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Drug Interactions: The Most Common, the Worst, and What to Do About Them in Long-Term Care

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ABSTRACT

The medical community is aware of the issue of medication interactions and has made significant attempts to track them, but they have been unsuccessful so far in predicting and preventing drug interactions. Unfortunately, there was no foolproof way to anticipate medication interactions; instead, people had to wait for them to show up in the scientific literature. Known drug interactions may not occur in all patients taking the medicine or even another drug in the same class, adding more complexity and unpredictability to the already difficult process of prescribing medications. Most medication interactions are unpredictable and happen with chronic drug usage. This article focused on the effects, cause, treatment, and prevention of potentially lethal medication interactions that may arise in long-term care settings. The possibility for adverse events and the processes behind them are best understood in the context of long-term care medication combinations.

Keywords;Genser 2008

INTRODUCTION

Medications can help people live healthy for a prolonged period. Although medicines are prescribed often, it is important to know than ever about the medicines administered and should be used with caution (Genser 2008). Medications, both prescription and over-the-counter, are used every day to treat acute and chronic illness. Taking several different medicines due to polypharmacy or having more than one health condition carry the risk of adverse interactions, such as drug interactions (Paul et al., 2000). Whenever two or more drugs are taken concurrently there is a chance of an interaction among the drugs that could manifest as an increase or decrease in their effectiveness or an adverse reaction or a totally new side effect that is not seen with either drug alone that can be severe enough to alter the clinical outcome and warrant hospital admissions (Ansari 2010). The likelihood of these interactions is increased if certain drugs in combination used for longer period. There is less emphasis of physicians on drug interaction on long term care. This article addressed dangerous drug interactions on long term care for commonly used drug combinations.

WARFARIN – NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDs) (Chan 1995)

The most dangerous drug combinations in the nursing home population involve warfarin interactions with nonsteroidal anti- inflammatory drugs (NSAIDs).

Impact:

Potential for serious gastrointestinal bleeding and increased INR.

Mechanism of Interaction:

NSAIDs increase gastric irritation and erosion of the protective lining of the stomach causing gastrointestinal bleeding which is likely to be more severe if warfarin is also given. Additionally, NSAIDs decrease the cohesive properties of platelets and inhibits aggregation necessary in clot formation. Altogether leads to severe gastrointestinal bleeding.

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Prevention:

Avoid concomitant use of an NSAID with warfarin. Identify reason for NSAID therapy. If anti-pyretic effects are desired, then consider acetaminophen. Acetaminophen in doses less than 2g/day on a short-term basis does not appear to affect the INR. Long- term use of acetaminophen for anti-pyretic and analgesic effects is controversial. If anti-inflammatory effects are necessary, then consider cyclooxygenase-2 (COX-2) inhibitor therapy. These agents minimization of gastric irritation combined with the lack of anti- platelet action, support the cautious use of COX-2 inhibitors in anticoagulation patients. There are some case reports discussing the elevation of INRs with COX-2 inhibitors (Shaefer et al., 2003). If analgesic effects are desired, caution should also be exhibited with the use of tramadol; there are a few case reports describing an elevation of the INR with concomitant administration of tramadol with warfarin (Dumo et al., 2006).

Management:

Dosage reduction of 25-30% in warfarin followed by Prothrombin time and international normalized ratio (INR) should be monitored every week with co-administration of an NSAID. Signs and symptoms of an active bleed should be monitored with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffeegrinds (hemoptysis), gum bleeding, nose bleeds, cola- or tea-colored urine (hematuria), or black, tarry stools (hemoccult positive).

WARFARIN - SULFA DRUGS (Cook et al., 1994; Ahmed et al., 2008)

Impact:

Increased effects of warfarin, with potential for bleeding

Mechanism of Interaction:

Clinicians hypothesize that warfarin's activity is prolonged due to inhibition of warfarin metabolism and decreased production of vitamin K by intestinal flora affected by systemic antibiotic administration. Sulfa drugs also cause the displacement of warfarin from protein binding sites and increases free drug concentration and increases prothrmbin time (Wen et al., 2002).

Prevention:

Avoid concomitant use of a sulfa drug with warfarin, particularly sulfamethoxazole and trimethoprim. Consider use of any other antibiotic alternative to sulfa drugs with warfarin. If use of a sulfa drug is imperative, then reduce warfarin dose by 50% during antibiotic administration and for one week following completion of the antibiotic. If sulfamethoxazole-trimethoprim therapy is required, then monitor INR every other day for elevating trends.

Management:

Prothrombin time and INR should be monitored every week during co-administration of warfarin with a sulfa drug. Also monitor for vitamin K levels at regular intervals. Signs and symptoms of an active bleed should be monitored daily with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffee grinds (hemoptysis), gum bleeding, nose bleeds, hematuria, and black, tarry stools (hemoccult positive).

