DRUG THERAPHY FOR NEUROHUMORAL ABNORMALITIES IN CHF

Ilodigwe E. E.
Dept Of Clinical Pharmacy & Biophamacy,
School of Pharmacy, College of Medicine, University of Lagos, Lagos.

SUMMARY

Congestive heart failure (CHF) is on the increase in Nigeria (though there is lack of accurarte epidemiological data) and mortality and morbidity rates are high. Approaches to treatment of CHF have been largely based on correcting hemodynamic abnormilities. The current understanding is that CHF results from left ventricular dysfunction which leads to complex activation of neurohumoral reflexes. This paper discusses current approaches and highlights the importance of prevention and control of CHF especially for first gear economies.

INTRODUCTION

CHF is a progressive syndrome resulting from the heart's inability to adequately perfuse and oxygenate peripheral tissues. This syndrome is manifested by symptoms of fatigue, dyspnea and congestion.

In the United States, the annual mortality rate is high ranging from 10% to 15% for patients with New York Heart Association (NYHA) funtional classes I and II (Table I), to 50% for the sickest patients (NYHA class IV). In Nigeria, comparable data is unavailable. It has become increasingly apparent that the view of heart failure as primarily a hemodynamic disorder is incomplete. Heart failure also results in wide spread neurohumoral activation.

Left ventricular dysfunction results in decreased cardiac output and a reduction in systemic blood pressure. Arterial underfilling activates baroreceptores in the left ventricle, aortic arch, and carotid sinus, which then stimulates the vasomotor regulatory centres in the medulla. The result is activation of the syumpathetic nervous system, the renin-angiotensinaldosterone system, and the arginine-vasopressin system, which leads to increased heart rate, myocardial contractility, peripheral vasoconstriction, and sodium and water retention. Natriuretic peptides, which promote sodium excretion and diuresis, are secreted from the atria and ventricles in response to volume overload and increasing intramyocardial pressure. Initially, these compensatory mechanisms maintain cardiac output and blood pressure. Ultimately, however, these mechanisms increase preload, afterload and myocardial work.

Increase in left ventricular end-diastolic pressure and left ventricular wall stress leads to further reduction in cardiac output, further volume retention and, eventually, pulmonary congestion. This downward spiral can develop acutely or chronically, depending on the balance of these factors.

Neurohumoral activation is the cardinal pathophysiologic condition responsible for progression of heart failure. This paper reviews therapies targeted at neurohumoral abnormalities in CHF.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

Patients treated with angiotensin-converting enzyme (ACE) inhibitors in several large multicentre trials show significant survival benefits (Table 2). The enzyme renin is released by the kidney when renal perfusion pressure is decreased. Renin acts to convert angiotensinogen present in the blood into angiotensin I which is further metabolized to angiotensin II under the influence of angiotensin converting enzyme (ACE).

Angiotensin II is a potent vasoconstrictor and also stimulates aldosterone release by the adrenals. It also may directly stimulate norepinephrine release. ACE inhibitors prevent (inhibit) the conversion of angiotensin I to angiotensin II, leading to favourable hemodynamic effects of peripheral vasodilatation, reduced after load, and decreased blood pressure.

Angiotensin II (a potent myogenic agent) blood level reduction may attenuate abnormal left ventricular remodelling; and subsequent reduction in aldosterone

decreases sodium and fluid retention.

ACE inhibitors also cause down-regulation of sympathetic nervous system and improve baroreceptor function. The ACE also degrades bradykinin and other vasodilatory substances. Thus the beneficial effects of these drugs may be partially related to the accumulation of vasodilatory kinins or prostaglandins.

Captopril is the prototype of ACE inhibitors and its arterial vasodilatory effect is relatively selective for the renal vasculature, resulting in increased blood flow and no adverse effects on the glomerular, filtration rate. This effect coupled with its indirect inhibition of aldosterone lead to mild diuretic response, a distinct benefit over other vasodilator compounds such as hydralazine and prazosin.

