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COX-2-Selective NSAIDs: mission not yet accomplished

CURRENT CLINICAL ISSUES

Goal: To increase awareness of the evidence for the risk of ulcer complications with the two COX-2 selective NSAIDs currently marketed in the United States.

Objectives:

1. Explain the proposed mechanisms involving the cyclooxygenase type 1 and type 2 enzymes that are believed to predict a difference in the gastrointestinal toxicity of the COX-2 selective NSAIDs compared to nonselective NSAIDs
2. Discuss the results of the Celecoxib Long-Term Arthritis Safety Study (CLASS).
3. Discuss the results of the Vioxx Gastrointestinal Outcomes Research Study (VIGOR).
4. Describe the epidemiological data of NSAID induced ulcer complications.
5. List the risk factors that have been shown to be associated with NSAID induced ulcer complications.

Introduction:

The development of cyclooxygenase 2 (COX-2) selective inhibitors is a significant achievement in the process of designing drugs based on detailed knowledge of pharmacology and physiology. Many studies have been conducted *in vitro*, in animal models, short-term studies in normal volunteers, and short term studies in patients based on the outcome

of endoscopically identified gastroduodenal ulcers. These studies have provided substantial evidence for the potential of these drugs to provide efficacy in the treatment of pain and inflammation, while reducing or eliminating the risk of nonsteroidal anti-inflammatory drug (NSAID) gastropathy. The next logical step in the development process with these drugs was to obtain long term outcome data of the safety of these drugs in a patient population representative of those in whom the drugs are indicated. This is analogous to the landmark MUCOSA trial in which misoprostol was demonstrated to reduce the risk of serious NSAID induced gastrointestinal complications in patients with rheumatoid arthritis (Silverstein, 1995). The MUCOSA trial was significant because it was the first randomized controlled study to evaluate clinically significant gastrointestinal (GI) complications, not just endoscopically identified ulcers. Similar studies have recently been published for celecoxib and for rofecoxib; they are reviewed below. However, the results from these studies are far from conclusive regarding overall safety.

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The diversity of results from the various types of studies has prompted wide ranging conclusions and public statements about the significance of these drugs from one extreme of "COX-2 specific inhibitors represent a major therapeutic advance and will replace conventional NSAIDs in the future" (Moskowitz, 2000) to "a massive fraud has been perpetrated on people in this country who have spent billions of dollars on drugs that are not arguably any better." (Wolfe, 2001)

Epidemiology of NSAID gastropathy

The year 1999 marked the 100th anniversary that aspirin, the first nonsteroidal anti-inflammatory drug, was synthesized. "Approximately 40 years elapsed before Douthwaite and Lintott provided endoscopic evidence that aspirin could cause gastric mucosal damage." (Wolfe, 1999) Starting in the early 1970's several new nonsteroidal anti-inflammatory drugs were developed that were initially believed to be free of gastrointestinal toxicity. These drugs are one of the most widely used classes of drugs with estimates of more than 111 million prescriptions, and more than \$ 1.8 billion in over the counter sales annually in the United States. (Laine, 2001)

Although NSAIDs are generally well tolerated, adverse gastrointestinal events ranging from mild dyspepsia to fatal gastrointestinal ulcer complications may occur. Depending on the definition of specific gastrointestinal complications, differences in patient populations, drugs, doses, and duration of therapy, the reported frequency of adverse effects varies widely. At least 10 to 20 percent of patients have dyspepsia while taking an NSAID. Within a 6-month treatment period 5 to 15 percent of patients discontinue NSAID therapy because of dyspepsia. (Wolfe, 1999)

Data prospectively collected by the Arthritis Rheumatism and Aging Medical Information System (ARAMIS) show that the annual incidence of serious GI complications requiring hospitalization while taking NSAIDs is 1.3 % for patients with rheumatoid arthritis (RA), and 0.73% for patients with osteoarthritis (OA). (Singh, 1999) The relative risk for GI complications in this population when taking NSAIDs compared to when they are not taking NSAIDs is 2.51 for OA and 6.77 for RA patients. NSAID gastropathy is fatal in about 10-15% of hospitalizations for upper GI bleeding.

Prospective outcome studies indicate the annual incidence of complicated GI events (perforation, obstruction, major bleeding) in arthritis patients is approximately 1.5%, and the annual rate of all clinical GI events (complicated events plus ulcers found on evaluation for significant symptoms) is approximately 3% to 4.5%. (Laine, 2001).

Based on data from ARAMIS, and conservative estimates of the number of people in the United States who take a NSAID regularly, the number of hospitalizations for serious GI complications each year would be 103,000 and the number of deaths would be 16,500. (Singh, 1999) NSAID gastropathy has been referred to as a silent epidemic because many physicians and patients are unaware of the magnitude of this problem, and only one in five persons who have a serious GI complication will have any warning symptoms. Even though dyspepsia is a common side effect of NSAID use it is poorly correlated with endoscopic ulcers or GI bleeding.

Since GI side effects are not a reliable warning sign, it is important to identify risk factors to predict which patients are more likely to experience clinically significant events, and then determine how to reduce that risk. Risk factors consistently found to be associated with serious NSAID gastropathy are: age, risk increases linearly with age; history of ulcer or GI bleeding; higher doses of NSAIDs; concomitant therapy with corticosteroids or anticoagulants; and serious comorbid conditions. *H. pylori* infection and NSAID use are independent risk factors for the development of ulcers. It is unclear if *H. pylori* infection potentiates the development of NSAID induced gastropathy. (Singh, 1999 Wolfe, 1999, and Laine, 2001)

Cyclooxygenase Theory

Inhibition of prostaglandin synthesis is thought to account for both the therapeutic and adverse effects of the nonselective NSAIDs. Prostaglandins are formed from arachidonic acid by the catalytic activity of cyclooxygenase. It is now recognized that there are two related but distinct isoforms of cyclooxygenase, termed COX-1 and COX-2. COX-1 is expressed constitutively (stably expressed under basal conditions) in most tissues and is thought to produce prostaglandins. COX-1 is present in platelets and in the gastric epithelium. In the gastric epithelium prostaglandin is produced which is gastroprotective. In platelets thromboxane A2 is produced which stimulates platelet aggregation.

