

RGH Pharmacy E-Bulletin

Volume 44 (2): October 17, 2011

A joint initiative of the Patient Services Section and the Drug and Therapeutics Information Service of the Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia. The RGH Pharmacy E-Bulletin is distributed in electronic format on a weekly basis, and aims to present concise, factual information on issues of current interest in therapeutics, drug safety and cost-effective use of medications.

Editor: Assoc. Prof. Chris Alderman, University of South Australia – Director of Pharmacy, RGH

© Pharmacy Department, Repatriation General Hospital, Daw Park, South Australia 5041

Drug toxicity and Gilbert's syndrome

Gilbert's syndrome is a hereditary (usually autosomal recessive) condition caused by impaired hepatic bilirubin clearance. Gilbert's syndrome is present in 5–10% of Western European populations, with one in three of those affected unaware that they are affected. Gilbert's syndrome is characterised by mild unconjugated non-haemolytic hyperbilirubinaemia. Diagnosis of the disorder is often made after an incidental finding of isolated hyperbilirubinaemia on routine liver biochemistry testing.

Bilirubin is the normal by-product of the breakdown of red blood cells (derived from haemoglobin). People with Gilbert's syndrome have a polymorphism in the gene that encodes for uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), which results in a reduction in the liver's ability to conjugate bilirubin. This subsequent increase in the serum concentration of unconjugated bilirubin can lead to intermittent episodes of non-pruritic jaundice, which can be precipitated by fasting, infections, dehydration, surgery, physical exertion and lack of sleep.

UGT1A1 is involved in the glucuronidation of some drugs, but plasma clearance of most drugs that undergo glucuronidation is unaffected. However, established toxicity reactions have been reported with irinotecan, atazanavir and indinavir. Irinotecan is a pro-drug and is metabolised to the active SN-38 metabolite (SN-38 is mainly inactivated by UGT1A1). Those with Gilbert's syndrome may have an increased risk of neutropenia and diarrhoea due to impaired metabolism of SN-38. People with Gilbert's syndrome who are receiving atazanavir or indinavir may be at an increased risk of experiencing hyperbilirubinaemia.

For some other UGT1A1 substrates that are listed below, the clinical relevance is predominantly theoretical and is yet to be fully determined.

Established toxicity reactions

- irinotecan
- atazanavir
- indinavir

UGT1A1 substrates (potential risk?)

- gemfibrozil
- ezetimibe
- simvastatin, atorvastatin, fluvastatin
- ethinylestradiol
- buprenorphine
- ibuprofen, ketoprofen
- olanzapine

Altered metabolism of paracetamol has been demonstrated in a subgroup of patients with Gilbert's syndrome, but no cases of toxicity have been reported after therapeutic doses. One study found no correlation between the capacity to glucuronidate paracetamol, the UGT1A1 genotype and the bilirubin serum level, and concluded that paracetamol was likely to be the substrate of a UGT isoform other than UGT1A1.

Acknowledgment – This E-Bulletin is based on work by Tricia Warrick, Senior Pharmacist, DATIS, RGH.

FOR FURTHER INFORMATION – CONTACT THE PHARMACY DEPARTMENT ON 82751763 or email: chris.alderman@rgh.sa.gov.au
Information in this E-Bulletin is derived from critical analysis of available evidence – individual clinical circumstances should be considered when making treatment decisions. You are welcome to forward this E-bulletin by email to others you might feel would be interested, or to print the E-Bulletin for wider distribution. Reproduction of this material is permissible for purposes of individual study or research.