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Risk of myocardial infarction and antiretroviral therapy—an update of the DAD Study

Prolonged use of antiretroviral agents has been shown to reduce morbidity and mortality associated with human immunodeficiency virus (HIV) infection. However, the long term use of antiretroviral agents can result in adverse metabolic effects, including hyperlipidemia, insulin resistance, and diabetes. All of these metabolic consequences are risk factors for coronary artery disease and myocardial infarction. To determine the risks of heart disease with antiretroviral therapy, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study was initiated in 1999. Specifically, the primary goal of the DAD study was to assess the effects of antiretroviral therapy on the risk of myocardial infarction. The DAD study was comprised of 11 established cohorts, with a total of 23,468 patients with HIV infection. Data were collected at 8-month intervals beginning in 1999 and included information on myocardial infarction, antiretroviral therapy, and cardiovascular risk factors.

Results of the DAD study—2003 and 2007 reports

The first results of the DAD study were published in 2003 and reported that combination antiretroviral therapy increased the risk of myocardial infarction. With 36,199 person-years of observation and 126 myocardial infarctions (3.5 events per 1000 person-years), the relative risk of myocardial infarction was 1.26 (95% CI, 1.12-1.41) per additional year of exposure to combination antiretroviral therapy. In 2007, a second series of results from the DAD cohort were published, with an analysis of myocardial infarction risk for 2 classes of antiretroviral therapy—protease inhibitors and nonnucleoside reverse transcriptase inhibitors (NNRTIs). During 94,469 person-years of observation, 345 myocardial infarctions

occurred, for an incidence of 3.65 events per 1000 person-years. When the occurrence of myocardial infarction was assessed for each of the antiretroviral classes, protease inhibitors were found to increase the risk of myocardial infarction with a relative risk of 1.10 per additional year of exposure (95% CI, 1.04-1.18). However, no additional risk was seen for exposure to NNRTIs (RR 1.00 [95% CI, 0.93-1.09]). The authors' suggested that this additional risk with protease inhibitors was due to the effect of these drugs on serum lipids.

Results of the DAD study—2008 report

The most recent report from the DAD study group evaluated the effects of nucleoside reverse transcriptase inhibitors (NRTIs) on the risk of myocardial infarction. Five NRTIs were included: zidovudine, stavudine, didanosine, lamivudine, and abacavir. This analysis was conducted after 157,912 person-years of observation. A total of 517 myocardial infarctions had occurred, for an incidence of 3.3 events per 1000 person-years. The risk of each NRTI was assessed separately, with outcomes adjusted using 3 different models—cumulative, recent (considered current use or use within 6 months), and past exposures. Long-term exposure to zidovudine, stavudine, and lamivudine, as determined by the cumulative exposure model, showed no increase in the risk of myocardial infarction. However, both didanosine and abacavir showed significantly increased risks of myocardial infarction—with relative risks of 1.06 and 1.14, respectively, per additional year of exposure. Additional results are given in Table 1.

The risk of myocardial infarction with didanosine and abacavir remained significant for any recent exposure (after adjustment for cumulative exposure and cumulative, recent, and past exposure) over non users. Past exposure,

however, did not increase the risk of myocardial infarction with didanosine or abacavir, or with any of the other NRTIs evaluated.

Table 1. Risk of myocardial infarction with NRTIs.

