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Hypnotic Activity of Melatonin

ABSTRACT & COMMENTARY

Synopsis: *Timing is everything! Melatonin just may work if given at the right time.*

Source: Stone BM, et al. *Sleep* 2000;23(5):663-669.

The purpose of this study was to establish the effect of melatonin on sleep. Stone and colleagues conducted two experiments. In the first experiment, varying doses (0.1-10 mg) of melatonin were administered to eight healthy volunteers at 23:30. Sleep time was from 23:30 to 07:30. Core body temperature, sleep structure, and dim light melatonin onsets (DMLO) were measured. This study was placebo-controlled, double-blinded, and included a crossover comparison with temazepam (20 mg). Melatonin had no significant effect on sleep compared with placebo, but temazepam resulted in classic benzodiazepine-induced changes of increased sleep efficiency, increased stage 2 sleep, and increased rapid eye movement (REM) sleep latency compared with placebo.

In the second experiment, varying doses of melatonin were administered at 18:00, and sleep time was from 18:00 to 24:00. Core body temperature, sleep structure, and DMLO were measured. This study was also placebo-controlled and double-blinded, and included a crossover comparison with temazepam (20 mg). In this study, all doses (range, 0.1-10 mg) increased total sleep time, sleep efficiency, and stage 2 sleep. There was an absence of dose response over the range of 0.5-10.0 mg. These changes were similar to those induced by temazepam.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH & CARL BOETHEL, MD

Melatonin is a pineal hormone that is secreted during darkness. In people with normal sleep-wake schedules, melatonin levels begin to rise approximately two hours before sleep, and begin to decline prior to the termination of sleep. There is a strong correlation between the time course of endogenous melatonin production and sleep propensity.[1] Further, daytime exogenous melatonin administration increases subjective sleepiness but impairs cogni-

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tion.[2] Because melatonin is a "food supplement" not regulated by the FDA, rigorous testing of safety, efficacy, and dose-response curves has not been done. It appears that the dose response curve may be flat, with effects noted at extremely low doses (< 1 mg), and little increase in toxicity at extremely high doses (> 1000 g). Because of these properties, melatonin has been recently touted in the lay press as a cure for insomnia and sleep disorders associated with abnormal daytime sleep schedules such as shift work and jet lag.

In this report, Stone et al produce evidence that melatonin given at 23:30 has no significant clinical effect on nocturnal sleep in healthy good sleepers. However, they found that melatonin given at 6 pm (presumably before endogenous levels begin to rise) has immediate hypnotic activity similar to 20 mg temazepam. This suggests that melatonin is unlikely to result in useful hypnotic activity in healthy people when taken around the normal time of sleep, but may be beneficial for sleep induction for "out-of-phase" sleeping.

Another finding of this study is that doses of melatonin above 0.5 mg did not further improve sleep. We have learned something useful about dosing melatonin.

This study's findings may not be extrapolated to all populations. It is notable that Stone et al studied healthy young men, who had high baseline sleep efficiencies (92%) to begin with. But it strongly suggests that 0.5 mg of melatonin has an effect comparable to temazepam for sleep induction in the evening, which could be very beneficial to time zone travelers and shift workers. (*Dr. Boethel is a Fellow in Pulmonary and Critical Care Medicine, Department of Internal Medicine, University of Kentucky College of Medicine, Lexington, Ky.*) ❖

References

1. Dijk DJ, et al. *Sleep Research* 1995;24A:162.
2. Hughes RJ, Badia P. *Sleep* 1997;20:124-131.

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Catheter Replacement Before Antimicrobial Therapy for Symptomatic UTI

ABSTRACT & COMMENTARY

Synopsis: *This study suggests a simple intervention: changing the indwelling urinary catheter can improve clinical and bacteriological outcomes both during and after therapy by about 50%.*

Source: Raz R, et al. *J Urol* 2000;164:1254-1258.

