil does not appear to result in the development of tolerance. In one study, 830 patients with mild to moderate hypertension were treated with

urapidil 60-180 mg daily for up to 2 years, with no apparent tolerance.[42] In an open, multicenter study of 182 patients, SBP was reduced by 25 mmHg and DBP by 17 mmHg after 1 year of treatment with urapidil 60-180 mg/day.[43] At the same average dose, this BP reduction persisted in the second and third years of treatment, indicating that there was no decrease in urapidil effect. In another study, reduction in BP was maintained without tolerance to the antihypertensive effect in 73 patients treated with urapidil 30-120 mg/day for up to 3 years.[44]

Therapeutic Effects with Intravenous Administration

Hypertensive Crises

Hypertensive crises refer to a severe elevation of BP, either with acute end-organ damage (hypertensive emergency) or without (hypertensive urgency).[45] Hypertensive emergencies are rare but can be life threatening and control of hypertension must be rapid in these situations. Many antihypertensive drugs are used to treat hypertensive crises, although evidence on the effects of treatment and the optimal first-line therapy is limited.[46]

Intravenous administration of urapidil results in a rapid antihypertensive effect within 2 minutes and is not associated with reflex tachycardia, which means it may be a useful treatment option for hypertensive crises. Indeed, national guidelines in France recommend intravenous urapidil for the treatment of hypertensive emergencies,[47] with use as first-line therapy also recommended in Austrian guidelines.[48]

Several small, noncontrolled studies have shown that intravenous urapidil is effective and safe in the treatment of hypertensive crises.[49-52] Other studies have shown intravenous urapidil to be associated with higher response rates when compared with other treatments (Table 3). In a prospective study in an outpatient population, intravenous urapidil was compared with sublingual nifedipine for the treatment of hypertensive urgencies (BP >200/110 mmHg).[53] Response to treatment was defined as a stable reduction of BP below 180/100 mmHg 15 minutes after application of a single dose of either intravenous urapidil 25 mg (n=26) or sublingual nifedipine 10 mg (n=27). If required, patients received a second dose of urapidil 12.5 mg or nifedipine 10 mg. After a single dose, response rate was 92% in the urapidil group compared with 70% in the nifedipine group. Two patients required a second dose of urapidil, both of whom responded, while eight patients required a second dose of nifedipine, half of whom had no reduction in BP.

In a subsequent study, intravenous urapidil 25 mg (n=48) was compared with intravenous enalaprilat 5 mg (n=43), sublingual nifedipine capsule 10 mg (n=47) and sublingual nifedipine spray two times 5 mg (n=30) in patients admitted to the emergency department with a hypertensive urgency (SBP >210 mmHg and/or DBP >110 mmHg) or a hypertensive emergency (DBP >100 mmHg and evidence of end-organ damage).[54] Intravenous urapidil had the highest response rate (96%) compared with 70% with enalaprilat, 71% with nifedipine spray and 72% with nifedipine capsule (P<0.05, urapidil versus other treatments). The authors concluded that urapidil should be used as a first-choice drug in critically ill patients with hypertensive crisis. In another randomized study by the same group, treatment with intravenous urapidil had a similar response rate as intravenous sodium nitroprusside in 81 patients with hypertensive emergencies (89% vs. 97%; P=0.18).[55] However, only 2% of patients in the urapidil group had re-elevation of BP in a 4-hour follow-up period compared with 24% of patients in the

Table 3. Controlled studies of intravenous administration of urapidil for hypertensive crises including pre-eclampsia.

