Chapter 10. Agents for the Treatment of Heart Failure

Simon F. Campbell and John C. Danilewicz

Pfizer Central Research, Sandwich, Kent, England

Introduction - Heart failure exists when cardiac function is compromised to a point that the needs of peripheral organs are not satisfied. Wagner and Cohn[1] offer the following classification:- systolic failure, in which the left ventricle fails to contract adequately, diastolic failure, in which the left ventricle fails to relax sufficiently and overload of the heart, which includes volume overload states. Burch[2] points out that cardiac failure should not be viewed solely as a low output state and stresses the importance of an appropriate balance between right and left heart function. This interesting view has been the subject of very recent comment.[3]

Drugs used for treating heart failure are primarily the cardiac glycosides and diuretics. The cardiac glycosides are positive inotropic agents, i.e. increase the force of myocardial contraction, though their effect on cardiac rhythm may also be important. Diuretics relieve symptoms of congestion by reducing plasma volume but are not considered in this review. Recently, attention has been turning to the response of the peripheral vasculature to the failing heart and vasodilators are being increasingly investigated. A number of new inotropic agents also appear to be in various stages of development. This review is primarily concerned with developments over the last two years.

Cardiac Glycosides - The side effects of cardiac glycosides are well recognised[4] though in a prospective study involving 649 patients on maintenance therapy with digitoxin, a low incidence (5.8%) was found.[5] This was ascribed to careful usage of the glycoside. Cardiac glycosides are particularly effective in cases where cardiac rhythm is accelerated.[6] Indeed, their use in failure accompanied by normal sinus rhythm has been questioned.[6-9]

Currently there is a debate of considerable interest on the mechanism of action of cardiac glycosides. One view is that the positive inotropic activity of these agents is due to the inhibition of myocardial cell membrane Na^+-K^+ transport ATPase (Na^+-pump). The function of this system is to exchange intracellular Na^+ for extracellular K^+, which is achieved in a ratio of approximately 3:2. The trans-membrane ion fluxes involved in the excitation-contraction process are complex and have been recently discussed.[10,11] Considering only Na^+, the process is visualised to function as follows: (a) Na^+ rapidly enters the cell on excitation, (b) increasing intracellular $[Na^+]$ progressively activates the pump to the point when Na^+ extrusion balances entry and peak $[Na^+]$ is achieved, (c) the pump, by then fully activated, coupled with reduced passive membrane permeability to Na^+, repolarises the cell by returning $[Na^+]$ to resting levels. The

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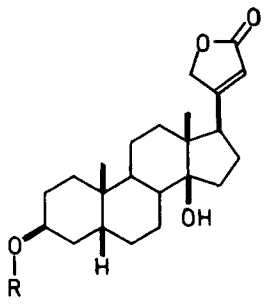
temporary increase in intracellular [Na^+] is termed the "Na^+ transient". Pump inhibition will allow Na^+ entry to persist at a higher rate, reach a greater maximum concentration and reduce its rate of extrusion from the cell. The Na^+ transient is thus increased, resulting in a greater mobilisation of Ca^{++}, which controls contraction.[12,13] With only partial inhibition, it is not necessary to invoke net Na^+ accumulation at therapeutic doses of cardiac glycosides. However, as doses increase, the pump will be inhibited to a degree that the extrusion of Na^+ will be incomplete before the beginning of the next depolarisation cycle. This results in progressive Na^+ accumulation and eventually to myocardial intoxication. Toxicity and therapeutic effect are seen therefore to depend on the same biochemical mechanism and this poses considerable problems when searching for agents of this class with a greater margin of safety.

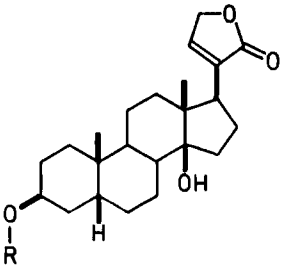
The alternative view is that the positive inotropic activity of the cardiac glycosides can be achieved independently of Na^+-pump inhibition. In cardiac tissue exposed to ouabain, the inotropic effect disappears in minutes after wash-out whilst cardiac toxicity persists for several hours.[14,15] In isolated guinea-pig atria, starting with low doses (10^{-9}-10^{-8}M) of ouabain, inotropism is associated with stimulation of the Na^+-pump. Concentrations above this range cause further increases in systolic tension but with pump inhibition.[16] Furthermore, in the same tissue there are high and low affinity ouabain-specific binding sites linked to pump stimulation and inhibition respectively.[17] Positive inotropic activity has been demonstrated with ouabain *in vivo* in the dog without pump inhibition;[18] whilst measurement of myocardial K^+ content during the development of digoxin positive inotropism suggests pump stimulation.[19] How pump stimulation results in a greater mobilisation of Ca^{++} remains to be explained but the demonstration that an inotropic effect is possible without pump inhibition, which is known to be associated with toxicity, should give encouragement for a more vigorous search for safer agents.[20]