Other ACE inhibitors include benazepril, enalapril, lisinopril, quinapril and ramipril. Lisinopril (the lysine derivative of enalaprilat) and captopril are active as parent compounds while the other ACE inhibitors are prodrugs that require enzymatic conversion by esterolytic enzymes to active metabolites e.g. (benazeprilat, enalaprilat, ramiprilat (3).

There is no apparent clinical consequence of these differences other than a slightly delayed onset of effet with the first dose (two to six hours for capropril, four to twelve hours for the others). The newer ACE inhibitors have longer half-lives compared to captopril, offering the theoretical advantage of once or twice daily dosing.

Despite the proven survival benefit of ACE inhibitors in patients with heart failure, many eligible patients either do not receive this therapy or take doses lower than those of proven benefits in large clinical trials. The recently published Assessment of Treatment with lisinopril and survival (atlas) trial(4) was designed to define the optimal dosing of ACE inhibitors. In this trial, 3,164 patients with NYHA class II, III or IV heart failure and an ejection fraction of 30% or less were assigned to receive wither a low dose 2.5 to 5mg/day or a high dose (32.5 to 35mg/day) of Lisinopril for $3^{1/2}$ to 5 years. Both treatment groups experienced similar improvements in symptoms and functional class. But those who received the high dose had a 12% lower relative risk of death or hospitalization and 24% fewer hospitalizations for heart failure. Although the ATLAS trial did not include a central group, patients who received a low dose had considerable survival benefit compared to placebo groups from previous large trials focused on ACE inhibitors. Results of the ATLAS study suggest that physicians should have a high target dose for ACE inhibitor therapy independent of symptomatic relief or hemodynamic effect (2). Low-dose ACE-inhibitor therapy should be used if high doses are not tolerated because of hypotension, renal insufficiency, or hyperkalaemia.

One theoretical advantage of the newer ACE inhibitors over Captopril is the lack of a sulfhydryl group as part of their clinical structures. The sulfhydryl group (also found in penicillamine) is associated with a high incidence of rashes, ageusia (transient loss of taste), proteinuria and neutropenia (3). The clinical significance of this difference remains to be determined, especially because captopril side effects have declined since clinicians have begun to use lower doses. Benazepril, enalapril, fosinopril and lisinopril usually are well tolerated except for chronic cough, occasional gastrointestinal upset or vasodilator induced headache, flushing and vertigo. Cough may be more common with enalapril than with captopril and least common with fosinopril.

ANGIOTENSIN II RECEPTOR BLOCKERS (ARBS)

Angiotensin II receptor blockers (ARBs) do not inhibit breakdown of the vasodilator bradykinin but can block angiotensin II from all pathways at the receptor level. They have similar haemodynamic effects to ACE inhibitor and do not produce a cough.

AT_1 receptor produces vasoconstriction and induces the muscle cell proliferation when activated, the AT_2 receptor produces anti-proliferative effects upon activation. Currently available ARBs (e.g. losartan and valsartan) selectively block the AT_1 receptor, producing vasodilation and

inhibiting muscle cell proliferation. Selective stimulation of AT_2 receptors may contribute to attenuation of abnormal ventricular remodelling.

Recent trials in elderly patients with heart failure - ELITE (5, 6) has shown that Losartan has a beneficial effect on functional class and the combined end-point of death and/or progressive heart failure. Also the Valsartan Heart Trial (Val-HeFT)7 has suggested that there may be a role for combination therapy with valsartan and ACE inhibitors in patients who cannot tolerate blockers.

BETA BLOCKERS

One of the copensatory mechanisms of a failing heart is the activation of the sypathetic nervous system. Adrenergic activity is increased in an attempt to maintain cardiac performance (8, 9). This compensatory mechanism may improve contractility and provide hemodynamic support. However, as heart failure progresses this mechanism is overwhelmed and becomes pathphysiological. Chronic adrenergic stimulation can cause myocardial damage due to changes in left ventricular remodelling, loss of cardial cells and abnormal gene expression (10).

Three adrenergic receptors ($beta_1$, $beta_2$, $alpha_1$) are present in human cardiac myocytes, and each is associated with a unique biological response (Table 3). A continuously increased adrenergic drive in congestive heart failure patients delivers adverse biologic signals to the cardiac myocytes via $beta_1$ and possibly through $beta_2$ and alpha adrenergic receptors (11).

