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circuit

clinical initiatives, research and current updates in treatment

Management of postmenopausal osteoporosis (PMO): something new on the horizon?

Osteoporosis is a skeletal disease characterized by low bone mineral density (BMD) and deterioration of microarchitecture that reduces bone strength and increases the risk of fracture. The World Health Organization (WHO) has officially declared osteoporosis a major public health concern, affecting nearly 200 million individuals worldwide, including a third of women aged 60 to 70 years and two-third of women aged 80 years or older. In Australia, someone is admitted to a hospital with an osteoporotic fracture every 5-6 minutes and this is expected to rise to every 3-4 minutes by the year 2021 as the population both increases and ages. Osteoporotic fracture is a significant cause of mortality and morbidity. Osteoporosis is most common in women after menopause as a decrease in estrogen triggers a rapid rise in bone-eroding cells which reduce bone density and strength.

Despite the high prevalence of osteoporosis and the availability of effective drugs, this 'silent epidemic' is underdiagnosed and undertreated. Despite accurate diagnosis and treatment, patients often do not take medication correctly or discontinue therapy against medical advice prior to obtaining benefit from a reduction in fracture risk. Studies on patients' adherence to osteoporosis treatments have found that less than half of patients are compliant after 1 year. Strategies to improve compliance to therapy include reducing the frequency of drug dosing and simplifying drug administration.

Current drugs used for the prevention and treatment of osteoporosis are classed as antiresorptive (anticatabolic) or anabolic (bone-forming) according to their effect on bone modeling. Antiresorptive drugs include estrogens, bisphosphonates (alendronate, risedronate, ibandronate and zoledronic acid), raloxifene (an estrogen agonist/antagonist or selective estrogen-receptor modulator (SERM)) and calcitonin. The anabolic drugs are teriparatide and recombinant human parathyroid hormone. Strontium ranelate has both antiresorptive and anabolic properties.

Denosumab, previously AMG 162, trade name Prolia® is a fully-humanised monoclonal antibody currently being developed by Amgen. Denosumab is in late-stage development and works through a novel mechanism of action. Denosumab inhibits osteoclast-mediated bone resorption by binding with high affinity and

specificity to receptor activator of nuclear factor- κ B ligand (RANKL), a key mediator of osteoclast differentiation, function and survival. In published phase 2 and phase 3 studies examining the effect of denosumab in postmenopausal women with low bone mass, denosumab treatment inhibited bone resorption and remodeling as measured by increases in BMD at all measured skeletal sites and decreased biomedical markers of bone turnover.

The proposed therapeutic dose of denosumab is 60 mg subcutaneous (SC) every 6 months and has been used in studies for the prevention and treatment of PMO. Cummings et al. enrolled 7868 postmenopausal women with osteoporosis and randomly assigned them to receive either denosumab or placebo subcutaneously every 6 months for 3 years. As compared with placebo, denosumab reduced the 3-year incidence of new vertebral fractures from 7.2% to 2.3% (a 68% decrease), of hip fractures from 1.2% to 0.7% (a 40% decrease) and of all nonvertebral fractures from 8.0% to 6.5% (a 20% decrease).

Oral bisphosphonates are widely used antiresorptive therapy for PMO. Brown et al. compared the efficacy and safety of denosumab (60mg SC every 6 months) with alendronate (70mg oral weekly) in postmenopausal women with low bone mass. Treatment with denosumab resulted in greater increase in BMD at all measured skeletal sites than alendronate therapy and the safety profile of these agents was similar and both appeared to be well tolerated by subjects in this study.

There is concern about long-term use of denosumab and its possible effects on the rate of infection and neoplasm as RANKL is expressed not only on bone cells but on immune cells. Neither Cummings et al. nor Smith et al. observed an increased rate of serious infections related to denosumab. Brown et al. observed no significant increase in rate of neoplasm related to denosumab as compared to alendronate therapy. However, Cummings et al. reported significant increases in rates of eczema and hospitalisations for cellulitis related to denosumab as compared to placebo. These findings are limited and support ongoing surveillance of patients on denosumab therapy especially when the drug is used in the community setting in patients with coexisting illnesses that might have excluded them from participating in clinical trials.