COX-1 is involved in production of prostaglandin in the kidney to maintain homeostatic function. (Crofford, 2000)

COX-2 is undetectable in most tissues in the absence of stimulation but is induced by bacterial lipopolysaccharides, growth factors, and cytokines and subsequently plays a role in inflammatory responses. COX-2 is present in synovial tissues of patients with arthritis. Glucocorticoids and anti-inflammatory cytokines can inhibit COX-2 expression and prostaglandin production. (Buttar, 2000)

Subsequently the theory says, if you inhibit COX-2 selectively you can achieve therapeutic efficacy in inflammation and pain without the adverse effects on the gastrointestinal tract caused by inhibition of COX-1. However, there are already data to indicate that as with most biologic systems, it is not quite that simple. Nitric oxide and other peptides are known to play a role in maintaining GI mucosal integrity and COX-2 may have an accessory role in the GI tract that is more important than previously thought. Other physiologic functions are being identified for COX-2. (Beejay, 1999)

COX-2 appears to have a role in adenomas and carcinomas of the colon. Specific inhibition of COX-2 has been shown to cause regression of preexisting adenomas in patients with familial adenomatous polyposis (celecoxib has been approved by the FDA for treatment of this condition). COX-2 also has a normal physiologic role in the central nervous system, female reproductive function, maintenance of renal function, and may have a role in bone formation. COX-2 is thought to play a role in production of prostacyclin by the endothelium; prostacyclin is antithrombogenic. (Schnitzer, 2001)

The full role of COX-2 is still being defined. It is clear that it is involved in the production of prostaglandins that mediate inflammation, pain, and fever. But as noted above, it is also involved in normal physiologic functions. The full implications of selective inhibition are not known. There is no expectation that COX-2 inhibitors will be more effective than nonselective NSAIDs; current data are consistent with that. There is also no expectation that selective COX-2 inhibitors will eliminate the potential for edema, hypertension, and congestive heart failure; again current data are consistent with this. There is speculation that selective inhibition of COX-2 may increase the risk of thrombosis because

of a lack of thromboxane inhibition coupled with inhibition of prostacyclin. (McAdam, 1999)

CLASS Study

In the CLASS study (Silverstein, 2000), patients with osteoarthritis or rheumatoid arthritis (27 % had rheumatoid arthritis) were randomized to blinded treatment with celecoxib 400mg twice per day (n=3987), ibuprofen 800mg three times per day (n=1985), or diclofenac 75mg twice per day (n=1996). These patients were recruited from 386 clinical sites in the United States and Canada. The average age of subjects in the trial was 60 years and approximately 70% were women. A history of gastrointestinal bleeding was present in approximately 1.6% of subjects and a little over 8% had a history of gastrointestinal ulcer. Of this population 21% were taking low dose aspirin, 30% were taking corticosteroids, 1% were taking anticoagulants and 81% had been taking NSAIDs at study entry.

The primary objective of the study was to compare the frequency of clinically significant upper gastrointestinal events (defined as gastroduodenal ulcer complications of perforation, obstruction, or bleeding). The combined endpoint of ulcer complications plus symptomatic ulcers was also assessed as a secondary outcome. Other secondary outcomes included parameters for cardiovascular, renal, dermatologic, hepatic and general safety. Although this was not intended as an efficacy study arthritis assessments consisted of patient's global assessment of arthritis and of arthritis pain, SF-36 quality of life assessment, and the Health Assessment Questionnaire Functional Disability Index.

The results of the primary hypothesis of a difference in the rate of ulcer complications between celecoxib and the combined rate from the two NSAIDs was not statistically significant. The annualized incidence of upper GI ulcer complications was 0.76% in the celecoxib patients and 1.45% in the NSAID group, p=0.09. The secondary outcome of ulcer complications plus symptomatic ulcers did demonstrate a significant difference. The annualized rate of this endpoint was 2.08% in the celecoxib group and 3.54% in the NSAID combined group. The relative risk for celecoxib compared to the NSAIDs for this secondary outcome was 0.59 and the 95% confidence interval was 0.38-0.94.

Individual data on the two NSAIDs were not reported in the published article, but were presented to the FDA Arthritis Advisory Committee (USFDA, 2001). The individual results of the comparison of celecoxib vs. ibuprofen and vs. diclofenac are very interesting. None of the gastrointestinal event data demonstrated any difference between celecoxib and diclofenac regardless of the event analyzed, the time period in the study, or the analysis based on the subgroups with or without concomitant aspirin use. Any differences that were demonstrated between celecoxib and the combined NSAID event rates were due to a difference with ibuprofen, but not with diclofenac. This creates a dilemma; does this mean that celecoxib has lower GI risk than some NSAIDs but not all? Does it mean the comparison with diclofenac failed to achieve significance because of inadequate study power? It should also be noted that the study power may have been less than intended since only 57% of patients completed 6 months of treatment. These questions can not be definitively answered with the available data.

It has also been argued that a significant difference in the primary outcome could have been missed because the event rate with celecoxib was higher than predicted. This higher than expected rate was probably due to the use of low dose aspirin in 21% of patients. In the subgroup of patients **not** taking aspirin the annualized incidence of ulcer complications in the celecoxib group was 0.44% compared to 1.27% for the combined NSAID group; this was statistically significant ($p=0.04$). The subgroup taking low dose aspirin had an annualized incidence of ulcer complications of 2.02% for patients taking celecoxib and 2.12% for the combined NSAID group ($p=0.92$). For ulcer complications plus symptomatic ulcer, the event rates were 4.7% for celecoxib and 6.00% for the NSAID group ($p=0.49$). These data appear to indicate that any potential advantage of reduced GI toxicity of celecoxib is lost when patients are taking low doses of aspirin. Considering that the population of patients with arthritis also frequently has concomitant cardiovascular disease, the need for low dose aspirin for prevention of cardiovascular events will be encountered often in the clinical setting.

