Indapamide

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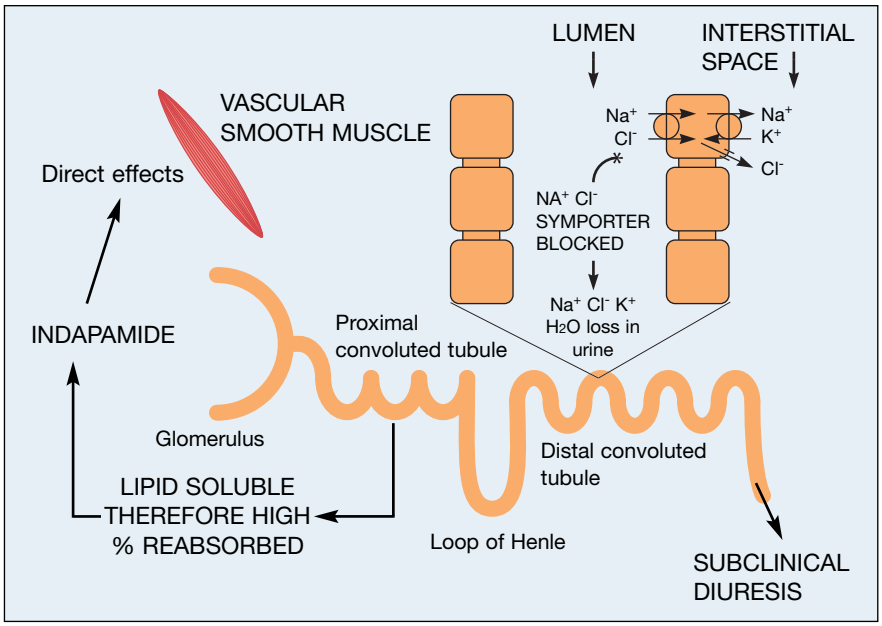
Introduction

Hypertension is a risk factor for the development of diabetic microvascular and macrovascular complications. In the UK diuretics are recommended as possible second line therapy after an ACE-inhibitor or angiotensin-II receptor blocker in patients with diabetes and hypertension. Bendroflumethiazide is the most commonly prescribed diuretic, but there are concerns about side effects such as hypokalaemia, glucose intolerance, dyslipidaemia and hyperuricaemia. Indapamide was synthesised by Servier Laboratories in 1969 as part of a programme to produce a sulphonamide that would dissociate the thiazide-like antihypertensive effects from the diuretic effects, with the intention of creating a drug with less side effects.

Figure 1. Pharmacological action of indapamide



Pharmacology

Figure 1 outlines the pharmacological action of indapamide. Indapamide is a 2-methyl indoline derivative of 4-chloro-3-sulfamoyl benzamide. It is referred to as a thiazide-like diuretic as it lacks the benzothiadiazine heterocycle seen with the thiazide group of drugs, although it retains a sulphonamide moiety. The molecular mechanism of action is similar to the thiazide diuretics. It inhibits sodium and chloride reabsorption from the distal convoluted tubule by blocking the sodium/chloride co-transporter (symporter). Dose response studies have shown that indapamide lowers blood pressure (BP) at doses below that needed to elicit a diuresis, and appears to have antihypertensive effects other than diuresis, though this may also hold true in the mechanism of action of thiazide diuretics. It is also thought to have effects on vascular smooth muscle by decreasing inward calcium currents and decreasing vascular reactivity to vasoactive substances such as norepherine and angiotension II.

Indapamide is rapidly absorbed from the gastrointestinal tract and peak plasma concentrations are seen 1–2 hours after dosing. Because of its long half-life it is effective in once-daily dosing. Indapamide is extensively metabolised, with only about 7% of the total dose administered recovered in the urine as unchanged drug during the first 48 hours after administration. It is usually 10–12 weeks before treatment effect is seen.

It is commercially available as indapamide 2.5mg (non-proprietary); Natrilix 2.5mg (Servier), Natrilix SR 1.5 mg, or in combination with perindopril as Coversyl Plus (perindopril 4mg and indapamide 1.25mg, Servier).

Trials of safety and efficacy

Several studies in the late 1970s demonstrated that indapamide was an effective antihypertensive drug, which was well tolerated and free of significant side effects. A very small (20 patients) randomised trial comparing indapamide and bendroflumethiazide found significant reductions in BP in both groups but no difference between the groups. Both groups had small but significant decreases in potassium.

Specific evidence for use in diabetes

Indapamide has been used in trials examining the effect on microvascular and macrovascular complications in people with diabetes and hypertension. These trials have tended to use indapamide in combination with perindopril, and have generally shown positive results.

The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) evaluated the effects of a perindopril-based regimen with or

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without indapamide (2.5mg) *vs* placebo in 6105 patients with established cerebral ischaemia. It included hypertensive and non-hypertensive patients. A total of 761 patients had diabetes at baseline (12%).[1] After an average follow up of four years, the risk of stroke was reduced by 38% in patients with diabetes in the active arm. The benefit was mainly due to subjects being on combined therapy, and subjects on perindopril alone in the active arm effectively saw no significant benefits. This may be explained by the additional BP reduction seen in the combination group.

