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INSIDE

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FDA Approves Vioxx and Avandia

By William T. Elliott, MD, FACP

Merck's entry into the cox-2 market, the highly anticipated **rofecoxib** (**Vioxx**) was approved by the FDA on May 21. The drug was approved for the treatment of osteoarthritis pain, menstrual pain and acute pain in adults. Rofecoxib joins **Searle's celecoxib** (**Celebrex**) as the only drugs in this class of "safer" NSAIDs. Celecoxib was approved in December for the treatment of osteoarthritis and rheumatoid arthritis, and Merck is hoping that the pain indication for rofecoxib will be a marketing edge in what promises to be a very competitive drug class. Merck provided studies to the FDA that demonstrated equivalency of refocoxib to existing NSAIDs for the treatment of pain, the standard the FDA required for the indication. COX-2 inhibitors have a lower tendency to induce gastroduodenal ulcers than standard NSAIDs, and have no affect on platelet function. Their effect on renal blood flow is the same as existing NSAIDs. Rofecoxib is available in 12.5 and 25 mg tablets, and is taken once a day. The recommended dose is 12.5-25 mg/d for arthritis, and up to 50 mg/d for pain. The drug will cost about $2.50 per tablet for both strengths.

The FDA has also approved **SmithKline Beecham's rosiglitazone** (**Avandia**) for the treatment of type 2 diabetes as monotherapy, or, in combination with metformin. The drug is a thiazolidinedione similar to **Warner Lambert's troglitazone** (**Rezulin**), a drug that was recently the subject of new FDA restrictions because of the risk of liver toxicity. Although no liver toxicity was found in trials with rosiglitazone, the FDA is recommending liver enzyme monitoring every two months for the first two years of therapy. SmithKline is quick to point out however that they feel the risk for liver toxicity is low since it metabolized differently than troglitazone, and is less likely to cause drug - drug interactions. **Lilly/Takeda's pioglitazone** (**Actos**), the third drug is this class is also nearing approval.

One of the most important prevention trials is recent years is enrolling patients. **The Study of Tamoxifen and Raloxifene** (**STAR**) trial will enroll over 20,000 women who are at risk for breast cancer to compare effectiveness of the two drugs in preventing breast cancer. The study is being run by the National Cancer Institute at 400 centers in the US, Canada, and Puerto Rico. Women will be randomized to either tamoxifen 20 mg/day or raloxifene 60 mg/day for five years. Tamoxifen was shown to effectively reduce the rate of breast cancer in high-risk women in the Breast Cancer Prevention Trial published in 1998. Raloxifene is currently approved for the treatment of osteoporosis, but early studies suggest that it may be effective

in preventing breast cancer. The STAR study is a head to head study, with no placebo group.

Should **low molecular weight heparin** become the standard for the treatment of inpatient **deep venous thrombosis**? While physicians and patients love the ease and the safety of low molecular weight heparin, hospital administrators have been concerned about the costs. A new study looked at the cost effectiveness of low molecular weight heparin vs standard unfractionated heparin, and found that the overall costs of care were similar with the two drugs. Cost savings favored low molecular weight heparin therapy if any of the following were true: there were fewer late complications, as few as 8% of the patients were treated as outpatients, 13% or more of patients were eligible for early discharge, or pharmacy costs were reduced by at least 31% (*Ann Int Med* 1999;130:789-799). These are all likely scenarios, especially when many hospitals are discharging the majority of patients early to self-administer the drug.The authors analysis suggests that low molecular weight heparin is cost-effective for this indication.

The FDA has issued a warning regarding Immunex's recently approved rheumatoid arthritis drug **etanercept** (**Enbrel**). Postmarketing reports point to a higher than expected incidence of sepsis and other serious infections in treated patients, some of them fatal. The company has issued a "Dear Doctor" letter urging caution when using the drug in patients with infections or patients that are at risk of developing infections. Etanercept is a tissue necrosis factor (TNF) inhibitor that is given by subcutaneous injection twice weekly. The drug was initially studied as a potential therapy for sepsis, but the studies were halted when it was found that the mortality rate was higher in etanercept treated patients. According to the FDA, approximately 25,000 RA patients have been treated with etanercept, with reports of 30 serious infections including sepsis. Immunex plans to perform large, prospective studies to assess the risk of infection in patients treated with etanercept. In related news, the FDA recently granted etanercept an indication for juvenile arthritis. Immunex is also reporting early results from Phase III studies demonstrating effectiveness in slowing progression and reducing signs of early RA.