Since there is debate about the clinical value of examining organ specific differences in toxicity as opposed to overall safety of these drugs, it is useful to examine overall adverse events. The most common adverse events causing withdrawal in this study were GI symptoms, ulcer, rash, and elevation

of liver function tests. During the study 22.4% of celecoxib patients, 26.5% of diclofenac patients, and 23.0% of ibuprofen patients withdrew because of an adverse event. The rate of withdrawal was significantly less for celecoxib compared to diclofenac but not compared to ibuprofen. A total of 500 patients experienced serious adverse events during or up to 28 days after the study. Serious adverse events included: abdominal pain, unstable angina, atrial fibrillation, cardiac failure, cerebrovascular disorder, chest pain, coronary artery disorder, deep vein thrombophlebitis, GI hemorrhage, myocardial infarction, and syncope. The rate of any serious event (per 100 patient years) was 11.6 for celecoxib patients, 10.3 for diclofenac, and 10.6 for ibuprofen. These rates were not statistically different.

The results of the CLASS trial demonstrated that: there was no significant advantage of celecoxib in the primary outcome of ulcer complications, there was no difference in mortality, no difference in overall serious adverse events or rate of withdrawal due to adverse events, and there was no difference in efficacy for arthritis. Celecoxib did have a lower rate of ulcer complications plus symptomatic ulcer compared to the combined NSAIDs, and compared to ibuprofen alone, but not compared to diclofenac alone. There was also a statistically significant reduction in the incidence of bleeding related anemia with celecoxib compared to the nonselective NSAIDs (2.0% of patients versus 4.4%). Concomitant use of low dose aspirin appears to eliminate any significant advantage for celecoxib.

VIGOR Study

The VIGOR study (Bombardier, 2000) was designed to compare the rate of clinically important upper gastrointestinal events (defined as perforation, obstruction, bleeding plus gastroduodenal ulcer) of rofecoxib to naproxen among patients with rheumatoid arthritis. The study was conducted at 301 centers in 22 countries. A total of 4047 patients were randomized to receive rofecoxib 50mg daily and 4029 were randomized to receive naproxen 500mg twice daily. The average age of patients was 58 years, 80% were female, 83% had prior use of NSAIDs, 56% were being treated with glucocorticoids, 56% were being treated with methotrexate, and 45% were receiving other rheumatoid arthritis disease modifying drugs. A history of a clinically significant gastrointestinal event was present in 8%. Low dose aspirin, other

antiplatelet drugs, or anticoagulants were not permitted in the VIGOR study.

The primary hypothesis was that upper gastrointestinal events would be lower in the rofecoxib group. A secondary hypothesis was that the risk of confirmed complicated events (perforation, obstruction, bleeding) would also be less. Cardiovascular events were assessed for a future planned meta-analysis, but a separate analysis of these events was not specified in the study design. The VIGOR study was not an efficacy study; however, the patient and the investigator answered a Global Assessment of Disease Activity questionnaire at baseline, 6 weeks, 4 months, 12 months and at the end of the study or when treatment was discontinued. The Modified Health Assessment questionnaire was administered only to patients enrolled in the United States at baseline, at 6 weeks, at the end of the study or when treatment was discontinued.

The median follow-up was 9 months in both groups (range 0.5 to 13 months), and 71% continued to take the assigned medication until the end of the study. The rate of confirmed upper gastrointestinal events per 100 patient years was 2.1 in the rofecoxib group and 4.5 in the naproxen group (relative risk 0.5, 95% CI 0.3-0.6, $p < 0.001$). The rate of confirmed complicated upper GI events per 100 patient years was 0.6 in the rofecoxib group and 1.4 in the naproxen group (relative risk 0.4, 95% CI 0.2-0.8, $p = 0.005$). These event rates are very similar to the results of the CLASS study except that the rate of 4.5 for upper gastrointestinal events in the naproxen group is higher than the comparable rate of 3.54 in the NSAID group of CLASS. It should be noted that the events are in different populations, with adjudication by different committees, so any comparison between the studies is rough at best. In addition the VIGOR population was not allowed to take low dose aspirin, which increased event rates in the CLASS study, and has been clearly demonstrated in other studies to increase the risk of GI events.

The GI event rates for rofecoxib in this study were clearly demonstrated to be less than the comparator naproxen. This should not be interpreted to represent superiority over the results of celecoxib in the CLASS study as there was an absence of low dose aspirin in VIGOR, and the GI event rate of naproxen was higher in VIGOR than the corresponding adverse GI event rates for NSAID in CLASS. It has been suggested in previous studies

that naproxen may have a higher event rate than ibuprofen or diclofenac, so the higher rate in VIGOR is not surprising. It should also be noted that the event rate of 2.1 confirmed GI events per 100 patient years with rofecoxib is within the range of the rates for the standard NSAID warning label.

The general safety experience of rofecoxib compared to naproxen in the VIGOR study is in contrast to the GI safety. Serious adverse experiences occurred in 9.3% of the rofecoxib group and 7.8% of the naproxen group ($p = 0.013$). The incidence of serious adverse experiences considered by the investigator to be drug related was 0.9% in the rofecoxib group compared to 1.7% in the naproxen group (p value not specified). Discontinuation due to adverse experiences was essentially equal, 15.9% with rofecoxib and 15.8% with naproxen. There were 22 deaths in the rofecoxib group (0.5%) and 15 in the naproxen group (0.4%). Serious cardiovascular events occurred in 2.5% of rofecoxib patients compared to 1.1% on naproxen ($p < 0.05$). The biggest difference in cardiovascular events between the groups was in acute myocardial infarction, which occurred in 20 rofecoxib patients (0.5%) compared to 4 naproxen patients (0.1%) $p < 0.05$. It can not be determined from this study if this difference represents a protective effect from naproxen or an increased risk from rofecoxib. As with the CLASS study, some of these additional data are not included in the published article but are available from the FDA review documents. (USFDA, 2001)

