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INSIDE

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Analgesics and the Risk of Hypertension

ABSTRACT & COMMENTARY

By Joseph Varon, MD, FACP, FCCP, FCCM

Clinical Professor of Medicine at the University of Texas Health Science Center, Houston; Adjunct Professor of Medicine at The University of Texas Medical Branch at Galveston.

Dr. Varon reports no financial relationship to this field of study.

Synopsis: *Non-narcotic analgesic use is associated with a moderate increase in hypertension in men. This association is greater with the use of non steroidal anti-inflammatory agents among obese and overweight men.*

Source: Forman JP, et. al. *Arch Intern Med.* 2007;167:394-399.

THIS PROSPECTIVE STUDY WAS AIMED AT EVALUATING THE association between the use of non-narcotic analgesics and the prevalence of hypertension in the United States. The study was part of the Health Professional Follow Up Study, which is an ongoing cohort study of 51,529 male health care professionals that began in 1986. The investigators, in 2000, sought detailed information about analgesic use. Men were excluded if they died before 2000, had prevalent hypertension at baseline, were using antihypertensives or did not return the survey instrument.

The final study sample included 16,031 men and in the year 2002 a repeat survey was sent. The mean age of respondents was 64.6 years and the mean body mass index (BMI) was 24.8. A smoking history was more common with increased analgesic use.

During the study period, the investigators found a significant independent association between the frequency of analgesic use and the risk of newly diagnosed hypertension. For example, compared to non-analgesic users, men who took acetaminophen 6-7 times per week had a relative risk (RR) for hypertension of 1.34. For non-steroidal anti-inflammatory agents (NSAID) the RR was 1.38 and 1.26 for aspirin.

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The study also showed that among men who took acetaminophen, the incidence of hypertension was greater in those who had a body mass index of less than 25. This was in contrast to those men who took NSAIDs, in whom the incidence of hypertension was greater in those overweight and obese and lower in those with BMI less than 25.

COMMENTARY

This article is interesting because it provides conclusive evidence that the use of non-narcotic analgesics in men is associated with incidental hypertension. Similar results have been shown in women in the Nurse's Health Study.[1]

The association between acetaminophen and hypertension may be mediated through a variety of cellular mechanisms and production of mediators. For example, acetaminophen produces analgesia by inhibiting prostaglandin H_2 synthetase, which is the same enzyme targeted by NSAIDs and aspirin.[2] This inhibition of vasodilatory prostaglandins is partially responsible for the elevated blood pressure. Other postulated mechanisms include increases in cellular oxidative stress and reduction of endothelial function.

In other studies, analgesics have been shown to increase the risk of hypertension. In a small, randomized study of patients with known hypertension, the administration of acetaminophen given four times a day for 4 weeks vs placebo led to a 4 mm Hg increase in systolic blood pressure.[3]

A concern that arises when evaluating these studies is the fact that patients who take analgesics do so as the result of pain, which by itself increases the sympathetic tone and blood pressure. However, based on the study by Forman and associates,[4] clinicians should be cautious about their use of non-narcotic analgesics for prolonged periods of time among their patients, as the risk of hypertension is real. ■

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Do Naps Get a Bad Rap?

ABSTRACT & COMMENTARY

By Barbara A. Phillips, MD, MSPH

Professor of Medicine, University of Kentucky; Director, Sleep Disorders Center, Samaritan Hospital, Lexington.

Dr. Phillips reports no financial relationship to this field of study.

Synopsis: *Regular napping in healthy people is associated with reduced coronary mortality, especially for working men.*

Source: Natasha A, et al. Siesta in healthy adults and coronary mortality in the general population. *Arch Intern Med.* 2007;167:296-301.

