

Prepared by the Adverse Drug Reactions Advisory Committee (ADRAC) and the Adverse Drug Reactions Unit (ADRU) of the TGA. Members of ADRAC are:
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AUSTRALIAN ADVERSE DRUG REACTIONS BULLETIN

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- ☆ Adverse reactions with botulinum toxin A (Botox, Dysport)

 - ☆ Proton pump inhibitors and possible fracture risk
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Please report **all** suspected reactions to these **Drugs of Current Interest**

Duloxetine (Cymbalta)
Ezetimibe and simvastatin (Vytorin)
Moxonidine (Physiotens)
Paliperidone (Invega)
Pramipexole (Sifrol)
Pregabalin (Lyrica)

Ranibizumab (Lucentis)
Rosuvastatin (Crestor or Viacor)
Sitagliptin (Januvia)
Strontium ranelate (Protos)
Varenicline (Champix)

1. Adverse reactions with botulinum toxin A (Botox, Dysport)

Botulinum toxin type A (Botox; 100 U/vial) is a neurotoxin approved for the treatment of strabismus, blepharospasm and facial nerve disorders, spasmodic torticollis, various spasticity disorders (including dynamic equinus foot deformity due to cerebral palsy), spasmodic dysphonia, axillary hyperhidrosis, and treatment of brow furrow (glabellar) lines. A haemagglutinin complexed form of botulinum toxin type A (Dysport, 500 U/vial) is also available for similar but more limited indications.

Importantly, Botox and Dysport are not interchangeable and it is essential that each product is used strictly in accordance with its own indications and dosing instructions as specified in the respective Product Information.

The United States Food and Drug Administration and Health Canada have received reports of serious systemic reactions including respiratory compromise and death following the use of botulinum toxin.^{1,2} The reactions are suggestive of botulism, which occurs when the toxin spreads in the body beyond the site where it is injected.

In the US, deaths occurred mainly in children treated for cerebral palsy-associated limb spasticity; the most serious non-fatal cases included respiratory insufficiency requiring gastric feeding tubes and ventilatory support.¹ Deaths associated with respiratory insufficiency have been reported in adults and children in Canada.²

Since mid 1994 the TGA has received 45 reports in connection with the use of botulinum toxin, none of which have described a fatal outcome. The reports involve 36 females and 9 males ranging in age from 2 to 79 years (median 45 years); 5 involved children under 10 years.

Reactions reported most commonly are of muscle weakness (16 cases) at sites adjacent to or distant from the injected area. These include 8 reports of dysphagia, including at least 2 severe enough to warrant hospitalisation; 3 of respiratory failure or dyspnoea associated with intercostal and/or diaphragmatic muscle weakness following injection of botulinum toxin to lower limbs; and 7 of generalised muscle weakness. Other reactions reported most commonly are of rash or other allergic reaction (10), diplopia (6) and fatigue (4).

Seven of the Australian reports cited 'off label' use (tension headaches, achalasia, bruxism, neurogenic detrusor overactivity, urinary incontinence) and 17 cited use for cosmetic reasons ("crows feet or other skin wrinkling") but the others cited reasons for use which were in accord with the approved indications (focal spasticity or muscle spasm).

Sixteen reports documented complete recovery: 6 of these specified a recovery period of 1-3 months after treatment but recovery occurred after 6 months in 1 case. The remaining reports indicated that the outcome was either 'unknown' or 'not yet recovered' at the time of reporting. Many of the 'not yet recovered' outcomes represent persistence (from 1 month up to 1 year) of symptoms/disability, which is consistent with the long-term effect of the toxin. Some reports have described recovery of adverse effects around the time the beneficial effects of the drug diminish, which is also consistent with the pharmacology of botulinum toxin.

Based on local and overseas experience, most adverse effects with botulinum toxin appear to be non serious, of 'mild to moderate intensity' and transient. Serious adverse reactions are rare and usually relate to 'leakage' of the toxin to non-target areas (*vis*, dysphagia, muscle weakness and sequelae such as aspiration pneumonia), generally, but not always, attributed to excessive volume of injection which in turn relates to the concentration used or incorrect administration.