Chronic indwelling urinary catheters are frequently associated with urinary tract infections (UTIs). The inner surface of the catheter becomes coated with a dense bacterial biofilm. Organisms may become embedded in this biofilm and survive due to decreased diffusion of antimicrobials into it. This explains why bacterial counts are higher in urine specimens aspirated from a chronic in situ catheter compared with a specimen obtained after catheter replacement. While routine catheter replacement in non-infected individuals does not lead to better outcomes, would catheter replacement prior to instituting antibiotic therapy for UTI result in improved outcomes in patients with chronic indwelling catheters in long-term

Table

Catheter Replacement in UTI: Clinical and Bacteriological Outcomes

	During Rx Day 3		Post Rx Day 7		Post Rx Day 28	
	REP	**NO REP**	**REP**	**NO REP**	**REP**	**NO REP**
No growth on urine culture (%)	89%	30% $P < 0.001$	67%	33% $P = 0.01$	48%	19% $P = 0.02$
Clinical cure or improvement (%)	93%	41% $P < 0.001$	93%	78%	89%	54%
Clinical relapse rate (%)			7%	29%	11%	41% $P = 0.015$

catheter replacement (REP)
no catheter replacement (NO REP)

care facilities? Raz and colleagues conducted a prospective, randomized, open clinical trial at two long-term care facilities to answer the question.

Fifty-four nursing home residents, 21 male and 33 female, mean age 72.6 years with a clinical diagnosis of UTI were enrolled in the study. Those with gross hematuria or obstruction were excluded from the study. Twenty-seven cases were randomized to either catheter replacement or no replacement before antibiotics were begun. Ciprofloxacin or ofloxacin was used and treatment was continued for 14 days. Clinical and bacteriological outcomes were assessed after three days of therapy, and then seven and 28 days after therapy completion.

The two groups, catheter replacement and no replacement, had similar characteristics. There were similar numbers of diabetics in both groups, and the presenting features, including fever, leucocytosis, bacteremia, and the organisms cultured were also similar. Catheter replacement was associated with a shorter duration of fever, 2.9 ± 1.9 days compared with 4.6 ± 1.9 days ($P = 0.05$) for those without catheter replacement. Catheter replacement was also associated with improved clinical and bacteriological outcomes during and post-therapy (*see Table*). The relapse rate 28 days post-therapy was only 11% in those with catheter replacement compared with 41% in those without replacement ($P = 0.015$). There were only two deaths and both were inpatients without catheter replacement.

COMMENT BY KAMALJIT SETHI, MD, FACP

Up to 10% of elderly long-term care individuals have chronic indwelling urinary catheters. Polymicrobial bacteriuria and serious invasive UTIs are serious complications and contribute to both morbidity and mortality. While it is accepted that asymptomatic bacteriuria should not be treated, clearly symptomatic UTI with and without bacteremia merits therapy. This study suggests a simple intervention: changing the indwelling urinary catheter can improve clinical and bacteriological outcomes both during and after therapy by about 50%. This means better, faster, and less expensive care for a common clinical problem. It makes sense to consider that removal of the catheter and hence, adherent biofilm in symptomatic UTI, would lead to improved outcomes. ❖

High Carbohydrate Diets Induce Hypertriglyceridemia

ABSTRACT & COMMENTARY

Synopsis: *High carbohydrate diets may have a number of metabolic effects that may run counter to expectations.*

Source: McLaughlin FA, et al. *J Clin Endocrinol Metab* 2000;85:3085-3088.

Reaven and associates demonstrated the relationship between carbohydrate intake and triglyceride elevations more than 30 years ago.[1] Are we closer to understanding why?

The association between the hyperinsulinemia and hypertriglyceridemia was later extended to include correlations between: 1) insulin resistance and compensatory hyperinsulinemia; 2) hyperinsulinemia and hepatic

very-low density lipoprotein (VLDL)- triglyceride (TG) synthesis and secretion; and 3) hepatic VLDL-TG secretion rate and plasma TG concentrations.

McLaughlin and colleagues point out that as a result of acute studies done by other investigators, an opposing view has emerged. Thus, it has been proposed that insulin inhibits hepatic VLDL and TG secretion. "As a consequence, it is argued that hypertriglyceridemia occurs in association with insulin resistance due to a loss in insulin's ability to inhibit VLDL-TG secretion in resistant individuals."

