THE EFFECTS OF FORGOTTEN DRUG INTERACTIONS

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AT DALLAS

Interests: Management of the Difficult Patient. Computerized medical education, psychosocial interviewing, evaluation and feedback of resident performance, mass casualty evaluation and triage, Persian Gulf illnesses. Dermatological manifestations of systemic disease.

This is to acknowledge that Robert Goldsteen, D.O. has not disclosed financial or other relationships with commercial concerns related directly or indirectly to this program.

Dr. Goldsteen will not be discussing off-label uses in his presentation.

Effects of acetaminophen on hemorrhagic risks.

Background-

It has been long known that aspirin and NSAIDS increased bleeding risks by inhibition of platelet function (COX-1). Additionally, cyclo-oxygenase (COX-2 inhibitors) selectively inhibits COX-2 while allowing COX-1 to remain intact. COX-2 plays a very important role in inflammation. Cox-2 is involved in converting arachidonic acid to prostaglandins for an inflammatory response. There is continual stimulation of COX-1 as compared to COX-2 which only is stimulated by the immune response.[1] COX2 inhibitors have been shown to have a modest, less than 10% increase in INR.[2] COX-1 inhibitors (NSAIDS) have an effect on clotting by inhibiting Thromboxane A_2.

Acetaminophen and bleeding-

Less clinical studies have been performed on the effects of acetaminophen on bleeding. There are no large scale trials that assess the risk of bleeding for acetaminophen. Multiple small scale studies have been completed, the largest of which was conducted by Hylek et al. [3] Hylek completed a perspective cohort study looking at the comparison of 93 case patients' versus 196 controlled patients with similar characteristics. 52 cases (56%) and 70 control cases (36%) reported taking acetaminophen in the week leading up to the study. They found a dose dependent relationship to the effect on INR that was stratified based on quantity of acetaminophen.[2] [4]For patients taking four, 325 mg acetaminophen per day for greater than 1 week the odds of having an INR (on warfarin) were increased by tenfold (95% CI-2.6, 37.9). For acetaminophen intake level between 2275 mg and 4549 mg (greater than 7 tablets per week), the adjusted odds ratio was 3.5(95% CI-1.2, 10). For greater than 4550mg of acetaminophen to 9099 mg acetaminophen per week the adjusted relative odds ratio was 6.9 (95% CI-2.2, 21.9).[3]

In conclusion, there was a statistically significant increase in the risk of bleeding associated with the higher doses of acetaminophen (higher INR). Several similar small trials of this nature show similar results. More additional high quality studies are needed to definitively show these effects. Unfortunately, over-the-counter medication studies often lack pharmaceutical monetary support to investigate this finding further. Also, warfarin is generic and is prone to the same lack of interest.

Laboratory studies have demonstrated the mechanism of the acetaminophen effecting blood clotting. The exact mechanism has been suggested, but not proven. Findings include decrease functional factor VII in patients on warfarin and acetaminophen. Also, acetaminophen has been correlated with decreased Factor IX levels, thus interfering with vitamin K function.[5] Also; both warfarin and acetaminophen are metabolized by cytochrome P450. Studies of enzymatic degradation using P450, CYP1A2 and CYP3A4 have shown both competitive and non-competitive inhibition of both these enzymes[6]. It has been recognized that acetaminophen is a significant inhibitor of CYP3A4. Additionally, there are genetic differences affecting warfarin metabolism as well as the effects of CYP enzyme with aging.