Study	Patients	Design	Results
Hirschl et al (1993)[53]	Hypertensive urgency (BP >200/110 mmHg).	Urapidil 25 mg (n=26) or sublingual nifedipine 10 mg (n=27).	In the nifidepine group, significant reductions (P<0.05) in SBP (207±27 to 164±25 mmHg), DBP (129± 10 to 95±23 mmHg) and mean BP (155± 20 to 118±24 mmHg) were observed in 19 (70%) patients. In the urapidil group, significant reductions (P<0.05) in SBP (206± 17 to 164±14 mmHg), DBP (126± 16 mmHg to 91±18 mmHg), and mean BP (1.53± 17 mmHg to 115±17 mmHg) were observed in 24 (92%) patients. Response rate of 92% in the urapidil group versus 70% in the nifedipine group (response defined as a stable reduction in BP to <180/100 mmHg).
Hirschl et al (1996)[54]	Hypertensive urgency (SBP >210 mmHg and/or DBP >110 mmHg) or hypertensive emergency (DBP >110 mmHg and evidence of end-organ damage).	Urapidil 25 mg (n=48), intravenous enalaprilat 5 mg (n=43), sublingual nifedipine capsule 10 mg (n=47) or sublingual nifedipine spray 2 × 5 mg (n=30).	Intravenous urapidil had the highest response rate (96%) compared with 70% with enalaprilat, 71% with nifedipine spray and 72% with nifedipine capsule (P<0.05, urapidil versus other treatments).
Hirschl et al (1997)[55]	Hypertensive emergency (DBP >110 mmHg and evidence of end-organ damage).	Randomized. Urapidil 25 mg (n=46) or intravenous sodium nitroprusside (n=35).	Primary response to treatment was observed in 34 (97%) nitroprusside patients and in 41 (89%) urapidil patients (P=0.18). SBP was lowered at an average of 65 mmHg in the nitroprusside group and of 48 mmHg in the urapidil group (P<0.01). DBP decreased at an average of 30 mmHg in the nitroprusside group and 24 mmHg in the urapidil group (P<0.01). A significant trend of heart rate reduction was observed in both treatment groups within 90 minutes (nitroprusside: –8.2±2.4 beats/min, P=0.01; urapidil: –9.2±3.2 beats/min, P<0.01).
Woisetschläger et al (2006)[56]	Hypertensive urgency (SBP >220 mmHg and/or DBP >110 mmHg).	Randomized, double blind, double dummy. Urapidil 12.5 mg (n=27) or oral captopril 25 mg (n=29).	Area under the curve (first 12 hours after administration) was 163/85 mmHg in the urapidil group and 159/88 in the captopril group. The course of SBP and DBP did not differ significantly between groups.
Wacker et al (1998)[58]	Pre-eclampsia and hypertension in pregnancy.	Randomized, open label. Urapidil (6.25 mg bolus, repeated if necessary) then 2-4 mg/hour (mean dose in first 4 hours was 21 mg) (n=13) or intravenous dihydralazine (mean dose in first 4 hours was 11 mg (n=13).	During the initial observation period of 6 hours, SBP decreased by 21 mmHg in the urapidil group (P<0.001) and 6 mmHg in the dihydralazine group (P<0.002), while DBP decreased 13 mmHg in the urapidil group (P<0.001) and 18 mmHg in the dihydralazine group (P<0.001). Between-group differences not reported. Effective prolonged control of blood pressure (values consistently <150/100 mmHg) was achieved in all patients.
Wacker et al (2006)[59]	Pre-eclampsia and pregnancy-induced hypertension.	Randomized, open label. Urapidil (12-25 mg bolus,) (n=21) or intravenous dihydralazine (5 mg bolus) (n=21).	Mean SBP and DBP were reduced by approximately 20 mmHg in both groups with no between-group differences. One patient in the dihydralazine group still had hypertension (220/140 mmHg) after 1 hour.

DBP=diastolic blood pressure; SBP=systolic blood pressure.

nitroprusside group. In addition, major side effects were more frequent with nitroprusside than urapidil (seven vs. two; *P*=0.04). In a further randomized, double-blind trial of 69 patients with hypertensive urgency, intravenous urapidil and oral captopril 25 mg resulted in similar reductions in SBP and DBP.[56]

There are few data evaluating the effects of urapidil in patients whose BP was not controlled with other antihypertensives, although one study showed that intravenous urapidil was effective and well tolerated in hypertensive emergencies after inadequate response to oral nifedipine.[57]

Pre-eclampsia and Eclampsia

Two studies have reported that intravenous urapidil and intravenous dihydralazine were similarly effective in reducing BP in women with pre-eclampsia. However, urapidil had more predictable hemodynamic effects and was better tolerated.[58,59] In another study, the use of intravenous urapidil for treatment of pre-eclampsia was associated with fewer effects on cardiovascular parameters than intravenous dihydralazine in newborns.[60] Dihydralazine is no longer recommended for hypertension in pre-eclampsia because of an excess of perinatal adverse effects. Austrian, French, and German guidelines all recommended intravenous urapidil for the treatment of pre-eclampsia.[47,48,61]

Perioperative Hypertension

Intravenous urapidil has also been shown to be effective in the management of perioperative hypertensive episodes in patients undergoing a variety of surgical operations, in particular coronary artery surgery.[62-70] Intravenous urapidil has also been shown to be useful in the treatment of hypertensive episodes in patients during abdominal aorta surgery,[71] neurosurgery,[72] and during tracheal intubation under general anesthesia,[73] as well as for the prevention of hypertensive episodes in patients undergoing preparation for surgery of pheochromocytoma.[74]

