

Bendroflumethiazide

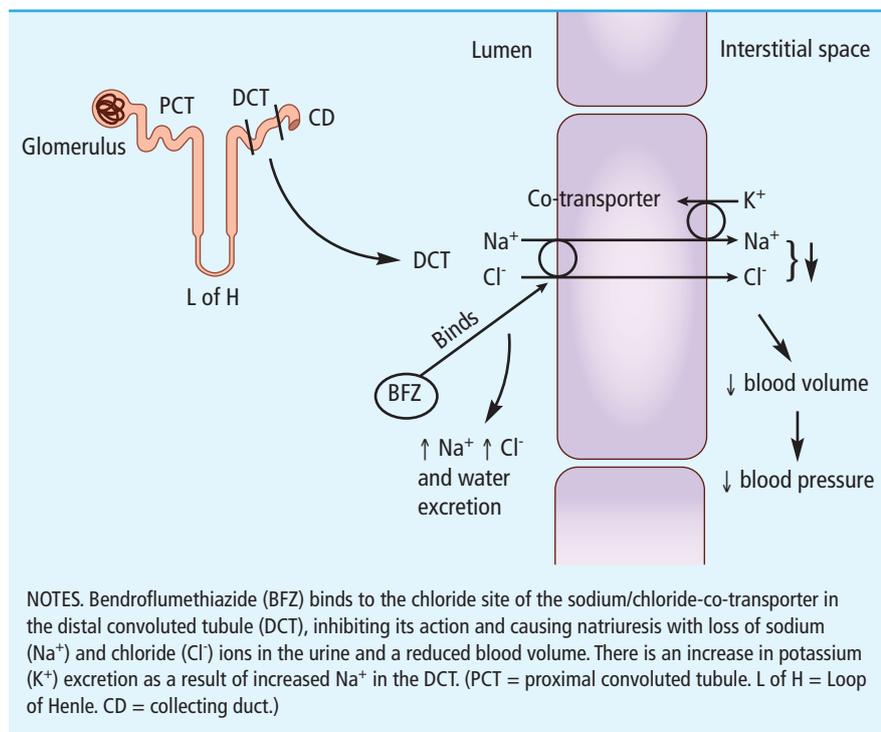


Figure 1. Pharmacological action of bendroflumethiazide

Introduction

Hypertension is common in people with diabetes. While ACE-inhibitors (ACE-Is) and angiotensin II receptor antagonists remain first-line antihypertensive agents, adequate blood pressure (BP) reduction may require two or three drugs including thiazide-like diuretics. Chlorthalidone was the diuretic used in several large diabetes hypertension studies such as SHEP and ALLHAT, but in routine clinical practice bendroflumethiazide is the most frequently prescribed thiazide diuretic in the UK.

Pharmacology

Bendroflumethiazide is a thiazide diuretic that acts on the distal convoluted tubule in the kidney. It binds to the chloride site of the sodium/chloride-co-transport system, inhibiting its action and causing natriuresis with loss of sodium and chloride ions in the urine and a reduced blood volume (Figure 1). Bendroflumethiazide is well absorbed from the GI tract and excreted in the urine, mainly by tubular secretion. The maximum effect is at about 4–6 hours with duration of 8–12 hours.

Side effects include hypokalaemia, metabolic alkalosis, hyperuricaemia, hyponatraemia, hypercholesterolaemia, and hyperglycaemia. There are several proposed mechanisms for thiazide-induced hyperglycaemia. Some studies have shown a significant correlation between the degree of diuretic-induced hypokalaemia and increased plasma glucose. Hyperkalaemia stimulates insulin secretion and insulin in turn induces cellular uptake of potassium. Conversely, hypokalaemia may impair insulin secretion and so increase plasma glucose. One study demonstrated a significant increase in 2-hour OGTT glucose levels after four weeks of bendroflumethiazide with corresponding fall in potassium levels, but there was no change in OGTT after treatment with amiloride (a potassium-sparing diuretic).

