

Pharmacokinetics Small Group III

Date: Wednesday August 9th, 2017, 1:00-2:00pm

Learning Objectives

1. Discuss the factors to take into account when co-administering two drugs simultaneously.
2. Identify potential cases of drug-drug interactions based upon drug-specific pharmacokinetic and pharmacodynamics properties
3. Interpret the effects of genetic polymorphisms and drug-drug interactions on patient-specific pharmacokinetic parameters
4. Demonstrate the ability to communicate and work effectively with peers in a small group setting

Question 1

A 79-year old man with long-standing anxious depression was undertaking a trial of mirtazapine, an atypical antidepressant, at a dose of 30 mg/day. He was also taking nifedipine to treat his hypertension, which appeared to be well controlled. However, the patient was not able to tolerate the sedative side effects of the mirtazapine. Consequently, his psychiatrist decided to discontinue this drug and instead begin a trial of fluoxetine that was gradually titrated upwards until a dosage of 20 mg/day was achieved. Approximately 3 weeks after replacing the mirtazapine with fluoxetine, the patient was attempting to get out of bed and experienced a syncopal (fainting) episode. The patient's son called an ambulance and when the paramedics arrived and took the man's supine blood pressure it was 80/50 mm Hg (normal is 120/80 mm Hg).

Please describe how drug-drug interactions may have contributed to the patient's syncopal episode and low blood pressure.

Answer:

Important concept: Effect of a CYP450 inhibitor added to a substrate

- *Nifedipine is a 3A4 substrate*
- *Fluoxetine is an inhibitor of 3A4*
- *Mirtazapine is a 3A4 substrate*

- *Initially the patient's hypertension is adequately controlled with nifedipine without any side effects.*

- *Increasing the titration of fluoxetine to a final dose of 20 mg/day leads to inhibition of 3A4 activity and a decrease in the metabolism of nifedipine leading to an increase in the nifedipine serum concentration*
- *Increased serum concentrations of nifedipine result in increased pharmacological activity resulting in an exaggerated activity of nifedipine activity (Calcium channel blocker) causing the patient's blood pressure to significantly fall, and the corresponding syncopal episodes*
- *Although mirtazapine, like nifedipine, is a 3A4 substrate it apparently did not have a significant effect on the metabolism of nifedipine, as the patient did not report any problems with his blood pressure control.*
- *It is possible that the initial co-administration of nifedipine (3A4 substrate) and mirtazapine (3A4 substrate) may have resulted in competitive inhibition of mirtazapine metabolism, thereby explaining the initial intolerance to the sedative effects to the antidepressant.*

Question 2.

A 22-year old woman has been diagnosed with both bipolar I disorder and panic disorder. Her symptoms have been well controlled on a regimen of carbamazepine (800mg/day), a mood stabilizer, and alprazolam (4mg/day), a benzodiazepine drug with mild sedative properties. During one of her routine follow up visits, complete blood counts revealed an ongoing leukopenia, a rare but dangerous side effect associated with carbamazepine. As a result, the carbamazepine was immediately discontinued and she began a trial of lithium. Initial titration of lithium to a dosage of 900 mg/day was uneventful, and this dosage was well tolerated. However, three weeks later the patient experienced marked sedation, which interfered with her ability to do her job. Her psychiatrist reduced the alprazolam dosage to 1.5 mg/day, which continued to effectively prevent panic attacks and which she tolerated without sedation.

Please describe how drug-drug interactions contributed to excessive sedative side effects experienced by the patient?

Answer

Important concept: Effect of reversal of CYP450 induction

- *Alprazolam is a 3A4 substrate*
- *Carbamazepine is a potent 3A4 inducer.*
- *When carbamazepine and alprazolam were initially co-administered, the alprazolam would have been titrated until a stable clinical effect was observed*

at a dosage that took into account a stable degree of 3A4 induction caused by carbamazepine. Because of the 3A4 induction this dose of alprazolam would likely be greater than the normal dose of the drug typically used.