Thijssen et al. [7] evaluated the vitamin K cycle with regard to the use of acetaminophen and warfarin. In an in vitro study, the authors noted that NAPQI, the metabolite of acetaminophen, is capable of irreversibly inactivating the key enzyme gamma decarboxylase thereby decreasing the coagulation proteins with the shortest half life, namely factor VII. This could result in an increase in INR.[8]

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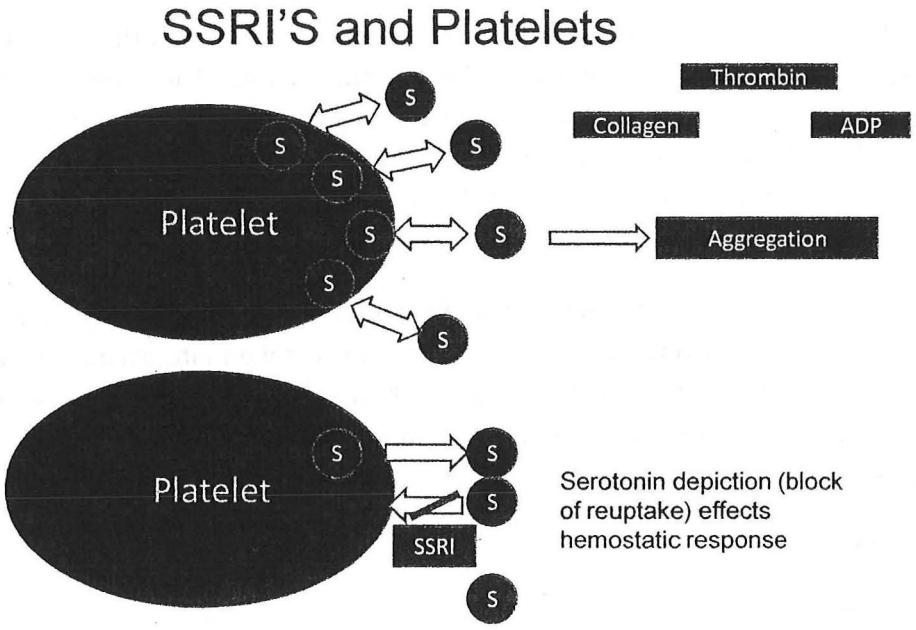
Selective serotonin reuptake inhibitors on bleeding risks.

Several clinical reports over the last 15 years has reported increased incidence of bleeding disorders such as purpura, ecchymosis, epistaxis, and gastrointestinal bleeding associated with use of serotonin reuptake inhibitors (SSRIs). A recent 2003 population based cohort study of 26,005 antidepressant users in Denmark found that upper gastrointestinal bleeding was 3 times more prevalent than expected. (95% confidence interval, 2.7-4.7). [9] This also corresponded to a difference of 3.1 episodes per 1000 treatment years. When SSRIs were combined with nonsteroidal anti-inflammatory agents (NSAIDS) or low-dose aspirin, the risk increases to 12.2 (95% confidence interval, 7.1 to 19.5) and 5.2 (95% confidence interval 3.2 to 8.0), respectively. A second study by Francisco Jose DeAbajo. Et al.[10] was a retrospective population case control study in the United Kingdom. The study looked at 1651 cases of upper gastrointestinal bleeding between April 1993 and September 1997. An SSRI was indentified in 3.1 percent of patients (52 out of 1651) with upper gastrointestinal bleeding compared to 1% of control patients. This gave an adjusted risk ratio of 3.0 (95% confidence interval 2.1 to 4.4).

It has been postulated that selective serotonin reuptake inhibitors increase risks of bleeding through a serotonin mechanism. The release of serotonin from platelets is a critical step in the platelet aggregation process. It has been hypothesized that the depletion of serotonin from the platelets would impair the "hemostatic response" to vascular injury.[11]



Effects of statins on reduced platelet activity.

In a trial by Bruni, et al., Investigators looked at effects on platelet aggregation using atorvastatin, simvastatin and pravastatin, their observation was that oxidized LDL cholesterol is a potent platelet agonist, promoting platelet aggregation. These oxidized LDL receptors are present in platelets. They found that these statin agents decreased the oxidized LDL by 9 days, decreasing platelet aggregation. Therefore, it was concluded that there are direct effects of statins on platelet activity.[12]

There have been several additional studies that have looked at the incidence of thrombocytopenic purpura (TTP) in statin in patients. Several case reports have been published noting theTTP side effect. Now TTP is listed in most statin drug monographs[13] Kearney et al. summarized some additional effects of HMG co A reductase inhibitors. Authors noted a reduction in the generation of thrombin with statins. This reduction was thought to be from the antiplatelet effects through direct inhibition of Thromboxane A_2. It has also been investigated that the decrease in cholesterol content of platelet membranes also contributes to reduced platelet activity.[14] In an in vivo study Szapary et al. determined that atorvastatin affected a number hemorrhagic factors including Von Willebrand factor, whole blood viscosity, collagen induced platelet aggregation and relative cell transit time in clotting. [15]

Monitoring of methadone treatment, side effects

The QTc problem.