WARFARIN – MACROLIDES (Penti et al., 1992)

Impact:

Increased effects of warfarin, with potential for bleeding

Mechanism of Interaction:

Macrolides inhibits the metabolism and subsequent clearance of warfarin from the body. The activity of warfarin may also be prolonged due to alterations in the intestinal flora and its production of vitamin K for clotting factor production (Woldtvedt et al., 1998)

Prevention:

The interaction between warfarin and macrolide antibiotics is highly probable and often delayed. Concomitant use of a macrolide with warfarin should be avoided; switch to an alternative antibiotic. Microbial pathogen identification prior to antibiotic initiation will decrease the prevalence of unnecessary drug interaction risk. Consider culture sensitivity screening as research indicates cautious use of any antibiotic with warfarin.

Management:

If use of a macrolide is imperative, then monitor prothrombin time every other day and adjust warfarin dosing as necessary (Oberg 1998). Signs and symptoms of an active bleed should be monitored daily with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffee grinds (hemoptysis), gum bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemoccult positive)(WHO 2004).

WARFARIN- QUINOLONES (Carroll et al. 2008, Cade B Jones et al. 2002)

Impact:

Increased effects of warfarin, with potential for bleeding

Mechanism of interaction:

The exact mechanism for the warfarin-quinolone drug interaction is unknown. Reduction of intestinal flora responsible for vitamin K production by antibiotics is probable as well as decreased metabolism and clearance of warfarin. Displacement of warfarin from protein binding sites could be another possible reason for potentiation of warfarin effect (Carroll et., al. 2008)

Prevention:

Culture and identify microbial pathogen prior to initiation of antibiotic therapy. Consider culture sensitivity

screening. The metabolism of warfarin may be delayed in patients administered enoxacin, ciprofloxacin, norfloxacin, or ofloxacin; thus, quinolone selection should focus on one of the newer agents that has not demonstrated significant impairment of warfarin metabolism. Additionally, microbial pathogen identification and sensitivity prior to antibiotic initiation will decrease the prevalence of unnecessary drug interaction risk (Carroll et., al. 2008).

Management:

Prothrombin time and INR should be monitored during co-administration of warfarin with a quinolone. If use of ciprofloxacin is imperative, then monitor INR every other day and adjust warfarin dose as necessary. Signs and symptoms of an active bleed should be monitored daily with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffee grinds (hemoptysis), gum bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (hemoccult positive).

WARFARIN- PHENYTOIN (Panegyres and Rischbieth 1991)

Impact:

Increased effects of warfarin and/or phenytoin

Mechanism of Interaction:

Phenytoin may increase or decrease the anticoagulant effect of warfarin. A decrease in the effect has been attributed to increase in the metabolism of warfarin as phenytoin causes hepatic enzyme induction. Increase in the effect has been attributed to displacement of warfarin from plasma protein binding sites by phenytoin. In addition phenytoin itself can prolong prothrombin time (Levine and Sheppard 1984).

Prevention:

Obtain baseline phenytoin levels prior to initiation of warfarin. Monitor prothrmbin time and INR during coadministration.

Target INR should be towards the lower end of the therapeutic range.

Management:

Prothrombin time, INR , and phenytoin levels should be monitored during co-administration.Signs and symptoms of an active bleed should be monitored daily with particular attention to the appearance and patterns of bruises. Signs of an active bleed include: coughing up blood in the form of coffee grinds (hemoptysis), gum bleeding, nose bleeds, cola- or tea-colored urine (hematuria), and black, tarry stools (WHO 2004).

ACE INHIBITORS -POTASSIUM SUPPLEMENTS (Palmer et al., 2004)

Impact:

Elevated serum potassium

Mechanism of Interaction:

Inhibition of ACE results in decreased aldosterone production and potentially decreased potassium excretion.

Prevention:

Measure serum potassium level prior to initiation of ACE-inhibitor in a patient. Monitor potassium levels for 3 to 5 days after initiation of therapy and with each dose increment, followed by one week later.

Management:

Potassium levels greater than 5 should be monitored carefully due to risk of severe hyperkalemia and EKG changes. Watchrenal function (BUN, SCr) also. Adjust potassium supplementation if levels increase

ACE INHIBITORS – SPIRONOLACTONE (Bauersachs et al., 2000 ; Eike Wrenger et al., 2003)

Impact:

Elevated serum potassium levels

Mechanism of interaction:

Unknown, possibly an additive effect.

Prevention:

Evaluate need for additional drug therapy**.** Measure serum potassium level prior to initiation of spironolactone in a patient.

Monitor potassium levels for 3 to 5 days after initiation of therapy and with each dose increment, followed by one week later.

Management:

Potassium levels greater than 5 mmol/L should be monitored carefully due to risk of severe hyperkalemia and EKG changes. Watch renal function (BUN, SCr) also. Avoid potassium supplements in patients taking this combination of medications, unless the need is documented and the patient is monitored closely for hyperkalemia (Pitt et al., 1999).

