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EFFECTIVE TREATMENT FOR METHANOL POISONING

LIGHT BROUGHT TO A STANDSTILL

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FEBRUARY 2001

HIGHLIGHTS AND PRACTICAL POINTS

2-1 LOW BACK PAIN

This long review comments on diagnostic evaluation (physical examination and imaging), natural history, and therapy.

For patients with non-specific low back pain, a precise pathoanatomical diagnosis is often impossible. This leads to various imprecise diagnoses (eg, sprain or strain). The natural history is favorable, and patients need this reassurance. Bed rest is not recommended for the treatment of low back pain or sciatica. A rapid return to normal activities is usually the best course.

The use of plain radiography can be limited to patients with clinical findings suggesting underlying systemic disease. More advanced imaging can be reserved for potential candidates for surgery.

Surgery is appropriate for a small proportion of patients. It is most successful in those with sciatica or pseudoclaudication that persists after non-surgical therapy has been tried.

2-2 ASPIRIN AND THE TREATMENT OF HEART FAILURE IN THE ELDERLY

In elderly patients with heart failure and coronary heart disease there was a strong association between use of aspirin and lower mortality.

Practical point: When there is likelihood that coronary atherosclerotic disease contributes to heart failure in elderly patients (as it most often does), low dose aspirin should be prescribed.

2-3 SYSTEMATIC REVIEW OF LONG TERM ANTICOAGULATION OR ANTIPLATELET TREATMENT IN PATIENTS WITH NON-RHEUMATIC ATRIAL FIBRILLATION

"The heterogeneity between the trials and the limited data result in considerable uncertainty about the value of long term anticoagulation compared with antiplatelet treatment. The risks of bleeding and the higher cost of anticoagulation make it an even less convincing treatment."

Practical point: Aspirin is effective preventive treatment. For the many patients for whom anticoagulation is not suitable, aspirin should be prescribed.

2-4 CARDIOVASCULAR DISEASE AND MORTALITY IN OLDER ADULTS WITH SMALL ABDOMINAL AORTIC ANEURYSMS DETECTED BY ULTRASONOGRAPHY:

Total mortality and cardiovascular disease were higher in participants with AAA than in those without. This was independent of age, sex or other cardiovascular disease.

We too often concentrate on the AAA itself, and not on the associated atherosclerotic disease. AAA is, by itself, evidence of prevalent atherosclerotic disease. It is a major risk factor for progression of cardiovascular disease.

Practical point: Patients with AAA should receive utmost efforts to reduce all possible risk factors for atherosclerosis.

2-5 PREFERENCES OF PATIENTS FOR PATIENT CENTERED APPROACH TO CONSULTATION IN PRIMARY CARE:

Observational Study

Analysis suggested 3 domains of patient preferences: 1) communication; 2) partnership; and 3) health promotion.

One in three patients did not want an examination; only a quarter wanted a prescription.

2-6 TOWARD A GLOBAL DEFINITION OF PATIENT CENTRED CARE

Patients want care which (a) explores the patients' main reason for the visit, concerns, and need for information; (b) seeks an integrated understanding of the patients' world— that is, their whole person, emotional needs, and life issues; (c) finds common ground on what the problem is and mutually agrees on management; (d) enhances prevention and health promotion; (e) enhances the continuing relationship between the patient and the doctor. "Here, then, is the beginning of a truly international definition."

Practical point: Long term primary care provides the greatest opportunity for patient centered care.

2-7 LONGITUDINAL ASSESSMENT OF NEUROCOGNITIVE FUNCTION AFTER CORONARY-ARTERY-BYPASS SURGERY

Cognitive decline is common and persistent after CABG. The pattern suggests an early improvement followed by a later decline. Older age, lower educational levels and presence of a decline immediately post CABG predicted greater 5-year declines.

This is bad news indeed for the elderly contemplating CABG. It accentuates the importance of primary prevention.

Practical point: This would tilt some patients toward high-intensity medical treatment and toward choosing PTCA instead of CABG if they are reasonable alternatives.

2-8 EFFECT OF RISEDRONATE ON THE RISK OF HIP FRACTURE IN ELDERLY WOMEN

The bisphosphonate, risedronate (*Actonel*), significantly reduced risk of hip fracture among elderly women with osteoporosis. It did not reduce risk of hip fracture among the subset of women who had increased risks for falling.

Practical point: To prevent hip fractures, interventions to prevent falls should be added to treatment of osteoporosis.

2-9 ALENDRONATE AND NAPROXIN ARE SYNERGISTIC FOR DEVELOPMENT OF GASTRIC ULCERS

Both alendronate and naproxin can cause gastric ulcers. The combination appears to synergistically increase risk.

Practical point: Combined NSAIDs (including aspirin) and bisphosphonates should be used with caution.

2-10 EFFECT OF AGGRESSIVE VERSUS CONVENTIONAL LIPID LOWERING ON ATHEROSCLEROSIS PROGRESSION IN FAMILIAL HYPERCHOLESTEROLEMIA

Aggressive LDL-cholesterol reduction was accompanied by regression of carotid intima-media thickness in patients with FHC.

Practical point: Primary care clinicians will encounter patients with familial hypercholesterolemia. Early detection and treatment of the disease in family members will save lives.

2-11 INTERPRETATION OF THYROID FUNCTION TESTS.

In many laboratories, the highly sensitive TSH assay (limit of detection < 0.1 mU/L) alone is used for initial screening. This is satisfactory as long as some limitations are appreciated. T3 or T4 estimation alone as initial screen will miss subclinical thyroid dysfunction and is not advised.

In individuals with a strong clinical suspicion of thyroid diseases, all 3 tests should be done. If all 3 are normal, thyroid disease can be confidently excluded.

The article comments on the pattern of thyroid function tests in sick patients. This is the most common abnormal pattern of interest to primary care.

2-12 ASPIRIN AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AMONG ELDERLY SURVIVORS OF HOSPITALIZATION FOR AN ACUTE MYOCARDIAL INFARCTION

The benefit of ACE and aspirin in patients at discharge from hospital, either alone or combined, was associated with a reduction in mortality at 1 year.

Practical point: The best practice appears to be to combine the two drugs.

2-13 INHALED HUMAN INSULIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Pulmonary delivery of insulin in type 2 diabetic patients who required insulin improved glycemic control, was well tolerated, and demonstrated no adverse pulmonary effects.

Pulmonary administration still does not match the physiological passage of insulin through the liver.

Practical point: This application requires much more experience.

2-14 EFFICACY OF INHALED HUMAN INSULIN IN TYPE 1 DIABETES MELLITUS: A Randomized Proof-Of-Concept Study

The study offers proof of the concept that inhaled insulin can be effectively and safely used in type 1 diabetes. It is a well tolerated alternative to subcutaneous insulin.

2-15 ANTIBIOTIC SUSCEPTIBILITY OF STREPTOCOCCI AND RELATED GENERA CAUSING ENDOCARDITIS:

Analysis of UK Reference Laboratory Referrals January 1996 To March 2000

Gentamicin plus penicillin remains appropriate for most patients, with vancomycin plus gentamicin a universally active alternative for those who are allergic to penicillin or who have more resistant isolates.

2-16 TERMINAL SEDATION, SELF-STARVATION, AND ORCHESTRATING THE END OF LIFE.

"Orchestrating the end of life" refers to systematically and skillfully creating conditions to help the patient enjoy and control what is left of life."

The desire to be dead is generally not a desire to be no longer alive, but an overwhelming feeling that being dead is preferable to "living this way". When all is said and done, powerlessness, social isolation, and incapacitation are more feared than pain. If we can change the way in which patients live at the end of life (as we often can through good palliative care) the desire to die will vanish or diminish.

Much can be done to optimize a patient's capacity for controlling his or her own wishes into consequent action. This is a central feature of "orchestrating the end of life".

Practical point: This article convinced me that I should never suggest to a patient that he or she should discontinue food or drink to hasten the end of life. RTJ

2-17 RENAL ARTERY STENOSIS

There seems to be a shift away from identifying patients with renovascular hypertension because of the known benefits of medical therapy and the lack of sustained cure after revascularization. Indeed, hypertension is seldom cured by revascularization, except in patients with fibromuscular dysplasia.

There is a shift toward identifying patients with renal-artery stenosis who are at risk for excretory dysfunction. Because of this shift, medical therapy (including aspirin) and modification of risk factors to limit atherosclerosis are essential in all patients, regardless of whether they have undergone revascularization.

2-18 FOMEPIZOLE FOR THE TREATMENT OF METHANOL POISONING.

Fomepizole, an inhibitor of alcohol dehydrogenase, appears to be safe and effective in the treatment of methanol and ethylene glycol poisoning..