Trials of safety and efficacy

In 1985, the MRC treatment of mild hypertension trial showed active treatment reduced stroke rates and the incidence of all cardiovascular (CV) events in 17 354 hypertensive patients. In a subgroup analysis, the stroke rates were 0.8, 1.9, and 2.6 per 1000 patient

Lyn D Ferguson¹

BSc (Med Sci) (Hons), MB ChB (Hons), MRCP (UK), Core Medical Trainee

Gerry McKay¹

BSc (Hons), FRCP, Consultant Physician

Miles Fisher¹

MD, FRCP, Consultant Physician

¹Glasgow Royal Infirmary, Glasgow, UK

Correspondence to:

Professor Miles Fisher, Wards 3, 4 & 5, Glasgow Royal Infirmary, Glasgow G4 0SF; email: miles.fisher@ggc.scot.nhs.uk

years for bendroflumethiazide, propranolol, and placebo, respectively. The percentage reduction on bendroflumethiazide was significantly greater than that on propranolol ($p=0.002$). Both drugs were associated with slightly reduced rates of all CV events (6.6 per 1000 patient years on bendroflumethiazide, 6.7 on propranolol, and 8.2 on placebo). The trial concluded that bendroflumethiazide was perhaps better than propranolol in preventing stroke, but propranolol may have prevented coronary events in non-smokers.

The HAPPY (Heart Attack Primary Prevention in Hypertension) trial randomised 6569 men with a diastolic BP between 100–130mmHg to either a diuretic (bendroflumethiazide or hydrochlorothiazide; $n=3272$) or a beta-blocker (atenolol or metoprolol; $n=3297$) with a mean follow up of 45.1 months. Patients with a history of MI, angina, stroke, or diabetes were excluded. Bendroflumethiazide was as effective as beta-blockers in managing hypertension and preventing coronary heart disease (CHD), with an odds ratio of 0.93 (95% confidence interval 0.64–1.37) for fatal CHD. In addition, there was no difference in the incidence of new-onset diabetes (6.1 per 1000 patient years in the diuretic group and 6.9 per 1000 patient years in the beta-blocker group).¹

In 1988, the MAPHY (Metoprolol Atherosclerosis Prevention in Hypertensives) trial randomised 3234 mildly hypertensive men to metoprolol, hydrochlorothiazide, or bendroflumethiazide.² After a median time of 4.2 years, the difference in total mortality was 48% in favour of metoprolol. In centres comparing metoprolol with bendroflumethiazide, there were 4.5 vs 10.2 deaths per 1000 patient years at median follow up, respectively. The difference in mortality was due to fewer deaths from CHD and stroke.

More recently, the larger Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) compared amlodipine and perindopril vs bendroflumethiazide and atenolol in 19 257 patients with hypertension and at least three other CV risk factors. In the amlodipine-perindopril regimen, there was a non-significant reduction in the primary endpoint of non-fatal MI or fatal CHD (HR 0.90, $p=0.1052$),

with significant reductions in stroke (HR 0.77, $p=0.0003$), total CV events (HR 0.84, $p<0.0001$) and all-cause mortality (HR 0.89, $p=0.025$). The incidence of developing new-onset diabetes was 30% less on the amlodipine-based regimen (HR 0.70, $p<0.0001$).³

Specific evidence for use in diabetes

In hypertensive patients with type 2 diabetes, treatment with higher-dose bendroflumethiazide (5mg) has been shown to cause a significant increase in fasting plasma glucose ($2.0\pm 0.5\text{mmol/L}$) and HbA_{1c} ($1.0\pm 0.2\%$) compared with low-dose bendroflumethiazide (1.25mg).⁴ In addition, high-dose bendroflumethiazide produced a 13% reduction in peripheral insulin sensitivity compared to baseline. In contrast, low-dose bendroflumethiazide produced no change in peripheral insulin action compared to baseline.

