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Therapeutic Goods Administration

Medicines Safety Update

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Accidental paracetamol poisoning

The hepatotoxic effects of paracetamol when taken as an intentional overdose are well-known. However, paracetamol hepatotoxicity can also occur in other situations, including accidental overdose and use at normal doses.

Paracetamol-induced hepatotoxicity at therapeutic doses

In many patients with hepatotoxicity, the paracetamol was taken for therapeutic purposes only. In a study of 662 patients with severe paracetamol-induced hepatotoxicity, 48% had not exceeded the recommended maximum daily dose of 4g.[1]

A 45-year-old woman suffered fatal paracetamol-induced liver failure after receiving paracetamol at a therapeutic dose. She had been hospitalised for subacute bowel obstruction and treated with paracetamol 1g 'qid' for 8 days while remaining nil by mouth.[1]

Risk factors for paracetamol hepatotoxicity include fasting, regular excessive alcohol use, and concomitant use of drugs that induce cytochrome P450 (CYP) 2E1 (e.g. ethanol). Paracetamol is normally metabolised through conjugation in the liver and excreted in urine. A small proportion of paracetamol is converted by CYP enzymes 2E1 and 3A4 to the hepatotoxic compound *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is then conjugated with glutathione and excreted. Prolonged fasting depletes the substrates necessary for conjugation, including glutathione, leading to a build-up of NAPQI.[1,2]

Accidental overdose

A three-year-old chronically malnourished boy with a history of gastric dysmotility syndrome was hospitalised with fever and vomiting. Being intolerant of oral medication, he was prescribed the intravenous formulation of paracetamol, Perfalgan 150 mg (15 mL). Due to confusion between mg and mL he was given a single dose of 150 mL (1500 mg).[3] He experienced transient hepatotoxicity, which responded to treatment with *N*-acetylcysteine. To avoid this type of dosing error, specify the dose volume in mL when prescribing, particularly in neonates and infants.[4]

Concomitant administration of oral and intravenous paracetamol is another cause of hepatotoxicity. When administering paracetamol, it is advisable to check no other sources of paracetamol have been given.

Information for health professionals

Australian guidelines for the management of paracetamol overdose include an updated treatment nomogram, and recommended investigations and *N*-acetylcysteine dosing regimens.[2]

REFERENCES

1. Lubel JS, Angus PW, Gow PJ. Accidental paracetamol poisoning. Med J Aust 2007;186:371–2.
2. Daly FF, Fountain JS, Murray L, Graudins A, Buckley NA; Panel of Australian and New Zealand clinical toxicologists. Guidelines for the management of paracetamol poisoning in Australia and New Zealand. Med J Aust 2008;188:296-301.
3. Berling I, Anscombe M, Isbister GK. Intravenous paracetamol toxicity in a malnourished child. Clin Toxicol (Phila) 2012;50:74-6.
4. Dear Healthcare Professional Letter. Bristol-Myers Squibb Australia Pty Ltd. 2012 May.

Correction

This should read:

"In a study of 662 patients with acute liver failure, 275 were cases of severe paracetamol-induced hepatotoxicity. 131 (48%) of these 275 cases were the result of an unintentional overdose and 19 (7%) of the 275 patients had not exceeded the recommended maximum daily dose of 4g".

The correct reference for this paragraph is:

Larson AM, Polson J, Fontana RF, Davern TJ, Lalani E, Hynan LS, et al. Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology 2005;42:1364-72.

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TGA Health Safety Regula

MEDICINES SAFETY UPDATE

Strontium ranelate and venous thromboembolism and serious skin reactions

Health professionals are advised of additional contraindications and precautions for strontium ranelate (Protos), to help manage the risk of venous thromboembolism (VTE) and serious skin hypersensitivity reactions.

Strontium ranelate, marketed as Protos, is indicated for the treatment of postmenopausal osteoporosis to reduce the risk of fracture, and for the treatment of osteoporosis in men at increased risk of fracture.

The European Medicines Agency (EMA) recently completed a review of Protos.[1] It concluded that while Protos remains an important treatment for osteoporosis, changes were required to the information provided to health professionals to better manage the associated risks.

Risk of VTE

The risk of VTE was found to be higher in patients with a previous history of VTE, and in patients who are temporarily or permanently immobilised. A higher rate of VTE was also identified in elderly patients aged >80 years receiving Protos, compared to placebo.

Risk of serious skin hypersensitivity reactions

Post-marketing surveillance has identified cases of severe skin reactions, such as drug rash with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), in patients prescribed Protos. However, the overall occurrence of serious skin reactions was low. Since these conditions are best managed with early diagnosis and immediate discontinuation of any suspect medicines, it is important that health professionals are aware of the time-to-onset, signs and symptoms of these conditions.