2-19 LIGHT BROUGHT TO A STANDSTILL

“Scientists in two separate laboratories at Harvard University have brought light to a complete standstill.”

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REVIEW ARTICLE

2-1 LOW BACK PAIN

(I abstracted this article in some detail because of the importance of low back pain in primary care practice. Most primary clinicians are quite aware of these points, but some may find a refresher course helpful. RTJ)

About two of every 3 adults suffer from low back pain at some time. It is one of the most common symptom-related reasons for visits to physicians. There are wide variations in type of care. This suggests there is professional uncertainty about

the optimal approach. There is evidence of excessive imaging and surgery in the US. The problem may have been "overmedicalized".

The great majority of patients with low back pain cannot be given a precise pathoanatomical diagnosis. The association between symptoms and imaging results is weak. Thus nonspecific terms such as "sprain" or "strain" are commonly used. Neither sprain nor strain have been anatomically or histologically characterized. These patients can be said to have "idiopathic low back pain".

Back pain may originate from many spinal structures — ligaments, facet joints, vertebral periosteum, paravertebral musculature and fascia, blood vessels, the annulus fibrosus, and spinal nerve roots. Perhaps the most common are musculo-ligamentous injuries and age-related degenerative processes in the intervertebral disks and facet joints. Spinal stenosis (narrowing of the central spinal canal or its lateral recesses typically from degenerative changes in spinal structures) is another common problem.

Diagnostic evaluation

Because a precise anatomical diagnosis is elusive, diagnostic evaluation is often frustrating. It is useful to address 3 questions: 1) Is a systemic disease causing the pain? 2) Is there neurological compromise that may require surgical evaluation? 3) Is social or psychological distress amplifying or prolonging the pain?

- 1) Clues to underlying systemic disease include the patient's age, history of cancer, unexplained weight loss, injection drug use, chronic infection, and the presence of night-time pain.
- 2) Neurological involvement is suggested by presence of sciatica or pseudoclaudication (mimicking ischemic claudication). There is often associated numbness or paresthesia. Sciatica due to disk herniation typically increases with cough, sneezing, or the Valsalva maneuver.
Bowel or bladder dysfunction may be a symptom of severe compression of the cauda equina (cauda equina syndrome). This is caused by a tumor or massive midline disk herniation. It is rare. Urinary retention with overflow is usually present. Sensory loss in the saddle distribution, bilateral sciatica, and leg weakness may be present.
- 3) Depression, somatization, substance abuse, job dissatisfaction, pursuit of disability compensation, and involvement in litigation may be associated with persistent unexplained symptoms.

Physical Examination

Among patients with sciatica and pseudoclaudication, a straight-leg raising test should be performed. However, the test is often negative in patients with spinal stenosis. An elevation of less than 60° is abnormal, suggesting compression or irritation of the nerve roots. A positive test reproduces the symptoms of sciatica, with pain that radiates below the knee, not merely to the back or hamstrings.

Ipsilateral straight-leg raising (the test) has high sensitivity for herniated disk. In patients who have a herniated disk, a positive test is usually present — few false negative tests. But, the specificity of the test may be low. Patients who do not have a disk may also have a positive straight leg raising test -- many false positives.

A crossed straight-leg raising test (eg, raising the right leg produces pain in the left leg) is not sensitive, but highly specific for herniated disk. In patients who actually have a disk, many will have a false negative test — will not have crossed-over pain. Conversely, if the patient does not have a disk, he or she is not likely to have crossed-over pain – few false positives.

The remainder of the neurological exam should focus on ankle and great toe dorsiflexion strength (L5 and S1 roots); plantar flexion strength (S1); ankle and knee reflexes (S1 and L4) and dermatomal sensory loss. L5 and S1 are involved in approximately 95% of lumbar disk herniations.

Spondylololosis is as common among asymptomatic persons as in those with low back pain. Its role in causing pain remains ambiguous.

Imaging

Imaging is indicated in patients with fever, unexplained weight loss, history of cancer, neurological defects, alcohol or drug abuse, age over 50, and trauma. Failure to improve in 6 weeks should prompt radiography. The radiologist should help determine methods — plain X-ray? CT? MRI? The use of the latter 2 should be reserved for patients for whom there is a strong clinical suggestion of underlying infection, cancer, or persistent neurological defect. CT and MRI have similar accuracy in detecting spinal stenosis and herniated disks.

Degenerated, bulging, and herniated disks are frequently incidental findings, even among patients with low back pain, and may be misleading.

Evaluation of older adults

Among those over age 65, diagnostic probabilities change. Cancer, osteoporosis, compression fractures, spinal stenosis and aortic aneurysms become more common. "Because drug therapy may prevent further osteoporotic fractures, early radiography is recommended for older patients."

Spinal stenosis is due to hypertrophic degenerative processes and degenerative spondylolithesis. It is more common in the elderly. Pseudoclaudication is the classic symptom. Symptoms are often diffuse, because the disease is often bilateral and involves several vertebrae. Pain, numbness, and tingling may occur in one or both legs. Symptoms are usually relieved by spinal flexion. Patients report less pain when they are sitting or pushing a grocery cart. Pain is increased by extension of the lumbar spine. Diagnosis can usually be made by CT or MRI.

Natural history

Recovery from non-specific low back pain is generally rapid. In one study, 90% of patients seen within 3 days of onset recovered in 2 weeks. However, a large subset did not recover until 7 weeks. Recurrences are common. An emerging picture is that of a chronic problem with intermittent exacerbations, analogous to asthma, rather than an acute disease that can be cured.

The natural history of herniated disk is also favorable. Improvement is the norm, although it is slower than in low back pain alone. Only 10% have sufficient pain after 6 weeks that surgery is considered. The herniated part of the disk tends to regress with time. In contrast, spinal stenosis usually remains stable or gradually worsens.

Return to work is influenced by clinical, social, and economic factors.

Low back pain is rarely permanently disabling.

Therapy

Nonspecific low back pain.

NSAIDs and muscle relaxants may be helpful for symptom relief. In general, drugs should be prescribed on a regular schedule rather than on an as-needed basis. Spinal manipulation and physical therapy are alternative treatments, but their effects are limited. The author defers recommending these interventions until 3 weeks after onset, because half of the patients recover in this period. For most patients the best recommendation is a rapid return to normal activities, with neither bed rest nor exercise in the acute phase. Some tempering of activity will depend on the degree of low back stress placed by usual work. Clinical trials suggest spinal manipulation has some efficacy. Reviews have found little support for acupuncture.

Exercise programs that combine conditioning with specific strengthening of the back and legs can reduce the frequency of recurrence.

Herniated Intervertebral Disk

In the absence of the cauda equina syndrome or progressive neurological deficit, patients with suspected disk herniation should be treated non-surgically for at least a month. Narcotic analgesics may be necessary, but must be used with caution.

Epidural corticosteroid injections offer temporary symptomatic relief for some patients.

Effectiveness of microdiscectomy, is similar to that of standard discectomy.

Spinal Stenosis

Surgery results in better pain relief and functional recovery than non-surgical treatment. However, at 4 years, about 30% have severe pain and 10% have undergone re-operation.

Chronic Low Back Pain

Many patients have no radiculopathy or anatomical abnormalities that clearly explain their symptoms. Central nervous system changes may perpetuate the perception of pain in the absence of ongoing tissue injury.

Intensive exercise reduces pain and improves function. Maintaining adherence to a program is often difficult. Anti-depressant drugs are helpful in the many patients who have low back pain and depression. Evidence of effectiveness in those without depression is conflicting. The author does not advocate long-term use of opioids.

Referral to a multidisciplinary pain center may be appropriate for some. Complete relief of symptoms may be unrealistic.

Conclusions

For patients with non-specific low back pain, a precise pathoanatomical diagnosis is often impossible. This leads to various imprecise diagnoses. (Eg, sprain or strain) The natural history is favorable, and patients need this reassurance. The favorable natural history may partly explain the proliferation of unproved treatments that may seem to be effective.

The use of plain radiography can be limited to patients with clinical findings suggesting underlying systemic disease. More advanced imaging can be reserved for potential candidates for surgery.

Bed rest is not recommended for the treatment of low back pain or sciatica. A rapid return to normal activities is usually the best course.

Surgery is appropriate for a small proportion of patients. It is most successful in those with sciatica or pseudoclaudication that persists after non-surgical therapy has been tried.

NEJM February 1, 2001; 344: 363-70 Review article, first author Richard A Deyo, University of Washington, Seattle.

2-2 ASPIRIN AND THE TREATMENT OF HEART FAILURE IN THE ELDERLY

Most patients with heart failure (**HF**) have coronary artery disease. Aspirin has been associated with improved survival in patients with left ventricular dysfunction. However, the most recent guidelines warn about the combined use of antiplatelet agents and diuretics.

