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Self-test questions

The following statements are either true or false (answers on page 139)

1. Digoxin remains the first-line treatment for patients with heart failure who are in sinus rhythm.
2. Beta blockers are contraindicated in heart failure.

Beta blockers in heart failure

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SYNOPSIS

Recent trials have shown the unequivocal benefits of beta blockers in patients with chronic systolic heart failure. These benefits include improved survival (30-35%) and a reduced need for hospitalisation. However, beta blockers may also make a patient with heart failure worse, especially when treatment begins. Complications can generally be avoided by starting with extremely low doses and increasing the dose very slowly. Beta blockers should be added to optimal conventional therapy for heart failure, and started only when the patient is stable.

Index words: carvedilol, digoxin, metoprolol.

(Aust Prescr 2000;23:120–3)

Introduction

Traditional teaching was that beta blockers should be avoided in patients with heart failure. The rationale was that the sympathetic nervous system was overactive and provided a crucial level of compensation for the failing heart. To remove this by using a beta blocker would risk precipitating or exacerbating heart failure.

Recent trials have seriously challenged this conventional wisdom. The risks remain, but now need to be balanced against the major long-term benefits of beta blockade in chronic systolic heart failure (see box).

History

The Scandinavians have been promoting the use of beta blockers in systolic heart failure since the mid-1970s. A number of relatively small trials showed benefits, primarily in patients with non-ischaemic dilated cardiomyopathy. The MDC trial of Metoprolol in Dilated Cardiomyopathy in 1985 failed to show either harm or benefit.

In 1998 there was a meta-analysis of 18 double-blind placebo-controlled trials of beta blockers in chronic systolic heart failure (see Table 1).[1] The overall reduction of total mortality from chronic beta blockade was 32%, with a 41% reduction in sudden deaths and a 37% reduction in hospitalisation.

Mechanism of action

The benefit of beta blockers almost certainly depends on blockade of beta-1 receptors. This action is consistent with the large body of data documenting high plasma catecholamines in severe heart failure, and more sophisticated studies demonstrating increased cardiac sympathetic activity and catecholamine release. Possible mechanisms for beta receptor blockade improving survival include:

- antiarrhythmic action
- anti-ischaemic action
- attenuation of catecholamine toxicity
- reduced cardiac remodelling.

Metoprolol and bisoprolol are both cardioselective beta blockers acting primarily on beta-1 receptors. By comparison,

Beta blockers in systolic heart failure

In patients with primarily severe systolic heart failure (low ejection fraction) beta blockade has the following long-term benefits which must be balanced against the short-term risks.

Long-term benefits	*Short-term risks*
• improved survival	• worsening heart failure
• improved control of heart failure	• bradyarrhythmias
• reduced need for hospitalisation	• prolonged intraventricular conduction
• improved quality of life	• hypotension
• improved left ventricular ejection fraction	• worsening renal function

carvedilol is a non-selective beta blocker with additional alpha-receptor blocking and antioxidant properties. Based on the unequivocal treatment benefits seen in the CIBIS[2] and MERIT[3] studies, the principal mechanism by which these drugs improve outcome in heart failure is likely to be via their beta-1 receptor blocking action. We will not know if the additional properties of carvedilol are important, and whether carvedilol actually produces a larger benefit than standard beta blockers, until the results of current head-to-head comparisons are reported.

Indications other than systolic heart failure

There are two other types of heart failure where use of beta blockers provides clear benefits and little risk.

Atrial fibrillation

In some patients, atrial fibrillation with rapid ventricular response is a major factor which worsens the severity of their heart failure. In this situation, controlling the ventricular response alone can produce a major improvement in heart failure. Digoxin is usually effective in this situation. Beta blockers are also effective in slowing the ventricular rate, and rarely worsen the situation providing ventricular systolic function is reasonably well preserved.

Diastolic heart failure

Possibly as many as one third of patients with heart failure have normal ventricular systolic function. In these patients, the primary cardiac abnormality leading to heart failure is an abnormality of ventricular filling. They have so-called 'diastolic heart failure'. In this situation, beta blockers can also produce improvement with little risk of the patient deteriorating. The drugs slow the heart rate and allow a longer period for diastolic filling, particularly if atrial fibrillation is also present. Patients with mitral stenosis are the best example. Beta blockers can also facilitate diastolic filling by improving abnormal myocardial relaxation, for example in patients with diastolic failure due to severe left ventricular hypertrophy. This is generally in patients with severe, long-standing, poorly-controlled hypertension.

Clinical trials in systolic heart failure (Table 1)

Patients with primarily **systolic heart failure** with low ejection fraction may deteriorate when given a beta blocker. Paradoxically, it is this very group of patients that had unequivocal long-term benefits in recent trials (see box).