NRTI	Cumulative exposure only (RR [95% CI])	Adjusted for cumulative and recent exposure (RR [95% CI])	Adjusted for cumulative, recent, and past exposure (RR [95% CI])
Zidovudine			
Cumulative exposure	1.03 [0.99-1.08]	1.04 [0.99-1.09]	1.04 [0.99-1.09]
Any recent exposure		0.97 [0.76-1.25]	1.22 [0.82-1.81]
Past exposure			1.29 [0.89-1.85]
Didanosine			
Cumulative exposure	1.06 [1.01-1.12] ^a	1.01 [0.95-1.08]	1.00 [0.93-1.07]
Any recent exposure		1.49 [1.14-1.95] ^a	1.53 [1.10-2.13] ^a
Past exposure			1.08 [0.84-1.39]
Stavudine			
Cumulative exposure	1.04 [0.99-1.10]	1.05 [0.98-1.11]	1.02 [0.95-1.09]
Any recent exposure		1.00 [0.76-1.32]	1.22 [0.84-1.77]
Past exposure			1.24 [0.93-1.66]
Lamivudine			
Cumulative exposure	1.03 [0.98-1.08]	1.00 [0.94-1.07]	0.99 [0.93-1.06]
Any recent exposure		1.25 [0.96-1.61]	1.69 [1.02-2.80]
Past exposure			1.45 [0.88-2.40]
Abacavir			
Cumulative exposure	1.14 [1.08-1.21] ^a	1.01 [0.93-1.09]	1.00 [0.92-1.08]
Any recent exposure		1.90 [1.47-2.45] ^a	1.94 [1.48-2.55] ^a
Past exposure			1.29 [0.94-1.77]

^aStatistically significant vs. no exposure

The risk of myocardial infarction with didanosine or abacavir remained high even after adjustment for the 10-year risk of coronary heart disease. For patients with recent use, the relative risk of myocardial infarction was 1.49 (95% CI, 1.14-1.95; p=0.004) for abacavir and 1.89 (95% CI, 1.47-2.25; p=0.0001) for didanosine compared to no exposure or only past exposure. Adjustment for

characteristics such as CD4 cell counts, viral load, glucose or lipid measurements, blood pressure, and use of antihypertensive or lipid-lowering agents did little to change the risk of myocardial infarction associated with the recent use of didanosine or abacavir.

Summary

The findings of the DAD study indicate that current use of either didanosine or abacavir is associated with an increased risk of myocardial infarction. This risk was not seen for other NRTIs, such as zidovudine, lamivudine, or stavudine. In addition, the risk with didanosine and abacavir remained little changed when the results were controlled for potential underlying cardiovascular risks including lipid measurements, blood pressure, diabetes, and predicted 10-year coronary heart disease risks. The mechanism of risk with these 2 agents is unclear. The authors of the DAD study suggested vascular inflammation as a possible cause, in part because the effects of exposure were reversed when therapy with didanosine or abacavir was discontinued for 6 months or more.

Drug induced suicidality

In recent years, the number of drugs associated with suicidality appears to be growing. Although there is not a universally accepted definition of suicidality, it can include suicidal ideation, suicidal attempts, and completed suicides and can occur in patients experiencing symptoms of depression or behavioral changes. Many of the medications found to be linked to suicidality have resulted in labeling changes either as precautions, warnings, or boxed warnings. Medications associated with suicidality according to the Food and Drug Administration (FDA) MedWatch database are summarized below. Mefloquine (Lariam), although contraindicated in patients with active depression, is not included in this summary as suicidality has been rarely reported and not confirmed to be linked to the drug.

Antidepressants

Suicidality associated with use of certain antidepressants in the pediatric population was first issued as a public health advisory by the FDA in 2003. Ongoing reviews of studies and postmarketing reports culminated in a boxed warning describing the risk of suicidality in children, adolescents, and young adults up to the age of 24 for all antidepressants in 2007. Healthcare professionals, caregivers, and patients are advised to monitor for sudden behavioral or mood changes, new or worsening depression, anxiety, agitation, insomnia, irritability, aggression, and suicidal thoughts or attempts. These changes may be particularly prominent within the first few months of therapy and after dose changes. Prescribers are advised to use the lowest possible dose of these agents. If discontinuation of therapy is required, the medication should be tapered and patients are advised

not to abruptly discontinue therapy. Although the FDA review did not establish the same risk in adults over the age of 24 and found a decreased suicidality risk in patients over the age of 65, patients in these age groups should also be monitored for behavioral and mood changes. Some antipsychotics, such as quetiapine (Seroquel®) and aripiprazole (Abilify®), approved for use in certain types of depression also carry similar warnings.