Discussion

The results of these large clinical trials provide the most useful evidence of the potential safety of the COX-2 selective NSAIDs compared to the nonselective drugs. As noted, these results are not reassuring that overall safety has been improved. In some groups of patients it is not even clear if GI safety has been improved in a clinically significant way. The original proposed pharmacologic and physiologic arguments support the belief that improved safety should be achieved, however evidence also exists that would provide biologic plausibility to a hypothesis that continued caution is necessary. For example; COX-2 induction has been demonstrated in *H. pylori* associated gastritis, and in inflammatory bowel disease. Whether specific COX-2 inhibitors are harmful in the presence of GI inflammatory conditions may depend on the extent that the COX-2 enzyme becomes the predominant source of protective prostaglandins. (Hawkey, 1999)

COX-2 is also induced with gastric injury and at the rim of ulcers in humans. Animal studies have shown COX-2 inhibitors retard ulcer healing. (Hawkey, 1999) It appears that additional data are required to demonstrate the subgroup of patients who will experience increased GI safety of COX-2 inhibitors without an increase in the risk of cardiovascular events.

The United States Food and Drug Administration Arthritis Advisory Committee addressed the issue of COX-2 inhibitor safety at its meeting February 7-8, 2001. (USFDA, 2001) After two days of extensive review and discussion of the two key long-term safety studies, material from the original NDA databases, post-marketing surveillance data, and additional epidemiological evidence, the conclusion was "inconclusive." Multiple issues of generalizability of the results were discussed including the doses used, the risk level of the subjects for ulcer complications and cardiovascular events, the selection of the comparison drugs, concomitant drug therapies, and how the outcomes are classified.

Celebrex™ and Vioxx™ are two of the fastest rising drugs in sales volume in history with \$2 billion and \$1.5 billion respectively in retail sales in the United States for the year 2000. Vioxx™ alone was responsible for 5.7% of the overall growth in spending on prescription drugs in the United States last year. These two drugs are the top two in sales in the antiarthritic category and have cornered 57.1% of that market in just two years. (NIHCM, 2001) It would appear that these new drugs are currently being prescribed preferentially to previously available NSAIDs. Based on available evidence, the question of a safety advantage and the cost effectiveness of these new drugs for many of these patients is in doubt.

The Department of Veterans Affairs Medical Advisory Panel and Pharmacy Benefits Management Strategic Healthcare Group, has produced an extensive review of the evidence of safety of the COX 2 inhibitors, strategies to assess individual patient risk, and criteria for use of these drugs. This document is a good resource for groups or individuals trying to make rational decisions about the cost effective use of these two new drugs. (Department of Veterans Affairs, 2001)

The mission of the COX-2 inhibitors may not yet be accomplished, but stay tuned. Dr Jay L Goldstein, University of Illinois at Chicago, presented data

from the SUCCESS I trial at the Digestive Disease Week conference in Atlanta, May 25, 2001 (Wilson 2001). This study is a 12-week trial in 13,274 patients with osteoarthritis comparing celecoxib to naproxen and diclofenac. Results presented at the meeting indicate a reduction in risk of ulcer complications, ulcers, and adverse events leading to withdrawal. Further details from this study will add to the database to support decision making in the use of NSAIDs.

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From the Indexers:

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Accreditation Information

The University of Iowa College of Pharmacy is approved by the American Council on Pharmaceutical Education as a provider of continuing pharmaceutical education. The ACPE program number is 020-000-01-020-H01. The University of Iowa will award 1 contact hour (0.1 CEU) of continuing pharmacy education for satisfactory completion of this monograph.

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Assessment Questions

Circle the most appropriate answer

1. Why is the MUCOSA trial considered particularly significant in research related to the prevention of NSAID induced gastrointestinal complications?
 - a. it was the first study of a COX-2 selective NSAID
 - b. it documented a reduction in serious GI complications not just endoscopically identified ulcers
 - c. it was conducted in normal volunteers
 - d. it was a nonrandomized follow-up study
2. Based on data from ARAMIS approximately how many deaths occur in the United States each year as a result of NSAID induced gastropathy?
 - a. 1 million
 - b. 103,000
 - c. 16,500
 - d. 1000
3. Which of the following results was statistically significant for the comparison of celecoxib to nonselective NSAIDs in the CLASS study?
 - a. the rate of ulcer complications was less
 - b. the rate of serious adverse reactions was greater
 - c. the rate of withdrawal due to adverse reactions was less
 - d. the rate of the combined endpoint of ulcer complications plus symptomatic ulcers was less
4. Which of the following is true regarding the results of the comparison of celecoxib to nonselective NSAIDs in the subgroup taking low dose aspirin in the CLASS study?
 - a. the rate of ulcer complications with celecoxib was reduced
 - b. the rate of ulcer complications with celecoxib was greater than with nonselective NSAIDs
 - c. the potential benefit of celecoxib with respect to GI toxicity was eliminated
 - d. the rate of cardiovascular complications in the nonselective NSAID group was increased
5. In the VIGOR study the patients were allowed to take low dose aspirin.
 - a. True
 - b. False
6. Which of the following is true regarding the results of the comparison of rofecoxib to naproxen in the VIGOR study?
 - a. the rate of ulcer complications was not significantly different
 - b. overall safety favored rofecoxib
 - c. cardiovascular events occurred more frequently in patients receiving rofecoxib
 - d. less than 50% of subjects completed the trial on assigned therapy
7. The FDA Arthritis Advisory Committee gave a strong recommendation to add a statement to the product labeling for Celebrex and Vioxx to indicate that they have a safety advantage over nonselective NSAIDs.
 - a. True
 - b. False
8. Which of the following might be a useful resource to assist with decision making about the cost effective use of the new COX-2 inhibitors.
 - a. the Department of Veterans Affairs Medical Advisory Panel and Pharmacy Benefits Management criteria for use of COX-2 inhibitors in veterans
 - b. the PDR
 - c. the Merck Manual
 - d. studies of the differences in rates of ulcers detected by endoscopy
9. Which of the following has **NOT** been consistently shown to be a risk factor for the development of NSAID induced gastropathy?
 - a. age
 - b. history of gastric or duodenal ulcer
 - c. *H. pylori* infection
 - d. high doses of NSAIDs
10. Which of the following is true regarding the cyclooxygenase theory behind the development of COX-2 selective NSAIDs.
 - a. COX-1 is an inducible isoform of the cyclooxygenase enzyme
 - b. COX-1 is expressed constitutively and produces prostaglandins in the gastric epithelium that serves a protective role
 - c. COX-2 has little or no role in normal physiologic functions
 - d. COX-2 inhibition produces an antithrombotic effect and therefore protects against cardiovascular events

Directions

Select the most appropriate answer for each of the following questions and circle the corresponding letter on the answer sheet.

