

# Insulin analogues: fears, facts and fantasies

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## Abstract

IGF-1 and insulin, acting through both IGF-1 and insulin receptors, have been studied widely to evaluate their oncogenic and teratogenic properties. These two properties need to be studied for each new insulin analogue, in addition to measurements of their metabolic and pharmacodynamic features. This editorial critiques a study in this issue of the journal of several insulin analogues in their action in vitro on several cancer-related cell lines. The conclusions and limitations of these studies are highlighted, especially as they influence guidelines for using these analogues patients. Copyright © 2009 John Wiley & Sons, Ltd.

The recent availability of insulin analogues (with very rapid onset of action or basal insulin action) has been welcomed with enthusiasm by clinicians, because these insulin analogues are believed to facilitate insulin therapy in patients with Type 1 and Type 2 diabetes mellitus. Several clinical trials have shown that insulin analogues allow patients to reach target blood glucose concentrations with fewer hypoglycemic events and to improve their quality of life (1). Therefore physicians see insulin analogues as the best tools with which to tailor insulin therapy to the needs of individual patients.

In this issue of DMRR, Weinstein and coworkers report that several insulin analogues show more IGF-I-like activity on cell proliferation compared with native, wild type insulin, raising suspicions about the long term safety of these widely prescribed drugs. Structural modifications of insulin result in the generation of new molecules with different binding affinities to the insulin receptor and/or IGF-IR hybrid receptor, with the possibility of increased risk of an altered pattern of receptor activation. Weinstein's data demonstrate that insulin analogues display some biological effects typical of IGF-I on colorectal, prostate and breast adenocarcinoma-derived cell lines. This paper adds to the several papers that have been published in the last years, where controversial and contrasting data leave this issue unresolved (3-8). The proliferative effect on cell type models is an important finding that sustains the idea of a potential link between insulin analogues and increased risk of cancer and teratogenic effects.

How do these findings translate into clinical practice? In vitro models reproduce only parts of the in vivo physiology. In vivo studies in animals and in humans so far have not reported any carcinogenic effects of insulin analogues. Two meta-analyses that compared long-acting (9) and short-acting insulin analogues (10) with human insulin have been reassuring; as yet, no oncogenic adverse events have been reported associated with the use of insulin analogues. Both papers, however, underline the relatively short follow-up period of all studies and the need for more studies of better design and longer duration before reaching definitive conclusions about long term safety.

Diabetes mellitus is a chronic condition that can cause complications after many years of disease and typically requires life long treatment. Such treatments must be safe and able to reduce blood glucose as well as prevent complications. The studies completed before the introduction of each analogue, were designed to demonstrate efficacy on glucose metabolism and

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short term safety. They were performed on a modest number of patients for a relatively short time, precluding firm conclusions about carcinogenic or teratogenic effects.

The answers to these questions will emerge with strict well designed and executed post-marketing studies. At present, physicians should prescribe for the non-pregnant patient those insulins that afford the best metabolic control, but also recognize that these new drugs may have adverse effects (like oncogenesis) that may appear only many years after their introduction into clinical practice.

The pregnant diabetic patients present an even more delicate situation. Offspring of diabetic mothers who receive standard therapy have an increased prevalence of birth defects, making it more difficult to detect whether a new drug is enhancing teratogenesis. Given the uncertainties, the potential for harm, and the relatively modest benefits of the new analogues, all use of new insulin analogues in pregnant diabetics should be avoided until much more extensive data are available for analysis by experts in the field.

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