This study was initiated to test the hypothesis that endogenous hypertriglyceridemia results from a defect in the ability of insulin to inhibit the release of VLDL-TG from the liver. To accomplish this goal, plasma glucose, insulin, free fatty acid (FFA), and TG concentrations were compared in 12 healthy volunteers in response to eucaloric diets consumed for 14 days, containing either 40% or 60% of total calories as carbohydrate (CHO). All subjects consumed both diets with a two-week washout period between each diet. The protein content of the two diets was similar (15% of calories), and the fat content varied inversely with the amount of CHO (45% or 25%). The ratio of saturated, polyunsaturated, and monounsaturated fat was the same for each diet.

On the last day of the diet, hourly blood samples were drawn fasting, and then hourly beginning one hour after the first study meal, for glucose, insulin, FFA, and TG concentrations. There was no effect on blood glucose concentrations from either diet. The 60% CHO diet, however, resulted in higher day-long insulin ($P = 0.01$) and TG ($P = 0.001$) concentrations, and lower FFA responses ($P = 0.001$).

If the role of insulin is to inhibit hepatic TG secretion, the fasting day-long higher insulin levels on the 60% CHO diet should have resulted in a decrease, not an increase, in plasma TG concentrations.

COMMENT BY RALPH R. HALL, MD, FACP

There are important clinical implications of this study. A high CHO, low-fat diet often results in hypertriglyceridemia and a lowering of the high-density lipoprotein cholesterol. There is also a tendency for the low-density lipoprotein cholesterol, to become smaller and more dense, thus more atherogenic.[2] However, as McLaughlin et al point out, if weight loss in overweight individuals occurs, with ad libitum high CHO diets, hypertriglyceridemia does not develop.

Unless physicians use weight loss in addition to a low-fat diet, it will be more effective to prescribe a diet with reduced saturated fat and instead of increasing carbohydrates, add polyunsaturated and monounsaturated fats—a Mediterranean diet, if you will. ❖

References

1. Reaven GR, et al. *J Clin Invest* 1967;46:1756-1767.
2. Knopp, et al. *JAMA*1997;278:1509-1515.

Comparing Hypertensive Therapies and Outcomes

ABSTRACTS & COMMENTARY

Synopsis: *In these studies, end points were similar, independent of therapy used.*

Sources: Hansson L, et al. *Lancet* 2000;356:359-365; Brown MJ, et al. *Lancet* 2000;356:366-372.

These two studies have the same goal; namely, to determine whether important cardiovascular (CV) end points are differently affected according to the choice of antihypertensive treatment when compared to traditional therapy with either a diuretic, β-blocker, or both. The Nordic Diltiazem (NORDIL) study compared treatment with diltiazem (initially short-acting but later long-acting) to thiazide diuretic or β-blocker—or both—and used as its primary combined end point fatal and nonfatal stroke, myocardial infarction (MI), or other CV death. In the diuretic and β-blocker group, step 1 was either a thiazide diuretic or β-blocker. Step 2 was their combination. Step 3 was an added ACE inhibitor or α-blocker. Step 4 was the addition of any other agent. In the cardiazem group, step 1 was 180-360 mg diltiazem. Step 2 was an added ACE inhibitor. Step 3 added a diuretic. Step 4 was any other antihypertensive drug. A total of 10,916 patients were randomized in this multicenter trial. The mean age was 60 years.

Over the course of the NORDIL study, mean blood pressure averaged 154.9/88.6 mm Hg in the diltiazem group and 151.7/88.7 mm Hg in the diuretic β-blocker group. The primary end point occurred in 403 patients in the diltiazem group and in 400 patients in the diuretic and β-blocker group. There were 159 fatal plus nonfatal strokes in the diltiazem group and 186 in the diuretic and β-blocker group. There were 183 fatal and nonfatal MIs in the diltiazem group and 157 in the diuretic and β-blocker group. Hansson and colleagues conclude that the two treatment approaches were almost indistinguishable for the primary combined end

point (whether the patient had type 2 diabetes mellitus) and stated that the difference in MI/stroke outcome may have been due to chance.