Stroke and Intracerebral Hemorrhage

Although no studies have specifically investigated the efficacy of urapidil in stroke management, there is some evidence to suggest that urapidil has properties that may be useful in the treatment of acute stroke.[75] Intravenous urapidil has been reported to be slightly more effective than nifedipine in reducing BP and cerebral symptoms in patients with hypertensive emergencies.[75] BP reduction with urapidil is generally not associated with an increase in intracranial pressure and cerebral perfusion pressure is not affected.[76] Urapidil has also been shown to have a potential protective effect against ischemia, with neuroprotective effects being shown in rodents.[77] Intravenous urapidil is one of the agents recommended in European guidelines for lowering blood pressure in the management of acute stroke.[78]

In the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage (INTERACT) study, early intensive BP lowering was well tolerated and reduced hematoma growth in patients with intracerebral hemorrhage compared with standard guideline management of BP.[79] Of the 203 patients randomized to intensive BP lowering in this trial, almost half (47%) were treated with urapidil. Hematoma growth is a strong predictor of poor outcomes in intracerebral hemorrhage and these results support the hypothesis that early intensive BP lowering may be beneficial.

Tolerability and Safety

The tolerability of urapidil has been reviewed previously.[13] Urapidil is generally well tolerated. Adverse events in clinical trials tended to be mild, and transient, mostly occurring in the first

week of therapy and subsiding with continued treatment. These included dizziness, nausea, headaches, fatigue, and orthostatic disorders. Compared with other antihypertensive agents, the incidence of adverse events with urapidil is generally similar.[13] However, because of its dual mode of action, urapidil may have a lower incidence of tachycardia and orthostatic hypertension compared with other alpha-blockers. The safety profile of urapidil in combination with other agents appears to be similar to urapidil monotherapy. In the study by Zanchetti,[14] the most frequent adverse events were gastrointestinal complaints, fatigue, headache, and palpitations (1% to 2% of patients). Orthostatic hypotension was not reported. In addition, urapidil does not appear to be associated with an increased risk of heart failure.

DISCUSSION

Successful control of BP remains challenging, despite the availability of a range of effective antihypertensive treatments and the widespread use of multiple drug therapy. Alpha-blockers are effective in reducing BP in patients whose hypertension is inadequately controlled with other agents and may have other therapeutic benefits, including improvements in lipid profile and glucose metabolism, and symptoms of BPH.[11] As such, alpha-blockers may have a particular role as second-line or subsequent-line therapy in hypertension management, particularly in patients with concomitant metabolic abnormalities or BPH.

However, the use of alpha-blockers to treat hypertension has declined since the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) reported increased rates of congestive heart failure (CHF) in patients randomized to first-line therapy with doxazosin compared with chlorthalidone.[80] However, CHF was not a prespecified individual endpoint in this study, but a component of a composite secondary endpoint. Moreover, the criteria for diagnosing CHF (one symptom and one sign) were not consistent with modern practice, and may explain the extremely high incidence of clinical CHF reported (5.35 and 8.89% per 4 years on chlorthalidone and doxazosin, respectively) and the equal distribution and low incidence of the hard endpoint of death from CHF (0.60 and 0.65% per 4 years, respectively).[81] Despite this criticism of the study, its findings mean that alpha-blocker use is no longer being recommended by some guidelines (eg, The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure [JNC-VII], 2003[82]), although others (eg, European Society of Cardiology [ESC]/European Society of Hypertension [ESH], 2007[7]) still indicate their potential as add-on therapy or in particular patient groups (eg, men with BPH). More recently, the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) reported that the use of doxazosin as third-line therapy was effective and safe, with no increase in the occurrence of heart failure.[83] Heart failure was a prespecified secondary endpoint in this trial and was defined and evaluated rigorously according to stricter, more robust criteria than in ALLHAT. After addition of doxazosin to antihypertensive therapy, mean BP fell 11.7/6.9 mmHg ($P<0.0001$) from 158.7/89.2 mmHg and 29.7% of participants achieved target BP after 12 months. Doxazosin was associated with modest favorable effects on plasma lipid profiles, but a small rise in fasting plasma glucose was reported. In addition, an observational study of doxazosin as add-on antihypertensive therapy in patients