Is **low-dose hormone replacement therapy** (HRT) effective in preventing osteoporosis? A recent study looked at the lowest available dose of conjugated estrogen (0.3 mg/d) and medroxyprogesterone (2.5 mg/d) as a daily HRT regimen in preventing osteoporosis in women over the age of 65 (*Ann Intern Med*. 1999;130:897-904). When used with at least 1000 mg/ day of calcium and vitamin D, bone density increased by 3.5% over 3.5 years in an intention-to-treat analysis, and by 5.2% among patients with greater than 90% adherence to therapy. This compares favorably with reports of studies of higher dose regimens in elderly women. Adverse reactions to HRT tend to be dose-related, and many women desire lower dose regimens, hence the importance of this study.

Preven, **Barr** and **Gynetic's** new emergency contraceptive kit has hit an unusual road block in marketing its product, many drug stores refuse to carry it. The kit, which is for use within 72 hours of unprotected sex, is mistakenly being called an "abortion drug," even though the primary effect of this combination kit of high- dose oral contraceptives is to prevent pregnancy. Recently Wal-Mart, one of the largest retail pharmacy chains in the country, announced that they would not stock Preven, and many local pharmacies have followed suit. The American College of Obstetricians and Gynecologists has roundly criticized this trend, arguing that the drug is no different in concept from other forms of contraception, and its ready availability will likely reduce the number of abortions in this country each year. ■

Trovafloxacin Tablet and Azithromycin for Oral Suspension (Trovan/Zithromax Compliance Pak-Pfizer)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

In december, the fda approved a product for the dual treatment of two common sexually transmitted diseases caused by *Neisseria gonorrhea* and *Chlamydia trachomatis*. Marketed by Pfizer under the trade name Trovan/Zithromax Compliance Pak, the combination contains a fluoroquinolone, trovafloxacin, and an azalide, azithromycin.

Indications

Trovafloxacin/azithromycin is indicated for the treatment of uncomplicated urethral gonorrhea in males and endocervical and rectal gonorrhea in females caused by

N. gonorrhea and nongonococcal urethritis and cervicitis due to *C. trachomatis*.

Dosage

The contents of the azithromycin (1 g) packet should be mixed thoroughly with 2 oz of water and taken orally. This should be followed by an additional 2 oz of water to ensure that the complete packet is consumed. The trovafloxacin tablet should be taken with the second portion of the liquid. The product may be taken without regard to meals but should be taken at least two hours before or two hours after aluminum- or magnesium-containing antacids, sucralfate, citric acid/sodium citrate, formulations containing buffers such as didanosine, or metal cations such as iron.

Patients should refer their sex partners for evaluation, testing, and treatment. Patients should be instructed to abstain from sexual intercourse for seven days after a single-dose regimen.[1]

Trovan/Zithromax is supplied as a 100 mg tablet of trovafloxacin and 1 g azithromycin for oral suspension.

Potential Advantages

The Trovan/Zithromax Compliance Pak provides a convenient single-dose dual therapy for gonococcal and chlamydial infections. Trofloxacin has shown in vitro activity against strains of *N. gonorrhea* that are relatively resistant to ciprofloxacin and ofloxacin.3 Single-dose azithromycin is more convenient than doxycycline, which is dosed for seven days and may actually be cost-effective despite higher initial drug cost.[5]

Potential Disadvantages

Quinolones are contraindicated for pregnant women.[1] Most common side effects associated with the combination of trovafloxacin and azithromycin include nausea (50%), abdominal pain (25%), and dizziness/lightheadedness (15%).[3] Although rare (< 1%) in the United States, *N. gonorrhea* resistant to fluoroquinolones has been reported in other parts of the world, especially in Asia.[1] The prevalence of quinolone-resistant *N. gonorrhea* is expected to increase in the United States.[1]