As denosumab is given subcutaneously twice yearly and could be self-administered, precluding the need for a clinic visit and intravenous infusion, it might improve adherence. Long-term bisphosphonate use is associated with potential adverse events including osteonecrosis of the jaw and (debatably) atypical femoral subtrochanteric fracture although these complications appear rare, there might be an advantage to the use of denosumab. Furthermore,

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bisphosphonates are cleared by the kidney and contraindicated in patients with renal insufficiency. Denosumab is cleared by nonrenal metabolism and may prove to be a safer alternative in these patients.

Denosumab has been fast tracked by the U.S. Food and Drug Administration (FDA) for treatment and prevention of PMO, in addition to treatment and prevention of bone loss in hormone treated prostate and breast cancer patients. However, FDA has delayed approval of denosumab in October 2009 as they needed more information on its post-marketing surveillance plan and requested a new clinical program to support approval of the drug. In Australia, the Advisory Committee on Prescription Medicines (ACPM) has recommended the approval of denosumab for the treatment of PMO in February 2010 and is pending approval from the Therapeutic Goods Administration (TGA).

In summary, denosumab is a promising agent for the treatment of PMO by decreasing bone resorption and increasing BMD through the inhibition of RANKL. In women with PMO, denosumab reduces risk of vertebral, hip and nonvertebral fractures compared with placebo and increases BMD and decreases bone turnover markers more than alendronate. The safety and tolerability of denosumab is favourable when compared to placebo or alendronate.

References available on request

Antiplatelet Therapy

Haemostasis is a process by which the circulatory system restores its integrity following damage to the vessel wall. A platelet plug formed at the injury site seals the breach formed as a result of the injury. This is primary haemostasis. Platelets adhere via cell surface adhesion molecules and their membrane receptors such as glycoprotein Ib/IX and von Willebrand factor. The glycoprotein IIb/IIIa receptor is exposed following platelet activation. Aggregation results when this receptor forms bridges using fibrinogen. This is followed by secondary haemostasis which is blood coagulation due to exposure of tissue factor. This results in thrombin and fibrin generation and stabilization of the thrombus. Under normal conditions the fibrinolytic system prevents the blood vessel from becoming occluded by the clot during its formation and later dissolves the thrombus. But in a diseased state excess amounts of thrombin are formed resulting in thrombosis. This can occur in both arterial disease (like myocardial infarction and stroke) and in venous thromboembolic disorders (like deep vein thrombosis and pulmonary embolism). Antiplatelet medications play an important role in inhibiting platelet aggregation by a variety of mechanisms. Currently approved antiplatelet medications for use in Australia include:

- 1) Aspirin
- 2) Thienopyridines (Clopidogrel, Ticlopidine, Prasugrel)
- 3) Glycoprotein IIb/IIIa receptor blockers (Abciximab, Eptifibatide, Tirofiban)
- 4) Phosphodiesterase inhibitors (Dipyridamole)

Aspirin

Aspirin (acetylsalicylic acid) irreversibly inhibits COX-1 in platelets and thereby blocks the formation of the prothrombotic substance Thromboxane A₂ (TXA₂). The COX-1 cannot be regenerated hence the antiplatelet effect remains for the life of the platelet.

Formulation strengths currently available in Australia range from 100mg to 500mg.

Aspirin is readily absorbed from the GI tract. On oral administration, 160mg dose of soluble Aspirin will inhibit platelet function within 30 minutes. Hence it is given as a loading dose for rapid antiplatelet effect. The recommended daily dose of Aspirin is 75-150mg for long term prevention of serious vascular events in high risk patients. Higher doses are no more effective and are associated with an increased incidence of adverse effects.

The main adverse effect of Aspirin involves GI toxicity including nausea, heartburn, epigastric pain etc. Some of these symptoms may be ameliorated by using enteric coated formulations, however GI toxicity is largely a result of

systemic effects of aspirin. Aspirin increases the risk of bleeding when used with other agents associated with bleeding like NSAID's, anticoagulants and corticosteroids.