A complicating factor in the interpretation of the mode of action of the cardiac glycosides *in vivo* is that they have neuroexcitatory activity. A significant vagomimetic action has been demonstrated at therapeutic doses[21-23] and this probably accounts for their effectiveness in atrial flutter and fibrillation.[24] Additionally, sympathetic nerve stimulation has been shown to coincide with the onset of arrhythmia in animals.[25] One group conclude that the primary site of action is within the peripheral nervous system,[26] whilst another find it to be central in origin.[25] Reserpine, guanethidine and β-blockers[27] as well as clonidine[25] protect against cardiac glycoside-induced arrhythmias in animals, thus implicating the involvement of the sympathetic nervous system. It has been suggested therefore that a cardiac glycoside which does not enter the brain may have a safety advantage.[24]

Cardiac Glycoside Analogues - An aminosugar cardiac glycoside , ASI-222 (1) produced a greater maximum increase in contractile force than ouabain and digoxin in the dog with a more rapid onset of activity, greater potency and less evidence of toxicity.[28-30] A study including a close analogue, ASI-254 (2), showed that the greater therapeutic index of these compounds is not



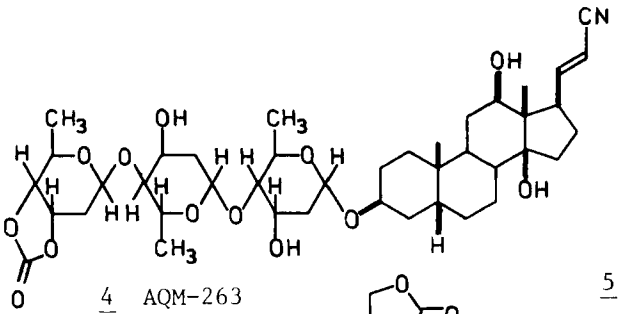
1 ASI-222, R=4-amino-4,6-dideoxy-β-D-galactopyranosyl.



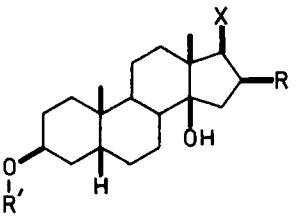
3 AY-22,241 R=β-D-glucopyranosyl.

2 ASI-254, R=4-amino-4,6-dideoxy-β-D-glucopyranosyl.

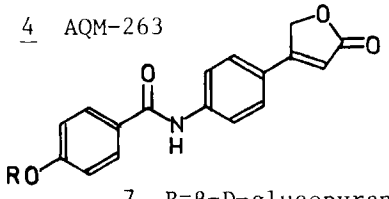
associated with reduced inhibition of Na^+-K^+ATPase.[31] In the rat 3β-acetylthio-3-deoxydigitoxigenin may have a toxicity advantage over 3-O-acetyl-digitoxigenin.[32] In a comparative study with ouabain in anaesthetised dogs, Actinogen (actodigin, AY-22,241) (3) was inotropic at lower fractions of the toxic dose. The onset of activity and recovery from toxicity were also more rapid.[33] This paralleled results obtained with the isolated Na^+-K^+ATPase enzyme[34] and though not effective on acute administration to patients with congestive heart failure, actodigin proved very effective in controlling atrial fibrillation.[35] In a volunteer study, AQM-263 (4)[36] has shown slightly greater potency than digoxin.[37] This follows from the earlier demonstration that the activity of digitoxigenin could be essentially retained by replacing the lactone ring by some open chain α,β-unsaturated systems.[38] However, it is now clear that the presence of an α,β-unsaturated system is not necessary for inotropic or Na^+-K^+ATPase inhibitory activity. The furan analogue (5) shows comparable inotropic activity to digitoxin in isolated guinea-pig atria[39] and a greater margin of safety than digitoxin in the anaesthetised dog.[40] A compound, SC-4453, in which the 17β-lactone ring of digoxin is replaced



4 AQM-263



5 R=OH, X=3-furyl, R'=4-O-(2,6-dideoxy-D-ribohexopyranosyl)-2,6-dideoxy-D-ribohexopyranosyl.



7 R=β-D-glucopyranosyl

6 R=H, X=4-pyridazinyl, R'=6-deoxy-3-O-methyl-α-L-glucopyranosyl.

by a 4-pyridazinyl group, has shown similar Na^+-K^+ATPase inhibitory activity to digoxin.[41] An analogue, SC-4362 (6) is a tenth as potent and is claimed to have been effective in a case of cardiac failure.[42] Replacement of the steroid system in cardiac glycosides by alternative simplified structures has been disappointing. An interesting exception is compound (7) which has shown greater inotropic efficacy than ouabain in isolated hearts with considerably less evidence of toxicity.[43]