Comments

Routine dual treatment for *N. gonorrhea* and *C. trachomatis* is generally recommended, as coinfection is common. Dual treatment may also hinder the development of resistant strains of *N. gonorrhea* since both doxycycline and azithromycin are active against *N. gonorrhea*.[1] Current recommendations of the CDC for dual treatment include azithromycin or doxycycline for chlamydia and ceftriazone 125 mg IM, cefixime 400 mg, ciprofloxacin 500 mg, or ofloxacin 400 mg[1] for gonorrhea. Azithromycin single dose is more convenient than doxycyline 100 mg twice daily for seven days. Single-dose trovafloxacin has been reported to be equivalent to ofloxacin both bacteriologically and clinically.[4] Cure rate was 99% for trovafloxacin and 98% for ofloxacin. This compares favorably to ceftriazone (99%), ciprofloxacin (99.8%), and cefixime (97%).[1]

At the time of this printing, Pfizer has not yet launched the product and cost was not available.

Clinical Implications

Chlamydial and gonorrheal genital infections are common in the United States and often exist as coinfections. Chlamydial infections are commonly asymptomatic in both males and females, while gonorrhea tends to be asymptomatic in females. Notwithstanding transmission, serious sequelae can result from these infections, including pelvic inflammatory disease, ectopic pregnancy, and infertility. To ensure compliance, medications should be dispensed on site at the time of diagnosis and the administration of the medication should be directly observed. Currently, there are convenient and highly effective dual treatments. Trovan/Zithromax Compliance Pak offers a single-prescription, oral, one-time treatment that is highly effective. Patients do not need to be retested for cure after completing treatment unless symptoms persist or reinfection is suspected. ■

References

1. *MMWR* 1998;47(RR-1):1-118.
2. Knapp JS, et al. *Antimicrob Agents Chemother* 1995;39(4):987-989.
3. Trovan/Zithromax Product Information. Pfizer 1999.
4. Jones RB, et al. *Am J Med* 1998;104:28-32.
5. Magid D, et al. Ann Intern Med 1996;124(4):389-399.

Lansoprazole, Amoxicillin, and Clarithromycin (Prevpac—TAP)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Helicobacter pylori infection is associated with 90% of non-NSAID-related peptic ulcers. The bacterium, which commonly infects the

upper GI tract, has also been implicated as a risk factor for gastric adenocarcinoma and low-grade gastric lymphoma of mucosa-associated lymphoid tissue.[1] In January, the FDA approved TAP's Prevpac, an administration pack containing one of the highly effective regimens for the eradication of *H. pylori*—the antibiotics clarithromycin and amoxicillin and a proton pump inhibitor, lansoprazole.

Indications

Prevpac is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease.

Dosage

Prevpac provides a daily dose of lansoprazole 30 mg (1 capsule), amoxicillin 1000 mg (2 capsules), and clarithromycin 500 mg (1 tablets) taken twice daily before meals (morning and evening) for 10 or 14 days.

Prevpac is supplied as a daily administration pack containing a sufficient number of capsules and tablets of the three-drug regimen.

Potential Advantages

Prevpac provides a highly effective and convenient regimen for the eradication of *H. pylori*. It is the only highly effective regimen in which all the components are available as a dispensing unit. This regimen also minimizes the risk of bacterial resistance since the rate of *H. pylori* resistance to either clarithromycin or amoxicillin is low, especially compared to metronidazole. A proton pump inhibitor-based triple-therapy regimen may be better tolerated with amoxicillin than with metronidazole.[1] Dosing of this combination is convenient (twice daily) compared to the four times daily dose for bismuth subsalicylate, metronidazole, and tetracycline (e.g., Helidac). Compliance and side effects have been reported to be problematic with bismuth regimens.[3]

Potential Disadvantages

Prevpac should not be used in patients with penicillin allergy, these who are pregnant, or those who are receiving concomitant therapy with cisapride, astemizole, or pimozide.[2] Potential drug interactions may occur between clarithromycin and ergotamine, triazolam, HMG-CoA reductase inhibitors, carbamazepine, cyclosporine, tacrolimus, phenytoin, disopyramide, alfentanil, bromocriptine, valproate, rifabutin, digoxin, protease inhibitors (e.g., ritonavir, indinavir), and warfarin.[2] Lansoprazole may affect the absorption of ketoconazole, iron, and digoxin by reducing gastric acidity.[2] Most common side effects reported with Prevpac are diarrhea (7%), headache (6%), and taste perversion (5%).[2]