The fundamental basis for treatment with beta-adrenergic antagonists is to halt the increased drive and to the adverse effects of chronic adrenergic stimulation.

Currently, three classes of beta-blockers are known. The first class consists of non-selective beta blockers and includes such drugs as propranolol and timolol. The second class consists of selective blockers of $beta_1$ receptor subtypes and includes metoprolol. The third class consists of non-selective beta-blockers and $alpha_1$ blockers. They include labetolol, carvedilol and bucindolol.

Bucindolol and carvedilol produce less "inverse agonism" than most other beta blockers (12). Inverse agonism is the ability of a beta blocker to inactivate active state receptors. The beta blockers with the most inverse agonism, like propranolol, produce the greatest negative chronotropic and inotropic effects. Thus, bucindolol and carvedilol produce relatively fewer negative chronitropic and inotropic effects when compared with beta blockers like propranolol.

Until recently, beta blockers were contraindicated in left ventricular systolic dysfunction because of negative inotropic effects. It is now evident that beta blockers improve left ventricular function, improve symptoms and functional class, and prolong survival in patients with CHF due to left ventricular systolic dysfunction(12). Large randomized trials involving more than 10,000 patients most of whom had stable NYHA class II or III heart failure, have demonstrated significant reduction in all cause mortality rate on treatment with various beta blockers (Table 4).

When each beta-blocker is viewed independently, there seems to be quite a bit of difference. Metaprolol and bisoprolol reduce all-cause mortality by about the same amount - 34%. Carvedilol gave a 65% reduction. Bucindolol only lowered all-cause mortality by 9%. Carvedilol has many actions besides beta receptor blocking. It is a vasodilator, anti oxidant, and has some anti-endothelin effect. It is unclear why bucindolol did not give benefits as great as the other tested beta-blockers.

Only patients with major contraindications should be excluded from beta-blocker treatment for CHF (Table 5). Contraindications exclude signs of clinically unstable heart failure. Such patients are usually critically dependent on the adrenergic drive, and beta blockade may worsen symptoms of heart failure.

Relative contraindications include chronic obstructive pulmonary

disease, asthma sensitive to beta agonists, significant bradycardcia (<60 beats per minute), second-or third-degree heart block, or hypotension (<100mmHg systolic).

If a patient is considered a suitable candidate for therapy, careful initiation and gradual increases in beta-blocker dose are crucial to avoid clinical deterioration (13). Patients should first be stable on standard therapy for CHF, including ACE inhibitors, diuretics, and digoxin. A beta- is then added at low starting dose that is gradually increased until the maintenance levels derived from the mortality trials are achieved. The increase in dose should generally occur at 2-3 week intervals, and patients should undergo revaluation before any adjustments are made.

Carvedilol therapy is usually started at 3.125mg twice daily for 2 weeks. The dose is doubled at 2-week intervals until the target level is achieved. 2mg twice daily for patients who weigh less than 85kg and 50mg twice daily for patients who weigh 85kg or more. Bisoprolol is started at 1.25mg once daily, and the dose is increased by 1.25mg every 1-2 weeks to a target dose of 10mg once daily. Metoprolol controlled release (extended release) is usually started at 25mg once daily, and the dose is doubled at 2-week intervals until a goal of 200mg once daily is reached. For patients with relatively severe symptoms (NYHA) class III or IV), a starting dose of 12.5mg once daily may be appropricte.

Patients should be told that improvement in symptoms may take several months and that they may notice signs of fatigue during the first few weeks of therapy. This is due to drop in sympathetic drive.

When symptoms do not improve, patients should be reminded that treatment can reduce the risk of progression of disease and improve long-term survival even when symptoms are present.

ALDOSTERONE ANTAGONISTS

Patients with heart failure have plasma aldosterone levels that are 20 times higher than normal, owing to increased activation of the renin-angiotensinaldosterone system from decreased effective renal perfusion and decreased hepatic clearance (14).