Ticlopidine

Ticlopidine inhibits ADP induced platelet aggregation. The first in its class to be marketed in Australia, this agent has now been largely superseded by the arrival of clopidogrel, seen as a safer option particularly in relation to the incidence of neutropenia, thrombocytopenia and thrombotic thrombocytopenic purpura.

Clopidogrel

An oral loading dose of 300-600mg Clopidogrel shows a significant antithrombotic effect within 2 hours. If loading dose is not used, repeated daily dose of 75mg is required to achieve maximal platelet inhibition.

The main adverse effect of Clopidogrel is diarrhea and skin rash. Though it is not associated with GI toxicity like aspirin, it does cause impaired healing of preexisting GI erosions and ulcerations. As with the other antiplatelet agents, clopidogrel prolongs bleeding time and should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other pathological conditions e.g. active peptic ulcer disease. Of particular note is the recent attention within the medical media surrounding a potentially significant drug interaction between clopidogrel and proton pump inhibitors (PPI's). Though there is ample evidence of a pharmacokinetic interaction resulting in decreased plasma levels of the active metabolite of clopidogrel (most significantly with omeprazole), the clinical significance of this interaction is yet to be fully determined.

Prasugrel

Prasugrel has been recently approved for use in Australia. It is usually administered as 60mg loading dose then 10mg daily as maintenance dose. Studies have shown Prasugrel with Aspirin to be more potent in antiplatelet effect than Clopidogrel with Aspirin yet this combination is also associated with an increased risk of bleeding. Caution is urged when giving prasugrel to patients who have an increased risk of bleeding i.e. recent surgery, recurrent gastrointestinal bleeding, active peptic ulcers, concomitant drugs, such as oral anticoagulants, non-steroidal anti-inflammatory drugs and fibrinolytics. In view of the bleeding risk Prasugrel is contraindicated in patients with active bleeding, a previous stroke or TIA or severe hepatic impairment. Prasugrel should only be used in high risk patients if the expected benefits outweigh the harm of serious bleeding.

Glycoprotein IIb/IIIa receptor blockers

These agents are primarily used in hospital environment. After IV administration of glycoprotein IIb/IIIa receptor blockers such as Abciximab, platelet activity is 90% inhibited within 2 hours but it takes about 2 days for the platelet activity to return to normal. These agents are currently indicated for the treatment of unstable angina and non-ST segment elevation myocardial infarction (non-STEMI), (Eptifibatide, Tirofiban) in high risk patients, and patients undergoing Percutaneous Coronary Intervention (PCI), (Abciximab, Eptifibatide).

Dipyridamole

Dipyridamole is a phosphodiesterase inhibitor. It has both vasodilator and antiplatelet properties. It is available as a modified release formulation which significantly increases its absorption. It is also available in combination with Aspirin which has been shown to be more effective than Aspirin alone. The most common side effect of Dipyridamole is headache which often leads to discontinuation of therapy.

Perioperative Management

Unless clinical need dictates (i.e. high thrombotic risk) antiplatelet agents like Aspirin or Clopidogrel should be ceased 7 to 10 days before the procedure as a result of their irreversible effect on platelets. They can be restarted approximately 24 hours following the surgery.

Combined use

Combination antiplatelet therapy is not recommended for primary prevention of coronary or cerebral events, nor is it recommended in the acute post-stroke or TIA phase until bleeding risk has been fully evaluated. The most appropriate

indications for the use of combined clopidogrel and aspirin therapy are the treatment of acute coronary syndromes and the prevention of coronary events after placement of a stent. This combination has been shown to reduce ischemic events associated with unstable angina (up to 9 months), non-STEMI (from at least 1 month to up to 12 months), MI (during hospital stay and up to four weeks) and those undergoing intracoronary stenting (from at least 1 month to up to 12 months). There is ongoing debate in the medical literature as to optimal length of treatment for achieving maximal benefit from combined use of antiplatelets versus excessive risk.

In the post ischaemic stroke setting clinician's choice between clopidogrel alone or a combination of aspirin/dipyridamole is governed largely by patient preference, side effect profile and/or expense.

Australian approved combination products include: Aspirin and Clopidogrel (CoPlavix®, DuoCover®), Aspirin and Dipyridamole (Asasantin SR®).