- *When carbamazepine was discontinued, there was a reversal of 3A4 induction, which resulted in a decrease in the level of 3A4 expression and a corresponding decrease in the level of alprazolam metabolism. As a result, the levels of active alprazolam increased leading to the alprazolam side effect of increased sedation.*
- *In the absence of the carbamazepine the psychiatrist was able to reduce the dose of alprazolam to 1.5 mg day, which was sufficient to control the patient's symptoms, without inducing side effects*

Question 3

A 25-year old man with bipolar I disorder had recently been discharged after a 4-week stay at an in patient facility, where his acute mania episode had been successfully treated with olanzapine, a second generation antipsychotic drug, at a dosage of 20 mg/day. Prior to his admittance into the facility the patient had been a habitual 2-pack a day smoker. However, the facility had a strict no smoking policy. Following his discharge he immediately resumed his smoking habit. Within 3-weeks the patient was readmitted following another acute manic episode. A trial of quetiapine was tried and the patient again improved and was discharged, but this time remained stable for a sustained period.

A. Please provide an explanation for why the patient's initial treatment with olanzapine failed following discharge, whereas the quetiapine was more successful at controlling his symptoms

Answer:

Important concept: Effect of a CYP450 inducer added to a substrate

- *Olanzapine is a 1A2 substrate*
- *Cigarette smoking is a significant inducer of 1A2*
- *Quetiapine is not a 1A2 substrate, but is a substrate of 3A4*
- *When the patient resumed smoking following discharge, the expression of 1A2 was induced resulting in an increase in the metabolism of olanzapine. In fact, smoking is known to reduce the concentration of olanzapine by as much as 40%.*
- *The increase in olanzapine metabolism and reduction in olanzapine serum levels is responsible for the failure of the olanzapine to control the patient's manic episodes following discharge.*

- *In contrast, quetiapine is not a substrate of 1A2 and hence its metabolism will be unaffected by smoking.*

B. St. John's wort is a herbal medication that is routinely used to treat depressive symptoms. What would be the likely effect for the patient if he were to now begin taking this medication?

Answer:

Important concept: St. John's wort is an inducer of CYP3A4

- *Quetiapine is not a 1A2 substrate, but is a substrate of 3A4*
- *St. John's wort is a potent inducer of 3A4*

- *If the patient were to now begin taking St. John's wort, the likely outcome would be clinical failure of the quetiapine due to 3A4 induction and increased metabolism of the quetiapine, resulting in an increased likelihood of the patient developing another manic episode*

Question 4.

A 58-year old female with type 2-diabetes is being treated with the glimepiride, sulfonylurea class of drugs that works by stimulating the pancreas to produce insulin. Her hyperglycemic symptoms have been adequately controlled on the same dose of glimepiride for the last 10 months and she has not experienced any significant side effects. Due to recent back pain the patient begins taking aspirin at 600 mg/day. Shortly after beginning the aspirin the patient experiences heart palpitations, shakiness, sweating, anxiety and an intense desire for food, all symptoms of hypoglycemia. Her blood glucose level registers 52 mg/dL (normal range 80-100 mg/dL). After consuming some orange juice and crackers her symptoms resolve. She discontinues the aspirin and does not experience any further problems.

What are the underlying mechanisms that explain the occurrence of this patient's hypoglycemic symptoms?

Answer:

Important concept: Drug displacement from serum proteins increases the concentration of unbound active drug

Both aspirin and glimepride are highly protein bound drugs, therefore addition of a high dose of aspirin can displace glimepiride from serum albumin, increasing the availability of the free unbound glimepiride that in turn can induce increased levels of insulin production resulting in the hypoglycemic reaction (i.e. overproduction of insulin).