There has been an abundance of individual case reports of prolonged QTc in the ECG associated with methadone treatment that the CSAT (Substance Abuse and Mental Health Services Administration) assembled an expert panel to set forth recommendations for the monitoring of methadone. Methadone can prolong the QTc interval and result in arrhythmias such as torsade de pointes. Often the onset of torsade is multifactorial including contributions from drugs, electrolytes and other metabolic derangements. It has been found the risk of methadone induced arrhythmia is dose dependant.[16]

A careful history and physical examination should be obtained prior to initiation of methadone therapy. Consideration for structural heart disease, history of syncope, arrhythmia etc. should be taken into account before prescribing methadone therapy. Given the long half life of methadone (up to 190 hrs) [15] when torsade de pointes occurs, the patient may remain hemodynamically unstable for a prolonged period of time. The CSAT panel will publish their report in the January 6, 2009 Annals of Internal Medicine(future).

The CSAT Panel's preliminary recommendations include:

1. *Informing the patient of methadone arrhythmia risks.*
2. *Assessing for history of structural heart disease, syncope, or prior history of arrhythmia.*
3. *Perform a baseline EKG before starting therapy including the measurement of the QTc interval.*
4. *Repeating the ECG at 30 days after initiation of therapy, and then yearly.*

5. Watch for drugs that promote electrolyte disturbances and hypokalemia.

It was suggested that patient's are at significant risk with a QTc of 450 to 500 milliseconds. A discussion should be made as to whether or not they wish to taper or discontinue the methadone or be monitored more frequently. When QTc's are greater than 500 milliseconds, the panel recommends consideration of discontinuation of therapy.[17] In conclusion, careful monitoring must be maintained with this drug, and risks for arrhythmia are associated with increasing doses.

Methotrexate

A common side effect of methotrexate therapy is bone marrow suppression including leukopenia, thrombocytopenia, anemia, and liver function abnormalities. Further, liver derangements from methotrexate are not always seen by labs, although liver fibrosis can be present from doses greater from accumulative 1.5 grams cumulative lifetime dose.[18]

Other drug interactions with Methotrexate

With ongoing use of trimethoprim/ sulfamethoxazole for urinary tract infections, and more recently for oral treatment of MRSA (methicillin resistant staff aureus), it is easy to forget about the increased propensity for higher levels of Methotrexate. The trimethoprim has additive antifolate effect; increasing risk for bone marrow suppression. Sulfonamides can increase the level of methotrexate by displacing the active drug from plasma protein binding sites.[19] The result is a "double threat".

The combination of methotrexate with nonsteroidal anti-inflammatory agents (NSAIDS) represents a significant drug interaction. Both salicylates and non steroidal anti-inflammatory agents can displace methotrexate from their plasma binding proteins, mainly albumin. Since anti-inflammatories, salicylates, tetracyclines /cyclines etc. are all weak acids, similar to methotrexate. The methotrexate can easily be displaced from its protein binding sites. Furthermore, NSAID therapy can lower the rate of clearance of methotrexate. This results in an increase in methotrexate levels which can result in increased hematologic and gastrointestinal toxicity. Also, renal excretion of methotrexate occurs in addition to excretion from enterohepatic circulation coupled with liver elimination. Active tubule secretion occurs with methotrexate, particularly during the first phase of its elimination. [20]

Cytochrome P450 inhibitors

Another common source of drug interactions is combining medications that are eliminated by cytochrome P450's isoenzymes with those medications that inhibit P450. A classic example is the use of certain antibiotics along with statin agents as well as antidepressants, antiretrovirals, antifungals and grapefruit juice. (Table 2)

Chart 1 below shows how methotrexate, when co- administered with a drug that inhibits methotrexate metabolism increases the methotrexate level.