THIS REPORT COMES FROM A SECONDARY ANALYSIS OF the Greek cohort of the European Prospective Investigation into Cancer and Nutrition [EPIC] study. The report results from a 6-year follow-up of 23,681 individuals who had no history of coronary heart disease, stroke, or cancer at enrollment. The study team hypothesized that regular napping would reduce coronary mortality. The authors were able to control for multiple health, anthropometric, and lifestyle variables, including age, smoking status, years of education as a socioeconomic status indicator, employment status, body mass

index, waist-hip ratio, level of physical activity, and diet. Napping was categorized as:

1. never;

2. systematically (midday naps regularly, at least 3 times per week, with average nap duration of at least 30 minutes); and

3. occasionally (either once or twice per week [frequently on weekends] or short midday naps with average duration of less than 30 minutes, irrespective of the weekly frequency).

Mortality ratios for relevant variables did indeed show the expected positive relationships between age, smoking, central obesity and coronary mortality, as well as the expected inverse relationships between education, physical activity and adherence to the Mediterranean diet and coronary mortality. Most of the associations appeared stronger for women than for men, except that employment status was the strongest predictor of coronary mortality in men, with a two-fold increase in cardiac deaths in unemployed men, even after controlling for all other variables. Employment status was not associated with mortality in women. Compared with those who never napped, those who napped occasionally had a 12% lower rate of coronary death (mortality ratio 0.88, 0.48-1.60), and those who napped systematically had a 37% lower coronary death rate (mortality ratio 0.63, 0.42 0.93). When the authors separated the male part of the cohort into employed and unemployed men (there were not enough women working outside the home for meaningful analysis), they found that the benefit of napping was much greater for working men than for non-working men (mortality ratio 0.36 for working, CI 0.16-0.77, mortality ratio 0.64 for non working CI 0.33-1.21). Although the unemployed men were older, this relationship was not changed after adjusting for age.

COMMENTARY

Napping is a hot topic! The prevalence of napping increases with age, and more than half of those over the age of 65 years in this country nap regularly.[1] Several population-based studies in countries where the siesta is culturally ingrained have examined the relationship between napping and mortality.[2-6] These studies have mostly indicated a positive association between napping and mortality However, small, well-controlled studies have suggested that planned naps can improve mood, alertness and blood pressure.[7-9] The big question has always been: does napping kill, or is napping simply a marker of an underlying illness which is the real culprit? In addition, most studies of napping have not been able to carefully control for physical activity, which tends to be both cardioprotective and also to be associated with a reduced likelihood of napping.

My reading of this paper and the authors' careful analysis is that this report trumps the previous work on this topic. It is likely that employment status (especially for men), is a very important variable that affects both propensity to nap and mortality, and this will need to be rigorously controlled in future studies. Now we need studies of the effects of napping in cultures where women are more likely to be employed and where napping is less common than in the Mediterranean. From the present study, it is not possible to draw many conclusions about differences in coronary mortality rates between employed and unemployed women, since very few women in this Greek population were working outside the home. But the preliminary analysis suggests that the effects of being employed or unemployed are very different for men and women. For now, encouraging, rather than discouraging, regular napping seems like the way to go, especially in employed men. ■

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Fecal Blood Testing for Colorectal Neoplasia

ABSTRACT & COMMENTARY

By Malcolm Robinson, MD, FACP, FACG

Emeritus Clinical Professor of Medicine, University of Oklahoma College of Medicine, Oklahoma City.

Dr. Robinson reports no financial relationship to this field of study.

Synopsis: *Immunochemical testing of stool for human blood appears to be a more sensitive and specific test for advanced colon neoplasia than current guaiac-based tests.*

Source: Zohar Levi, et al. A Quantitative Immunochemical Fecal Occult Blood Test for Colorectal Neoplasia. *Ann Inten Med.* 2007:146;244-255.

An ideal screening test for colorectal neoplasia should be noninvasive, inexpensive, and accurate. High sensitivity should be coupled with specificity to best identify early colon cancer and advanced adenomas (those adenomas with dysplasia and/or villous features). Since colonoscopy is invasive and expensive, a positive noninvasive screening test should minimize the need for colonoscopy in cases unlikely to have significant colon neoplasia. Guaiac-based fecal occult blood tests have been the office mainstay for many years, but these tests do not specifically identify human hemoglobin. Guaiac testing is relatively insensitive to the presence of advanced colon neoplasia although the employment of even this seemingly inadequate test seems to reduce mortality from colon cancer in screened patient groups. Nevertheless, a better test for occult GI bleeding seems to be highly desirable. The present study assessed a laboratory-based immunochemical test that is specific for human hemoglobin, requires no dietary restrictions, and that can be reliably quantitative.