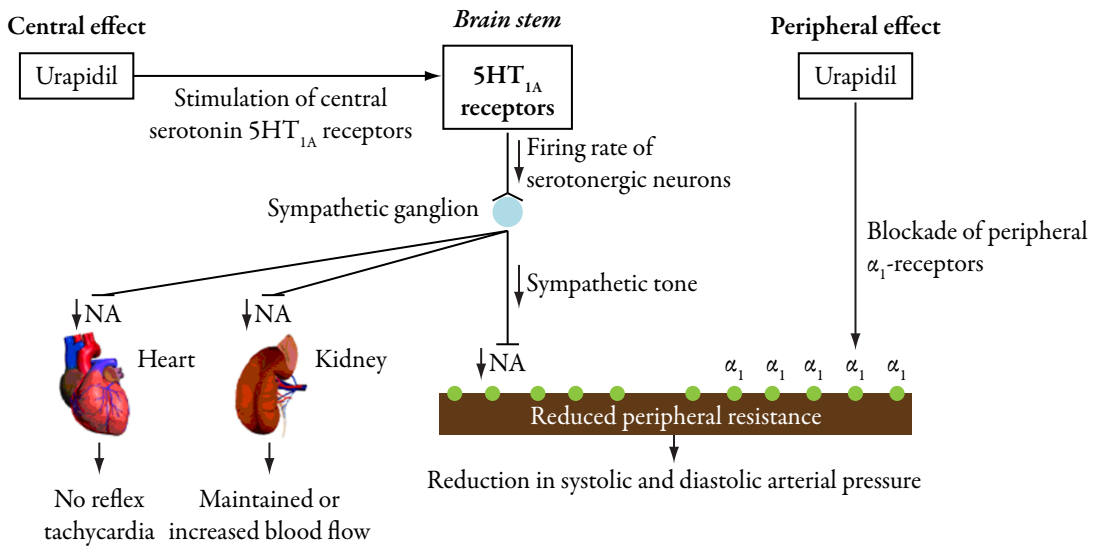
with CHF did not demonstrate any increase in CHF complications.[84]

While the primary effect of urapidil is as an alpha-blocker, it also has a central sympatholytic effect mediated via stimulation of serotonin $5HT_{1A}$ receptors in the central nervous system (Figure 4). The $5HT_{1A}$ agonist effects of urapidil decrease the firing rate of serotonergic neurons, which inhibit their excitatory input to sympathetic neurons. This inhibition depresses sympathetic nervous system activity at the receptor level.[12] In addition to contributing to the reduced peripheral resistance, this reduced sympathetic tone appears to suppress the reflex tachycardia often associated with vasodilator therapy.[12]

Studies have reported that urapidil is associated with either no significant change in heart rate or a slight transient increase.[85,86,13] In a randomized, double-blind, placebo-controlled, crossover study in 12 healthy male volunteers, resting heart rate was significantly increased by doxazosin ($P<0.05$) but not by urapidil, although both were equally effective at reducing BP.[87] In addition, doxazosin but not urapidil significantly increased the rate pressure product at rest and recovery (ie, the increasing effect of doxazosin on heart rate appeared more pronounced than its lowering effect on SBP). The authors postulated that this might be one reason to explain the increased incidence of heart failure and stroke observed with doxazosin compared with chlorthalidone in ALLHAT.

Unlike other antihypertensive drug classes, alpha-blockers, including urapidil, may have beneficial effects on glucose and lipid metabolism and so may be of particular use in the high proportion of hypertensive patients with concomitant type 2 diabetes, metabolic syndrome, and/or hyperlipidemia. Achieving BP targets in these patients is difficult, even with combination therapy, and alpha-blockers may represent an underutilized but useful treatment option. In addition, urapidil has a positive effect on urinary symptoms in patients with BPH or neurogenic bladder dysfunction. These effects of alpha-blockers may suggest a particular role in older hypertensive patients, given the greater need for multiple drug therapy

Figure 4. Double mode of action of urapidil. NA=norepinephrine release.



and increasing prevalence of comorbidities with age. The potentially useful role of urapidil in the treatment of older hypertensives has previously been suggested.[88]

CONCLUSION

Hypertension is a major cause of mortality and morbidity worldwide, despite the availability of effective treatments. Although their use in hypertension has declined over the past decade, alpha-blockers remain an effective and well-tolerated treatment option for second-line and subsequent-line therapy, and represent an important option in the antihypertensive therapeutic armamentarium. Urapidil, which has a central hypotensive action in addition to its alpha-blocking effect, may offer a useful option for the lowering of BP in a variety of clinical settings and its role in the management of hypertension is worthy of reappraisal.

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REFERENCES

1. Ezzati M, Lopez A, Rodgers A, Vander Hoorn S, Murray CJL, eds. Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors. Geneva: World Health Organization; 2004.

2. Chobanian AV. Shattuck Lecture. The hypertension paradox - more uncontrolled disease despite improved therapy. N Engl J Med. 2009;361:878-887.