To receive one hour of continuing education credit (0.1 CEU) for successful completion of this program, you must:

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ANSWER SHEET

- | | | | | | | | | | |
|----|---|---|---|---|-----|---|---|---|---|
| 1. | a | b | c | d | 6. | a | b | c | d |
| 2. | a | b | c | d | 7. | a | b | c | d |
| 3. | a | b | c | d | 8. | a | b | c | d |
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Overall quality	5	4	3	2	1
Relevance to practice	5	4	3	2	1
Value of content	5	4	3	2	1
	Agree				Disagree
Important to pharmacists	5	4	3	2	1
Increased my knowledge	5	4	3	2	1
Achieved stated objectives	5	4	3	2	1
Was educational and not promotional	5	4	3	2	1

It took me _____ hours and _____ minutes to read this article and complete the assessment questions.



Prevention: Which *IDIS* disease terms to use or not to use? V07., V07.2 or 99.3

Prevention is an integral part of today's practice of medicine.

The benefits of **immunization** in the prevention and spreading of childhood infectious diseases have been proven by a sharp decrease during the last fifty years in the incidence of once common and sometimes debilitating diseases such as rubella, mumps, measles, whooping cough, tetanus, diphtheria or poliomyelitis. How is immunization covered in *IDIS*?

A search of the term "*Immunization*" in the Thesaurus brings up four entries crossed to two defined terms:

- Active Immunization See INOCULATION AND VACCINATION **99.3**
- Immunization, Active See INOCULATION AND VACCINATION **99.3**
- Passive immunization See PROPHYLAXIS, IMMUNOTHERAPY **V07.2**
- Immunization, Passive See PROPHYLAXIS, IMMUNOTHERAPY **V07.2**

In **active immunization**, the vaccine, either in the form of a live weakened or killed microbe or its components, trigger an immunological mechanism in the vaccinee to confer a protective specific immunity against that specific organism. A search with the valid term "*HEPATITIS, VIRAL B 070.2*" in the *IDIS* disease field retrieves all articles related to hepatitis B in our database (1,663 citations—through May 2001 Update). "*HEPATITIS, VIRAL B 070.2*" combined with "*INOCULATION AND VACCINATION 99.3*" using the Boolean operator "and" in the disease field retrieves 820 citations specific to hepatitis B vaccination.

Not all vaccines are indexed in the database under "*INOCULATION AND VACCINATION 99.3*". Articles related to intravesical BCG vaccine used in the treatment of urinary bladder cancer are not indexed under "*INOCULATION AND VACCINATION 99.3*". This disease term is used only when the intent is to mount a cell-mediated immune response against a specific organism, such as *Mycobacterium tuberculosis* in the case of BCG vaccine.

In **passive immunization**, the administration of a therapy containing antibodies or lymphocytes confers a rapid but short duration immunity to prevent an imminent specific infection. An *IDIS* search conducted with the term "*PROPHYLAXIS, IMMUNOTHERAPY V07.2*" yields over 500 citations related to the use of immune globulins such as RSV immune globulin, varicella-zoster immune globulin, hepatitis b immune globulin and antirabies serum. The same search conducted with the additional term "*HEPATITIS, VIRAL B 070.2*" combined with the Boolean operator "and" in the disease field retrieves approximately 100 articles pertaining to the prophylactic use of immunotherapy for hepatitis B, i.e. HEPATITIS B IMMUNE GLOBULIN 80040017.

Immunotherapy in the context of allergenic desensitization is indexed under "*DESENSITIZATION, ALLERGEN V07.1*" and not "*PROPHYLAXIS, IMMUNOTHERAPY V07.2*".

Some drugs can be very effective but their safety profile is such that it limits their use. **Prophylaxis** measures are needed to minimize an anticipated frequent and serious drug side-effect. Oral corticosteroids are often used in the treatment of rheumatological diseases. Evidence has shown that their long-term use at moderate to high doses can cause bone loss leading to osteoporosis.

Search example: What are the drugs used in the prophylaxis of drug-induced osteoporosis? A search in the thesaurus done with the term “*prevent**” brings up the entry “Treatment, Preventive, Unspecified See PROPHYLAXIS NEC V07.”. Conducting a search in the disease field by combining the valid search terms “*PROPHYLAXIS NEC V07.*” with “*OSTEOPOROSIS 733.0*” and “*TX/AE-DRUG/CHEMICAL E999.*” using the Boolean operator “and” retrieves 60 articles related to the prevention of drug-induced osteoporosis. (May 2001 Update)

The term “*PROPHYLAXIS NEC V07.*” can also be used to retrieve articles pertaining to the prevention of postoperative complications such as nausea and vomiting, transplant rejection as well as non-iatrogenic conditions such as postmenopausal osteoporosis or coronary heart disease.

If you have any search questions, please do not hesitate to contact us. An *IDIS* pharmacist will gladly assist you.



ThaiBinh TonThat, R.Ph., Pharm.D.

