

# DRUG TREATMENT OF HEART FAILURE

Allen K Brown, Consultant Physician  
Royal Lancaster Infirmary

In my early years in Lancaster I remember my senior colleague Dr W J Hay asking whether or not digoxin and diuretics remained routine treatment for congestive cardiac failure; in fact there had been little change, in that digoxin was being used less often. Recently there have been three important alterations in management. These are:-

- (1) improved diagnostic capabilities,
- (2) the introduction of new drugs, particularly ACE inhibitors, and
- (3) the reappraisal of older drugs including hydralazine, nitrates and digitalis. Finally we have seen the establishment of cardiac transplantation, various attempts at mechanical cardiac assistance and cardiomyoplasty which are outside the scope of this article but which need to be borne in mind when drugs fail.

## INVESTIGATION OF PATIENTS WITH CARDIAC FAILURE

Routine tests should include a full blood count to exclude anaemia, a profile to check renal function, hepatic function and electrolyte status; an ECG for such information as previous infarction or right or left ventricular enlargement and a chest X-ray to show pulmonary venous hypertension, cardiac enlargement and possibly to give clues to underlying pathology such as mitral valve disease. Thyroid tests are worthwhile as thyroid disease may be difficult to diagnose in patients with cardiac failure.

In hospital, all patients would have two dimensional echocardiographic examination to exclude treatable causes of failure such as aortic stenosis and pericardial effusion. In theory this should apply to all patients but because of sheer numbers (up to 5% of people over 65 years suffer from heart failure) it is necessary to look to special groups; these include all patients with murmurs and those with no obvious underlying cause. Radionuclide ejection fraction studies are being used increasingly (see later).

## DRUG MANAGEMENT

Before starting treatment it is wise to review the current drugs in case the patients are taking agents which can promote failure or make it worse. Calcium channel inhibitors and beta blockers reduce myocardial contractility and substitution by nitrates may be dramatically helpful in occasional patients. NSAIDs increase sodium and water retention and antacids with high sodium content should be replaced by a low sodium compound, e.g. Algicon instead of Gaviscon. All patients should receive advice on a low sodium intake.

### a) Diuretics

Diuretics remain the mainstay of the management of heart failure, especially loop diuretics such as frusemide and bumetanide. They are the most potent agents with an onset

of action within one hour and duration of four hours. The milder thiazide diuretics are used less in the management of cardiac failure now and tend to be reserved for mild failure in patients with hypertension.

Hypokalaemia remains a problem with diuretic therapy. Potassium salts are rarely prescribed as they are seldom of value in the doses given, particularly when combined with other diuretics. There is a choice of three potassium-sparing mild diuretics: amiloride, spironolactone and triamterene, and combinations are frequently used, e.g. amiloride with frusemide (Frumil, Lasoride), with bumetanide (Burinex A) or spironolactone with frusemide (Lasilactone). Triamterene and amiloride may cause hyponatraemia particularly in mature-onset diabetics on chlorpropamide.

There is no precise scientific information on when to use a potassium-sparing diuretic but recent advice suggests they are necessary when serum potassium is under 3.2 mmol/l, when digoxin is used, when arrhythmias are a problem and if there is renal, hepatic or a gastrointestinal tract disorder. The renin-angiotensin system comes into the equation with frusemide doses of 120mg per day and the specific aldosterone antagonist spironolactone is indicated. Potassium-sparing drugs are unnecessary and potentially hazardous in most patients on ACE inhibitors.

### b) Newer drugs and new views on older ones

#### 1. ACE Inhibitors

Angiotensin converting enzyme inhibitors are rapidly altering our management of heart failure. They are mixed venous and arteriolar vasodilators which reduce both preload and afterload via inhibition of angiotensin II formation from angiotensin I. Captopril (Acepriil, Capoten) is a short acting drug whereas enalapril (Innovace) and lisinopril (Zestril, Carace) are long acting. Although newer ACE inhibitors including quinapril and perindopril are marketed now, the major trials have used enalapril or captopril in chronic heart failure and have confirmed beneficial effects on morbidity and mortality. These trials have required considerable ingenuity on behalf of the investigators to produce suitable acronyms and the most important are:-

CONSENSUS I<sup>(1)</sup> (Co-operative North Scandinavian Enalapril Survival Study 1986). This showed that enalapril improved survival, quality of life and symptoms in patients with severe heart failure. Mortality at one year was reduced from 52% to 36%.

SOLVD<sup>(2)</sup> (Studies of left ventricular dysfunction). This trial was particularly important because it extended the use of enalapril to milder heart failure and was designed in two parts. In the "treatment" group there were 2569 patients with mild or moderate congestive cardiac

failure already treated with drugs. Enalapril up to 10mgs b.d. was added. There was a significant reduction in mortality after a mean follow-up of three and a half years and significantly fewer patients required admission to hospital for heart failure compared with a placebo group. In the "prevention" arm of the study, 4228 patients who were not on digitalis or diuretics, were randomised to placebo or enalapril. They were included on the basis of an ejection fraction under 35%. There was a statistically insignificant reduction in mortality but a dramatic improvement in morbidity; this included a 39% reduction in congestive cardiac failure in the treated group over five years, and a reduction in hospital admissions. Both treatment and preventive arms of SOLVD showed a highly significant reduction in ischaemic events such as acute myocardial infarction, unstable angina and sudden cardiac death. There is an exciting suggestion that enalapril may produce structural improvement in the heart because reduction in left ventricular dilatation persisted even after the drug was discontinued.