The INSIGHT study compared treatment with 30 mg nifedipine in a long-acting gastrointestinal-transport system (GITS) formulation with co-amilozide (hydrochlorthiazide 25 mg + amiloride 2.5 mg). Dose titration was by dose doubling and addition of either atenolol 25-50 mg or enalapril 5-10 mg. The primary outcome was CV death, MI, heart failure, or stroke. A total of 6321 patients ranging in age from 55 to 80 years were randomized in this multicenter trial. Over the course of the study, a mean blood pressure of 138/82 mm Hg was achieved for both groups. There were 200 primary outcomes in the nifedipine group and 182 in the co-amilozide group. The difference is not statistically significant. Neither treatment selectively improved an individual risk factor.

COMMENT BY MICHAEL K. REES, MD, MPH

In 1997, the Joint National Committee (JNC) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure issued its sixth report, which—like all preceeding reports—emphasized selection of either a diuretic or a β-blocker as initial treatment of uncomplicated hypertension.[1] These two major randomized, controlled trials provide further evidence of the validity of this long-term recommendation, reporting no difference in cardiovascular primary outcomes when hypertension is treated with either a diuretic, a β-blocker, nifedipine GITS, or cardizem long-acting, and this was true whether or not the patient had type 2 diabetes mellitus. Although neither of these studies demonstrated a selective difference in outcome (that is, one drug better for reduction in stroke vs another better for reduction of heart disease), Hansson et al and Brown and colleagues note that there were too few primary outcomes to detect a statistical difference. Thus far, the risk reduction achieved when treating patients with uncomplicated hypertension should be attributed to the degree of blood pressure control achieved, as predicted by the Framingham Risk Profile.[2] ❖

References

1. The Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Arch Intern Med* 1997;157: 2413-2440.
2. Anderson KM, et al. *Am Heart J* 1990;121:293-298. (You can calculate your patients' risk profile on line at http://www. hyp.ac.uk/bhs/risk.xls. Cholesterol and HDL can be entered in either mg/dl or mmol/l).

Infective Endocarditis Prophylaxis

ABSTRACT & COMMENTARY

Synopsis: *Of the patients who underwent a procedure where IE prophylaxis was indicated, 13.2% did not follow their physician's advice to take IE prophylaxis.*

Source: Seto TB, et al. *JAMA*2000;284:68-71.

Physicians often perform procedures of the genitourinary tract in which antibiotic prophylaxis may be indicated for patients with certain cardiac conditions. But is infective endocarditis (IE) prophylaxis being used appropriately?

Seto and colleagues surveyed a group of 108 patients with cardiac diagnoses derived from transesophageal echocardiograms performed at a university-based cardiology laboratory during a month-long period. These patients were initially classified for IE risk using the American Heart Association 1997 guidelines as high, moderate, and negligible risk. Of eligible patients, 80% completed a survey within 6-9 months following their echocardiograms.

Of the patients studied, 49.5% were candidates for IE prophylaxis based on high or moderate risk diagnoses. Approximately 45.9% of all patients reported physician recommendation for IE prophylaxis. Most (88.9%) of the high-risk patients received physician instruction to take IE prophylaxis, but only 61.1% of moderate-risk patients were instructed to take IE prophylaxis. Additionally, 26.4% of negligible risk patients were instructed to take IE prophylaxis. Of those who underwent a procedure where IE prophylaxis was indicated, 13.2% did not follow their physician's advice to take IE prophylaxis.

COMMENT BY ELLEN L. SAKORNBUT, MD

The 1997 American Heart Association guidelines classify cardiac lesions in the following manner:

1. High-risk patients include all patients with a previous diagnosis of infective endocarditis, all patients with prosthetic heart valves, cyanotic congenital heart disease, and patients with surgical pulmonary shunt procedures.
2. Moderate-risk patients include other congenital malformations (except isolated secundum atrial septal defect), mitral valve prolapse with regurgitation or thickened mitral valve leaflets, acquired valvular disease, and hypertrophic cardiomyopathy.