Changes to the Product Information

The Australian Product Information has been updated to include strengthened advice for managing the risk of VTE and serious skin hypersensitivity reactions (see below).

REFERENCE

1. European Medicines Agency confirms positive benefit-risk balance of Protelos/Osseor, but recommends new contraindications and revised warnings [press release]. European Medicines Agency. 2012 Mar.

New contraindications and precautions for strontium ranelate (Protos)*

New contraindications

- Current or previous venous thromboembolic events, including deep vein thrombosis and pulmonary embolism
- Temporary or permanent immobilisation (e.g. post-surgical recovery or prolonged bed rest)

New precautions

Venous thromboembolism:

- In patients over 80 years at risk of VTE, ongoing treatment with Protos should be re-evaluated
- In the event of an illness or a condition leading to immobilisation, Protos should be discontinued as soon as possible and adequate preventive measures taken. Therapy should not be restarted until the event has resolved and the patient is mobile.
- Protos should be stopped if VTE occurs

Serious skin hypersensitivity reactions:

- Patients should be advised of the signs and symptoms and monitored closely for skin reactions
- The highest risk for occurrence of SJS or TEN is within the first weeks of treatment and usually around 3–6 weeks for DRESS
- If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) or DRESS (e.g. rash, fever, eosinophilia and systemic involvement (e.g. adenopathy, hepatitis, interstitial nephropathy, interstitial lung disease)) are present, Protos treatment should be discontinued immediately
- Early diagnosis and immediate discontinuation of the suspected drug is associated with a better prognosis of SJS, TEN or DRESS. Recovery from DRESS could be slow and recurrences have been reported in some cases after discontinuation of corticosteroid therapy.
- If the patient has developed SJS, TEN or DRESS with the use of Protos, Protos must not be re-started

* For full prescribing information, see the Protos Product Information available on the TGA website

MEDICINES SAFETY UPDATE

Better information on medicine labels – have your say

Health professionals are invited to submit comments on the TGA's consultation paper for the Medicine Labelling and Packaging Review. In particular, the TGA is interested in comments from health professionals on the relevance and impact of the proposed changes on the quality use of medicines and consumer safety.

The objective of the review is to develop appropriate regulatory solutions that effectively address the consumer safety risks posed by the following issues:

- active ingredients prominence
- look-alike medicine branding, also known as brand extension or trade name extension
- look-alike and sound-alike medicine names
- look-alike medicine packaging
- standardised formats for information included on medicines labels and packaging
- mandatory space for dispensing stickers
- information provided on blister strips
- information included on small containers
- information provided in pack inserts.

The aim of the proposed changes is to reduce the risk of errors by health professionals and facilitate consumer access to the information they need to:

- make informed choices where they are self-managing minor conditions, such as a headache or a cold
- safely use a medicine that they have been prescribed by a health practitioner for the treatment of a more serious condition.

Full details of the process and the consultation paper can be found on the TGA website: www.tga.gov.au/newsroom/consult-labelling-packaging-review-120524.htm

What to report? You don't need to be certain, just suspicious!

The TGA encourages the reporting of all **suspected** adverse reactions to medicines, including vaccines, over-the-counter medicines, herbal, traditional or alternative remedies. We particularly request reports of:

- all suspected reactions to new medicines
- all suspected medicines interactions
- suspected reactions causing death, admission to hospital or prolongation of hospitalisation, increased investigations or treatment, or birth defects.

Reports may be submitted:

- **using the 'blue card'** available from the TGA website
- **online** at www.tga.gov.au
- **by fax** to (02) 6232 8392
- **by email** to ADR.Reports@tga.gov.au

For more information about reporting, visit www.tga.gov.au or contact the TGA's Office of Product Review on 1800 044 114.

For the latest safety information from the TGA, subscribe to the TGA Safety Information email list via the TGA website

For correspondence or further information about Medicines Safety Update, contact the TGA's Office of Product Review at ADR.Reports@tga.gov.au or 1800 044 114

Medicines Safety Update is written by staff from the Office of Product Review

Editor:
Dr Katherine Gray

TGA Principal Medical Advisor (acting):
Dr Tony Gill

Contributors include:
Dr Claire Behm
Dr Richard Hill

DISCLAIMER

Medicines Safety Update is aimed at health professionals. It is intended to provide practical information to health professionals on medicine safety, including emerging safety issues. The information in Medicines Safety Update is necessarily general and is not intended to be a substitute for a health professional's judgment in each case, taking into account the individual circumstances of their patients. Reasonable care has been taken to ensure that the information is accurate and complete at the time of publication. The Australian Government gives no warranty that the information in this document is accurate or complete, and shall not be liable for any loss whatsoever due to negligence or otherwise arising from the use of or reliance on this document.