Captopril has been less well investigated in chronic heart failure but two recent studies, although less well organised or with fewer patients, have suggested similar benefit to the enalapril trials<sup>(3)(4)</sup>.

## 2. Other vasodilators

Nitrates are venodilators and reduce preload and also act as coronary vasodilators in ischaemic heart disease. They have been used with hydralazine, which is an arteriolar dilator and reduces afterload.

### V-HeFT I and II<sup>(5,6)</sup> (Vasodilator – Heart Failure Trial)

V-HeFT I, in which patients received hydralazine and isosorbide dinitrate, was the first trial to give convincing evidence of improved mortality in heart failure. In the second V-HeFT trial enalapril was compared with the hydralazine and isosorbide dinitrate combination. Mortality over a two year period was reduced from 34% with placebo to 25% with the combined drugs and to 18% with enalapril, confirming the superiority of the ACE inhibitor. There was a better exercise performance in patients with hydralazine and isosorbide, and ejection fraction and cardiac size improved but side effects unfortunately caused poor tolerance because of headache 18%, fatigue 19% and dizziness 7%.

### Hy C Trial

This study compared captopril and isosorbide dinitrate with hydralazine and captopril in patients with severe failure being evaluated for transplantation. Survival at one year was 81% in the captopril – isosorbide group and 51% in the hydralazine – captopril group.

## 3. Digitalis

The digitalis story goes on forever; most of the trials in patients with sinus rhythm have been poor, but an overview suggests that digitalis gives improved symptoms, morbidity and effort tolerance. The RADIANCE study which was reported at the American College meeting in spring 1992, shows highly significant increases in heart failure problems when digoxin is withdrawn in patients stabilised on digoxin, diuretics and ACE inhibitors. In general therefore it seems that digitalis has a part to play in the management of congestive cardiac failure with patients in sinus rhythm and it is the only

acceptable oral positive inotrope (i.e it improves myocardial contractility).

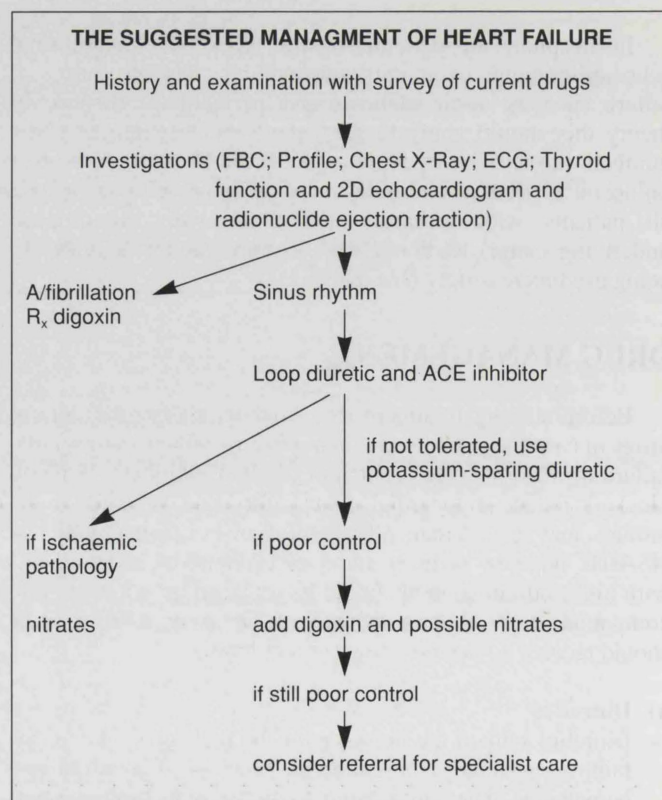
## 4. Phosphodiesterase inhibitors (P.D.E.)

In 1978 PDE inhibitors were presented as the successors to digoxin but invariably subsequent investigations have been disappointing. In contrast to the ACE inhibitor trials, the largest trial of a PDE inhibitor, the Milrinone Survival Evaluation Trial had to be stopped because of a significantly increased mortality in patients treated with milrinone; the only use of this class of drugs appears to be in the short term while patients are waiting transplantation when enoximone seems to be of some value.

## A STRATEGY FOR THE MANAGEMENT OF HEART FAILURE

After a careful history and examination to find an underlying cause and to identify drugs which may exacerbate cardiac insufficiency, routine investigations, preferably with echocardiography, are performed (see Table). The predominant question is when to introduce ACE inhibitors. In a leading article in the Lancet<sup>(7)</sup> comments were made about the reluctance of non-cardiologists to use ACE inhibitors because of worries about hypotension and renal dysfunction. The effectiveness and safety of the drugs in the major trials should dispel these worries and the leader goes on to state categorically that "to prescribe a diuretic and delay an ACE inhibitor is insupportable". Nevertheless hypotension and renal insufficiency are relative contraindications to the use of these drugs and they should be avoided if the creatinine level is over 300mgs/l. Intractable cough remains the most frequent reason for withdrawal of the drugs.