3. Negligible-risk patients include patients with mitral valve prolapse without regurgitation, isolated secundum atrial septal defect, pacemaker or defibrillator implantation, and functional heart murmurs.

Additional patients needing IE prophylaxis include those with acquired valvular heart disease secondary to appetite-suppressant drugs, classified by the FDA as valvular stenosis, at least mild aortic regurgitation, thickened mitral leaflets with at least mild regurgitation, or moderate mitral or tricuspid regurgitation. In addition, although dental procedures and surgical procedures are commonly remembered as a possible risk to patients with valvular heart disease, any significant focal infection may create a risk for IE in patients in the moderate-to high-risk group.

The report by Seto et al is disturbing both in the failure of physicians to uniformly recommend IE prophylaxis to high- and moderate-risk patients and the failure of patients to follow their physicians' recommendations. Some may consider it less concerning that IE prophylaxis was recommended for patients with negligible risk. Nonetheless, the use of antibiotics without clear medical indication should be considered as an issue not only of cost, but also of possible contribution to the development of antibiotic resistance. Patient education, identification, and implementation of treatment protocols should be conducted in a manner most likely to uniformly accomplish IE prophylaxis as indicated, perhaps incorporating antibiotic regimens in standard order sheets and screening questions in prenatal forms. (*Dr. Sakornbut is Associate Professor, University of Tennessee-Memphis.*) ❖

Pharmacology Update

Methylphenidate Extended-Release Tablets (Concerta—Alza)

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

The fda has approved an extended-release formof methylphenidate for the treatment of attention deficit hyperactivity disorder (ADHA). Methylphenidate has been available for more than 30 years for this indication; however, the drug is a short-acting stimulant with a duration of action of 1-4 hours, and the necessity for frequent dosing has limited its usefulness in children. A currently available extended-release formulation has a duration of action of about eight hours. The newly approved formulation is a once-daily preparation due to a novel drug delivery system (osmotic controlled-release) developed by Alza. The new product will be marketed by Alza and McNeil under the trade name Concerta.

Indications

Methylphenidate extended-release tablets (Concerta) are indicated for the treatment of ADHA. Efficacy has been established in children 6-12 years of age.[1] Methylphenidate should be a part of a total treatment program that may include psychological, educational, and social measures.[1]

Dosage

Concerta is administered orally once daily in the morning. The tablets may be administered without regard to food and must be swallowed whole and not chewed, divided, or crushed.[1] The recommended starting dose for patients not currently taking methylphenidate is 18 mg once daily. Dose can be adjusted in 18 mg increments up to a maximum of 54 mg per day. Adjustments may proceed at roughly weekly intervals.[1] For patients who are taking methylphenidate 5 mg two or three times a day, or methylphenidate SR 20 mg/d, the Concerta dose is 18 mg every morning. Those on 10 mg two or three times daily, or methylphenidate SR 40 mg/d, the Concerta dose is 36 mg every morning. For those taking 15 mg two or three times daily or 60 mg of methylphenidate, SR the Concerta dose is 54 mg per day.[1]

Patients should be advised that the tablet remains intact during its passage through the gastrointestinal (GI) tract and not to be alarmed to notice the intact tablets in the stool.

Concerta is supplied as 18 mg and 36 mg.

Potential Advantages

A pharmacokinetic study indicated that the plasma concentration time profile of Concerta more closely reflected that of intermediate-release methylphenidate dosed three times daily compared to the SR formulation (i.e., Ritalin SR).[2] In addition, Concerta provides a lower peak concentration compared to the IR and SR formulations.[2]

Potential Disadvantages

Concerta is only available in doses of 18 mg and 36 mg. Since there is marked individual variability in dose-

response, it is not clear if there is sufficient dose flexibility for individual titration to optimize response.