Comments

Patients with peptic ulcers who have evidence of *H. pylori* infection benefit from eradication of the organism. Effective treatment promotes ulcer healing and reduces the rate of ulcer recurrence. Efficacious treatment regimens should have a cure rate of 90% and greater on per-protocol analysis and 80% or greater on intent-to-treat analysis.[1] Prevpac has reported eradication rates of 81-86% on intent-to-treat analysis and 84-92% on per-protocol analysis.[2] The intent-to-treat analysis is considered more reflective of clinical practice as this analysis includes patients who did not complete the treatment regimen for various reasons.[7] A 10-day regimen appears to be as efficacious as a 14-day regimen.[4] Lansoprazole also appears to be as efficacious as omeprazole.[5]

The cost of a 14-day treatment regimen with Prevpac is about $200. A combination of bismuth, metronidazole, and tetracycline (Helidac) with a proton pump inhibitor is about $170.

Clinical Implications

H. pylori infection is a common infection; however, most infected individuals are asymptomatic. Treatment is beneficial to those who have peptic ulcer disease or gastric mucosa-associated lymphoid tissue lymphoma.[1] *H. pylori* eradication with one of the appropriate regimens should be first-line therapy for infected patients with peptic ulcer. *The Guidelines for the Management of Helicobacter pylori Infection* by the Ad Hoc Committee on Practice Parameters of the American College of Gastroenterology stated that the highest eradication rates are achieved with a proton pump inhibitor, clarithromycin, and amoxicillin or metronidazole for two weeks, ranitidine bismuth citrate, clarithromycin, and ether amoxicillin, metronidazole, or tetracycline for two weeks, or a proton pump inhibitor, bismuth, metronidazole, and tetracycline for 1-2 weeks.[1] Diagnostic testing for *H. pylori* should only be performed if treatment is intended. There is no clear evidence that eradication of *H. pylori* will relieve symptoms of nonulcer dyspepsia.[1] While *H. pylori* eradication significantly reduces ulcer recurrence, a recent meta-analysis indicated that 20% of patients had ulcer recurrence within six months. Laine and colleagues suggest that non-*H. pylori* or non-NSAID ulcers may be more common than previously believed.[6] Prevpac is a regimen that is highly efficacious, convenient, and also minimizes the risk of developing bacterial resistance. ■

References

1. Howden CW, et al. *Am J Gastroenterol* 1998;93(12): 2330-2338.
2. Prevpac Product Information. January 1999. TAP

Pharmaceuticals.
3. Dobrucali A, et al. *Wien Med Wochenschr* 1998; 148(20):464-468.
4. Fennerty MB, et al. *Arch Intern Med* 1998; 158(15):1651-1656.
5. Bazzoli F, et al. *Helicobacter* 1998(3):195-201.
6. Laine L, et al. *Am J Gastroenterol* 1998;93(9): 1409-1415.
7. William MP, et al. *Drugs* 1998;65(1):1-10.

Bedtime Insulin Plus Metformin Prevents Weight Gain and Reduces Frequency of Hypoglycemia in Type 2 Diabetes

Source: *Yki-Jarvinen H, et al. Ann Intern Med 1999; 130:389-396.*

This excellent study compared four different bedtime insulin regimens to evaluate weight gain, frequency of hypoglycemic episodes, and glycemic control in patients with type 2 diabetes. Yki-Jarvinen and associates randomly assigned 96 patients with type 2 diabetes to one year of treatment with bedtime insulin plus glyburide and placebo, metformin and placebo, glyburide and metformin, or a second injection of insulin.

All patients in each group injected intermediate acting neutral human isophane insulin at 9 p.m. Additional therapy consisted of glyburide (10.5 mg). Given as one 3.5 mg tablet before breakfast and two 3.5 mg tablets before dinner plus four tablets of metformin placebo; metformin 2 g given as two 500 mg tablets before breakfast and two 500 mg tablets before dinner, and three tablets (1 before breakfast and 2 before dinner) of glyburide placebo; metformin (2 g), and glyburide (10.5 mg), given as described; or a second injection of neutral human isophane insulin before breakfast. Thus, the trial was only partially blinded.

