bestpractice

Issue 8

September 2007

GOUT

CAVEDILOL

PREXIGE

CO-ENZYME Q10

bpac nz
better medicine

Contact us:

Mail P.O. Box 6032 Dunedin
Email editor@bpac.org.nz
Free-fax 0800 27 22 69

Best Practice Journal (BPJ)
ISSN 1177-5645

BPJ is published and owned by bpac^{nz}
Level 8 10 George Street Dunedin

BPJ, Issue 8, September 2007

Bpac^{nz} is an independent organisation that promotes health care interventions which meet patients' needs and are evidence based, cost effective and suitable for the New Zealand context.

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UPFRONT

THE ROLE OF CO-ENZYME Q10 SUPPLEMENTS IN MEDICAL TREATMENT

It is becoming increasingly common for natural health products to be promoted as supplements to common medicines such as antibiotics and statins. They are readily available in supermarkets and health stores and now some pharmacy chains are actively promoting these products for sale with prescriptions.

On a recent visit to a pharmacy, a GP was surprised to be encouraged by a pharmacist to purchase a natural health supplement, co-enzyme Q10 (CoQ10), to accompany his prescription for cardiac medication. He was handed an information sheet with both pharmacy chain and natural health product company branding. It claimed that supplementation with CoQ10 was recommended, especially with statins, beta-blockers and tricyclic antidepressants to 'avert the negative effects of a CoQ10 deficiency'. It was claimed that statins and beta-blockers inhibit CoQ10 and 'the status of CoQ10 together with tricyclic antidepressants may be compromised'. As a prescriber and user of these drugs the GP was somewhat surprised at these claims, and asked us what the evidence was.

www.bpac.org.nz keyword: **"CoQ10"**

Co-enzyme Q10 was discovered in the 1950s and its mechanisms and uses are still being investigated

CoQ10 (also known as ubiquinone) assists in the production of energy within cells and helps protect internal and external cell membranes against oxidation. Organs with the greatest energy requirements such as the heart, lungs and liver have higher concentrations of CoQ10. Approximately half of the body's CoQ10 is obtained through dietary fat ingestion, with the remainder from cellular synthesis.

Supplementation of CoQ10 is used as a treatment for serious mitochondrial disorders and other metabolic syndromes, when people are unable to produce enough CoQ10. Current research focuses on its role in the treatment of neurodegenerative and cardiovascular disease. CoQ10 is a common ingredient in skin-care products and CoQ10 supplements are marketed by the cosmetics industry as 'skin boosters'.

Routine use of co-enzyme Q10 with statins is not necessary

The rationale for using CoQ10 in association with statin medication seems to focus on the role it may play in alleviating symptoms of myopathy – a relatively rare side effect of statin use. Statin treatment reduces circulating levels of CoQ10.[1, 2] However, studies on human subjects have shown that intramuscular levels of CoQ10 are not reduced by low-dose statin treatment. Effects may differ with the type of statin and dose.[2] Data on a causal association between low levels of intramuscular CoQ10 and statin induced myopathy is limited and contradictory.[2]

In a recently published systematic review in the Journal of the American College of Cardiology, Dr Leo Marcoff and Dr Paul Thompson concluded that there is insufficient evidence at present to prove the role of CoQ10 deficiency in statin induced myopathy. They state that routine supplementation of CoQ10 with statin use is neither justified nor recommended. However they noted that as there are no known risks associated with CoQ10, it may be trialled for people who develop statin associated myalgia.[2] Other reviews of research and literature have come to similar conclusions.[3, 4]

No compelling evidence as yet for using co-enzyme Q10 in cardiovascular disease

In the pharmacy-supplied CoQ10 information sheet, beta-blockers were highlighted as medications that would benefit from concurrent administration of CoQ10 supplements.

There has been some research on using CoQ10 as a treatment for hypertension. A recent meta-analysis of clinical trials concluded that CoQ10 'has the potential' to lower blood pressure in hypertensive patients.[5] In contrast, a study conducted among healthy individuals found that CoQ10 had only a mild and transient effect on systolic blood pressure.[6] While there is some emerging evidence of a beneficial effect of CoQ10 in hypertensive patients, there is less evidence for its use in cardiovascular disease as a whole. Large-scale trials are needed to find any compelling evidence of clinical effect.

No evidence for supplementing tricyclics with CoQ10

Although the pharmacy information sheet highlighted tricyclic antidepressants as benefiting from supplementation of CoQ10, we could not find any research to support this.

No clinical evidence of neuroprotection role for CoQ10 in Parkinson's disease

The mechanisms of Parkinson's disease are not yet fully known, but there is emerging evidence that cellular energy depletion and oxidative stress are contributing factors. CoQ10 is known to be a potent antioxidant and energy stimulant, therefore its potential role as a neuroprotectant is being investigated.

A recently published trial testing whether CoQ10 has beneficial effects on the symptoms in mid-stage Parkinson's disease, found that, while it was safe and well-tolerated, there was no difference between patients receiving CoQ10 and those who did not receive the supplement.[7] Other researchers have found no evidence of a clinically significant effect of CoQ10 in alleviating symptoms or halting the progression of Parkinson's disease, but suggest that further study is warranted.[8,9] One researcher notes that caution must be applied to the use of CoQ10 without certainty of its efficacy, especially since it is readily available over-the-counter and may expose patients to unnecessary risk and significant expense.[10]

So what does all this mean?

Current evidence on the use of CoQ10 supplements, alongside medications such as statins, beta-blockers and tricyclic antidepressants and as a treatment for hypertension or neurological disorders, shows that while there is no evidence of harm in taking this supplement clinical benefit is not proven.

There are good dietary sources of CoQ10 including oily fish, offal (e.g. liver, kidney), nuts, soy, sesame and some vegetables. In addition, there are other non-pharmacological strategies for managing conditions such as hypertension e.g. increased exercise, weight loss, decreased alcohol consumption and dietary modifications.[11] The use of supplements introduces a relatively substantial cost, with the recommended dose of 30–90 mg costing on average 60c – $1.80 a day.

While there is no safety issue preventing the promotion of the blanket use of CoQ10, we question whether it is ethical to use a prescription as the basis for promoting a supplement, that has little evidence of clinical benefit.

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TREATMENT OF GOUT

HIT THE TARGET

TARGET SERUM URIC ACID <0.36 mmol/L

KEY ADVISER

Dr Nicola Dalbeth, Rheumatologist and Senior Lecturer, Department of Medicine, University of Auckland

ACKNOWLEDGEMENTS

We are grateful to Dr Peter Gow and Dr Doone Winnard for their review of this article.

www.bpac.org.nz Keyword: ***"Gout"***

SUMMARY POINTS

1. ***Gout is a major cause of arthritis in New Zealand, with high rates of severe disease in Māori and Pacific patients***
2. ***Gout causes significant disability in Māori and Pacific men of working age***
3. ***All patients with gout should have cardiovascular disease (CVD) risk assessment, and intensive management of modifiable risk factors***
4. ***Long-term preventive therapy with allopurinol is critical for effective gout management:***
   - *Prescribe early, before development of tophi*
   - *Monitor serum uric acid levels*
   - *Aim for target serum uric acid <0.36 mmol/L*
   - *Introduce gradually: 'start low and go slow'*
   - *Use colchicine prophylaxis*
5. ***Minimise diuretic therapy in patients with gout***

WHAT IS GOUT?

Gout is an arthritis caused by the inflammatory response to intra-articular monosodium urate crystals. Supersaturation of urate typically occurs in physiological fluids above concentrations of 0.42 mmol/L. In early disease, gout presents as recurrent episodes of self-limiting acute inflammatory attacks ('flares') of arthritis. These attacks most often affect the 1st metatarsophalangeal joint, midfoot and ankle. In the presence of prolonged hyperuricaemia, some patients develop recurrent polyarticular attacks, chronic tophaceous disease, erosive arthritis (images are available in the online version of this article visit www.bpac.org.nz) and renal disease (urate nephropathy and uric acid stones).

NATURAL HISTORY OF GOUT

If untreated, the evolution of gout follows four stages:

1. ***Asymptomatic hyperuricaemia*** – asymptomatic hyperuricaemia has traditionally remained untreated with drugs. Although evidence is building, linking hyperuricaemia with cardiovascular and renal disease, treatment remains unproven. Identification of hyperuricaemia presents an opportunity to suggest diet and lifestyle changes to patients and also to look for possible underlying causes for the raised uric acid. Of those with hyperuricaemia, 20% will go on to develop acute symptomatic gout.

2. ***Acute attacks*** – typically the first attack involves one joint but it can also be polyarticular. Without specific treatment, an attack of acute gout is likely to resolve within 7–10 days. In practice, the severe pain usually forces patients to seek pharmacological relief.

3. ***Intercritical gout*** – the length of time between attacks can vary widely. Some patients only ever have one attack, but for the majority, a second attack will occur within a year. If the urate level remains high (>0.36 mmol/L) despite the patient being symptom free, there can be ongoing joint inflammation and hence joint damage and tophi formation.

4. ***Chronic tophaceous gout*** – tophi are firm white translucent nodules in connective tissue arising from the deposition of urate crystals. They can take at least 10 years after the initial attack to develop. As well as causing joint destruction, they are disfiguring and also cause physical hindrance. Tophi can become inflamed or infected and can exude tophaceous material.

DIAGNOSIS OF GOUT

The diagnosis of gout can be made according to the American College of Rheumatology (ACR)/Wallace criteria[1]:

A. The presence of characteristic urate crystals in the joint fluid,

B. A tophus proved to contain urate crystals by chemical means or polarized light microscopy (images are available in the online version of this article visit www.bpac.org.nz)

OR

C. Six of the following 12 clinical criteria

a. Maximum inflammation within the first day

b. More than one attack of acute arthritis

c. Monoarticular arthritis

d. Redness observed over joints

e. First metatarsophalangeal joint pain attack

f. Unilateral metatarsophalangeal joint attack

g. Unilateral tarsal joint attack

h. Suspected tophus

i. Hyperuricaemia

j. Asymmetric swelling within a joint on x-ray

k. Subcortical cysts with no erosions on x-ray

l. Negative bacterial culture of joint fluid

It is important to note that gout and sepsis can co-exist. The presence of urate crystals in synovial fluid does not exclude a diagnosis of sepsis.[2]

Although hyperuricaemia is a key risk factor for gout, it is not sufficient to make the diagnosis of gout; ***only 20% of patients with hyperuricaemia will develop gout***, and serum urate concentrations may be normal in patients during an acute gout flare.[3]

TREATMENT OF GOUT

Treatment of acute gout flares

Presenting symptom: Acute gout

- Treat acute attack with NSAIDs.
- Use corticosteroids when NSAIDs are contraindicated.

- Treat resistant cases with ***addition*** of low dose colchicine.
- Treat those at risk of NSAID side effects with colchicine ***alone***.

Evaluate and manage risk factors
(weight, alcohol, diuretics, dietary purines)

- ***NSAIDs:*** given at regular intervals until the severe pain abates, at which time the dose may be reduced (e.g. starting with naproxen 500 mg bd or diclofenac 75 mg bd). Always watch for renal impairment, heart failure and peptic ulceration. If patients are already taking low dose aspirin for cardiovascular risk reduction it should be continued.

- ***Oral corticosteroids:*** in view of the toxicity of colchicine, corticosteroids may be preferred to treat acute gout in patients in whom NSAIDs are contraindicated, provided sepsis has been excluded. The initial dose is 15–40 mg prednisone daily, gradually reduced over 10 days. Intra-articular corticosteroids are useful if monoarthritis is present to reduce risks of systemic therapy.

- ***Colchicine:*** can be a useful adjunct to NSAIDs in resistant cases, particularly when tophi are present, as monotherapy or to prevent flares when starting allopurinol.

- ***Allopurinol:*** If a patient has been taking allopurinol regularly at the time of developing an acute attack it should be continued at the same dose.

