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Member hospitals

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Blacktown-Mt.Druitt
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Broken Hill
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Canterbury
Coffs Harbour
Concord
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Fairfield
Gosford
Goulburn
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Lismore
Lithgow
Lower Hunter Area
Macquarie
Manly
Mona Vale
Moruya
Nepean
Newcastle Mater
New Children's
Orange
Prince of Wales
Royal North Shore
Royal Prince Alfred
Rozelle
Ryde
Shell Harbour
St George
St Vincent's
Sutherland
Sydney
Tamworth
Tweed Heads
Wagga Wagga
Westmead
Wollongong-Port Kembla
Wyang

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An initiative of
NSW TAG funded by
NSW Health

Aspirin and Clopidogrel for Acute Coronary Syndromes

Question

I have been asked by our coronary care department whether the use of combined treatment with aspirin and clopidogrel to treat patients with Acute Coronary Syndrome (ACS) has been generally adopted and incorporated into local or other guidelines for coronary care. Can you help? (Hospital Pharmacist NSW)

Answer

In the CURE study[1], 12,592 patients presenting within 24 hours after the onset of symptoms were randomly assigned to receive clopidogrel (300mg stat followed by 75mg daily for 3 to 12 months) or placebo, in addition to aspirin 75-325 mg. Clopidogrel significantly reduced the risk of the composite outcome of death from cardiovascular causes, non fatal myocardial infarction or stroke [9.3% vs 11.4%; relative risk 0.80 (95% CI 0.72-0.90; p<0.001)]. The absolute risk reduction was 2.1% which corresponds to the number needed to treat (NNT) for the primary endpoint of 48. When the results were analysed for the outcome measure of cardiovascular death only, the difference in the groups was not significant (relative risk 0.93; 95% confidence interval 0.79 to 1.08). The 12-month data showed no significant reduction in mortality. The incidence of major bleeding was significantly greater in the clopidogrel and aspirin group compared with the placebo group (3.7% vs 2.7%; relative risk 1.38, 95% CI 1.13-1.67; p<0.001). The absolute risk increase was 1%, which translates to the number needed to harm (NNH) of 100 ie for every 100 patients treated one additional patient will suffer major bleeding. Thus for every 2 events prevented by clopidogrel there will be one more case of major bleeding than compared with using aspirin alone.

The definitive Australasian guidelines in the area of acute coronary syndromes are the 'Management of Unstable Angina Guidelines-2000', conjointly produced by the National Heart Foundation and the Cardiac Society of Australia and New Zealand. The

guidelines are directed at caring for patients presenting with ACS without electrocardiographic ST segment elevation, and therefore include unstable angina and non Q-wave myocardial infarction. In that document it is noted that clopidogrel was currently being assessed in patients with unstable angina (CURE trial) [1]. In October 2001 an addendum was completed to the document, taking into account results of the CURE and TACTICS [2] studies, with the following recommendations:-

*Welcome to the July 2002
edition of the TAGNet
Bulletin.*

*In this issue we look at the
use of aspirin and
clopidogrel in acute coronary
syndromes.*

- Early treatment with aspirin, clopidogrel and tirofiban/ heparin should be considered in patients with non-ST elevation ACS and high risk features (ST depression or elevated serum markers). The use of clopidogrel should be avoided in patients likely to require emergency coronary bypass surgery (patients with severe widespread ST depression or haemodynamic instability). If possible, clopidogrel should be discontinued 5 days prior to coronary bypass surgery.
- An early invasive strategy (4-48 hours) is recommended in patients without ST elevation who have high-risk features.

The addendum does not, however, specify the *optimum duration* of clopidogrel therapy.

The American College of Cardiology and the American Heart Association (ACC/AHA) have also recently updated their practice guidelines for the treatment of unstable angina and non-ST-segment elevation myocardial infarction (MI) [3]. They recommend

that aspirin should be given as soon as possible after presentation, and continued indefinitely, and clopidogrel should be given to hospitalized patients unable to take aspirin because of hypersensitivity or major gastrointestinal intolerance. In hospitalised patients in whom an early non-interventional approach is planned, clopidogrel should be added to aspirin as soon as possible on admission and given for at least one month and for up to 9 months. In patients for whom a percutaneous coronary intervention (PCI) is planned, clopidogrel should be started and continued for at least one month, and up to 9 months in patients who are not at a high risk of bleeding. However, in patients taking clopidogrel in whom coronary artery bypass grafting (CABG) is planned, the drug should be withheld for at least 5 days and preferably 7 days.