Table

	Mean weight gain	Hypoglycemic episodes
BT insulin + glyburide	3.9 kg	3.4
BT insulin + metformin	0.9 kg	1.8
BT insulin + glyburide & metformin	3.6 kg	3.3
BT insulin + a.m. insulin	4.6 kg	3.9

Yki-Jarvinen et al's conclusions were that good glycemic control for one year was achieved by using simple bedtime insulin regimens in patients whose disease is poorly controlled with sulfonylurea therapy. Additionally, insulin and metformin gave better glycemic control, prevented weight gain, and induced less hypoglycemia than the other regimens tested.

Comment by Ralph R. Hall, MD, FACP

This study is consistent with a growing number of studies that show the advantages of metformin in the management of weight in type 2 diabetes.[1,2] The use of bedtime insulin has previously been shown to improve control but usually with weight gain as a side effect.[3] The decrease in hypoglycemic episodes is also a distinct plus. Further, the use of insulin rather than another oral hypoglycemic agent significantly decreases the cost of treatment.

Although there has been a great deal of skepticism regarding the decrease in cardiovascular events in the UKPDS studies when metformin was used alone, this potential advantage remains. In my view, it is another reason to consider metformin as the drug of choice.

Two new troglitazone-like preparations will be coming on the market within the next few months and will also need to be considered. Similar information should soon be available regarding acarbose and miglitol, which have great potential for some patients used alone or with insulin.

The important issue is that all studies demonstrate a significant reduction in microvascular disease with good glucose control. It is helpful to know that we can get better control and at the same time reduce cardiovascular risk factors. ■

References

1. Bell DSH, Mayo MS. *Endo Practice* 1998;4:360-364.
2. Giugliano D, et al. *Eur J Clin Pharmacol* 1993;44: 107-112.
3. Cusi K, Cunningham GR. *Diabetes Care* 1996;18: 843-850.
4 UKPDS Study Group (UKPDS 34). *Lancet* 1998;352: 854-865.

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Antidepressants and Pregnancy

By Lucy J. Puryear, MD

Depression occurs most commonly in women during the reproductive years, ages 22-45. The treatment of depression during pregnancy raises difficult issues. Many women and/or physicians are reluctant to use antidepressant medications during pregnancy; however, untreated depression may also have deleterious consequences for the fetus. As such, withholding antidepressant medication during pregnancy may not be the safest option in many circumstances. Fortunately, some antidepressant medications are considered relatively safe in pregnancy, although a thorough evaluation of the risk:benefit ratio is prudent.

If the mother is experiencing only mild depressive symptoms, psychotherapy alone may be useful.[1,2] In this situation, the patient exhibits no impairment in day-to-day functioning and has no accompanying thoughts of death. Psychotherapy alone is particularly indicated if there is no past history of more severe depression. Major depression, or clinical depression, is characterized by decreased energy, anhedonia (loss of interest in usual activities), tearfulness, excessive guilt, altered sleep and appetite, and suicidal thoughts or thoughts of death. In these cases, initiation of antidepressant medication may be necessary. Additionally, many women become pregnant while taking antidepressants, thereby raising the question of medication discontinuation.

If the woman has a history of recurrent, moderate-to-severe episodes of major depression, it is generally unwise to stop medication because the risk of recurrence is high. If there have been previous suicide attempts or hospitalizations, then antidepressants will need to be continued throughout the pregnancy and into the postpartum period. In these circumstances a choice needs to be made whether to remain on the current effective medication or to change to one with the most safety data. This is a decision best made in collaboration with the prospective parents.

Fluoxetine (Prozac), a selective serotonin reuptake inhibitor, is arguably the safest antidepressant during pregnancy. The manufacturer (Eli Lilly and Company) has a large database of women who have taken fluoxetine while pregnant without adverse fetal outcomes.[3,4] In a 1993 study of 128 women taking fluoxetine during pregnancy, there was no increase in congenital anomalies or perinatal complications compared to women taking nortriptyline, a tricyclic antidepressant.[3] The only study to date with a possible negative outcome is a study of 228 women who were exposed to fluoxetine in the first or second trimesters only vs. those who took the medication throughout the entire pregnancy.[5] Although this study suggests that exposure in the last trimester of pregnancy may be problematic, there were many other maternal variables not controlled for that may have affected outcome. Maternal age was higher in the fluoxetine-treated group, and depressive illness was not present in the control group. This is an important confound because untreated depression, in and of itself, may be associated with more neonatal complications.

