Editorial

Cost Effective Management of Myocardial Infarction

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Prevention

Although mycocardial infarction is falling in urbanised societies it is rising in countries which are becoming more affluent. There have been dramatic reductions in mortality in hospitalised patients over the last decade, but we should bear in mind that, at least in urban conditions, about half of the deaths occur before any medical intervention is possible. Many of these deaths are sudden and many are unheralded. This emphasises the need for a strong preventative approach, taking in the clearly proven factors, particularly smoking, hypertension, saturated fat intake and lack of exercise. Since the "damaging" lipid appears to be oxidised LDL, there is increasing evidence of the value of antioxidants (Vit E & Vit C) in food, particularly fruit.

Emergency Treatment of Acute Myocardial Infarction (AMI)

Thrombolysis

After many years of confusion, with small and contradictory trials GISSI-1[1] and ISIS-2[2] showed that i/v Streptokinase (SK) could reduce mortality by about a quarter in a wide range of patients including women, the elderly and all sites of infarction, with the possible exception of subendocardial infarction (i.e ST depression, not elevation, on the initial ECG). In these trials, where invasive procedures were unusual, there was only about 1% risk of bleeding. Although there was an increase in cerebral haemorrhage, as might be expected, there was a slightly greater shortfall in embolic/thrombotic (ischaemic) stroke; so overall, the feared excess of stroke did not materialise. About 8% of SK treated develop minor allergic reactions but these were not dangerous.

ISIS-2[2] randomised patients up to 24 hours from the onset of AMI. Later entered patients still showed benefit, although less than those treated within the first 4-6 hours. So unless there are strong contraindications to SK (e.g. recent surgery, stroke, or GI bleeding, or traumatic resuscitation), it should be used in AMI, particularly in those at high risk of dying — large anterior MI and/or fit elderly patients. As well as reducing mortality there are also benefits in terms of reduced infarct size and LV damage. Newer agents such as a derivative of SK, APSAC, which has the convenience of use as a 3-5 minute bolus, and recombinant tissue plasminogen activator rt-PA, which is non allergenic, are about ten times more expensive than SK. Fortunately 2 very large trials ISIS-3 (42,000 patients)[3] and GISSI-2 and its international extension (20,000 patients)[4,5] showed that they were not only no better than SK for first time treatment, but caused a small (0.2% - 0.4%) but significant excess of stroke[3]. rt-Pa does have a role for second time use, since a previous SK dose produces antibodies which are long lasting and which may neutralise the therapeutic effect of a second SK dose.

Aspirin

ISIS-2[2] also tested the effect of half an aspirin (160mgs enteric coated), the first tablet chewed immediately and then continued

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daily. Mortality at five weeks was reduced by over 20% and this reduction applied both in the absence and in the presence of SK (when it was additive to the SK benefit). This regimen of SK+Aspirin more than halved 5 week and longer term mortality in patients treated in less than 4 hours.

Furthemore it was remarkably well tolerated (as well as placebo!) and gave rise to no excess of cerebral or major bleeding, even in the presence of SK; stoke was also almost halved. This remarkable effect, which astonished us, is probably due to the fact that even while intense fibrinolysis (natural or pharmacological) is occurring the fragmenting clot is highly attractive to circulating platelets, so that both lysis and thrombosis are occurring simultaneously. Aspirin probably helps push the equation in the direction of lysis. This Aspirin/SK regimen can be safely used in small community hospitals.

Heparin

In the presence of an effective dose of Aspirin ISIS-3 and GISSI-2 showed that 25,000 units/day of s/q Heparin for 7 days increased the risk of bleeding including cerebral bleeds, and gave no long-term mortality benefit. Others have argued that i/v Heparin should be given routinely, at least with tPA. This will certainly be more risky and has not been adequately tested in large trials. My own current practice is to use i/v Heparin only in those at high risk (poor LV function, arrhythmia, and aneurysm).

Nitrates

Although these are very widely used, they have not been tested in large mortality trials. Overviews of the smaller trials suggest they do reduce mortality, as well as relieving pain and left ventricular failure[6,7]. Intravenous nitrates are fashionable and may be slightly more effective, but in many cases oral therapy (which is much cheaper) will suffice. Remember to leave a nitrate free period of several hours each day — usually at night — to prevent the development of nitrate tolerance. Sublingual GTN is effective and cheap.