Carvedilol trials

In the meta-analysis of beta blockade[1], there were eight trials of carvedilol, with a total of 1657 patients. Carvedilol appeared to reduce total mortality by 49%. However, only one of the eight individual carvedilol trials produced a statistically significant reduction in total mortality. This trial markedly influences the overall estimate of the treatment benefit of carvedilol. The ANZ trial was the largest of the carvedilol trials (415 patients). Although it found a 27% reduction in total mortality and a 30% reduction in hospitalisation, neither result was statistically significant. None of the carvedilol trials were sufficiently powered to be able to detect a significant difference in these end-points.

It was pooled data from a number of relatively small trials of carvedilol which convinced the Therapeutic Goods Administration to approve carvedilol for systolic heart failure in 1998. Carvedilol requires an authority prescription under the Pharmaceutical Benefits Scheme.

Table 1

Summary of beta blocker trials in chronic systolic heart failure

Trial	*Meta-analysis of 18 pre-1998 trials*[1]	*Carvedilol meta-analysis*	*CIBIS-II 1999*[2]	*MERIT-HF 1999*[3]	*COPERNICUS 2000**
Number of patients	3023	1657	2647	3991	2289
Severity†			III/IV	II/III	III/IV
Placebo mortality	156/1305 (11.9%)	62/665 (9.3%)	228/1320 (17.3%)	217/2001 (11.0%)	NA/1133 (18.6%)
Beta blocker mortality	130/1718 (7.5%)	47/992 (4.7%)	156/1327 (11.8%)	145/1990 (7.2%)	NA/1156 (11.4%)
Reduction in relative risk: total mortality	32%	49%	34%	34%	35%
Number needed to treat††			23	26	14
Reduction in relative risk: sudden death	41%		44%	41%	NA
Reduction in relative risk: hospitalisation	37%	40%	20%		

* Not yet published, data preliminary and incomplete
† New York Heart Association functional class
†† Number of patients who must be treated with beta blocker for one year to prevent one death
NA = not available

CIBIS-II

CIBIS stands for **C**ardiac **I**nsufficiency **Bi**soprolol **S**tudy.[2] Bisoprolol is a beta-1 selective blocker not available in Australia. A total of 2647 patients, mostly in Class III heart failure, had either bisoprolol or a placebo added to optimal therapy. (Most patients were taking a loop diuretic and ACE inhibitor in reasonable doses, and 50% were taking digoxin.) The trial was stopped early because of an unequivocally statistically significant reduction in total mortality of 34%. There were also significant reductions in sudden death (44%) and in hospitalisation for congestive cardiac failure (20%).

MERIT-HF

MERIT-HF stands for **Me**toprolol **R**andomised **I**ntervention **T**rial in **H**eart **F**ailure.[3] Metoprolol is a beta-1 selective blocker which has been available in Australia for many years. However, this trial used a slow-release formulation not currently available in Australia. A total of 3991 patients, with predominantly Class III heart failure, were randomised to have either a placebo or metoprolol, added to the optimal conventional therapy of a loop diuretic and ACE inhibitor. The trial was stopped early because of an unequivocally statistically significant reduction in total mortality of 34%. There was also a significant reduction in sudden death (41%).

COPERNICUS

This stands for **C**arvedil**o**l **P**rosp**e**ctive **R**a**n**dom**i**zed **Cu**mulative **S**urvival Trial. This trial compared carvedilol with placebo in 2289 patients with severe Class III/IV heart failure and ejection fraction of less than 25%. Carvedilol or placebo was added to optimal conventional therapy for heart failure. The trial has been stopped prematurely because of a beneficial effect of carvedilol on the primary end-point of all cause mortality. The results have been presented at an international meeting, but have not yet been published. Carvedilol was associated with a 35% reduction in total mortality.

In COPERNICUS, the annual mortality in the placebo group (18.6%) was higher than in either the MERIT (11.0%) or CIBIS (13.2%) studies. This reflects a generally sicker group of patients in COPERNICUS with more severe heart failure. As a result, the same **relative** risk reduction has resulted in a larger **absolute** mortality benefit and a smaller number needed to treat. However, the relative risk reduction was similar between the three studies.

Unresolved issues

Severity of heart failure

Both the CIBIS and MERIT trials enrolled predominantly patients with Class III heart failure. The number of patients with more severe Class IV heart failure was small (17% and 3% respectively) and the treatment benefit was not statistically significant in this sub-group. Nevertheless, on average, the **magnitude** of benefit was not different in the patients with more severe failure. The COPERNICUS study enrolled more patients with Class IV heart failure, yet produced virtually the same relative reduction in total mortality. It must be emphasised that patients with very severe heart failure are a much more difficult group in which to start beta blockers because of the risk of exacerbating their already severe heart failure.

Co-medication

Digoxin

Approximately 50% of patients in both the CIBIS and MERIT studies were taking digoxin. Randomisation was not performed in relation to digoxin, but there was no difference between the treatment benefit from beta blockade in those taking and those not taking digoxin. Given that there is no mortality benefit from digoxin[4], it seems logical to recommend that patients in sinus rhythm should have a beta blocker added to optimal therapy before digoxin is introduced. However, this recommendation is **not** based on any definitive data.

