medizine
update in medication
A monthly newsletter for nurses about medicines and their safe administration
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Doubts raised about Quinine

Quinine should not be prescribed for routine muscle cramps according to a new guideline from the American Academy of Neurology. The advice is based on an evidence-based review that linked the use of quinine for this indication with serious side effects.

Serious but uncommon side effects associated with its use include kidney and blood problems according to the review, published in *Neurology* (2010;74:691). Milder but more common side effects include headache, sweating, blurred vision and tinnitus. In 2006, an FDA advisory notice warned against the off-label use of quinine sulphate and its derivatives for treating muscle cramps. It said 93 deaths had been linked to quinine use since 1969.

Lead author of the recent study said: "Quinine should be considered only when cramps are very disabling, when no other drugs relieve the symptoms, and when side effects are carefully monitored."

As alternatives to quinine, naftidrofuryl should be considered, it is already used for symptoms of intermittent claudication, calcium channel blockers such as diltiazem, and vitamin B, the guideline recommends. Details of their effectiveness based on evidence from the 24 trials are included in the review.

However, the drug is widely used for nocturnal leg cramps. The British National Formulary states that 200–300mg of quinine salts at bedtime are effective in reducing frequency of nocturnal leg cramps by around a quarter in mobile patients.

Paroxetine & Tamoxifen

Concomitant use of paroxetine and tamoxifen increases the risk of death from breast cancer, a Canadian study reports (*BMJ online*, 2010;340:c693). The finding is attributed to a documented interaction between the two medicines.

Mechanism of interaction

Tamoxifen is a prodrug that is metabolised by cytochrome P450 enzymes in the liver to its active metabolites 4-hydroxytamoxifen and endoxifen, which have a higher affinity for oestrogen receptors. Of these metabolites, endoxifen could be considered more important as it reaches higher plasma concentrations. The conversion of tamoxifen to endoxifen is catalysed by CYP2D6.

Selective serotonin reuptake inhibitors inhibit CYP2D6 to varying degrees. The authors of this study describe paroxetine as "an exceptionally potent CYP2D6 inhibitor" and "the only SSRI to exhibit 'suicide' inhibition" — ie, it causes irreversible enzyme loss, meaning that metabolic function cannot restart until new CYP2D6 is synthesized.

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BP Lowering reducing heart failure risk

Lowering blood pressure in hypertensive patients is helping to reduce the risk of people developing heart failure.

In the UK heart failure costs the NHS £625m per year. Its management also takes a large proportion of health professionals' time, the Health Foundation report "Bridging the quality gap" states.

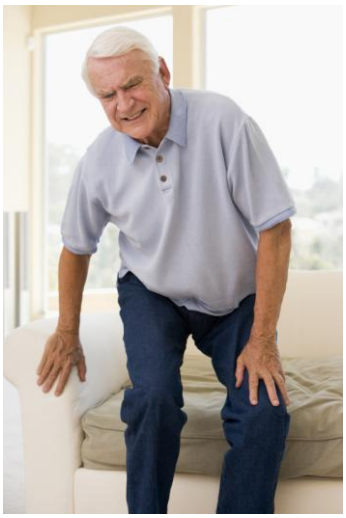
In primary care, heart failure patients have an average of 11 to 13 contacts with community health professionals per year with drug costs for the syndrome accounting for 9 per cent of the total care cost.

Evidence cited by the report shows that where preventive measures are put in place, incidence of heart failure is reduced. A meta-analysis from 2009 found that a 10mmHg reduction in systolic blood pressure or a 5mmHg lowering of diastolic blood pressure using thiazides, beta-blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor blockers or calcium channel blockers reduced incidence of heart failure by 25 per cent, with no increase in non-vascular mortality.

The report also gives evidence for cost-effectiveness of treatments. One study from 2007 found ACE inhibitors, beta-blockers, selective aldosterone receptor antagonists, aspirin and statins were all cost-effective, with ratios ranging from £223 per life year gained for beta-blockers in patients in hospital to £3,093 per life year gained for statin use in community patients.

Another study found the highest health gains in terms of quality-adjusted life years were made from three interventions: extending prescribing of ACE inhibitors, extending compliance and making earlier diagnoses. "All the interventions together have the potential to reduce the current burden of disease by 24 per cent, and the annual number of deaths by 1,300," the report says.

NSAIDs and cardiac disease



Patients with cardiac disease should not use NSAIDs at high doses for prolonged periods unless unavoidable.

Non-steroidal anti-inflammatory drugs (NSAIDs) are associated with increases in cardiovascular risk and should only be used by patients with cardiovascular disease at high doses for prolonged periods if unavoidable, according to the latest *Drug and Therapeutics Bulletin* (March 2010).

Evidence from randomised controlled trials and observational studies of NSAIDs was examined to assess the effects of the drugs on cardiovascular health.

NSAIDs are associated with small increases in cardiovascular risk, with particular harm possible when patients with cardiovascular disease are administered high doses for long periods, the independent review concluded.

Consideration should always be given to whether an NSAID is really necessary and, if the therapy is thought unavoidable, then it should be used in the lowest possible dose for the shortest possible time, the bulletin advises. Of the non-selective NSAIDs currently in wide use naproxen is associated with the lowest risk, evidence suggests. Diclofenac appears to be associated with the highest risk.