Correct injection technique and expert knowledge of human anatomy relevant to the specific indication are prerequisites for the administration of botulinum toxin. Treatment should be initiated with the lowest effective dose and repeated at the longest interval consistent with effectiveness.

Adherence to the specific recommendations for use of botulinum toxin-containing products is essential and patients should be warned about the possibility, *albeit* slight, of long-term adverse effects.

References:

1. http://www.fda.gov/cder/drug/early_comm/botulinum_toxins.htm
2. Botulinum toxin type A (Botox) and distant toxin spread. *Canadian Adverse Reactions Newsletter* Oct 2008; 18/4.

2. Proton pump inhibitors and possible fracture risk

Proton pump inhibitors (omeprazole, pantoprazole, lansoprazole, rabeprazole and esomeprazole) have been available in Australia since the mid 1990s.

To date three large retrospective studies have suggested an association between proton pump inhibitors (PPIs) and an increased incidence of fractures.^{1,2,3}

A Canadian review of administrative data (electronic bills submitted by medical professionals) spanning 1996-2004 showed an increased risk of hip fractures for people exposed to PPIs for 5 years or more. After 7 or more years of exposure to PPIs the risk of hip fractures increased even further (OR = 4.55, 95% CI 1.68-12.29, $p = 0.002$).¹

A review of data from the year 2000 in the Danish National Hospital Discharge Registry (where clinicians code admission diagnosis according to ICD criteria) showed that exposure to PPIs within the preceding year was associated with an increased overall fracture risk and an even greater risk of hip fracture (OR 1.45, 95% CI 1.28-1.65).²

Similarly, a US study of the UK General Practice Database (from 1987–2003) identified a statistically significant increase in hip fractures with PPI exposure of more than 1 year, and also found that the risk increased with increasing duration of therapy and high dose therapy.³

These studies are observational in design and consequently are subject to confounding. Further study is necessary to verify and more clearly define the association.

The biological mechanism underlying this possible association is unknown. One explanation may be that the absorption of dietary calcium is dependent on a low pH in the stomach and as PPIs are potent inhibitors of acid secretion from the gastric parietal cells, there will be an increase in

pH.⁴ However the effect of this, if any, on bone density in the long term is still unknown and it is certainly possible that other factors contribute to the observed increase in fracture risk.

To date, we have received only two reports of cases where a PPI has been associated with a pathological fracture and/or osteoporosis; the PPI was the sole suspect in only one of these cases. This low reporting rate may reflect a low index of clinical suspicion given the high prevalence of hip fractures in Australia and the common prescription of PPIs.

Despite the limitations of the available data, it would seem reasonable to consider the potential for increased fracture risk when prescribing and maintaining patients on PPI therapy. Clinicians should prescribe the lowest effective dose for recognised indications and periodically re-evaluate individual cases to determine whether PPI therapy remains necessary.

ADRAC also reminds prescribers to be aware of the potential cumulative risk for individuals taking more than one medication known to increase fracture risk. This risk should also be taken into account when prescribing concomitant medicines known to increase the risk of falls.⁵

References:

1. Targownik, L, Lix L, Metge C, *et al.* Use of proton pump inhibitors and risk of osteoporosis related fractures. *CMAJ* 2008; 179: 319-326.
2. Vestergaard P, Rejnmark L, Mosekilde L. Proton pump inhibitors, histamine H2 receptor antagonists, and other antacid medication and the risk of fracture. *Calcif Tissue Int* 2006; 79:76-83.
3. Yang Y, Lewis J, Epstein S, Metz D. Long term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; 296: 2947–2953.
4. Richards J, Goltzman D. Proton pump inhibitors: balancing the benefits and potential fracture risks. *CMAJ* 2008; 179: 306-307.
5. Bannwarth B. Drug induced musculoskeletal disorders. *Drug Safety* 2007; 30: 27-46.

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 website: <http://www.tga.gov.au/adr/bluecard.pdf> or from the Adverse Drug Reactions Unit ☎ 02-6232-8744.

Reports can also be submitted electronically, by going to the TGA website <http://www.tga.gov.au> and clicking on "report problems" on the left, by fax: 02-6232-8392, or email: ADR.Reports@tga.gov.au

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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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