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Delapril plus Indapamide
A Review of the Combination in the Treatment of Hypertension

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Abstract

Although many data indicate that the management of hypertension has improved over the last two decades, there is still a large proportion of hypertensive individuals who do not receive adequate management of their blood pressure (BP). Combination therapy with two or more antihypertensive agents from different drug classes is increasingly being recognised as the most effective means of achieving target BP values by pharmacological means, particularly in the large number of patients in whom monotherapy proves to be ineffective.

Use of an angiotensin-converting enzyme (ACE) inhibitor combined with a diuretic is a well established antihypertensive combination that is very effective because of the different, yet synergistic, mechanisms of actions of agents from these two drug classes. Delapril is a potent antihypertensive ACE inhibitor, and indapamide is a thiazide-like diuretic with additional antihypertensive properties. The combination of delapril and indapamide provides renoprotective effects, and indapamide is also cardioprotective. Use of these two drugs together is therefore a rational selection for combination therapy, and one that has consistently demon-

strated lowering of BP to target values with a level of efficacy that is at least as good as other combinations of ACE inhibitors and diuretics. This combination has also been found to provide favourable effects on haemodynamic parameters, including left ventricular mass index and ejection fraction. Furthermore, combining an ACE inhibitor and a thiazide-type diuretic has been associated with a decreased risk of stroke and is recommended for patients with cerebrovascular disease, a setting in which the combination of delapril and indapamide has therapeutic potential.

Because of the additive mechanisms of delapril and indapamide, the dose required for an effective antihypertensive effect is relatively low, and the combination is well tolerated at such doses. In particular, metabolic effects normally associated with diuretics are rare at the therapeutic dose of indapamide used in combination with delapril, making the combination suitable for patients with metabolic disorders in whom diuretic therapy would otherwise not be recommended. Delapril 30mg and indapamide 2.5mg have been combined in a fixed combination, offering the convenience of a one-tablet-per-day antihypertensive drug regimen for most patients, which, along with good tolerability, helps to address the issue of noncompliance.

In spite of convincing data that the awareness and management of hypertension have improved, hypertension remains a leading cause of cardiovascular morbidity and mortality, accounting for approximately 4.4% of the global disease burden and for an estimated 7.1 million hypertension-associated deaths annually.[1,2] Suboptimal blood pressure (BP) [systolic BP >115mm Hg] is the single most common attributable risk factor for death, and is responsible for an estimated 49% and 62% of cases of ischaemic heart disease and cerebrovascular disease, respectively.[2]

While the number of hypertensive patients receiving therapy has improved, there are still a significant number of individuals with hypertension worldwide who are not being managed adequately, or even managed at all.[1,3,4] Experience in recent years has shown that monotherapy does not adequately control BP in up to one-half of patients,[4] and combination therapy with two or more drugs from different classes is increasingly being recognised as important. It has also become apparent that lower BP targets than those previously recommended are needed to decrease morbidity and mortality. Previous recommendations of a systolic BP goal of <160mm Hg for many patients were based primarily on observational data. Recent studies have indicated that for low- to medium-risk hypertensive patients, systolic BP <140mm Hg and diastolic BP <90mm Hg are beneficial.[4] The respective systolic and diastolic pressure targets for patients with hypertension complicated by established cardiovascular disease, diabetes mellitus or renal insufficiency are <130 and <80mm Hg.[4] Focus should also be on achieving systolic BP goals, as in most patients aged >55 years, diastolic BP goal will also be achieved concurrently.[4] In general, antihypertensive therapies that achieve these goals at the lowest possible doses are preferred.

There are many fixed-combination products available now for the treatment of hypertension. Fixed-combination products offer the advantage of convenience for the patient[1] and they improve patient compliance[3,5] and persistence with therapy[6] by reducing the number of tablets that need to be taken. This is important, as many hypertensive patients have co-morbid conditions and require polypharmacy. Furthermore, low doses of both drugs can be administered, reducing the likelihood of adverse effects.[3] The majority of available fixed combinations contain a diuretic combined with another diuretic or drug from another antihypertensive

class, with the exception of a few that combine an angiotensin-converting enzyme (ACE) inhibitor with a calcium channel antagonist. The combination of an ACE inhibitor and a diuretic is particularly effective,[7,8] as these two drug classes offer different mechanisms of action that produce an additive antihypertensive effect.[9] The fixed combination of delapril and indapamide (Delapride®, Promedica, Italy)[1] has been extensively researched in Italy and appears to offer a well tolerated and effective option for managing hypertension. This article reviews the pharmacology, clinical efficacy and safety of the combination of delapril and indapamide for the management of hypertension.

