



THE TRUTH BE TOLD

Recent studies have linked human insulin and insulin analogues to cancer. Dr Kevin Tan, Vice-President, Diabetic Society of Singapore, sieves through the results to bring you this report.

No tabloid headlines screaming, 'Insulin causes Cancer'. No stern warnings to 'Stop Insulin Now'. Perhaps the H1N1 flu was hogging the world's attention or perhaps the media finally decided to be responsible (for once!) since it would be reckless to perpetuate and compound everyone's fears.

Nevertheless, the medical community has been made aware of this subject and it would only be responsible to communicate this information to the general community and, in particular, those with diabetes.

In the Beginning

It all started when a German paper investigating the risk of malignancies (cancer) in diabetic patients treated with human insulin or insulin analogues was published in the medical journal *Diabetologia*.

The study was conducted to examine the risk of cancer and death in those on human insulin compared to three insulin analogues – rapid acting lispro (Humalog), aspart (Novorapid) and long-acting glargine (LANTUS). The paper concluded that there were 'safety concerns surrounding the mitogenic (cancer causing) properties of LANTUS in diabetic patients'.

The data was obtained from 127,031 patients listed with the largest German health insurance fund – these

were mostly likely persons with Type 2 diabetes.

The data available was for seven and a half years from January 1998 to June 2005. It required three years of being cancer-free and therefore the longest follow-up was from January 2001 to June 2005, a mere four and a half years - too short for a proper cancer study.

In any case the information was not from a properly designed follow-up or prospective study into the link between insulin and cancer, but a 'backwards' (retrospective) data-gathering exercise, which is usually exposed to various limitations. For example, confounding factors like body weight, smoking, social status and duration of diabetes, all of which could independently increase cancer risk could not be corrected for.

Furthermore, the conclusion of the study was confusing – the absolute cancer incidence was actually 15% lower with LANTUS being used alone; death from all causes was also considerably lower with LANTUS. Only when a complicated statistical analysis was done did it show a dose-dependant increase in cancer risk with LANTUS.



What is the quantum of risk that we are talking about?

Compared with people using similar doses of human insulin, out of every 100 people who are on LANTUS for an average of one and a half years, one will be diagnosed with cancer. The increased risk is dependant on the dose of insulin. A dose of 10 units of LANTUS is associated with a 9% increased risk, while a dose of 50 units is associated with a 31% increased risk.

The editor of Diabetologia and the President of the European Association for the Study of Diabetes (EASD) on recognising the implications of the paper, commissioned studies from the databases of Sweden, Scotland and the UK to confirm or refute the data.

The results added to the confusion!

The Swedish study found that persons on LANTUS insulin alone had double the risk of breast cancer compared to those on other insulins. However, the death rate was lower in these women on LANTUS!

The Scottish study suggested that those on LANTUS insulin alone had an increased risk of cancer, but those using LANTUS insulin together with other insulins had a lower risk!

And finally, the UK study found no link between LANTUS insulin and cancer. At the same time, a 'ray of light' shone in the midst of all this gloom; the oral agent, metformin, if used alone, carried the lowest risk of cancer. On top of that, combining metformin with insulin (as is commonly done in daily practice) reduced the progression to cancer.

At this juncture, it is pertinent to point out that diabetes itself is associated with a higher risk of certain cancers especially of the colon (large intestine), pancreas and breast. Some of the association may be with obesity which is common in Type 2 diabetes or with insulin resistance, which underlies Type 2 diabetes, or even insulin itself which not only binds to its own receptors on cells, but also cross-binds with a 'growth' receptor called IGF-1 (insulin-like growth factor-1). A very complex picture indeed!

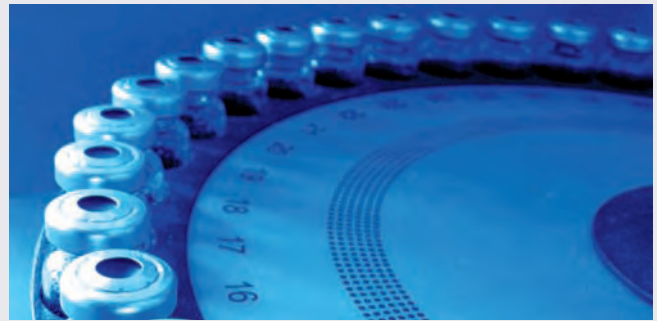
So how are we to respond to this current controversy?

The natural response is in one of two ways:

Reject insulin altogether as a form of therapy

This is ill-advised! Insulin is the oldest form of treatment for diabetes since its discovery by Banting and Best in the 1920s. Oral medication for Type 2 diabetes came much later in the 1950s.

Blood sugar control remains of paramount importance in preventing and minimising the dreaded complications of poorly controlled and long-duration diabetes.



Insulin is, by far, the most potent blood glucose lowering medication available. Unlike the majority of oral tablets, it does not require an intact or healthily functioning pancreas. There is also no dose-limit to insulin.

Reject LANTUS insulin

Before you do this, consider that since the introduction of LANTUS as a 24-hour long-acting insulin, with a relatively peak-less mode of action, insulin used in combination with oral tablets has been made easier and safer for doctors and patients alike.

More are open to insulin use, earlier in the course of diabetes. For Type 1 patients, the advent of LANTUS and levemir, the other long-acting insulin analogue, has opened the way for basal-bolus therapy with once a day LANTUS/levemir and thrice daily pre-meal insulin boluses with the rapid acting analogues. This is the 'ultimate' in terms of insulin regimens to control blood glucose levels.

If indeed LANTUS insulin is rejected, what are the alternatives?

The options would be to return to human insulins – NPH insulin (insulatard or humulin N) or the alternative insulin analogue, levemir. The other option would be to switch to pre-mixed insulins, both human (e.g. Mixtard 30/70 or Humulin 30/70) or analogues (Novomix and Humalog-Mix).

Is there a far better response ?

In terms of clinical practice, there does not appear to be sufficient evidence to recommend against the use of LANTUS insulin. Doctors who treat diabetes have a variety of potential treatment regimens in their armamentarium, and they should continue to individualise their recommended therapy based on each patient's situation. Persons with diabetes should adopt a healthy lifestyle to prevent cancer and they should also follow current recommendations regarding screening tests for cancer (mammogram, colonoscopy) and avoid dangerous habits (smoking) regardless of the specific treatment program followed.

In the meantime, leave it to the experts to sieve through the complexities of the data and wait for more news and developments in this area.