There are few data regarding exposure to antidepressants and long-term behavioral outcome. One of the few studies published recently found no long-term effects on IQ, speech, or behavior in 55 children up to the age of 8 who had been exposed to fluoxetine in utero.[9] Although this information is preliminary, it appears that there are no long-term complications to children whose mothers have taken fluoxetine. There are no long-term behavioral outcome data about other antidepressants.

Several newer serotonergic medications are also available, although there are fewer data regarding their use during pregnancy. A recent retrospective study found no teratogenic effects following exposure to sertraline, paroxetine, and fluvoxamine.[6] These preliminary data are encouraging, but the sample included only 267 women in total, which is substantially less than the combined fluoxetine data. Among the older antidepressants, nortriptyline remains a reasonable choice if the serotonin reuptake inhibitors cannot be tolerated due to side effects or if the patient is unresponsive to SSRIs. Older data suggested that the tricyclic antidepressants may have been associated with limb deformities; however, newer evidence does not support this finding.[7,8] The advantage of nortriptyline is its therapeutic window of 50 to 150 ng/mL, which allows for the use of blood levels to guide dosing.

There is currently no database available on the use of bupropion, nefazodone, mirtazepine, or venlafaxine during pregnancy. Use of these agents must be undertaken with caution in pregnancy until human data are available. The *Physician's Desk Reference* pregnancy category has created some confusion. Although the SSRIs are listed as Class C drugs and bupropion as Class B, the difference between these two classifications has no clini-

cal use. Class B means that animal studies show no risk or show some risk but there are no well-controlled studies in animals or women. Class C means animal studies may show adverse risk but there are no well-controlled studies in women. These distinctions are not helpful when trying to ascertain safety for human use during pregnancy.

In addition, many more women are choosing to breastfeed. Data to date indicate that nortriptyline, clomipramine, sertraline, and fluoxetine are excreted in small quantities and the amount the infant receives is negligible.[10,11] An elegant study assessing the amount of sertraline excreted in breast milk and analyzing infant exposure has shown sertraline and the metabolite desmethylsertraline to be minimally detectable in the infant. On the basis of these data, if the mother becomes depressed in the postpartum period and wishes to breastfeed, sertraline is currently a first-line treatment. However, if the mother has been treated during pregnancy with fluoxetine, many clinicians will continue to use this medication during the postpartum period and allow the mother to breastfeed.[12]

In summary, depression during pregnancy can be safely treated with minimal risk to both the fetus and the mother. A careful psychiatric history is imperative. If medication can be avoided, then this is obviously the first choice. However, women have increased risks for depressive illness that often coincide with reproductive events. Antidepressant treatment is often necessary to insure a good outcome for all concerned. ■

References

1. Weissman MM. The many uses of interpersonal therapy. *Harv Ment Health Lett* 1998;14(10):4-5.
2. Spinelli MG. *Am J Psychiatry* 1997;154(7):1028-1030.
3. Pastuszak A, et al. *JAMA* 1993;269(17):2246-2248.
4. Goldstein DJ, et al. *Obstet Gynecol* 1997;89(5 Pt 1): 713-718.
5. Chambers CD, et al. *N Engl J Med* 1996;335(14):1010-1015.
6. Kulin NA, et al. *JAMA* 1998;279(8):609-610.
7. Altshuler LL, et al. *Am J Psychiatry* 1996; 153(5): 592-606.
8. Lewis-Hall FC, et al. *J Womens Health* 1997;6(3): 337-343.
9. Nulman I, et al. *N Engl J Med* 1997; 336(4):258-262.
10. Stowe ZN, et al. *Am J Psychiatry* 1997;154(9):1255-1260.
11. Llewellyn A, Stowe ZN. *J Clin Psychiatry* 1998;59 (Suppl 2):41-52.
12. Taddio A, et al. *J Clin Pharmacol* 1996;36(1):42-47.

Cost-Effectiveness of Therapy in Nonvalvular Atrial Fibrillation

Source: Catherwood E, et al. Ann Intern Med 1999; 130:625-636.

