HEART DISEASE

(3) ACUTE CORONARY SYNDROMES

By Helen Williams, DipPharmPrac, MRPharmS

This third article in a series on heart disease discusses the management of acute coronary syndromes, including acute myocardial infarction.

identify gaps in your knowledge

1. Are you up to date with the drugs used to treat ACS?
2. How should ACS be managed?
3. What can pharmacists do to contribute to the acute care of cardiac patients?

This article relates to the Royal Pharmaceutical Society’s core competency of “common disease states and their drug therapies” (see “Medicines, ethics and practice — a guide for pharmacists”, number 26, July 2002, pp105–6). You should consider how it will be of value to your practice.

T he term “acute coronary syndromes” (ACS) encompasses a number of diagnoses that represent a spectrum of disease. Three distinct diagnoses are recognised, but these cannot be distinguished by assessment of their presenting symptoms alone. Electrocardiogram changes and cardiac enzyme levels need to be investigated to determine the underlying disease and appropriate treatment course. Myocardial infarction (MI) is defined as death of a segment of heart muscle following interruption of its blood supply. In most cases this occurs acutely following rupture of an atherosclerotic plaque and the subsequent release of prothrombotic and platelet-activating factors, which leads to thrombus formation. The resulting thrombus can fully or partially occlude a blood vessel. Partial occlusion may or may not lead to heart muscle death, depending on the extent to which blood flow is restricted.

Figure 1 shows a normal ECG. In addition to symptoms, patients with elevation of the ST-segment with or without changes in the levels of cardiac enzymes that indicate myocardial damage (usually creatinine kinase or troponin) are considered to have suffered an acute “ST-elevation MI”. Patients with raised cardiac enzymes (usually troponin) in the absence of ST-segment elevation are considered to have suffered a “non ST-elevation MI” and are at a higher risk of further events. Although the true incidence of MI is unknown, it is estimated that approximately 300,000 people in the United Kingdom suffer ST-elevation MI each year, resulting in about 140,000 deaths.1

“Unstable angina” is diagnosed where there is a sudden deterioration in angina symptoms, but no ST elevation or changes in cardiac enzymes. Despite the use of standard therapies, the risk of death, infarction, refractory angina or readmission to hospital following an episode of unstable angina is as high as 30 per cent within six months.2 Chapter 3 of the National Service Framework for Coronary Heart Disease highlights three key areas for the management of ACS: pre-hospital interventions, hospital interventions and continuing care.

PRE-HOSPITAL INTERVENTIONS

Pre-hospital interventions include early recognition of symptoms and early initiation of therapies. Delays in seeking medical advice in patients suffering ACS are well documented as having a significant impact on subsequent mortality and morbidity. Factors that may lead to delay include absence of typical symptoms, misinterpretation of symptoms, denial and fear. Increased public awareness of the signs and symptoms of ACS may aid early presentation for treatment and the NSF calls for the education of patients with known CHD — a role that pharmacists are ideally placed to fulfil or support. Panel 1 (p748) lists typical MI symptoms, but not all heart attacks are sudden or intense — some may occur without any identifiable symptoms.

A number of pre-hospital drug therapies are recommended:

1. Oxygen to relieve ischaemia
2. Diamorphine for pain relief — this also has anxiolytic and vasodilating effects
3. Aspirin for its antiplatelet effect — at least 300mg should be chewed or dispersed in water to aid early absorption

Myocardial ischaemia rapidly leads to the development of arrhythmias that can result in sudden cardiac death and as a result, up to two-thirds of MI deaths occur out of hospital.1 Cardiopulmonary resuscitation and early access to defibrillators is therefore essential. To improve resuscitation outcomes, a target response time of eight minutes has been set for the ambulance service where MI is suspected. Many training schemes, such as the Heartstart Emergency Life Support scheme funded by the British Heart Foundation and others offered by British Red Cross and St John Ambulance are now available to members of the public to facilitate basic life support in the community. Debate over the potential benefits of locating automated external defibrillators in public places continues.

