New drugs, but old habits die hard!

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Considerable time was spent this year at the EASD Annual Meeting in Vienna hearing about SGLT-2 inhibitors, a relatively new class of oral antidiabetic drugs. First launched in the UK in 2013, there are now three different SGLT-2 inhibitors licensed for use in the UK and Europe. They work by inhibiting reabsorption of glucose in the proximal renal tubule in the kidney, resulting in increased glucose excretion in the urine. A range of studies have been reported for each drug and overall there is an expected HbA1c fall of 5–15mmol/mol (0.5–1.5%).

One of the significant benefits of this class of drugs is the reported weight loss. On average, across the class a weight reduction of 2.5–4% is expected within the first 26 weeks with very little reported nausea or vomiting. A low risk of hypoglycaemia is another reported benefit to patients. However, no class of drug is without its concerns and SGLT-2 inhibitors are no exception. Initial concerns regarding an increase in bladder cancer have led to the exclusion of their use in patients with a history of bladder cancer, and to this outcome being included in one of the major cardiovascular outcomes trials (DECLARE-TIMI 58). The cause of raised lipids with these drugs is unknown and the longer-term effect of this remains unclear. Blood pressure appears to fall, but heart rate rises – again the implications of this for cardiovascular outcomes remains uncertain.

However, an oral presentation at the EASD in Vienna in September this year cast some light on the body’s capacity to adapt to pharmacological attempts to reduce both hyperglycaemia and obesity. Ferrannini and colleagues presented the results of a study investigating the effects of an SGLT-2 inhibitor on the energy balance of the body. They used the data from 86 patients with type 2 diabetes who had completed a 90-week trial of an SGLT-2 inhibitor. Using a mathematical model to simulate the time-course of weight loss for a given change in calorie balance, they were able to calculate the predicted weight loss for the estimated calorie loss (based on estimated urinary glucose excretion). The observed weight loss of 3.2±4.2kg was only 38% of what was predicted (8.7±2.4kg) from the patients’ estimated glycosuria. Given that previous studies show that these drugs do not affect resting energy or post-meal energy use, the most likely explanation is that patients compensate by increasing their energy intake.

It seems that the brain compensates for the weight loss induced by these drugs by increasing appetite and food intake. Perhaps this should be no surprise to us as clinicians who see our patients try to lose weight only to find it increasing again several months or years later. However, this study does provide an elegant explanation of what is seen in clinical practice and reminds us that the body has many ways of adapting and compensating for metabolic changes we may induce through new drugs. Whether this class of drugs can show longer-term weight benefit remains to be seen, but don’t underestimate the body’s capacity to adapt and surprise.

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References