NHS
NPC
National Prescribing Centre

MeReC Monthly

No.30 September 2010

MeReC Publications

Higher doses of insulin glargine associated with cancer

An observational study[1] of people with type 2 diabetes found that higher mean daily doses of insulin glargine, but not other types of insulin, were associated with a five times higher relative risk of cancer after adjusting for confounders. Although more research is required, this study adds to the evidence and provides a further signal about the long-term safety of high doses of insulin glargine.

Action

NICE guidance on type 1 and type 2 diabetes suggests that long-acting insulin analogues, including insulin glargine and insulin detemir, should not be used first-line routinely. A health economic analysis in the NICE guidance for type 2 diabetes found that the cost effectiveness of long-acting insulin analogues was not favourable. The incremental cost effectiveness ratio (ICER) compared with conventional insulin was greater than £100,000 per quality-adjusted life-year (QALY) in all scenarios, and in some cases in excess of £400,000 per QALY. However, prescribing data for England indicate extensive prescribing of insulin analogues in primary care (about 40% of all intermediate/long-acting insulin items) and it may be appropriate for prescribers and prescribing managers to review the use of these drugs to see if their current use is in line with NICE guidance and consider alternatives where this is not the case.

What did the study find?

This nested case-control study involved a cohort of 1,340 outpatients with type 2 diabetes (free of previous malignancies) starting insulin. It assessed the association between the incidence of cancer and use of different insulin analogues, considering different insulin doses and several confounders. Over a median follow-up of 75.9 months, there were 112 cases of incident cancer, which were compared with 370 controls (matched with respect to follow-up time, age, sex and body mass index). A statistically significantly higher mean daily dose of insulin glargine was observed in cases, compared with controls (0.24 vs. 0.16 units/kg/day, P=0.036). A dose of insulin glargine $\geq$0.3 units/kg/day was associated with a significantly higher risk of incident cancer, compared with controls, even after adjusting for comorbidity score, other types of insulin administration, and metformin exposure (OR 5.43, 95%CI 2.18 to 13.53, P<0.001). The association of cancer was evident in younger, but not older people (i.e. $\geq$70 years).

Although this observational study took many confounding variables into account it is likely that some remain, and the study does not confirm that high doses of insulin glargine cause cancer. Nevertheless, it does suggest that dosages should be considered when the possible association between cancer and insulin and its analogues is assessed.

More details of this study can be found in *MeReC Rapid Review 1652*.

What is the current regulatory advice?

As reported in *MeReC Rapid Review 374*, in July 2009, the EMEA's Committee for Medicinal Products for Human Use reviewed the available evidence from four earlier studies on a possible relationship between insulin analogues, in particular insulin glargine, and the risk of cancer. Due to methodological limitations and inconsistencies in the findings, no relationship between insulin glargine and cancer could be confirmed or excluded. The EMEA concluded that the available data did not provide a cause for concern and that changes to the prescribing advice were therefore not necessary, but requested more research be carried out in this area.

Reference

1. Mannucci E, et al. Doses of insulin and its analogues and cancer occurrence in insulin-treated type 2 diabetic patients. Diabetes Care 2010. Published online before print June 14, 2010, doi:10.2337/dc10-0476

All information was correct at the time of publication (September 2010)

New insulin safety guidance issued to reduce dosage errors

In June 2010, the NPSA issued guidance[1] across England and Wales aimed at reducing the number of wrong dose incidents involving insulin.

Action

Recommended actions should be put in place by all NHS and independent sector organisations by the deadline of 16th December 2010.

What does the NPSA recommend?

All organisations in the NHS and independent sector should ensure that:

1. All regular and single insulin (bolus) doses are measured and administered using an insulin syringe or commercial insulin pen device. Intravenous syringes must never be used for insulin administration
2. The term 'units' is used in all contexts. Abbreviations, such as 'U' or 'IU', are never used
3. All clinical areas and community staff treating patients with insulin have adequate supplies of insulin syringes and subcutaneous needles, which staff can obtain at all times
4. An insulin syringe must always be used to measure and prepare insulin for an intravenous infusion. Insulin infusions are administered in 50ml intravenous syringes or larger infusion bags. Consideration should be given to the supply and use of ready to administer infusion products e.g. prefilled syringes of fast-acting insulin 50 units in 50ml sodium chloride 0.9%
5. A training programme should be put in place for all healthcare staff (including medical staff) expected to prescribe, prepare and administer insulin. An e-learning programme is available from: www.diabetes.nhs.uk/safe_use_of_insulin
6. Policies and procedures for the preparation and administration of insulin and insulin infusions in clinical areas are reviewed to ensure compliance with the above.

What has prompted this guidance?

The NPSA received 3,881 wrong-dose incident reports involving insulin between August 2003 and August 2009. These included one death and one severe harm incident due to 10-fold dosing errors from abbreviating the term 'unit'. Three deaths and 17 other incidents between January 2005 and July 2009 were also reported where an intravenous syringe was used to measure and administer insulin. Some of these errors have resulted from insufficient training in the use of insulin by healthcare professionals.

Further information can be found in *NPCi Blog 1705*.

