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Increased risk of mortality associated with tiotropium Respimat▼ in COPD

A meta-analysis of randomised controlled trials (RCTs)[1] found that tiotropium delivered via mist inhaler (Spiriva Respimat▼) 5 micrograms/day (the recommended UK dose) was associated with a 46% relative increased risk of death in people with COPD compared with placebo. Taking into account the baseline risk of death (1.8% / year), this suggests that one excess death would be expected for every 121 patients (95% CI 51 to 5556) treated with 5 micrograms/day of tiotropium Respimat for one year.[2] Earlier evidence included in previous MHRA guidance found no such increased risk with the tiotropium HandiHaler device.

Action

Health professionals looking after people with COPD should continue to follow NICE guidance. A long-acting bronchodilator (either a long-acting muscarinic antagonist [LAMA — e.g. tiotropium] or a long-acting beta agonist [LABA — e.g. salmeterol]) should be offered for people who experience exacerbations or persistent breathlessness despite use of a short-acting bronchodilator. If a LABA is chosen for severe to very severe COPD (FEV1 <50% predicted) it should be offered in combination with an inhaled corticosteroid (ICS). NICE does not give preference to either a LAMA or a LABA. Health professionals should follow current MHRA advice on tiotropium Respimat.

When decisions are made around which long-acting bronchodilator to use, choice in individual patients should take account of their response to a therapeutic trial, potential side-effects, patient preference (e.g. suitability of different inhaler devices, individual tolerability), and cost. These new safety data on tiotropium Respimat should also feature in discussions with patients.

This new study does not answer the important question of whether tiotropium Respimat carries a particular risk compared with the HandiHaler device. A 2-year head-to-head study between tiotropium Respimat and HandiHaler is ongoing to help clarify the situation.

What did this study find?

The relative risk of mortality for tiotropium Respimat (5 micrograms/day) compared with placebo was 1.46 (95% CI 1.01 to 2.10, p=0.04) in this study. Although this relative increased risk of death for tiotropium Respimat of 46% may appear alarming, this needs to be put in perspective of the baseline risk (1.8% / year). The absolute risk increase in the risk of death was only 0.8%/year, compared with placebo. This translates into an annual number needed to harm (NNH) of 121 (i.e. the number of patients who would need to be given tiotropium Respimat 5 microgram/day tiotropium for a year for one additional death to occur compared with patients given placebo).[2] However, there is considerable uncertainty around this estimate (NNH 95% CI 51 to 5556). MeReC Rapid Review No. 4012 contains a Cates plot illustrating the one-year mortality data for tiotropium Respimat 5 micrograms/day, which may be useful when explaining risks and benefits to patients.

MHRA advice on tiotropium Respimat reminds prescribers to use tiotropium Respimat with caution in patients with known cardiac rhythm disorders. For both tiotropium Respimat and HandiHaler, prescribers should not exceed the recommended once-daily dose (two puffs of 2.5 micrograms for Respimat, one 18 microgram capsule for HandiHaler). The MHRA continues to review the cardiovascular (CV) safety of all inhaled anticholinergics and any suspected adverse reactions to tiotropium Respimat (and HandiHaler) should be reported via the Yellow Card scheme.

In terms of cost, tiotropium Respimat is more expensive (£440.08/year) than either tiotropium HandiHaler (refill £386.93/year) or any single component LABA preparation (range £144.08/year to £426.49/year).

Further information on this study can be found in MeReC Rapid Review No. 4012.

References

1. Singh S, et al. Mortality associated with tiotropium mist inhaler in patients with chronic obstructive pulmonary disease: systematic review and meta-analysis of randomised controlled trials. BMJ 2011;342:d3215
2. Cates C. Safety of tiotropium. Indirect evidence suggests the Respimat inhaler is riskier than the Handihaler. BMJ 2011;342:d2970

All information was correct at the time of publication (September 2011)

Observational study of LABAs compared with tiotropium in older patients with COPD

An observational study[1] found that initial prescribing of tiotropium for older people with COPD was associated with a 14% relative increased risk of death compared with initial prescribing of a LABA. However, this appears to contrast with a finding from the POET-COPD RCT,[2] in which there was no significant difference in mortality between COPD patients randomised to tiotropium or salmeterol. Important limitations in both studies limit the conclusions which may be drawn from them.

Action

As stated above, NICE guidance on COPD advises that people who experience exacerbations or persistent breathlessness despite use of a short-acting bronchodilator should be offered either a LAMA or a LABA. NICE does not give a preference for either a LABA or a LAMA. If a LABA is chosen for severe to very severe COPD (FEV1 <50% predicted) it should be offered in combination with an inhaled corticosteroid (ICS).

Given that a choice of treatment for an individual patient has to be made, health professionals and patients may wish to consider the outcomes of this study and the POET-COPD study, along with other factors such as the suitability to the individual of different inhaler devices, individual tolerability to treatment and possible adverse effects of ICS.

What did this study find?