One thousand consecutive ambulatory patients scheduled for colonoscopy had quantitative immunochemical testing of three separate stool specimens for hemoglobin content. Some patients were having routine screening colonoscopies, and others had various worrisome symptoms or other high risk profiles for colonic neoplasia. Hospitalized patients, those with inflammatory bowel disease, and patients having hematuria or active menstruation at the time of stool sampling were excluded. Some patients were taking NSAIDs, and some had been anticoagulated. Forty-nine patients with incomplete colon exams were excluded. Polyps were enumerated, assessed histologically, and classified by location. Mean age was 63.2, about 10% of patients had been found to have positive guaiac-based tests, and about 35% had a history of previous colon neoplasia. Ninety-one patients had significant neoplasia found at colonoscopy including 17 cancers and advanced adenomas in 74 patients. A hemoglobin threshold of 75 ng/mL of buffer seemed to have particularly high sensitivity and specificity for neoplasia, 94.1% and 87.5% respectively. The authors pointed out that stool sample size depended on fecal consistency, and they noted that the overall population studied was at increased risk of colon neoplasia. For this reason, the test performance in average-risk populations might be quite different.

COMMENTARY

Despite the medically recognized value of colorectal cancer screening, the rates of actual screening in the total population remain low (far lower than rates of breast and cervical cancer screening). Immunochemical stool testing for human blood content has considerable appeal as a potentially much more sensitive and specific test for important colon neoplastic lesions than guaiac-based tests as currently used. However, immunochemical tests are relatively expensive ($18-$30) and have not been widely adopted in the United States. In the present study, 16 of 17 cancers found at colonosocpy were Dukes A or B. This is typical of the relatively early ca cers found during colonoscopic screening programs.

In an accompanying editorial,[1] some of the particular advantages of a quantitative stool hemoglobin test were explored. Specificity and sensitivity at various levels could be utilized for different types of screened patients, eg, those with pre-test high or low likelihoods of colon neoplasia. For example, patients currently thought to be at high risk might still be able to avoid colonoscopy if cancer sensitivity level of the test was extremely high (averting colonoscopy if the test were negative). Although the concept of immunochemical fecal occult blood testing seems appealing in many ways, this reviewer doubts that such testing will be widely utilized anytime soon. First, the less expensive guaiac type testing has been found to be clinically effective despite its drawbacks. Physicians are very accustomed to employing this test and to its interpretation. Unless there is strong guideline-based pressure to change, and unless the cost of immunochemical testing drops, guaiac-based testing may continue to be selected by most physicians

as their preferred approach. ■

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Having Sons Reduces the Risk of Prostate Cancer

ABSTRACT & COMMENTARY

By William B. Ershler, MD

INOVA Fairfax Hospital Cancer Center, Fairfax, VA; Director, Institute for Advanced Studies in Aging, Washington, DC

Dr. Ershler reports no financial relationship to this field of study.

Synopsis: *In a family-based research cohort, men were followed for up to 40 years after the birth of their children, and those with only daughters had a 40% higher risk of prostate cancer compared with men with at least one son. The findings support the hypothesis that Y chromosome loci are involved in the pathogenesis of prostate cancer.*

Source: Harlap S, Platiel O, Friedlander Y, Calderon-Margalit R, Deutsch L, Kleinhaus KR, Manor O, Neuget AI, Opler M, Perrin MC, Terry MB, Tiram E, Yanetz R. Prostate cancer in fathers with fewer male offspring: The Jerusalem Perinatal Study Cohort. *J Natl Cancer Inst.* 2007;99:77-81.