Antiepileptics

An FDA review of clinical studies of 11 antiepileptic drugs revealed an increased risk of suicidality with their use compared to placebo (0.43% vs. 0.22%, respectively). An FDA alert was issued to healthcare professionals and consumers in January 2008. Prescribers are advised to monitor patients for changes in behavior, including depression, as the increased suicidality risk was evident within 1 week of starting treatment and persisted through 24 weeks. Patients with epilepsy were found to have a relatively higher risk than those patients receiving the medications for other conditions. Based on these data, labeling changes are likely to occur for the entire antiepileptic drug class.

Accutane

In 2002, Roche Laboratories updated its warnings for isotretinoin (Accutane®) to inform prescribers and patients of the potential for depression and suicidality. Patients with psychiatric conditions, severe acne, or those with a family history of mental health problems may be at increased risk. Patients should be evaluated for symptoms of depression, mood changes, aggression and suicidality prior to starting isotretinoin (Accutane®) and during therapy. If symptoms do occur, patients should discontinue therapy immediately and contact the prescriber for further monitoring. Although most cases occurred within the first 4 months of therapy, depression was observed later in the course of therapy and even after discontinuation. According to the manufacturer, there have been at least 7 published cases of suicidal ideation or attempts. Systematic reviews and a retrospective review have found a weak association between suicidality and isotretinoin use. However, until larger scale studies are conducted, healthcare professionals should continue to monitor patients for behavioral and mood changes.

Strattera

The FDA, in 2005, required the manufacturer of atomoxetine (Strattera®) to add a boxed warning to its prescribing information and to provide a Patient Medication Guide describing increased suicidality risk in children and adolescents taking atomoxetine (Strattera®). A review of 12 trials with 1,357 patients on atomoxetine (Strattera®) and 851 on placebo revealed a risk of 4 events of suicidal ideation per 1,000 patients on atomoxetine (Strattera®) compared to 0 events in patients receiving placebo. In addition, 1 suicide attempt occurred in a patient on atomoxetine (Strattera®) compared to none in the placebo group. Prescribers and caregivers are advised to observe patients closely, especially at initiation of therapy and after

dose changes, as the risk was found to be greater during the first few months of therapy. The analysis did not find a similar risk in adults receiving atomoxetine (Strattera®).

Chantix

Risk of neuropsychiatric symptoms, including behavioral changes, agitation, depression, suicidal ideation, attempted and completed suicide with varenicline (Chantix®) use was identified in post marketing reports in 2007 and escalated to a warning in 2008 after further FDA review. Symptoms are not necessarily attributable to nicotine withdrawal since some patients receiving varenicline (Chantix®) had not yet quit smoking. Of additional concern is that symptoms may occur even after discontinuation of varenicline (Chantix®). Patients with preexisting psychiatric conditions, such as schizophrenia, bipolar disorder, and major depression, may be at an increased risk.

Singulair

Post marketing adverse events of suicidality were added to montelukast's (Singulair®) labeling information in October 2007 followed by an FDA announcement in March 2008 of an ongoing safety review of a possible association of use of the drug with suicidality. According to the FDA, the analysis may take as long as 9 months. Patients should not stop taking the medication. However, prescribers are advised to monitor for symptoms of suicidality and behavioral and mood changes.

Alpha and beta interferons

Warnings of neuropsychiatric disorders including suicidal ideation, suicidal attempts and completed suicide appear as a boxed warning and a precaution in the labeling information for alpha interferons. Discontinuation of therapy may or may not alleviate symptoms. Patients should be monitored for signs of depression and suicidality during and after therapy.