References available on request

The Serotonin Syndrome

Serotonin Syndrome is a consequence of over stimulation of central (CNS) and peripheral serotonergic receptors. Current thinking favours the spectrum concept of 'serotonin toxicity' as a continuum of the serotonergic effects of a medicine. This progresses from barely perceptible side effects through to life-threatening toxicity. Therefore it is a form of poisoning rather than an idiosyncratic reaction.

This can be the result of an excessive dose of one medication that increases serotonin, or multiple medications that increase serotonin levels when prescribed concurrently.

The symptoms of serotonin syndrome can be divided into three classes:

- Cognitive symptoms which include confusion, agitation, hyperactivity and restlessness
- Autonomic symptoms which include hyperthermia, sweating, diarrhea, tachycardia, hypertension, pupil dilation, flushing and shivering
- Neuromuscular symptoms which include hyperreflexia, tremor, muscle rigidity and a lack of coordinated movement particularly of the lower limbs.

The acronym FLUSH (Flushing of the skin, Loss of awareness, Uncoordinated movement, Sweating, Hyperreflexia) is often used to describe these symptoms

Presentation

- Not all of the symptoms described above are consistently present in every patient with the disorder
- Mild cases may present as afebrile, tachycardic, shivering, sweating, mydriasis, intermittent tremor or myoclonus, as well as hyperreflexia.
- Moderate toxicity may present as above with the addition of, hypertension, hyperthermia, hyper reactive bowel sounds, horizontal ocular clonus, mental status changes including mild agitation or hyper vigilance, and slightly pressured speech.
- Severe cases - significant hypertension, tachycardia, agitated delirium, muscle rigidity and hypertonicity, core temperature over 41°C (when poorly managed may lead to metabolic acidosis, rhabdomyolysis, renal failure, seizures, and disseminated intravascular coagulopathy), and frank shock.

The onset of symptoms is usually rapid. Approximately 60% of patients with Serotonin Syndrome present within 6 hours after initial use of medication, an overdose, or a change in dosing. Mild cases may be difficult to detect or assign causation whilst severe cases may progress rapidly to death.

Drugs Associated with Serotonin Syndrome

The most common medications that are implicated in Serotonin Syndrome are members of, but not limited to, a variety of antidepressant drug classes (see the table opposite).

Class Drugs	
Class	Drugs
Antidepressants	SSRI's Citalopram (Celapram), Escitalopram (Lexapro), Fluoxetine (Lovan), Fluvoxamine (Luvox), Paroxetine (Aropax), Sertraline (Zoloft)
	TCA's Amitriptyline (Endep), Nortriptyline (Allegron), Imipramine (Tolerade), Clomipramine (Placil), Dothiepin (Dothep), Trimipramine (Surmontil), Doxepin (Deptran)
	MAOI's Phenelzine, Tranylcypromine • As well as Moclobemide (Aurorix),
	SNRI's Venlafaxine (Efexor), Duloxetine (Cymbalta)
Other	St John's Wort
Opioids	Tramadol, Pethidine, Fentanyl, Dextromethorphan
Stimulants	Phentermine (Duromine), Sibutramine (Reductil), Pseudoephedrine, Methylphenidate (Ritalin, Attenta, Concerta)
Others	Illicit Drugs e.g. LSD, Ecstasy, Cocaine as well as Selegiline, Tryptophan, Lithium, Linezolid, Ondansetron, Granisitron, Metoclopramide

Management

There are no accepted guidelines for the treatment of serotonin syndrome. Treatment includes the removal of the offending drug(s) and supportive care including IV hydration, and control of agitation, autonomic instability, and hyperthermia. Intensity of therapy is dependant upon the severity of toxicity. Mild cases often respond to supportive care, removal of offending agent and the use of benzodiazepines. Benzodiazepines can be used to control agitation and muscle rigidity.

Moderately affected patients should receive aggressive management of cardiorespiratory and thermal abnormalities with close monitoring of temperature, pulse, blood pressure and urine output. These patients may also benefit from the administration of the 5-HT_{2A} antagonist – cyproheptadine, which in addition to its serotonin antagonist properties causes sedation of the patient.