"Allopurinol should not be started at the time of the attack"

RISK FACTORS FOR GOUT

The key risk factors for gout are

- Hyperuricaemia
- Male sex
- Māori and Pacific ethnicity*
- Chronic renal impairment
- Hypertension
- Obesity
- Diuretic use**
- Coronary heart disease
- High intake of meat, seafood and alcohol (particularly beer)

*Māori patients with normal uric acid levels have been shown to have a reduced excretion of urate. This suggests an underlying renal mechanism.[4]

**Diuretic therapy is a risk factor for the development of hyperuricaemia and recurrent gout attacks. Diuretic therapy should be minimised and avoided wherever possible.

Adverse effects with Colchicine

Colchicine has a narrow therapeutic margin and considerable variation in absorption between individuals. Toxic effects include diarrhoea, nausea and vomiting, electrolyte imbalance, alopecia, haematological effects, pancreatitis, and failure of kidneys, liver or respiratory system. High doses can be fatal.

Colchicine dosing for acute gout

Due to recent concerns about toxicity, colchicine is no longer considered first line treatment for acute gout. In addition colchicine should be used at a lower dose than has been recommended in the past.

"…The recommended dose for colchicine in the treatment of acute gout is 1.0 mg stat, followed by 0.5 mg six hourly, up to a maximum dose of 2.5 mg per 24 hours…"

New Zealand Rheumatology Association (NZRA), endorsed by Medsafe.[5]

(full statement available at www.rheumatology.org.nz/colchicine.htm)

After the first 24 hours, the dose should be reduced to 0.5 mg one or two times daily, according to renal function. Prescribed in this way colchicine is safe and effective. The risk of diarrhoea and other toxic effects is minimised. Many patients report that one or two colchicine tablets taken within the first few hours of the onset of pain can avoid a major flare.

Adverse effects with Allopurinol

The most common adverse effect is a rash (1–2%), which may be more common in patients with renal impairment.[12] *Allopurinol hypersensitivity syndrome (AHS) is extremely rare but potentially fatal. It is characterised by fever, rash, eosinophilia, hepatitis and renal failure. Adverse effects can occur at any dose.*[13]

INDICATIONS FOR URIC ACID LOWERING THERAPY[6-8]

All patients with any one of the following should receive long-term uric acid lowering therapy:

- Recurrent gout attacks (≥2 attacks/year)
- Tophi
- Gouty arthropathy
- Radiographic damage
- Early onset, family history and serum uric acid >0.60 mmol/L

It should be noted that although effective treatment of gout can lead to regression of tophi, management is far more difficult once tophi develop, due to the high total body urate load.

"Early treatment of gout, before onset of tophi and erosive disease, is recommended"

HITTING THE TARGET IN GOUT: AIM FOR A SERUM URIC ACID CONCENTRATION OF <0.36 mmol/L

Several recent studies have emphasised the importance of excellent long-term control of serum uric acid in order to suppress gout attacks and achieve regression of tophi. These studies have identified a serum uric acid level of <0.36 mmol/L as the target required for dissolution of monosodium urate crystals within the joints and subcutaneous tissues.[9–11] This target has been endorsed in the recent European League Against Rheumatism (EULAR) guidelines for management of gout.[7]

Reduction of the serum uric acid level requires both pharmacological and non-pharmacological management. Allopurinol is the first choice urate-lowering drug unless there is a history of allopurinol allergy/ intolerance.

"Patients with gout should be encouraged to think of their uric acid level in the same way that patients with diabetes think of their HbA1c"

Allopurinol prescribing: a how-to guide

1. Wait for at least two weeks after an acute gout attack before starting allopurinol

2. *'Start low and go slow'*. Start with allopurinol 100 mg daily, and increase by 100 mg every two weeks until the serum uric acid level is <0.36 mmol/L. For most patients with normal renal function, a dose of 300 mg daily is needed to achieve this target. Patients with renal impairment may require less allopurinol to achieve this target. Sudden changes in the serum uric acid level are likely to precipitate gout attacks. Gradually increasing the dose of allopurinol is less likely to trigger a gout attack

3. Use prophylaxis against acute attacks. Prophylaxis with colchicine (0.5 mg daily to twice daily) or NSAIDs for the first three months of starting allopurinol (or until serum uric acid <0.36 mmol/L) should be prescribed to reduce the risk of gout attacks.[14]

4. Ensure the patient knows that the colchicine is for gout prevention and the dose should not be altered without medical advice if an acute episode occurs.

5. Monitor serum uric acid levels on a monthly basis while establishing allopurinol. Once serum uric acid is <0.36 mmol/L, monitor uric acid and renal function on a three-monthly basis.

6. Allopurinol should be continued as life-long therapy for management of gout, except in the case of allopurinol intolerance. Do not stop taking allopurinol during an acute attack of gout.

Other urate-lowering drugs

The uricosuric agent probenecid is an effective urate-lowering drug in patients with normal renal function and urate under-excretion. This agent is particularly useful in combination with allopurinol if there is persistent hyperuricaemia despite therapeutic doses of allopurinol, or in allopurinol intolerance.[15] A typical dose is 250 mg twice daily for two weeks, then 500 mg twice daily thereafter.

Probenecid is contraindicated in patients with a history of renal stones. Patients should be advised regarding the importance of high fluid intake while taking probenecid, around eight glasses of water per day.

LIFESTYLE INTERVENTIONS

Weight management is the key component in dietary management of gout. A 5% loss in body weight leads to a 10% reduction in serum uric acid level.[16,17] Diets very low in purines are generally unpalatable and poorly tolerated over time. Patients are more likely to accept advice to reduce purine-rich foods than to be told not to eat them at all (Table 1). Patients should be encouraged to eat regular meals and to drink plenty of water.

Table 1. Dietary advice for patients with gout

What to reduce in your diet	What to include in your diet
Red meat, shellfish, oily fish[18]	*Vitamin C[19]
Sugar and sugar-sweetened drinks[20]	Low fat dairy products[18,21]
**Alcohol, especially beer[22]	***Coffee[23,24]

**Studies suggest that Vitamin C might be beneficial in the prevention and management or gout and other urate-related diseases.[19]*

***Beer confers a larger risk than spirits. Moderate wine intake does not increase risk[22]*

****Refer to Bandolier article, page 33*

WHEN TO REFER TO A RHEUMATOLOGIST

Referral is appropriate when there is:

- Persistent hyperuricaemia or gout attacks despite maximum tolerated allopurinol treatment
- Doubt about the diagnosis
- Failure to achieve prompt resolution of acute attacks
- Development of progressive bone and joint damage on x-ray

URATE

Cam Kyle and Stephen Du Toit
Chemical Pathologists

About one third of body urate comes from the diet, two thirds from endogenous tissue catabolism. Underexcretion of urate by the kidneys is the cause of high serum levels in over 80% of adult patients. Insulin resistance (metabolic syndrome) is associated with increased urate resorption and higher serum urate levels.

About 20% of males have a serum urate above 0.42 mmol/L, but this has been chosen as the upper end of the male range because at that level urate becomes supersaturated in body fluids at 37°C, resulting in increased crystal deposition in tissues. Above this level the 5–year risk of gout rises fifty-fold from about 0.1% below 0.42 mmol/L to 5% above 0.54 mmol/L. Above 0.60 mmol/L the 5–year prevalence of gout is about 30%.

An upper limit of 0.36 mmol/L is used for women because their levels before menopause average 0.06 mmol/L lower than men. After menopause, levels in women approach those in men and the risk of gout increases, being similar to men over age 60.

Serum urate is the most important predisposing risk factor for gout, but is not used alone to make the diagnosis. Most patients with high urate levels do not develop gout and, conversely, serum urate may be normal, especially during acute attacks. Visual identification of crystals from joint fluid or tophi is the gold standard.

For patients with clinical gout on long-term treatment, a target urate level of 0.36 mmol/L has been recommended by some international bodies. The long-term risk of gout recurrence is much lower when levels are maintained below this threshold and it also favours the slow dissolution of chronic tophi, being well below the solubility constant of urate.

D-News, Diagnostic Medlab, August 2007 Available from: http://snipurl.com/1ptr8

CONSIDER CVD RISK AND METABOLIC SYNDROME FOR EVERY PATIENT WITH GOUT

There is increasing recognition that asymptomatic hyperuricaemia is an independent risk factor for development of CVD.[25] However, there is no current evidence that treatment of asymptomatic hyperuricaemia reduces the risk of subsequent CVD events.

Re-analysis of the Multiple Risk Factor Intervention Trial (MRFIT) has addressed the association of acute myocardial infarction (MI) in patients with gout. In this study, gout was associated with increased risk of acute MI (OR 1.3, $p < 0.001$), even after adjusting for BMI and metabolic syndrome.[26] In patients attending gout clinics in Auckland, 59% are at high risk of CVD events (>15% in the next five years) based on Framingham risk tables.[27]

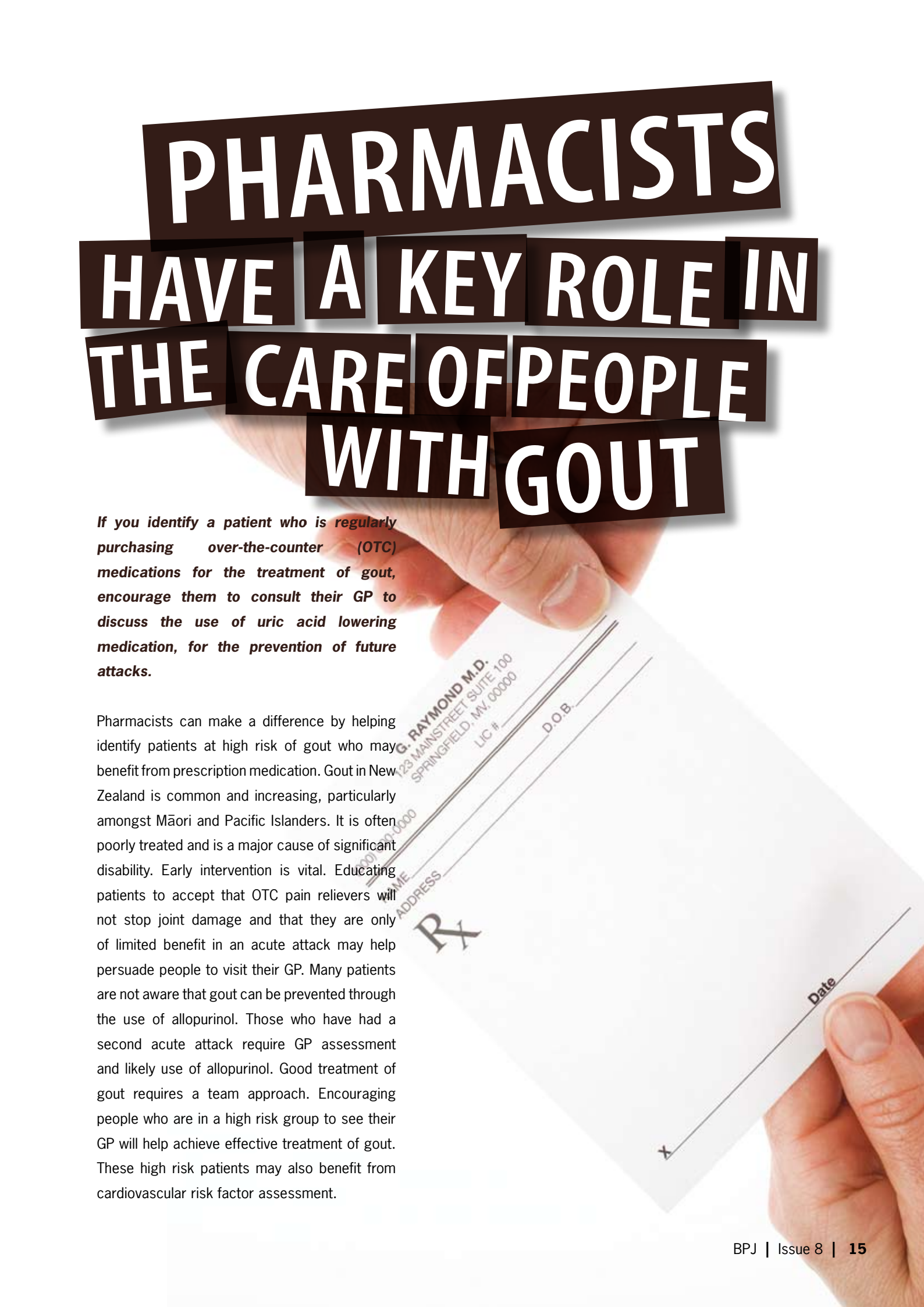
Recent analysis of the National Health and Nutrition Examination Survey (NHANES III) showed that gout is associated with increased risk of metabolic syndrome (OR 3.4, $p < 0.001$).[28] In patients attending gout clinics in Auckland, 87% have metabolic syndrome (using the revised Adult Treatment Panel (ATPIII) definition).[27]

"All patients with gout should have CVD risk assessment, and intensive management of modifiable risk factors"

PHARMACISTS HAVE A KEY ROLE IN THE CARE OF PEOPLE WITH GOUT

If you identify a patient who is regularly purchasing over-the-counter (OTC) medications for the treatment of gout, encourage them to consult their GP to discuss the use of uric acid lowering medication, for the prevention of future attacks.

