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Reducing the risk of gastrointestinal adverse effects by NSAIDs. Guidelines recommend non-steroidal anti-inflammatory drugs (NSAIDs) as a management option for a number of conditions (e.g. low back pain and rheumatoid arthritis). NSAIDs are associated with serious gastrointestinal (GI), cardiovascular (CV) and renal adverse effects (AEs); a UK study of hospital admissions (n=18,820) in 2004 found that 6.3% of the admissions were related to an adverse drug reaction of which 30% were caused by NSAIDs. A review on ways to reduce the risk of NSAID related GI effects was recently published ***(DTB June 2020;58(6):89-92)***. **GI AEs (including ulcers, perforation, obstruction and bleeding) are the most common complications associated with NSAIDs;** these are thought to occur mainly due to inhibition of cyclo-oxygenase 1 enzyme (COX-1), even though other mechanisms are involved. COX-2 inhibitors are associated with a lower risk of serious ulcer complications than non-selective NSAIDs. **The relative risk differs between non-selective NSAIDS, with azapropazone, ketorolac and piroxicam having higher risk, diclofenac and naproxen having intermediate risk and low-dose ibuprofen having lower risk**. A NICE Clinical Knowledge Summary includes the following risk factors for a patient on NSAIDs developing GI complications:

- Patients aged >65 years
- High dose of NSAID
- A history of GI ulcer or GI bleeding
- Concomitant use of medicines that increase the risk of GI complications (e.g. antiplatelets, anticoagulants, selective serotonin reuptake inhibitors and corticosteroids)
- Serious comorbidity (e.g. CV disease, hepatic/renal impairment, diabetes, hypertension)
- Smoking and/or excessive alcohol consumption
- Previous adverse reaction to NSAID
- Prolonged requirement for NSAID

Patients without any risk factors are regarded as low risk for GI complications, those with 1 or 2 risk factors have moderate risk and those with >2 risk factors have high risk. It is recommended that for those at low risk, a non-selective NSAID should be considered; those at moderate risk, a COX-2 alone or non-selective NSAID with PPI considered and those at high risk a COX-2 inhibitor with PPI should be prescribed. A recent network analysis (82 trials; n=125,053) compared the effectiveness of multiple strategies (non-selective NSAIDs alone or with a PPI, a H2-receptor antagonist or misoprostol, or COX-2 inhibitors alone, or with a PPI or misoprostol) for preventing NSAID-induced toxicity. The results of the study suggested that co-prescribing a PPI with an NSAID appears to be more effective than using a H2-receptor antagonist or misoprostol. A COX-2 inhibitor plus PPI may offer slightly better GI protection than a non-selective NSAID plus a PPI or a COX-2 inhibitor alone. It should be remembered that long-term use of PPIs have also been associated with AEs (e.g. *Clostridium difficile*, bone fractures, hypomagnesaemia and vitamin B12 deficiency). In addition to GI AEs, CV and renal AEs are also associated with use of NSAIDs. COX-2 inhibitors, aceclofenac, diclofenac and high dose ibuprofen should not be prescribed in patients with ischaemic heart disease, peripheral arterial disease, cerebrovascular disease and congestive heart failure. All NSAIDs and COX-2 inhibitors should be prescribed with caution in patients with or at risk of renal impairment.

Alternative treatment should be considered prior to prescribing an oral NSAID including physiotherapy, exercise and strength training, topical NSAIDs and non-NSAID oral analgesics. The decision to prescribe an NSAID should take into account patients' CV and renal risk factors. **If oral NSAIDs are prescribed, they should be prescribed at the lowest effective dose for the shortest period of time.** Healthcare professionals should carefully discuss the potential benefits and harms associated with NSAIDs and PPIs to help patients decide on the most appropriate strategy.