THERE HAVE BEEN RECENT STUDIES SUGGESTING THE involvement of loci on the Y chromosome in the pathogenesis of prostate cancer. Because mutations or variants in sex chromosomes might influence the gender of offspring, the current study was designed to determine whether the risk of prostate cancer is associated with offspring gender. For example, mutations on the Y chromosome associated with prostate cancer (as postulated) may also reduce the likelihood of male offspring.

To address this question, investigators surveyed vital status and cancer incidence in fathers from the Jerusalem Perinatal Study, a family-based research cohort.[1] Over a 13-year period (1964-1976), all births to residents in western Jerusalem (n = 92,408) were recorded and demographic features of parents and grandparents abstracted. By linking with the Israel Cancer Registry it was discovered that a total of 712 of the fathers had developed prostate cancer. Compared with men who had at least one son, men with only daughters had an increased risk of prostate cancer (adjusted relative risk [RR] = 1.40, 95% confidence interval [CI] = 1.20 to 1.64, P < 0.0001). In men with one, two, or three or more offspring, the relative risks associated with absence of sons were 1.25 (95% CI = 1.00 to 1.56), 1.41 (95% CI = 1.04 to 1.91), and 1.6 (CI I.05 to 2.43), respectively. Men with no daughters showed no statistically significant altered risk, compared with men who had offspring of both sexes. The relative risk of prostate cancer decreased as the numbers of sons increased (Ptrend < 0.0001) but did not change with the number of daughters.

■ COMMENTARY

These findings support the hypothesis that Y chromosome loci are involved in prostate cancer and provide an excellent example of how careful epidemiological investigation can provide basic clues to the pathogenesis of disease. Of course, other explanations may be forwarded. One that came to mind was that perhaps men with daughters are more likely to be screened and thus diagnosed. However, if such were the case, earlier diagnosis would be expected in those with daughters and better survival observed. This was not the case. Furthermore, the lack of sons appeared to have biological significance, as it becomes increasingly important as family size increases.

Although the postulated genetic loci on the Y chromosome remain to be identified, further research capitalizing on this observation may be productive. Prior work had suggested involvement of sex chromosomes, both X.[2, 3] and Y. The incidence of prostate cancer is increased in some[4, 5] families carrying mutations in BRCA1 or BRCA2. In such families, regardless of whether they include men with prostate cancer, male carriers have a lower percentage of male offspring than the general population.[6, 7] This was also found in two case-control studies of the offspring of BRCA-associated prostate cancer patients.[8, 9] Thus, the Jerusalem Perinatal Study provides additional evidence that function of the Y chromosome is altered in some ways in at least some with prostate cancer. Further investigation in the laboratory, but using clinical samples, may ultimately reveal the specifics of this Y chromosome defect. ■

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Pharmacology Update

Mesalamine Delayed Release Tablets (Lialda™)

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; Assistant Clinical Professor of Medicine, University of California, San Francisco; Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA.

Drs. Chan and Elliott report no financial relationship to this field of study.

THE FIRST ONCE-DAILY MESALAMINE FORMULATION has been approved for the treatment of ulcerative colitis. The formulation uses the Multi Matrix System (MMX) technology designed to deliver the drug throughout the colon. Lialda is under license from Guiliani SpA Italy and marketed by Shire Pharmaceuticals, Inc.

Indications

Mesalamine (MMX) is indicated for the induction of remission in patients with active, mild to moderate ulcerative colitis.[1]

Dosage

The recommended dose is two to four 1.2 g tablets taken once daily. Tablets may be taken whole and without regard to meals.[1]

Mesalamine (MMX) is available as 1.2 g tablets.

Potential Advantages

Mesalamine MMX can be given once-daily while other mesalamine products (Pentasa Asacol) and prodrugs (sulfasalazine, balsalazide) require dosing 2 to 4 times a day.

Potential Disadvantages

Treatment duration longer than 8 weeks has not been studied.[1] Mesalamine MMX is currently not FDA approved for Crohn's disease or for maintenance of disease remission.