Perspective from an *IDIS* Subscriber



Re: Amiodarone (Cordarone™) associated pulmonary disease

DATA: VITALS – blood pressure 121/63; pulse 68; respiratory rate 24; temperature 97.4 on admission; ALLERGY – penicillin; 88 Year-old White Male; 69 inches/171 lbs; calculated creatinine clearance value of 27 mL/min (4/23); White Blood Cell 11.4 (4/16) – 8.8 (4/22); Thyroid Stimulating Hormone 6.6 (4/23); FT₄ 0.86;

Liver Function Tests – within normal limits except Alkaline Phosphatase 1.2 x ULN; Erythrocyte Sedimentation Rate – not done; (arterial pCO₂-49, pO₂ 52 on admission)

HISTORY OF PRESENT ILLNESS: The patient was seen in Emergency Room for the complaint of increasing shortness of breath, a non-productive cough, and anorexia for 14 days prior to admission. He denied any other symptoms. His chest film report noted diffuse bilateral inflammatory findings with probable right pleural effusion. His most recent chest film on 2/12/01 revealed only cardiomegaly. He was admitted to medicine to rule out pneumonia and then to Medical Intensive Care Unit to rule out acute myocardial infarction. By 4/25/01 he had improved and was transferred to the geriatric evaluation team for assistance with placement.

PRIOR MEDICAL HISTORY: Coronary Artery Disease (CAD) – status post, Acute Myocardial Infarction (AMI) 1999, Peripheral Vascular Disease (PVD), Congestive Heart Failure (CHF), Chronic Obstructive Pulmonary Disease (COPD), Gastroesophageal Reflux Disease (GERD), Benign Prostatic Hyperplasia (BPH), hypothyroidism, legally blind.

MEDICATIONS: (Outpatient) levothyroxine 0.88 mg qd, amiodarone 200 milligrams every day (begun 11/16/00), Lansoprazole 30 milligrams qAM, Timolol 0.5% 1 drop every 12 hours right eye, multivitamin with minerals daily.

LITERATURE: Amiodarone was first used as a coronary vasodilator in Europe in the 1960's. Reports of amiodarone's antiarrhythmic efficacy after intravenous administration and oral administration were published in 1970 and 1974 respectively. Initially it was believed that amiodarone was an "ideal" antiarrhythmic agent. It was effective for various refractory arrhythmias, produced few acute adverse effects, and had no clinically important negative inotropic effects. It also was the first oral agent that could be administered once daily (Pollak 1998, Singh 1983).

The desire of some clinicians for rapid, dramatic results and a preference for high dose monotherapy, led to amiodarone dosing that resulted in toxicity and limited its acceptability. Amiodarone's toxicity profile eventually included dermatologic, ophthalmologic, neurologic, thyroid, hepatic and pulmonary adverse effects. By the time amiodarone was available in the United States it was being reserved for patients with life-threatening or severely symptomatic arrhythmias who were resistant or intolerant to standard therapy. Amiodarone was available in the United States as an investigational drug and had been used in 432 patients by the time Sobol and Rakita published their six patient series of amiodarone pneumonitis and pulmonary fibrosis in 1980. The incidence of amiodarone pulmonary toxicity based on that limited data was 1.4% (Sobol, 1982).

Based on Sobol's research there had been no reports of amiodarone pulmonary toxicity in the world literature prior to 1980. Rotmensch had published a case of possible amiodarone associated pneumonitis in 1980 (Rotmensch, 1980). In spite of widespread use of amiodarone in Europe for almost two decades with documented use for more than 500,000 patient-years in one country, there were no published reports of pulmonary toxicity. Several reviews of amiodarone pulmonary toxicity (APT) have recently been published (Marchlinski et al. 1982, Martin 1988, Pitcher 1992, Fraire 1993, Adams et al. 1986).

In the 1990's the use of new lower maintenance doses is thought to have decreased the frequency of side effects of amiodarone while maintaining efficacy. Amiodarone has reemerged as a preferred drug for the treatment of ventricular arrhythmias in the setting of heart disease.

The common clinical presentation of APT is the insidious onset of non-productive cough, dyspnea, weight loss, and occasionally fever with chest x-ray findings of infiltrates with a diffuse interstitial pattern. The symptoms usually do not precede changes in the chest film. This syndrome is thought to be rare in patients receiving less than 400 mg of amiodarone daily like This Patient. There is another type of presentation with a "more acute onset," often associated with fever, that mimics infectious pneumonitis.

Signs and symptoms of APT are non-specific and include:

- Dyspnea is initially present in one-half to three-fourths of patients and in all patients as the disease progresses. (Dyspnea is worse on exertion.)
- Cough is typically nonproductive.

Other symptoms may include:

- Fever is present in one-third to one-half of patients.
- Chest pain, usually pleuritic, is present in many cases.
- Weakness and weight loss are commonly reported.

Physical examination findings include:

- Bilateral rales are typically reported.

Laboratory abnormalities include:

- Leukocytosis is commonly described.
- Increased erythrocyte sedimentation rate reported in >50% of cases.
- Increased lactate dehydrogenase.

Pulmonary function tests results:

- (see discussion in references 2 and 4.)
- A normal D_{co} would make APT unlikely.

Radiographic findings include:

- Chest x-ray film appearances are widely variable. Abnormal findings will usually be bilateral and diffuse, but may be patchy and focal. The most common finding is a pattern including both alveolar and interstitial features. Pleural effusion is said to be uncommon.

EDITOR'S NOTE: From time to time, we publish articles contributed by *IDIS* subscribers. An article from Dave Mace, B.S.Pharm., is included in this issue. Dave Mace is from an institution that is a long-standing *IDIS* subscriber, utilizing the database on a regular basis. His consult illustrates *IDIS* database use contributing directly to patient care outcomes. The responsibility for errors is the author's alone. The consult does not necessarily represent hospital views and recommendations. We hope you find the information interesting and useful and welcome comments. If you are interested in sharing your experiences using the *IDIS* database, please contact donna-brus@uiowa.edu.



Donna Brus, Editor

COMMENT:

If the patient did not have either infection or heart failure

Patient	Dyspnea grade	Cough	Pleuritic pain	Fever	Crackles	Pleural rub
Adams 32	IV	+	0	0	+	0
Adams 33	IV	0	0	0	+	0
Adams 34	IV	+	+	+	+	+
Adams 35	III	+	0	0	+	0
Adams 36	III	0	+	0	+	0
Adams 37	IV	0	0	+	+	0
This Patient	III	+	0	0	+	0

Adapted from reference number 1.

at the time of his recent admission, APT may be a realistic possibility. His total cumulative dose of amiodarone is at least 30.4 G at the time of presentation on 4/16/01. At that time he had been on amiodarone 200 mg daily, for at least 152 days. In Adam's prospective study of APT in 34 patients taking amiodarone, one of the patients who developed APT had been taking a mean daily dose of only 238 mg for 180 days (Adams 1986).