3. Wolf-Maier K, Cooper RS, Kramer H, et al. Hypertension treatment and control in five European countries, Canada, and the United States. Hypertension. 2004;43:10-17.

4. Thoenes M, Neuberger HR, Volpe M, Khan BV, Kirch W, Böhm M. Antihypertensive drug therapy and blood pressure control in men and women: an international perspective. J Hum Hypertens. 2010;24:536-544.

5. Antikainen RL, Moltchanov VA, Chukwuma C Sr, et al. WHO MONICA Project. Trends in the prevalence, awareness, treatment and control of hypertension: the WHO MONICA Project. Eur J Cardiovasc Prev Rehabil. 2006;13:13-29.

6. Falaschetti E, Chaudhury M, Mindell J, Poulter N. Continued improvement in hypertension management in England: results from the Health Survey for England 2006. Hypertension. 2009;53:480-486.

7. Mancia G, De Backer G, Dominiczak A, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2007;28:1462-1536.

8. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ 2009;338:(doi: 10.1136/bmj.b1665).

9. De Bacquer D, De Backer G. The prevalence of concomitant hypertension and hyper-cholesterolaemia in the general population. Int J Hypertens. 2006;110:217-223.

10. Heran BS, Galm BP, Wright JM. Blood pressure lowering efficacy of alpha blockers for primary hypertension. Cochrane Database Syst Rev. 2009;4:CD004643.

11. Zusman RM. The role of alpha 1-blockers in combination therapy for hypertension. Int J Clin Pract. 2000;54:36-40.

12. van Zwieten PA, Blauw GJ, van Brummelen P. Pharmacological profile of antihypertensive drugs with serotonin receptor and alpha-adrenoceptor activity. Drugs. 1990;40(suppl. 4):1-8.

13. Dooley M, Goa KL. Urapidil. A reappraisal of its use in the management of hypertension. Drugs. 1998;56:929-955.

14. Zanchetti A. Addition of urapidil or metoprolol to the treatment of hypertensive non-responders to

nifedipine monotherapy: efficacy and metabolic effects. Italian Urapidil Study Group. Blood Press Suppl. 1995;3:38-46.

15. Mizuno K, Fukuchi S. Antihypertensive effectiveness of urapidil alone and in combination with nifedipine in mild to moderate essential hypertension. Curr Ther Res. 1991;50:274-281.

16. Fariello R, Dal Palu C, Pessina A, et al. Antihypertensive efficacy of urapidil versus hydrochlorothiazide alone in patients with mild to moderate essential hypertension and of their combination in nonresponders to monotherapy. Drugs. 1990;40(suppl. 4):60-62.

17. Kaneko Y. Double-blind comparison of urapidil and prazosin in the treatment of patients with essential hypertension. Drugs. 1988;35(suppl. 6):156-163.

18. Takeda T, Kaneko Y, Shionoiri H, et al. Urapidil in patients with severe hypertension and in long-term treatment. J Hypertens Suppl. 1988;6:S37-42.

19. Mancia G, Grassi G, Zanchetti A. New-onset diabetes and antihypertensive drugs. J Hypertens. 2006;24:3-10.

20. Elliott WJ, Meyer PM. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. Lancet. 2007;369:201-207.

21. Fariello R, Boni E, Corda L, Zaninelli A, Noseda A, Spinazzi A. Influence of a new multifactorial antihypertensive on blood pressure and metabolic profile in essential hypertension associated with non-insulin-dependent diabetes mellitus. Eur Heart J. 1992;13(suppl. A):65-69.

22. Oren S, Turkot S, Paran E, Flandra O, Slezak L, Hof B. Efficacy and tolerability of slow release urapidil (ebrantil) in hypertensive patients with non-insulin dependent diabetes mellitus (NIDDM). J Hum Hypertens. 1996;10:123-127.

23. Goto Y. Effects of sustained-release urapidil on essential hypertension and hyperlipidaemia: a multicenter clinical trial. Curr Ther Res. 1992;51:870-876.

24. Ferrara LA, Leonetti G, Fogari R, Mazzola C, Mancini M, Zanchetti A. Urapidil in hypercholesterolemic hypertensive patients. Blood Press Suppl. 1994;4:39-44.

25. Pattenier JW, von Heusinger FC. Effect of urapidil treatment on lipid metabolism in patients with hypertension. Royal Soc Med Int Congr Symp. 1992:196:61-67.

26. Gerber A, Weidmann P, Marone C, Uehlinger D, Riesen W. Cardiovascular and metabolic profile during intervention with urapidil in humans. Hypertension. 1985;7:963-971.