This study examined the use of aspirin as a discharge medication among elderly patients who survived hospitalization for both HF and coronary artery disease (**CAD**).

Conclusion: Use of aspirin was associated with lower mortality at 1 year.

STUDY

1. Multicenter, retrospective cohort study of over 1000 consecutive patients hospitalized with

HF associated with CAD. All were over age 65.

2. Determined prescription of aspirin at discharge.
3. Determined mortality at 1 year.

RESULTS

1. At discharge 41% received a prescription for aspirin.
2. Patients for whom aspirin was prescribed had a lower 1-year mortality compared with those not receiving aspirin. (Odds ratio = 0.7)
3. At one year, 27% in the non-aspirin group died; 20% in the aspirin group. [NNT(benefit-1year)= 14]

DISCUSSION

1. The current American Heart Association guidelines for patients with CAD recommend use of aspirin.
2. Despite this, the use of aspirin for patients with HF, many of whom have CAD, has been controversial. The rationale was based on a potential harm resulting from inhibition of prostaglandins by aspirin.
3. This study identified a strong association between use of aspirin and lower mortality among patients with both HF and CAD.
4. There was no suggestion of significant harm from aspirin.

CONCLUSION

In elderly patients with HF and CAD, there was a strong association between use of aspirin and lower mortality. Archives Int Med February 26, 2001; 161: 577-82, Original Investigation, first author Harlan M Krumholz, Yale University School of Medicine, New Haven Conn. www.archinternmed.com

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2-3 SYSTEMATIC REVIEW OF LONG TERM ANTICOAGULATION OR ANTIPLATELET TREATMENT IN PATIENTS WITH NON-RHEUMATIC ATRIAL FIBRILLATION

Warfarin is used widely in preference to aspirin to prevent thromboembolism in patients with non-rheumatic atrial fibrillation. (AF)

Previous reviews have reported considerably more benefit from warfarin than from aspirin. "From these reviews it might be concluded that long-term anticoagulation results in substantially greater benefit in non-rheumatic atrial fibrillation."

These investigators considered that comparison of the two treatments might be biased by different selection criteria, leading to differences in prognosis unrelated to treatment and overestimation of treatment effects.

Conclusion: Heterogeneity between trials resulted in uncertainty about the value of long-term anticoagulation as compared with aspirin.

STUDY

1. Meta-analysis of 5 randomized trials (over 3200 patients) compared outcomes of antiplatelet drugs (mainly aspirin) with anticoagulation (warfarin) in patients with chronic non-rheumatic AF.
2. Calculated odds ratios and 95% confidence intervals to estimate treatment effects.

RESULTS

1. Fatal vascular events: 82 in the anticoagulation; 95 in the aspirin group.
2. Individual trial sizes were small. "The pooled odds ratios . . . showed non-significant trends in favor of anticoagulation in deaths from stroke (odds ratio 0.74; 95% confidence interval = 0.39 to 1.46 and vascular death (odds ratio 0.86; confidence interval = 0.63 to 1.46)
3. Primary annual event rates varied from 1.7% to 10.6% reflecting a marked clinical heterogeneity in risk among patients included in the different trials.
4. Only one trial reported greater benefits from long term anticoagulation. "These results must be interpreted with caution because methodological quality of this trial was lower than in the other trials." (*See page 323 for comments on this point.*)
5. Major bleeding events were more common in the anticoagulation groups. Bleeding would probably be more common in routine clinical practice.

DISCUSSION

1. "The evidence for current clinical practice in long-term anticoagulation for patients with non-rheumatic atrial fibrillation is not strong." "For vascular deaths, anticoagulation may be up to 37% better than aspirin, or as much as 17% worse."
2. Costs of anticoagulation are much greater.
3. "Given the uncertainty over the greater efficacy of anticoagulation, its undoubted hazards, and considerations of cost effectiveness we should strongly favour antiplatelet drugs in preference to long term anticoagulation."
4. For patients who are already receiving anticoagulation and are happy and stable on this treatment, these results show that there is little to choose between the two treatments except cost. For new patients, some doctors may consider it unwise to risk the potential hazards of major bleeding with the associated higher costs and will choose an antiplatelet drug. Patient preferences also need to be taken into account.

CONCLUSION

"The heterogeneity between the trials and the limited data result in considerable uncertainty about the value of long term anticoagulation compared with antiplatelet treatment. The risks of bleeding and the higher cost of anticoagulation make it an even less convincing treatment."

BMJ February 10, 2001; 322: 321-26 Original investigation, first author F C Taylor, University of Bristol, UK

www.bmj.com/cgi/content/full/322/7282/321

Comment:

So . . . where does this leave us? Warfarin treatment in the US is now so ingrained in practice that it will be difficult to change many minds. Warfarin is considered standard treatment. Possibly so much so that variation from this practice might lead to charges of malpractice should a stroke occur.

I do believe, however, that the article would tilt us toward more use of aspirin in patients who have higher risk of bleeding from warfarin (eg, the elderly frail) and in those who have difficulty in the strict compliance necessary with anticoagulation therapy.

I believe aspirin is a beneficial treatment. But, is warfarin so much better that it should be advised in almost all patients, or can we begin to be more liberal in the use of aspirin? RTJ

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2-4 CARDIOVASCULAR DISEASE AND MORTALITY IN OLDER ADULTS WITH SMALL ABDOMINAL AORTIC ANEURYSMS DETECTED BY ULTRASONOGRAPHY: The Cardiovascular Health Study

Persons with abdominal aortic aneurysms (AAA) have a high mortality. The UK small AAA trial reported no long-term benefit with early surgery. Even after successful repair, the average life expectancy is less than that of the general population.

This observational study was designed to identify AAA as a risk factor for development and progression of cardiovascular disease.

Conclusion: Mortality and incident cardiovascular disease were higher in patients with AAA.

STUDY

1. Longitudinal cohort study followed over 4500 patients, all older than age 65 (mean age 75), recruited from Medicare lists.
2. Screened all for AAA by ultrasound.
3. Determined mortality and incident cardiovascular disease over 4.5 years.

RESULTS

1. Prevalence of AAA was 9%; 90% were 3.5 cm or less in diameter.
2. Outcome per 1000 person-years at 4.5 years

	Total mortality	Cardiovascular mortality	Incident CVD
AAA	65	34	47
No AAA	33	14	31
Relative risks	1.3	1.4	1.6

3. Outcomes were determined after adjustment for age, risk factors, and presence of other cardiovascular disease.
4. Rates of rupture and repair were low.

DISCUSSION

1. In this cohort of older persons with AAA, mortality and incident cardiovascular disease were higher than in those without AAA, independent of other risk factors.
2. Risk of rupture was small and not detectable in those with AAA of less than 4.0 cm in diameter.
3. Use of infrarenal-to-suprarenal aortic diameter ratio did not substantially increase prediction of risk.
4. Of interest — ankle/arm BP index of 0.9 occurred in 24% in AAA group vs 12% of normal aorta group.
5. "These findings reinforce the current practice of repairing aneurysms at a diameter of 5 cm."
6. The risk for mortality exceeds the risk for rupture with smaller aneurysms (those 4.0 to 5.0 cm in diameter). It will be difficult to discern a benefit of elective repair in those with diameter < 5.0 cm.

7. Patients with small AAA should be advised to modify risk factors while under surveillance for increase in the size of the AAA.

CONCLUSION

Total mortality and cardiovascular disease were higher in participants with AAA than in those without. This was independent of age, sex or other cardiovascular disease.

Annals Int Med February 6, 2001; 134: 182-90 Original investigation, first author Anne B Newman, University of Pittsburgh PA. www.annals.org

Comment:

Note that about 1 in every 10 persons mean age 75 had a small AAA.

I abstracted the article because we too often concentrate on the AAA itself, and not on the associated atherosclerotic disease. AAA is, by itself, evidence of prevalent atherosclerotic disease. It is a major risk factor for progression of cardiovascular disease. Patients with AAA should receive utmost efforts to reduce all risk factors for atherosclerosis possible. RTJ

Recommended Reading

2-5 PREFERENCES OF PATIENTS FOR PATIENT CENTERED APPROACH TO CONSULTATION IN PRIMARY CARE: Observational Study

The patient-centered approach (**PCA**) is widely advocated. Implementation in practice is limited and related to characteristics of both doctors and patients.

One influential PCA model encompasses 5 principles:

Exploring the experience and expectations of disease and illness: patient's

ideas about the problem, their feelings, expectations for the visit, and effects on function.

Understanding the whole person" (feeling emotionally understood and the context of the illness

(how the family and life has been affected).

