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Statins and the Risk of Dementia

ABSTRACT & COMMENTARY

Synopsis: *The study demonstrated that individuals 50 years of age and older who were prescribed statins had a substantially lower risk of developing dementia independent of the presence or absence of untreated hyperlipidemia or the exposure to nonstatin lipid-lowering agents.*

Source: Jick H, et al. *Lancet.* 2000;356:1627-1631.

Cognitive impairment in elderly people, also known as senile dementia, is a heterogeneous condition that in most cases has pathological and clinical features consistent with Alzheimer's disease (AD).[1] There is evidence to suggest a relationship between lipids and vascular changes involving the brain in patients with dementia, although the precise mechanism is poorly understood at the present time.[2-5]

Jick and associates from the Framingham Heart Study, Boston University, and the Department of Epidemiology of the Harvard School of Public Health evaluated information obtained from 368 practices which contributed data to the UK-based General Practice Research Database. Patients 50 years of age and older were separated into three groups: group 1 consisted of all individuals with a clinical diagnosis of untreated hyperlipidemia, group 2 included those individuals who received lipid-lowering agents, and group 3 consisted of all cases with a computer-recorded clinical diagnosis of dementia. The study demonstrated that individuals 50 years of age and older who were prescribed statins had a substantially lower risk of developing dementia independent of the presence or absence of untreated hyperlipidemia or the exposure to nonstatin lipid-lowering agents.

COMMENT BY HAROLD L. KARPMAN, MD, FACC, FACP

Dementia effects an estimated 10% of the population older than 65 years of age. As many as 90% of the patients diagnosed with either dementia or AD by the database practitioners in the United Kingdom were found on detailed analysis to have progressive dementia.[6] The Jick et al study of this data clearly demonstrated that patients in the United Kingdom who were pre-

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INSIDE

scribed statin drugs had a risk of clinically diagnosed dementia that was 30-70% lower than those individuals who do not have hyperlipidemia and were not put on lipid-lowering drug therapy. The statin drugs themselves, therefore, appear to reduce the risk of dementia although one cannot exclude the possibility that some of the characteristics of the statin recipients not measured in this study may be associated with a lowered risk of dementia.

Statins are known to competitively inhibit the synthesis of cholesterol thereby preventing the conversion of 3hydroxy-3methylglutaryl-coenzyme A (HMG-CoA) to mevalonate. They also reduce the formation and entry of LDL cholesterol into the circulation, upgrade LDL receptor activity, lower serum LDL cholesterol and triglycerides, and increase HDL cholesterol.[7] Statins also apparently have beneficial effects on the microvasculature which may be of major importance since some investigators have suggested that cerebral perfusion is decreased in affected areas of the brain in patients with AD. Statins may improve cerebral perfusion both because of specific beneficial effects of these drugs on the cerebral capillary endothelium as well as other properties of the agents. A second question addressed by the study was whether the positive effects of the statin drugs in the treatment of dementia might also be noted when using statin drugs in the treatment for other dementing disorders. Jick et al, therefore, determined the relative risk of dementia in the group diagnosed as "dementia" compared with those diagnosed as "Alzheimer's disease" and found no material difference in drug effect suggesting that there may be a common risk factor for dementia which is positively effected by statin drug therapy.

The base population in the study consisted of 24,480 individuals who were users of lipid-lowering agents, 11,421 patients with a diagnosis of hyperlipidemia who did not receive lipid-lowering agents, and 25,000 patients who did not receive lipid-lowering agents and did not have a recorded diagnosis of hyperlipidemia. Despite the significantly large number of patients in the three examined groups, it is important to recognize that Jick et al's study is a purely observational study, and that its results correlated well with findings of another recently published study on this subject.[8] The positive findings of these two studies suggest that the use of statins may significantly reduce the risk of dementia in the elderly either by delaying its onset or by stabilizing (or even reversing) specific or general age-related changes that result in cognitive impairment. It is therefore critically important that additional well designed, double-blind, placebo-controlled studies of an acceptable size be mounted as soon as possible since most clinicians would almost certainly recommend statin therapy to broad segments of their patient population if these studies demonstrated the unequivocal efficacy of the statins in preventing senile dementia. ❖

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If a Little is Good, is More Better?