HOSPITAL INTERVENTIONS

Although there are many similarities between the management of ST-elevation MI and other ACS (eg, oxygen and diamorphine), the use of some key drugs, notably thrombolytics and glycoprotein IIIb/IIIa inhibitors, is determined by the specific cardiac diagnosis, ie, accurate diagnosis is essential at this point. Table 1 (p748) shows two drug therapy menus.

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Figure 1: A normal electrocardiogram

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Aspirin and clopidogrel  It is well known that administration of aspirin reduces mortality and protects against subsequent events. A 300mg dose should be given as early as possible in all ACS, followed by 75–150mg daily thereafter (the lower dose may limit adverse effects in the long-term). In the ISIS-2 trial a 23 per cent reduction in mortality was seen following aspirin therapy at five weeks post-acute event compared with placebo.3

Clopidogrel, another anti-platelet drug, has not been studied in the acute setting of ST-elevation MI, but the CURE trial demonstrated the benefit of using this drug with aspirin in the management of other ACS.4 A reduction in cardiac events was seen within the first 24 hours of therapy and an absolute reduction in risk of death, MI or stroke of approximately 2 per cent (20 per cent relative risk reduction) was observed in the group treated with aspirin plus clopidogrel over the course of the study. However, controversy remains over the optimal duration of therapy in such circumstances (opinion varies between one month and life-long therapy).

Thrombolysis  Thrombolytic therapy aims to break down clots in coronary arteries through the lysis of fibrinogen bonds. In trials, successful thrombolysis has been assessed by measuring the patency of the affected vessel 90 minutes post-thrombolysis but longer-term outcomes are more important in clinical practice. An 18 per cent relative risk reduction in mortality at 35 days post MI has been attributed to thrombolytic therapy.

All patients diagnosed with ST-elevation MI should receive thrombolytic therapy without delay, unless contraindicated, because early treatment gives greater benefits in terms of survival. One study4 quoted a mortality rate of 1.2 per cent in those treated within 70 minutes of symptom onset compared with 8.7 per cent in those who received therapy later and it has been estimated that for every hour earlier a patient is treated there is a 1 per cent absolute reduction in mortality, resulting in 10 more lives saved per 1,000 treated.6

The NSF has been a key driver for change. It sets a “call-to-needle time” (time between seeking help and administration of thrombolytic therapy) target of within one hour, and a “door-to-needle time” (time between reaching hospital and administration of therapy) target of within 30 minutes. Improvements in door-to-needle time have been achieved in many trusts through more accident and emergency departments offering thrombolysis, improved systems of triage and diagnosis of MI and the roll-out of a national MI audit project (MINAP) to monitor adherence to the NSF standard. Projects investigating the feasibility of pre-hospital thrombolysis initiated by paramedics are ongoing.

There is no strong evidence that any individual thrombolytic agent has superior efficacy, but the agents can be distinguished in terms of mode of administration, duration of effect, risk of haemorrhage or other adverse effects and cost. Until recently, the most commonly used agents in the UK were streptokinase and alteplase (rt-PA), given by intravenous infusion. The newer thrombolitics, tenecteplase (TNK-tPA) and reteplase, are growing in popularity due to their ease of administration (single or double-bolus, respectively), which may be significant in terms of achieving door-to-needle time targets.7

The indication of thrombolytic therapy should be considered carefully. Absolute contraindications include previous haemorrhagic stroke (a stroke caused by a bleed as opposed to a clot — “ischaemic stroke”), any cerebrovascular event within the previous year, internal bleeding and suspected aortic dissection. Other contraindications must be considered on a patient-by-patient basis. These include uncontrolled hypertension (systolic blood pressure >180mmHg), anticoagulant therapy, recent (within the past four weeks) trauma or major surgery, prolonged cardiopulmonary resuscitation and pregnancy. Complications of thrombolytic therapy include haemorrhagic stroke (occurs in approximately 1.2 per cent of patients, with a greater risk in the elderly and those with hypertension), other bleeds, allergic reactions (primarily with streptokinase) and systemic emboli.