A second mechanism of interaction comes from the fact that aspirin and the salicylates can positively modify the efficiency of the insulin-signaling pathway, thereby synergizing with insulin-inducing drugs such as the sulfonylureas to enhance the

*insulin response (i.e. enhanced glucose uptake leading to the risk of hypoglycemia). In this case, aspirin has been shown to inhibit the activity of the I κ B - **Note- the students will likely not be aware of this mechanism as they have not yet had lectures on aspirin and the salicylates***

While glimepiride is metabolized by 2C9, Aspirin is primarily metabolized by Phase II conjugation reactions, although 2C9 may also play a role. Hence, it is additionally possible that there could be competition between the two drugs that could lead to an effect on glimepiride levels.

Question 5.

A 27-year old man with chronic paranoid schizophrenia was being stably maintained on the second generation antipsychotic, olanzapine, at a dose of 25 mg/day. He developed some consistent heart burn and visited his primary care physician who diagnosed acid reflux disease and prescribed the histamine H₂ receptor antagonist, cimetidine, at 300 mg four times a day. After 5 days, the patient experienced increased sedation and constipation. When his psychiatrist was consulted, he decreased the dosage of olanzapine to 15 mg/day, which promptly led to a remission of the patient's symptoms. The patient was successfully maintained on 15 mg/day of olanzapine together with 300 mg of cimetidine four times daily for the following two years. However, due to a worsening of his GI symptoms the patient's primary care physician decided to discontinue the cimetidine and begin omeprazole at 20 mg/day. Within 3 weeks the patient begins to experience auditory hallucinations and paranoid delusions, which worsened until the patient required hospitalization. The patient was treated with an escalating titration of olanzapine that was effective at treating his psychosis at a dosage of 40 mg/day.

- A. Why did the patient likely experience sedation and constipation following the initial prescription of cimetidine?
- B. Why did the patient's symptoms resolve when his olanzapine dosage was reduced to 15 mg/day?
- C. Why did the patient experience a relapse and development of psychotic symptoms when the cimetidine was discontinued and the omeprazole was added?
- D. Why did the patient require a higher dose of olanzapine (40 mg/day) to finally control his psychosis?

Answer:

Important concept: Effect of a CYP450 inhibitor added to a substrate followed by reversal of inhibition and addition of an inducer to a substrate

- *Olanzapine is a 1A2 substrate (also metabolized by 2D6)*
- *Cimetidine is a strong inhibitor of 1A2, 2D6 and 3A4*
- *Omeprazole is an inducer of 1A2*

- *Cimetidine is a potent inhibitor of 1A2, 2D6 and 3A4- when it was added to the olanzapine it would have inhibited the metabolism of olanzapine, resulting in an increase in the serum concentration of the drug and a corresponding increase in olanzapine-induced adverse effects i.e. sedation and constipation.*

- *The reduction of the olanzapine dosage to 15 mg/day takes into account the effects of cimetidine. At this level, the antipsychotic efficacy is maintained and the dose is low enough to avoid side effects*

- *When cimetidine was discontinued 1A2, 2D6 and 3A4 became disinhibited and regained their full metabolic activity.*

- *Consequently, 1A2 was more efficient at metabolizing the olanzapine, resulting in a significant decrease in the blood levels of olanzapine, which led to a decrease in efficacy of the drug and contributed towards the patient's relapse*

- *Omeprazole is an inducer of 1A2, which results in increased expression of 1A2 and enhanced 1A2-mediated metabolism. This contributes to further increased metabolism of olanzapine and a corresponding further decrease in the blood concentration of olanzapine, again contributing towards the patient's relapse and development of psychotic symptoms. Note: Although Omeprazole is also listed as a 1A2 inhibitor, it is a weak inhibitor, hence this effect is minimal compared to its ability to induce expression of the enzyme.*

- *Since omeprazole is an inducer of 1A2, there is more 1A2 available to metabolize olanzapine, meaning that more olanzapine is converted to its inactive metabolites. Consequently, a higher dosage of olanzapine is required to overcome the higher levels of 1A2 in order to achieve a serum concentration that is sufficient to effectively treat the patient's psychosis.*

Question 5.