Pharmacists can make a difference by helping identify patients at high risk of gout who may benefit from prescription medication. Gout in New Zealand is common and increasing, particularly amongst Māori and Pacific Islanders. It is often poorly treated and is a major cause of significant disability. Early intervention is vital. Educating patients to accept that OTC pain relievers will not stop joint damage and that they are only of limited benefit in an acute attack may help persuade people to visit their GP. Many patients are not aware that gout can be prevented through the use of allopurinol. Those who have had a second acute attack require GP assessment and likely use of allopurinol. Good treatment of gout requires a team approach. Encouraging people who are in a high risk group to see their GP will help achieve effective treatment of gout. These high risk patients may also benefit from cardiovascular risk factor assessment.



PREVALENCE AND IMPACT OF GOUT

MAORI AND PACIFIC PEOPLE OVER-REPRESENTED IN GOUT CLINICS

Gout is the most common form of inflammatory arthritis affecting men.[29] Gout is uncommon in pre-menopausal women. Most women with gout are post-menopausal and taking diuretics.

Gout is on the increase in New Zealand.[30] Recent data from primary care in Auckland shows that gout affects 14.9% Pacific men, 9.3% Māori men and 4.1% European men (Richard Hulme, East Tamaki Health Care, 2006). The same data has shown that gout is more frequently diagnosed than Type II diabetes in Māori and Pacific Island men.

Gout is now the most frequent cause for new patient referral to the rheumatology outpatient clinic in South Auckland, and accounts for more than 200 inpatient admissions to Middlemore Hospital each year.[31] Māori and Pacific patients with severe gout are over-represented within gout clinics in the Auckland area (Table 1).

Table 1. Percentage of Māori and Pacific Island people presenting to gout clinics in Counties Manukau DHB.[13]

	% DHB population	*% presenting to gout clinics*
Māori	17%	25.6%
Pacific Island	16%	46.0%

Māori and Pacific patients attending these rheumatology clinics have higher serum uric acid levels, more work disability and lower levels of musculoskeletal function than European patients (N. Dalbeth, unpublished data).

Why is gout such a problem in Māori and Pacific communities?

A study of gout patients in South Auckland has revealed some key issues (personal communication, Dr K Lindsay, CMDHB).

- There is minimal knowledge about gout and the medications used in treatment.
- Amongst the Pacific Island community in particular, there is a normalisation of gout, a stoicism and tolerance of the pain.
- Often knowledge of gout is based on jokes about over-indulgence, old age or unhelpful myths.
- These beliefs contribute to denial and result in missed opportunities for early diagnosis.
- Families take up the burden of caring for gout patients and these patients rarely present to general practice.
- Typically patients will use pain relief but not preventative medications, with a resulting increase in the number of joints involved, the size of tophi, the frequency of attacks and number of days off work. Without appropriate use of allopurinol, their gout is progressive and becomes chronic.

Genetic research into the causes of gout

Renal excretion of urate is controlled by a number of organic anion transporters and URAT1, the specific urate transporter that reabsorbs urate from the proximal renal tubules into the bloodstream. Genetic variants in URAT1 have been demonstrated to be a primary cause of gout in overseas populations. Researchers at the University of Otago, in collaboration with the New Zealand Rheumatology Research Network and Ngati Porou Hauora, are testing the URAT1 gene and other urate transport molecules for genetic variants causative of gout in patients of Māori and Pacific ancestry. Patients with variants in URAT1, that are a primary cause of gout, may benefit from treatment with uricosuric agents such as benzbromarone and probenecid which specifically inhibit the activity of URAT1. (J.Hollis-Moffatt,personal communication)

Further resources

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Pharmaceutical society of NZ. Gout. Self care pamphlet. 2007. (Available from Pharmacies)

www.rheumatology.org.nz

www.arthritis.org.nz

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A SLOW DEATH FROM **COLCHICINE**

CONTRIBUTED BY SAFE USE OF QUALITY MEDICINES

A patient wakes in the middle of the night with gout related pain. He reaches for his recently prescribed bottle of colchicine and swallows 30 of the tablets – he wants to go back to sleep. Three hours later he wakes with vomiting, diarrhoea and stomach pain. He sees his GP who refers him to hospital where he is admitted. There he suffers progressive CVS collapse and liver failure and dies three days later. There is nothing anyone can do once the overdose has occurred. Why did he take 30 tablets despite the correct directions being on the bottle - English was not his first language, it was the middle of the night and he was in pain!

How can you stop this happening again?

- Only prescribe colchicine for acute gout if the patient has contraindications to the first-line treatments, NSAIDs or oral steroids
- Forget the directions you were taught at medical school for colchicine (unless very recently qualified), these have been superseded
- Take colchicine off your favourites list or change the dose instructions to the recommendations below
- Consider prescribing a maximum of 12 colchicine tablets if the prescription is for acute gout
- Ensure patients for whom English is a second language understand the directions and risks
- Children are vulnerable to colchicine poisoning and very small doses can be fatal. Please remind people to store out of reach of children and grandchildren[1]
- **Do the bpac '10 Minute Audit'. See page 26.**

Current dose recommendations for colchicine in acute gout[2]

- Initial dosage 2 tablets (2 x 0.5 mg) followed every six hours by one tablet until relief is obtained, up to a maximum of five tablets (2.5 mg) in the first 24 hours
- In elderly patients, patients with renal or hepatic impairment, or patients weighing less than 50 kg use lower doses
- A cumulative oral dose of 6 mg over four days should not be exceeded (additional colchicine should not be administered for at least three days after a course of oral treatment)
- Patients should be told to discontinue colchicine immediately if they develop abdominal pain, diarrhoea, nausea or vomiting even if the symptoms of the acute attack have not been relieved

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IS CARVEDILOL SUPERIOR TO METOPROLOL IN HEART FAILURE?

KEY POINTS

- *Carvedilol may be an option if metoprolol succinate is poorly tolerated.*
- *In patients with heart failure who have not previously used a beta-blocker, carvedilol may be considered as the first choice agent.*
- *Strategies for initiating carvedilol are discussed in the following article.*

www.bpac.org.nz Keyword: ***"betablockercarvedilol"***

BACKGROUND

There has been much debate concerning the relative effectiveness of different types of beta-blockers, particularly carvedilol and metoprolol. Several large clinical trials have been conducted comparing these drugs.

Carvedilol is a non-selective beta-blocker with α_1, β_1 and β_2 adrenergic receptor blockade properties. It has shown to be effective in the treatment of hypertension, coronary heart disease (anti-ischaemic and anti-anginal properties), chronic heart failure and left ventricular dysfunction following acute myocardial infarction.[1]

Metoprolol is a cardioselective beta-blocker, that is it blocks β_1 adrenergic receptors (mainly cardiac in origin) at lower doses than those needed to block β_2 adrenergic receptors (mainly located in the bronchi and peripheral vessels). There are two chemical forms of metoprolol. They are different salts of the same drug; metoprolol succinate (Betaloc CR) and metoprolol tartrate (Lopressor, Slow Lopressor). In New Zealand, the succinate is only available as a slow release preparation designed for once daily dosing. The tartrate is available as an immediate release (twice or three times daily dosing) or a once daily slow release preparation. Metoprolol tartrate is indicated for the treatment of hypertension, angina, disturbances of cardiac rhythm, functional heart disorder with palpitation, hyperthyroidism and migraine prophylaxis.[2] In addition, metoprolol succinate is also indicated for maintenance treatment after myocardial infarction and for chronic heart failure, as an adjunct to other heart failure therapy.[3]

COMPARING CARVEDILOL AND METOPROLOL: RESULTS OF THE COMET TRIAL

The Carvedilol or Metoprolol European Trial (COMET) compared overall mortality in patients with heart failure, randomised to receive either carvedilol or metoprolol tartrate.[4] The doses used were carvedilol 25 mg twice daily and metoprolol tartrate 50 mg twice daily. The results of the trial showed that carvedilol was associated with a 15% relative risk reduction in all cause mortality, compared to metoprolol tartrate.[5] Carvedilol extended median survival by 1.4 years (95% CI: 0.5–2.3 years) compared with metoprolol and was associated with significantly lower rates of death from stroke and new-onset diabetes. There were no observed differences between carvedilol and metoprolol tartrate in rate of hospitalisation, adverse events or drug withdrawal.[6]

Based on the results of the COMET trial, the authors concluded that carvedilol, at a dose of 25 mg twice daily, provides superior morbidity and mortality benefit compared to metoprolol tartrate at a dose of 50 mg twice daily. However there is some controversy surrounding the conclusions drawn from this study, with debate focusing on whether the doses of the two drugs were comparable. It has been suggested that metoprolol tartrate should have been titrated to a higher dose (up to 200 mg per day). However, there is no agreement on what the optimal dose equivalence between the two drugs should be and in addition it is unproven whether higher doses of metoprolol tartrate confer lower mortality.[6]

It is important to note that in the COMET trial, carvedilol was compared with metoprolol tartrate. The MERIT-HF trial compared metoprolol succinate to placebo and it was found that metoprolol succinate reduced the mortality rate by 34% in patients with heart failure.[7] This is comparable to carvedilol.[6]

While carvedilol appears to be preferable to metoprolol tartrate for patients with heart failure, there is currently no evidence to demonstrate that it is superior to higher doses of metoprolol tartrate (e.g. 200 mg per day) or metoprolol succinate. Carvedilol is a more complex, non-selective beta-blocker and may represent a more comprehensive antagonism of the characteristics of heart failure than a cardioselective beta-blocker such as metoprolol.[5] However, these characteristics also mean that carvedilol is not an appropriate medication for people with respiratory disease due to risk of bronchoconstriction (*see BPJ Issue 1 page 38, and BPJ Issue 7 page 48 for more information*).

CARVEDILOL MAY BE AN OPTION IF METOPROLOL SUCCINATE IS POORLY TOLERATED.[1]

There is no advantage in changing to carvedilol for people who are already taking metoprolol succinate at effective doses. However, carvedilol may be an option if metoprolol succinate is poorly tolerated. In patients with heart failure who have not previously used a beta-blocker, carvedilol may be considered as the first choice agent.