Finding common ground regarding management (partnership): problems,

priorities, goals of treatment, and roles of doctors and patient.

Health promotion: health enhancement, risk reduction, early detection of illness

Enhancing the doctor-patient relationship: sharing power; the caring and

healing relationship.

And, adding a 6th domain, the realistic use of time.

This study identified patient's preferences for patient centered consultations in general practice. Patients in waiting rooms were asked to complete a short questionnaire before their consultation, asking their opinions about what they wanted the doctor to do in the consultation.

Results: Analysis suggested 3 domains of patient preferences: 1) communication; 2) partnership; and 3) health promotion.

One in three patients did not want an examination; only a quarter wanted a prescription.

Patients who wanted good communication were more likely to feel unwell, to be high attenders, to have no paid work.

Patients strongly want a patient-centered approach. Those who had a very strong preference for patient centeredness were those who were vulnerable either socioeconomically, or because they were feeling particularly unwell or worried.

The patient's ideas about the problem and expectations for treatment are closely related to mutual discussion and partnership.

Many patients want patient centeredness rather more than they want a prescription. Patients presenting with psychosocial problems are more likely to be satisfied with a patient centered consultation style.

Doctors should be sensitive to those patients who are likely to have a particularly strong preference for patient centeredness; patients who are vulnerable, either psychosocially or because they are feeling particularly unwell.

BMJ February 24, 2001; 322: 468-72 Original investigation, first author Paul Little, University of Southampton, UK.
[www.bmj.com/cgi/content/full/ 322/7284/468](http://www.bmj.com/cgi/content/full/322/7284/468)

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2-6 TOWARD A GLOBAL DEFINITION OF PATIENT CENTRED CARE

(This editorial comments and expands on the preceding article.)

The best way of measuring patient centeredness is an assessment made by patients themselves. Patient centeredness is becoming a widely used, but poorly understood, concept in medical practice. It may be most commonly understood for what it is not — technology centered, doctor centered, hospital centered, disease centered.

Definitions of patient centered care seek to make the implicit in patient care, explicit.

Questions: What is it? Do patients want it? What are the benefits?

The answer to the second question is a resounding "yes". Patients want care which (a) explores the patients' main reason for the visit, concerns, and need for information; (b) seeks an integrated understanding of the patients' world— that is, their whole person, emotional needs, and life issues; (c) finds common ground on what the problem is and mutually agrees on management; (d) enhances prevention and health promotion; (e) enhances the continuing relationship between the patient and the doctor. "Here, then, is the beginning of a truly international definition."

As for the 3rd question— there is evidence of a tangible benefit; patient centered communication is positively associated with patient satisfaction, adherence, and better health outcomes.

Some express doubt — patients may not prefer a patient centered approach and hence universal adoption may be unwise. This concern rests on a misconception. Being patient centered does not mean sharing all information and all decisions. It actually means taking into account the individual patient's desire for information and for sharing decision making.

"Patient centered clinical practice is a holistic concept in which components interact and unite in a unique way in each individual patient-doctor encounter."

BMJ February 24, 2001; 322: 444-45 Editorial by Moira Stewart, University of Western Ontario, London, Ontario, Canada.
www.bmj.com/cgi/content/full/322/7284/444

Comment:

Key points: Establishing a connection with the patient — mutuality in understanding the problem and concurring on management. Enhancing a continuing relationship. Here is the challenge to primary care.

Specialist care is most often brief and disease-oriented. As valuable as this is, and as empathetic as specialists are, brevity and disease orientation do not lead to an understanding the patient's world.

Primary care clinicians have the opportunity to understand the patient's world. This requires a commitment to long-term care. Development of the relationship requires multiple visits, each of which may, by circumstance, be limited in time. RTJ

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2-7 LONGITUDINAL ASSESSMENT OF NEUROCOGNITIVE FUNCTION AFTER CORONARY-ARTERY-BYPASS SURGERY

Cognitive decline has been recognized as a complication of cardiac surgery. Although advances in anesthesia and surgery have made substantial reductions in mortality, the incidence of post-surgery cognitive decline has remained stable. Depending on the measurement used, some cognitive decline has been reported after cardiac surgery in up to 80% of patients at discharge, up to 50% of patients at 6 weeks, and up to 30% at 6 months.

Elderly patients with multiple health problems are now able to undergo surgical procedures late in life more safely. They are, however, at higher risk for neurological and neurocognitive complications. Perioperative cognitive decline appears to be transient in a substantial number of patients. This study assessed the course of cognitive change after CABG surgery

Conclusion: Cognitive decline was common immediately after CABG. There was some improvement at 6 months, followed by further decline at 5 years.

STUDY

1. Performed neurocognitive tests preoperatively (baseline) on over 250 patients (mean age 61) who underwent CABG. Repeated tests at 6 weeks, at 6 months, and at 5 years.
2. Defined a decline in cognitive function as a drop of 1 standard deviation or more in scores on tests of any one of 4 domains of cognitive function.
3. Overall neurocognitive status was assessed with a composite cognitive index score.

RESULTS

1. Patients with cognitive decline:

At discharge	53%
Six weeks	36%
Six months	24%
Five years	42%
2. Older age, lower level of education, and evidence of decline at discharge were significant predictors of decline at 5 years.

DISCUSSION

1. Patients whose cognitive function declined immediately after CABG were at increased risk of long-term cognitive decline.
2. The change between cognition at baseline and at 5 years was more than 2 to 3 times that demonstrated in longitudinal assessments of cognitive function of over 5500 Medicare patients followed for 5 years.
3. Adjectives such as "subtle", "transient", and "subclinical" have been used to describe the cognitive decline that occurs after CABG. Such descriptions minimize the importance of these changes.
4. A downward change of 1 SD in a domain of cognition indicates a reduction of approximately 20% in cognitive function in that domain. In the Digit Symbol subtest, for which good age-related normative data exist, a 20% reduction is similar to the difference in function between 40- and 60- year-old subjects.
5. These data demonstrate a significant association between cognitive decline immediately after CABG and the incidence and the severity of cognitive decline five years later.

CONCLUSION

Cognitive decline is common and persistent after CABG. The pattern suggests an early improvement followed by a later decline. Older age, lower educational levels and presence of a decline immediately post CABG predicted greater 5-year declines.

NEJM February 8, 2001; 344: 395-402 Original investigation by the Neurological Outcome Research Group, and the Cardiothoracic Anesthesiology Research Endeavors Investigators, first author Mark F Newman, Duke University Medical Center, Durham NC. www.nejm.com

An editorial in this issue (p 451) comments:

Beside the cognitive decline, stroke (1.5% to 5%) and postoperative delirium (10% to 30%) occur after CABG. Post operative delirium may be related in part to anesthesia. These patients are more likely to have stroke.

After CABG some patients are described as being "just not the same". Cognitive changes are often subtle, involving problems with following directions, mental arithmetic, and planning complex actions. Family members may note the patient is more short-tempered, is less able to withstand frustration, and has wider mood swings.

Is it possible that many patients contemplating CABG are not cognitively normal. They have symptomatic coronary disease, and may also have cerebrovascular disease. A high rate of preexisting brain injury due to silent ischemia has been reported in patients undergoing CABG. Showers of embolic material can enter the cerebral vessels during surgery, probably arising during manipulation of the aorta.

Comment:

This is bad news indeed for the elderly contemplating CABG. It accentuates the importance of primary prevention. It would also tilt some patients toward high-intensity medical treatment and toward choosing PTCA instead of CABG if it is a reasonable alternative.

Cardiac surgeons as well as primary care clinicians should inform patients about this possibly devastating complication.

Short-term cognitive changes have also been reported in elderly patients who have undergone non-cardiac surgery. RTJ

2-8 EFFECT OF RISEDRONATE ON THE RISK OF HIP FRACTURE IN ELDERLY WOMEN

Risedronate (*Actonel*), a bisphosphonate, has been shown to increase bone mineral density (BMD) and decrease the risk of vertebral and non-vertebral fractures in post-menopausal women.

This study assessed effect on incidence of hip fractures

Conclusion: Risedronate reduced risk of hip fracture among some elderly women with confirmed osteoporosis. It did not protect against fractures due to falls.

STUDY

1. Followed over 5000 women age 70-79 with confirmed osteoporosis (BMD at the femoral neck more than 4 standard deviations below mean peak value for young women).
2. And over 3500 women at least 80 years old who had low BMD at the hip, and at least one non-skeletal risk factor for hip fracture (eg, difficulty in standing from a sitting position, poor tandem gait, fall related injury in the previous year, low psychomotor score, poor hand-eye coordination, smoking).
3. Randomized to: risedronate 2.5 or 5 mg/d, or 2) placebo.
4. Gave the usual precautions regarding bisphosphonates — Take tablets with a cup of water on an

empty stomach 30 to 60 minutes before breakfast; remain upright for 60 minutes thereafter. Women also received supplemental calcium and vitamin D.