27. Held K, Cremer P, Hundertmark E, Seidel D. Effects of long-term antihypertensive therapy with Urapidil (Ebrantil®) on lipometabolism. Hochdruck. 1985;5:2.

28. Liebau H, Wurst W, Harder I, Solleder P. Metabolically neutral therapy of hypertension. An open, multicenter, prospective long-term study of the tolerance, safety and effectiveness of urapidil [in German]. Fortschr Med. 1988;106:651-654.

29. Haenni A, Lithell H. Urapidil treatment decreases plasma fibrinogen concentration in essential hypertension. Metabolism. 1996;45:1221-1229.

30. Ernst E, Resch KL. Fibrinogen as a cardiovascular risk factor: a meta-analysis and review of the literature. Ann Intern Med. 1993;118:956-963.

31. Danesh J, Lewington S, Thompson SG, et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis. JAMA. 2005;294:1799-1809.

32. Sebeková K, Fedelesová V, Blazícek P, Dzúrik R. Acute effect of urapidil on peripheral serotonin metabolism. Cor Vasa. 1990;32:274-281.

33. Smith CC, Betteridge DJ, Prichard BN. Platelet in vitro responses to urapidil and prazosin. Drugs. 1990;40(suppl. 4):48-51.

34. Storck J, Ochs JG, Kirsten R. Effects of urapidil on 5-hydroxytryptamine induced platelet aggregation and on 14C-5-hydroxytryptamine uptake in platelets. Int J Clin Pharmacol Ther Toxicol. 1990;28:303-308.

35. Kawabe K, Tsuchida S, Shimazaki J, Morita T, Yasuda K, Kageyama S. Effect on urapidil on benign prostatic hypertrophy: a multicenter, double-blind study. Urol Int. 1993;50:27-32.

36. Yasuda K, Yamanishi T, Kawabe K, Ohshima H, Morita T. The effect of urapidil on neurogenic bladder: a placebo controlled double-blind study. J Urol. 1996;156:1125-1130.

37. Yamanishi T, Yasuda K, Homma Y, Kawabe K, Morita T. A multicenter placebo-controlled, double-blind trial of urapidil, an alpha-blocker, on neurogenic bladder dysfunction. Eur Urol. 1999;35:45-51.

38. Yamanishi T, Yasuda K, Kamai T, et al. Combination of a cholinergic drug and an alpha-blocker is more effective than monotherapy for the treatment of voiding difficulty in patients with underactive detrusor. Int J Urol. 2004;11:88-96.

39. Ikeda Y, Takagi N, Takeda K. Clinical evaluation of urapidil in hypertensive patients with renal failure. Shinyaku to Rinsho. 1992;41:622-631.

40. de Leeuw PW, van Es PN, de Bruyn HA, Birkenhäger WH. Renal haemodynamic and neurohumoral responses to urapidil in hypertensive man. Drugs. 1988;35(suppl. 6):74-77.

41. Lavrijssen AT, Kroon AA, Fuss-Lejeune M, Schiffers PM, de Leeuw PW. Renal haemodynamics and sodium excretory capacity during urapidil treatment in patients with essential hypertension. J Hypertens. 2000;18:963-969.

42. Liebau H, Wurst W, Harder I, Solleder P. Metabolically neutral therapy of hypertension. An open, multicenter, prospective long-term study of the tolerance, safety and effectiveness of urapidil. Fortschr Med. 1988;106:651-654.

43. Liebau H, Solleder P, Harder I, Wurst W. Long-term antihypertensive therapy with urapidil. A 3-year open, multicenter trial of tolerance, safety and effectiveness. Fortschr Med. 1990;108:325-328.

44. Haerlin R. Treatment of primary and secondary hypertension. Long-term use of urapidil (Ebrantil®). Clinical Trials J. 1985;22:215-225.

45. Cherney D, Straus S. Management of patients with hypertensive urgencies and emergencies: a systematic review of the literature. J Gen Intern Med. 2002;17:937-945.

46. Perez MI, Musini VM. Pharmacological interventions for hypertensive emergencies. Cochrane Database Syst Rev. 2008;1:CD003653.

47. Agence Française de Sécurité Sanitaire Des Produits de Santé (AFSSAPS). Poussees hypertensives de l'adulte: elevation tensionnelle sans souffrance viscerale immediate et urgences hypertensives [in French]. Agence Française de Sécurité Sanitaire Des Produits de Santé, Saint Denis, France, May 2002. Available at www.afssaps.fr/var/afssaps_site/storage/original/application/460262f69aa6b448962c08cba7d8be4f.pdf. Accessed May 24, 2010.