Aldosterone has multiple effects that promote progression of heart failure, including sodium retention, sympathetic activation, parasympathetic inhibition, baroreceptor dysfunction, and myocardial and vasclar fibrosis. Until recently, aldosterone antagonists have not been widely used in heart failure because of their weak diuretic activity, concerns about hyperkalemia, and the assumption that ACE inhibitors would sufficiently block aldosterone production and negate its neurohormonal effects. Recent evidence that aldosterone levels may be only transiently suppressed with ACE inhibitor therapy has spawned new interest in aldosterone antagonists.

A recent study, the Randomized Aldactone Evaluation Study - RALES(15) has demonstrated that spironolactone therapy in patients with NYHA class III or IV heart failure who were already being treated with ACE inhibitor lead to significant reduction in risk of death, slowed progression of heart failure and improvement in functional class. Currently spironolactone therapy is considered in patients with severe symptomatic heart failure in the absence of significant renal insufficiency or hyperkalaemia.

OTHER NEWER NEUROHORMONAL AGENTS

(a) Endothelin Antagonists.

The endothelium has a central role in the regulation of vasomotor tone. In patients with heart failure, endothelium-dependent vasodilation in peripheral blood vessels is impaired and may be the mechanism of exercise limitation (16). The cause of abnormal endothelial responsiveness is complex but relates to abnormal release of both nitric oxide and vasoconstrictor substances, such as endothelin. Preliminary data indicate that the major sources of circulating endothelin in heart failure is the pulmonary vascular bed.

Endothelin has many actions that potentially contribute to the pathophysiology of heart failure: vasoconstriction, sympathetic stimulation, renin-

angiotensin system activation and left ventricular hypertrophy Bosentan, endothelin antagonist has been shown in animal models to prevent the progression of left Ventricular dysfuntion and in preliminary human studies has demonstrated favourable hemodynamic effect. However, large studies are needed to establish a role for these agents.

(b) Vasopeptidase Inhibitors

A trial natriuretic peptide (ANP) is released from atrial myocytes in response to stretch. ANP induces diuresis, natriuresis, vasodilation and suppression of the renin-angiotensin system. Levels of circulating ANP are increased in congestive cardiac failure and correlate with functional class, prognosis and haemodynamic state (16). Vasopeptidase inhibitors inhibit both ACE and neutral endopeptidase, an enzyme that metabolizes ANP. This results to an increased circulating ANP and vasodilatory peptides such as bradykinin.

Omapatrilat, a vasopeptidase inhibitor has been shown to improve exercise tolerance and may reduce hospitalizations and death from worsening CHF. These drugs might have a therapeutic role in the future.

Brain Natriuretic Peptide (BNP)

Brain natriuretic peptide is synthesized in the ventricles and is elevated early on in patients with left ventricular dysfunction. It has effects similar to ANP. Nesiritide (a recombinent human BNP) has been shown to be effective in CHF in a recent study.

Table 1 New York Heart Association Funtional Classificcation

Functional class	Limitation of physical activity
Class 1	No limitation of activity Ordinary activity dose not cause undue fatigue, palpitation, dyspnea.
Class II	Slight limitations of physical activity Patient is comfortable at rest. Ordinary activity results in fatigue, Palpitation, dyspnea or anginal pains.
Class III	Marked limitation of physical activity Patient is comfortable at rest, but less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
Class IV	Inability to carry out physical activity without discomfort. Symptoms of congestive heart failure may be present, even at rest. Increased discomfort with any physical activity.

Table 2: Mortality Benefits of ACE Ihhibitors in Major Trials.

Trial Name	Study Group	Drugs	All Cause Mortality Reduction
CONSENSUS	253 Patients with NYHA Class IV CHF	Enalapril Vs, Placebo	27%
SOLVD	2,569 Patient with Class II,III or IV CHF	Enalapril vs, Placebo	16%
V-HeFT II	804 Patients with Class II, III, or IV CHF	Enalapril Vs. Hydralizine HCL phu isosorbide dinitrate	28% with Enalapril

Table 3: Biological Response Mediate By Adrenergic Receptors in the Human Heart.