Chart 1: Action of inhibitors of Cytochrome P450

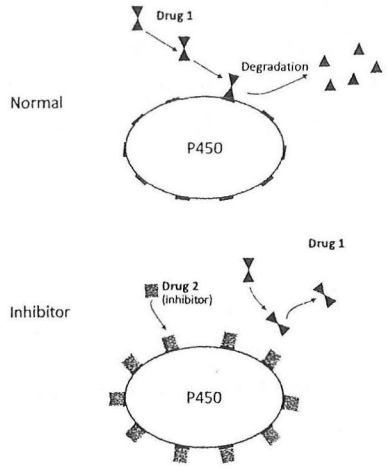


Table 1: Effect of Co-administered drug on Native drug concentrations

Statin Agent	Coadministered drug	% increase need of drug concentration
Rosuvastatin	Itraconazole	28 to 39%
Rosuvastatin	Gemfibrozil	Up to 120%
Rosuvastatin	Fluconazole	14%
Rosuvastatin	Fenofibrate	7 to 21%
Atorvastatin	Fosamprenavir/Ritonavir	153 to 184%
Atorvastatin	Digoxin	20%
Atorvastatin	Fenofibrate	17%
Atorvastatin	Itraconazole	150%
Atorvastatin	Rifampin	40 to 80%
Simvastatin	Diltiazem	360 to 480%

Source: Drugdex register,micromedex healthcare series

Cholelithiasis associated with fibrates

Several studies have looked at the cholesterol saturation index of bile in vitro. Four good studies were completed that demonstrated a statistically significant increase in lipid concentrations in the common bile duct. Epidemiologic studies also have shown increases in the incidence of cholelithiasis in patients treated with fibrates. Caroli-Bosc ,et al. revealed that the relative risk for cholelithiasis was 1.7 (P value was 0.04).[21] P values in other studies were also statistically significant.

One must also recall the risk for pancreatitis for patients presenting with upper abdominal pain. This is a known side effect of many statins. This consideration should remain in the differential diagnosis of the patient that presents with abdominal pain after initiation of therapy.[22]

Selective serotonin reuptake inhibitors (SSRI's) are a class of antidepressants that interact with tricyclic antidepressants. Tricyclic drugs such as amitriptyline, imipramine and doxepin all have significant serotonergic effects. Concomitant use of mainstream of SSRI's can increase the risks of serotonin syndrome, and decrease the clearance of the tricyclic agent. SSRI's such as paroxetine and fluoxetine are the most potent SSRI agents for inhibiting isoenzymes responsible for the metabolism of the tricyclic antidepressants, mainly CYP2D6 and or CYP3A4. In addition to anticholinergic side effects severe cases can result in seizures or even death. It is important to closely monitor patients who are on SSRI's plus tricyclics. Sertraline and citalopram are the least inhibiting SSRI's. [23]

Statin induced Rhabdomyolysis with Macrolide antibiotics

Case reports have been prevalent that note that the interaction between macrolide antibiotics and statin agents. Macrolides, mainly clarithromycin and erythromycin inhibit CYP 3A4 metabolism of the statin. Thus, the drug levels increase resulting in potential for rhabdomyolysis.[24] Underlying renal insufficiency can also exacerbate this effect as demonstrated in case reports.[25]

Table 2: P450 Inhibitors

P450 Inhibitors

	1A2	2C8	2C9	2D6
STRONG	Fluvoxamine Ciprofloxacin	Gemfibrozil	Fluconazole	Bupropion Fluoxetine Paroxetine quinidine
MODERATE		Trimethoprim	Amiodarone	Duloxetine Terbinafine

http://www.medicine.iupui.edu/Flockhart/table.htm

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