ABSTRACT & COMMENTARY

Synopsis: *Longer sleep was not associated with increased quality of well-being, but greater sleep satisfaction was.*

Source: Jean-Louis G, et al. *Sleep*. 2000;23:1115-1121.

Jean-louis and colleagues recruited a total of 273 San Diego adults aged 40-64 years by random telephone dialing. Subjects underwent interviews, collection of demographic data, and administration of the Quality of Well-Being (QWB) and Center for Epidemiologic Studies-Depression (CES-D) scales. They also wore wrist actigraphs at home for 3 days to record level of activity and exposure to light. Greater quality of well-being (QWB) was associated with greater sleep satisfaction, younger age, less obesity, non-Hispanic White ethnicity, and greater light exposure. Sleep duration was not associated with QWB. Depression (CES-D) scores correlated positively with QWB and negatively with self-rated sleep satisfaction and habitual sleep time.

COMMENT BY BARBARA A. PHILLIPS, MD, MSPH

As a result of the development of electricity and the 24-hour society, we may be getting only about three-fourths as much sleep as did Americans of the last century.[1] Citing numerous publications decrying the reduction of sleep since the development of electricity,[2-4] these seasoned sleep epidemiologists set out to learn if America's rampant sleep deprivation is affecting well-being. They found that it did not, at least in this middle-aged, sun-exposed population who reported sleeping an average of about 7 hours per night. I chose this paper, not because I believe they are correct (I don't), but because it addresses a "hot" topic, and because Jean-Louis et al found that satisfaction with sleep was associated with improved quality of life and reduced depression scores.

With regard to sleep deprivation/reduction, it matters a great deal whether sleep is curtailed voluntarily to make way for other activities or because of insomnia. Individuals who have reduced sleep because of insomnia almost invariably report reduced quality of life.[4,5] It also matters whether the reduction is acute or chronic, and how severe it is. Acute sleep deprivation adversely affects mood and alertness,[6,7] but gradual and moderate sleep reduction may not.[8,9]

In addition to "soft" variables like depression and quality of life, the effects of reduced sleep on measures such as car wrecks, work performance, and life expectancy are of interest. The sleep community is united in its opposition to sleep reduction in commercial drivers.[10,11] There are less clear-cut data on the effects of sleep loss in physicians-in-training.[12,13] And life expectancy is actually shorter for those sleeping more than 8 hours than it is for those sleeping less than 7.[14,15]

What does this mean to you? It is probably more important to ask the patient is he is satisfied with his sleep than how long he sleeps. In fact, if you only have time to ask one question about sleep (and if you ask even 1 question about sleep, you'll be doing better than most), it should probably be, "Are you satisfied with your sleep?" ❖

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Delayed HAV Vaccine Boosting

ABSTRACT & COMMENTARY

Synopsis: *Patients who miss their booster dose of Havrix do not have to restart the series.*

Source: Pappas VJ, Jr. *Vaccine.* 2001;19:339-402.

A question frequently asked of infectious disease specialists is whether patients who received a single dose of Hepatitis A vaccine (Havrix, SmithKline Beecham Biologicals), but who missed the booster dose

within 6-12 months, should repeat the series as recommended or proceed with a single booster dose. Pappas and colleagues assessed whether a delay in the administration of the booster dose of Havrix reduces the response rate. Two groups of patients were selected for study: 124 travelers who received either a single dose of Havrix 1440 IU or two doses of Havrix 720 IU more than 24 months earlier, and a control group of 125 travelers who received the primary dose of Havrix 1440 IU 6-12 months earlier. Subjects were matched by age and gender.

The median duration of time between receipt of their initial vaccine and enrollment was 35 months (range, 24-66 months) for those receiving delayed vaccination compared with 9 months (range, 6-14 months) for controls. HAV titers before and 30-40 days following the administration of a single booster dose of vaccine (1440 IU) were compared between groups.