Reference

1. NPSA. Safer administration of insulin. Rapid response report NPSA/2010/RRR013. June 2010

CV risk reduction in diabetes: law of cumulative benefits, diminishing returns

This modelling study[1] illustrates the 'law of cumulative benefits' or conversely the 'law of diminishing returns' with intensification of BP-lowering and lipid-modifying therapy in patients with diabetes. It suggests a personalised approach based on baseline CV risk could maximise a patient's net benefit from treatment.

Action

Health professionals should continue to follow NICE guidance on the management of type 2 diabetes. NICE guidance recommends reducing blood pressure (BP) to below 140/80 mmHg (below 130/80 mmHg if there is kidney, eye or cerebrovascular damage). Simvastatin 40mg daily is the usual choice and dose of statin, with an increase to 80mg daily if the total cholesterol is more than 4mmol/L **and** the LDL-cholesterol is more than 2mmol/L on treatment (note MHRA advice on the use of simvastatin 80mg). In people with type 2 diabetes and existing or new cardiovascular (CV) disease, or increased albumin excretion, NICE advises **considering** intensifying lipid lowering treatment to achieve a total cholesterol of less than 4mmol/L **or** an LDL-cholesterol of less than 2mmol/L. However, in line with good medical practice, such a decision should take into account the patient's informed preference, including the benefits and risks of treatment.

Health professionals may wish to consider the implications of this study and the earlier ACCORD BP and lipids trials with respect to the risks and benefits of intensifying antihypertensive and lipid-modification treatment, especially if aiming for BP and lipid targets below or at the lower end of the standard target levels set by NICE.

What did this study find?

A model using data from a large US cohort was developed and used to predict the net benefits of treating patients with diabetes to aggressive risk factor targets, including

the net benefits for individual treatment steps. Compared with no treatment, treating to an LDL-cholesterol target of 2.6mmol/L resulted in gains of 1.50 QALYs of lifetime treatment-related benefit. Treating to a BP target of 130/80mmHg predicted a gain of 1.35 QALYs of lifetime treatment-related benefit. These QALYs declined to 1.42 and 1.16, respectively, after accounting for treatment-related harms. Most of the total benefit was limited to the first few steps of medication intensification or to tight control for a limited group of very high-risk patients. Intensifying treatment beyond the first step (simvastatin 20mg – 40mg/day) for the LDL-cholesterol target or the third step (thiazide plus ACE inhibitor plus beta-blocker) for the BP target resulted in either limited benefit or net harm for patients with below-average risk.

In line with the ACCORD BP and lipids trials, this study suggests that the diminishing benefits of more aggressive therapy might not only be inefficient but potentially harmful. The study also found that the benefit patients receive from preventative interventions is strongly related to their baseline absolute risk of the outcome. More details can be found in *MeReC Rapid Review 1655*.

The principle around the 'law of cumulative benefits' or conversely the 'law of diminishing returns' has been discussed in some detail in workshop 3 of the Information Mastery 4 — communicating risks and benefits floor of NPCi.

Reference

1. Timbie JW, et al. Variation in the net benefit of aggressive cardiovascular risk factor control across the US population of patients with diabetes mellitus. Arch Intern Med 2010;170:1037–44

Financial conflicts of interest linked to authors' views on MI risk with rosiglitazone

A systematic review[1] found a link between authors' financial conflicts of interests with pharmaceutical companies and their views on the association of rosiglitazone with increased risk of MI.

Action

This review reinforces the need for readers of scientific literature to consider the authors' financial conflicts of interests and the potential influence this may have on their writing. Healthcare professionals should base their prescribing decisions on evidence-based information from organisations with a public sector ethos such as NICE, CKS, SIGN, Cochrane, CRD, Clinical Evidence, DTB and the NPC. These decisions should be based on consideration of the entire body of evidence and not rely on the claims made in individual publications or reports.

What did this review find?

Financial conflicts of interests were disclosed by authors in only 108 of the 202 articles (53%) commenting on rosiglitazone, with 90 of the authors (45%) having financial conflicts of interest. Authors who had a favourable view of the risk of myocardial infarction (MI) with rosiglitazone were more likely to have financial conflicts of interest with rosiglitazone manufacturers, than authors who had an unfavourable view (rate ratio 4.29, 95%CI 2.63 to 7.02).

The EMEA is currently reviewing the impact of new data from recent publications that point towards an increased risk of CV events with rosiglitazone. While this review is ongoing, the MHRA have issued a reminder for healthcare professionals about current advice for the use of rosiglitazone in the treatment of diabetes. In view of the growing evidence of CV risk, healthcare professionals should closely observe the current contraindications, warnings and precautions and monitoring requirements, and consider alternative treatments where appropriate.

Reference

1. Wang AT, et al. Association between industry affiliation and position on cardiovascular risk with rosiglitazone: cross sectional systematic review. BMJ 2010;340:c1344

The National Institute for Health and Clinical Excellence (NICE) is associated with MeReC Publications published by the NPC through a funding contract. This arrangement provides NICE with the ability to secure value for money in the use of NHS funds invested in its work and enables it to influence topic selection, methodology and dissemination practice. NICE considers the work of this organisation to be of value to the NHS in England and Wales and recommends that it be used to inform decisions on service organisation and delivery. This publication represents the views of the authors and not necessarily those of the Institute.

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