If a decision is made to switch from metoprolol succinate to carvedilol there are some important considerations:[8]

1. Adequate beta-blockade must be maintained to avoid precipitating ischaemia or arrhythmia.
2. Initial dosing must be low enough to avoid hypotension resulting from vasodilation.
3. A stable heart failure regimen (e.g. ACE inhibitor, diuretic, etc) must be in place.
4. The patient must not be acutely decompensated.

STRATEGIES FOR CHANGING TO CARVEDILOL

Two strategies have been suggested for changing from metoprolol succinate to carvedilol; either a ***non-overlapping protocol*** where a straight switch is made, or an ***over-lapping protocol*** where the dose of metoprolol succinate is gradually reduced whilst simultaneously up-titrating carvedilol.[8] Whichever method is used, co-existing heart failure medication should be stable and the patient should be relatively euvolaemic.

An overlapping method may be considered if the patient is taking high doses of metoprolol. In this method, the dose of metoprolol is gradually reduced while the dose of carvedilol is increased. Most patients seem to tolerate a simple approach without an overlap period, particularly if they are taking relatively low doses (i.e. <95 mg daily) of metoprolol.[8] In this method, the metoprolol is stopped upon initiation of the carvedilol, which is titrated to the target or maximum tolerated dose (Table 1).

Table 1: Non-overlapping method for switching from metoprolol succinate to carvedilol

Adapted from Abraham et al. [8]

	Carvedilol (twice daily)			
Previous daily metoprolol succinate dose	Initiate	week 2	week 4	week 6*
≤47.5 mg	6.25 mg	12.5 mg	25 mg	25 mg
>47.5 mg	12.5 mg	25 mg	25 mg	25 mg

**At week 6, the dose of carvedilol can be increased to 50 mg twice daily, in patients >85 kg, unless* congestive heart failure (*CHF) is severe.*

INITIATING CARVEDILOL IN PATIENTS WITH STABLE CHRONIC HEART FAILURE[1]

- All other medication (e.g. digoxin, diuretics, ACE inhibitors) should be stabilised prior to starting carvedilol
- Carvedilol should be given twice daily
- Recommended starting dose is 3.125 mg, twice daily, for two weeks
- Increase dose at intervals of at least two weeks, to 6.25 mg, 12.5 mg then 25 mg, twice daily, as tolerated
- Maximum dose for patients with severe CHF, or weighing less than 85 kg, is 25 mg twice daily. In patients with mild to moderate CHF and over 85 kg, the maximum recommended dose is 50 mg twice daily
- Signs of intolerance to carvedilol include bradycardia (<50 bpm), systolic BP <80 mmHg or fluid retention

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LUMIRACOXIB
LINKED TO DEATHS IN AUSTRALIA

Lumiracoxib (Prexige), a COX-2 inhibitor anti-inflammatory drug, has been withdrawn in Australia due to the emergence of serious adverse reactions, including liver failure (leading to transplant) and death. In New Zealand, Medsafe has just announced that approval for Prexige 400 mg tablets has been revoked (100 mg tablets are still available).

Lumiracoxib (Prexige) is a selective inhibitor of cyclo-oxygenase-2 (COX-2). As with all COX-2 inhibitors (coxibs), lumiracoxib is not recommended for people at high risk of heart attack or stroke, for those already taking aspirin, or for routine pain relief, except where the person is at high risk of developing a serious gastrointestinal adverse effect from other standard anti-inflammatory drugs.[1]

Lumiracoxib was deregistered from the Australian market on August 11th, 2007 after the Australian Therapeutic Goods Administration (TGA) received eight reports of serious liver adverse reactions, including two deaths and two patients requiring liver transplants. People were advised to stop taking lumiracoxib immediately and consult their doctor for an assessment of any clinical or biochemical evidence of liver damage. All doses of Prexige were withdrawn. Lumiracoxib has been available in Australia since July 2004 but has only become widely used since being listed on the Pharmaceutical Benefits Scheme in 2006. All eight cases have occurred since March 2007, with six of the cases emerging in the last six weeks. While full details are not yet available, it appears that prolonged use of 200 mg tablets is a risk factor.[2]

There are limited data available on the hepatic side-effects of lumiracoxib. However clinical trial data suggested that if a person developed abnormal liver function while on the drug, their results were likely to normalise when the drug was ceased. In several of the Australian cases, the patients did not improve after lumiracoxib was ceased, due to the severity of their hepatic damage.[2]

Lumiracoxib does not have a significant market share in New Zealand and is not subsidised by PHARMAC. Until now, it was indicated for the symptomatic treatment of osteoarthritis, acute pain, primary dysmenorrhoea and acute gout and was available in 100 mg and 400 mg tablets.[3] Medsafe and the Medicines Adverse Reactions Committee (MARC) reviewed safety data from Australia, Singapore and the United Kingdom and concluded that the increased risk of liver damage seen with higher doses of Prexige outweighs any of its potential benefits.[4] Medsafe therefore has revoked consent for the 400 mg Prexige tablet and it is being recalled. According to Medsafe Interim Manager, Dr Stewart Jessamine, this recall is likely to affect around 1000 people who take Prexige 400 mg in New Zealand.[4]

Recommendations:

Patients using Prexige 100 mg tablets for osteoarthritis, should have their liver function checked and monitored monthly. GPs should report any abnormalities found in these tests to CARM (Centre for Adverse Reactions Monitoring).

Patients using Prexige 100 mg tablets for acute pain should be encouraged to use other suitable analgesics, as it is no longer approved for this use.

Patients using Prexige 400 mg tablets should cease use immediately and be assessed for any signs of adverse effects.

Medsafe also reviewed the safety of the 100 mg daily dose but concluded that severe liver damage with this dose is rare.[4] Dr Jessamine said that a review of New Zealand adverse reactions data showed no reports of liver damage associated with Prexige.[5] At this stage, Prexige 100 mg will still remain on the market, however its safety will be closely monitored.

Changes to Prexige approval include;

- Maximum daily dose now decreased to 100 mg
- Approved indication now limited to osteoarthritis
- Warning statements added to prescriber and patient information sheets, advising that patients should have a liver function test prior to starting treatment and every month thereafter

While the association between coxibs and adverse events has been evident for several years, lumiracoxib is the first of this type of drug to have been withdrawn by a government agency. Rofecoxib (Vioxx) was voluntarily withdrawn by its manufacturer in 2004 after it was found to be associated with an increased risk of heart attack and stroke. This was followed by the voluntary withdrawal of valdecoxib (Bextra) in 2005 after reports of serious skin reactions began to emerge.

An assessment of the clinical pharmacology of lumiracoxib found that liver function test abnormalities were more frequent with lumiracoxib (2.57%) than with comparator NSAIDs (0.63%).[6] Information from the Medsafe drug data sheet indicates that one year trials with lumiracoxib 200 mg and 400 mg, were associated with more frequent elevations of ALT/AST (2.6% >3 x ULN) than lower doses, for shorter time periods. Rare cases of hepatitis have been reported.[3]

There is little evidence of clinical reports of hepatic adverse effects of lumiracoxib in the literature. However it is known that all NSAIDs (including coxibs) are associated with an increased risk of hepatotoxicity.

** For more information on cardiovascular risk and coxibs, see BPJ Issue 1, October 2006.*

Doctors in Singapore recently reported that three patients presented with acute hepatitis after being prescribed nimesulide, an NSAID with COX-2 selectivity, for joint pain. One of these patients subsequently died from hepatic failure.[7] Nimesulide has been associated with many reports of adverse reactions and has never been approved for use in New Zealand. There have been rare reports of hepatic injury attributable to coxibs. One report describes two cases in which patients developed severe hepatotoxicity shortly after the initiation of rofecoxib for arthritic pain. In these cases there was rapid improvement in liver function once the drug was discontinued.[8] A case analysis of hepatic disorders in people taking NSAIDs concluded that, the safety profile of coxibs was no worse than that of traditional NSAIDs.[9]

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Ten minute Audit

Identifying your patients on colchicine

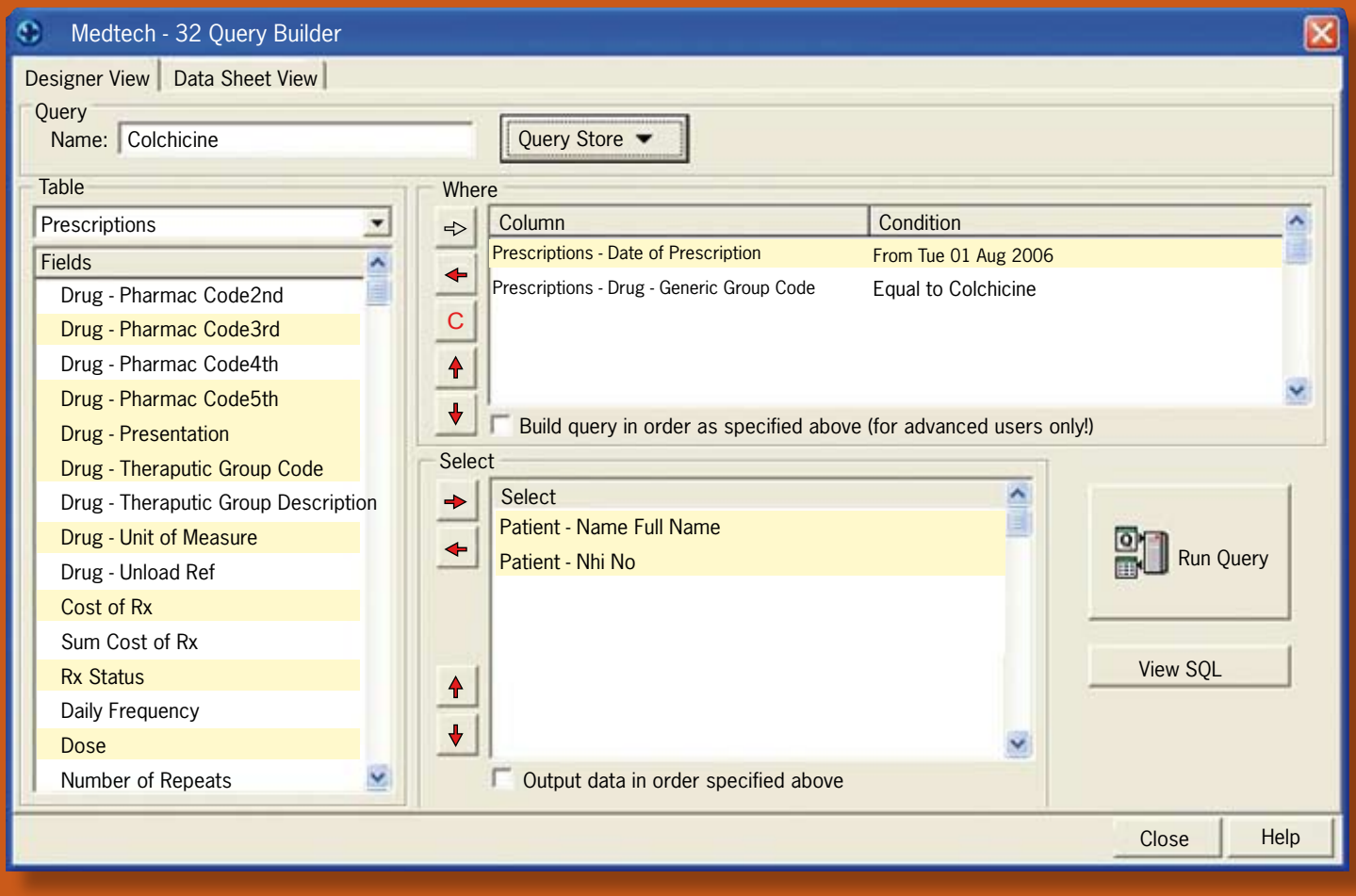
There has been recent concern about the toxicity of colchicine which has lead to a revision of the dosing regimen. This audit is designed to identify patients who have been prescribed colchicine in the past so that they can be informed of the changes in dosing. Many patients are used to starting colchicine as soon as an attack of gout starts. Outdated instructions on packaging may cause these patients to take doses that are toxic. Please refer to the gout article in this issue for further information on the safe use of colchicine.

