Therapeutics Today

February 2020
Number 2

Decreased renal function and oral anticoagulants (OAC). Warfarin and non-vitamin K OACs [NOACs] are used in the management of atrial fibrillation (AF). All NOACs (dabigatran, rivaroxaban, apixaban and edoxaban) are partially eliminated by the kidneys, and different doses of each NOAC are recommended according to a patient's renal function or a combination of renal function and other factors (e.g. age and body weight). **Worsening renal function (RF) is common in patients with AF**. Dose adjustment may be required in patients treated with NOACs who experience worsening RF, however it is not known the extent this happens in clinical practice. A US study of patients with AF treated with OACs who were enrolled in a prospective, multicentre nationwide registry from February 2013 to July 2016 was undertaken ***(Heart 2019;doi:10.1136/heartjnl-2019-316099).*** The study aimed to: 1) evaluate the changes in patients' RF over time, 2) assess the frequency that patients required NOAC dose adjustment due to worsening RF over time and 3) assess how often these patients received dose adjustment of the NOAC. Patients enrolled in the study were those with a new diagnosis of AF in the previous 6 months or those started on NOACs for AF in the previous 3 months. Serum creatinine (Cr) was collected at baseline and at follow-up visits every 6 months for 2 years; worsening RF was defined as a decrease of >20% of creatinine clearance (CrCl) from baseline. The study which had 6682 patients (median age 72 years; median CrCl at baseline 80.1mL/min) had a median follow-up period of 361 days. The study found that 5566 (83.3%) of patients were treated with NOACs and 1116 (16.7%) were treated with warfarin. **There were 1543 patients (23%) who met the definition of worsening RF during the follow-up; those with worsening RF were older, more likely to be female, have higher CrCl at baseline and more likely to have a history of anaemia and cardiovascular comorbidities**. A continuous decline in CrCl over time was observed regardless of the type of OAC. The rates of all renal outcomes including WRF were significantly higher in patients treated with warfarin than those on NOACs. **There were 4120 patients on doses of NOACs of which 154 patients (3.7%) met the dose reduction criteria based on the FDA dosing guidelines; of these only 31 patients (20%) had their NOAC dose appropriately reduced**. Patients with appropriately reduced NOACs doses were more likely to have a history of cerebrovascular disease and chronic kidney disease; those patients who did not have appropriate NOAC dose reduction were more likely to experience bleeding complications (major bleeding: 1.7% vs 0%; bleeding requiring hospitalisation: 2.6% vs 0%) at 1 year. The authors of the study advise that further efforts to improve the quality of care of patients with AF in terms of dose adjustment of NOACs based on regular serum Cr are required.

Information on novel coronavirus. The 2019- novel coronavirus (2019-nCoV) is a virus previously not seen in humans which was first identified in Wuhan, China in December 2019. As readers are aware the WHO declared the 2019-nCoV outbreak a public health emergency of international concern on the 30th January 2020; the situation is rapidly evolving. The Health Protection Surveillance Centre (HPSC) has useful guidance documents for healthcare professionals (HCPs) on 2019-nCoV (www.hpsc.ie). These documents include: algorithms for Irish healthcare settings (e.g. 1) risk assessment for use by ambulance services when primary point of contact, 2) risk assessment for the primary care setting, 3) public health investigation of a close contact of a confirmed case and 4) risk assessment for use in a hospital setting), clinical management for novel coronavirus, guidance for educational settings and infection prevention and control guidance. The Health Service Executive website also has information on 2019-nCoV which includes guidance for patients https://www2.hse.ie/conditions/coronavirus.html.