Spironolactone

In the recently published RALES trial[5] there was a highly significant 30% reduction in total mortality when a low dose of spironolactone (25 mg daily) was added to conventional therapy in patients with very severe heart failure. Only 10% of the patients were taking beta blockers. The patients in this study had much more severe heart failure than in most of the beta blocker studies. As a result of this trial, many physicians are now including low dose spironolactone as part of 'optimal conventional therapy' in patients with very severe heart failure before introducing a beta blocker.

Antiarrhythmics

There is no consensus on the role of conventional antiarrhythmics in severe heart failure. What is clear is that the beta blocker trials have shown a clear reduction in the very substantial risk of sudden death. This is assumed to be because they prevent ventricular tachyarrhythmias. It seems logical to recommend that, in the absence of documented sustained ventricular tachycardia, beta blockers should be used **before** any consideration of antiarrhythmic drug therapy.

Recommendations

A beta blocker should be considered for all patients with systolic heart failure who are stable on optimal doses of a diuretic and ACE inhibitor. If patients are not stable on optimal treatment, then digoxin and perhaps spironolactone should be added before a beta blocker.

Which beta blocker to use?

Both carvedilol and standard beta-1 blockers appear to be effective. There are currently multiple trials in progress of carvedilol in various different groups of heart failure patients. The results should tell us if carvedilol is more effective than standard beta-1 blockers. Carvedilol has the advantage of a lower dose formulation for starting treatment. However, carvedilol is also much more expensive than standard beta blockers (up to 10 times the cost of the standard form of metoprolol).

What dose for starting therapy?

Starting a beta blocker can make heart failure worse, so low doses are used. For most patients you can cautiously start with carvedilol 3.125 mg twice a day or metoprolol 12.5 mg twice a day. Patients with very severe heart failure should probably start on only a morning dose.

How rapidly can the dose be increased?

The dose can be doubled every 2–4 weeks providing the patient is stable. If the heart failure has deteriorated, the doses of diuretic, ACE inhibitor or digoxin should be adjusted first before any further increase in beta blocker. The dose of beta blocker may need to be reduced, particularly if there is undue bradycardia or worsening cardiac conduction.

What is the target dose?

For carvedilol, the target dose is 25 mg twice a day. For metoprolol it is 100 mg twice a day. Many patients will not reach these doses. Substantial benefits are almost certainly achieved with doses which are lower than these targets.

What about patients who are already taking a beta blocker?

Some patients who have been taking beta blockers long term for other indications such as angina or hypertension will develop heart failure. The clinician must first determine why the patient has developed heart failure (for example, new atrial fibrillation, silent myocardial infarction). Both the underlying cause and the heart failure must be treated appropriately. In many patients the degree of heart failure may not be too severe, and the beta blocker will be able to be continued. In other patients it may be necessary to either reduce the dose or even withdraw the beta blocker completely until the heart failure is under control. Once this has been achieved, the beta blocker should be cautiously reintroduced.

Who should manage the patient?

These patients are extremely fragile and difficult to treat. Occasional patients will deteriorate markedly after starting a beta blocker and may even require intensive or coronary care with intravenous beta agonist support. In Australia carvedilol can only be started in hospital patients. General practitioners should always consider involving a physician or cardiologist before starting or changing beta blocker therapy.

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FURTHER READING

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Self-test questions

The following statements are either true or false (answers on page 139)

3. Patients with heart failure should be treated with an ACE inhibitor and a diuretic before starting a beta blocker.
4. Beta blockers reduce total mortality in heart failure, but do not reduce sudden deaths.

Medicinal mishaps

Allergy to an antihistamine

Prepared by Christian Hamilton-Craig and J. McNeece, Royal Adelaide Hospital, Adelaide

An 18-year-old woman took a dose of a friend's nizatidine for an upset stomach. About one hour after taking 150 mg of nizatidine she experienced shortness of breath, tachypnoea, wheezing and a mild visible swelling of the neck. On presentation to the Emergency Department she was visibly distressed. Her lung expansion was poor with diffuse coarse polyphonic inspiratory and expiratory wheezes. There was no rash. After treatment with adrenaline, promethazine and prednisolone, she improved rapidly.

We can only find two other reports of allergic reactions to nizatidine[1,2], (although cases of allergy to other H_2 histamine receptor antagonists have been published). The first report described a leukocytoclastic vasculitis associated with nizatidine. The second described a situation which was very similar to our case. In the report the patient was rechallenged with nizatidine and other H_2 antagonists. Results of the oral challenge were negative for cimetidine, ranitidine and famotidine. However, within 15 minutes of nizatadine administration the patient again experienced laryngeal oppression, dysphonia, dysphagia, dry mouth, moderate flushing and generalised pruritis.

The ability of H_2 histamine antagonists to increase serum histamine by displacing it from its receptors is well known, particularly after a rapid intravenous infusion. A similar effect would account for the appearance of anaphylactoid symptoms on some occasions. However, the second study[2] suggested an anaphylactic, rather than anaphylactoid, mechanism caused the symptoms as there was no reaction to the other H_2 antagonists.

Our case also shows the dangers of using other people's medicines.

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