Primary angioplasty (an interventional procedure to unblock the occluded artery) is a useful option in patients in whom thrombolysis is contraindicated. Furthermore, it has been shown to be superior to thrombolytic therapy in acute MI, achieving improved vessel patency, limiting infarct size, protecting against reinfarction and reducing the risk of cerebrovascular bleeds. The DANAMI-2 investigators, reported a 40 per cent relative reduction in risk of death, stroke or reinfarction with primary angioplasty versus thrombolysis.8 Unfortunately, limited access to interventional cardiac units means the procedure cannot be offered comprehensively in the UK.

Glycoprotein IIb/IIIa inhibitors  Although thrombolysis significantly reduces mortality in ST-elevation MI, it can be associated with increased mortality and non-fatal infarction in non-ST-elevation MI and other ACS.9 In contrast, antithrombotic strategies have been shown to reduce the risk of death, MI and hospital admission in these patients. The introduction of potent intravenous anti-platelet drugs, the GPIIb/IIIa inhibitors, into clinical practice in the 1990s further highlighted the need for early diagnosis and stratification to appropriate treatment strategies. Abciximab, eptifibatide, and tirofiban block the final common pathway for platelet aggregation, by preventing the binding of fibrinogen to GPIIb/IIIa receptors on platelets. Abciximab is a long-acting monoclonal antibody fragment that targets GPIIb/IIIa receptors and blocks platelet aggregation by stearic hindrance. It has a place in the reduction of complications during procedures such as angioplasty and intra-coronary stent placement, but has not been shown to improve outcomes in ACS.

In contrast, eptifibatide and tirofiban (known as the small-molecule GPIIb/IIIa receptor antagonists) have been shown to reduce mortality and morbidity associated with episodes of ACS. GPIIb/IIIa inhibitors reduce the risk of patients with unstable angina or non ST-elevation MI going on to develop an ST-elevation MI. The PRISM-plus study compared tirofiban plus heparin with heparin alone in a high-risk population (ECG abnormalities or non-ST-elevation MI) and demonstrated a 34 per cent reduction in death, MI and refractory ischaemia.10 The impact of these GPIIb/IIIa receptor antagonists persists beyond the acute treatment phase, with favourable results at six months and beyond.

Recently issued guidance from the National Institute for Clinical Excellence has indicated that GPIIb/IIIa inhibitors should be considered early in the management of ACS (except ST-elevation MI) even if coronary intervention is planned.12 To maximise benefits, high risk patients with characteristics including increasing age, comorbidities (eg, diabetes), prolonged chest pain at rest, previous MI, ongoing chest pain despite initial management strategies, dynamic or unstable ischaemic ECG changes, haemodynamic instability or raised cardiac troponins should be targeted. Tirofiban and eptifi-
Heart failure is a common complication of acute ischaemic events and may require diuretic therapy, angiotensin converting enzyme inhibitors or other supportive measures. Electrolytes should be monitored closely and abnormalities quickly corrected to avoid precipitating or exacerbating arrhythmias. Arrhythmia management is important, but must be approached cautiously because many anti-arrhythmics have been shown to increase mortality post-MI, with only amiodarone being considered safe and potentially beneficial in this setting.

**CONTINUING CARE**

Continuing care means reducing cardiovascular risks through lifestyle changes and secondary prevention drug therapy (eg, aspirin, beta-blockers, statins). Cardiovascular risk reduction post-myocardial infarction will be discussed in the next article.

**CONCLUSION**

A number of interventions made in timely manner can significantly improve outcomes for patients with ACS. The pharmacist’s role in the acute stage could involve educating patients with CHD, recognising and responding appropriately to acute cardiac symptoms, ensuring availability of acute drugs in appropriate areas, training staff regarding the use and administration of acute drug therapy and developing clear and practical clinical guidelines.

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**REFERENCES**