1. Combination Therapy in Hypertension

Starting antihypertensive treatment with low-dose monotherapy and switching to another low-dose agent if the first agent fails to control BP may help identify the agent that is most effective for the patient. However, this can be a time-consuming and frustrating process for both the patient and the physician.[3] Current international guidelines recognise that two or more antihypertensive agents are likely to be necessary to reach BP targets in the majority of patients.[1,3,4,10] While starting with combination therapy has the potential to expose the patient to a drug unnecessarily, combination therapy increases the probability of controlling BP by providing drugs that act through two BP-lowering mechanisms. Fixed-dose combination therapy should include two or more antihypertensive agents from different drug classes,[1] with the agents being chosen on a rational basis. This approach increases the number of potentially complementary antihypertensive mechanisms and reduces the incidence and magnitude of adverse effects. Antihypertensive combinations commonly used include a diuretic combined with an ACE inhibitor, an angiotensin II type 1 receptor antagonist (angiotensin receptor blocker [ARB]), a β-adrenoceptor antagonist, a centrally acting agent or another diuretic, or an ACE inhibitor combined with a calcium channel antagonist.[1]

1.1 ACE Inhibitor plus Diuretic

The combination of an ACE inhibitor and a diuretic has long been established as a rational and highly effective combination for controlling BP. According to a review by Pessina,[11] response rates with such combinations typically exceed 80%. This high response rate has been largely attributed to the additive pharmacodynamic effect of two drugs with different mechanisms of action,[9] but it has also been hypothesised that a potentiation effect of diuretics on the action of ACE inhibitors on the renin-angiotensin system plays a part.[12] It has been suggested that stimulation of the renin-angiotensin system as a result of diuretic-induced decreased sodium levels results in increased antihypertensive activity of ACE inhibitors. Indeed, it has been shown that a reduction in sodium levels enhances the antihypertensive effect of ACE inhibitors.[13] At the same time, ACE inhibitors may inhibit diuretic-associated activation of the renin-angiotensin system and augment the antihypertensive effect of diuretics.[12] Data from a clinical study support the potentiation hypothesis; reductions in BP were greater with the combination of an ACE inhibitor and diuretic than with either agent alone.[8] Another important aspect of the ACE inhibitor plus diuretic combination is that ACE inhibitors block production of angiotensin II, which may reduce the antihypertensive activity of the diuretic,[4] thereby creating conditions for the ACE inhibitor to function with its maximum antihypertensive effect. Furthermore, because the dosages of each agent in the combination needed to achieve adequate BP control are less than those required when these agents are used as monotherapy, the tolerability of combined ACE inhibitor and diuretic therapy is favourable.[11]

2. Pharmacology of Indapamide and Delapril

2.1 Indapamide

Indapamide, an indoline clorosul-fenidic derivative,[11] is a thiazide-like diuretic with antihyperten-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

sive action[14,15] that offers several advantages over thiazide diuretics.[11] The diuretic effect of indapamide is dose-proportional[16] and is proposed to occur via inhibition of sodium chloride co-transporters in the cortical segment of the distal convoluted tubule.[14]

Indapamide also has direct vascular effects, as demonstrated by alterations in vascular reactivity to agonists in the presence of the drug[16,17] and its potent calcium antagonist activity,[18] resulting in reductions in intracellular calcium levels.[14] *In vivo* and *in vitro* studies (reviewed by Campbell and Brackman[17]) have suggested a cardiovascular protective role for indapamide through enhanced prostaglandin-mediated antithrombotic and vasorelaxant activity, free radical scavenging and reduced endothelium-dependent vasoconstrictor reactivity.

The diuretic and the antihypertensive effects of indapamide appear to occur at different dosages. Significant, consistent diuretic activity of indapamide is only seen at dosages above 2.5 mg/day.[19] In contrast, a dose-ranging study found indapamide had antihypertensive efficacy at a dosage of 1 mg/day and attained maximal BP lowering at a dosage of 2.5 mg/day, with no additional antihypertensive benefit attained by increasing the dose above 2.5 mg/day.[20] Moreover, the dampening effect of indapamide on vascular reactivity has been observed in subjects receiving indapamide 2.5 mg/day.[19] Taken together, these findings suggest that the antihypertensive action of indapamide occurs at subdiuretic doses and is likely to result from the drug's direct vascular effect, which appears to be independent of its diuretic activity. This gives indapamide the advantage over other thiazide diuretics of antihypertensive efficacy at dosages at which only a mild diuretic effect is seen,[20] which in turn reduces the likelihood of the unwanted cardiac and renal effects usually associated with diuretic action.[11] Indapamide also has well established dose-dependent natriuretic and kaliuretic effects, but it exerts its maximum natriuretic effect at a lower dose than that required to exert its maximum kaliuretic effect, allowing it to increase sodium excretion without causing hypokalaemia.[21]