5. Follow-up = 3 years.

RESULTS

1. BMD at the femoral neck and trochanter increased in the treatment groups. (Somewhat greater in the 5.0 mg group.)
2. Overall risk of hip fracture in the younger women was 3.2% in the placebo groups vs 1.9% in the treatment group. (Absolute difference = 1.3%; NNT(benefit 3 years) = 77).
3. In the older age group there was no significant difference in incidence of hip fracture. (Most of these women had non-skeletal risk factors for fracture — ie, increased risk of falling.)
4. Adverse effects were reported in a high percentage of both active treatment groups and placebo group without any difference between them. Any upper GI adverse effect occurred in 22% of patients of all 3 groups. Esophagitis in 1.7 to 1.9%. (Higher in the placebo group.)

DISCUSSION

1. Risedronate was associated with a decreased incidence of hip fracture over 3 years in some women who had low BMD at the femoral neck.
2. There was no benefit in women who had non-skeletal risk factors for hip fracture.
3. "Risedronate was well tolerated. Overall, the incidence and types of adverse events were similar to those observed with use of placebo, even in women 80 years of age and older." The reasons for discontinuance associated with adverse effects were similar between groups.

CONCLUSION

The bisphosphonate, risedronate, significantly reduced risk of hip fracture among elderly women with osteoporosis. It did not reduce risk of hip fracture among the subset of women who had increased risks for falling.

NEJM February 1, 2001; 344: 333-40 Original investigation, first author Michael R McClung, Oregon Osteoporosis Center, Portland. www.nejm.com

See also: "Risedronate: A Clinical Review: Archives Int Med February 12, 2001; 161: 353-360

Review article of 9 randomized, controlled trials:

Risedronate prevents postmenopausal bone loss, decreases fractures in those with established osteoporosis, effectively treats Paget disease of bone, and prevents corticoid-induced bone loss.

Unknown — long term toxic effects and efficacy; optimal duration of therapy; potential use in combination with other agents. The review comments on adverse effects — "Adverse effects . . . are similar to those of patients taking placebo, and do not include notable upper gastrointestinal tract adverse event rates of serious adverse events."

A direct comparison with alendronate (safety and effectiveness) has not been done.

Comment:

The authors stress an important point — broken hips and vertebra are caused by falls as well as low BMD. Applications to prevent falls in the elderly are as important as interventions to increase BMD.

I believe the report of adverse effects will prove to be misleading. The investigators must have believed risedronate has some irritating effect on the GI tract. Otherwise, why should they advise such caution in its administration? Toxic effects will be more evident in general use than in a controlled trial.

Caution in the use of combined NSAIDs and bisphosphonates!

See the following study. RTJ

2-9 ALENDRONATE AND NAPROXIN ARE SYNERGISTIC FOR DEVELOPMENT OF GASTRIC ULCERS

The most common adverse effects of alendronate (*Fosamax*) are abdominal pain and discomfort. Studies have reported associated esophageal damage. In small endoscopic studies, visible gastric mucosal injury was present in over 50% of those receiving the drug. Overall, 7% developed gastric ulcers.

The target population for alendronate (and other bisphosphonates) and the population most likely to take NSAIDs (and aspirin) are similar.

This study asked — Do naproxin (*Naprosin*) and alendronate (*Fosamax*) act synergistically in causing gastric ulcers?

Conclusion: The combination acts synergistically to cause gastric ulcers.

STUDY

1. Endoscopist-blind randomized crossover study compared: 1) Alendronate alone (10 mg), 2) Naproxin alone 500 mg twice daily, and 3) the combination.
2. Twenty six healthy volunteers age 30-50 took the drugs for 10 days in each phase of the study with a 1 to 4 week washout period between evaluations.

RESULTS

- | | | | |
|---------------------------------|-------------------|----------------|-------------|
| 1. Incidence of gastric ulcers: | Alendronate alone | Naproxin alone | Combination |
| | 2/26 | 3/26 | 10/26 |
2. No esophageal injury was seen in any group.
 3. Side effects were mild, and reported by 6 in the naproxin group; 14 in the alendronate group; 18 in the combined group. Abdominal pain and diarrhea were reported more often in the combined group.

DISCUSSION

1. "The evidence is now overwhelming that the use of alendronate alone can cause gastric ulcers."
The study did not address the combined use of alendronate and COX-2 inhibiting— COX-1 sparing NSAIDs.
2. Alendronate combined with naproxin was more likely to produce severe gastric mucosal damage and abdominal symptoms than either drug used alone. The combination produced ulcers in more than one third of those studied.
3. These results are consistent with a follow-up study of over 800 women who filled prescriptions for alendronate. About 1/4 discontinued the drug primarily because of GI complaints.
4. "Yet, prospective studies of alendronate have not reported an increase in ulcer complications."

CONCLUSION

Both alendronate and naproxin can cause gastric ulcers. The combination appears to synergistically increase risk.

Comment:

Admittedly, a small study. Note that the study was carried out in relatively young healthy volunteers. Adverse effects would be more common in the elderly frail population.

Caution should extend to all bisphosphonates and to the combination with aspirin.

Several recent investigations I have reviewed claim that the adverse effects of bisphosphonates are equivalent to placebo. Based on common sense, I do not believe this to be true. Undoubtedly, bisphosphonates are irritating to the upper GI (eg, the occurrence of esophagitis is well-known and leads to the directions about taking the drugs with a full glass of water and maintaining an upright posture for 30 to 60 minutes.

These valuable drugs should be used with caution and with full explanation of possible adverse GI effects. Patients should be followed closely and advised to report any GI symptoms. RTJ

2-10 EFFECT OF AGGRESSIVE VERSUS CONVENTIONAL LIPID LOWERING ON ATHEROSCLEROSIS PROGRESSION IN FAMILIAL HYPERCHOLESTEROLEMIA

B-mode ultrasound allows assessment of atherosclerotic changes in the walls of the carotid arteries. Intima media thickness (**IMT**) in the carotid arteries can be measured. Carotid IMT is associated with cardiovascular risk factors and prevalence of cardiovascular disease. Changes in carotid IMT over time enable prediction of coronary artery disease (**CAD**).

Patients with heterozygous familial hypercholesterolemia (**FHC**) have increased IMT.

This study postulated that aggressive lowering of LDL-cholesterol in patients with FHC would favorably influence carotid atherosclerosis as measured by IMT.

Conclusion: High dose atorvastatin therapy was accompanied by regression of carotid IMT.

STUDY

1. Randomized double-blind trial entered over 300 patients with FHC.
2. Randomized to: 1) atorvastatin (*Lipitor*) 80 mg/d, or 2) simvastatin (*Zocor*) 40 mg/d.
3. Measured change in IMT over 2 years.

RESULTS

1. Baseline IMT overall was similar between groups (0.93 mm vs 0.92 mm).
2. Mean LDL-cholesterol levels mg/dL (mmol/L):

	Baseline	2 years	% change
Atorvastatin	307 (8.00)	149 (3.88)	-50%
Simvastatin	320 (8.33)	177 (4.61)	- 41%

3. After 2 years, IMT decreased in the atorvastatin group by a mean of -0.031 mm — increased in the simvastatin group by + 0.036 mm.
4. Regression of IMT occurred in 2/3 of the atorvastatin group.
5. HDL-cholesterol rose in both groups. Both drugs were well tolerated.

DISCUSSION

1. Aggressive lowering of LDL-cholesterol is warranted to modify IMT progression.
2. The most recent NCEP guidelines endorse aggressive LDL-cholesterol lowering to less than 100 mg/dL in patients with established CAD. Since LDL-cholesterol levels are higher in patients with FHC these goals are rarely met. Even if the goal is not met, atherosclerosis regression can occur.
3. IMT is increasingly used to predict future cardiovascular events. "The clinical relevance of progression of IMT as a marker for cardiovascular disease is beyond doubt."

CONCLUSION

Aggressive LDL-cholesterol reduction was accompanied by regression of carotid intima-media thickness in patients with FHC.

Lancet February 24, 2001; 357: 577-81 Original investigation, first author T J Smilde, University Medical Center, Nijmegen, Netherlands www.thelancet.com

An editorial in this issue (p 574) comments:

FHC is the commonest potentially lethal genetic disorder in societies of European descent. It is dominantly inherited. If untreated, half of the males and 15% of females die before age 60.

The doses of the 2 drugs were the highest approved at the start of the study. Eighty mg of simvastatin is now approved. (*I do not think the investigators attributed any benefit of atorvastatin to factors other than LDL lowering. RTJ*)

"The lower, the better" should be applied wherever possible.