The effectiveness of Concerta longer than four weeks has not been studied in controlled clinical trials.[1]

Comments

Concerta is a novel drug delivery system. The tablet is made up of an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate release overcoat. After oral administration, the overcoat dissolves releasing a portion of the dose. As water permeates the core of the tablet through the semipermeable membrane, the osmotically active polymer excipients expand pushing the drug through a laser-drilled orifice in a controlled rate.[1] There is a gradual increase in plasma concentration with a peak at 6-8 hours. This formulation appears to be more similar to multiple dosing of the IR formulation than the SR formulation.[2] There are currently no published studies comparing Concerta with the other SR form of methylphenidate and IR methylphenidate. The manufacturer labeling describes controlled studies comparing Concerta with IR methylphenidate dosed three times a day. However, the primary comparison of interest in all these trials was Concerta vs. placebo.[1]

The cost for Concerta is $2.20 for a 18 mg tablet and $2.30 for 36 mg. This compares to $1.33 for a 20 mg tablet of Ritalin SR and $1.10 for the generic formulation.

Clinical Implications

Methylphenidate is commonly used to treat ADHD. Controlled-release formulations have improved compliance because of the problematic midday dose that usually occurs during school hours.

In addition, data suggest that there may be a greater abuse potential with IR compared to a controlled-release formulation.[3] Concerta may offer an advantage over the SR (Ritalin SR) formulation, which shows a fall-off in efficacy earlier than a three times a day regimen with the IR formulation. Patients stabilized on a three times a day regimen of IR methylphenidate in whom compliance with the midday dose is problematic may benefit from Concerta. ❖

References

1. Concerta Product Information. Alza Pharmaceuticals. July 2000.
2. Modi NB, et al. *J Clin Pharmacol* 2000;40:379-388.
3. Kollins SH, et al. *Exp Clin Psychopharmacol* 1998; 6(4):367-374.

CME Questions

30. The optimal dose of melatonin (above which the dose-response curve is flat) for evening induction of sleep is:

a. 0.1 mg.
b. 0.5 mg.
c. 1.0 mg.
d. 5.0 mg.
e. 10.0 mg.

31. In patients in long-term care facilities with indwelling urinary catheters, catheter replacement should be considered:

a. when bacteriuria is documented.
b. when symptomatic UTI occurs, prior to therapy.
c. on a regularly scheduled basis every 4-8 weeks.

32. Which one of the following statements is correct?

a. High carbohydrate diets appear to stimulate the liver's secretion of triglycerides.
b. During weight loss, a high carbohydrate diet increases plasma triglycerides.
c. A high carbohydrate diet usually increases HDL-cholesterol.

33. The NORDIL and INSIGHT studies compared either long acting diltiazem or nifidipine GITS (respectively) to thiazide diuretics and/or b-blockers as treatment of hypertension. The combined primary outcome of both studies was fatal and non-fatal MI, stroke, or other CV death. (INSIGHT also included congestive heart failure). Which statement is correct?

a. The studies demonstrate that cardizem reduces combined primary outcome when compared to all other therapies tested.
b. The studies demonstrate that nifedipine GITS reduces combined primary outcome when compared to all other therapies tested.
c. The studies demonstrate that either a thiazide diuretic or a β-blocker or both reduces combined primary outcome when compared to all other therapies tested.
d. The studies demonstrate that all therapies are approximately equivalent in their effect on combined primary outcome.

34. A patient presents to your office for treatment of abnormal uterine bleeding. She is obese and asks for "diet pills." She was on them previously and would like to resume. You examine her and hear a soft holosystolic murmur beat along the lower left sternal border. What diagnostic and treatment approaches are safest?

a. Refuse to prescribe appetite suppressant medication and recheck her in six months.
b. Do not prescribe the medication. Order an echocardiogram to determine if she has valvular incompetence.
c. Perform an endometrial biopsy and plan to have her cleared by a cardiologist if she needs surgery.