Indapamide has been found to offer reno- and cardioprotective effects, including reversal of ventricular hypertrophy and regression of microalbuminuria in humans, and decreased incidence of stroke and prevention of nephrosclerosis in animal models of hypertension.[17,21,22] Limited *in vitro* and *in vivo* animal studies suggest that indapamide also has anti-atherosclerotic actions, including favourable effects on lipid profiles and reduction of atherosclerotic lesions in animal studies.[23-25]

Indapamide is associated with fewer metabolic adverse effects than true thiazide diuretics when used at the subdiuretic doses required for treating hypertension. As reviewed previously, indapamide is associated with smaller reductions in potassium levels or a lower incidence of hyperkalaemia,[11,26] and does not significantly affect glucose metabolism.[11,26,27] Treatment with indapamide for 36 months in patients with type 2 diabetes and mild hypertension was not associated with any changes in postprandial or basal glucose or glycosylated haemoglobin levels.[28] Thiazide diuretics may have a dose-dependent effect on triglyceride and low-density lipoprotein cholesterol levels that is evident even at low doses,[26] whereas indapamide at antihypertensive doses has a lower propensity to cause dyslipidaemia[11,29] or hyperuricaemia[11] than thiazide diuretics. Pessina[11] suggested that the lack of these metabolic effects relative to true thiazide diuretics makes indapamide a suitable option for treating hypertensive patients who also have diabetes, gout or hyperlipidaemia.

There are additional actions of indapamide that may be clinically beneficial. Indapamide has been shown to be at least as effective as, and better tolerated than, hydrochlorothiazide in controlling urinary calcium levels in patients with recurrent nephrolithiasis and renal hypercalciuria.[30] Furthermore, there are indications from preclinical studies that indapamide may have osteoprotective effects, which may make use of this agent more appropriate than thiazide diuretics in patients with co-morbid osteoporosis.[31,32]

2.2 Delapril

Delapril is an ACE inhibitor without a sulfhydryl group.[33] The proline moiety present in enalapril and captopril is replaced with an indanyl-glycine substituent, making delapril more lipophilic. It has been hypothesised that ACE inhibitors with increased lipophilicity will have superior tissue ACE inhibition.[33,34] The substitution of the proline moiety may also make delapril a more potent antihypertensive than other ACE inhibitors; in an animal study, delapril inhibited vascular wall ACE activity to a greater degree than enalapril,[35] presumably because of the drug's higher lipophilicity and thus greater affinity for the vascular wall. It is believed that various ACE inhibitors act at different binding sites on ACE, including ionic and van der Waals type sites.[33] Lipophilicity may therefore be important in determining which binding sites a given ACE inhibitor interacts with, and, consequently, the concentrations of ACE inhibitors in lipophilic membranes.[33] Using tissue samples from humans, it was shown that the main active metabolite of delapril has a higher affinity for the C-domain on ACE.[36,37] Bevilacqua and colleagues[36] concluded that this finding fits well with the model that ACE inhibitors that have large side chains and are hydrophobic generally have a higher affinity for the C-domain; conversely, those with shorter side chains and hydrophilicity have a greater affinity for the N-domain. It was also observed that the specificity of an ACE inhibitor for N- and C-sites was influenced by the organ involved, and it has been proposed that organ-specific glycosylation of ACE affects the affinity of ACE inhibitors for N- or C-sites in human ACE.[36]

Once-daily administration of delapril 30mg has been shown to confer a smooth reduction in BP over 24 hours.[38-40] The ratio between the average of the 24-hour BP changes after trough and its standard deviation (the 'smoothness' index) was high for all delapril recipients.[39] Additionally, the trough-to-peak ratio of once-daily delapril 30mg has been found to be >50% in patients who experienced significant reductions in BP while receiving the agent.[38,40]