Medsafe[1] has issued the following advice:

"Prescribers should be aware that patients might still have supplies of colchicine at home with previous dosage advice, including instructions to continue dosing until diarrhoea occurs. Prescribers need to inform patients of the revised dosage advice for colchicine and stress the importance of not exceeding the lowered maximum doses. Clear dosage advice (including the maximum daily and cumulative doses) should be written on the prescription so that this information can be included on the pharmacy label that is read by the patient. Patients should be warned of the symptoms of colchicine toxicity, and advised to immediately discontinue therapy and see their doctor, if symptoms occur."

Identifying your patients on colchicine

Medtech 32 Query Builder



If you are using MedTech you simply complete the query builder form as shown above.

Select items from the box on the left and transfer them to the appropriate box on the right of the screen.

Once patients are identified we suggest you contact them via a patient recall or letter so that clear instructions can be given on the safe use of colchicine. You can download a form letter from the bpac website: **www.bpac.org.nz** keyword: ***"colchicineform"***

Reference

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etc

evidence that counts

Effect of Exercise on HDL

Published in Journal Watch General Medicine June 14, 2007
Available from http://general-medicine.jwatch.org/cgi/content/full/2007/614/5

Bottom line: In this meta-analysis, aerobic exercise raised HDL cholesterol levels only modestly, and an exercise duration of less than 30 minutes per session failed to raise HDL. However, these results should not discourage exercise, which is associated with numerous benefits regardless of effect on lipids.

A meta-analysis finds that duration of aerobic exercise, but not frequency or intensity, is associated with change in HDL levels.

We routinely advise patients to increase aerobic exercise as a means of raising HDL cholesterol levels. These researchers conducted a meta-analysis to assess the overall effect of aerobic exercise on HDL levels and to determine which properties of an exercise program have the greatest effect. A total of 35 trials, including about 1400 subjects (mean intervention period, 27 weeks), were included in the analysis.

After exercise training, HDL levels were a mean of 2.53 mg/dL higher in patients randomized to exercise than in controls — a significant difference. Duration of exercise was significantly associated with change in HDL: Increases in HDL were significant only beyond thresholds of 120 minutes per week for total duration and 30 minutes for individual sessions. More frequent exercise sessions (independent of total duration) and more strenuous exercise were not associated with increased HDL.

— Jamaluddin Moloo, MD, MPH

Reference

Kodama S et al. Effect of aerobic exercise training on serum levels of high-density lipoprotein cholesterol: A meta-analysis. Arch Intern Med 2007 May 28; 167:999-1008.

Both conventional and atypical antipsychotics increase risk of femoral fracture in elderly patients

National Electronic Library for Medicines

Bottom Line: The authors conclude that their study found both atypical and conventional antipsychotic agents to be associated with an increase in risk of femoral fracture in elderly, institutionalised patients. These drugs should therefore be used with caution in elderly patients, especially those at increased risk of falls.

A case-control study has found that in institutionalised elderly patients, both conventional and atypical antipsychotic drugs increase the risk of femoral fracture. Conventional antipsychotics have been linked to an increase in risk of fracture in the elderly, via an increase in the risk of falling due to effects on gait and movement. Some trial evidence suggests a lower risk with the atypical antipsychotics, and this study aimed to clarify whether this was so by examining risk of hospitalisation for femoral fracture in relation to use of drugs in either group.

Study subjects were nursing home residents from six US states. Cases consisted of 1787 patients with fractured femur, who were compared with 5606 controls with no fracture living in the same institution at the same time. After adjusting for potential confounding factors, the risk of fracture for those taking atypical antipsychotics was statistically the same as those in the conventional drugs: relative to non-users, the odds ratios were 1.37 (95% CI 1.11 to 1.69) and 1.35 (95% CI 1.06 to 1.171) respectively. Numbers were sufficient to calculate risks for three individual agents - risperidone (OR, 1.42; 95% CI 1.12 to 1.80), olanzapine (OR, 1.34; 95% CI 0.87 to 2.07), and haloperidol (OR, 1.53; 95% CI 1.18 to 2.26).

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Atypical antipsychotics raise risk of femoral fracture in nursing home residents. J Clin Psychiatry 2007; 68: 929-934.

Rosiglitazone: More Data, Continuing Concern

Published in Journal Watch General Medicine June 12, 2007 Available from http://general-medicine.jwatch.org/cgi/content/full/2007/612/2

Bottom Line: By itself, this interim analysis doesn't settle the question of whether rosiglitazone increases risk for MI or death. However, the results are not reassuring: The primary endpoint is in the "wrong direction" for rosiglitazone (although not statistically significantly so), and the increased risk for heart failure is striking. This report — superimposed on the earlier meta-analysis — convinces an editorialist that clinicians should no longer feel comfortable prescribing rosiglitazone. I agree.

An editorialist concludes that clinicians should no longer feel comfortable prescribing the diabetes drug.

In a recent meta-analysis, rosiglitazone was associated with increased risk for myocardial infarction and possibly cardiovascular mortality (Journal Watch May 24 2007). The authors noted that the industry-sponsored RECORD trial, specifically designed to examine cardiovascular outcomes associated with rosiglitazone, was still in progress. Because of the controversy sparked by the meta-analysis, the RECORD investigators conducted this interim analysis (about two thirds of the way through the trial).

Researchers in Europe and Australasia enrolled 4447 type 2 diabetic patients taking metformin or sulfonylurea monotherapy. Half the patients were randomized to receive add-on rosiglitazone; in the control group, metformin users received add-on sulfonylurea, and sulfonylurea users received add-on metformin. During an average follow-up of 3.75 years, the primary endpoint (cardiovascular death or cardiovascular hospitalization) occurred in 217 rosiglitazone patients and 202 controls (hazard ratio, 1.08; P=0.43). For secondary endpoints, the only statistically significant finding was an increased risk for heart failure in the rosiglitazone group compared with the control group (38 vs. 17 events; P=0.006). A slight excess of MIs in the rosiglitazone group was not significant (43 vs. 37 events; P=0.5).

— Allan S. Brett, MD

Reference

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Nathan DM. Rosiglitazone and cardiotoxicity — Weighing the evidence. N Engl J Med 2007 Jun 5; [e-pub ahead of print]. (http://dx.doi.org/10.1056/NEJMe078117)

Role of statins for the primary prevention of cardiovascular disease in patients with type 2 diabetes mellitus

National Electronic Library for Medicines

Bottom Line: The authors conclude, "Current ADA recommendations may be too aggressive as available evidence suggests that the decision to initiate pharmacotherapy with a statin in patients with type 2 diabetes mellitus who do not have pre-existing CHD should be individualised rather than based solely on the diagnosis of type 2 diabetes mellitus."

The authors of this American article review and evaluate the major statin trials that included a significant number of patients with diabetes without pre-existing coronary heart disease (CHD). They also discuss the role statins should play in primary prevention. The following primary prevention trials are discussed in the article:

- Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT)
- Heart Protection Study (HPS)
- Anglo–Scandinavian Cardiac Outcomes Trial–Blood Pressure Lowering Arm (ASCOT-BPLA)
- Collaborative atorvastatin diabetes study (CARDS)
- The atorvastatin study for prevention of coronary heart disease endpoints in non-insulin-dependent diabetes mellitus (ASPEN)

Guidelines from the American Diabetes Association (ADA) recommend statin therapy in the majority of patients with diabetes. The authors note that the first 4 studies above (which included a significant number of patients with diabetes and no history of CHD) have had an impact on treatment guidelines. However, they also add that these studies had various methodological flaws and some non-significant results. ASPEN was the most recent trial published since the ADA guidelines were issued. This trial found that in patients with diabetes at lower CHD risk, atorvastatin 10 mg was not superior to placebo in reducing time to the first major CV event or procedure.

Reference

Lancet 2007; 370: 292, 293-4, 319-28

etc

evidence that counts

Cannabis use associated with increase in risk of psychotic disorder

National Electronic Library for Medicines

Published evidence is consistent with an increased risk of psychosis in cannabis users, according to a systematic review published today. The review, which has inevitably generated considerable media interest, was funded by the UK Department of Health.

As cannabis is the most frequently used illegal substance in many countries, there is considerable concern over whether it has any long-term adverse effects. Increase in use at younger ages, while the brain is still developing, has sharpened this concern. There is strong evidence that use can provoke transient psychotic and affective experiences, and this review aimed to determine whether there was any evidence for any longer term effect. The authors searched a wide range of sources for published population-based longitudinal studies or case-control studies within longitudinal designs that looked at psychotic or affective mental health outcomes in association with cannabis use. Study quality was assessed on a range of factors including methods to address bias and confounding factors, reverse causation, missing data, response rates, etc.

The initial literature search yielded 4,804 references of which 173 were considered potentially relevant on the basis of title and abstract. Of these, 143 were excluded after full examination to leave 35 for analysis: 11 for psychosis (from 7 cohorts) and 24 for affective disorders (from 15 cohorts). Unadjusted results from all studies on psychosis showed an increased risk with cannabis use in all seven cohorts, which remained positive in six after adjustment for confounding. Pooled estimates showed an increased risk of psychosis associated with cannabis use, with an adjusted odds ratio of 1.41 (95% CI 1.20 to 1.65).

Where the data were available, there was evidence for a dose-response effect with the OR in most frequent users being 2.09 (95% CI 1.54 to 2.84). The evidence for effects on depressive outcomes was much weaker - effect sizes were small and many of the included studies were too small.

The authors conclude that the published evidence is consistent with the view that use of cannabis is associated with an increased risk of psychosis. They discuss in some depth the steps taken to try and minimise the weaknesses of the studies included, the most important being confounding factors (people who use cannabis are also those at greater risk for other reasons) and reverse causation (people with early symptoms are more likely to use cannabis in an attempt to relieve these). While considerable efforts were made to reduce these, they can never be eliminated in observational studies. In the studies of affective outcomes in particular, reverse causation was poorly addressed. These factors are unlikely to be resolved, as proof would require a large randomised controlled trial that is not feasible. An estimate suggests that up to 14% of psychotic outcomes in young adults in the UK would not occur in the absence of cannabis use, however this relies on the assumptions that the link is causal and the pooled estimate is accurate. Incidence figures do not show parallels between schizophrenia and trends in cannabis use, however time lags and lack of reliable incidence data may affect these.

Overall, therefore, they consider that although causality cannot be proven, and confounding cannot be ruled out, the evidence for a link between cannabis use and increased risk of psychotic illness is sufficiently strong to justify public health warnings on the issue. Although the individual lifetime risk for even regular users is low (<3%), on a population level the impact would be significant because of the drug's widespread use.

Cochrane review: saline irrigation effective in chronic rhinosinusitis

National Electronic Library for Medicines

Nasal irrigation in chronic rhinosinusitis does appear to be worthwhile, despite the patient effort involved, according to a Cochrane review. The authors note that nasal irrigation as a treatment for chronic nose and sinus problems originated in some alternative medical practices and has become more common as a mainstream therapy. It may often involve considerable efforts by the patient, however, and it is not clear how beneficial it is: this review aimed to determine whether there was good published evidence to support the practice. The authors carried out a comprehensive literature search for randomised controlled trials in which saline was evaluated against placebo, no treatment, against other treatments, or as an adjunct to other treatments. They also looked for studies comparing isotonic with hypertonic saline.

