

Drugs in the News 7/1/09 – Insulin Glargine (Lantus) and Cancer

Three epidemiological studies (observational studies) conducted in Sweden, Germany and Scotland, all suggesting a possible link between the use of insulin glargine (Lantus) and an increased risk of cancer compared to human insulin, have been published in *Diabetologia*.

An additional study from the UK found no association with the insulin analogues and an increased risk of cancer above that of human insulin. All of these studies, alongside a statement from the European Association for the Study of Diabetes (EASD), an expert commentary (webcast) and information for patients, are available on the *Diabetologia* Web site at <http://www.diabetologia-journal.org/cancer.html>.

The results of the studies were:

German Cohort Study

Data for this study were provided from the largest statutory German health insurance fund between Jan 1998 and June 2005 on 127,031 adults receiving first-time insulin therapy for diabetes with an average follow-up of 1.63 years. A positive association between cancer incidence and insulin dose was found for all insulin types; when adjusted for dose, a dose-dependant increase in cancer risk was found for treatment with insulin glargine compared with human insulin: HR 1.09 (95% CI 1.00 to 1.19) for daily dose of 10 IU; 1.19 (1.10 to 1.30) for 30 IU; and 1.31 (1.20 to 1.42) for 50 IU.

Swedish Study

This study was conducted at request by the EASD and involved a total of 114,841 individuals who had at least one prescription for insulin dispensed between July and December 2005. The outcome of interest was the occurrence of a first diagnosis of a primary malignancy, occurring between Jan 2006 and Dec 2007. Individuals using insulin glargine as monotherapy were found to have an increased risk of breast cancer (RR of 1.99; 95% CI 1.31-3.03) compared to users of other types of insulin. No statistically significant findings were obtained for other cancer types studied or for the category “all malignancies”.

Scottish Study

This study used a nationwide diabetes clinical database. The subset of patients using insulin glargine alone (n=447) had a higher incidence of all cancers than those using other insulins only (n=32295) (HR 1.55, 95% CI 1.01–2.37, p=0.045). These authors concluded that insulin glargine use was not associated with an increased risk of all cancers or site-specific cancers in Scotland over a 4 year

time frame based on other findings presented taking into account overall use, for example, use in combination with other insulins.

UK Study

This retrospective cohort study involved 62,809 subjects. Patients were divided into groups according to whether they received monotherapy with metformin, combination therapy with metformin and a sulfonylurea, or insulin. The risk of progression to any solid tumour for those on basal human insulin alone was not statistically significantly different compared to those on insulin glargine alone (HR 1.24; 95% CI 0.90 1.70), although in general those on insulin of any kind were more likely to develop solid cancers than those on metformin.

Causality?

The following is our analysis of a possible cause and effect relationship between the use of insulin glargine and cancer using the Bradford-Hill Criteria.

Criterion 1 -- Strength of Association

Strength of Association is somewhat subjective, however, there was an over 3-fold increased risk of breast cancer found in the Swedish Study. In interpreting this safety data the upper limit of the 95% confidence interval is used to estimate the worst case scenario.

Criterion 2 – Consistency of the Association

All four studies demonstrated an increased risk of some types of cancer, however, not all of these results were statistically significant.

Criterion 3 – Biologically Plausible Mechanism

There is a possible mechanism for the epidemiological findings, in that insulin is a growth factor for a number of epithelial tumors in cell culture systems, and hyperinsulinemia also produces a secondary increase in the availability of IGF-1 (Insulin Like Growth Factor – 1) which is a known tumour growth factor that is mediated by a reduction in IGF binding protein-1 levels (IGFBP-1). Changes in the insulin–IGF-1 axis have the potential to support self sufficiency in growth signals and resistance to apoptosis, and may thus offer an adaptive advantage to cancer foci struggling to survive in a hostile environment.

Criterion 4 – Dose Response Relationship

The German Cohort Study found a dose dependent (dose response) increase in cancer risk with the use of insulin glargine.

Human Insulin and Long Acting Insulin Analogues

The available science does not support important differences, if any, for the long acting insulin analogs, including insulin glargine, over human insulin.^{1, 2, 3}

Conclusion

It may be argued that the Bradford Hill Criteria have not been fully met for a clear presumption of causality between insulin glargine and cancer. Nevertheless, there is sufficient concern about a link to approach the prescribing and recommendation of this long acting insulin analogue cautiously.

There is no compelling scientific reason that patients concerned about insulin glargine and cancer cannot successfully use human insulin.

Copyright and Disclaimer

Lake Erie College of Osteopathic Medicine, School of Pharmacy Center for Drug Information and Research (CDIR).

All material subject to this copyright may be photocopied or digitally reproduced only for noncommercial educational and scientific uses. Please contact the Center for Drug Information and Research director in writing for permission to reprint articles or portions of articles. Proper credit and copyright must accompany all reprinted material. Opinions expressed by individuals in this (newsletter, website, etc.) do not necessarily represent the official position of the Lake Erie College of Osteopathic Medicine or LECOM School of Pharmacy unless otherwise noted.

¹ Bazzano LA, Lee LJ, Shi L, Reynolds K, Jackson JA, Fonseca V. Safety and efficacy of glargine compared with NPH insulin for the treatment of Type 2 diabetes: a meta-analysis of randomized controlled trials. *Diabet Med*. 2008 Aug;25(8):924-32.

² Monami M, Marchionni N, Mannucci E. Long-acting insulin analogues versus NPH human insulin in type 2 diabetes: a meta-analysis. *Diabetes Res Clin Pract*. 2008 Aug;81(2):184-9.

³ Horvath K, Jeitler K, Berghold A, Ebrahim SH, Gratzner TW, Plank J, Kaiser T, Pieber TR, Siebenhofer A. Long-acting insulin analogues versus NPH insulin (human isophane insulin) for type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):CD005613.