3. Pharmacokinetics of Indapamide and Delapril

3.1 Indapamide

Indapamide is rapidly absorbed once released from its formulation and its bioavailability is not affected by food (reviewed previously by Caruso et al.[16]). Following administration of immediate-release forms, indapamide plasma concentration increases and peaks rapidly.[16] In the fixed combination tablets of indapamide/delapril 30mg/2.5mg, the maximum concentration (C_{max}) of indapamide occurs within 2 hours of administration.[41] Indapamide area under the concentration-time curve (AUC_∞) values for indapamide 2.5mg (administered with delapril) were 1597 and 1536 ng • h/mL for single-dose and once-daily dosing for 7 days, respectively.[42] Indapamide is 76% bound to plasma protein.[43] It is extensively bound to erythrocytes in blood but its distribution in blood is significantly affected by binding to serum plasma proteins, particularly α_1-acid glycoproteins.[43] Removal of indapamide from the blood follows a biphasic pattern, and the elimination half-life ($t_{1/2}$) is relatively long at approximately 16 hours after administration of indapamide[16] and 14 hours after administration of indapamide/delapril 2.5mg/30mg.[42] Indapamide is extensively metabolised, and around 70% of its metabolites are excreted in the urine with only a small percentage being excreted in the faeces.[16]

Indapamide has no clinically relevant effects on the pharmacokinetics of delapril following coadministration of therapeutic single doses.[44] Furthermore, repeated coadministration over 7 days does not alter the pharmacokinetic parameters of indapamide compared with single-dose administration.

3.2 Delapril

Delapril is a prodrug that after oral ingestion is rapidly absorbed and then quickly and extensively metabolised after administration alone or in combination with indapamide;[44] absorption of delapril is not influenced by intake of food.[33] AUC_∞ values

following a single dose of delapril 30mg (administered with indapamide) were 281 ng • h/mL for delapril, and 2178, 739 and 716 ng • h/mL for its metabolites, delaprilat, M-2 and M-3, respectively.[42] Following a single dose of delapril 30mg, C_{max} values for the active metabolites delaprilat and M-3 were 579.2 and 175.9 ng/mL, respectively, and occurred after 1.2 and 1.6 hours, respectively.[44] The respective $t_{1/2}$ values for these metabolites were relatively short at 1.3 and 1.4 hours, and the concentrations were no longer quantifiable 8 and 3–4 hours after administration. About half of the administered dose of delapril (56%) is excreted in the urine within 24 hours, mainly as delaprilat (21.4%) and M-3 (30.4%).[33] Repeated daily administration of delapril 60mg for 7 days indicated there is no accumulation of delapril or any of its metabolites.[33]

Delapril has clinically relevant effects on the pharmacokinetics of indapamide following coadministration of therapeutic single doses.[44] Furthermore, repeated coadministration over 7 days does not alter the pharmacokinetic parameters of delapril compared with single-dose administration.

4. Drug Interactions: Indapamide and Delapril

Most drug-drug interactions associated with the combination of delapril and indapamide consist of interactions that would occur with the individual component agents.

4.1 Indapamide

Diuretics can cause reduced potassium or magnesium levels, and this may be exacerbated by concomitant administration of corticosteroids, corticotrophin, amphotericin B or carbenoxolone.[41] Indapamide-induced electrolyte disturbances may predispose patients to digitoxin- or digoxin-induced arrhythmias.[45] Patients receiving such combinations should undergo plasma potassium and magnesium monitoring. If low levels of these electrolytes occur, supplementation should be considered along with prevention of further losses through dietary sodium restriction or use of potassium-sparing diuretics. Combining ACE inhibitors and potassium-sparing diuretics such as amiloride, spironolactone and triamterene may result in hyperkalaemia in some high-risk (e.g. renally impaired) patients.[45] Orthostatic hypotension may occur when the fixed combination of indapamide plus delapril is administered in the presence of barbiturate, alcohol or opioid use.[41]

4.2 Delapril

Antacid administration may reduce absorption of delapril.[41] Because ACE inhibitors may increase the concentration of concomitant lithium and lead to neurotoxicity, concomitant administration of lithium and delapril should be undertaken cautiously with careful monitoring of serum lithium concentrations. Antihyperglycaemic agent concentrations may be increased when the latter are administered concomitantly with ACE inhibitors, resulting in hypoglycaemia, particularly during the first few weeks of treatment or in patients with renal insufficiency.[41] Anaesthetics administered during surgery in the presence of ACE inhibitors can produce additive hypotensive effects that require corrective measures.[41] Concomitant administration of salicylates may reduce the antihypertensive effect of ACE inhibitor therapy.[45] Whenever coadministration of delapril and a salicylate is necessary, BP and haemodynamic parameters should be monitored, and a change in therapy should be considered if haemodynamic adverse effects occur.[45]

5. Clinical Efficacy of Delapril plus Indapamide Combination Therapy

5.1 BP-Lowering Effect

Clinical studies investigating the combination of delapril plus indapamide in patients with mild to moderate hypertension have consistently demonstrated that the combination is more effective than placebo in reducing BP compared with baseline values,[46,47] and better in this respect than either drug administered on its own[47,48] (table I). Periodic and continuous ambulatory BP monitoring have also shown that BP reduction with delapril plus indapamide is maintained over a 24-hour period,[48-50]

