Topic 6. PHARMACOGENETICS OF ANTIEPILEPTIC AGENTS AND ANALGESICS

DRUGS USED FOR FOCAL (PARTIAL ONSET) SEIZURES

Carbamazepine is a prototype of the antiseizure drugs primarily used in the treatment of focal onset seizures. In addition to being effective in the treatment of focal seizures, carbamazepine is indicated for the treatment of tonic-clonic (grand mal) seizures. The most popular drugs for the treatment of focal seizures are carbamazepine, lamotrigine, phenytoin, and lacosamide; levetiracetam is also commonly used. It was initially marketed for the treatment of trigeminal neuralgia, for which it is highly effective; it is usually the drug of first choice for this condition. In addition, carbamazepine is a mood stabilizer used to treat bipolar disorder. The structure of carbamazepine is similar to that of tricyclic antidepressants such as imipramine, but unlike the tricyclic antidepressants, carbamazepine does not inhibit monoamine (serotonin and norepinephrine) transporters with high affinity; therefore, carbamazepine is not used as an antidepressant despite its ability to treat bipolar disorder.

Carbamazepine is a prototypical sodium channel-blocking antiseizure. Peak levels are usually achieved 6–8 hours after administration. Typically, the half-life of 36 hours observed in subjects after an initial single dose decreases to as little as 8–12 hours in subjects receiving continuous therapy. Considerable dosage adjustments are thus to be expected during the first weeks of therapy. This reaction is primarily catalyzed by CYP3A4. Carbamazepine stimulates the transcriptional up-regulation of CYP3A4 and CYP2B6. This autoinduction leads not only to a reduction in steady-state carbamazepine concentrations but also to an increased rate of metabolism of concomitant antiseizure drugs including phenytoin, ethosuximide, valproic acid, and clonazepam. Some antiseizure drugs such as valproic acid may inhibit carbamazepine clearance and increase steady-state carbamazepine blood levels. Other antiseizure drugs, notably phenytoin and phenobarbital, may decrease steady-state concentrations of carbamazepine through enzyme induction. These interactions may require dosing changes.

Adverse Effects. Carbamazepine may cause dose-dependent mild gastrointestinal discomfort, neurological disorders (dizziness, blurred vision, diplopia, or ataxia), leukopenia. The variant allele *HLA-B*15:02* is strongly associated with greater risk of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) in patients treated with carbamazepine or oxcarbazepine. According to Pharm KGB and FDA carbamazepine application need preliminary screening of patients with ancestry in genetically at-risk populations (patients of Asian descent) for the presence of the *HLA-B*1502* allele should be carried out prior to treatment due to a high risk of serious and something fatal dermatologic reactions. It also notes that a moderate association has been found between *HLA-A*3101* and the risk of developing hypersensitivity reactions to carbamazepine, though it does not mention testing for this allele.

Phenytoin, first identified to have antiseizure activity in 1938, is the oldest nonsedating drug used in the treatment of epilepsy. It is prescribed for the prevention of focal seizures and generalized tonic-clonic seizures and for the acute treatment of status epilepticus. Phenytoin is a sodium channel-blocking antiseizure drug that acts in a similar fashion to carbamazepine and other agents in the class.

Phenytoin is extensively (~90%) bound to serum albumin and is prone to displacement in response to a variety of factors (eg, hyperbilirubinemia, hypoalbuminemia, or drugs such as warfarin or valproic acid), which can lead to toxicity due to raising of free phenytoin level in

plasma. Phenytoin is metabolized by CYP2C9 and CYP2C19 to inactive metabolites that are excreted in the urine. The elimination of phenytoin depends on the dose. At low blood levels, phenytoin metabolism follows first-order kinetics. However, as blood levels rise within the therapeutic range, the maximum capacity of the liver to metabolize the drug is approached (saturation kinetics).

Half-life – 4 hrs (first order kinetics, unsaturation kinetics)

Initial concentration – 200 mg/kg

After 4 hrs – 100

After 8 hrs – 50

After 12 hrs – 25

Alcohol – during 1 hrs it is metabolized 10 gr (zero order kintecs, saturation kinetics)

Initial concentration 200 gr

After 1 hr – 190 gr

After 2 hrs – 180 gr

After 3 hrs – 170 gr

Early signs of phenytoin administration include nystagmus and loss of smooth extraocular pursuit movements. Diplopia and ataxia are the most common dose-related adverse effects requiring dosage adjustment; sedation usually occurs only at considerably higher levels. Gingival hyperplasia and hirsutism occur to some degree in most patients; the latter can be especially unpleasant in women. Long-term use is associated in some patients with coarsening of facial features and with mild peripheral neuropathy.