The effects on insulin sensitivity and glycaemic control of treatment with captopril alone or in combination with low-dose bendroflumethiazide have been investigated in 15 hypertensive patients with type 2 diabetes.⁵ The combination lowered BP significantly (6/3mmHg), but increased fasting plasma glucose levels ($9.6\pm 2.6\text{mmol/L}$ for combination therapy vs $8.5\pm 1.6\text{mmol/L}$ for captopril alone), in keeping with a thiazide-induced decline in peripheral insulin sensitivity. It was concluded that, through the additional BP lowering effects of combination therapy, low-dose bendroflumethiazide could be beneficial in reducing CV events.

The ASCOT-BPLA trial performed a subgroup analysis on 5137 patients with type 2 diabetes and at least two additional risk factors; 2565 patients were randomised to amlodipine plus perindopril vs 2572 patients given atenolol plus bendroflumethiazide. The amlodipine-based regimen reduced the incidence of total CV events and procedures by 14% compared to the atenolol-based regimen (HR 0.86, 95% CI 0.76–0.98). Fatal and non-fatal strokes were reduced by 25% ($p=0.017$), non-coronary revascularisation procedures by 57% ($p<0.001$), and peripheral arterial disease by 48% ($p=0.004$).⁶ BP was radically reduced by both antihypertensive regimens, but more effectively

Key points

- ACE-inhibitors and angiotensin II receptor antagonists remain first-line agents in hypertension management in diabetes
- Bendroflumethiazide should be included as an additional option in those requiring two or more agents to achieve target blood pressure control
- In hypertensive patients without diabetes, bendroflumethiazide produces a small (<1% per year) increased risk of new-onset diabetes. This should be balanced against its antihypertensive properties

by the amlodipine-based treatment, contributing to the difference in CV events between groups.

Discussion

It is increasingly apparent from UKPDS and other studies that tight BP control is of paramount importance in reducing CV mortality in type 2 diabetes. Originally, beta-blockers and diuretics were first-line therapies for the treatment of hypertension in diabetes. The results of trials such as ASCOT and CAPPP (Captopril Prevention Project), with evidence that ACE-Is and angiotensin II receptor antagonists may have additional cardioprotective benefits beyond BP lowering, have meant these newer agents are now regarded first-line therapies, with calcium channel blockers as second line.

Patients with diabetes frequently require two or more agents to reach BP targets and so diuretics are still a reasonable addition to ACE-Is and/or calcium channel blockers. While there is relatively little specific evidence for bendroflumethiazide, the existing evidence suggests that it is as effective as other more proven diuretics.

In patients without diabetes, an additional consideration is the slight but significant increase in risk of new-onset diabetes compared to ACE-Is, which may protect against development of diabetes, and calcium channel blockers, which are neutral.

Declaration of interests

There are no conflicts of interest declared.

References

References are available online at www.practicaldiabetes.com.

References

1. Wilhelmsen L, *et al.* Beta-blockers versus diuretics in hypertensive men: main results from the HAPPHY trial. *J Hypertens* 1987;5:561–72.
2. Wikstrand J, *et al.* Metoprolol versus thiazide diuretics in hypertension. Morbidity results from the MAPHY study. *Hypertension* 1991;17:579–88.
3. Dahlöf B, *et al.*; for the ASCOT investigators. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet* 2005;366:895–906.
4. Harper R, *et al.* A comparison of the effects of low- and conventional-dose thiazide diuretic on insulin action in hypertensive patients with NIDDM. *Diabetologia* 1995;38:853–9.
5. McLaughlin DM, *et al.* Comparison of effects of combined ACE inhibitor and low-dose thiazide diuretic with ACE inhibitor alone on insulin action in patients with hypertension and type 2 diabetes: a double-blind crossover study. *Diabet Med* 2008;25:631–4.
6. Ostergren J, *et al.*; for the ASCOT investigators. The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure lowering limb: effects in patients with type II diabetes. *J Hypertension* 2008;26:2103–11.