Table I. Antihypertensive efficacy of delapril (DEL) plus indapamide (IND) in clinical studies of patients (pts)[a] with mild to moderate hypertension

Study duration	Mean age (y)	Regimen[b] (mg/day)	No. of pts	Mean BP[50] or mean seated[7,46,48,49,51-54]/supine[47] BP (mm Hg)			Responders (at study end, unless stated otherwise) [% pts][c]	Ref
				baseline	interim timepoint	study end		
Noncomparative studies								
4wk	49	DEL 30 + IND 1.25	30	160/100	140/90** [wk 2]	137/88**		56
24wk	69	DEL 30 + IND 1.25	28	156/101	142/86*** [wk 8]	133/73***		55
24wk	56	DEL 30 + IND 2.5	50	168/104	157/98** [wk 2]	145/90**	96	57
Comparative studies vs PL and/or DEL and IND monotherapy								
4wk[d]	51	DEL 15 + IND 1.25	37	162/104		144/93****†	70†	52
		DEL 15 + IND 2.5	36	166/102		146/91****†	71†	
		DEL 30 + IND 1.25	33	163/103		146/91****†	83†	
		DEL 30 + IND 2.5	35	161/104		141/88****†	88†	
		PL	35	162/102		157/101	18	
6wk	51	DEL 30	52	162/102			73[e]	54
		IND 2.5	52	163/102			77[e]	
		DEL 30 + IND 2.5	53	165/102			94‡[e]	
30d	48	DEL 30	48[f]	159/103		149/94		53
		IND 2.5	48[f]	159/103		143/94		
		DEL 30 + IND 2.5	48[f]	159/103		141/92		
		PL	48[f]	159/103		148/96		
Comparative studies vs other combination therapies								
12wk	55	DEL 30 + IND 2.5	87	160/102			92	7
		FOS 20 + HCT 12.5	84	161/101			87	
12wk	≈54	DEL 30 + IND 2.5	80	162/102		134/84***	93	59
		LIS 20 + HCT 12.5	79	162/102		131/84***	91	
6mo	53	DEL 30 + IND 1.25[g]	80	105[g]	101[h] [d30]	88*[h]	79‡ [d30]	60
		CAP 50 + HCT 15[g]	72	103[g]	100[h] [d30]	91*[h]	63 [d30]	
6mo	54	DEL 30 + IND 1.25[g]	396	161/102	142/89 [d30]	135/85***‡‡	93‡‡‡	58
		CAP 50 + HCT 15[g]	394	160/101	145/91 [d30]	138/86***	85	

a One study[53] enrolled pts with newly diagnosed or inadequately treated hypertension and DBP of ≥95 and ≤114mm Hg.

b All drugs administered orally once daily (where reported).

c Response defined as a reduction from baseline in DBP of ≥10[7,46,48,51,52,54] or ≥15[53] mm Hg, and included pts with normalised BP in some trials, i.e. with a DBP of <90[48] or ≤90[7,46,51-54] mm Hg.

d 4-wk randomised treatment followed by 4-wk open-label, dose-titration period (results not presented here).

e Evaluable pt numbers were 51 (DEL), 49 (IND) and 50 (DEL + IND).

f This study was of crossover Latin-square design; 48 pts were enrolled, each pt received each treatment.

g Doses were increased in nonresponders at 1 mo as follows: HCT dose was increased to 25 mg/day; doses for other diuretics were doubled.

h DBP.

CAP = captopril; **d** = day; **DBP** = diastolic BP; **FOS** = fosinopril; **HCT** = hydrochlorothiazide; **LIS** = lisinopril; **mo** = month; **PL** = placebo; **pt** = patient; **wk** = week. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$; **** $p < 0.0001$ vs baseline; † $p < 0.0001$ vs PL; ‡ $p < 0.05$; ‡‡ $p < 0.01$; ‡‡‡ $p < 0.001$ vs active comparators.

and that the circadian BP profile is unaltered by treatment.[48,49] While it is apparent that once-daily administration achieves a progressive and gradual antihypertensive effect, the data indicate that the

major BP-lowering effect occurs within the first 2–4 weeks of therapy[51] and is maintained during long-term treatment.[49,51,52] A trend for further decreases in mean BP following weeks 2–4 of treatment is often seen in clinical trial data, but is usually not significant.

Fogari et al.[46] investigated the antihypertensive effects of four possible dose combinations of delapril 15 or 30mg and indapamide 1.25 or 2.5mg. They found that there was a trend for lowest efficacy with delapril 15mg and indapamide 1.25mg, highest efficacy with delapril 30mg and indapamide 2.5mg, and similar intermediate efficacies for the two intermediate combinations.