The Framingham risk equation underestimates the risk of CHD in patients with FHC. Most individuals are not overweight, and do not have other risk factors such as diabetes or hypertension. The high LDL-cholesterol levels from birth accounts for the greatly increased risk.

Comment:

As noted in the January 2001 issue of *Practical Pointers*, primary care clinicians will inevitably encounter an occasional index case. Family members should then be screened for hypercholesterolemia. The yield will be high. Lipid control beginning at an early age will save lives. There is an increasing tendency for pediatricians to begin treatment. RTJ

REFERENCE ARTICLE

2-11 INTERPRETATION OF THYROID FUNCTION TESTS.

The introduction of highly sensitive thyrotropin measurements and free thyroxine (free T4) and free triiodothyronine (free T3) has simplified the interpretation of thyroid tests.

Thyrotropin (thyroid stimulating hormone — TSH) is the pituitary hormone regulating the thyroid. Interpretation is generally straightforward. More than 90% of patients investigated have normal thyroid function. However, important pitfalls and difficult cases still exist. There are cases where TSH, free T4 and free T3 are misleading, pointing in different directions.

In many laboratories, the highly sensitive TSH assay (limit of detection < 0.1 mU/L) alone is used for initial screening. This is satisfactory as long as some limitations are appreciated. T3 or T4 estimation alone as initial screen will miss subclinical thyroid dysfunction and is not advised.

If TSH is abnormal, a free T4 should be obtained. When TSH is low, a free T3 should be obtained. In difficult cases, all 3 should be obtained. This will usually avoid misdiagnosis.

Other tests such as thyroid anti-thyroid peroxidase autoantibodies may be of value in determining cause of a thyroid disturbance.

In individuals with a strong clinical suspicion of thyroid diseases, all 3 tests should be done. If all 3 are normal, thyroid disease can be confidently excluded.

The author goes on to discuss 6 combinations of the three tests which require special interpretation:

The combination most important to primary care is:

Low free T3 or low free T4 (or both)

And a low or normal TSH

This pattern represents a typical pattern in unwell patients with non-thyroidal illness (previously termed the sick euthyroid syndrome). The most common pattern is a low T3 with a normal TSH.

The same pattern (a low T3 with a normal TSH) can be seen in pituitary disease with secondary hypothyroidism. TSH normally should be high in response to the low T3. But TSH in the normal range may occur in this situation, since the pituitary fails to respond adequately to low thyroid hormone concentrations. (The TSH may, of course, be low.) The diagnosis is important, because concomitant hypo-adrenalism could be life-threatening. An unsuspected large pituitary tumor can cause local pressure effects. A history of pituitary or cranial irradiation, even 20 years previously, can provide the explanation.

In most cases, interpretation of thyroid function tests with free hormone assays and TSH is straightforward. Unusual conditions, however, can generate common patterns of thyroid function easily confused with more straightforward diseases. In many cases, correct diagnosis of rare thyroid conditions can be made from thyroid function tests.

Lancet February 24, 2001; 357: 619-24 Review article by Colon M Dayan, Bristol Royal Infirmary, Bristol UK

2-12 ASPIRIN AND ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AMONG ELDERLY SURVIVORS OF HOSPITALIZATION FOR AN ACUTE MYOCARDIAL INFARCTION

Both aspirin and angiotensin-converting enzyme inhibitors (**ACE**) are prescribed for patients with acute myocardial infarction (**MI**). The American Heart Association recommends both for secondary prevention. Aspirin is considered beneficial for all patients; ACE for patients with left ventricular systolic dysfunction. Indeed, ACE have been suggested for use in all patients following MI.

However, recent studies have pointed out the possibility of harm when aspirin is added to ACE. Aspirin blocks prostaglandin production; ACE tend to increase it. Aspirin may block ACE-induced vascular relaxation. The combination may have an adverse effect on renal function.

This study evaluated the effect of the interaction of ACE and aspirin among elderly patients who survived hospitalization after a MI.

Conclusion: Benefit was evident from the combination.

STUDY

1. Observational study evaluated the effect and interaction of aspirin and ACE on mortality in over 14 000 patients who survived MI. All over age 65.
2. At discharge from hospital, 25% received aspirin alone; 20% received ACE alone; 40% received both; 15% received neither.
3. Follow-up = 1 year

RESULTS

1. Compared with those who received neither drug, patients who received both aspirin and ACE had a significantly lower mortality. (Adjusted risk ratio = 0.86.)
2. Compared with those who received aspirin alone or ACE alone, risk ratio of mortality was 0.81 compared with those who received both. But the difference was not statistically significant.

DISCUSSION

1. The study found no evidence of an adverse interaction between ACE and aspirin.
2. Use of either alone or the combination was independently associated with a reduction in mortality at 1 year.
3. Benefits were consistent with previously reported studies. Aspirin alone was associated with a 15% reduction in mortality; ACE alone with a 15% reduction in mortality. The combination produced a somewhat greater benefit, but not significantly so.

CONCLUSION

The benefit of ACE and aspirin in patients at discharge from hospital, either alone or combined, was associated with a reduction in mortality at 1 year.

The best practice appears to be to combine the two drugs.

Archives Int Med February 26, 2001; 538-44 Original investigation, first author Harlan M Krumholz, Yale University School of Medicine, New Haven Conn. www.archinternmed.com

2-13 INHALED HUMAN INSULIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

A dry powder insulin formula along with an aerosol system that permits inhalation of rapid-acting insulin has been developed.

This study assessed the efficacy and safety of pulmonary delivery in patients with type 2 diabetes who required insulin.

Conclusion: Inhaled insulin was effective and safe.

STUDY

1. Open label study entered 26 patients who were on a stable insulin schedule (2 or 3 injections daily).
2. During a 4-week baseline lead-in phase, patients continued their usual insulin regimen, were instructed in diet, performed home glucose monitoring, and underwent pulmonary function tests.
3. Then instructed in self-administration of inhaled insulin. Dry powder insulin was packaged in foil-blister packs containing either 1 mg or 3 mg of insulin. One mg delivers to the circulation the rough equivalent of 3 units of subcutaneous insulin. Only 10% to 30% of the insulin is absorbed.
4. Each blister was aerosolized using a specialized hand-held inhaler which delivered the insulin in a single inhalation. The median diameter of the aerosolized particles was approximately 3.5 microns, making it suitable for alveolar deposition.
5. Patients received 3 inhalations daily before meals at starting doses between the equivalent of 3 to 18 units of insulin. In addition they received a bedtime injection of ultralente insulin (Humulin-U; long-acting).
6. Dose titration was then based on preprandial glucose response targeted to 100 to 160 mg/dL.

7. Follow-up = 12 weeks.

RESULTS

1. Inhaled insulin for 3 months significantly improved glycemic control compared with baseline:
Mean HbA1c levels decreased by 0.7%. (From 8.7% to 8.0%). [*Not an exemplary result. RTJ*]
2. Patients received an average of 15 mg/d of inhaled insulin, and 36 units of ultralente daily by the end of the study. This compared with 19 units/d of regular and 51 units/d of ultralente given at end of baseline.
3. An average of fewer than 1 mild to moderate hypoglycemic events occurred each month.
4. No weight change. No change in pulmonary function.

DISCUSSION

1. "Inhaled insulin improved glycemic control, was well tolerated, and demonstrated no adverse pulmonary effects."
2. Despite demonstrated benefits, tight glucose control remains a largely unmet clinical challenge.
Multiple daily injections are inconvenient. Patient acceptance and adherence are poor. There is difficulty matching postprandial insulin availability to postprandial requirements.
3. Peptides, such as insulin, pass easily from the alveoli into the blood. The feasibility of pulmonary insulin delivery has been demonstrated in humans. Systemic absorption is confirmed by increased serum insulin levels.
4. Inhaled insulin appears to have an earlier onset of action than subcutaneous insulin. One mg of inhaled insulin has a peak level similar to approximately 3 units of insulin, with a similar glucose nadir.

CONCLUSION

Pulmonary delivery of insulin in type 2 diabetic patients who required insulin improved glycemic control, was well tolerated, and demonstrated no adverse pulmonary effects.

Annals Int Med February 6, 2001; 134: 203-07 Original investigation by the Inhaled Insulin Study Group, first author William T Cefalu, University of Vermont College of Medicine, Burlington. www.annals.org

Study supported by Pfizer.

An editorial in this issue (pp 242-44) comments:

Subcutaneous delivery has been the mainstay, but delayed and variable absorption interferes with true physiological replacement therapy.

This study represents only a preliminary demonstration of the biological activity and short-term safety of inhaled insulin. The final and defining issue will be *long-term* effectiveness and safety.