Biological Response	Adrenergic Receptor
Cardial myocyte growth	beta, $beta_2$ alpha
Positive inotropic response	beta, $beta_2$, alpha, (minimal)
Positive chronotropic response	beta, $beta_2$
Myocyte toxicity	beta, $beta_2$ (?$beta_2$,<beta)
Mycocyte apoptosis	$beta_1$

Table 4: Selected Mortality trials with beta receptor antagonists in patients with chronic heart failure.

Trials (date length of folow-up)	No of patients enrolled	NYHA Class II/III/IV symptoms (% per group)	Ejection fraction	Mortality reduction (95%C.I)	Agent and targer dose
US carvedilol Heart failure study (1996 6.5mo)	1,094	53/44/3	23%	65% (39%-80%)	Carvedilol, 25-50mg bid
CIBIS-II (1999, 1.3YR)	2,647	0/83/17	28%	34% (19%-46%)	Bisoprolol 10mg qd.
MERIF-HF 1999,1.0yr)	3,991	41/55/4	28%	34% 19%-47%)	Metroprolol CR/XL 200mg qd

CI = Confidence interval
CIBIS = Cardiac Insufficiency Bisoprolol study II
MERIT - HF = Metoprolol CR/XL Randomized intervention Trial in Congestive Heart failure.

Major and Relative Contraindications to beta-blocker Therapy for Congestive Heart Failure

-Signs of clinically unstable heart failure in the previous 2 weeks.
-Increase in body weight
-Increase in diuretic dose
-Need for intravenous therapywith diuretic or inotropic agents
-Need for hospitalization for cardiac symptoms
-Presence of episodic worsening of heart failure symptoms
-Bronchial asthma or emphysema sensitive to beta agents
-Brady cardia (heart rate<60 beats per minute
-Hypotension (systolic blood pressure<100 mmHg)
-Second or third degree heart block

PREVENTION AND CONTROL OF CHF

Many less developed countries including Nigeria have "first-gear" economies; health infrastructure is over burdened and socio-economic conditions are abysmally poor. Unfortunately, near-epidemics of cardiovascular diseases including heart failure are already occurring in these countries already grappling with the burden of persistent infection, malnutrition, cancer and threat of AIDS. As a result, the available scarce resources are widely dispersed. Therefore primary prevention and control of heart failure should be the policy thrust in these countries and the pharmacist is well positioned to participate.

Education strategy that targets all sections of the community and all ages is an appropriate preventive approach and should aim at altering the norms of behaviour within the population and removing the underlying causes of heart failure. Individuals should be encouraged to adapt healthy life style by keeping a normal body weight, cessation of tobacco smoking, eating less salt, consuming less alcohol and increasing physical activity. Industries, restaurants and shops should be educated on the importance of providing healthier foods.

The success of this approach depends on the sustenance of collaborative efforts between health professionals, policy makers, industry, media, and other opinion formers.

The control of heart failure should involve two complimentary approaches: the

population(public health) approach and the individual (clinical approach). The goals of the population approach are to increase awareness about HF and its consequences, detect HF individuals and promote life style measures which minimize controllable risk factors of HF.

Achievement of these goals depends on proper education of the public health professionals and patients with HF.

Public education may entail informing the community about the nature, causes and complications of HF, the life style measures useful in its management and the contributory role of other cardiovascular risk factors. Health professionals including the pharmacist should be better trained to detect, manage and prevent HF. For instance the easy accessibility of the pharmacist to the population positions him for early detection of HF if well trained in recognizing the symptoms and probably signs associated with different functional classes of HF.

Patients should be educated about his condition and its consequences, the need for effective managemnt and the benefits of life style changes. He must be educated on the importance of compliance to health care advice and the need for regular monitoring and periodic visit to the physician or pharmacists to discuss the effects of therapy. The informed participation of family members should be enlisted. The messages and effective methods of delivery especially for public and patient education must consider cultural, economic, environmental and geographical differences. The message must be simple and repeated. Radio, television, publications, community centres and religious centres could be used for information delivery.

The individual approach essentially involves educating people with established HF on the need for life style modification as an adjunct to drug theray and compliance. The succesful management of HF should not be based only on improving the functional class of the patient and improving the quality of life but also by the appropriateness of the resources used.