Medicines in the news

- **Previous EMA advice on PPI and clopidogrel use updated**

Previous advice from the European Medicines Agency to discourage the concomitant use of proton-pump inhibitors (PPIs) and clopidogrel (Plavix) unless absolutely necessary has been replaced with a warning stating that only concomitant use of clopidogrel and omeprazole (Losec) or esomeprazole (Nexium) should be discouraged.

The new advice comes after the EMA's Committee for Medicinal Products for Human Use became aware of new studies that brought into question the clinical significance of a class interaction between PPIs and clopidogrel. However, two studies completed in August 2009 confirmed that omeprazole can reduce the levels of the active form of clopidogrel in the blood and reduce its antiplatelet effect, says the EMA.

- **Doubts cast over benefit of BP control in type 2 diabetes patients**

Intensive management of blood pressure and treatment with multiple lipid lowering drugs do not reduce cardiovascular events in patients with type 2 diabetes who are at high risk of these occurring.

This is the researchers' conclusion based on new results from the ACCORD (action to control cardiovascular risk in diabetes) trial. The results are published online in two papers in *The New England Journal of Medicine* (14 March 2010).

The ACCORD lipid trial reveals that a combination of fenofibrate and simvastatin does not reduce the rate of heart attack, stroke or death from cardiovascular disease when compared with simvastatin alone (see panel below). However, analysis of the results suggests that the combination therapy may benefit men but not women (*P*=0.01 for interaction).

Findings from the ACCORD lipid trial

Patients with type 2 diabetes who were at high risk for cardiovascular disease events were selected from 77 clinical sites. In total, 5,518 patients with type 2 diabetes were treated with simvastatin alone or in combination with fenofibrate. The primary outcome was non-fatal heart attack or stroke, or death from cardiovascular causes. Patients were followed up for just under five years.

The annual rate of primary outcome was 2.2 per cent in the fenofibrate group compared with 2.4 per cent in the placebo group.

There may also be a possible benefit for patients with a high baseline triglyceride level and low baseline level of high-density lipoprotein cholesterol (*P*=0.057 for interaction), say the researchers. They conclude that, for patients with "substantial dyslipidemia," there may be a benefit of adding fenofibrate to statin therapy.

The latest results from the ACCORD trial, which involved more than 10,000 people overall, suggest that flexible goals should be applied to the control of blood pressure, dyslipidaemia and hyperglycaemia in patients with type 2 diabetes, taking into account individual factors of clinical importance.

Blood pressure control and stroke risk

The ACCORD blood pressure trial found that intensive lowering to a target systolic blood pressure of less than 120mmHg, compared with less than 140mmHg, did not reduce the rate of cardiovascular events. However, lowering blood pressure to below 120mmHg seemed to reduce the risk of stroke by about 40 per cent, the researchers note. But these patients were also more likely to have complications, such as abnormally low blood pressure or hyperkalaemia, they add. In light of this, the researchers recommend that patients weigh the risks and benefits of intensive management to lower their blood pressure.

- **HbA1c useful diagnostic test**

Glycated haemoglobin (HbA_{1c}) is a better marker than fasting glucose for identifying long-term cardiovascular risk, especially at values above 6.0 per cent, thus supporting its use as a diagnostic test for diabetes, the authors of a recent study suggest (*New England Journal of Medicine* 2010;362:800).

Results from the study, which involved 11,092 participants, suggest that glycated haemoglobin and fasting glucose are similarly associated with a risk of diabetes and more strongly associated with risks of cardiovascular disease and death from any cause.

Study questions if screening cuts breast cancer deaths

A study from Denmark published on bmj.com (27 March, 2010) **finds no effect of the Danish screening programme on breast cancer deaths.**

Similar results have been seen in other countries, including the UK, leading the authors to question whether screening has delivered the promised effect on breast cancer mortality.

A 2005 study suggested that screening had reduced breast cancer deaths by 25% in Copenhagen. But Karsten Jørgensen and Peter Gøtzsche from the Nordic Cochrane Centre in Copenhagen, together with Per-Henrik Zahl from Folkehelseinstituttet in Oslo, identified important problems in this study and decided to undertake a more comprehensive analysis of the data.

They compared annual changes in breast cancer deaths in two Danish regions offering publicly organised screening programmes (Copenhagen and Funen county) with non-screened regions across the rest of Denmark.

Their analysis covered 10 years after screening could have had an effect on breast cancer mortality. For comparison, they also looked at the 10-year period before screening was introduced.

Data for each area were divided into three age bands. Women aged 55-74 years, who could benefit from screening, and women aged 35-55 years and 75-84 years, who were largely unaffected by screening.

They found that in women who could benefit from screening (55-74 years) breast cancer mortality declined by 1% per year in the screened areas and by 2% per year in the non-screened areas. In women too young to benefit from screening (35-54 years), breast cancer mortality declined by 5% per year in the screened areas and by 6% per year in the non-screened areas during the same period.

For the older age groups (75-84 years), there was little change over time both in screened and non-screened areas.

"We were unable to find an effect of the Danish screening programme on breast cancer mortality," conclude the authors. "The reductions in breast cancer mortality we observed in screening regions were similar or less than those in non-screened areas and in younger age groups, and are more likely explained by changes in risk factors and improved treatment than by screening mammography."

"Our results are similar to what has been observed in other countries with nationally organised programmes. We believe it is time to question whether screening has delivered the promised effect on breast cancer mortality," they add.