New therapies in the management of diabetes and cardiovascular disease

This report is from a symposium that took place on 15 November 2007 at the Primary Care Diabetes Society conference in Birmingham. The event was sponsored by Novartis.

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Professor Anthony Barnett

Anthony Barnett, Professor of Medicine and Honorary Consultant Physician, Birmingham.

Introduction

As a prelude to the 2007 Primary Care Diabetes Society National Conference, Novartis hosted an interactive dinner symposium focusing on the latest treatment in the management of diabetes and cardiovascular disease. State-of-the-art lectures from leading UK healthcare professionals examined how new treatments fit into current management models. The emphasis was on the implications for practical, day-to-day management provided by healthcare professionals in primary care.

Symposium Chair Anthony Barnett, Professor of Medicine and Honorary Consultant Physician, Birmingham, introduced a panel of experts from across the UK with the aim of explaining the mechanisms of the new pharmacotherapies recently made available for diabetes and cardiovascular care in the UK and interpreting clinical trial evidence into recommendations for everyday practice.

'Diabetes care has experienced the London bus phenomenon,' Anthony said. 'We've been waiting for years for a new therapy and now several have all come along at once!'

Incretins and DPP-4 inhibition

The discovery of the importance of the incretin hormones in diabetes care was first eluded to in 1964 when McIntyre et al showed that intravenously administered glucose gave a lower insulin response than ingested glucose. This is due to signalling between the intestinal tract and the pancreas via incretin hormones that enhance the insulin response to nutrient ingestion.

'In 1986, Nauck and colleagues compared people with type 2 diabetes to matched controls and demonstrated a diminished incretin effect in those with diabetes,' explained Cliff Bailey, Head of Diabetes Research and Professor of Clinical Science, Aston University, Birmingham. This introduced the possibility of utilising incretins, in particular glucagon-like peptide 1 (GLP-1), as novel therapy to up-regulate insulin production in type 2 diabetes,.

GLP-1 prompts glucose-dependent secretion of insulin from the pancreas, decreases glucagon secretion, increases satiety and slows gastric emptying (Flint et al, 1998; Nauck et al, 1996; Larsson et al, 1997; Drucker, 1998; Green et al, 2006). However, the peptide only has a half life of around 1–2 minutes as it is rapidly degraded by dipeptidyl peptidase-4 (DPP-4; Parkes et al, 2001). 'DPP-4 is essentially a pair of scissors snipping where the second N-terminal amino acid of a peptide is alanine or proline,' Cliff said.

To promote the beneficial effects of GLP-1, it is possible to administer an incretin hormone that mimics the actions of GLP-1 but is structurally different enough not to be recognised by DPP-4 (Drucker, 2003). The GLP-1 analogue exenatide has a half-life of several hours and at a dose of 5 µg/kg can reduce HbA_{1c} by, on average, 0.6 % and reduce weight by 1.6 kg over 6–12 months (DeFronzo et al, 2005; Kendall et al, 2005).

An alternative strategy to improving the insulin output of the pancreas via the incretin system is to block the action of DPP-4. DPP-4 inhibitors occupy the active site at the centre of the DPP-4 enzyme so that it cannot bind to and degrade GLP-1; the net effect being an increase in the availability of GLP-1 (Nauck et al, 1986; Kieffer et al, 1999; Druker, 2003).

'Currently, sitagliptin is the only DPP-4 inhibitor available in the UK,' Cliff said. 'But vildagliptin will be available soon and saxagliptin, among others, is in the pipeline.' Using data presented at the 2006 EASD conference, Cliff showed that vildagliptin could reduce HbA_{1c} by 1.0–1.1 % versus placebo when added to metformin and sitagliptin by 0.6–1.1 % (Bosi et al, 2007). 'DPP-4 inhibitors can decrease post prandial glucose by 2–3 mmol without causing hypoglycaemia as the GLP-1 system is glucose-dependent,' he explained (Aschner et al, 2006; DeJager et al, 2006; Itamar et al, 2006; Nonaka et al, 2006; Rosenstock et al, 2006).

