Thiazolidinediones and reduced bone density

Renal impairment with zoledronic acid

Dangers associated with chronic ingestion of colloidal silver

Please report all suspected reactions to these Drugs of Current Interest

Atomoxetine (Strattera)  Rosuvastatin (Crestor / Viacor)
Ezetimibe/Simvastatin (Vytorin)  Strontium ranelate (Protos)
Moxonidine (Physiotens)  Varenicline (Champix)
Pregabalin (Lyrica)  Ziprasidone (Zeldox)
Ranibizumab (Lucentis)
1. Thiazolidinediones and reduced bone density

Thiazolidinediones include rosiglitazone (Avandia and Avandamet) and pioglitazone (Actos). These medicines act to increase insulin sensitivity and are widely prescribed to treat type II diabetes mellitus. Recent evidence suggests thiazolidinediones are associated with an increased risk of peripheral fractures in post-menopausal women.

The ADOPT study\(^1\) was a randomised, double-blind, parallel group study that followed the progression of 4360 recently diagnosed patients with diabetes mellitus for a median of 4.0 years. The incidence of fractures in women taking rosiglitazone was 9.3% (2.7 patients per 100 patient years), compared with 5.1% (1.5 patients per 100 patient years) in those taking metformin and 3.5% (1.3 per 100 patient years) in those taking glibenclamide. The majority of fractures in these patients were in the humerus, hand, or foot. The incidence of fractures of the hip or spine in women and the incidence of fractures in males were similar among the 3 treatment groups.

A sponsor-initiated review of fracture risk in pioglitazone-treated patients treated for up to 3.5 years also found more fractures in female patients taking pioglitazone than those taking a comparator. There was no increased risk of fracture identified in men.

The sponsors of rosiglazone\(^2\) and pioglitazone\(^3\) have updated product information documents for these medicines and issued letters to healthcare professionals describing the above findings.

The mechanism for increased fracture risk was examined in a 14 week study in 50 healthy postmenopausal women in New Zealand.\(^4\) This study showed reductions in markers of bone formation in women taking rosiglitazone 8 mg/day compared with placebo. These changes were evident after 4 weeks and persisted for the duration of the study. There were also small reductions in hip and lumbar spine bone density in women taking rosiglitazone.

The full clinical significance of these recent findings is yet to be determined. However, the risk of fracture should be considered for all patients, especially women, taking or being considered for treatment with thiazolidinediones. For these patients, as for all patients with type 2 diabetes mellitus, attention should be given to assessing and maintaining bone health according to current standards of care.

References:
2 GlaxoSmithKline Australia Pty Ltd: Avandia, Avandamet
3 Eli Lilly Australia: Actos

2. Renal impairment with zoledronic acid

There is a well-known risk of deterioration in renal function with intravenous bisphosphonates administered at a rapid infusion rate. ADRAC has received few reports of renal impairment or failure with pamidronate and the oral bisphosphonates risedronate and alendronate, but there is a significant number with zoledronic acid (31 from a total of 268 reports for this drug). While the deterioration in renal function with zoledronic acid (Zometa) was usually acute, in many cases it did not appear to be related to a rapid infusion rate.

The 31 reports in association with zoledronic acid describe either renal failure (16) or renal impairment (15). It was the only suspected drug in 20 of the 31 reports. Interstitial nephritis was described in 3 of the reports. Ages ranged from 44 to 88 years (median 63 years). Time to onset in about two thirds of the reports was between 1 and 3 months after starting zoledronic acid.

Recovery was mostly unknown or unspecified.

Zoledronic acid was being used for a variety of indications with multiple myeloma (13 cases) the most common but also breast cancer (5), prostate cancer (4), plasmacytoma, malignant melanoma, osteoporosis, bone metastases and osteomyelitis (1 case each). Only 4 reports did not specify the reason for use.

The Zometa product information\(^1\), under \textit{Precautions}, includes comprehensive information on the need to monitor renal function and use in

\(\text{18} \quad \text{Aust Adv Drug Reactions Bull 26(5), Oct 2007}\)
patients with pre-existing renal impairment. It also provides detailed information on risk factors for renal adverse events which include dehydration, pre-existing renal impairment, multiple cycles of bisphosphonates, as well as the use of other nephrotoxic drugs, or using an infusion time shorter than 15 minutes. Renal impairment and renal failure are both mentioned under Adverse Reactions as common (1-10%) and uncommon (0.1-1%) respectively.