Comment:

Pulmonary administration still does not match the physiological passage of insulin through the liver.

This application requires much more experience. I abstracted the article mainly because patients may ask about inhaled insulin. The study and editorial comment may help primary care physicians clarify the present state of knowledge. If long-term safety and effectiveness are confirmed, patient acceptability will have to be assessed.

Small observational studies are likely to report more optimistic results than larger studies. And, when the application is entered into clinical practice, results are likely to be even less beneficial. RTJ

2-14 EFFICACY OF INHALED HUMAN INSULIN IN TYPE 1 DIABETES MELLITUS: A Randomized Proof-Of-Concept Study

Control of type 1 diabetes (insulin-dependent) requires at least two, and generally three or more insulin injections daily. Despite known effectiveness, tight control with aggressive insulin therapy has been slow to gain acceptance in general practice. Limitations include inconvenience and poor patient-acceptability.

Inhaled insulin offers an alternative.

A new dry powder of pure insulin and a new aerosol delivery device have been developed. The inhaler separates the patient's breathing maneuver from the generation of the respirable aerosol cloud, enabling reproducible dosing. The blister is opened within the inhaler, and the powder is dispersed by the inhaler (with an air-assist mechanism) into a discrete aerosol cloud which is captured in a holding chamber.

The purpose of the new delivery aerosol is to quantify and facilitate reproducible dosing.

The insulin is packaged in individual blisters containing either 1 or 3 mg of powdered recombinant human insulin. One inhalation of 1 mg delivers to the systemic circulation the equivalent of 3 units of subcutaneously injected insulin. But only 10% to 30% of the insulin is absorbed. Thus, assuming a 10% bioavailability, to make 36 units of insulin available systemically, 12 mg of powder would have to be inhaled. One mg of powder contains about 30 units of insulin; 12 mg contains about 350 units. The delivery is wasteful and expensive. In addition to the inhaled insulin, subcutaneous long acting insulin is required at bedtime.

This study was similar to the preceding, but limited to type 1 diabetes. One group received inhaled insulin; the other continuation of injected insulin. At the end of the 12 weeks, there was no difference between groups in HbA1c, fasting and postprandial glucose, and occurrence and severity of hypoglycemia. The inhaled insulin was well tolerated — no effect on pulmonary function.

The authors conclude that the study offers proof of the concept that inhaled insulin can be effectively and safely used in type 1 diabetes. It is a well tolerated alternative to subcutaneous insulin.

Lancet February 3, 2001: 357: Original investigation by the "Inhaled Insulin Phase II Study Group" first author Jay S Skyler, University of Miami School of Medicine. www.thelancet.com

An editorial in this issue (p 324) comments:

The aerosolized insulin peaks at least as rapidly as fast-acting subcutaneous insulin, and has a longer duration of action. Inhalation delivers a small, but reproducible, fraction of the inhaled dose safely and rapidly into the blood stream. As the authors state, the study is no more than a "proof of concept".

Comment:

Inhaled insulin, an exciting concept, has a long way to go before being clinically applicable. RTJ

2-15 ANTIBIOTIC SUSCEPTIBILITY OF STREPTOCOCCI AND RELATED GENERA CAUSING ENDOCARDITIS: Analysis of UK Reference Laboratory Referrals January 1996 To March 2000

This study reports over 600 isolates from patients with endocarditis referred from over 150 hospitals in the UK. About 85% were "viridans" group streptococci, which again documents this group as the most common agent for endocarditis. Five species of viridans accounted for over 2/3 of the isolates. The great majority was still susceptible to penicillin.

Other species and genera comprised fewer than 20 isolates each. Both isolates of *Abiotrophica defecta* and 6 of 15 isolates of *A. adjacens* had reduced susceptibility to penicillin

All isolates of *S. pneumoniae* and Lansfield groups A, B, C, and G streptococci were susceptible to penicillin

Overall 89% of isolates were susceptible to penicillin (minimum inhibitory concentrations ≤ 0.125 mg/L. Minimum inhibitory concentrations of 0.25 mg/L were seen in 4%. Minimum inhibitory concentrations of 4 to 8 mg/L were seen in 1%.

All isolates were susceptible to vancomycin. None had high level of resistance to gentamicin.

Some guidelines advocate that endocarditis on a native valve caused by streptococci that are susceptible to penicillin should be treated for 2 weeks with penicillin plus gentamicin, provided the patients lack thromboembolic disease and cardiac risk factors, have small vegetations, and respond clinically within the first week. A combination of penicillin and gentamicin is recommended for streptococcal endocarditis by British and American authorities. Vancomycin replaces penicillin in penicillin-allergic persons.

In patients not fulfilling these criteria, or with infection of a prosthetic valve, 4 weeks of penicillin plus gentamicin is recommended. Four weeks is also recommended for patients with streptococci with reduced susceptibility to penicillin. The American Heart Association advocates penicillin for at least 4 weeks, with gentamicin for the first 2 weeks, if the minimum inhibitory concentration of penicillin is 0.25 mg/L, or for at least 4 weeks if it exceeds this value.

Gentamicin plus penicillin remains appropriate for most patients, with vancomycin plus gentamicin a universally active alternative for those who are allergic to penicillin or who have more resistant isolates.

BMJ February 17, 2001; 3221; 395-96 Original investigation, first author Alan P Johnson, Central Public Health Laboratory, London, UK www.bmj.com/cgi/content/full/322/7283/395

RECOMMENDED READING

2-16 TERMINAL SEDATION, SELF-STARVATION, AND ORCHESTRATING THE END OF LIFE.

(This commentary will interest ethicists and primary care clinicians who care for terminal patients. The abstract consists mainly of quotes. RTJ)

"Orchestrating the end of life" refers to systematically and skillfully creating conditions to help the patient enjoy and control what is left of life.

The desire to be dead is generally not a desire to be no longer alive, but an overwhelming feeling that being dead is preferable to "living this way". When all is said and done, powerlessness, social isolation, and incapacitation are more feared than pain. If we can change the way in which patients live (as we often can through good palliative care) the desire to die will vanish or diminish.

Skillful pain control is more than merely obliterating pain. It is aimed at dealing with the whole concept of suffering and not only with the sensation of physical pain. *(The goal of good palliation is the relief of suffering as much as possible. Suffering extends far beyond physical pain. RTJ)* Much can be done to optimize a patient's capacity for controlling his or her own wishes into consequent action. This is a central feature of "orchestrating the end of life".

Despite the best palliative care and orchestration, some patients still might feel that they wish to terminate their lives, and might ask their physician for help. Two questions must be asked and answered as forthrightly as possible: 1) Who is entitled to decide what should be done? 2) Who is being treated?

1) Ethicists agree that patients who have decisional capacity are free to reject any and all forms of therapy for themselves. Conversely, patients are not free to expect that all demands for treatment be met.

2) The question — who the patient is, or ought to be, can be a difficult one to address. Often it is the family, the team, the institution, or the law that is, in fact, "being treated". The author urges that we be clear about whom we are treating and that we carefully examine our reasons and our justification for doing so. When, at least in our Western culture, we fail to put the patient as the center of our concerns, we need to have compelling reasons for doing so. Beware lest family and community interests be placed before those of the patient.

Terminal sedation:

Terminal sedation places a patient under anesthesia during the dying process. Supportive care is stopped and patient is given sufficient drugs to render him unconscious. It is done with the full knowledge that no further active treatment will be done, and that the patient will now die as rapidly as possible as a result of the underlying disease. The claim is made that, while providing maximal relief of pain and suffering, the death of the patient is "not intended". But that is, to say at least, disingenuous. (*Lacking in candor; giving a false appearance of simple frankness; not straightforward. RTJ*) That the patient should die in comfort is clearly the goal of terminal sedation. The death is clearly foreseen. It is in fact the end point of what is being done. Clearly the intent here is more than just the goal of relieving suffering. Because the goal can be attained only by obtunding the patient until death ensues, death becomes the end-point and therefore one of the intended goals. These goals do not differ from those of physician-assisted suicide, or for that matter, voluntary euthanasia.

Patients injected with overdoses of a drug with the intention of causing death, or patients kept unconscious until death ensues are in the end both very much dead. To say that the former (directly causing death) was the intended consequence, but in the latter to deny the death was the intended consequence, seems to again be disingenuous. The difference is maintained for 2 reasons: to escape legal difficulties, and as a form of self-delusion aimed at giving comfort to the physician and medical team. Self-delusion is not something to be encouraged.

The author states he is clearly *not* opposed to maximal analgesia and sedation for patients at this stage of life. He sees no rational or human argument against it. But he opposes the idea that we should engage in this practice as a charade for our own and the court's sake. Ethics, if it must be anything, must be honest.