Significantly fewer patients receiving delayed boosting had detectable HAV antibody levels (> 33 m IU/mL) at entry to study compared with controls (68% vs 89%; $P < .001$). Nonetheless, both groups responded equally well to a single booster dose of vaccine. There was no statistically significant difference in the geometric mean titers between the two groups in response to boosting.

COMMENT BY CAROL A. KEMPER, MD, FACP

Receipt of a booster dose of Havrix up to 66 months after primary vaccination appears to be as successful as the recommended dosing schedule. Patients who miss their booster dose of Havrix do not have to restart the series. (*Dr. Kemper is Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases, Stanford, Calif.*) ❖

Ursodiol Use is Associated with a Lower Prevalence of Colonic Neoplasia

ABSTRACT & COMMENTARY

Synopsis: *Cancer risk is increased in ulcerative colitis, and administration of oral ursodiol might reduce the risk of carcinogenesis.*

Source: Tung BY, et al. *Ann Intern Med.* 2001;134:89-95.

Patients with both ulcerative colitis (uc) and sclerosing cholangitis have a particularly high risk of colonic neoplasia. Adenocarcinoma may occur in 50% of such patients with longstanding colitis, a rate at least twice that of UC without cholangitis. Ursodiol improves liver biochemical indices of liver function in sclerosing cholangitis, and it incidentally appears to result in dramatic lowering of cancer risk (adjusted odds ratio, 0.14; confidence interval, 0.03-0.64).

Many experts believe that UC is associated with an increased risk of colonic adenocarcinoma (0.5-1%/y of disease). Primary sclerosing cholangitis (PSC) is an inflammatory condition of the bile ducts occurring in 2-4% of patients with UC. Combined UC and PSC are associated with a markedly increased risk of colonic adenocarcinoma to as high as 50% of all such patients after 25 years of colitis. Factors important in development of colorectal cancer in the general population include a high fat diet that predisposes to formation of secondary bile acids. Use of aspirin and NSAIDs has been associated with reduced risk for cancer and colon polyps. Ursodiol is often given to patients with sclerosing cholangitis since it appears to improve liver function. Ursodiol seems to inhibit colon carcinogenesis in animal models.

The present study included 59 patients with UC and PSC. Forty-one had used ursodiol and 18 had not done so. Dysplasia on biopsies was found in 32% of patients who had ever used ursodiol and in 72% of patients who had never been exposed to this medication.

COMMENT BY MALCOLM ROBINSON, MD, FACP, FACG

Although this small study does not definitely prove that ursodiol will prevent or reduce dysplasia and neoplasia in UC, these results are certainly intriguing. Controlled, prospective, randomized studies should be undertaken. Moreover, this apparently benign medical intervention could also prove useful in the prevention of colonic neoplasia in other settings. Further information about ursodiol and carcinogenesis in other groups with increased risk of colon cancer will be awaited with great interest. ❖

Pharmacology Update

Beclomethasone Dipropionate HFA Inhalation Aerosol (QVAR—3M)

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

A new steroid inhaler for the treatment of asthma has been released in a nonchlorofluorocar-

bon (CFC) metered dose form. Beclomethasone dipropionate has been reformulated in a nonozone-depleting propellant, hydrofluoroalkane-134a. The new formulation is a solution rather than a suspension, resulting in smaller particle sizes and better airway deposition. The product is manufactured by 3M Riker and comarketed by Johnson and Johnson as QVAR. The product represents the first hydrofluoroalkane (HFA) inhaled corticosteroid and the second HFA product following albuterol-HFA approved in the United States.

Indications

Beclomethasone-HFA (BDP-HFA) is indicated for the maintenance treatment of asthma as prophylatic therapy in patients 12 years of age and older. It is also indicated for asthma patients who require systemic corticosteroid administration where the addition of BDP-HFA may reduce or eliminate the need for systemic corticosteroids.[1]

Dosage

The recommended starting dose for BDP-HFA is 40-80 mcg twice daily in patients on bronchodilators alone. For patients previously on inhaled corticosteroids, the recommended starting dose is 40-160 mcg twice daily. If adequate response has not been achieved after 3-4 weeks, a dose increase should be considered. The maximum dose is 320 mcg twice daily.[1] For stable patients maintained on systemic steroids, a reduction in steroid dose may be considered after 1-2 weeks of therapy with BDP-HFA. Systemic steroid withdrawal should be done slowly and each decriment should not exceed 2.5 mg of prednisone or equivalent.[1]

The manufacturer indicates that QVAR does not need to be used with a spacer.