An incremental cost-effectiveness analysis of the long-term (25 year) use of aspirin, clopidogrel, or both for secondary prevention in patients with known coronary disease has recently been published [4]. The authors concluded that aspirin use for secondary prevention of coronary disease is attractive from a cost-effectiveness perspective under a wide range of assumptions. Clopidogrel, as currently priced, has an attractive cost-effectiveness ratio when used for patients with contraindications to aspirin, but not in those who can tolerate aspirin.

Anecdotally, many hospitals within the TAG network are using aspirin and clopidogrel together, but this is not universal. Most TAG hospitals reported in February 2002 that the findings from the CURE study had not been incorporated into their guidelines at that time. As the bleeding risk with aspirin/ clopidogrel combination is higher than with aspirin alone, some hospitals are using the combination on a case by case basis. Since clopidogrel appears to increase the risk of surgical bleeding, some clinicians consider tirofiban a better alternative in patients who are possible surgical candidates (i.e. if CABG is the outcome of diagnostic angiogram).

At present, the Pharmaceutical Benefits Scheme provides subsidy for prescribing of clopidogrel only in the following indications:

- secondary prevention of ischaemic stroke or transient ischaemic events in patients with a history of cerebrovascular ischaemic episodes while taking low-dose aspirin, where low-dose aspirin poses an unacceptable risk of GIT bleeding or where there is a history of anaphylaxis, urticaria or asthma within 4 hours of ingestion of aspirin, salicylates or NSAIDs.
- secondary prevention of myocardial infarction or unstable angina in patients with a history of cardiac ischaemic episodes while taking low-dose aspirin, where low-dose aspirin poses an unacceptable risk of GIT bleeding or where there is a history of anaphylaxis, urticaria or asthma within 4 hours of ingestion of aspirin, salicylates or NSAIDs.

References

1. CURE Investigators, *Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation*. N Engl J Med, 2001. **345**: p. 494-502.

2. Cannon, C.P., et al., *Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/ IIIa inhibitor tirofiban*.

N Engl J Med, 2001. **344**: p. 1879-1887.

3. Braunwald, E., et al., *ACC/AHA guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina)*. 2002.

Available at:

<http://www.acc.org/clinical/guidelines/unstable/unstable.pdf>, 2002.

4. Gaspoz, J.M., et al., *Cost effective-ness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease*.

N Engl J Med, 2002. **346** (23): p. 1800-1806.

NSW TAG Staff and Board News

Maria Kelly shares the role of Executive Officer with Karen Kaye. Maria is available in the office on Thursdays, or e-mail nswtag@stvincents.com.au

Following the Annual General Meeting in October 2001, two new members were elected to the Board. **Rosemary Burke** is the Director of Pharmacy at Concord Hospital and immediate Past President of the Society of Hospital Pharmacists (NSW Branch). **Professor Jo-anne Brien** holds the Pharmacia Chair in Clinical Pharmacy, The University of Sydney (St Vincent's Hospital).

Clinical Representatives

NSW Therapeutic Assessment Group provides representatives to the following NSW Health committees:-

Contract Advisory Group for Pharmaceuticals
(A/Prof Ian Whyte)

Infection Control Advisory Group Sub-committee on Multi-resistant Organisms (Jennie MacDonald)

Integrated Incident Management Steering Group (Karen Kaye)

Clinical Information Access Project (CIAP)
Management Committee (Karen Kaye)

If you have any issues which you would like brought to the attention of these committees please contact the TAG secretariat for contact details for the representative concerned.

NSW TAG Projects

Review of Pain Guidelines and New Guidelines on General Principles for Management of Chronic or Recurrent Non-Malignant Pain

With the support of NSW Health, NSW TAG prepared guidelines in 1998 for general practitioners for prescribing for migraine and low back pain. In 1999/2000, NSW TAG coordinated an evaluation of the guidelines by GPs in clinical practice. Useful features of the guidelines were identified, and also the need for inclusion of more recently marketed drugs, clarification of some terminology and more specific guidelines for use of codeine-containing products. GPs participating in the project also identified a need for additional guidelines in other areas of chronic pain management.