The Preterax in Albuminuria Regression (PREMIER) study compared a combination of perindopril 2mg (increasing to a maximum of 8mg) plus indapamide 0.625mg *vs* enalapril dose of 10mg (increasing to a maximum of 40mg) on microalbuminuria in 457 patients with type 2 diabetes and hypertension over 52 weeks.[2] The combination arm had a significantly greater reduction in systolic and diastolic BP compared to enalapril alone, and the combination arm was more effective at reducing urinary albuminuria excretion rate compared to enalapril, by a mean of -42% *vs* -27%. The benefit was partially independent of BP changes. There were less cardiovascular adverse events in the combination arm (2.5% *vs* 6.3%, p=0.036). Metabolically, both groups had a small but statistically significant increase in HbA1c% (enalapril +0.2%, perindopril/indapamide +0.6%) and the combination group saw a small but significant increase in triglycerides.

The Natrilix SR versus Enalapril Study in hypertensive Type 2 diabetics with MicrOalbuminuRia (NESTOR) was a randomised, one-year study comparing indapamide SR 1.5mg *vs* enalapril 10mg in 570 hypertensive patients with diabetes and microalbuminuria.[3] The study produced equivalent reductions in the albumin:creatinine ratio comparing indapamide and enalapril. Both arms showed improvement in microalbuminuria to normoalbuminuria (indapamide 40% *vs* enalapril 42%), microalbuminuria levels were maintained with no deterioration in half of each of the arms (indapamide 51% *vs* 52% enalapril) and less than 10% in each arm showed some deterioration, with no difference between the two groups. The reduction in systolic BP was greater with indapamide, and different results might have been obtained if a larger dose of enalapril had been used. A small but significant deterioration was seen in total cholesterol and HbA1c% in the indapamide arm.

The Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) trial recruited 11 140 subjects with type 2 diabetes and one other vascular risk factor, randomised to combination treatment (perindopril 2mg and indapamide 0.625mg) or placebo.[4] The average follow up was 4.3 years. The active arm had a reduction in BP of 6/2mmHg and a relative risk reduction of 9% in total macrovascular and microvascular events, but there was no significant difference for macrovascular or microvascular events separately. Significant reductions were seen in total mortality and cardiovascular mortality, and in the development of microalbuminuria. There was no statistical difference in cerebrovascular or eye events. It is noteworthy that greater than 50% of the patients in the control group were taking open-label perindopril by the end of the study, making the major difference in treatment between the two arms being the use of indapamide (or, put another way, combination treatment *vs* perindopril on its own).

Discussion

These trials raise a number of interesting issues regarding indapamide, but their design means many questions are left unanswered. In each of the studies the reduction in BP was greater in the study group compared to the control groups. In PREMIER, there was a greater reduction in microalbuminuria with perindopril + indapamide compared to enalapril, but the authors claim that these differences persisted after correction for BP differences. In NESTOR, indapamide alone was more effective at lowering BP than low-dose enalapril, leading to the same reduction in microalbuminuria. In PROGRESS, perindopril + indapamide reduced strokes compared to placebo, and in ADVANCE perindopril + indapamide reduced mortality compared to placebo. In each of these studies the BP differences may be sufficient to explain the benefits demonstrated. Small but significant deteriorations in HbA1c% and lipid profiles were observed with indapamide in some of these studies, and it is uncertain if this would have a significant adverse effect on long-term cardiovascular prognosis. Despite the favourable outcomes in these trials there is not enough evidence to support indapamide as the diuretic drug of choice in managing hypertension in patients with diabetes when there are no comparative trials with other diuretics.

Key points

- Indapamide is a thiazide-like diuretic that is structurally different from thiazide diuretics
- It has been studied in several large trials in people with diabetes, but the study designs have meant that it is not proven whether it has any advantages over other diuretics or other antihypertensive drugs
- Indapamide affects glucose tolerance, leading to increases in HbA1c in patients with diabetes

Conflict of interest statement

Glasgow Royal Infirmary was a centre in the ADVANCE study, and Dr Fisher was the principal investigator for the centre. Dr McKay was a co-investigator in the ADVANCE study when he previously worked as a Consultant Physician at Monklands Hospital, Airdrie.

References

1. Berthet K, Neal BC, Chalmers JP, *et al*; on behalf of the PROGRESS Collaborative Group. Reductions in the risks of recurrent stroke in patients with and without diabetes: the PROGRESS trial. *Blood Pressure* 2004; **13:** 7–13.
2. Mogenson CE, Viberti G, Halimi S, *et al*. Effect of low-dose perindopril/indapamide on albuminuria in diabetes. Preterax in albuminuria regression: PREMIER. *Hypertension* 2003; **41:** 1063–1071.
3. Marre M, Puig JG, Kokot F, *et al*. Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with Type 2 Diabetes: the NESTOR study. *J Hypertens* 2004; **22:** 1613–1622.
4. ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular complications in patients with type 2 diabetes (the ADVANCE trial): a randomised controlled trial. *Lancet* 2007; **370:** 829–840.