BDP-HFA is supplied as 40 mcg or 80 mcg in 7.3 g canisters providing 100 actuations.

Potential Advantages

The HFA formulation provides much smaller droplets compared to the CFC formulation. About 55-60% of the actuated dose of BDP in the HFA formulation is deposited in the lungs compared to 4-7% with the BDP in the CFC formulation.[2] In general, CFC and dry powder formulations deposit about 5-30% of the drug in the lungs with the remainder deposited in the oropharynx. About one-half the dose of BDP-HFA is needed for asthma control compared to BDP-CFC.[3,4] BDP-HFA may have a more favorable therapeutic ratio than BDP-HFA as the greatest systemic availability did not appear to be associated with greater adrenal effects at the same dose of BDP-CFC.[5,8] This was based on the affect on 24-hour urinary free cortisol comparing doses of 800 mcg per day of BDP-HFA and BDP-CFC for 14 days.[8] HFA does not contain chlorine, does not deplete ozone, and has a shorter life in the atmosphere than CFCs.[5] BDF-HFA is a solution and, as such, does not have to be shaken before use and provides a consistent delivery of drug throughout the life of the inhaler.

Potential Disadvantages

The most common side effects are headache (25%) and pharyngitis (27%).[1] All inhaled corticosteroids have shown dose-related systemic side effects. These include adrenal suppression, growth suppression in children, increased risk of osteoporosis, development of posterior subcapsular cataracts, and thinning and bruising of the skin.[6] The doses per actuation between QVAR and current beclomethasone products (Vanceril, Beclovent) are similar, 40 or 80 mcg for QVAR and 42-84 mcg for Vanceril and Beclovent. Care must be taken to avoid confusion over dosing which may result in a higher than optimal dose of QVAR.

Comments

QVAR is the reformulation of a commonly used inhaled corticosteroid, beclomethasone. The HFA (1,1,1,2 tetrafluoroethane) formulation is more environmentally friendly and provides a much smaller particle size (1.1 microns vs 3.5 microns) and better lung penetration. BDP-HFA is about twice as potent as BDP-CFC. Patients switched from BDP-CFC to BDP-HFA should begin with one half the previous dose.[7] Studies comparing QVAR to other inhaled steroids are limited. The average cost per day ranges from about $1 to $2.

For an equivalent dose, the 80 mcg strength is about 60% less costly than the 40 mcg strength ($1.60-3.30). QVAR prices are generally competitive with the other inhaled corticosteroids.

Clinical Implications

CFCs are being phased out as common propellants for aerosols. Alternative propellants include powder inhalers (budesonide) and hydrofluoroalkanes (albuterol HFA). Inhaled steroids continue to be the mainstay anti-inflammatory drugs for the management of mild-to-severe persistent asthma. QVAR provides an environmentally safe, twice-a-day alternative to the other inhaled steroids on the market. ❖

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CME question No. 6 in the January 29 issue of *Internal Medicine Alert* contained an error. The question will be omitted from the CME test. Please leave the space blank on your answer sheet. A reminder will also be sent with your CME Scantron. We regret any confusion this may have caused. ❖

CME Questions

17. Greater Quality of Well-Being is associated with:
a. sleep satisfaction.
b. longer sleep duration.
c. older age.
d. obesity.
e. reduced light exposure.

18. Ursodiol is currently widely accepted in the treatment of:
a. ulcerative colitis.
b. Crohn's disease.
c. adenocarcinoma of the colon.
d. primary sclerosing cholangitis.
e. None of the above

19. Patients 50 years of age or older who were prescribed statins:
a. had a higher risk of developing dementia.
b. had a lower risk of developing dementia.
c. always developed dementia.
d. never developed dementia.