DIGOXIN – AMIODARONE (Fenner et al., 2009)

Impact:

Digoxin toxicity

Mechanism of Interaction:

Multiple theories exist, but actual mechanism is unknown. Digoxin does not undergo any metabolism via the cytochrome P450 (CYP450) enzyme system but rather is a major substrate for the efflux pump known as multidrug resistance-associated protein (MDR) or more commonly called, P-glycoprotein (P-gp) (Cavet et al., 1996). Amiodarone is inhibitor of P-gp. Since digoxin is a major substrate for P-gp and amiodarone is a known inhibitor of P-gp, leads to decrease digoxin clearance, resulting in prolonged digoxin activity. There may also be an additive effect on the sinus node of the heart (Koonlawee et al., 1984).

Prevention:

Obtain digoxin level prior to initiation of amiodarone therapy. Then, Consider reducing digoxin dosing by 50% when givingit with amiodarone, and monitor digoxin levels once weekly for several weeks.

Management:

Maintain digoxin level between 1-2. Monitor for signs and symptoms of digoxin toxicity (abdominal pain, anorexia, bizarre mental symptoms in the elderly, blurred vision, bradycardia, confusion, delirium, depression, diarrhea, disorientation, drowsiness, fatigue, hallucinations, halos

around lights, reductionin visual acuity, mydriasis nausea, neuralgia, nightmares, personality changes, photophobia, restlessness,vertigo, vomiting, and weakness).

DIGOXIN – VERAPAMIL (Pedersen et al., 1981)
Impact:
Digoxin toxicity

Mechanism Of Interaction:

Synergistic effect of slowing impulse conduction and muscle contractility, leading to bradycardia and possible heart block. The mechanism of the digoxin-verapamil interaction consists of decreases in both renal and extrarenal clearance of digoxin by verapamil. Since the creatinine clearance does not change under the influence of verapamil, the decreased renal clearance of digoxin appears to be due to an inhibition of tubular secretion. The elevated plasma digoxin concentration induced by verapamil is associated with an inotropic effect as assessed by a measurement of systolic time intervals. When the serum digoxin levels are markedly elevated as a result of coadministration of verapamil, lethal cardiac toxicity may occur (Klein et al., 1982).

Prevention:

Monitor heart rate and EKG–PR interval. Evaluate selection of verapamil and digoxin. If patient has CHF, note that verapamil has no proven benefit in reducing mortality or morbidity; furthermore, digoxin offers no additional benefit in mortality, but does improve symptomatology (Zatuchni 1984).

Management:

Monitor heart rate and EKG–PR interval. Monitor for signs and symptoms of digoxin toxicity (abdominal pain, anorexia, bizarre mental symptoms in the elderly, blurred vision, bradycardia, confusion,delirium, depression, diarrhea, disorientation, drowsiness, fatigue, hallucinations, halos around lights, visualacuity, mydriasis, nausea, neuralgia, nightmares, personality changes, photophobia, restlessness, vertigo,vomiting, and weakness) (Matthew 2016).

THEOPHYLLINE – FLUOROQUINOLONES (Radandt et al., 1992**)**
Impact:
Theophylline toxicity

Mechanism of Interaction:

The fluoroquinolones have been shown to interact with the hepatic metabolism of theophylline and increase serum theophylline concentrations. The quinolone metabolite, 4-oxoquinolone, inhibits the N-demethylation of theophylline, leading to a decrease in the clearance of theophylline. The resultant rise in theophylline concentrations corresponds with the decrease in clearance and possible toxicity (Matuschka and Vissing 1995).

Prevention:

Obtain theophylline level prior to administartion of a quinolone and the dosage of theophylline may need to be reduced in order to avoid toxicity. Of the quinolones, enoxacin and ciprofloxacin reduce theophylline clearance by 30-84%. In contrast, ofloxacin and norfloxacin cause less inhibition of the metabolism of these compounds, and reduction of the theophylline dosage is not routinely required. Hence, switching to gatifloxacin, levofloxacin, moxifloxacin, or trovafloxacin; these agents appear not to inhibit theophylline metabolism can prevent theophyllin toxicity (Wijnands and Vree 1988).

Management:

Reduce the dose and monitor theophylline levels. Maintain level within targeted range of 5-15mcg/mL; however, theophylline toxicity may result even when the level is within the targeted range. Signs and symptoms of theophylline toxicity include nausea, vomiting, irritability with unrest, anxiety, trouble sleeping, seizures or a fast heartbeat (Sano et al., 1988).

CONCLUSION

It is desirable to understand the basic pharmacology of drugs so as to avoid giving drugs that are additive in nature or those acting on the same or multiple sites. Special care is needed while prescribing certain drugs with the greatest propensity for interactions. It would be easy to conclude from the above facts that it is extremely risky to give a patient more than one drug not only on long term even for short term. It is prudent to remember the subsets of populations like the elderly, critically ill, and those suffering from chronic disease as they are more susceptible. Recommended future research.

LIST OF ABBREVIATIONS

NSAIDs : Non Steroidal Anti-inflammatory DrugsCOX-2 : Cyclooxygenase-2INR : International Normalized Ratio SCr : Serum Creatinine
P-gp : P-glycoprotein

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