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Imidapril

Will Fewer Adverse Events Translate into Better Long-Term Outcomes?

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The history of ACE inhibition as a therapeutic approach dates back to the synthesis of captopril, now more than 30 years ago. Currently, ACE inhibitors are widely used in clinical practice to lower blood pressure (BP) and for the secondary prevention of cardiovascular and renal complications. According to the recent Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7),[1] compelling indications for ACE inhibitors include heart failure, post-myocardial infarction, a high risk of coronary heart disease, diabetes mellitus and renal disorders. ACE inhibitors are also recommended to prevent recurrent stroke,[1] although as monotherapy they are no better than placebo in preventing this condition.[2] The European Society of Hypertension-European Society of Cardiology 2003 guidelines[3] propose the use of ACE inhibitors in patients with congestive heart failure, left ventricular dysfunction, nondiabetic and type 1 diabetic nephropathy and proteinuria, as well as post-myocardial infarction.

According to UK National Institute for Clinical Excellence 2006 guidelines,[4] they are particularly suited to initiating antihypertensive treatment in patients younger than 55 years. Although current guidelines list compelling indications for ACE inhibitors, ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) indicated that the more cost effective thiazide diuretics are superior to ACE inhibitors in BP lowering and the prevention of stroke and combined cardiovascular disease.[5] In addition, ALLHAT participants randomised to lisinopril experienced a higher risk of stroke, combined cardiovascular disease and angioedema than those assigned to the calcium channel antagonist amlodipine, but conversely experienced less heart failure.[5,6]

In general, ACE inhibitors are well tolerated. Class-specific adverse events, like dry cough and dysgeusia, diminish adherence to therapy. Five years after randomisation into the ALLHAT,[5] persistence of first-line treatment was significantly lower with lisinopril than amlodipine (76.6% vs 80.4%). As reviewed by Robinson et al.[7] in this issue of *Drugs*, the incidence of dry cough is lower with imidapril than with other ACE inhibitors.

Although the precise mechanism underlying dry cough, airway symptoms and angioedema remains unknown, it appears to involve bradykinin and substance P. ACE inhibitors promote the accumulation of these compounds with the subsequent formation of arachidonic acid and nitric oxide (figure 1). *In vitro* data suggest that imidaprilat might inhibit bradykinin metabolising enzymes less than enalaprilat.[8] Among all drug classes that inhibit the renin system, the accumulation of bradykinin is specific to ACE inhibitors (figure 1).

In guinea pigs, ACE inhibitors induced a higher airway sensitivity to ozone, with imidapril eliciting the lowest degree of hypersensitivity compared with enalapril or captopril.[9] The reduction in forced expiratory volume seen in patients receiving enalapril is not observed in patients receiving

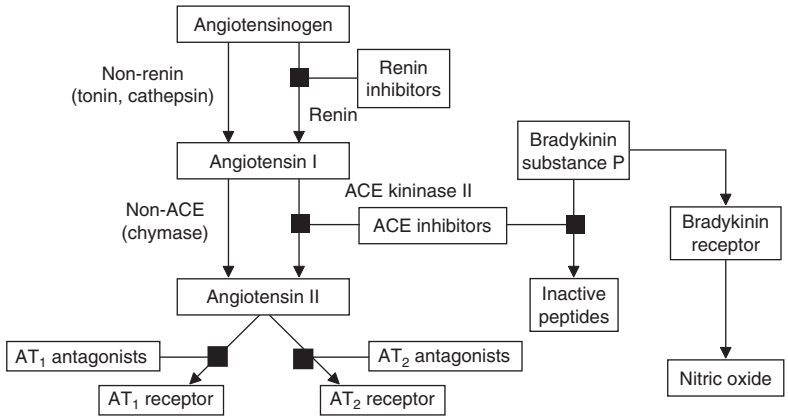

Fig. 1. The renin-angiotensin-aldosterone system. Arrows indicate metabolic pathways and black squares represent sites of inhibition. **AT**$_1$ = angiotensin 1, **AT**$_2$ = angiotensin 2.

imidapril.[10] This effect may contribute to a beneficial effect of imidapril on exercise capacity in patients with chronic heart failure.[11]