20. Patients who miss their booster dose of Havrix:
a. must restart the series.
b. must have a double booster dose.
c. do not have to restart the series.
d. None of the above

21. QVAR:
a. is the first HFA inhaled corticosteroid approved in the United States.
b. is environmentally safe, it does not deplete ozone.
c. does not need to be used with a spacer.
d. provides a consistent delivery of drug throughout the life of the inhaler.
e. All of the above

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By Louis Kuritzky, MD

Effect of Alcohol Consumption on Myocardial Infarction

The epidemiologically observed favorable association between moderate alcohol consumption and cardiovascular end points has been demonstrated in multiple populations. Multiple mechanisms for this association have been proposed, though none have been confirmed in randomized, placebo-controlled, interventional trials. The current study examined participants in the Physicians' Health Study (PHS) comparing relative risk (RR) for myocardial infarction (MI) in persons with various genetic profiles in reference to alcohol metabolism.

Comparing genetic alcohol slow-metabolizers (A-SM) with alcohol rapid metabolizers (A-RM) there was a 35% reduced risk of MI among the A-SM group. As has been previously described, moderate alcohol consumption was associated with favorable reduced incidence of MI across all genetic profiles. Of persons who consumed moderate amounts of alcohol, those with the homozygous A-SM genetic makeup enjoyed the greatest RR reduction (RR = .14). These persons also had the highest HDL levels.

Apparently, the slower metabolism of alcohol, possibly by reducing alcohol clearance, favorably affects MI risk. A-SM persons demonstrated higher HDL levels, but analysis indicated that only half of the beneficial risk reduction could be attributed to HDL. Hines and associates comment that variation in MI risk associated with genetic makeup would argue against previous thoughts that non-alcoholic components, like flavonoids, are etiologic in alcohol benefits, since only alcohol, and not flavonoids, is affected by the different alcohol dehydrogenase genetic patterns. ❖

Hines LM, et al. N Engl J Med. 2001; 344:549-555.

Eradication of House Dust Mite from Homes of Atopic Asthmatic Subjects

Most asthmatic patients demonstrate allergic responses to inhaled allergens, of which house dust mites are the most consistent offenders. Although living in altitudes unfavorable for mites (high altitudes) favorably affects allergic symptoms, upon return to lower altitudes, symptoms recur. Mite reduction through steam cleaning and acaracides has produced transient benefit in some trials. Htut and associates report a new treatment method used in Sheffield, England, in which technicians used dry heat to achieve a mattress temperature of 80° centigrade, after which 2 minutes of steam was applied. Additionally, a ventilation system filtering air at 1 air exchange rate per hour was placed above the rooms of the actively treated participants. The placebo group received treatment with the same equipment, but no heat or steam was applied. House dust mite concentration was measured by ELISA prior to and immediately after the intervention, as well as 6 and 12 months later.

In addition to a durable reduction of dust mite concentrations in actively treated sites, bronchial hyperreactivity decreased 4-fold compared to sham-treated sites, and was maintained at this level through the 12 months duration of the trial. The cost of the heat treatment ($800) and installation of ventilation ($640) are not insubstantial. ❖

Htut T, et al. J Allergy Clin Immunol. 2001;107:55-60.

Intake of Fruits and Vegetables and Risk of Breast Cancer

The bulk of epidemiologic evidence suggests that increased fruit and vegetable intake is associated with reduced likelihood of breast cancer. However, the strength of these observations has been affected by the potential recall and selection bias in the dominantly case-control methodologies that have been used.

To help address such issues, Smith-Warner and associates performed a pooled analysis of prospective cohort studies in which a validation study of diet intake (or similar method) was used. The population from which data was drawn included 7377 women with breast cancer among 351,825 women for whom appropriate baseline diet data was available.

No favorable association of fruit or vegetable intake was discernible in this population. Smith-Warner et al conclude that there is no relationship between fruit and vegetable intake and breast cancer. ❖

Smith-Warner SA, et al. JAMA. 2001; 285:769-776.