Caution is advised in the use of beta interferon in patients with a history of depression and other mood disorders. Depression and suicidality occur more frequently in patients receiving interferons. In some cases, symptoms improved once therapy was discontinued.

Amantadine

Suicidal attempts and completed suicides have been reported in patients receiving amantadine for influenza prophylaxis or treatment. The effects occurred in patients with or without a history of mental disorder. Patients should be monitored for symptoms of disorientation, insomnia, somnolence, behavioral/mood changes, agitation, aggression, and other psychotic behaviors.

Summary

Healthcare professionals need to be aware of the suicidality risk associated with a variety of medications. The mechanism of this serious adverse event is unknown for most medications. However, patients receiving these medications and their caregivers should be advised to

report changes in mood and behavior. In some instances, such as with Accutane, the medication can be stopped immediately with prompt follow up with the healthcare provider. Patients receiving other medications, such as antidepressants, should not abruptly discontinue the medication but should report the symptoms to their provider immediately. Cessation of therapy may not be sufficient as symptoms have been reported even after discontinuation of certain medications.

Medication errors in US children’s hospitals

Traditional methods to detect and quantify medication errors in a hospital setting include voluntary reporting, chart review, and direct observation. Problems exist with these methods including an unwillingness to report errors and the potential to miss errors during a chart review. It is widely believed that medication error rates are higher than those seen with traditional methods. Based on this potential discrepancy, Takata and colleagues developed a tool to identify medication errors in pediatric patients and tested the tool in 12 children’s hospitals in the US.

This tool uses an approach known as the “trigger method”, which uses specific items to help identify medication errors. The trigger approach involves a focused review of the medical record for information associated with medication errors and has been shown to be useful in previous studies for identifying medication errors in adults and neonates in the neonatal intensive care unit (NICU). The tool was developed in a phase I portion of the study from a chart review of 931 patients from the 12 children’s hospitals. The phase I chart review used an adult trigger tool and focused on comparing the tool to traditional methods and getting input to adapt the tool for pediatric patients. Examples of the triggers (in the final tool) used by Takata and colleagues for phase II of the study and potential errors associated with them are summarized Table 2.

Table 2. Examples of triggers to identify potential errors

Trigger	Potential errors identified
Diphenhydramine prescription	Drug allergy
Vitamin K use, elevated PTT	Excessive anticoagulation
Flumazenil, naloxone prescription	Benzodiazepine or narcotic overdose
Sodium polystyrene prescription	Potassium overdose
Serum creatinine elevation	Nephrotoxicity
Rash	Adverse reaction, allergy
Laxative, stool softener use	Drug-induced constipation
Abrupt discontinuation of a drug	Allergy or adverse effect

Phase II of the study was a retrospective chart review of randomly selected charts of children who were hospitalized for at least 2 days. Chart review was limited to the first 30 days of an admission; newborns and patients not meeting criteria during the specified time frame were excluded from review. Healthcare providers at the individual sites conducted the reviews and were extensively trained on the use of the tool and provided with an instruction manual. For the purposes of the trial, an adverse drug event (ADE) was defined as an injury caused by a drug or nonuse of a drug. The preventability of the ADE was also determined at the site by 2 reviewers. Reviewers also recorded ADEs not associated with a specific trigger.

The outcome measures were the rate of ADEs, number of triggers per patient, positive predictive value of the trigger, severity of the ADE, percentage of preventable ADEs, stage of the medication use process where the medication error occurred, diagnosis on discharge, and the hospital unit where the ADE occurred.

A total of 960 charts were reviewed, which represented 6806 patient days. Analysis of demographic data revealed an average length of stay of about 7 days, an average patient age of 5.9 years, 14.3 medications on average per patient with 90.5 doses. Overall, 2,388 triggers were identified, mean rate of 2.49 per patient (95% CI: 2.39 to 2.59). One hundred seven ADEs were found for a mean rate of 11.1 per 100 patients (95% CI: 9.13 to 13.5), 15.7 per 1000 patient days (95% CI: 12.9 to 19), and 1.23 per 1000 doses (95% CI: 1.01 to 1.49).