Beta Blockers i/v

ISSIS-1[8] tested 5-10mgs of i/v Atenolol in over 16,000 patients. It can only be used in low and medium risk patients without heart block or left ventricular failure. With these exceptions it reduced mortality by 15%. Hypotension may occur, but is not dangerous. It can usually be treated by raising the foot of the bed and/or giving Atropine.

Calcium Channel Blockers

In the immediate phase (first 4 hours) of AMI there is no place for any calcium channel blocker with possible exception of Diltiazem in non Q wave MI[9]. All the other trials of calcium blocking agents in this phase have been neutral at best and often negative.[10]

The dihydropyridines (e.g. nifedipine) have not been useful in secondary prevention either. Verapamil (120mgs 8 hourly) has recently been shown in DAVITT-2[11] to reduce reinfarction and mortality when started 3-4 days after MI and continued long term. It is therefore a useful alternative to longterm B.Blockade e.g. in patients with bronchospasm or peripheral vascular disease.

All calcium channel blockers impair LV function and this appears to be the reason for this adverse experience in the initial phase of AMI. Used later in patients with LV dysfunction Diltiazem was harmful and Verapamil neutral.

Antiarrhythmic Drugs

I find that severe arrhythmia is one of the most worrying, difficult and unscientific areas of treatment. The first rule is not to overtreat, particularly if the arrhythmia is well tolerated

clinically.

Lignocaine i/v

This used to be routine treatment for all AMI. Now we realise that although in high dosage (3-4mg/min, which is often toxic), it is effective in the prophylaxis of ventricular fibrillation (VF), it also causes asystole, which is very difficult to treat![12] We now only use lignocaine for recurrent VF or VT and. **not** for VEB, R on T, or short well tolerated runs of VT.

Class 1 Agents

These agents (flecainide, encainide and morcizine) have now been shown in the CAST, I, II, studies[13,14] to be pro arrhythmic and more harmful than placebo.

Verapamil

i/v Verapamil is effective against supraventricular arrhythmia, but can depress LV function further, so should be used with caution, particularly in hypotensive patients.

i/v Beta Blockade

This is well tolerated. In the ISIS-1 pilot[15] study we showed that both supraventricular and complex ventricular arrhythmias were significantly reduced. In the post CAST era they remain one of the first line agents. Used orally long term they reduce reinfarction and particularly sudden death[16].

Adenosine i/v

This drug block A-V node conduction, is a coronary vasodilator and apart from transient flushing and chest tightness, is well tolerated. It is very useful to block re-entry and A-V nodal tachycardia.

Amiodarone i/v

This is a toxic drug in longterm use but has proven highly effective in the coronary care field in the treatment of both supraventricular and ventricular arrhythmias which are causing haemodynamic problems. It is well tolerated, even by patients with poor LV function. It causes peripheral venous inflammation and thrombosis so is usually given by a central venous line in a dose of 600mgs/24hours.

Newer Drugs

Magnesium Sulphate

Previous small trials had suggested that i/v magnesium reduced mortality. A larger trial in 2,300 patients (LIMIT) from Leicester in the U.K.[17], has now shown a mortality reduction of 24% when about 80mg of $MgSO_4$ was infused over 24 hours. The infusion causes transient flushing but is otherwise non-toxic and can be used in conjunction with all the normal coronary care drugs, without adverse interactions. The main therapeutic benefit was not, as was expected, an anti-arrhythmic action but rather an improvement in LV function. This simple treatment is effective, non toxic and very inexpensive. It can be made in the hospital pharmacy. It is currently undergoing large scale testing in c.40,000 patients in ISIS-4.

Conclusion

The management of myocardial infarction is complex but need not be expensive. Aspirin (chewed immediately and continued indefinitely) and nitrites are "Best Buys". Streptokinase is relatively inexpensive and highly effective. In races with smaller stature it is probably effective (and cheaper) in half the normal dose, i.e. 750,000 units over 30-60 minutes. Heparin is of uncertain benefit in the persence of adequate (160mgs) aspirin daily. Lignocaine and calcium channel blockers are best avoided in the routine early management of

AMI. i/v beta blockade is of proven benefit and useful in patients without LV dysfunction.

Prevention is the cheapest strategy of all. Tax tobacco punitively, take a brisk walk every day, eat fruit and vegetables daily and reduce animal fat intake. Avoid obsesity, which increases blood pressure. After an MI or any other vascular event, all these, plus half an aspirin a day and, if can be tolerated and afforded, a beta blocking agent, will reduce the chance of a recurrence.

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