NICE National Institute for Health and Care Excellence

2021 exceptional surveillance of headaches in over 12s: diagnosis and management (NICE guideline CG150)

Surveillance report
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Surveillance decision

We will update recommendation 1.3.15 in the NICE guideline on headaches in over 12s on the use of metoclopramide and prochlorperazine for acute migraine in people in whom oral or nasal treatments for acute migraine are ineffective or not tolerated. This is currently a strong 'offer' recommendation but will be changed to a more cautious 'consider' recommendation.

Reason for the exceptional review

To assess the impact of the Medicines and Healthcare products Regulatory Agency (MHRA) drug safety update (DSU; 2014) and additional information on recommendation 1.3.15.

Methods

The exceptional surveillance process consisted of:

- Examining the MHRA DSU and underpinning European Medicines Agency (EMA) report about the risks of metoclopramide in children and young people.
- Searching PubMed to identify evidence for the benefits and risks of metoclopramide and prochlorperazine for the treatment of headaches in children and young people.
- Feedback from NICE clinical advisers and from external topic experts.
- Consulting with stakeholders on a proposal to amend the recommendation.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Discussion of the evidence

When the guideline was developed in 2012, the recommendation to offer the anti-emetics metoclopramide and prochlorperazine was based on moderate to very low quality evidence of their effectiveness for pain relief for migraine irrespective of whether a person

is experiencing nausea. The evidence for prochlorperazine included children in the study population (5 to 18 years). However, none of the evidence for metoclopramide included people under 18 years but the committee agreed that there were no additional considerations about metoclopramide for people 12 to 17 years.

It was noted by the committee that there is a small risk that anti-emetic drugs of this type (dopamine receptor antagonists) can trigger extrapyramidal side effects and the risk is higher in people younger than 20 years. The committee agreed that these side effects are rare and reversible, and that the benefits of metoclopramide or prochlorperazine justify their use with consideration of the side effects. Therefore, the committee decided to make an 'offer' recommendation reflecting clear evidence of benefit (see the section on wording the recommendations in developing NICE guidelines: the manual).

In 2014, the MHRA DSU provided further evidence of metoclopramide's association with extrapyramidal side effects and that this risk is higher in paediatric populations.

The MHRA DSU was informed by an EMA report that examined benefit and harm data from various indications of metoclopramide. Rates of extrapyramidal side effects were 6 times higher for children compared with adults. The report concluded that in paediatric populations, metoclopramide should only be used as a second-line option for preventing delayed chemotherapy-induced nausea and vomiting, and for treating established post-operative nausea, and that use should be short term (up to 5 days).

More evidence has since become available. PubMed searches for the risks associated with metoclopramide and other anti-emetics in children and young people were identified in a systematic review. This review of metoclopramide in paediatric populations indicated a small risk that was generally reversible (Lau Moon Lin et al. 2016). An observational study (Kirkpatrick et al. 2020) reports a small risk of dystonic reactions with metoclopramide and prochlorperazine and that the risk is relatively higher for prochlorperazine.

When recommendation 1.3.15 was developed in 2012, the guideline committee were confident in making a strong 'offer' recommendation for metoclopramide and prochlorperazine in children and young people. Although the EMA report and subsequent additional data are not direct evidence for harm in this population, they confirm the risks associated with metoclopramide, particularly in paediatric populations, and reduced the certainty of the original benefit–harm assessment made by the committee.

Topic expert feedback

Two topic experts in pain management and headache (from the NICE Centre for Guidelines Expert Advisers Panel) considered the MHRA DSU and the risks associated with metoclopramide and prochlorperazine. The experts concluded that these risks are well known and are usually reversible, and that recommendation 1.3.15 is appropriate and does not need to be reviewed and updated. However, they did highlight that the evidence underpinning the MHRA DSU was largely indirect with respect to the population covered by recommendation 1.3.15. They highlighted that the DSU conclusions were based on evidence that used safety data from people regularly using metoclopramide for various indications (not occasional use as with migraine treatment), and that it considered only very limited evidence for metoclopramide's benefit for migraine in children and adolescents.

Proposal

We propose reducing the strength of recommendation 1.3.15 by making it a 'consider' recommendation, reflecting that the evidence of benefit is less certain (see the section on wording the recommendations in developing NICE guidelines: the manual).

Prochlorperazine is also a dopamine receptor antagonist and is associated with extrapyramidal side effects. Kirkpatrick et al. (2020) reported that the risk of extra pyramidal side effects, although small, may be relatively higher for prochlorperazine compared with metoclopramide. Therefore, 'consider' will also apply to prochlorperazine.

We also propose adding advice about checking summaries of product characteristics (SPCs) to alert practitioners (particularly those who may not be pain management or headache specialists) to the safety issues associated with metoclopramide. The new wording will be as follows:

For people in whom oral preparations (or nasal preparations in young people aged 12 to 17 years) for the acute treatment of migraine are ineffective or not tolerated:

- consider a non-oral preparation of metoclopramide or prochlorperazine **and**

- if non-oral metoclopramide or prochlorperazine is used, consider adding a non-oral NSAID (non-steroidal anti-inflammatory drug) or triptan if they have not been tried. **[2012]**

  Note the special warnings and precautions for use in the summaries of product characteristics for metoclopramide and prochlorperazine, and discuss the benefits and risks with the person (or their parents or carers, as appropriate).

  In November 2015, only a buccal preparation of prochlorperazine was licensed for this indication (prochlorperazine was licensed for the relief of nausea and vomiting); nasal sumatriptan was the only triptan licensed for this indication in under 18s. This was an off-label use of metoclopramide in children and young people. See NICE's information on prescribing medicines.

Stakeholder consultation

Stakeholders were consulted to collect opinions on our proposal to amend recommendation 1.3.15, changing 'offer' to 'consider' and to add advice about checking SPCs. Two stakeholders responded: the Royal College of Paediatrics and Child Health, and the Royal College of Nursing. Both agreed with the decision to amend the recommendation as proposed. One stakeholder commented that using 'consider' rather than 'offer' in managing migraine better reflects the benefits and harms of these drugs. The second stakeholder commented that the rationale for the amendment is clear and noted that in their experience, metoclopramide is used regularly in practice because it is very effective and generally tolerated.

See appendix A for stakeholder consultation comments and our responses.

See ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual for more details on our consultation processes.

Equalities

No equalities issues were identified during the surveillance process.

Overall decision

We will amend recommendation 1.3.15 on the use of metoclopramide and prochlorperazine for the treatment of acute migraine, from a strong 'offer' recommendation to a 'consider' recommendation to better reflect the balance between the benefits and harms associated with their use. We will add wording that reminds healthcare professionals to check the SPCs of these drugs for any warnings or use precautions.

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