New Drugs for Type 2 Diabetes – No Sweetness, No Light

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The world epidemic of type 2 diabetes (T2DM) which is sweeping through Southern Asia represents a huge challenge for public health, and a huge commercial opportunity for pharmaceutical companies. The population-level response to this epidemic needs to be based on control of obesity, improvements in diet, promotion of exercise, and measures to reduce the cardiovascular risks which the condition carries. The response of the drugs industry, on the other hand, is to increase the development and marketing of new drugs which reduce blood sugar.

On the face of it, this seems perfectly logical. A sustained increase in blood sugar is the defining characteristic of the condition, and the main adverse outcomes of type 2 diabetes are the same as those of type 1 diabetes. The so-called macro-vascular harms include myocardial infarction and peripheral ischemia, and the so-called micro-vascular harms include visual loss and renal failure. Each of these shows a similar straight-line relationship to increasing levels of glycaemia, whether measured as fasting blood sugar or as glycated hemoglobin (HbA1c) [1].

So when we talk about the "new drugs for type 2 diabetes", we are generally talking about new drugs which reduce blood sugar, on the basis that each step in reducing sugar will be accompanied by an equal step in reducing the adverse effects on that straight-line graph. Unfortunately that is not the case for any known drug in type 2 diabetes. Moreover we have little idea of how any of these drugs affects the long-term progression of the condition; in particular how each drug might protect or damage the beta-cells of the pancreatic islets. Yet the current system of drug development and licensing is founded on the idea that any drug which reduces blood sugar without causing immediate harms is a useful addition to the clinical arsenal for treating type 2 diabetes.

The harm caused by this approach is literally incalculable. It cannot be calculated because we have no adequate, long-term, randomized controlled trials for any single agent used to reduce blood glucose in T2DM. It is really remarkable that drugs which are intended to be used for periods of many years or even decades for high-risk patients can be licensed on the basis of data which are rarely collected for more than 3 years. This period is far too short to judge long-term effects on macro-vascular or micro-vascular outcomes. These studies are also too short to predict significant long-term harms.

The effects of such willful ignorance are well illustrated by the glucose-reducing drug rosiglitazone (Avandia), which throughout the last decade earned annual profits of up to $3bn for its manufacturer, GlaxoSmithKline. There is evidence that the company knew from the start that the drug, far from reducing the cardiovascular risks associated with T2DM, might actually increase them [2]. Eventually, in 2010, the US Food and Drug Administration was forced to revoke its earlier approval of rosiglitazone when the burden of evidence of harm became too great. Even now, however, we cannot accurately quantify this harm, because properly designed studies were never conducted [3].

It would be good to report that the lessons of rosiglitazone have been well learned, and that from now onwards, all drugs intended to reduce the long-term vascular harms of T2DM will have to demonstrate that they actually do so before they can be used on patients. But to date the licensing requirements for diabetes drugs remain entirely unchanged. Expensive new classes of drugs, such as glucagon-like peptide analogues and dipeptidyl peptidase-4 inhibitors, are being widely marketed and used on millions of people without any long-term proof of efficacy or safety. These drugs are hailed as exciting developments on the basis of their novel modes of action. Huge potential benefits are predicted from the changes they produce in various surrogate disease markers, including blood sugar. But before you get blinded by this seeming blaze of science, remember that similar claims have been made for all previous drugs for T2DM. We actually know nothing about what the new drugs do in the long term to the outcomes that really matter - heart attacks, limb amputations, blindness and kidney

failure. And it is no good reducing sweetness, if you have no light to go by.

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