More severe forms involving high core temperatures should receive the above therapies as well as immediate sedation, neuromuscular paralysis, and orotracheal intubation. Clinicians requiring a parenteral form of 5-HT_{2A} antagonist may choose intravenous chlorpromazine although the evidence to support such a choice is not robust.

The prevention of Serotonin Syndrome requires health care professionals to be aware of the medications that may contribute to the condition as well as educating those patients receiving implicated medications, ensuring their awareness of potential drug interactions exposing them to increased risk of toxicity.

References available on request

New Drug Brief: Methylnaltrexone: Relistor®

Approved Indication^(1,2): Approved for treatment of opioid induced constipation in patients with advanced illness who are receiving palliative care when response to laxative therapy has not been sufficient.

Approved dosage⁽¹⁾: Presentation: 12mg/0.6mL solution for subcutaneous injection (conc. 20mg/mL). Bodyweight 38-62 kg: 8 mg (0.4 mL); 62-114 kg: 12 mg (0.6 mL); < 38 kg or > 114 kg: 0.15 mg/kg (to nearest 0.1 mL).

- Relistor® should be injected subcutaneously into the upper arm, abdomen or thigh. Avoid repeated injections at the exact same spot previously used
- Relistor® is administered as a single dose on alternate days. Doses may also be given with longer intervals, as needed. If there has been no bowel movement within 24 hours of the last dose, an additional dose may be given.

Efficacy and Safety^(1,2,3):

- The efficacy and safety of Relistor in the treatment of opioid induced constipation in patients receiving palliative care was demonstrated in two randomised, double blind, placebo controlled studies (Study 301 & Study 302)
 - Almost all trial participants were using laxatives at baseline but had not defecated for more than 48 hours or had had fewer than 3 bowel movements

in the previous week, with no clinically significant defecation in the previous 24 hours

- 50–60% of people defecated within 4 hours of the first.
- 30% did not respond to a single dose after 24 hours.
- **Methylnaltrexone does not reverse analgesia** - Mean pain scores and opioid withdrawal scores among trial participants receiving methylnaltrexone did not change from baseline.
- **Continue other therapies to prevent or treat opioid-induced constipation** - Trial participants using laxatives at baseline continued to use them throughout the trials of methylnaltrexone.
- Methylnaltrexone is not a treatment for constipation caused by factors other than opioids.
- In trials undertaken in palliative care patients, abdominal pain, flatulence, nausea and dizziness were reported more frequently in people taking methylnaltrexone than placebo.
- The PBAC recommended listing methylnaltrexone on the PBS on the basis of high clinical need, and high and uncertain but acceptable cost-effectiveness compared with placebo.

Accessibility⁽³⁾:

As of March 1st, 2010 Relistor® was made available on the Pharmaceutical Benefits Scheme (PBS) under Authority. Consult PBS website (<http://www.pbs.gov.au/html/healthpro/home>) for access details for Relistor®.

Readers Crossword - Test Your Knowledge!

Once completed, the highlighted letters make this 16 letter drug name mentioned within the newsletter: **M _ _ _ _ _ _ _ _ _ _ _ _ _ _ X**

ENTRIES MUST BE RECEIVED BY 5.00pm on Friday 30th July 2010

Submit this phrase with your full name, facility and contact details to **be in the draw for 1 of 4 \$100 Myer vouchers:**

- email: circuiteditor@aphs.com.au OR fax: 07 3394 5902 OR internal mail: to your APhS Pharmacy

Across:

1. Not a desirable outcome when using denosumab
6. Improvement in this area seen as a major advantage to the use of denosumab
7. Antiplatelet drug given intravenously
8. An adverse effect rarely seen with newer Thienopyridine derivatives
9. This drug sees its use both favoured and discontinued for reasons that are all in your head!
10. Type of drug interaction between clopidogrel and PPI's

Down:

2. One in the anabolic arsenal of medicines used to treat osteoporosis
3. Though not commonly implicated in Serotonin Syndrome, you would be a real Turkey not to pick this drug
4. If a drug is "bone-forming" it may be otherwise described as _____ in nature
5. Not a direct outcome in severe cases of Serotonin Syndrome



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