Comments

Mesalamine MMX is a delivery system that uses lipophilic and hydrophilic matrices in a coating that resists gastric pH. The coating begins to dissolve at a pH of 7 or higher and slowly releases mesalamine in the colonic lumen beginning in the distal ileum.[2] Efficacy was shown in two randomized, double-blind, placebo-controlled studies in adult patients (n = 517) with active, mild to moderate ulcerative colitis. This was defined as a score of 4-10 on a modified ulcerative disease activity index (UC-DAI) and sigmoidoscopy score.[1] Remission was defined as a UC-DAI score of 1 and 1-point reduction in sigmoidoscopy score.[1,2] Remission rates at 8 weeks, in the first study, were 34.1%, 29.2% and 12.9% for 1.2 g twice daily, 4.8 g once daily and placebo. In the second study, rates were 40.5%, 41.2%, and 22.1% for 2.4 g once daily, 4.8 g once daily, and placebo.[1,2] In the second study, Asacol (2.4 g three times a day), as an active comparator, showed a remission rate of 33.6% but not significantly different from placebo.[2] A larger trial would be needed to validate whether mesalamine MMX is more efficacious. Mesalamine MMX appears to be well tolerated. Adverse events include headache (3.4% to 5.6% vs 0.6% for placebo), flatulence (2.8% to 4% vs 2.8%), pruritus (0.6% to 1.1% vs 0%), and increase in ALT (0.6% to 1.1% vs 0%). The relative efficacy compared to other mesalamine formulations is not known. The wholesale cost for mesalamine MMX is $219 to $438 per month compared to about $170 for Asacol and Pentasa for induction of remission.

Clinical Implications

Ulcerative colitis is a chronic disease with a prevalence of about 250 per 100,000 individuals per year in the US.[3] Sulfasalazine and mesalamine are the mainstays of therapy for mild-moderate active colitis that is not limited to the distal colon.[4] However, mesalamine is generally better tolerated than sulfasalazine.[5] Regimen complexity, tablet quantity and dose frequency are key factors associated with poor adherence in these patients.[6] Mesalamine MMX provides a once-daily formulation with a low pill burden (2 to 4 tablets per day) that may be beneficial in patients in whom adherence is problematic. ■

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CME Questions

13. In the study by Forman and coworkers, the highest relative risk of having hypertension was found among those men taking:
a. acetaminophen
b. NSAIDs
c. aspirin
d. dihydropyridines
e. benzodiazepines

14. In the Greek cohort of the EPIC study, systematic napping resulted in reduced coronary mortality rates for:
a. women, but not for men
b. working women, but not for working men.
c. working men, but not for working women
d. working women, but not for working men

15. Colon cancer mortality has been demonstrated to be:
a. much lower with immunochemical testing of human fecal occult blood than with any guaiac-based occult blood testing technique
b. About the same with immunochemical occult blood testing of stool vs guaiac techniques
c. Better with guaiac-based occult blood testing than with any yet evaluated immunochemical test for human hemoglobin in stool
d. Improved with screening programs based on guaiac testing of stool
e. Improved with immunochemical testing of stool for blood

16 Based upon the Jerusalem Perinatal Study cohort, the risk for prostate cancer would be greatest in a man with:
a. three daughters, one son
b. two daughters, two sons
c. no daughters, one son
d. two daughters, no sons.

Answers: 13 (b);14 (c); 15 (d); 16 (d)

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CME Objectives

The objectives of *Internal Medicine Alert* are:

- to describe new findings in differential diagnosis and treatment of various diseases;
- to describe controversies, advantages, and disadvantages of those advances;
- to describe cost-effective treatment regimens;
- to describe the pros and cons of new screening procedures.

Clinical Briefs

By Louis Kuritzky, MD, Clinical Assistant Professor, University of Florida, Gainesville

Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim.