NSW TAG is currently undertaking a project to facilitate the review process and to build on the successes already achieved with the existing pain guidelines. The aims of the project are to revise the NSW TAG Guidelines for General Practitioners Prescribing for Migraine and Low Back Pain and develop an additional guideline for medical practitioners to complement the existing guidelines, focusing on general principles of pain management relevant to both community and hospital practice.

The new guidelines are expected to be released in December 2002.

If you would like additional information contact Karen Kaye: nswtag@stvincents.com.au

Evaluation of APAC Guidelines

The Commonwealth Department of Health and Ageing has commissioned NSW TAG to undertake a 6 month project (May to October 2002) to evaluate the implementation and effectiveness of the Australian Pharmaceutical Advisory Council National Guidelines to Achieve the Continuum of Quality Use of Medicines between hospital and community.

Current initiatives undertaken in Australia to progress elements of the Guidelines will be investigated via a comprehensive literature review, utilisation of the QUM Map and consultation with stakeholders. A survey of hospital staff and community health providers is currently being conducted across Australia. Alternative methods of facilitating the implementation of the Guidelines within health facilities in Australia will be considered.

Outcomes will be a detailed map of activities being undertaken in respect to the Guidelines implementation in Australia, and recommendations to the Department regarding future implementation of the guidelines, including alternative methods of facilitation and workable solutions.

For more information contact Karen Kaye: nswtag@stvincents.com.au

TREATMENT OF CYANIDE POISONING

The currently recommended antidote for clinically severe cyanide toxicity in Australia is dicobalt edetate¹. However, hydroxocobalamin has been preferred in Europe and animal studies and uncontrolled trials in humans suggest that hydroxocobalamin is safer and at least as effective². The suggested dose of hydroxocobalamin for cyanide poisoning is 5-15 g given over 30 mins (faster if necessary) accompanied by sodium thiosulphate 12.5 g over 10-20 min.

Hydroxocobalamin is available as a marketed product, Neo- Cytamen 1000 injection®, however this product contains only 1 mg of hydroxocobalamin per ampoule, and is clearly unsuitable for use in cyanide poisoning, as a minimum of 5000 ampoules would be required.

High dose hydroxocobalamin is available from Orphan Australia as a kit (brand name 'Cyanokit') containing 2 x 2.5g freeze dried hydroxocobalamin plus 2 x 100ml saline diluent with giving sets/transfer devices included. It is available under the SAS (Category A) but can be held in stock with TGA approval. Lead-time for orders is approximately 1-2 weeks. Cost is approximately \$1,850/kit. Orphan may be contacted at (03) 9769 5744.

NSW TAG's Life Saving Drugs Register can be found at the TAG web site: <http://www.nswtag.org.au>
www.nswtag.org.au

It contains indicative stock holdings in NSW public hospitals of marketed agents which may be required in emergencies.

Hypertox® software for emergency ward management, undergraduate and postgraduate teaching of clinical toxicology (poisoning) is available commercially. The current version contains a monograph on cyanide poisoning. Enquiries may be directed to:-

Meditox
PO Box 316
Kotara Fair NSW 2289
or fax 02- 49635371

¹Caswell, A. ed. MIMS Annual 2001; 20-1325.

²Braitberg, G., Vanderpyl, MMJ. Emergency Medicine 2000; 12: 232-240.

Off-Label Drug Therapy

NSW TAG is preparing a discussion paper to assist Drug Committees in formulating policy in this area. A working group has been convened and will consider issues relating to off-label use in paediatrics, oncology and other areas of therapeutics. If you would like more information contact Maria Kelly: nswtag@stvincents.com.au

Did you know that all our new resource documents can be found at the TAG web site: www.nswtag.org.au
or via CIAP: <http://www.clininfo.health.nsw.gov.au/>

The most recent ones include:-

- **Literature review of Proton Pump Inhibitors**
- **Tramadol 2001**
- **Erythropoietin for anaemia associated with chemotherapy**



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