48. Slany J, Magometschnigg D, Mayer G, et al. Klassifikation, Diagnostik und Therapie der Hypertonie 2007 - Empfehlungen der Österreichischen Gesellschaft für Hypertensiologie [in German]. J Hypertonie. 2007;11:7-11.

49. Zähringer J, Klepzig M, Greif J, Ludwig B, Strauer B. Therapy of the hypertensive crisis with urapidil. Various effects on patients with or without coronary disease. Fortschr Med. 1984;102:624-628.

50. Błaszyk K, Grajek S, Skorupski W, et al. Evaluation of the antihypertensive efficacy of urapidil in the treatment of hypertension emergencies [in Polish]. Pol Arch Med Wewn. 1995;94:512-517.

51. Alijotas-Reig J, Bove-Farre I, de Cabo-Frances F, Angles-Coll R. Effectiveness and safety of prehospital urapidil for hypertensive emergencies. Am J Emerg Med. 2001;19:130-133.

52. Jelakovic B, Grba-Bujevic M, Bosan-Kilibarda I, et al. Hypertensive crisis. Efficacy and safe of urapidil based protocol in out-of-hospital settings. J Hypertens. 2009;27(suppl. 4):S122, P11.305.

53. Hirschl MM, Seidler D, Zeiner A, et al. Intravenous urapidil versus sublingual nifedipine in the treatment of hypertensive urgencies. Am J Emerg Med. 1993;11:653-656.

54. Hirschl MM, Seidler D, Müllner M, et al. Efficacy of different antihypertensive drugs in the emergency department. J Hum Hypertens. 1996;10(suppl. 3):S143-146.

55. Hirschl MM, Binder M, Bur A, et al. Safety and efficacy of urapidil and sodium nitroprusside in the treatment of hypertensive emergencies. Intensive Care Med. 1997;23:885-888.

56. Woisetschläger C, Bur A, Vlcek M, Derhaschnig U, Laggner AN, Hirschl MM. Comparison of intravenous urapidil and oral captopril in patients with hypertensive urgencies. J Hum Hypertens. 2006;20:707-709.

57. Späh F, Grosser KD, Thieme G. Acute haemodynamic effects of urapidil and nifedipine in hypertensive urgencies and emergencies. Drugs. 1990;40(suppl. 4):58-59.

58. Wacker J, Werner P, Walter-Sack I, Bastert G. Treatment of hypertension in patients with pre-eclampsia: a prospective parallel-group study comparing dihydralazine with urapidil. Nephrol Dial Transplant. 1998;13:318-325.

59. Wacker JR, Wagner BK, Briese V, et al. Antihypertensive therapy in patients with pre-eclampsia: A prospective randomised multicentre

study comparing dihydralazine with urapidil. Eur J Obstet Gynecol Reprod Biol. 2006;127:160-165.

60. Schulz M, Wacker J, Bastert G. Effect of Urapidil in antihypertensive therapy of preeclampsia on newborns [in German]. Zentralbl Gynakol. 2001;123:529-533.

61. Deutsche Hochdruckliga e.V. DHL® - Deutsche Hypertonie Gesellschaft. Leitlinien zur behandlung der arteriellen hypertonie. Heidelberg, Germany, 2008. Available at: www.hochdruckliga.de. Accessed: May 24, 2010.

62. Olmos M, Vidarte MA, Ballester JA, Lasuen J, Escobar A. Efficacy of a single dose of urapidil for preventing arterial hypertension during the pre-bypass period in coronary surgery. Rev Esp Anestesiol Reanim. 2000;47:337-342.

63. Göb E, Barankay A, Richter JA. Control of hypertension during cardiopulmonary bypass with urapidil and phentolamine. Arzneimittelforschung. 1981;31:1479-1481.

64. Hess W. Urapidil versus clonidine. Acute haemodynamic effects during control of intraoperative hypertensive episodes. Drugs. 1990;40(suppl. 4):77-79.

65. Hess W, Schulte-Sasse U, Tarnow J, Veit S. Comparison of phentolamine and urapidil in controlling acute intra-operative hypertension in patients subjected to coronary artery bypass surgery. Eur J Anaesthesiol. 1985;2:21-27.

66. Petry A, Wulf H, Baumgärtel M. The influence of ketanserin or urapidil on haemodynamics, stress response and kidney function during operations for myocardial revascularisation. Anaesthesia. 1995;50:312-316.

67. van der Stroom JG, Van Wezel HB, Koolen JJ, Visser CA, Van Zwieten PA. Comparison of the effects of urapidil and nitroprusside on hemodynamics and myocardial function in hypertension following cardiac surgery. Blood Press Suppl. 1994;4:31-38.