Direct renin inhibition

Renin maintains blood pressure via vasoconstriction and is regulated by four mechanisms: pressure in the afferent arteriole, sympathetic nerve stimulation of the ß1 receptor in the juxtaglomerular apparatus, sodium ions at the macula densa and negative feedback from angiotensin II (Brown, 2007).

This can create challenges when managing hypertension as there are numerous compensatory pathways. However, by blocking a pathway that leads to renin secretion in addition to by eliminating sodium, in principle any patient can be treated to target. Thus, Morris Brown, Professor of Clinical Pharmacology and Honorary Consultant Physician, Cambridge, proposed that in the management of hypertension in people with diabetes, combination treatment targeting these two causes of blood pressure elevation could become routine.

Ramipril (an ACE inhibitor) alone can reduce diastolic blood pressure by 10.7 mmHg and aliskiren (a renin inhibitor) alone by 11.3 mmHg. However, when combined the two agents cause a significantly greater reduction in diastolic blood pressure: 12.8 mmHg (P<0.05). This additive effect was also shown in systolic blood pressure (ramipril alone: -12.0 mmHg; aliskiren alone: -14.7 mmHg; combination: -16.6 mmHg; P<0.05; Uresin et al, 2006).

In a study by Oparil et al (2007), aliskiren plus the ARB valsartan demonstrated significant additive effects on reducing both diastolic and systolic blood pressure versus monotherapy (P<0.001).

'Combination of a renin-angiotensin system blocker with a calcium channel blocker or diuretic is generally more effective than adding a second renin-angiotensin system blocker,' Morris said.

In conclusion, hypertension may best be managed in the future by an understanding and exploitation of the renin–sodium interaction.

What role do the new therapies play in the treatment paradigm and when should they be used?

Eugene Hughes, GP, Isle of Wight, agreed with Morris that most people with type 2 diabetes will need at least two agents to achieve target blood pressure. He also explained why so many people fail to achieve targets. 'Hypertension is asymptomatic, but therapy can make them feel ill!' He said, highlighting the importance of selecting an individualised regimen with minimal side effects.

After a comprehensive review of the pros and cons of metformin, sulphonylureas, meglitinides and insulin, Eugene shared some of his experiences of some of the newer therapies.

'Rimonabant is expensive – costing over £40 per month – and is licensed as a drug for obesity management. However, in my patients weight loss has been OK but they have shown remarkable improvements in glycaemia.'

Data have shown an increased number of small bone fractures in women taking glitazones, however the mechanism of action of this effect remains unknown. Most prominent in the literature is the debate over the CV safety of glitazones. 'This has laboured on for several months now,' Eugene said. 'And it seems to have lapsed into emotional rather than scientific arguments.'

While incretin mimetics have shown efficacy in controlling glycaemia with the added benefit of weight loss, as exenatide is an injectable formulation it may not be accepted by some individuals. 'But longer-acting preparations are on the way,' Eugene reminded delegates.

The glycaemic improvements, weight neutral and low risk of hypoglycaemia associated with the DPP-4 inhibitors all provide strong advantages for the class. Eugene addressed the argument that there have been no long-term outcome studies: 'This is inevitable due to the time it takes to get a drug to the market and the data collection will be ongoing. It is perfectly usual to start using agents before the availability of long-term studies and base clinical decision making on existing trials.'

Eugene concluded with a look at the draft NICE guidelines for diabetes management: metformin to be used first line and a sulphonylurea second line. 'I was disappointed as it looked like we were stepping back in history – no consideration of gliptins and exenatide was only mentioned in passing,' Eugene said. 'Unless these guidelines are comprehensively rewritten they will be of limited clinical use in a climate of abundant new therapies.' ■

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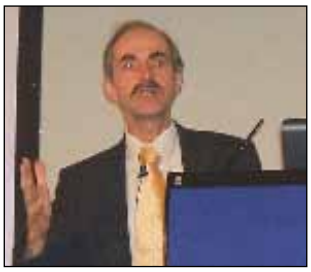

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