Published in the Slovak Republic
European Journal of Medicine
Has been issued since 2013.
E-ISSN: 2310-3434
2019, 7(1): 30-34

DOI: 10.13187/ejm.2019.1.30
www.ejournal5.com

Drug Interactions of Acetaminophen (Paracetamol) involving CYP and UGT Enzymes

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Abstract

Acetaminophen (Paracetamol) is the most frequently used Over-The-Counter (OTC) antipyretic and analgesic drug, worldwide. The metabolism of Acetaminophen is mediated by phase II reactions (UDP-glucuronosyl transferases (UGT)-mediated glucuronidation and sulfation) and phase I oxidative reactions mediated by Cytochrome P450 (CYP) enzymes including CYP2E1 and CYP1A2. The drugs inducing CYP2E1 and CYP1A2 enzymes and the drugs inhibiting UDP-glucuronosyl transferases (UGTs) may increase the exposure of NAPQI resulting in elevated risk of hepatotoxicity. The risk of acetaminophen-associated hepatotoxicity might be elevated due to concomitant use of certain medications including Isoniazid, Antiepileptic drugs, Tyrosine kinase inhibitors and Alcohol. Acetaminophen may increase the international normalized ratio (INR) by potentiating the anticoagulant effect of warfarin. To prevent possible adverse drug interactions, the prescribers and pharmacists must discuss with their patients about the use of OTC Acetaminophen.

Keywords: drug interactions, Acetaminophen, Paracetamol, CYP2E1, CYP1A2, UGT enzymes.

1. Introduction

Acetaminophen (Paracetamol) is an antipyretic and analgesic medication and it is the most frequently used Over-The-Counter (OTC) drug worldwide (Kontogiorgis et al., 2016). It is found in more than 200 OTC products used to treat pain, common cold and cough. The antipyretic effect of Acetaminophen occurs through the selective inhibition of cyclooxygenase (COXs) pathway in the brain as Acetaminophen crosses the blood brain barrier easily. Moreover, it has been proposed that Acetaminophen modulates endogenous cannabinoid system to produce analgesic effect (Ghanem et al., 2016).

Acetaminophen is metabolised majorly (>90 %) by phase II reactions (UDP-glucuronosyl transferases (UGT)-mediated glucuronidation and sulfation) to form non-toxic metabolites and a small fraction (5-10 %) is metabolised by Cytochrome P450 (CYP) enzymes including CYP2E1 and CYP1A2 to form toxic metabolite called N-acetyl-p-benzoquinoneimine (NAPQI) (Mazaleuskaya et al., 2015). The NAPQI formed by therapeutic doses of Acetaminophen, is detoxified by glutathione. However, intentional higher dose or non-intentional misuse may induce overdose or toxicity of paracetamol resulting in the formation of higher levels of NAPQI leading to hepatocellular injury (Caparrotta et al., 2017). The pediatric dose of 150 mg/kg of Acetaminophen could induce hepatic failure in children while a single dose of >7 gm of paracetamol needed to induce hepatocellular damage in adults (Hodgman et al., 2012).

Modification of effects of one drug (object drug) by the administration of another (precipitant) drug, supplement, tobacco smoke or alcohol is termed drug interaction (Maideen et

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al., 2018; Maideen, 2018) and the adverse drug interaction is defined as the drug interaction resulting in decreased therapeutic efficacy or increased rate of adverse effects (Pakkir Maideen NM, 2018). The risk of drug interactions is enhanced as the number of concurrent medications increases (Maideen et al., 2017). The addition of precipitant drugs alters the pharmacokinetic or pharmacodynamic profile of an object drug (Pakkir Maideen et al., 2018).

The drugs inducing CYP2E1 and CYP1A2 enzymes and the drugs inhibiting UDP-glucuronosyl transferases (UGTs) may increase the exposure of NAPQI resulting in elevated risk of hepatotoxicity.

2. Results

Isoniazid

Isoniazid (INH) is a first-line Antitubercular drug and it is an inducer of CYP2E1 enzyme (Hassan et al., 2018). Administration of Acetaminophen in patients taking INH resulted in enhanced risk of hepatotoxicity (Murphy et al., 1990; Moulding et al., 1991) which might be caused by CYP2E1-mediated metabolism of Acetaminophen leading to increased exposure to toxic acetaminophen metabolites (NAPQI). Caution is advised and administration of higher doses of Acetaminophen should be avoided in patients taking INH (Namdar et al., 2018).