Rappelli et al.[47] investigated the antihypertensive effects of delapril 30mg and indapamide 2.5mg each as monotherapy and in combination in a double-blind, randomised placebo-controlled trial with a balanced Latin-square design (table I). These investigators found that while there was generally a trend toward BP reduction with each monotherapy compared with placebo, only the effect of combination therapy reached statistical significance (mean change in supine diastolic BP from baseline of −5.3mm Hg with combination therapy vs +2.1mm Hg with placebo; $p < 0.05$). In contrast, Lechi and Arosio[48] found that the proportion of patients with normalised or improved BP following 6 weeks of combination therapy with delapril plus indapamide was significantly greater than with either agent on its own.

Cremonesi and colleagues[7,54] compared delapril plus indapamide with other ACE inhibitor plus diuretic combinations. When delapril plus indapamide was compared against hydrochlorothiazide plus fosinopril or lisinopril, there was no significant difference in treatment groups in terms of the proportion of patients who responded to treatment (table I). Similarly, there was no significant between-group difference in the proportion of responders in a study comparing delapril plus indapamide with hydrochlorothiazide plus captopril (45% vs 32%, respectively); however, when normalised patients (i.e. patients achieving a diastolic BP of ≤90mm Hg) were included, significant between-group differences were found (table I).[53] When Rosei et al.[52] compared delapril plus indapamide with hydrochlorothiazide plus captopril, delapril plus indapamide was significantly superior in terms of responders (table I). Interestingly, the between-group difference in this study was of similar magnitude to that in the fosinopril plus hydrochlorothiazide comparison by Cremonesi et al.[7]

5.2 End-Organ Protection

Both delapril and indapamide have renoprotective effects. Indapamide decreases BP and increases creatinine clearance in patients with renal impairment and moderate hypertension, while hydrochlorothiazide, a true thiazide diuretic, is associated with decreased creatinine clearance in such patients.[55] As such, indapamide may be effective for hypertension in patients with renal impairment when other diuretics are not.[56] An increased glomerular filtration rate is also seen when delapril and indapamide are combined.[57] The researchers postulated that this was probably due to 'synergistic' actions of delapril decreasing renal vascular resistance via vasodilatation together with the vasodilatory action of indapamide on glomerular vessel myocytes. The associated improvement in renal function makes the combination of delapril and indapamide particularly desirable as antihypertensive therapy for patients with poor renal function, including many elderly patients, in whom use of a combination of an ACE inhibitor with a true thiazide diuretic such as hydrochlorothiazide would increase the risk of renal failure.

The WHO recommends ACE inhibitor therapy for hypertensive patients with cardiac disease or type 1 diabetic nephropathy or nondiabetic nephropathy.[4] US and European hypertension guidelines include ACE inhibitors in their recommendations for patients with various cardiovascular diseases, renal diseases and diabetes.[1,3] Diuretics are also recommended for patients with heart failure or who are at high risk for coronary disease and diabetes.[1] The cardioprotective properties of the combination of delapril plus indapamide have been demonstrated in studies that have assessed cardiac

haemodynamics. In one study, mean ejection fraction increased significantly ($p < 0.01$) from a pretreatment value of 66.36% to 68.18% in 50 patients with hypertension treated for 24 weeks with delapril plus indapamide.[51] Additionally, significant decreases in left ventricular mass, end-systolic (telesystolic) stress and the thickness of the posterior wall and interventricular septum were also seen. No patient developed left ventricular hypertrophy during the study. Acanfora et al.[49] measured haemodynamic parameters in 15 elderly patients with hypertension and left ventricular hypertrophy who received delapril plus indapamide. They found that the baseline left ventricular mass index decreased from 167.5 to 152.2 g/m^2 after 24 weeks of treatment with delapril and indapamide ($p < 0.05$ vs baseline). Furthermore, the percentage of left ventricular mass index change correlated with the percentage change in the 24-hour diastolic BP AUC.