The cost-effectiveness of HF management must be optimal for the patient. In Nigeria, access to healthcare is constrained by economic factors. Strategies must therefore be simple with emphasis on efficacy, safety, and cost as guided by the essential drugs list (EDL)

A major component of costs in the management of HF is the financial cost of visits to the physician. The community pharmacist if empowered educationally and financially could reduce this cost as he is readily accessible to the patient. He can also ensure compliance and proper storage of the medications through frequent visits and montoring.

CONCLUSION

CHF is a progressive syndrome with significant morbidity and mortality rates. It has been established that multiple neurohormonal reflexes are activated as a result of left ventricular systolic dysfunction. Initially these physiological changes are compensatory but as HF progresses, these mechinisms are overwhelmed and become pathophysiologic. Contemporary therepy is aimed at correcting the deliterious effects of the neurohormones. In Nigeria access to health contemporary therapy is aimed at correcting the deliterious effects of the neurohormones. In Nigeria access to health care is constrianed by economic factors and drug costs is a factor in determining benefits from these drugs. Options open for us are health policy measures that emphasize prevention and control and cost-benefit measures that emphasize efficiency in resource use and expense.

REFERENCES

1. Parmley, W. W. (1996). Cost-effective management of heart failure. Clin. Cardiol; 19:240-2.
2. Parker RW and Mlen SA (2001). Slowing the progression of CHF. Postgraduate Medicine 104(3): 36-45.
3. Lloye YY and Koda-Kimble MA (1995). Applied Therapeutics. Applied Therapeutics Inc. USA.
4. Packer M, Armstron PW; Poole Wilson PA, et al (1999). Comparative effects of low and high doses of the angiotensin-converting enzyme inhibitor, lisinopril, on morbility and mortality in chronic heart failure. ATLAS Study Group. Circulation 100(23): 2312-8.
5. Pit B, Segal R; Martinez FA, et al (1997): Randomized trial of Losartan versus captopril in patients over 65 with heart failure (Evaluation of Losartan in the elderly study, ELITE). Lancet 349(9045): 747-52.
6. Pit B; Poole-WilsonP; Segal R, et al (1999). Effects of Losartan versus Captopril on mortality in patients with symptomatic heart failure, rationale, design and baseline characteristics of patients in the Losartan Heart failure survival study-Elite II. J. Card. Fail. 5(2): 146 - 54.
7. Cohn JN, Tognoni G for the Val-HefT investigators (2000): The effect of the angiotensin receptor blocker valsartan on morbidity and mortality in heart failure: The valsartan heart failure trial (Val HefT) - presented at a meeting of the American Heart Association 73rd Scientific Session, New Orleans.
8. Packer M. (1992): The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am. Coll. Cardiol 20(1): 248 -n54.
9. Eichhorn EJ; Bristow MR. (1946): Medical therapy can improve the biological properties of the chronically failing heart: a new era in the treatment of heart failure. Circulation 94(9): 2285 - 96.
10. Metra M; Nodari S; D'Aloia A, et al (2000): rationale for the use of beta-blockers as standard treatment for heart failure. Am. Heart. J. 139(3): 511 - 21.
11. Bristow MR. (2000): Beta-adrenergic receptor blockade in chronic heart failure. Circulation 101(5): 558 - 69.
12. Bruce TV, Heather MR; Peter BA (1998): Carvedilol: The new role of beta blockers in congestive heart failure. J. AFP.
13. Ravi KG; Mathew JS (2001): Beta blockers for CHF. J. Postgraduate Medicine 190(3): 49 - 56.
14. Fornarow GC (2000): Heart failure: recent advances in prevention and treatment. Rev. Cardiovasc. Med. 1(1): 25 - 33, 54.
15. Pit B; Zannad F; Remme WJ, et al (1999): The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone evaluation study. Investigators N. Eng. J. Med. 341(10): 709 - 17.
16. Parveen K, and Michael C. (2001): Clonical Medicine. Harcourt Publishers, London.
17. Colucci WS: Elkayam U; Horton DP, et al (2000): Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesiritide Study Group. N. Engl. J. Med. 343(4): 246 - 53.