Antiepileptic Drugs

The antiepileptic drugs such as Carbamazepine, phenytoin and phenobarbital induce many CYP enzymes (Zaccara et al., 2014). Acute liver failure occurred in a patient taking carbamazepine and Acetaminophen concomitantly and it is recommended to monitor the signs and symptoms of liver failure when chronic use of both drugs is necessary (Jickling et al., 2009).

Phenytoin and phenobarbital may also increase the risk of acetaminophen-associated hepatotoxicity through the inhibition of glucuronidation of acetaminophen via Uridin-glucuronyl transferases (UGTs) inhibition (Kostrubsky et al., 2015). The patients taking antiepileptic drugs such as carbamazepine, phenytoin or phenobarbital along with acetaminophen are advised to monitor for the signs and symptoms of hepatotoxicity.

Alcohol

Alcohol is a substrate of CYP2E1 enzyme (Cederbaum, 2012) and the chronic ingestion of alcohol increase the synthesis and activity of CYP2E1 enzyme along with decreased glutathione stores. Hence, the risk of acetaminophen-associated hepatotoxicity is enhanced in chronic alcoholics due to increased formation of NAPQI and decreased glutathjione levels (Yoon et al., 2016). The chronic alcoholics should be advised to consider dose reduction of acetaminophen from 4gm/day to 2gm/day (Lourenco, 2017).

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (TKIs) are anticancer agents useful to treat various malignancies and they include imatinib, gefitinib, erlotinib, sorafenib, sunitinib, and dasatinib (Hartmann et al., 2009). The TKIs such as imatinib, sorafenib and dasatinib may increase the risk of paracetamol hepatotoxicity through the inhibition of UGT (UGT1A9, UGT2B15 and UGT1A1)-mediated glucuronidation of Acetaminophen (Liu et al., 2011). Monitoring of liver function tests is advised in patients taking imatinib for longer period especially with concomitant use of Acetaminophen (Ridruejo et al., 2007).

Warfarin

Warfarin is an oral anticoagulant used effectively to prevent thromboembolic events in patients with atrial fibrillation, venous thromboembolism, and other conditions (Holbrook et al., 2005). Warfarin prevents the synthesis of hepatic synthesis of coagulation factors II, VII, IX, and X through the inhibition of vitamin K epoxide reductase (VKOR) which is responsible for the activation of vitamin K (Wu et al., 2018).

Concomitant use of warfarin and Acetaminophen may result in increased international normalized ratio (INR) (Olsen et al., 2018). It has been hypothesized that Acetaminophen may potentiate anticoagulant effect of warfarin by interfering the enzymes responsible for the synthesis of vitamin K-dependent coagulation factors (Mahé et al., 2006). The vitamin K cycle might be disrupted by the toxic metabolite of Acetaminophen (NAPQI) through the oxidation of vitamin K-hydroquinone, inhibition of vitamin K-dependent carboxylation and blockade of vitamin K-epoxide reductase (VKOR) activity (Lopes et al., 2011).

Monitoring of INR is recommended in patients taking warfarin and higher dose of Acetaminophen concomitantly for more than three consecutive days (Ornetti et al., 2005). Acetaminophen is the drug of choice as an analgesic in patients taking oral anticoagulants such as warfarin, acenocoumarol or phenprocoumon. Clinically relevant interaction may occur in patients taking more than 2gm/day of paracetamol with oral anticoagulants and monitoring of INR is recommended (Gschwind et al., 2013; Caldeira et al., 2015).

Food

Orally administered Acetaminophen is absorbed by passive diffusion into the bloodstream and hence the rate of gastric emptying determines the absorption of acetaminophen (Raffa et al., 2014). The rate of absorption of Acetaminophen might be decreased by the presence of food (DIVOLL et al., 1982; Bushra et al., 2011). It is recommended to administer oral Acetaminophen one hour before or two hours after food, to avoid such interaction (Ismail et al., 2009).

3. Conclusion

The drugs inducing CYP enzymes such as Isoniazid and antiepileptic drugs (Carbamazepine, Phenytoin and Phenobarbital) and the drugs inhibiting UDP-glucuronosyl transferases (UGTs) including Tyrosine kinase inhibitors (TKIs) (Imatinib, Sorafenib and Dasatinib) and antiepileptic drugs (Phenytoin and Phenobarbital) may increase the exposure of NAPQI resulting in elevated risk of hepatotoxicity. Acetaminophen may increase the international normalized ratio (INR) by potentiating the anticoagulant effect of warfarin. The rate of absorption of Acetaminophen might be decreased by the presence of food. To prevent possible adverse drug interactions, the prescribers and pharmacists must discuss with their patients about the use of OTC Acetaminophen.

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