Omeprazole is a proton pump inhibitor that is metabolized by CYP2C19 (major, 90%) and CYP3A4 (minor, 10%) to inactive metabolites that are further metabolized before phase II conjugation and subsequent excretion. The graphs below represent the serum concentration of omeprazole detected following administration of a 20 mg dose to a normal individual.

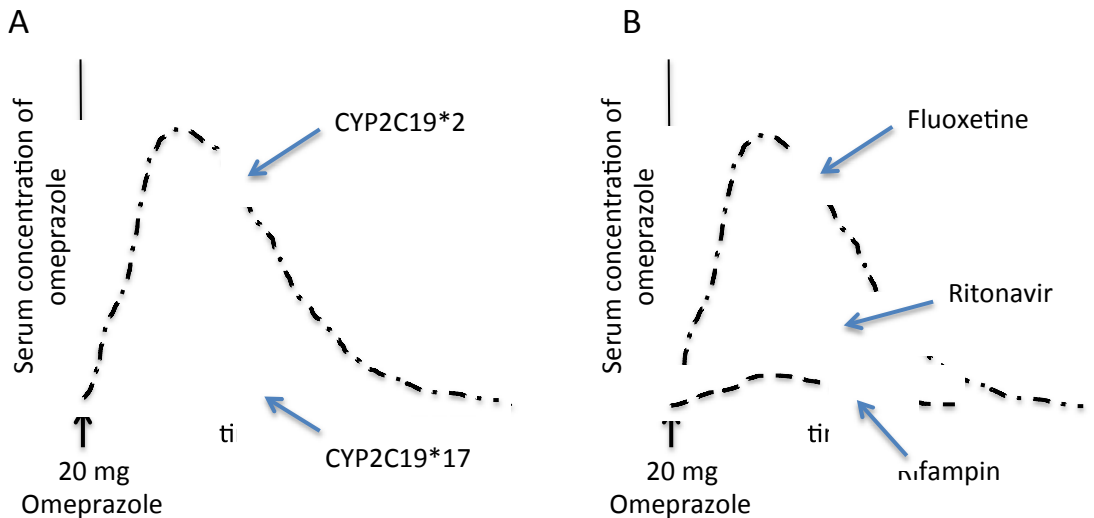
The CYP2C19 gene is polymorphic: CYP2C19*1 is the normal wild type allele; CYP2C19*2 is a non functional allele; and CYP2C19*17 is an allele that is expressed at higher levels than the wild type.

On **graph A** draw and label the curves that you would expect to obtain if 20 mg of omeprazole was administered to:

- (i) an individual homozygous for the CYP2C19*2 allele
- (ii) an individual homozygous for the CYP2C19*17 allele

On **graph B** draw and label the curves that you would expect to obtain if 20 mg of omeprazole was co-administered together with:

- (i) Fluoxetine
- (ii) Ritonavir
- (iii) Rifampin



A(i) The CYP2C19*2 allele is non functional- hence individuals who are homozygous for this allele will be unable to metabolize omeprazole by CYP2C19- this will result in an increase in the AUC of omeprazole relative to normal 2C19 metabolizers

A(ii) The CYP2C19*17 allele is expressed at a higher level than wild type and therefore displays enhanced 2C19 enzyme activity. As a result, these individuals are ultra rapid metabolizers and will efficiently metabolize omeprazole leading to a decrease in the AUC of the parental drug.

B (i) Fluoxetine is a potent inhibitor of 2C19, hence it will block 2C19-mediated metabolism of omeprazole leading to a significant increase in the serum concentration of the drug. Although the drug can still be metabolized by 3A4, this is a minor pathway and will not have significant effect.

B (ii) Ritonavir is a potent inhibitor of 3A4. However, because 3A4 only makes a minor contribution to omeprazole metabolism, the effects of ritonavir will be relatively minor and may only slightly (or not at all) increase the AUC.

B(iii) Rifampin is an inducer of multiple CYP450s including 2C19. Induction of 2C19 will lead to an increase in the expression of 2C19 and a corresponding increase in the metabolism of omeprazole resulting in a significant decrease in the AUC.