A Clue in the Pause

By Ken Grauer, MD

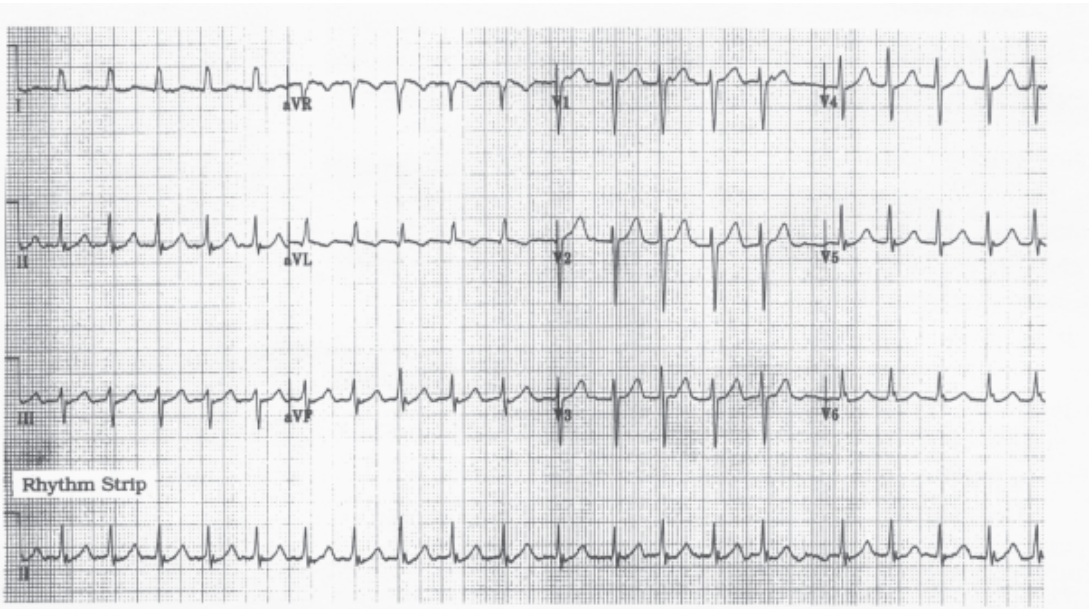

Figure. 12-lead ECG obtained from a woman with dyspnea.

Clinical Scenario: The tachycardia recorded in the 12-lead ECG shown in the Figure was obtained from a 73-year-old woman who presented with shortness of breath. What is the rhythm most likely to be?

Interpretation: The first step in determining the cardiac rhythm on any 12-lead ECG is to examine the rhythm strip. A lead II rhythm strip is seen at the bottom of the 12-lead tracing shown here, obtained simultaneously with the recording of the ECG. Lead II is generally preferred as the best single lead for rhythm determination because P waves are usually most easily seen in this lead, and because by definition P waves *must* be positive in lead II for there to be sinus rhythm (unless there is lead misplacement or dextrocardia).

The lead II rhythm strip in this Figure manifests a rapid and nearly regular rate. The most helpful clue for determining the rhythm lies with the brief pause that is seen toward the end of the tracing (this is the somewhat longer R-R interval between the 6th and 7th to last complexes on the rhythm strip). Atrial activity is clearly lacking except during this pause. Close attention to the baseline during the pause reveals the presence of 3 negative, small amplitude deflections that are regularly spaced from one another in a gentle sawtooth pattern at a rate that is close to 300/minute (the first negative deflection is just before the T wave in the pause; the other 2 follow the T wave). These signs of atrial activity occurring at a rate that is close to 300/minute strongly suggest that the underlying rhythm is atrial flutter. With the possible exception of lead V_1 (in which intermittent notching in various parts of the ST segment may represent flutter activity), this would mean that atrial flutter activity (at an atrial rate just under 300/minute with 2:1 AV conduction) is hidden throughout the rest of the tracing. One might seek to confirm this theory by noting the response to a vagal maneuver and/or from empiric use of Adenosine.

There are 2 take-home messages from interpretation of this ECG: 1) atrial flutter is by far the most commonly overlooked cardiac arrhythmia. As a result, one should always maintain a high index of suspicion for this arrhythmia (always assume that the cause of a regular SVT at a rate that is close to 150/minute is atrial flutter *until* proven otherwise); and 2) when confronted with a difficult-to-interpret tachycardia—look to any pause that may be present in the rhythm for clues to the etiology of the arrhythmia. ❖

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