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Insulin/ insulin analogues and cancer

Insulin is used medically to treat some forms of diabetes mellitus. Patients with Type 1 diabetes mellitus depend on external insulin for their survival because the hormone is no longer produced internally. Patients with Type 2 diabetes mellitus are insulin resistant, and may suffer from a relative insulin deficiency. Some patients with Type 2 diabetes may eventually require insulin when other medications fail to control blood glucose levels adequately.

An insulin analogue is an altered form of insulin, different from any occurring in nature, but still able to perform the same action as human insulin in terms of glycemic control. Through recombinant DNA technology, the amino acid sequence of insulin can be changed to alter its ADME (absorption, distribution, metabolism, and excretion) characteristics.

Adverse effect reports of malignancies have caused concern regarding the long term use of these therapies. Recently published studies investigating a possible relationship between insulin analogues, in particular insulin glargine, and the risk of cancer are currently under review of the EMEA. On the basis of the currently available data, a relationship between insulin glargine and cancer cannot be confirmed nor excluded. However, the concerns raised by these data require further in-depth evaluation.

A plausible biological mechanism for the adverse effects is lacking, but some studies suggested that unlike regular insulin some insulin analogues (*e.g.* insulin glargine) strongly activate the IGF-I receptor (IGF-IR) and the MAP kinase pathway and may be a strong mitogen for cells characterised by a high IGF-IR/insulin receptor ratio.

Areas of particular interest for research include:

- The effect of time and/or intensity of insulin treatment on the likelihood of developing malignancy.
- Elucidation of potential mechanisms *e.g.* cancer initiation/promotion.
- Dose-response effects.
- The limitations of the relatively short duration of the clinical development programs to study long-term safety *e.g.* the potential effects of long-term treatment on the initiation or promotion of malignancy.

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- Identification of risk factors for developing malignancy in patients treated with insulin of insulin analogues *e.g.* indication for treatment, age, sex, disease (including severity), body mass index (BMI), menopausal status, parity, socioeconomic status, prior and during treatment.
- Methodologies for early clinical detection of malignancy.
- Methodologies for screening/predicting patients at high risk of developing malignancy.
- Detection of differences between different insulins and insulin analogues.

Suitable research methodologies could include long-term epidemiological follow-up studies of diabetic populations, subgroup analyses to study risk factors and important effect modifiers, intensive monitoring studies as methods to capture early stages of diseases, and non-clinical mechanistic studies.

Examples of insulins and insulin analogues are

Normal unmodified insulin is soluble at physiological pH. Analogues have been created that have a shifted isoelectric point so that they exist in a solubility equilibrium in which most precipitates out but slowly dissolves in the bloodstream and is eventually excreted by the kidneys. These insulin analogues are used to replace the basal level of insulin, and may be effective over a period of about 24 hours. However, some insulin analogues, such as insulin detemir, bind to albumin rather than fat like earlier insulin varieties, and results from long-term usage (e.g. more than 10 years) have never been released.

Insulin glargine (trade names *Lantus, Optisulin*) is a longer lasting insulin analogue. It was created by modifying three amino acids. Two positively charged arginine molecules were added to the C-terminus of the B-chain, and they shift the isoelectric point from 5.4 to 6.7, making glargine more soluble at a slightly acidic pH and less soluble at a physiological pH. Replacing the acid-sensitive asparagine at position 21 in the A-chain by glycine is needed to avoid deamination and dimerisation of the arginine residue. These three structural changes and formulation with zinc result in a prolonged action when compared with biosynthetic human insulin. When the pH 4.0 solution is injected, most of the material precipitates and is not bioavailable. A small amount is immediately available for use, and the remainder is sequestered in subcutaneous tissue. As the glargine is used, small amounts of the precipitated material will move into solution in the bloodstream, and the basal level of insulin will be maintained up to 24 hours. The onset of action of subcutaneous insulin glargine is somewhat slower than NPH human insulin.

Insulin detemir (trade name *Levemir*) is a long-lasting insulin analogue for maintaining the basal level of insulin. The basal level of insulin may be maintained up to 20 hours, but the time is clearly affected by the size of the injected dose. This insulin has a high affinty for serum albumin, increasing its duration of action.

NPH insulin (trade names *Humulin N, Novolin N,Novolin NPH, NPH Lletin II, and isophane insulin*) is an intermediate-acting insulin.

Insulin lispro (trade name *Humalog*) is the first insulin analogue with "lispro" as a rapid acting insulin analogue. It is engineered so that the penultimate lysine and proline residues on the C-terminal end of the B-chain were reversed. This modification does not alter receptor binding, but blocks the formation of insulin dimers and hexamers. This allows larger amounts of active monomeric insulin to be available for postprandial (after meal) injections.

Insulin aspart (trade names *NovoLog/NovoRapid (UK-CAN)*) is a rapid acting insulin analogue. It is engineered so that the amino acid, B28, which is normally proline, is substituted with an aspartic acid residue. This analogue also prevents the formation of hexamers, to create a faster acting insulin.

Insulin glulisine (trade name *Apidra*) is a newer rapid acting insulin analog. It differs from regular human insulin by its rapid onset and shorter duration of action.