The combination of an ACE inhibitor with a diuretic or a diuretic alone are the two regimens recommended for treating hypertension in patients with cerebrovascular disease.[4] This recommendation is based in part on the findings of the PROGRESS (Perindopril pROtection aGainst REcurrent Stroke Study) trial, in which a perindopril plus indapamide combination had a significant protective effect against the occurrence of stroke compared with other regimens.[58] However, it is of interest that the original interpretation of the PROGRESS data by some reviewers was that the protective effect against stroke was attributable only to perindopril.[59] These interpretations subsequently formed the basis for approval of perindopril or an ACE inhibitor for hypertensive patients with cerebrovascular disease by a number of European regulatory authorities.[60] However, the reduction in stroke risk was not necessarily solely attributable to perindopril because risk reduction in this subgroup was only 5% compared with 43% in patients receiving perindopril plus indapamide.[58] It appears that the combination of an ACE inhibitor and a diuretic reduces the risk of stroke, at least when given at the dosages used in the PROGRESS study, which are the same as the Defined Daily Doses (DDD) recommended in the WHO Collaborating Centre for Drug Statistics Methodology Anatomical Therapeutic Chemical/Defined Daily Dose index.[61] Use of alternative agents at appropriate dosages from the same classes also seems reasonable if perindopril and/or indapamide are not available,[62] indicating that the combination of delapril 30mg plus indapamide 2.5mg has a potential role in this setting.

Pessina[11] concluded that the combination of delapril and indapamide would be expected to provide reliable antihypertensive effects and to be well tolerated because of the different mechanisms of action of the two agents and the relatively low dosages required. Use of large doses of delapril or indapamide would be inappropriate in any case, as both these agents have a flat dose-response curve. In stroke-prone spontaneously hypertensive rats (SHRsp), the combination of delapril and indapamide has also been shown to delay death when administered even at low doses, and to protect against infarctive and haemorrhagic cerebral lesions, degenerative renal lesions, and cardiac hypertrophy secondary to long-term hypertension (probably via 'synergistic' mechanisms).[63] In another experiment investigating the combination of delapril and indapamide or hydrochlorothiazide administered to SHRsp, the combination of delapril and indapamide at the lowest dosage significantly delayed animal death by protecting against proteinuria, although doses were below those necessary to lower BP adequately.[64] The researchers concluded that the combination of a low-dose ACE inhibitor and diuretic can protect against proteinuria, independent of antihypertensive effects. In a long-term follow-up study, Contri et al.[65] found that the combination of delapril and indapamide prevented the increase in extracellular matrix deposition in the thoracic aorta seen in rats receiving monotherapy with either drug. They postulated that indapamide may interact with ACE inhibitors to limit aortic fibrosis, a finding indicative of hypertension-associated vascular remodelling, independently of BP-lowering or diuretic effects.

Table II. Adverse effects associated with delapril and indapamide

Delapril[41,68]	Indapamide[41,69]
Cough	Acute gout
Dizziness	Blurred vision
First-dose hypotension	Cardiovascular (including orthostatic hypotension, palpitations)
Hepatotoxicity	Dermatological effects (including necrotising angiitis, pruritus, rash, vasculitis)
Hyperkalaemia (as a result of decreased aldosterone secretion)	CNS effects (including anxiety, depression, dizziness, drowsiness, fatigue, headache, insomnia, lethargy, light-headedness, nervousness, restlessness, vertigo, weakness)
Hypersensitivity reactions (including angioneurotic oedema)	Electrolyte disturbances, including hypokalaemia
Renal dysfunction	Gastrointestinal effects (including abdominal pain/cramping/bloating, anorexia, constipation, diarrhoea, dry mouth, gastric irritation, nausea, vomiting)
Skin rash	Glycosuria
Taste disorders	Hyperglycaemia
Teratogenic effects	Hyperuricaemia
	Impotence/reduced libido
	Neutropenia
	Muscle cramp or spasm
	Nocturia
	Rhinorrhoea

6. Tolerability

Adverse effects of the fixed combination of delapril and indapamide include the adverse effects associated with each component drug (table II). To date there is no evidence that the type of adverse effects associated with each component of the delapril plus indapamide fixed combination are any different to those associated with each component drug on its own, with the exception that delapril-induced hyperkalaemia and indapamide-induced hypokalaemia may negate each other.[41] In a trial comparing indapamide plus perindopril with placebo, hypokalaemia occurred in 13 of 138 patients receiving combination therapy, which was greater than the incidence in those receiving placebo, but hypokalaemia was mild in all cases, with potassium levels >3.0 mmol/L (hypokalaemia <3.4 mmol/L).[66] A *post hoc* analysis that assessed cardiovascular outcomes related to potassium levels in the HOPE (Heart Outcomes Prevention Evaluation) study found that use of the ACE inhibitor ramipril was associated with a lower incidence of hypokalaemia.[67] Of note, this effect was particularly marked in patients receiving diuretics, with patients receiving diuretics without ramipril having an increased incidence of hypokalaemia compared with those receiving the combination (5.95% vs 3.86%, respectively; p = 0.07).