Reports to ADRAC suggest renal impairment and renal failure may occur more commonly with zoledronic acid than with other bisphosphonates.

In several cases, the delayed onset of renal toxicity suggests the impairment was unrelated to the infusion rate; although the conditions in which zoledronic acid is used may predispose patients to renal impairment. Many of the reports described patients with pre-existing renal impairment, and the use of zoledronic acid in multiple myeloma is also a confounding factor.

ADRAC reminds prescribers of bisphosphonates to pay close attention to risk factors for renal impairment and to adhere strictly to the instructions for use.

Reference:

3. Dangers associated with chronic ingestion of colloidal silver

ADRAC has received four reports of silver toxicity (argyria) following ingestion of homemade products containing colloidal silver (tiny particles of metallic silver suspended in liquid) prepared using a “colloidal silver generator”:

- A 5 year old boy who ingested colloidal silver daily for several months developed grey discolouration of skin and tongue and abnormal hepatic function.
- An elderly man who drank colloidal silver daily for 6 months required hospital admission for debilitating fatigue accompanied by blue skin discolouration, dilated cardiomyopathy, amnesia and incoherent speech.
- An elderly man consuming liquid made using a “colloidal silver generator” over a 4 year period developed grey skin discolouration.
- An adult male ingesting homemade colloidal silver daily for 3 years and also applying it topically after shaving developed generalised skin discolouration.

In each case, the plasma silver concentration was many times higher than in subjects not knowingly exposed to silver (background levels up to 2.3 µg/L have been reported\(^1\)).

There are no products containing colloidal silver approved for marketing in Australia.\(^2\) With the exception of registered topical silver preparations, there is no evidence to support the safety or efficacy of silver regardless of its form or method of manufacture.\(^3\) In addition, silver has no known nutritional benefit and its well-defined toxicity can occur with all forms of the metal, including silver salts and colloids.\(^3,4\) Despite this, claims of therapeutic benefit continue to be made for colloidal silver products.

While the TGA will take action to stop the supply of unapproved colloidal silver products that make therapeutic claims, “colloidal silver generators” are currently exempt from regulation and therefore remain available in Australia.

Argyria is the main toxicity associated with chronic ingestion or topical absorption of silver, including colloidal forms of silver. It is characterised by an irreversible, generalised blue-grey discoloration of the subepithelial layer of skin. Later, the entire skin, deep tissues, mucous membranes, nails, conjunctiva, cornea, and lens may be affected.

Argyria discolouration may be misdiagnosed as cyanosis, methaemoglobinemia or haemochromatosis. Other toxicities associated with ingested silver may include peripheral neuropathies, seizures, and haematological, cardiac, hepatic and nephrotoxic derangements.\(^3,4\)

ADRAC has received no reports of argyria associated with legitimate therapeutic goods containing presentations of silver that remain appropriate, for example, topical silver nitrate for neonatal conjunctivitis or silver sulfadiazine for burns.
Patients seeking information on claimed benefits of colloidal silver should be advised of the lack of evidence for therapeutic benefit and the potential for toxicity associated with colloidal silver preparations. Patients should be strongly discouraged from using products made with “colloidal silver generators”.

References:
3. Federal Register: August 17, 1999 (Volume 64, Number 158)] [Rules and Regulations] Over-the-Counter Drug Products Containing Colloidal Silver Ingredients or Silver Salts

WHAT TO REPORT? (you do not need to be certain, just suspicious!)

ADRAC encourages the reporting of all suspected adverse reactions to medicines, including vaccines, OTC medicines, herbal, traditional or alternative remedies. ADRAC particularly requests reports of:

*ALL suspected reactions to new drugs (see drugs of current interest, front page)
*ALL suspected drug interactions
*Suspected reactions causing
  •Death
  •Admission to hospital or prolongation of hospitalisation
  •Increased investigations or treatment
  •Birth defects

For blue cards
Reports of suspected adverse drug reactions are best made by using a prepaid reporting form ("blue card") which is available from the front of the "Schedule of Pharmaceutical Benefits" and the "Australian Medicines Handbook", or from the Adverse Drug Reactions Unit ☏️ 02-6232-8744, or from the website: http://www.tga.gov.au/adr/bluecard.pdf

Reports can also be submitted electronically, by going to the TGA web site ( http://www.tga.gov.au ) and clicking on "report problems" on the left.

For further information from the ADRAC Secretariat:
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The Bulletin is also available on the Internet at: http://www.tga.gov.au/adr/aadrb.htm

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