The patient's presentation is very similar to the patients described in Adam's series.

During his admission to the ICU he was treated with IV steroids, for a presumed exacerbation of his Chronic Obstructive Pulmonary Disease, he was also treated with antibiotics, diuretics and bronchodilators. By the time of his transfer to our service he was said to have no signs of infection or pneumonia. But several days later he had

bilateral crackles when examined and his dyspnea on exertion persisted unchanged.

His clinical situation is consistent with the possibility of APT. Current pulmonary function tests with a diffusing lung capacity test for carbon monoxide would aid diagnosis. A normal diffusing lung capacity for carbon monoxide result would weigh against the diagnosis of APT.

If the results of pulmonary function tests are consistent with APT, the relative risk of APT versus his need for the amiodarone will have to be included in the decision to continue his amiodarone.

Dave Mace, R.Ph., Drug Information Specialist, wrote the article. Mace graduated from the University of Iowa College of Pharmacy in 1967. Since 1982 he has served as the Director of the Drug Information Center at BPVAMC, 10,000 Bay Pines Blvd., Bay Pines, FL 33744. His responsibilities include serving as a preceptor for drug information and Pharm.D. clerkship programs and responding to complex drug information requests from clinical staff.

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4. Martin WJ, Rosenow EC. Amiodarone pulmonary toxicity: Recognition and pathogenesis (Part I). *Chest* 1988; 93:1067-1075. (IDIS Article Number 315825)
5. Pitcher WD. Southwestern Internal Medicine Conference: Amiodarone pulmonary toxicity. *Am J Med Sci* 1992; 303:206-212. (IDIS Article Number 292312)
6. Pollak TP. Oral amiodarone: Historical overview and development. *Pharmacotherapy* 1998; 18: 121S-126S. (IDIS Article Number 417844)
7. Rotmensch HH, et al. Possible association of pneumonitis with amiodarone therapy. *Am Heart J* 1980; 100:412-413. (IDIS Article Number 122446)
8. Singh BN. Amiodarone: Historical development and pharmacologic profile. *Am Heart J* 1983; 106:788-797. (IDIS Article Number 176067)
9. Sobol SM and Rakita L. Pneumonitis and pulmonary fibrosis associated with amiodarone treatment: A possible complication of a new antiarrhythmic drug. *Circulation* 1982; 65:819-824. (IDIS Article Number 147109)

FDA DRUG/BIOLOGIC APPROVALS

Generic Name (FDA Therapeutic Classification) <i>Trade Name</i>	Sponsor (Approval Date)	Valid <i>IDIS</i> Drug Term Drug Number (<i>IDIS</i> Citations)*	Indication/Use	Valid <i>IDIS</i> Disease Term Modified ICD-9-CM Number
Alemtuzumab (NA) <i>Campath</i>	Millennium and ILEX Partners, LP (May 7)	ALEMTUZUMAB 10120196 (27 citations)	For the treatment of patients with B-cell chronic lymphocytic leukemia who have been treated with alkylating agents and who have failed fludarabine therapy	Leukemia, Lymphoid, Chronic 204.1
Almotriptan Malate (1S)** <i>Axert</i>	Pharmacia (May 7)	ALMOTRIPTAN 28081298 (5 citations)	Treatment of migraine	Migraine 346.
Caspofungin Acetate (1P)*** <i>Cancidas</i>	Merck (Jan. 29)	CASPOFUNGIN 8120411 (1 citation)	Treatment of aspergillosis in patients who cannot tolerate or are unresponsive to standard therapies	Aspergillosis 117.3
Formoterol Fumarate (1S) <i>Foradil</i>	Novartis (Feb. 16)	FORMOTEROL 12120046 (136 citations)	For long term, twice daily administration in the maintenance treatment of asthma and in the prevention bronchospasm in adults and children 5 years and older with reversible obstructive airway disease, including patients with symptoms of nocturnal asthma, who require regular treatment with inhaled short-acting beta2-agonists	Asthma Nec 493.
Galantamine Hydrobromide (1S) <i>Reminyl</i>	Janssen (Feb. 28)	GALANTAMINE 12040012 (31 citations)	Treatment of mild to moderate dementia of the Alzheimer's type	Alzheimer's Disease 331.0 Psychosis, Organic Nec 294.
Imatinib (1PV)**** <i>Gleevec</i>	Novartis (May 10)	IMATINIB 10120185 (6 citations)	Treatment of patients with chronic myeloid leukemia (CML) in blast crisis, accelerated phase, or in chronic phase after failure of interferon-alpha therapy	Leukemia, Myeloid, Chronic 205.1
Ziprasidone Hydrochloride (1S) <i>Pfizer</i>	Zeldox (Feb. 5)	ZIPRASIDONE 28160844 (66 citations)	Treatment of schizophrenia	Schizophrenia Nec 295.

* Through May 2001 Update. Complete bibliographic citations will be provided upon request.

** New molecular entity given standard review by FDA.

*** New molecular entity given priority review by FDA.

**** Orphan Drug

NA Not applicable

New Drug Selected Bibliography

This new drug selected bibliography provides a selection of key clinical studies and reviews of new drugs approved by the FDA January through May 2001. *IDIS/CD-ROM* was searched to retrieve key articles relevant to the new drugs and their approved uses.