Pregabalin related poisoning deaths in Ireland*.** The rates of prescribing of pregabalin which is authorised for the treatment of epilepsy, neuropathic pain and generalised anxiety disorder, has increased both nationally and internationally. Pregabalin was initially considered to have low abuse potential; however there is a potential risk for misuse with pregabalin due to its pharmacokinetic properties, the fast onset of its relaxant and sedative effects and reduced withdrawal symptoms. **Recent studies have reported misuse of pregabalin especially in those with a history of opioid misuse and those on opioid substitution treatment.** There is a growing body of evidence that pregabalin may be addictive in people with a history of dependence on other substances and that caution should be taken if prescribing to people with a history of opioid dependency. There have also been reports of pregabalin been involved in deaths in Sweden, Finland and the UK among people who use drugs of abuse. A recent study suggested a possible association between the increased use of pregabalin in Ireland with an increase in pregabalin-related poisoning deaths. A retrospective repeated cross-sectional study examined the factors associated with pregabalin-positive poisoning deaths (PPPD) in Ireland between 2013 and 2016 ***(Drug and Alcohol Dependence 2020 Jan 1;206:107741). The study used anonymous data from the National Drug-Related Deaths Index (NDRDI) which is a database that records all poisoning deaths by drugs and/or alcohol. The primary outcome was PPPD (all poisoning deaths with pregabalin present on toxicology reports) from 2013 to 2016, which was compared to all other poisoning deaths, referred to as pregabalin-negative poisoning deaths (PNPD). Analysis included univariate and multivariate logistic regression to measure unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for factors associated with PPPD. The study reported that of the total number of poisoning deaths (n=1489) recorded by the NDRDI during the study period, 16% (n=240) were identified as PPPD. The total number of poisoning deaths decreased over the 4 years, however **there was an increase in PPPDs compared to PNPD, rising from 5% (n=18) in 2013 to 27% (n=94) in 2016**. After adjustment for significant covariates (including age, gender, year of death, alone at time that lead to death, unemployed, homeless, alcohol dependency, opioid misuse and in receipt of treatment for drug misuse [e.g. methadone]), **an increased odds of PPPD was seen in women, history of opioid misuse, those in receipt of treatment for drug misuse and the year of death (2016 vs 2013),** while alcohol dependency was associated with a reduced odds of PPPD. **An increased odds of PPPD in men was seen with year of death (2016 vs 2013), history of opioid misuse and a lower odds seen in those with alcohol dependency. In women, an increased odds of PPPD was seen in those receiving treatment for drug misuse and year of death.** The study also found that polydrugs were present on all PPPD; **having ≥2 CNS depressant drugs (e.g. opioids, methadone and benzodiazepines), antidepressants, antipsychotics and or z drugs on toxicology reports were significantly associated with PPPD.** The authors of the study conclude that the increase in PPPD is in line with increasing use of pregabalin and the results suggests that there is inappropriate use of pregabalin among those who are known to misuse opioids and those receiving treatment for drug misuse. They recommend that enhanced training to prescribers and treatment providers is required on the potential risks associated with pregabalin, particularly among people who use drugs of abuse.

[**Editor's note**: The Medicines Management Programme recently published a Prescribing Tips and Tools on the appropriate prescribing of pregabalin. It is available on ***https://www.hse.ie/eng/about/who/cspd/ncps/medicines-management/prescribing-tips-and-tools/appropriate-prescribing-of-pregabalin.pdf].***

Prescribing in pregnancy*.** Two recent useful review articles have been published on prescribing in pregnancy. The first article covers some of the key issues that should be considered for women as part of pre-pregnancy care ***(Drug and Therapeutics Bulletin [DTB] 2019;57(11):168-172). The second article reviews the pharmacological treatment for women with mental illness in the perinatal period which affects up to 20% of women ***(DTB 2020;58(1):8-11)***.

[**Editor's note**: readers are reminded of the 3 bulletins published by the NMIC on prescribing in pregnancy. The first bulletin reviewed the principles of prescribing in pregnancy ***(NMIC 2018;Vol 24:No 2)*** and the second two bulletins ***(NMIC 2018; Vol 24: No 3 &4)*** covered frequently asked questions on prescribing in pregnancy received by the NMIC. These topics include the use of antidepressants, antihypertensives, antiemetics, antimicrobials, analgesics, topical corticosteroids and biologicals in pregnancy. The bulletins are available on our website www.nmic.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*