Self-starvation:

By "self-starvation" the author does not have in mind patients who stop eating and drinking by their own volition, but by what had better be called "physician-stimulated (or suggested) self-starvation." Ie, patients who are still able and willing to continue eating are advised by their physician when they ask for help in ending their lives, to stop eating and drinking.

This leaves physicians free to claim that they were not directly involved and are therefore not ethically culpable. Note that this does not apply to patients who truly choose to starve themselves and make their own decision. We are speaking of patients who are still able and willing to eat and drink, and who, if they ask for help, are advised that they can starve themselves. This is more than self-starvation, it is "physician-stimulated self-starvation". Suggesting to patients that they can starve themselves is not as much aimed at easing the patient's plight as it is aimed at letting the health care professional off the legal hook.

Persons at the end of life are often able to share less and less with family and friends. Their isolation is real. The atavistic thread of sharing food and drink, even if only a symbolic sip, connects the person at the end of life with others. Encouraging them to stop eating and drinking (instead of encouraging them to continue sharing food and drink with their family) is encouraging them to sever their last social ties with their own hands. It is encouraging them to commit social suicide. There is an enormous difference between *allowing* patients to decline food and *encouraging* them to do so. To encourage patients to stop eating and drinking before they truly wish to do so seems a cruel act of rejection. It is not ethically legitimate, or even a minimally acceptable option.

Archives Int Med February 12, 2001; 161: 329-32 "Commentary" by Erich H Loewy, University of California, Davis.

www.archinternmed.com

Comment:

Some individuals have no social nexus during the process of dying. This must be one of humankind's saddest moments.

What is the difference between 1) terminal sedation, and 2) sedation given to cause death (euthanasia)? There is a great difference:

1) Physicians wishing to relieve suffering in a terminal patient give only enough morphine to relieve the patient's distress. And cease to give morphine until and unless the pain or distress recur. The intention is clearly not to kill the patient.

2) In the case of euthanasia, despite relieving the suffering, one goes on giving more morphine (or gives a much higher dose than one thinks necessary), then clearly one not only foresees the patient's death, one intends it.

The "doctrine of double effect" (DDE) states that a harmful effect of treatment, even if it results in death, is ethically permissible if it is not intended, and occurs as a side-effect of a beneficial action. According to the DDE, if the patient dies after 1), the intention can be considered a side effect of treatment. If the patient dies after 2), death is intended and is not a side effect, and is not considered ethical.

This article convinced me that I should never suggest to a patient that he or she should discontinue food or drink to hasten the end of life. RTJ

REFERENCE ARTICLE

2-17 RENAL ARTERY STENOSIS

The article concludes:

Atherosclerotic renal-artery disease is a common manifestation of generalized atherosclerosis. It is frequently associated with hypertension and excretory dysfunction. However, the association with hypertension and renal insufficiency does not establish causation. The use of invasive diagnostic techniques and treatment early in the course of the disease still has no proven benefit.

There seems to be a shift away from identifying patients with renovascular hypertension because of the known benefits of medical therapy and the lack of sustained cure after revascularization. Indeed, hypertension is seldom cured by revascularization, except in patients with fibromuscular dysplasia.

There is a shift toward identifying patients with renal-artery stenosis who are at risk for excretory dysfunction. Because of this shift, medical therapy (including aspirin) and modification of risk factors to limit atherosclerosis are essential in all patients, regardless of whether they have undergone revascularization.

In patients with atherosclerotic renal-artery stenosis who are at risk of excretory dysfunction, percutaneous or surgical techniques may improve or stabilize renal function.

NEJM February 8, 2001; 344; 431-42 Review article, first author Robert D Safian, William Beaumont Hospital, Royal Oak, Mich.

Comment:

We must always remember that atherosclerosis is a generalized disease.

The article presents a list of clinical findings associated with renal-artery stenosis which are the first step in suspecting RAS. There is also an algorithm for evaluation and treatment.

A Venn diagram illustrates the interrelation between RAS, hypertension, and chronic renal failure:

Chronic renal failure and RAS may occur without hypertension.

Hypertension and RAS can occur without chronic renal failure.

RAS, hypertension, and chronic renal failure can occur together.

2-18 FOMEPIZOLE FOR THE TREATMENT OF METHANOL POISONING.

Methanol poisoning results in metabolic acidosis, blindness and death. Methanol itself is not highly toxic. It is metabolized by alcohol dehydrogenase to formaldehyde and subsequently to formic acid. These metabolites cause the toxic effects.

Inhibition of alcohol dehydrogenase, and in selected patients, hemodialysis, are the traditional treatments. Ethanol, a competitive substrate of alcohol dehydrogenase is commonly used in attempt to inhibit methanol metabolism.

Fomepizole is an inhibitor of alcohol dehydrogenase. It appears to have few of the adverse effects of ethanol.

This study evaluated fomepizole in a small number of patients with methanol poisoning.

Conclusion: Fomepizole appeared to be safe and effective therapy.

STUDY

1. Multicenter study evaluated effect of fomepizole in 11 patients with methanol poisoning. Eight had ingested windshield wiper fluid; one antifreeze — 6 in a suicidal attempt, 2 to cause inebriation, two accidentally.
2. All had serum methanol concentrations over 20 mg/dL. And 2 of 3 findings: 1) arterial pH < 7.3; 2) serum bicarbonate < 20 mmol/L; and 3) serum osmolality gap (determined by freezing point depression) of more than 10 mOsm per kilogram of water.
3. All received supportive therapy and supplemental folate. All had received ethanol before fomepizole treatment. Five patients received hemodialysis.
4. All received fomepizole iv for a mean of 30 hours.

RESULTS

1. Plasma formic acid concentrations fell and metabolic abnormalities resolved in all patients. Nine patients survived. The 2 who died had anoxic brain injury at the time of enrollment.
2. At entry 7 of the 9 survivors had visual abnormalities. At the end of the trial none had any detectable visual defects related to the methanol.

DISCUSSION

1. "Our findings suggest that fomepizole is a safe and effective antidote for methanol poisoning."
2. There were few adverse effects.
3. In the absence of a substantial accumulation of formic acid, as indicated by the absence of acidosis, hemodialysis is useful only to remove methanol itself. With the use of fomepizole, little methanol was metabolized. Since its elimination half-life is over 2 days, hemodialysis may be useful to remove methanol.
4. A comparison of fomepizole with ethanol could not be made. However, fomepizole is simpler to administer and with the dosing regimens used, reliable plasma concentrations can be achieved.

CONCLUSION

Fomepizole appears to be safe and effective in the treatment of methanol poisoning.

NEJM February 8, 2001; 344: 424-29 Original investigation by the Methylpyrazole for Toxic Alcohols Study Group, first author Jeffrey Brent, University of Colorado, Denver.

Comment:

Fomepizole (*Antizol*) was provided by Orphan Medical, Minnetonka, Minn. It is available in Charlotte. Other treatment recommendations include gastric lavage, and bicarbonate for the acidosis. Folate is recommended because the detoxification of formic acid requires tetrahydrofolate as a cofactor.

Methanol causes an anion-gap metabolic acidosis. The gap can be used to estimate the concentration of methanol.

Fomepizole is also effective therapy for ethylene glycol poisoning.

Few primary care physicians are likely to encounter a patient with methanol or ethylene glycol poisoning. This is an example of information to be tucked away and recalled in case of emergency. RTJ

2-19 LIGHT BROUGHT TO A STANDSTILL

(This is an unusual article published in a medical journal. It is not a practical point. It is fascinating. I do not pretend to understand it. RTJ)

"Scientists in two separate laboratories at Harvard University have brought light to a complete standstill."

Nothing goes faster than light in free space, where it has a velocity of 300 000 km/s. When light travels through transparent matter such as water or glass, it is slowed down a little, a change known as refraction. In water, the speed goes down by a quarter.

To reduce the speed of light to zero is an astonishing achievement. Two years ago, the physicists used ultracooled gas to slow the speed to 60 km/h. In a later development, they brought a light pulse to a stop inside a glass cell containing rubidium. A laser beam changed the rubidium atoms so the vapor turned transparent. They then entered a pulse of light. At the same time a control laser beam was gradually dimmed. This caused more and more atoms to pile around the light pulse. When the control beam was switched off the light pulse halted, imprisoned in the rubidium atoms, so no light emerged from the cell.

The light trapping is completely reversible.

Physicists are now close to the next challenge – to stop light in its tracks and then reverse it at will. And to build a quantum computer which does not depend on the 0 and 1 binary code.

BMJ February 17, 2001; 357; 496 Commentary by Simon Mitton, University of Cambridge, UK

Comment: The possibility of reversing light boggles my mind. One step beyond Einstein? RTJ