68. van der Stroom JG, van Wezel HB, Langemeijer JJ, et al. A randomized multicenter double-blind comparison of urapidil and ketanserin in hypertensive patients after coronary artery surgery. J Cardiothorac Vasc Anesth. 1997;11:729-736.

69. van der Stroom JG, van Wezel HB, Vergroesen I, et al. Comparison of the effects of urapidil and sodium nitroprusside on haemodynamic state, myocardial metabolism and function in patients during coronary artery surgery. Br J Anaesth. 1996;76:645-651.

70. Möllhoff T, Van Aken H, Mulier JP, Müller E, Lauwers P. Effects of urapidil, ketanserin and sodium nitroprusside on venous admixture and arterial oxygenation following coronary artery bypass grafting. Br J Anaesth. 1990;64:493-497.

71. van Hemelrijck J, Waets P, Aken H van, Lacroix H, Nevelsteen A, Suy R. Blood pressure management during aortic surgery - Urapidil compared to isosorbide dinitrate. J Cardiothorac Vasc Anesth. 1993;7:273-278.

72. Zander J, Puchstein C, Aken H van, Lawin P. Urapidil as a supplement to neuroleptanalgesia during neuroanaesthesia. Br J Anaesth. 1984;56:1304-1305.

73. Puchstein C, Van Aken H, Zander J, Lawin P. The use of urapidil in the postoperative period. Anaesthesist. 1984;33:224-227.

74. Gosse P, Tauzin-Fin P, Sesay MB, Sautereau A, Ballanger P. Preparation for surgery of phaeochromocytoma by blockade of alpha-adrenergic receptors with urapidil: what dose? J Hum Hypertens. 2009;23:605-609.

75. Späh F, Walsemann SO. Potential beneficial effects of urapidil in primary and secondary prevention of stroke. Blood Press Suppl. 1995;3:62-67.

76. Wüsten R, Hemelrijck J, Mattheussen M, Lauvers T, Anger C, van Aken H. Der einfluss von nifidepin und urapidil auf die autoregulation der zerebralen durchbtuling in gegenwart einer intrakraniellen raumforderung [in German]. Anasth Intensivther Notfallmed. 1990;25:140-145.

77. Prehn JH, Backhauss C, Karkoutly C, et al. Neuroprotective properties of 5-HT1A receptor agonists in rodent models of focal and global cerebral ischemia. Eur J Pharmacol. 1991;203:213-222.

78. European Stroke Initiative Executive Committee. European Stroke Initiative Recommendations for Stroke Management-update 2003. Cerebrovasc Dis. 2003;16:311-337.

79. Anderson CS, Huang Y, Wang JG, et al. Intensive blood pressure reduction in acute cerebral haemorrhage trial (INTERACT): a randomised pilot trial. Lancet Neurol. 2008;7:391-399.

80. ALLHAT Collaborative Research Group. Major cardiovascular events in hypertensive patients

randomized to doxazosin vs. chlorthalidone: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). JAMA. 2000;283:1967-1975.

81. ALLHAT officers and coordinators for the ALLHAT Collaborative Research Group. Diuretics versus alpha blockers as first-step antihypertensive therapy. Hypertension. 2003;42:239-246.

82. Chobanian AV, Bakris GL, Black HR, et al; Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. National Heart, Lung, and Blood Institute; National High Blood Pressure Education Program Coordinating Committee. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-1252.

83. Chapman N, Chang CL, Dahlöf B, et al. Effect of doxazosin gastrointestinal therapeutic system as third-line antihypertensive therapy on blood pressure and lipids in the Anglo-Scandinavian Cardiac Outcomes Trial. Circulation. 2008;118:42-48.

84. Spoladore R, Roccaforte R, Fragasso G, et al. Safety and efficacy of doxazosin as "add-on" antihypertensive therapy in mild to moderate heart failure patients. Acta Cardiol. 2009;64:485-491.

85. Belz GG, Matthews JH, Graf D, et al. Dynamic responses to intravenous urapidil and dihydralazine in normal subjects. Clin Pharmacol Ther. 1985;37:48-54.

86. Kobrin I, Amodeo C, Ventura HO, Messerli FH, Frohlich ED. Immediate hemodynamic effects of urapidil in patients with essential hypertension. Am J Cardiol. 1985:722-725.

87. Stoschitzky K, Stoschitzky G, Wonisch M, Brussee H. Differential effects of urapidil and doxazosin on heart rate. Eur J Clin Pharmacol. 2007;63:259-262.

88. Hansson L, Petitet A. Review of studies with urapidil in elderly hypertensives. Blood Press Suppl. 1995;3:21-25.