ALEMTUZUMAB

Osterborg A, Dyer MJ, Bunjes D et al. Phase II multicenter study of human CD52 antibody in previously treated chronic lymphocytic leukemia. *J Clin Oncol* 1997;15:1567-74. (*IDIS* Article Number 383720). **Researchers performed an open, multicenter, phase II study to evaluate the safety and efficacy of Campath-1H (alemtuzumab) via 30mg 2hr intravenous infusion thrice weekly, for a maximum period of 12 weeks, in 29 chemotherapy-refractory or relapsed chronic lymphocytic leukemia patients.**

ALMOTRIPTAN

Colman SS, Brod MI, Krishnamurthy A et al. Treatment satisfaction, functional status, and health-related quality of life of migraine patients treated with almotriptan or sumatriptan. *Clin Ther* 2001;23:127-45. (*IDIS* Article Number 460067). **A double-blind, multicenter, randomized, parallel-group study was conducted to compare treatment satisfaction, functional status, and health-related quality of life of 1173 migraine patients treated with oral almotriptan (12.5mg) versus sumatriptan (50mg) for acute treatment of migraine headaches.**

FORMOTEROL

Pauwels RA, Lofdahl CG, Postma DS et al. Effect of inhaled formoterol and budesonide on exacerbations of asthma. *N Engl J Med* 1997;337:1405-11. (*IDIS* Article Number 394992). **Researchers performed a double-blind, randomized, parallel-group, 12-month study of 852 asthmatic patients randomly assigned to one of four treatments, given twice daily by means of a dry-powder inhaler (100ug of budesonide plus placebo, 100ug of budesonide plus 12ug of formoterol, 400ug of budesonide plus placebo, or 400ug of budesonide plus 12ug of formoterol), to evaluate the effects of adding inhaled formoterol to both lower and higher doses of the inhaled glucocorticoid budesonide.**

Akpinarli A, Tuncer A, Saraclar Y et al. Effect of formoterol on clinical parameters and lung functions in patients with bronchial asthma: a randomised controlled trial. *Arch Dis Child* 1999;81:45-8. (*IDIS* Article Number 432164). **A six week, double blind, randomized, parallel group, placebo controlled study was conducted to investigate the effects of inhaled formoterol (12ug twice daily) in 32 children with moderate to severe bronchial asthma.**

Fitzgerald JM, Chapman KR, Cioppa GD et al. Sustained bronchoprotection, bronchodilatation, and symptom control during regular formoterol use in asthma of moderate or greater severity. *J Allergy Clin Immunol* 1999;103:427-35. (*IDIS* Article Number 426713). **A 6 month, multicenter, parallel-group, double-blind, placebo-controlled study was performed to compare the long term effects of formoterol (12ug twice daily), albuterol (200ug 4 times daily), and on-demand albuterol (100ug/puff) on bronchial hyperresponsiveness in 271 asthma patients receiving concomitant inhaled corticosteroids.**

Perpina M, Duce F, Burgos A et al. Effect of treatment with formoterol on indicators of ventilatory function and their relationship to quality of life in patients with asthma under daily practice conditions. *Curr Ther Res* 1999;60:207-19. (*IDIS* Article Number 424472). **An uncontrolled, 8 week, multicenter study was conducted to assess the relationship between indicators of ventilatory function and quality of life in 746 asthma patients receiving 12 or 24ug of formoterol twice daily.**

Ekstrom T, Ringdal N, Tukiainen P et al. A 3-month comparison of formoterol with terbutaline via turbuhaler, a placebo-controlled study. *Ann Allergy Asthma Immunol* 1998;81:225-30. (*IDIS* Article Number 415167). **A 12 week, parallel-group, double-blind, randomized study was conducted to compare the efficacy and safety of formoterol (12ug twice daily) and terbutaline (500ug four times daily) in 343 asthma patients.**

GALANTAMINE

Wilcock GK, Lilienfeld S, Ganens E et al. Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicenter randomised controlled trial. *BMJ* 2000;321:1445-9. (*IDIS* Article Number 456878). **Investigators conducted a six month, randomized, double blind, multicenter, placebo controlled trial to evaluate the efficacy and safety of galantamine maintenance doses of 24 or 32mg in 653 patients with mild to moderate Alzheimer's disease.**

Raskind MA, Peskind ER, Wessel T et al. Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. *Neurology* 2000;54:2261-8. (IDIS Article Number 449305). **A six month, randomized, multicenter, double-blind, placebo-controlled trial was used to evaluate the safety and efficacy of galantamine maintenance doses of 24 or 32mg in 636 patients, with mild to moderate Alzheimer's disease, followed by a 6-month open-label study of the 24 mg dose in eligible patients.**

Tariot PN, Solomon PR, Morris JC et al. A 5-month, randomized, placebo-controlled trial of galantamine in AD. *Neurology* 2000;54:2269-76. (IDIS Article Number 449306). **A five month, randomized, multicenter, placebo-controlled, double-blind study was preformed to investigate the tolerability and efficacy of galantamine maintenance doses of 8, 16, or 24mg/day in 978 patients with mild to moderate Alzheimer's disease.**

IMATINIB

Druker BJ, Sawyers CL, Kantarjian H et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. *N Engl J Med* 2001;344:1083-42. (IDIS Article Number 461597). **An on going pilot dose-escalation study designed to assess the antileukemic activity and safety of CGP 57138B (Imatinib) inhibition (300-1000mg/day) on BCR-ABL tyrosine kinase in 58 patients, 38 with myeloid blast crisis and 20 with lymphoid blast crisis.**

ZIPRASIDONE

Keck PE, Reeves KR, Harrigan EP et al. Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. *J Clin Psychopharmacol* 2001;21:27-35. (IDIS Article Number 458070). **Data was taken from two separate, randomized, multicenter, placebo-controlled, double-blind studies to assess the efficacy and safety of ziprasidone in a subset 115 hospitalized schizoaffective patients on 40, 80, 120, 160mg/day or placebo, for four to six weeks.**

Goff DC, Posever T, Herz L et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. *J Clin Psychopharmacol* 1998;18:296-04. (IDIS Article Number 411148). **A four week, randomized, multicenter, double-blind, exploratory, dose-ranging trial was conducted to assess the safety and efficacy of ziprasidone in 90 schizophrenic or schizoaffective patients on fixed doses of ziprasidone 4, 10, 40, 160mg/day or haloperidol 15mg/day.**

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