A total of eight eligible trials were located, comparing saline irrigation with no treatment (n=3), with placebo (n=1), with an intranasal steroid spray (n=1), and as an adjunct to intranasal steroid spray (n=1): there were two studies comparing different hypertonic solutions with isotonic saline. Analysis indicated that saline irrigation provided effective symptom relief as sole treatment, and also as an adjunctive therapy. It is less effective alone than intranasal steroid, however. There is some evidence that hypertonic solutions may give better results, but this is not clear. Overall, the authors conclude that saline nasal irrigations have beneficial effects in chronic rhinosinusitis, both as sole treatment and as an adjunct. Minor side effects are common, however for most patients these are outweighed by the benefits and the procedure is well tolerated.

Inhaled corticosteroids increase risk of pneumonia in elderly patients with COPD?

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According to the results of this nested case-control study, the use of inhaled corticosteroids among elderly patients with COPD is associated with an excess risk of hospitalisation due to pneumonia.

Researchers analysed data from health databases of a health insurance agency in Quebec (holds information on all 7 million residents), and identified all subjects aged 66 years or above who were dispensed at least one of the following between 1988 and 2001: any beta-agonist, theophylline, ipratropium bromide, sodium cromoglycate, nedocromil, or ketotifen. The cohort of patients with COPD was formed from this source population by identifying all subjects with three or more prescriptions for these medications in any 1-year period and on at least two different dates (subjects with a primary or secondary diagnosis of asthma were excluded). Cases were identified as those who were hospitalised for pneumonia during follow-up; all cases were age and time matched to four control subjects.

The main findings were as follows:

- The cohort included 175,906 patients with COPD of whom 23,942 were hospitalised for pneumonia during follow-up, for a rate of 1.9 per 100 per year, and matched to 95,768 control subjects.
- The case subjects had more severe respiratory disease, and more co-morbidity.
- The current use of inhaled corticosteroids was found to be associated with an increased risk of hospitalisation for pneumonia (adjusted rate ratio [ARR] of 1.70; 95% CI 1.63–1.77) and an increased risk of hospitalisation for pneumonia followed by death within 30 days (ARR 1.53; 95% CI 1.30–1.80).
- There was a dose–response relationship, with the rate of pneumonia greatest with the highest doses of inhaled corticosteroids, equivalent to fluticasone at 1,000 mcg/day or more (RR, 2.25; 95% CI, 2.07–2.44).
- All-cause mortality was similar for patients hospitalised for pneumonia, whether or not they had received inhaled corticosteroids in the recent past (7.4 and 8.2%, respectively).

The authors conclude that 'the use of inhaled corticosteroids is associated with an excess risk of pneumonia hospitalisation and of pneumonia hospitalisation followed by death within 30 days, among elderly patients with COPD'. They recommend that this adverse effect 'needs to be considered when prescribing these medications to patients with COPD'.

Reference

Inhaled Corticosteroid Use in Chronic Obstructive Pulmonary Disease and the Risk of Hospitalization for Pneumonia American Journal of Respiratory and Critical Care Medicine; Vol 176:162-166

Bandolier

Independent evidence-based thinking about health care

Gastrooesophageal reflux and BMI

Bandolier 160, www.ebandolier.com

There is a general understanding of a relationship between weight and increased prevalence of heartburn, or symptoms of gastrointestinal reflux. Indeed, there is a meta-analysis [1] indicating significant increase for those with a BMI of 25 kg/sq m or more compared with those with lower BMI.

However, this is something of a blunt analysis, and does not tell us much about gradations. For instance, is there a gradual increase in risk, or does the risk increase dramatically at any particular BMI? Is there any evidence of a U-shaped relationship, perhaps with higher rates in underweight people? A new study [2] fills in some of the fine details.

Study

Part of the US Nurses study, this survey involved a questionnaire to a random selection of 12,192 nurses, with questions about frequency, severity, and duration of heartburn or acid regurgitation, using validated definitions of both terms. Severity was defined as mild (can be ignored), moderate (cannot be ignored but does not affect lifestyle), severe (affects lifestyle), and very severe (markedly affects lifestyle). Frequent was an episode occurring at least weekly.

Information was collected regarding height, weight (at various ages), drugs, diet, exercise, tobacco and alcohol use, and concurrent disease. Analysis of results used these data to examine confounding variables. Controls were women without symptoms not taking acid suppressing medicines.

Results

The women in the survey had an average age of 66 years, and an average BMI of about 27. Women with symptoms were more likely to have a higher BMI, use medications for asthma or hypertension, or hormone preparations, consumed more calories, and were less active.

Over 10,500 questionnaires were returned, with an 86% response rate. No symptoms of heartburn or acid reflux were reported in 41% (1 in 10 of whom were using proton pump inhibitors), with the remaining 51% reporting symptoms less frequently than monthly, to daily (Figure 1). One woman in five (22%) had symptoms at least weekly. Of those with symptoms, most (95%) were moderate or mild, and only about 5% had symptoms that were severe or very severe, and most (55%) had both heartburn and acid reflux.

Using those women with frequent (at least weekly) symptoms, and women without symptoms as controls, there was increasing reporting of symptoms of heartburn or acid reflux with increasing BMI (Figure 2), even after adjusting for potential confounders. This was the case for mild, moderate and severe or very severe symptoms. With a BMI ≥25, 60% of the increased risk was accounted for by excess weight.

Figure 1: Frequency of symptoms

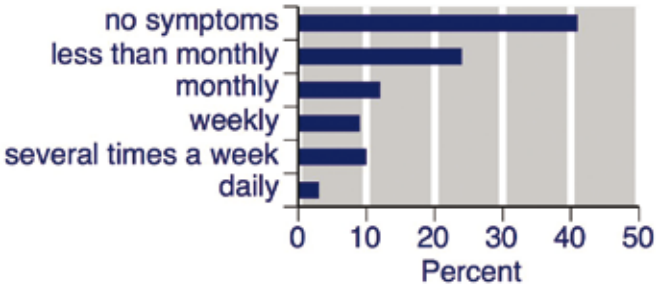
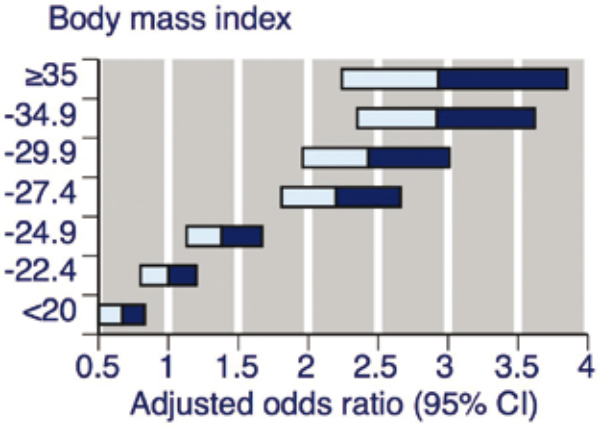


Figure 2: Odds ratio for heartburn or acid reflux at different BMI levels

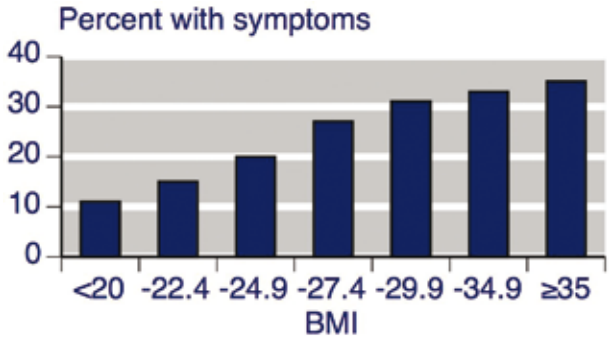


Among women who had gained weight during the previous 14 years, there was a dose-dependent increase in the risk of symptoms, with about a threefold increase in those whose BMI increased by 3.5 units. Conversely, there was a reduction in almost 40% in the risk of frequent symptoms in women who reduced BMI by 3.5 units or more.

Comment

This nicely captures the relationship between increased risk of heartburn or acid reflux and increased weight. Being or becoming overweight doubles the risk of having these symptoms at least once a week. A back-

Figure 3: Crude symptom rate and BMI



of-the-envelope calculation gives crude results for the prevalence of moderate or severe heartburn or acid reflux symptoms at least weekly for each band of BMI and shows the gradation (Figure 3). The bottom line is that this is yet another reason to avoid being overweight, along with all the others. If our populations keep growing out as well as in numbers, we will need to step up production of the antacids.

References:

H Hempel et al. Meta-analysis: obesity and the risk for gastroesophageal reflux disease and its complications. Annals of Internal Medicine 2005 143: 199-211.

BC Jacobson et al. Body-mass index and symptoms of gastroesophageal reflux in women. New England Journal of Medicine 2006 354: 2340-2348.

Statins, sepsis, and chronic kidney disease

Bandolier 160, www.ebandolier.com

Bandolier once came across a paper that claimed that at least half of all indications for drug use arose from observations made by perceptive clinicians, rather than from the original intentions for their use by pharmaceutical companies. It is interesting, therefore, to perhaps see one swim into our ken, and perhaps watch it develop. The case of the possible effect of statins in reducing sepsis may be one of these.

Study

A prospective observational study [1] has examined the use of statins and rate of sepsis in dialysis patients. Situated in the USA, the study began in 1995 to examine treatment choices and outcomes. Eligibility included long-term outpatient dialysis in the preceding three months in adults of at least 17 years, and it enrolled 1041 participants up to mid-1998, with observations continuing up to 2005.

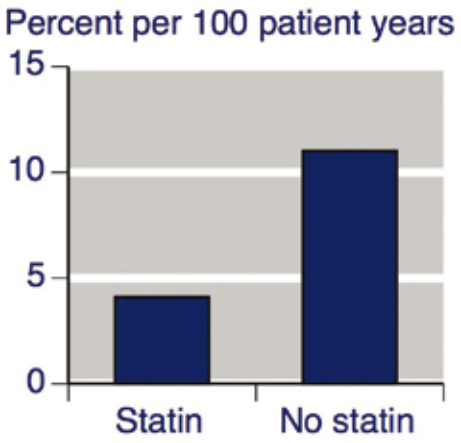
Statin use was determined by review of clinic notes and computerised records. Data collected was extensive, including demographics, comorbidity, drug therapy, and laboratory values. The primary outcome was hospital admission for sepsis, where sepsis was defined using ICD codes. A number of different statistical analyses were performed, including multivariate regression and propensity score matching.

Results

The mean age of patients was 57 years, about half men, and about 80% white. Statin users were more likely to be white, and have higher cholesterol levels, cardiovascular disease, and a history of sepsis, but were less likely to have used street drugs, and consumed less alcohol.

In the 1041 patients there were 303 hospital admissions for sepsis over the mean follow up of 3.4 years. The crude incidence rate was 4% per year in statin users and 11% per year in non-users (Figure 1). In the main statistical analysis, the crude incidence rate ratio was 0.37 (95% confidence interval 0.22 to 0.61). Using multivariate analysis with more complex interaction models, or propensity scoring, did not reduce the effect, but if anything made it larger. Various sensitivity analyses did not change the findings.

Figure 1: Crude rate of hospital admission for sepsis with and without statin



Comment

This was an extremely detailed study, with a moderate number of events, and with extensive efforts to discover possible sources of confounding, especially confounding by indication. It found none of these, and the result, a 60% reduction in the risk of sepsis with statins in dialysis patients looks strong.

Several other observational studies in bacteraemia or bacterial infection have also found improved outcomes in statin users, and a study of hospital admission for cardiovascular events found a lower incidence of sepsis with statin use. Moreover, there appears to be a biological plausibility, as the first statin was originally identified from a penicillin fungus, where it is theorised that it may have benefited the fungus by preventing replication of microorganisms requiring cholesterol for growth.

All in all an intriguing story based on some good observation. It will be interesting to see where it leads.

Reference:

R Gupta et al. Statin use and hospitalization for sepsis in patients with chronic kidney disease. JAMA 2007 297: 1455-1464.