In this study, adults (aged 66 years or older) who were initially prescribed tiotropium had a modest but statistically significantly higher adjusted rate of death than those initially prescribed a LABA (39.9% vs 36.5% respectively, adjusted hazard ratio 1.14, 95% CI 1.09 to 1.19; p<0.001). In addition, initial use of tiotropium was associated with a significantly greater risk of all secondary outcomes compared with a LABA; these included a composite of death, hospitalisation or an emergency department visit for COPD.

However, in the POET-COPD RCT of patients with moderate to very severe COPD there was a statistically significant benefit for tiotropium over salmeterol in its primary outcome (time to first moderate or severe exacerbation). Furthermore, safety monitoring data from this study suggested a possible reduction in mortality with tiotropium, although the difference was not statistically significant. This trial was reviewed in MeReC Rapid Review No. 3501.

Direct comparison of the results from the this study and the POET-COPD study is limited because of differences in the primary outcome and the populations studied, and both studies are subject to a number of limitations, making it difficult to draw firm conclusions from them, for example, lack of information and adjustment for smoking status and disease severity in this observational study and uncertainty over treatment with ICS in patients in the POET-COPD study. More details and discussion of this study, set in the context of the POET-COPD study, can be found in MeReC Rapid Review No. 3941.

Further information can be found on NHS Evidence and in NPC e-learning materials on COPD.

References

1. Gershon A, et al. Comparison of inhaled long-acting β-agonist and anticholinergic effectiveness in older patients with chronic obstructive pulmonary disease: a cohort study. Ann Intern Med 2011;154:583–92
2. Vogelmeier C, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011;364:1093–103

Even short-term treatment with NSAIDs can increase CV risk in patients with prior MI

A Danish cohort study[1] identified an increased risk of death or recurrent myocardial infarction (MI) with non-steroidal anti-inflammatory drugs (NSAIDs) in patients with prior MI. The risk appeared largely independent of the duration of treatment, and became apparent within the first weeks of treatment. Overall, the highest risk was associated with diclofenac and the lowest risk was associated with naproxen.

Action

This study suggests that particular care is required when prescribing NSAIDs (including coxibs) for patients with prior MI, and reinforces previous advice (see MeReC Extra 30) regarding the choice of NSAIDs. Where NSAIDs are required, prescribing should be based on the safety profiles of individual NSAIDs and on individual patient risk factors. All NSAIDs should generally be used **at the lowest effective dose and for the shortest period of time necessary** to control symptoms.

- Low-dose ibuprofen (≤1200 mg/day) is an appropriate first choice NSAID in view of its low risk of gastrointestinal (GI) and CV side effects.
- Low-dose ibuprofen or naproxen 1000 mg/

day would appear more appropriate than other NSAIDs for patients in whom CV risk is a significant consideration in decision making.

- Consider prescribing a proton-pump inhibitor (PPI) with any NSAID to reduce the risk of adverse GI effects, particularly in those who are at high GI risk (this includes anybody aged 65 years or older) and long-term NSAID users. Specific recommendations for co-prescribing of PPIs are provided in NICE clinical guidelines for osteoarthritis, rheumatoid arthritis, and low back pain.

- Although coxibs are associated with a lower risk of GI side effects than traditional NSAIDs, there is no good evidence to support the use of coxibs alone ahead of traditional NSAIDs co-prescribed with a PPI. Coxibs also have a higher CV risk than ibuprofen ≤1200 mg/day or naproxen 1000 mg/day.

What does this study add?

The results of this study in patients at high CV risk is consistent with many other studies (see MHRA webpage) that have demonstrated an increased risk of CV events both with coxibs (e.g. celecoxib, etoricoxib▼) and traditional NSAIDs (e.g. diclofenac, naproxen and ibuprofen). In this study, diclofenac was associated with the highest risk of death or recurrent MI, and in accordance with other studies naproxen was associated with the lowest CV risk. An increased risk of MI or death was apparent for most NSAIDs during the first few weeks of treatment, and the study suggests that the increased relative risk could be largely independent of the duration of treatment. Although this study adds to the evidence base, results need to be interpreted with caution because of inherent limitations, for example, inability to take account of potential confounders (e.g. CV risk factors), lack of information on dosage, and unrecorded use of medicines (e.g. over the counter ibuprofen). Nevertheless, this study supports current advice to limit the use of NSAIDs to the shortest time necessary to control symptoms.

Prescribers and prescribing managers should review local prescribing trends for NSAIDs as suggested in the document 'Key therapeutic topics – Medicines management options for local implementation', produced by the NPC as part of the QIPP programme.

For more details of the study see MeReC Rapid Review No. 3927. More information on NSAIDs can be found on NHS Evidence, and in NSAID national support materials and NPC e-learning materials on musculoskeletal pain.

Reference

1. Schjerning Olsen A-M, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction. A nationwide cohort study. Circulation 2011;123:2226–35

The National Prescribing Centre (NPC) is responsible for helping the NHS to optimise its use of medicines. NPC is part of the National Institute for Health and Clinical Excellence (NICE), an independent organisation providing national guidance on promoting good health and preventing and treating ill health.

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