LETTERS

Letters to the Editor

Genetic polymorphisms in opioid metabolism

Aust Prescr 2021;44:118
https://doi.org/10.18773/austprescr.2021.030

The article about serotonergic interactions between antidepressants and opioids[1] was a concise depiction of the influence of enzyme inhibitors and inducers of cytochrome P450 (CYP) 2D6 on the extent of the serotonergic, noradrenergic or opioid effects of codeine and tramadol. However, it is not simply drug–drug interactions, but also genetic polymorphisms that dictate the prevalence of serotonergic, noradrenergic, or opioid metabolites.

Equivalent drug doses can produce vastly different degrees of analgesia or serotonergic toxicity if the patient is an ultra-rapid metaboliser of CYP2D6 (the incidence is 1–28% of the worldwide population), or a poor metaboliser.[2,3] Without this caveat, it could be misleading to label codeine and tramadol as 'weak' analgesics.[3]

Codeine is a prodrug metabolised to therapeutically active morphine. In ultra-rapid metabolisers it can be a potent analgesic with risks that may not be appreciated if it is considered as a 'weak' opioid.[2] In contrast, codeine offers negligible analgesia to poor metabolisers.

Tramadol's opioid activity is dependent on metabolism to O-desmethyltramadol via CYP2D6. Ultra-rapid metabolisers experience a lower risk of serotonergic and noradrenergic adverse effects yet greater risks of mu-opioid-receptor agonism and respiratory depression.[4]

The table in the article showed the 'triptan' class of drugs as being 'likely' to increase the risk of serotonin toxicity.[1] They are primarily agonists of 5-HT_{1B} and 5-HT_{1D} subtypes, while the harms of serotonin toxicity are believed to be primarily mediated through 5-HT_{1A} and 5-HT_{2A} (as the authors note in other work).[5,6] Due to the clinical benefit of having a triptan and opioid analgesic available for the treatment of severe migraine, it may be counterproductive to suggest they should be combined only cautiously.

Tiernan McDonough
Community pharmacist, Kenmore Discount Drug Stores, Kenmore, QLD

REFERENCES

1. Perananthan V, Buckley NA. Opioids and antidepressants: which combinations to avoid. Aust Prescr 2021;44:41-4. https://doi.org/10.18773/austprescr.2021.004
2. Therapeutic Goods Administration. Safety review: codeine use in children and ultra-rapid metabolisers, Version 1.0, October 2015. www.tga.gov.au/alert/safety-review-codeine-use-children-and-ultra-rapid-metabolisers [cited 2021 Jun 9]
3. Kamenski G, Ayazseven S, Berndt A, Fink W, Kamenski L, Zehetmayer S, et al. Clinical relevance of CYP2D6 polymorphisms in patients of an Austrian medical practice: a family practice-based observational study. Drugs Real World Outcomes 2020;7:63-73. https://doi.org/10.1007/s40801-019-00177-4
4. Stamer UM, Musshoff F, Kobilay M, Madea B, Hoeft A, Stuber F. Concentrations of tramadol and *O*-desmethyltramadol enantiomers in different *CYP2D6* genotypes. Clin Pharmacol Ther 2007;82:41-7. https://doi.org/10.1038/sj.clpt.6100152
5. Buckley NA, Dawson AH, Isbister GK. Serotonin syndrome. BMJ 2014;348:g1626. https://doi.org/10.1136/bmj.g1626
6. Orlova Y, Rizzoli P, Loder E. Association of coprescription of triptan antimigraine drugs and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants with serotonin syndrome. JAMA Neurol 2018;75:566–72. https://doi.org/10.1001/jamaneurol.2017.5144

The Editorial Executive Committee welcomes letters, which should be less than 250 words. Before a decision to publish is made, letters which refer to a published article may be sent to the author for a response. Any letter may be sent to an expert for comment. When letters are published, they are usually accompanied in the same issue by any responses or comments. The Committee screens out discourteous, inaccurate or libellous statements. The letters are sub-edited before publication. Authors are required to declare any conflicts of interest. The Committee's decision on publication is final.