The positive predictive value of the trigger tool was 3.7%. The majority of ADEs, 104 (97.2%) of 107 were classified as resulting in temporary harm and requiring intervention. The remaining 3 (2.8%) were classified as resulting in temporary harm and requiring hospitalization (initial admission or extended length of stay). None of the events led to permanent harm, need for a life-saving intervention, or death. A total of 22% were classified as preventable ADEs, 17.8% could have been detected sooner, and 16.8% could have been resolved more effectively. This study also demonstrated the shortcomings of relying on error reports in the hospital setting, as only 4 (3.7%) of 107 were reported via the hospital’s occurrence reporting system. When the medication use process was examined, the monitoring phase (62.5%) was most commonly associated with preventable ADEs such as not assessing the regimen for continued need and not using clinical and laboratory monitoring when indicated. The second most common phase was prescribing or ordering (50%, errors could overlap in the process).

Analgesics/opioids was the class of drugs most frequently associated with ADEs (51%), and the events were most common in hematology/oncology units (18 per 100 patients). Pruritis was the most common ADE (17.8%).

The authors concluded that the trigger tool was effective in identifying ADEs in hospitalized pediatric patients, and that event rates were higher than described in previous literature. The majority of events caused temporary harm to the patients.

Following the release of Takata's study and in light of recent high profile medication errors in children, The Joint Commission issued a sentinel event alert on April 11, 2008 on this topic. The alert points out that children are at higher risk for medication errors and subsequent harm as compared to adults for several reasons:

- Commercially available dosage forms often need dilution or adjustment when given to pediatric patients.
- Facilities lack adequately trained clinicians, notably in the emergency department.
- Young children, as well as those who are small and/or ill may have less developed renal and hepatic function and may not tolerate an error to the same degree an adult would.
- Young children cannot communicate problems they are experiencing.

The alert contains data from the United States Pharmacopeial Convention's (USP) MEDMARK database for 2006 and 2007. The data reveal that incorrect dosing is the most common reason for errors (37.5%) followed by omission errors (19.9%). Errors in pediatric patients were most often linked to performance (43%) and knowledge (29.9%) deficits. Additional causes were calculation errors, computer entry errors, insufficient monitoring, and not using pumps correctly.

The Joint Commission's alert contains several strategies to reduce medication errors in this population (http://www.jointcommission.org/SentinelEvents/SentinelEventAlert/sea_39.htm). Some key recommendations include using oral syringes to administer oral medications to prevent inadvertent intravenous administration, orientation of all pharmacy staff to pediatric and neonatal pharmacy services, development of preprinted order forms to standardize care, and appropriate use of technology.

The Joint Commission also provides a list of 9 suggested actions to prevent medication errors in pediatric patients. The emphasis lies in accurate dosing and appropriate formulations. Initially an accurate weight in kilograms for pediatric patients should be obtained at the time of admission or within 4 hours of an emergency situation. Furthermore, prescriptions should contain the dose and the dose per weight to allow for a double-check prior to dispensing. Pediatric strength formulations should be stocked in the institution to the extent possible. Adult formulations should be clearly distinguished from pediatric formulations with warning labels.

Summary

Pediatric patients are more at risk for medication errors compared to adults for a variety of reasons such as immature organ function, lack of specific drug formulations, and lack of specialty practitioners available for consultation. Recent high profile medication errors involving the incorrect strength of heparin being used for neonates has increased the attention on errors in pediatric patients. Takata and colleagues' trigger tool represents a way for institutions to identify common ADEs allowing for analysis of root causes. Implementation of the strategies offered by The Joint Commission may further reduce the potential for errors in pediatric patients.

P&T Committee Formulary Action

Additions

Sevalamer cabonate

Deletions

Sevalamer HCl

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