Hypertension Treatment in "Real Life"

Data in the United States from the NHANES (National Health and Nutrition Examination Survey) have shown that rates of awareness, treatment, and control of blood pressure remain remarkably suboptimal, despite over three decades of periodic NHANES data reporting and diversification of therapeutic choices. Because most hypertension is treated in the primary care sector, specifically Family Medicine, a perspective on prevalence, treatment, and control in this population is valuable.

The burden of hypertension (HTN) in Canada appears similar to the USA. Petrella utilized a database of 150,000 patients from family practice clinics in Ontario to derive prevalence, treatment, and control assessments. HTN was defined as > 140/90 for the general population, >130/80 for diabetics, and >160 systolic for Isolated Systolic Hypertension.

Based upon these definitions, the majority of persons with hypertension were untreated (68.6%), and only 15.8% had blood pressure treated and controlled. When viewed in concert with US population data, the challenge of blood pressure control in North America remains daunting. ■

Petrella RJ, et al. J Clin Hypertension. 2007;9(1):28-35

Prevent Recurring Diabetic Foot Ulcers?

Diabetes remains the number one cause of atraumatic limb loss, the majority of which is secondary to diabetic neuropathy, subsequent infection, and tissue loss. Standard management for diabetic patients, including those with a history of foot ulcer, includes periodic clinician examination, education on maintenance of foot skin integrity, examination, prevention of injury, and daily foot self-inspection.

Lavery, et al assessed the comparative efficacy of standard management with what they termed Structured Foot Examination (SFM) and Enhanced Therapy (ENH) in a population of diabetics who would well be considered high risk because they had already sustained a diabetic foot ulcer. SFM included standard management plus training to perform a twice daily mirror-assisted foot examination seeking redness, discoloration, swelling, and local warmth. Results of the SFM were recorded in a logbook. ENH consisted of standard management plus personal instruction on use of a digital infrared thermometer. Foot temperature was measured with the digital infrared thermometer at six sites, and recorded in a logbook. Subjects in each group were advised to make clinician contact for any changes detected.

The primary outcome of the trial was foot ulceration during 15 months of followup. ENH was significantly superior to both standard management and SFM. Overall, there was a four-fold decrease in risk of developing a foot ulcer in the ENH group compared to other groups.

Once a patient has suffered a diabetic foot ulcer, recurrences may be as common as 25% annually or more. A patient-administered temperature monitoring device may substantially reduce this risk. ■

Lavery LA, Higgins KR, Lanctot DR, et al Diabetes Care 2007;30(1):14-20

Contact Sensitizers in Chronic Urticaria

Up to half of all persons who suffer chronic urticaria (URT) never learn the causative factor. Recently, dermatologists have noted that contact sensitizers are culprits in URT even though patients may NOT evidence irritation at the site of contact in daily life. To better ascertain the percentage of persons who might be suffering sensitivity to contact allergens, Guerra et al performed evaluations on 121 patients with URT who had already undergone "traditional" diagnostic tests including ESR, blood chemistry, urinalysis, food scratch testing, total IgE levels (as well as IgE specific to Anisakis and Echinococcus), HIV and hepatitis testing, thyroid testing, ANA, stool parasite analysis, Helicobacter testing, autologous serum skin testing, CXR, hereditary angioedema screening, urine electrophoresis, lymphocyte subpopulation analysis, and extractable nuclear antigens (Whew!). In addition, study subjects underwent an Italian made specialty Patch Testing system which includes metals, chemicals, cleaning agents, and cosmetics.

Fifty subjects (41%) had positive tests using the novel patch testing panel. None of these individuals had manifested signs of contact dermatitis at the actual sight of exposure in day-to-day activity. In addition to a positive patch test result, application of the culprit allergen to the skin resulted in a worsening of urticaria in approximately half of them. Of the 50 patch test positive patients, everyone who practiced avoidance of the demonstrated allergen enjoyed remission of URT! Contact sensitization is an underappreciated etiology of URT, but specialized testing panels may be required to detect it and intervene appropriately. ■

Guerra L, Rogkakou, et al J Am Acad Dermatol 2007;56:88-90.

In Future Issues: Global Cardiovascular Risk in Women