As previously stated, phenytoin is metabolized via the CYP2C9 enzyme. Due to the presence of the genotype of slow or intermediate metabolizers CYP2C9 genotype, a significant increase in the concentration of phenytoin appeared that can increase risk of adverse effects. That is why in case of *CYP2C9 * 3* allele presence, there is an increase in the risk of dermal complication that need to replace phenytoin with another drug. Also, in patients-carriers of *HLA-B*15:02* allele, there is an increased risk of Stevens-Jones syndrome (SJS) and toxic epidermal necrolysis (NET), so in such case it is possible to replace phenytoin with another drug, for example, ~~carbamazepine~~. The Consortium for the Implementation of Clinical Pharmacogenetics has proposed the Advanced Algorithm (CPIC).

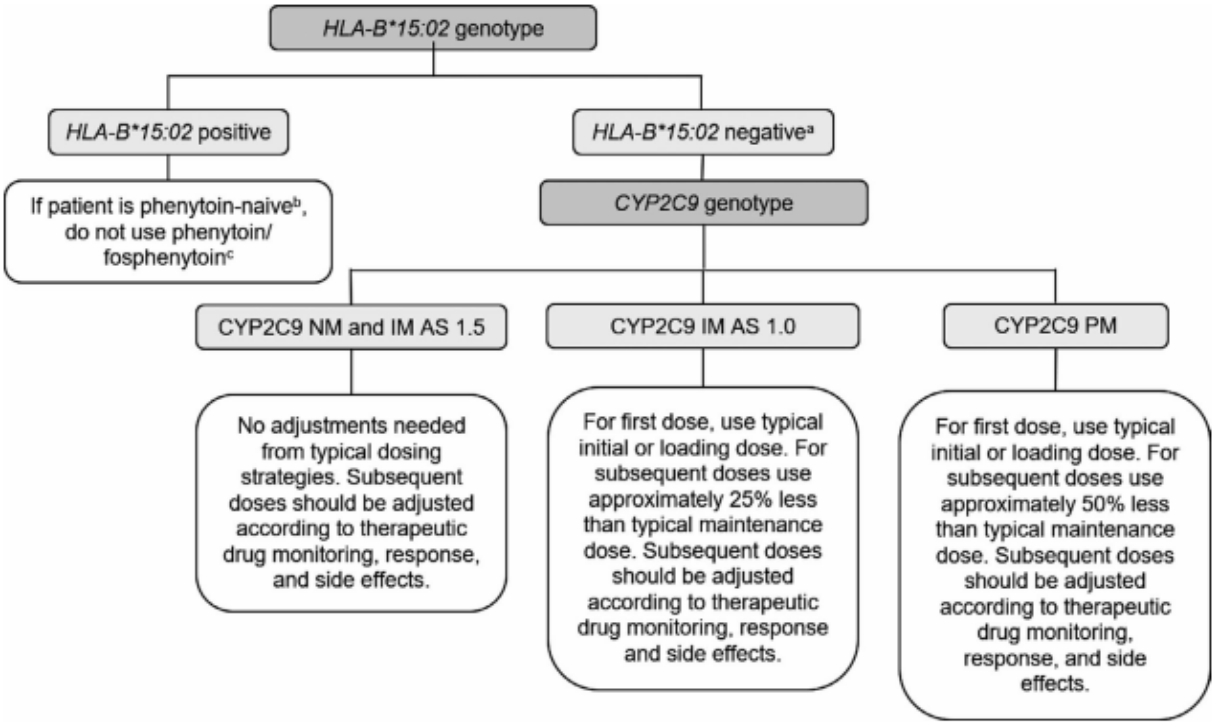


Fig. 1 Algorithm for therapy after detection of CYP2C9 and HLA-B * 15:02 genotype (guided by CPIC recommendations)

Narcotic (opioid) analgesics. Hepatic oxidative metabolism is the primary route of degradation of the phenylpiperidine opioids (fentanyl, meperidine, alfentanil, sufentanil) and eventually leaves only small quantities of the parent compound unchanged for excretion. However, accumulation of a demethylated metabolite of meperidine, normeperidine, may occur in patients with decreased renal function and in those receiving multiple high doses of the drug. In high concentrations, normeperidine may cause seizures. In contrast, no active metabolites of fentanyl have been reported. The P450 isozyme CYP3A4 metabolizes fentanyl by N-dealkylation in the liver. CYP3A4 is also present in the mucosa of the small intestine and contributes to the first-pass metabolism of fentanyl when it is taken orally.