If confirmed in long-term studies with appropriate sample sizes, the lower incidence of adverse events at the level of the airways might be a clinical characteristic differentiating imidapril from other ACE inhibitors. In ALLHAT, angioedema occurred in 38 patients in the lisinopril group, but only in 3 randomised to amlodipine.[5] Although fatalities resulting from angioedema are rare, one should consider that 30–40 million patients worldwide are exposed to ACE inhibitors, and that therefore this drug class might account for several hundred deaths per year.[12] That these are not just hypothetical numbers is underscored by cases of fatal angioedema in both ALLHAT[5,6] and the HOPE (Heart Outcomes and Prevention Evaluation)[13] trials and also by a recent report from a single coroner's office describing seven cases of asphyxiation associated with ACE inhibitors during a 3-year period.[14]

Although mostly considered an adverse event, accumulation of bradykinin is also beneficial because it contributes to the BP-lowering effect of ACE inhibitors. Moreover, ACE inhibitors probably attenuate the depletion of substance P, which is a common finding in aspiration pneumonia.[15] Post-stroke patients, in particular those with infarction of the basal ganglia, are at increased risk of this condition,[16] but if treated with ACE inhibitors they showed an improvement of asymptomatic dysphagia. Along similar lines, patients taking ACE inhibitors, including imidapril, experienced a lower risk of aspiration pneumonia, although the latter effect has only been observed in Asian patients.[17] From a theoretical point of view, moderate inhibition of the degradation of bradykinin to a degree that does not induce dry cough might therefore be beneficial, although this hypothesis remains to be tested in properly powered clinical trials.

ACE inhibitors can be divided into three groups according to their molecular structure. With captopril being the only sulfhydryl compound and fosinopril the only phosphonyl compound, all other ACE inhibitors, including imidapril, are dicarboxyl compounds. Table I lists the pharmacological properties of ACE inhibitors. Most compounds are registered for once-daily administration. However, only fosinopril, ramipril, imidapril and trandolapril have trough-to-peak effect ratios exceeding 50%,[18] with imidapril being one of the highest at 84%[7]. The half-life of imidapril is adequate for once-daily administration, but there are indications that the time of administration is of importance in selected clinical settings, such as non-dipping hypertensive patients.[19] Therapy with ACE inhibitors acutely reduces serum aldosterone levels; however, long-term ACE inhibition entails a reactive increase of ACE activity in the blood, which during chronic treatment reduces BP-lowering activity and leads to

Table I. Pharmacological properties of imidapril[22,23] and other ACE inhibitors[1,18,24]

	Imidapril	Benazepril	Captopril	Enalapril	Fosinopril	Lisinopril	Perindopril	Quinapril	Ramipril	Trandolapril
Prodrug	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Half-life (h)	5	11	1.7	2	12	12	3–10	2–4	13–17	16–24
Peak onset (h)	7.6	1–2	1.0–1.5	2–8	1	6–8	1–2	3	1–2	6–10
Bioavailability (%)	42	>37	75–91	60	36	6–60	75	>60	50–60	11
Renal excretion (%)	40	85	95	88	50	70	75	75	85	15
Hepatic elimination	No	No	No	No	Yes	No	No	No	No	Yes
Administration frequency	od	bid	tid	bid	od	od	od	od	od	od
Dose range (mg/dose)	10	2.5–20	25–100	2.5–20	10–40	2.5–10	4–8	10–40	2.5–10	1-4

bid = twice daily, **od** = once daily; **tid** = three times daily.

escape of adrenal aldosterone inhibition.[20,21] Imidapril probably does not behave differently in this regard.

International guidelines endorse inhibition of the renin-angiotensin system with ACE inhibitors as the first-line antihypertensive therapy in patients with diabetic and non-diabetic nephropathy.[1,3] Imidapril lowers BP more than placebo, and to a similar extent to other agents of this drug class.[7] A recent meta-analysis[25] has questioned the specific renoprotective effects of ACE inhibitors and angiotensin receptor antagonists on renal outcomes over and beyond those attributable to BP lowering *per se*. These controversial findings once more underscore the importance of vigorous BP control in the treatment of high-risk patients, regardless of the drug class prescribed.[26]

In conclusion, imidapril is an ACE inhibitor that has a more favourable adverse-event profile with less dry cough than other compounds of this drug class. Its pharmacokinetic properties allow once-daily administration. However, in contrast to other ACE inhibitors, such as captopril,[27,28] perindopril[29,30] and lisinopril,[5,31] no hard outcome data from long-term randomised clinical trials currently support the use of imidapril. One interesting hypothesis, which might be tested with imidapril as a pharmacological tool, is whether, as suggested by others,[32] angiotensin receptor antagonists provide less protection against myocardial infarction than ACE inhibitors. Imidapril might be used as the comparator in such a trial, which would provide more data supporting the licensing and marketing of the drug and at the same time answer an important medical question.

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