It may be suggested that use of delapril plus indapamide combination products would be generally better tolerated than monotherapy with either individual agent at the usual recommended doses because the additive actions of delapril and indapamide mean that hypertension can be well controlled at relatively low doses of each agent in combination.[11] Two clinical studies comparing the delapril plus indapamide combination therapy with monotherapy generally found no significant between-group differences in terms of tolerability.[47,48]

Compared with other ACE inhibitors, delapril is better tolerated in terms of tussive response to challenge tests,[70] probably because of its weaker bradykinin potentiation.[71] Cough is listed as a warning/precaution for the fixed combination indapamide plus delapril,[41] but there is evidence that it may occur less frequently with delapril than with other ACE inhibitors.[70,71] Saruta and Nishikawa[71] noted that enalapril-associated cough resolved in 6 of 12 patients when treatment was switched to delapril. When Ogihara et al.[70] investigated frequency of induced cough with captopril, enalapril and delapril in a small group of patients, they found that

delapril resulted in a smaller increase in cough frequency above control values than the other ACE inhibitors studied.

Adverse events with delapril plus indapamide generally did not interrupt clinical trial participation.[7,47-49,51-54,72,73] Furthermore, no significant alterations in cardiac parameters associated with delapril plus indapamide treatment have been reported in clinical trials.[7] Clinically relevant alterations in laboratory parameters have generally not been observed in clinical studies during delapril plus indapamide treatment, which lasted ≥1 year in some trials.[47,49-54,72,73] Indapamide-associated uricaemia has been reported occasionally,[48,54] but no more often in combination with delapril than when indapamide was administered on its own, since the proportion of patients with 'out of range' uric acid levels was not different with delapril plus indapamide combination therapy compared with indapamide monotherapy.[48]

7. Dosage and Administration

Delapride® is a fixed-combination product that contains delapril 30mg and indapamide 2.5mg, a dose combination that has been shown to be effective and generally well tolerated.[41] However, adverse events were found to be dose-related in a dose-ranging study,[73] resulting in the suggestion that combinations containing either delapril or indapamide at half the doses currently used in the fixed combination product may be useful for tailoring treatment to suit individual patient needs.[46] This aim can also be achieved by halving the current fixed-combination tablet.

Prior to starting treatment with delapril plus indapamide combination therapy, any pre-existing diuretic agents should be discontinued at least 1 day before starting the combination therapy.[41] One delapril plus indapamide 30mg/2.5mg tablet once daily, preferably taken in the morning, is required to control BP in most patients with moderate hypertension (diastolic BP >105mm Hg).[41] One half tablet of delapril plus indapamide 30mg/2.5mg once daily is sufficient to control BP in most patients with borderline hypertension (diastolic BP 90–95mm Hg).[41] The standard dosage should be sufficient to maintain BP below target values once this have been achieved.

Contraindications for use of the combination of delapril plus indapamide include known hypersensitivity to either agent, serious renal impairment and renal artery stenosis, serious hepatic insufficiency, pregnancy or breastfeeding, anuria, recent cerebrovascular accident, phaeochromocytoma or Conn's syndrome, and previous angioneurotic oedema, hypokalaemia or refractory hyponatraemia.[41] The combination should be used with caution and/or the dosage adjusted in patients with mild to moderate renal insufficiency, in elderly patients with compromised renal function, and in patients with mild to moderate hepatic insufficiency. Delapril plus indapamide combination therapy is not indicated for use in paediatric patients because of lack of efficacy and safety data.[41]

8. Conclusion

Combination therapy for treating hypertension is increasingly being recommended because initial monotherapy fails to provide adequate BP control in most patients. The combination of the ACE inhibitor delapril and the thiazide-like diuretic indapamide, which is available in some regions as a fixed combination, has been shown to be an effective and well tolerated option. Also, once-daily administration of a fixed combination in a single tablet helps improve patient compliance. Because of its greater lipophilicity, delapril appears to be a more potent antihypertensive than other ACE inhibitors, and indapamide offers improved efficacy and tolerability in patients with renal impairment compared with other diuretics. Together the two drugs exert a renoprotective effect, making them suitable for patients with renal dysfunction. The different mechanisms of action of delapril and indapamide provide additive antihypertensive effects, meaning that BP control can be achieved with relatively low doses. This in turn results in a favourable tolerability profile, particularly in terms of indapamide-associated metabolic effects, which may increase the suitability

of this combination therapy for patients with diabetes, hyperlipidaemia or gout.

Clinical studies have consistently demonstrated that the combination of delapril plus indapamide can reduce BP to target levels, and that this therapy is at least as effective as other combinations. Delapril plus indapamide combination therapy also improves haemodynamics and may help prevent stroke, making it a useful therapeutic option in patients with risk factors for cerebrovascular events.

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