Gout and drinking

Bandolier 160, www.ebandolier.com

People with gout, and their carers, tend to the obsessive when it comes to food, and especially drinking; alcohol and coffee are often banned completely. All of which makes for a bland existence, which is why a frequently asked question is what gout sufferers can drink without exacerbating their condition. A large US survey has reported on coffee, tea, and various forms of alcohol [1,2]. The results will warm the cockles of some hearts.

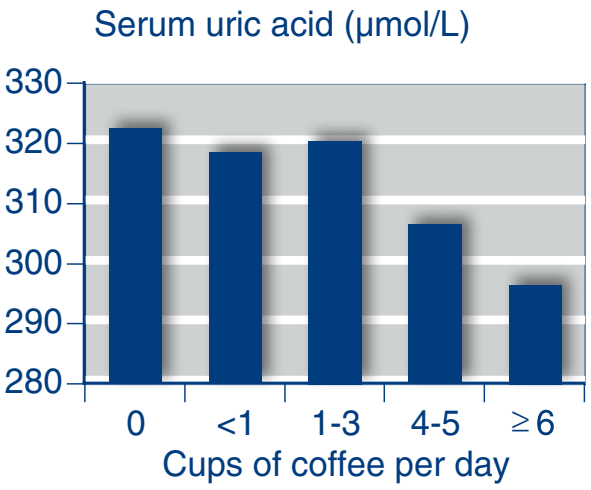
Studies

A representative sample of the US population was selected and studied between 1988 and 1994. Subjects were interviewed at home, and attended an examination, with blood and urine sample collection. During the interviews, a food frequency questionnaire was used which ascertained the frequency of consumption of coffee, tea, and alcoholic beverages, as well as soft drinks that might contain caffeine. Serum uric acid was measured also.

Results

The survey used data from over 14,000 people aged over 20 years of age. Those with gout, or taking allopurinol or uricosuric agents were excluded.

Figure 1: Reduction in mean serum uric acid levels according to quintiles of daily intake of coffee



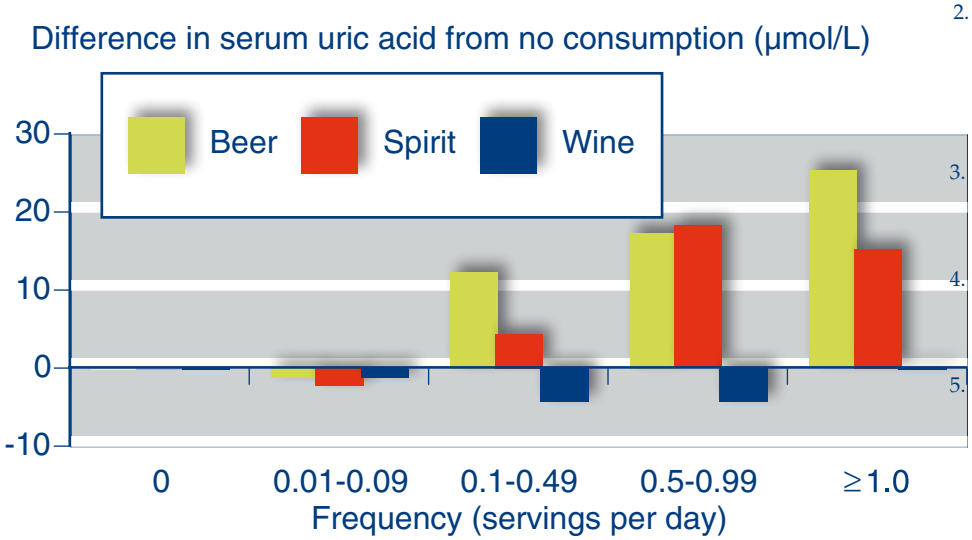
Coffee, tea, and caffeine

Using a quintile of consumption approach, uric acid levels were identical across quintiles of intake of total caffeine and tea. For coffee (including decaffeinated), drinking more than four cups of coffee a day significantly lowered serum uric acid levels, by about 8% at maximum (Figure 1). The reduction of uric acid by coffee remained after adjusting for a whole range of variables and dietary factors.

Alcohol

Using the quintile of consumption approach drinking wine did not affect serum uric acid levels at any level of consumption up to one serving per day or more. The consumption of spirits, and especially beer, did increase serum uric acid levels (Figure 2), even after adjusting for a whole range of factors. Beer and spirits drunk daily increased serum uric acid by about 10%; wine did not. The results were similar in men and women, and at lower and higher levels of BMI.

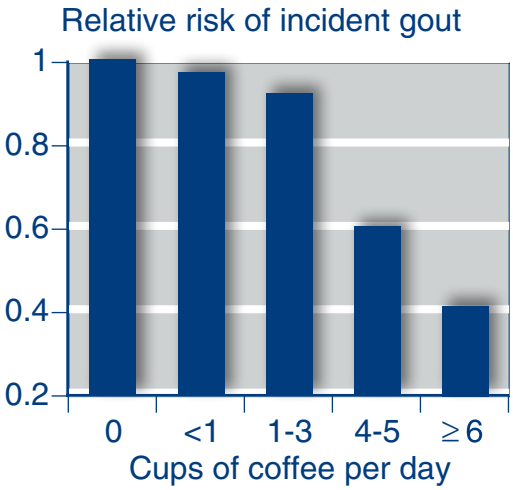
Figure 2: Effect of different daily consumption (quintiles) of different alcoholic beverages on mean serum uric acid levels



Comment

This constitutes useful additional knowledge about what gout sufferers might do to avoid increasing their serum uric acid, and perhaps precipitating an attack, or making the pain worse. Drinking beer and spirits are out, but tea and wine have no effect, while coffee actually seems to reduce uric acid levels. We have had some straws in the wind about coffee before, but this adds weight.

Figure 3: Relative risk of incident gout in 12-year follow up of 46,000 men, according to quintiles of daily coffee consumption



More weight comes from a large study of coffee consumption and incident gout in men [3], following 46,000 men with no history of gout at baseline for 12 years. There were 750 cases of incident gout, and the risk was lower with higher coffee consumption, before and after adjustment for a whole host of different possible confounding factors (Figure 3). So increased coffee drinking is linked with both reduced serum uric acid levels and reduced incidence of clinical gout.

We also have information about what we eat and the risk of incident gout [4]. This has been examined in detail on the Bandolier Internet site, but the main results are worth reiterating. Increased consumption of meat was associated with increased risk of gout, but only with beef, pork, and lamb. There was less association with seafood, and none with purine rich vegetables. Increased consumption of dairy food reduced the risk of gout. We find the same now for uric acid [5] where high meat and to a small extent seafood consumption is associated with higher uric acid levels, but dairy food with lower uric acid levels. Much food for thought for those with gout and for healthy eating.

References:

1. HK Choi, G Curhan. Coffee, tea, and caffeine consumption and serum uric acid level: third National Health and Nutrition Examination Survey. Arthritis & Rheumatism 2007 57: 816-821.
2. HK Choi, G Curhan. Beer, liquor, and wine consumption and serum uric acid level: third National Health and Nutrition Examination Survey. Arthritis & Rheumatism 2004 51: 1023-1029.
3. HK Choi et al. Coffee consumption and risk of incident gout in men. Arthritis & Rheumatism 2007 56: 2049-2055.
4. HK Choi et al. Purine-rich foods, dairy and protein intake, and the risk of gout in men. NEJM 2004 350:1093-1103.
5. HK Choi et al. Intake of purine-rich foods, protein, and dairy products and relationship to serum levels of uric acid. Arthritis & Rheumatism 2005 52: 283-289.

Fracture and quality of life in older women

Bandolier 161, www.ebandolier.com

Fractures in older people, especially older women, can be problematical. The impact of hip fracture can be devastating. Much treasure is spent on trying to prevent fracture through treatment of osteoporosis, and by trying to reduce loss of bone, especially in postmenopausal women. If we want to know how treatments compete in the clever world of cost effectiveness, then we have to measure the negative impact of fractures, and while much has been done in that area, a new, and very large, study [1] opens another window.

Study

This was part of a prospective longitudinal study of 200,000 postmenopausal US women aged at least 50 years, without a diagnosis of osteoporosis, no bone density measurement within 12 months, and not taking treatments for osteoporosis. For inclusion they has to have completed two mail or telephone surveys, the first at about 12 months after enrolment, and the second about 36 months after enrolment.

Both surveys elicited information of new fractures, health status using a SF-12 instrument, osteoporosis-related care, and fall history. Analysis of the SF-12 data was according to two composite scores, the physical component score (PCS) and mental component score (MCS). Reported new fractures (hip, spine, wrist, rib) between the first and second surveys formed the cases, with controls being women without fracture.

Results

The analysis included 86,128 women (88% white), whose mean age was about 65 years. Just 1.2% had suffered a fracture in the year before the first survey. Fractures between the first and second survey numbered 320 hip, 445 spine, 835 wrist, and 657 rib, 2.6% over the two years. There were 83,871 women without fracture who served as controls.

Women suffering a fracture more frequently had significantly reduced bone mineral density, and were 4-6 times more likely to have suffered a fracture during the 12 months before the first survey. They also had lower quality of life scores at the first survey.

After adjusting quality of life scores for these factors, women suffering a fracture in the two years between the two surveys had significantly reduced PCS scores compared with women without a fracture (Figure 1). Statistically significant reductions were found for hip, spine, wrist and rib fractures for younger postmenopausal women (50-64 years), and for hip, spine and rib fractures in older postmenopausal women (65-99 years).

Women suffering a fracture in the two years between the two surveys had greater reduction in MCS scores than women without a fracture (Figure 2). Statistically significant reductions were found for spine and rib fractures for younger postmenopausal women, and for hip and spine fractures in older postmenopausal women.

Figure 1: Reduction of physical quality of life compared with control

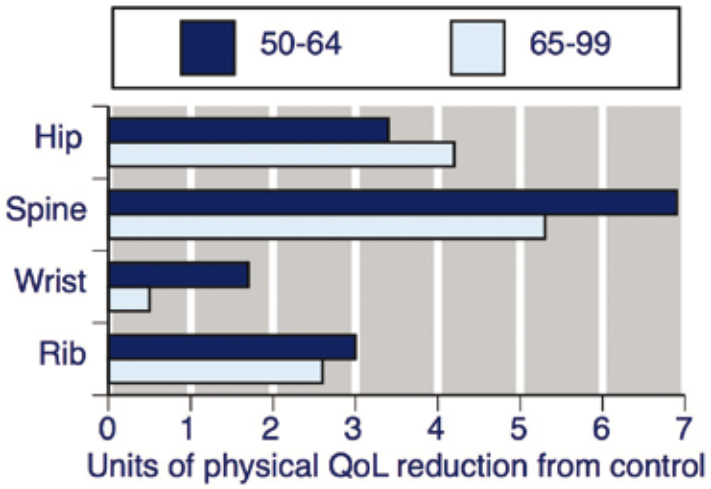
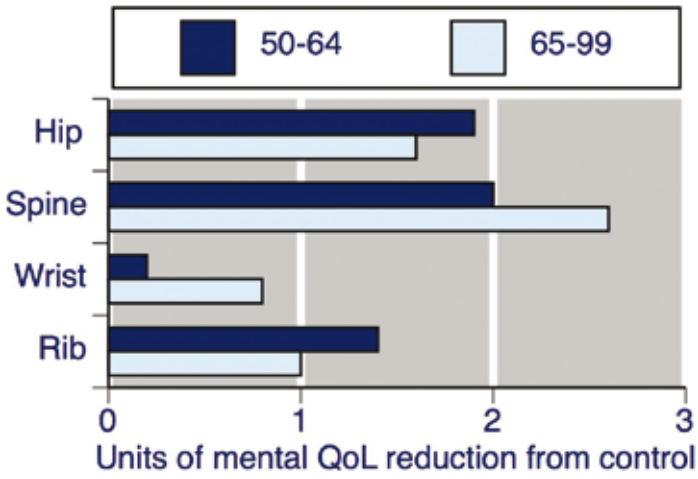


Figure 2: Reduction of mental quality of life compared with control



Comment

What makes this study worth thinking about is the combination of its size and detail, and that it provides quality of life results for different fractures in younger and older postmenopausal women. It also did some useful statistical stuff, like taking into account multiple comparisons, so that statistical significance was only reported when the probability value was 0.004, so it does not tell us about associations that crept into conventional levels of significance.