Risk of major bleeding with direct oral anticoagulants (DOACs) and interacting drugs. DOACs (dabigatran, rivaroxaban, apixaban and edoxaban), used for the treatment of thromboprophylaxis have been associated with a lower risk of major bleeding than vitamin K antagonists in clinical trials. However, uncertainties about their benefit-risk profile remain, such as their concomitant use with potentially interacting drugs and the effect on bleeding risk. A nested case-control study aimed to evaluate the association between combined use of DOACs (dabigatran, rivaroxaban and apixaban) with potentially pharmacokinetic (PK) and pharmacodynamic (PD) interacting drugs on major bleeding risk ***(Br J Clin Pharmacol 2020;86:1150-1164)***. Data for the study was obtained from the UK Clinical Practice Research Datalink linked to Hospital Episode Statistics (2008-2015). The study cohort included 23,492 DOAC users aged ≥18 years; there were 393 cases (defined as patients hospitalised with major bleeding) who were matched with 1494 controls (on age, sex, index date and region) from the study cohort. The PK and PD interacting drugs were obtained from the Summary of Product Characteristics and European Heart Rhythm Association Practical Guide; exposure to potentially interacting drugs were identified from the patients' records. The odds ratios (ORs) were assessed using conditional logistic regression; adjustments were made for covariates including BMI, smoking status, hypertension, kidney disease, hepatic impairment, history of major bleeding, gastritis, cancer, peptic ulcer disease, thrombocytopenia the year before the index date and other co-medication (e.g. glucocorticoids, proton pump inhibitors). The study found that **concurrent use of PD interacting drugs with DOACs was associated with a statistically significant increased risk of bleeding; adjusted OR of 1.92 (95% confidence interval, 1.40-2.66)**. The most frequently used PD interacting drugs were antiplatelet drugs and selective serotonin reuptake inhibitors. There was no statistically significant association with bleeding risk for use of potentially PK interacting drugs with DOACs in the study.

HPRA Drug Safety Newsletter May 2020. The most recent edition of the Health Products Regulatory Authority (HPRA) Drug Safety Newsletter highlighted and reminded healthcare professionals of some important safety issues ***(HPRA Newsletter May 2020 98th Edition).*** The topics include:

1) **Adverse reaction reporting during the COVID-19 pandemic** – reminder to report suspected adverse reactions to any of the medicinal products used in the treatment of patients with confirmed or suspected COVID-19
2) **Picato▼ (ingenol mebutate)** –recent EMA review concludes negative risk-benefit balance due to a risk of skin malignancy; it is no longer authorised in the EU
3) **Levetiracetam** – may cause psychotic symptoms and behavioural abnormalities including irritability and aggressiveness
4) **Cyproterone acetate** – use associated with increased risk of meningioma; contraindicated in patients with a meningioma or a history of meningioma
5) **Carbimazole and propylthiouracil** – use of ***carbimazole in pregnancy*** associated with increased risk of congenital malformations especially in the first trimester and at high doses; women of childbearing potential should use effective contraception during treatment and must only be administered during pregnancy after a strict individual benefit/risk assessment with close monitoring required. There is conflicting evidence regarding risk of congenital malformations associated with use of ***propylthiouracil during pregnancy***; individual benefit/risk should be undertaken
6) **Carbimazole** – use associated with increased risk of acute pancreatitis
7) **Testosterone-containing medicinal products** – topical, oral and injectable testosterone-containing medicinal products should be used with caution in patients with thrombophilia or risk factors for venous thromboembolism.

Full details of these safety issues are in the newsletter at www.hpra.ie

[**Editor's note:** readers are reminded that they can register directly with the HPRA to receive Drug Safety Newsletters and other safety alerts on www.hpra.ie]

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. References are available on request. **This newsletter is produced by the National Medicines Information Centre, St. James's Hospital (SJH) Dublin 8 and Dept. of Therapeutics Trinity College, Trinity Centre, SJH.** Tel: Direct Line (01) 473 0589 or 1850 727 727 Email: nmic@stjames.ie @NationalNmic