35. Concerta tablets:

a. may be administered without regard to food.
b. must be swallowed whole and not chewed, divided, or crushed.
c. remain intact during their passage through the GI tract.
d. are an extended-release form of methylphenidate with a duration of action of about eight hours.
e. All of the above

By Louis Kuritzky, MD

Polymorphisms in the Factor VII Gene and the Risk of MI

Myocardial infarction (mi) often results from the collusion of atherosclerotic coronary vascular disease and abnormal coagulation factors, including factor VII (F7). Elevated F7 levels have been reported in some (but not all) studies to be a predictor of mortality due to coronary heart disease, and are influenced by both environmental and genetic factors. Genetic polymorphisms result in variable levels of F7, and since some data suggest that F7 levels may either favorably, or unfavorably, affect the course of severe atherosclerosis, Girelli and colleagues selected a population (n = 444) of persons with angiographically proven severe multivessel coronary artery disease for evaluation of the relationship between F7 and vascular outcome.

Several different genetic polymorphisms were associated with statistically significantly different levels of F7. Similarly, some genotypes were found to be cardioprotective, in that they were associated with lesser frequency of MI than others. As anticipated, genotypes with the lowest mean activated F7 were also associated with reduced odds ratio for MI.

Girelli et al conclude that some of the difference in frequency of MI among persons with equally severe coronary artery stenosis may be secondary to differences in F7 levels, reflecting different underlying genetic polymorphisms. ❖

Girelli D, et al. N Engl J Med 2000; 343:774-780.

Arthritis Drugs and GI Toxicity

The commonly quoted risk of significant gastrointestinal (GI) ulcer complications of NSAID treatment is 2-4% per year from the older, nonspecific NSAIDs. Newer COX-2 specific agents have been developed intending safer GI toxicity profiles, with equal therapeutic efficacy. The current trial compared patients with osteoarthritis or rheumatoid arthritis treated with six months therapy of celecoxib (Celebrex), ibuprofen (Motrin, and others), or diclofenac (Voltaren, and others).

Approximately 8000 patients were randomized. The dose of celecoxib used was substantially higher than typically used in practice in the United States: 400 mg twice daily. Doses of ibuprofen (800 t.i.d.) and diclofenac (75 mg b.i.d.) were more typical of standard use.

The annualized rate of GI ulcer complications in the celecoxib group was approximately half that of persons taking nonspecific NSAIDs (0.76% vs 1.45%). For GI adverse events of sufficient effect to cause drug withdrawal, celecoxib was associated with equal or lower rates than nonspecific NSAIDs, with the exception of rash, which was about twice as common on celecoxib, and pruritus, which was about 1.5 times more frequent with celecoxib. On the other hand, overall GI symptoms were significantly less frequent on celecoxib than comparators.

Silverstein and associates conclude that celecoxib, even in doses 2-4 times greater than typically used, provides a greater safety profile than traditional NSAIDs. ❖

Silverstein FE, et al. JAMA 2000;284: 1247-1255.

Effect of Niacin in Patients with Diabetes and Peripheral Arterial Disease

Arteriosclerotic vascular disease remains the primary cause of death in diabetics, attributable to some degree to lipid aberrations often seen in this population. Although niacin treatment in nondiabetic populations demonstrates favorable effect on LDL, HDL, and triglycerides, concern about potential worsening of diabetic control as a result of niacin therapy has widely restricted its use. Conclusions that niacin is "relatively contraindicated" in diabetes stem from limited clinical data. Since lipid control and subsequent cardiovascular disease end points are of crucial importance, and expanding the therapeutic choices might enhance success in achieving normolipidemia, a trial in high-risk individuals with peripheral vascular disease (n = 468), of whom about 30% were diabetic, was performed to ascertain the potential role of niacin therapy. Patients received nicotinic acid at doses up to 3000 mg/d (or less, if not tolerated) for up to 60 weeks.

Niacin increased HDL (29%), and reduced LDL (8-9%) and triglycerides (23-28%) in diabetic and nondiabetic persons. There was no effect of niacin treatment from baseline on hemoglobin A1c, despite a small increase in glucose levels. Elam and colleagues conclude that niacin therapy may be safely and effectively prescribed in diabetics, and may serve as rational alternatives to patients who fail or do not tolerate statins or fibrates. ❖

Elam MB, et al. JAMA 2000;284: 1263-1270.

In Future Issues:

Effect of Losartin Compared with Captopril on Mortality in Patients with Symptomatic Heart Failure