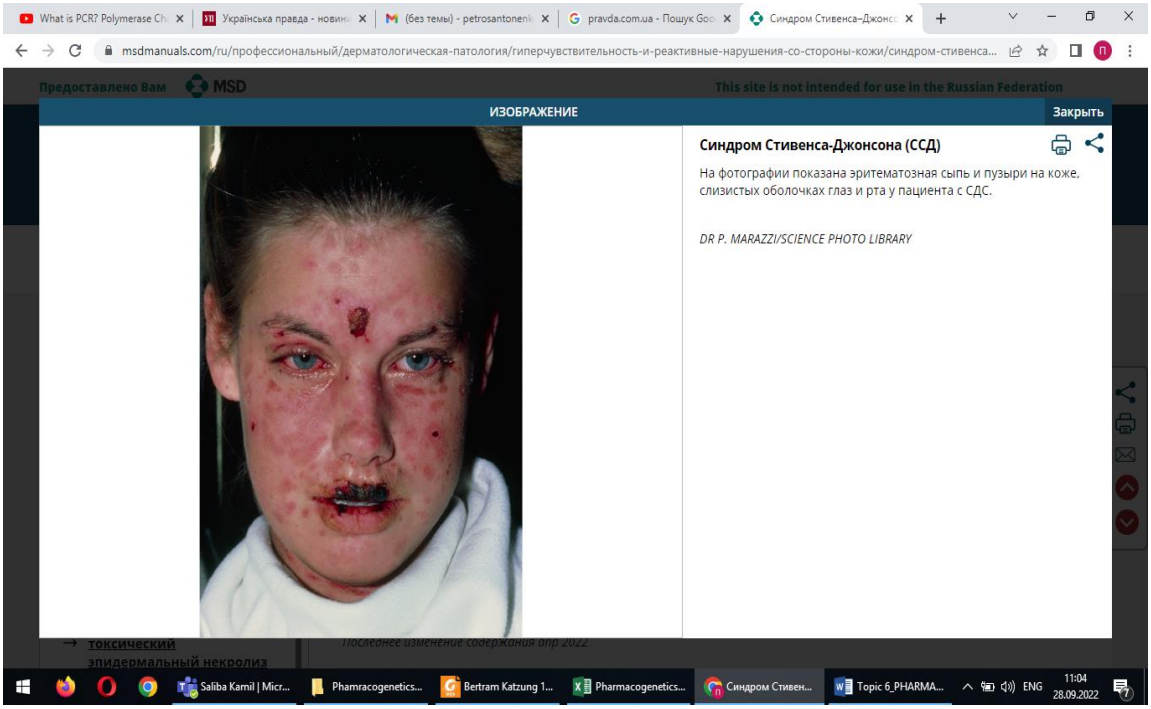
Codeine and related drugst undergo metabolism in the liver with the participation of the CYP2D6 enzyme, which leads to the formation of more active metabolites. For example, codeine is demethylated to form morphine, which is then conjugated; hydrocodone is metabolized to hydromorphone and, like morphine, is further conjugated with glucuronic acid. Genetic polymorphism of CYP2D6 is associated with differences in analgesic and adverse effects between patients when using codeine and tramadol. The conversion of codeine to morphine is important because codeine has a relatively low affinity for opioid receptors.

Therefore, in "slow metabolizers" during the use of codeine and tramadol, a significant weakening of the analgesic effect can be observed. On the contrary, in "ultra-rapid metabolizers" there can be a significant increase in the concentration of the active metabolite and increased toxicity of codeine, which can lead to respiratory depression and death. Therefore, codeine and tramadol are not used in children under 12 years of age in the United States. Methadone is metabolized by several CYP450 pathways, mainly CYP2B6. Although CYP450 genetic testing is not common, testing is gradually becoming cheaper and more accessible.

Non-steroidal anti-inflammatory drus (celecoxib, meloxicam, piroxicam, ibuprofen etc) are metabolized with participation of *CYP2C9*. In carriers of the "slow metabolizers" genotype or in the presence of the **3* allele, an increase in the concentration of drugs in the blood is observed. Therefore, for piroxicam, meloxicam and celecoxib, it is recommended to reduce the dose in "slow metabolizers" (up to 50% - for celecoxib). The question of replacing celecoxib in "slow metabolizers" in the treatment of juvenile rheumatoid arthritis is also being considered.

Diazepam, a well-known tranquilizer and anticonvulsant, is metabolized by the enzyme CYP2C19; in carriers of the "slow metabolizers" genotype, the concentration of the active substance in the blood may increase. The tetrahydrocannabinol derivative **dronabinol** is metabolized by the enzyme CYP2C9; in carriers of the *"slow"* or "*moderate metabolizers*" genotype, the concentration of the active substance in the blood may increase. The antiemetic metoclopramide is metabolized with the participation of the CYP2D6 enzyme; in carriers of the "slow metabolizers" genotype, the concentration of the active substance in the blood may increase, and its toxicity also increases.

In this case, it is suggested to reduce the dose of the drug. Proton pump inhibitors **(omeprazole, pantoprazole, rabeprazole)** are metabolized in the liver with the participation of the CYP2C19 enzyme. Carriers of the genotype "*slow*" and "*moderate metabolizers*" have an increase in the concentration of medicinal substances in the blood. In children with the genotype of "*slow metabolizers*", it is recommended to reduce the dose of pantoprazole.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