Frusemide 40mgs or bumetanide 1mg are usually prescribed and after a short period of stabilisation, enalapril 2.5mgs, increasing if tolerated to 10mgs b.d is introduced. It is recommended that the first dose of enalapril is given under clinical supervision because of the rare dramatic hypotension. This is usually done in hospital because the blood pressure



needs checking over several hours but as ACE inhibitors are used more extensively in the treatment of mild failure, it is likely that this procedure will be reviewed soon.

If ACE inhibitors are not tolerated, potassium-sparing diuretics often combined with a loop diuretic are acceptable. Spironolactone is best reserved for those patients requiring 120 mg frusemide or greater, and amiloride is the most widely prescribed drug. Digoxin should also be considered at this stage.

Two other aspects require discussion:-

**1. Arrhythmias:** sudden cardiac death, presumably arrhythmogenic, is responsible for up to half of all deaths in heart failure. Diuretic-induced potassium depletion must be avoided by regular electrolyte monitoring e.g. every 3-6 months and potassium-sparing diuretics should be used whenever ACE inhibitors are not tolerated or are otherwise unsuitable. Drugs such as quinidine, flecainide and propafenone are all strongly pro-arrhythmic and should be avoided. If an antiarrhythmic agent is essential then amiodarone is the most useful despite its side effect problems. It tends to be most successful in patients with cardiomyopathy rather than in cardiac failure secondary to ischaemic heart disease, and patients with an ejection fraction below 30% seem to benefit least. The decision to start amiodarone should be made by a specialist who is familiar with the problems associated with this "difficult" drug.

## **2. Resistant cardiac failure**

The management of patients who are resistant to routine therapy is usually best initiated in hospital, not least because of the potential for drastic electrolyte disturbances when large amounts of diuretic are used. Again it must be emphasised that a careful history should be taken to identify and then withdraw drug treatment such as NSAIDs, carbenoxolone, beta blockers and calcium channel inhibitors. The diet should be checked for sodium content and daily weighings possibly plus fluid balance monitoring are used to check the efficiency of fluid withdrawal.

The drugs should be checked so that optimal dosage is obtained, e.g. enalapril at 10mg b.d. The dose of diuretic is usually increased steadily but at 120 mgs frusemide (3mgs bumetanide), the addition of nitrates and possibly hydralazine should be considered, particularly if ACE inhibitors cannot be used. Nitrates are introduced earlier if there is a clear ischaemic aetiology and digitalis is indicated if atrial fibrillation is present. In patients with sinus rhythm, digitalis is still probably indicated as the only oral positive inotrope and should be introduced as a third line drug after a loop diuretic and an ACE inhibitor.

Most of the patients seen in a cardiac clinic or on the wards have been on large doses of loop diuretics. It may be necessary to use huge dosage eg. 500mg frusemide but whenever this is considered there are two alternatives to be tried. First, the addition of metolazone, a thiazide type of diuretic, which usually gives a massive diuresis when used with a loop diuretic. The main problem is renal and electrolyte deterioration and the electrolytes, urea and creatinine are measured daily. Once a stable condition is reached the minimal dose of metolazone is achieved by daily weighing and the drug is given only when the weight goes up by 2lbs. The second alternative is to use frusemide intravenously because there is evidence of poor alimentary absorption of the drug in severe fluid retention and 80mgs i.v., repeated as necessary can produce a good diuresis

when large doses orally have failed. The hospital management of these resistant cases is a time-consuming and expensive process, and extension of life span may not be associated with good quality of life. In the patient under 55 years serious consideration should be given to transplantation, the indications for which are beyond the scope of this article.

## **3. Post myocardial infarction**

In this special group of patients the same principles apply in the management of heart failure and many patients receive ACE inhibitors although hypotension excludes a substantial minority. Use of these drugs early after the infarct is controversial: a trial of intravenous enalapril was stopped because of lack of benefit but the results of the SAVE (Survival and Ventricular Enlargement) trial were reported at a recent meeting in the U.S.A. and suggested that captopril given 5-16 days post infarct reduced all mortality, recurrent infarction, hospitalisation and the benefits apply regardless of associated therapy. These patients were not in overt failure but had reduced ejection fractions and this raises the likelihood of a considerable increase in the use of ACE inhibitors in post MI patients with clear failure and also those with reduced left ventricular function without clinical failure.

## **CONCLUSION**

The drug management of cardiac failure has changed dramatically since the introduction of ACE inhibitors but loop diuretics still have the key role and digoxin remains the main positive inotrope with a lesser but definite value. Nitrates are particularly useful in ischaemic patients and drugs such as the potassium-retaining diuretics, hydralazine and metolazone are valuable in individual patients. The main areas of current debate are in the use of ACE inhibitors in the early stages of cardiac failure and the exciting possibility of using these drugs in patients with acute myocardial infarction to reduce morbidity and mortality.

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