Those in the know about such things may not have been surprised by the findings. For the rest of us, perhaps what stands out is the particular loss of life quality attendant on vertebral fractures. This may reflect the fact that vertebral fractures cannot be healed, and often come with a lot of back pain, and we do know that chronic pain has a large negative impact on quality of life.

It also helps to have some context. The negative impact on PCS scores for hip and spine were at the same level as those for COPD, hip impairment, or rheumatoid or osteoarthritis. Given that we will have more older people with low bone mineral density and at risk of these fractures, this should help in making sense of current and new therapy choices.

Reference:
SK Brenneman et al. Impact of recent fracture on health-related quality of life in postmenopausal women. Journal of Bone and Mineral Research 2006 21: 809-816.

Dear Dave

Dave and other members of the bpac[nz] team answer your clinical questions

Does the 'seven day rule' still apply with the concomitant use of combined oral contraceptives and all antibiotics?

In June 2006, the American College of Obstetricians and Gynaecologists (ACOG) released a practice bulletin on the use of hormonal contraception in women with coexisting medical conditions. This bulletin has cast some doubt over whether it is valid for GPs to advise their patients taking oral contraceptives that they need to use other methods of contraception for the duration of antibiotic treatment and the following seven days.

"Although there have been many anecdotal reports of oral contraceptive failure in women taking concomitant antibiotics, pharmacokinetic evidence of lower serum steroid levels exists only for rifampicin. Because oral contraceptive steroid concentrations are strikingly reduced in women concomitantly taking rifampicin, such women should not rely on combination oral contraceptives, progestin-only oral contraceptives or implants for contraceptive protection". ACOG[1]

The fact that rifampicin can cause oral contraceptive failure is unequivocal due to enzyme induction, increased oestrogen metabolism and resultant reduced plasma oestrogen concentrations. Most other antibiotics have been reported to be associated with oral contraceptive failure, but as stated in the ACOG Practice Bulletin, clinical studies have not demonstrated that antibiotics (other than rifampicin) decrease serum steroid concentrations.

There is a theoretical basis for an interaction in that antibiotics reduce gut flora which are responsible for increasing the reabsorption of oestrogens from the GI tract. Oestrogens are metabolised in the liver and conjugated with glucuronide, which is water soluble and can be excreted in the bile. Under normal gut flora conditions, bacteria cleave this conjugate and free up oestrogen, which can then be reabsorbed (enterohepatic recycling). Although the theory is not backed up by evidence from clinical studies, an interaction cannot be completely ruled out as in some women enterohepatic recycling may be crucial, in maintaining adequate oestrogen plasma concentrations. Clinical studies may also not represent the situation in practice where antibiotics or the underlying illness may cause diarrhoea or vomiting, which are known to reduce the effectiveness of oral contraceptives.

Bearing in mind that there is a background failure rate associated with oral contraception, it is not possible to prove that an antibiotic given concurrently is causative or contributory to a case of failure. Although an interaction and resultant contraceptive failure is probably extremely unlikely, the possibility cannot be completely excluded.

On moral and ethical grounds most authorities continue to sanction the cautious approach and continue to recommend the seven day rule.

Reference

Stockley's Text Book of Drug Interactions 2007.

1. ACOG Practice Bulletin. Clinical Management Guidelines for Obstetricians and Gynecologists. Number 73, June 2006.

If you have a clinical question email it to
dave@bpac.org.nz

Serotonin toxicity: "Is combining Reductil with tricyclic antidepressants really such a no-no or are the drug companies just being defensive over the unlikely occurrence of serotonin syndrome?"

Bob Buckham from the Christchurch Drug Information Centre was asked if he had come across this question in practice. His advice was as follows:

Sibutramine and amitriptyline work by inhibiting the reuptake of serotonin and noradrenaline. Concurrent use of these drugs is actively discouraged because of the potential for serotonin toxicity (which may range from mild symptoms, such as diarrhoea or sweating, through to coma and death). Furthermore, TCAs may cause weight gain and both agents lower the seizure threshold.

The risk would be (theoretically) greater with tertiary amine TCAs (compared to secondary amine) as they are more serotonergic. So it could be argued that nortriptyline might be 'safer' and less likely to cause serotonin toxicity than amitriptyline or imipramine. The concurrent use of sibutramine and clomipramine should definitely be avoided as this TCA has potent serotonerigic properties.

Similarly, it would be a dose-dependent effect, therefore the relevance of dose needs to be considered. However overall we try to discourage the combination and suggest trying orlistat (Xenical) first-line. If that is not an option then we would need to seriously weigh risk versus benefit and monitor carefully. We also make the same recommendation if the patient is taking an SSRI or a monoamine oxidase inhibitor (MAOI).

Serotonin toxicity

Instead of serotonin 'syndrome', we try to refer to it as serotonin toxicity, as most people usually know that the 'syndrome' is actually only rarely reported – so they tend to disregard it. Whereas 'toxicity' suggests a range of issues from mild symptoms, like diarrhoea and sweating, many probably wouldn't think to associate it with serotonin toxicity, to the serious signs like tremor, seizures, coma and death (the 'syndrome').

In summary, like other combinations which have the potential for toxicity (e.g. SSRIs + TCAs) the combination of sibutramine and a TCA may be uneventful in many people. The risk of an interaction is probably lower with low doses of nortriptyline than with other TCAs at high doses.

Concurrent use is governed by appreciation of risk versus benefit, recognition of the general advice against its use and the need to closely monitor patients if the combination is used.

Further reading about serotonin toxicity
http://snipurl.com/1ps35

Who is Dave?

Pharmaceutical Programme Manager Dave Woods is a graduate of Manchester University (B.Sc. [Hons]) and the University of Otago (MPharm). Dave has extensive experience in hospital pharmacy, drug information, rational use of drugs and quality assurance. He has published on a range of subjects and holds editorial positions for several international journals.

If you have a clinical question email it to dave@bpac.org.nz

Correspondence

Low dose aspirin and the risk of GI complications

Dear Editor

I would be grateful for your advice regarding best practice for patients on long term aspirin. An increasing number of middle-aged and elderly patients are on long term low dose aspirin – and I wondered what the current advice was as to whether they should also be on long term PPIs.

If a patient is at a high risk of GI complications or has a history of dyspepsia, a proton pump inhibitor can be added to low dose aspirin therapy.

It is well established that low dose aspirin produces significant inhibition of gastric mucosal prostaglandins, even when taken as an enteric coated tablet. Therefore, low dose aspirin has the potential to induce gastric lesions and GI complications even in normal healthy subjects.

Some factors to consider when assessing GI risk with low dose aspirin include; a history of peptic ulcer or GI bleeding, significant co-morbidity and previous NSAID gastropathy. Peptic ulcer disease is of particular importance because it leads to recurrent episodes of dyspepsia and is associated with significant complications of bleeding and perforation.

NICE guidelines recommend that patients taking low-dose aspirin, who have a history of dyspepsia, would benefit from concurrent treatment with a proton pump inhibitor (NICE Clinical Guideline 17).

It is therefore important to assess each patient on an individual basis – check for red flags (BPJ Issue 4, April 2007), assess risk and take into account any symptoms and other medications.

It is always worth considering the potential for adverse effects, particularly in elderly people. The most common side effects of proton pump inhibitors include headache, diarrhoea and skin rashes. Proton pump inhibitors may also increase the risk of gastrointestinal infections and pneumonia because of their acid suppressive effects.

In summary, PPIs can be considered for patients on long-term low dose aspirin therapy, with a high risk of GI complications or a history of dyspepsia.

References

- *NZGG. Management of Dyspepsia and Heartburn. June 2004. Available from http://www.nzgg.org.nz*
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- *NICE. Secondary prevention in primary and secondary care for patients following a myocardial infarction. 2007. Available from http://guidance.nice.org.uk/CG48*

IM injections

Dear Editor

Occasionally we need to give IM injections (other than immunisations) e.g. antibiotics or anti-emetics, to toddlers and young children.

1. *What is the preferred site and at what age can the gluteal site be used?*
2. *Is the use of lignocaine (plain) ok for dilution of antibiotics (adult use only) and if so, how much if say 4 ml total of fluid is required for the dilution?*

Unfortunately there is no simple answer to this. IM injections (excluding vaccines) are generally avoided in children. Many doctors would not use anti-emetics for childen, particulary not IM. Their use is mainly postoperative, for oncology or for special situations such as cyclical vomiting. IM antibiotics would usually only be given in an emergency situation, for example suspected meningitis en route to hospital. However, GPs, especially in rural areas, may have a different situation and environment to deal with. Some antibiotics, for example benzathine penicillin, can only be given by IM injection.

Preferred site of IM injection in children

There is little information on recommended sites for IM injections other than vaccines in children. Manufacturers' data sheets will often have information on the recommended site of administration. The Ministry of Health Immunisation Handbook (2006) states that the recommended sites for IM vaccines are:

For children under 15 months of age, the vastus lateralis muscle on the lateral thigh is used

For children over 15 months, both the vastus lateralis and deltoid sites may be used – the choice will be based on the vaccinator's professional judgement

For older children, adolescents and adults, the deltoid muscle is used

For injections, other than immunisations, there is no clear guidance and it may be wise to consult MedSafe datasheets. However there are some general areas of agreement:

The dorsogluteal site (upper outer quadrant): use of this site is associated with significant risk of damage to the sciatic nerve and superior gluteal artery. There is often a deep layer of subcutaneous fat in this region and the injection may not reach the muscle, resulting in the drug being deposited in the subcutaneous fat.

This site should not be used in children.

The ventrogluteal site: this is a good site for intramuscular injections in adults and children over seven months. The site provides the greatest thickness of gluteal muscle, is relatively free of major nerves and blood vessels and is easy to locate. However there is little experience of use of this site in New Zealand and consequently it is not used often.

The lateral thigh (vastus lateralis): This site is safer than the dorsogluteal site and is recommended for intramuscular injection of adrenalin in anaphylaxis. Patients can be taught to self-inject in this area.

The deltoid: This site is safe for low volume injections of non-irritating solutions for older children and adults, provided the deltoid muscle mass is located with care.

Using lignocaine to dilute antibiotics

Anyone considering using lignocaine for dilution should refer to the specific datasheet of each medicine to ensure that dilution with lignocaine is approved and compatible with the injectable antibiotic. However, some data sheets do not include this information, stating only that the antibiotic should not be mixed with other medicines, while acknowledging pain on IM injection. Note that some antibiotics (e.g. Augmentin) should not be given by the IM route.

Most injectable drugs that allow the use of a local anaesthetic as a diluent, will specify the same volume of diluent, be it water for injection or 1% lignocaine, to reconstitute the powder. However, great caution must be applied when using lignocaine in an IM injection, as inadvertent IV administration may result in serious cardiac adverse effects.

This advice was developed in consultation with Dr David Reith, Paediatrician, Alan McClintock, Pharmacist and Barbara Warren, Immunisation Co-ordinator.

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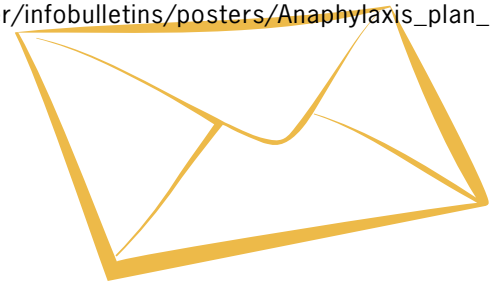

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