Catherwood and colleagues performed a cost-effectiveness analysis of treatment strategies in patients with nonvalvular atrial fibrillation. Catherwood et al expanded a previously published Markov decision analysis (), which favored cardioversion plus amiodarone by including health-related costs of the treatments and outcomes in the analysis. Eight different potential strategies were considered. These included rate control with either metoprolol or diltiazem, initial cardioversion followed by aspirin or warfarin at the time of relapse, initial cardioversion followed by quinidine or amiodarone at relapse, and quinidine or amiodarone along with cardioversion at presentation. The Markov model was based on a population of 70-year-old patients of both genders with nonvalvular atrial fibrillation. Patients were assumed to be hemodynamically stable with acceptable symptoms with only rate control. Probabilities of various outcomes for each strategy were estimated from data in the literature. Outcomes and costs were recalculated at three-month intervals over a five-year period. Results are reported as expected costs, increase in quality-adjusted life-years, and incremental cost-effectiveness.

Strategies involving initial cardioversion alone were most effective and less costly than those not involving this option. The cost-effectiveness of the various options after initial cardioversion could be predicted by the patient's risk of stroke. Among high- and moderate-risk patients, initial cardioversion followed by amiodarone and repeat cardioversion upon relapse were the preferred strategies. Costs were estimated to be $9300 and $18,900 per quality-adjusted life-year increments in these two cohorts, respectively. Among patients thought to be at low risk for stroke since they had no risk factors other than age, cardioversion followed by aspirin therapy on relapse was most cost effective. Sensitivity analysis showed that baseline risk for stroke, estimated stroke rate in sinus rhythm, efficacy of warfarin, and costs of warfarin and amiodarone were the major factors influencing the analysis. Catherwood et al conclude that cardiover-

sion alone should be the initial therapy of non-valvular atrial fibrillation, with amiodarone reserved for relapses

Comment by John P. DiMarco, MD, PhD

Atrial fibrillation is the most commonly encountered sustained arrhythmia at the present time. Catherwood et al present an analysis of the cost-effectiveness of various treatment strategies for patients presenting with new onset persistent atrial fibrillation. Although their model is very complex, it still does not take into account several important factors that may influence clinical decision making. Catherwood et al assumed that their hypothetical patients were asymptomatic and hemodynamically stable in atrial fibrillation on rate-controlling agents only. This is probably the case for those patients in whom atrial fibrillation is discovered by chance but frequently is not the case in patients who present with new onset arrhythmia. Evaluating the efficacy of rate control and the subtle effects of atrial fibrillation on quality of life can be difficult and these problems were not considered here. Problems with chronic warfarin anticoagulation are also frequent. The event rates used here are derived from large, randomized trials but these trials excluded up to one-third of the patients they screened because of real or perceived contraindications to long-term warfarin. Finally, only a minority of atrial fibrillation patients present with persistent atrial fibrillation without any other history of arrhythmia or heart disease. A careful clinical analysis to detect prior episodes of self-terminating episodes of arrhythmia, evidence for associated sinus node dysfunction, or structural heart disease can be helpful for predicting an individual's risk of arrhythmia recurrence.

The analysis here, therefore, strictly applies to only a narrow subset of atrial fibrillation patients. However, the clinician can use these data as a guideline when he or she is deciding on care for an individual patient. Considerations of symptoms, risk of therapy, and estimates of recurrence rate should be used in making the final clinical decision. ■

Reference

1. Disch DL, et al. Ann Intern Med 1994;120:449-457.

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CME questions

Testing form inserted in the July 1999 issue

16. The following statements are true about Trovan/Zithromax Compliance Pak *except*:

a. It is given as a single dose.
b. It cannot be used in pregnancy.
c. After treatment, patients need to abstain from sex for 2-3 weeks.
d. The most common side effect is nausea.

17. Which of the following statements are true?

a. Metformin plus insulin prevented weight gain but increased the number of hypoglycemic episodes.
b. Metformin plus insulin should only be used in diabetics with a BMI of 27 or less.
c. Insulin plus an oral agent increases weight gain more than two doses of insulin per day.
d. In the UKPDS studies, metformin used alone resulted in fewer cardiovascular events than other drugs used alone or in combination.

18. Cost-effectiveness in the management of nonvalvular atrial fibrillation is enhanced by:

a. initial cardioversion.
b. chronic warfarin therapy.
c. initial amiodarone therapy.
d. None of the above

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