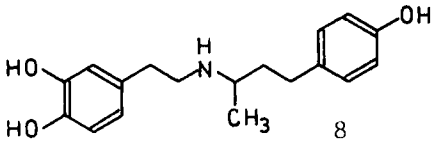
Vasodilators - The use and mechanism of vasodilators in the treatment of heart failure have been extensively reviewed in 1977.[44-48] Their mode of action is interpreted by considering three points:- preload, which determines ventricular filling pressure, the inotropic state of the heart, that is the ability to perform work and afterload, which is a measure of arterial impedance to the ejection of blood during systole.[48] In health, stroke volume can be maintained within limits in the face of varying outflow impedance and, therefore, vasodilatation may produce hypotension if cardiac output is not sufficiently augmented by the reflex increase in heart rate. In decompensated heart failure, however, where no cardiac reserve exists, stroke volume bears a much accentuated inverse relationship to output impedance so that a reduction in peripheral resistance causes an increase in stroke volume. Cardiac output can therefore be increased with little effect on blood pressure and heart rate under optimum conditions. Thus, by reducing output impedance, which is generally raised in heart failure, vasodilators exert a salutary effect on cardiac performance. Most dilators also cause venodilatation to varying degrees and so by reducing preload, will relieve symptoms of pulmonary congestion and decrease myocardial oxygen consumption by reducing heart size. However, if venous pooling predominates, as with the nitrates, the advantages gained in reducing afterload will be lost, with little overall change in stroke volume unless left ventricular end diastolic pressure is markedly raised, when the heart is presumably functioning on the descending part of the Frank-Starling curve. Therefore, in analysing the effects of vasodilators, it is important to consider both the overall haemodynamic effect and the pathophysiological state of the patient.[49,50]

The current position with respect to sodium nitroprusside, nitroglycerin and isosorbide dinitrate is summarised in the recent reviews.[44-48] The principal action of the nitrates appears to be on the venous circulation and though a reduction in preload is observed, the effect on cardiac output is variable. Sodium nitroprusside has a rather more balanced action on preload and afterload but its use is limited to parenteral administration. Oral phentolamine has shown a beneficial effect extending to four hours, though tachycardia may be a problem.[51] However, most of 40 patients benefited from a slow release formulation acting over 12 hours.[52] Ten patients with refractory heart failure have shown clinical improvement with hydralazine[53] and in a further report, cardiac output was shown to increase without alteration in venous compliance.[54] In fact, the relative lack of effect of hydralazine on the venous circulation may limit its utility in congestive heart failure and its beneficial combination with nitrates administered over a 3-10 month period has been reported.[55] Relevant in this context is that hydralazine has a direct cardiac stimulant

action which is mediated by β-adrenoceptors.[56] A patient who was unresponsive to nitrates responded to minoxidil with a significant increase in cardiac output without tachycardia or hypotension.[57] Oral trimazosin increased stroke volume in six patients, reducing both systemic and pulmonary vascular resistance.[58] Ten patients treated with prazosin showed beneficial effects persisting at least six hours, increased cardiac index being accompanied by a reduction both in arterial and venous tone.[59] The compound has also shown substantial benefit on daily administration over a two week period.[60] Its haemodynamic action on oral administration appears to be similar to that of parenteral sodium nitroprusside.[61]

Beta-Adrenoceptor Stimulants - Myocardial noradrenaline levels are markedly reduced in heart failure and there may also be a depressed inotropic response to released transmitter.[62,63] β-1 adrenoceptor agonists may therefore find use in heart failure but selective stimulation of force rather than rate of contraction is paramount. Controversy continues over the further sub-division of cardiac β-receptors into inotropic and chronotropic types, while in the whole animal any intrinsic force- or rate-selectivity of an agonist can be greatly modified by a whole range of compensatory mechanisms.[64-66]

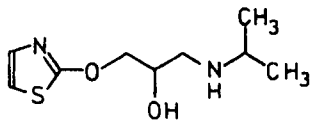
Dobutamine (Dobutrex) (8) was launched onto the UK hospital market in 1977 for use after myocardial infarction and cardiac surgery. The use of dopamine (Intropin) and dobutamine in heart failure has been reviewed.[67] The cardiac effects of both compounds are blocked by propranolol indicating β-receptor mediation. There is little evidence for the involvement of dopamine receptors. Dobutamine is reported to be superior to dopamine in low output patients[68,69] although its force/rate selectivity has been questioned.[70] Both catecholamines have to be given by intravenous infusion and have a short duration of action, although clinical improvement was maintained for at least one week after a 72 hr infusion of dobutamine.[71] Dopamine and nitroprusside have been combined advantageously.[72] The metabolism of dobutamine in dogs has been reported.[73]



8

dobutamine

Intragastric administration of tazolol (9) to conscious dogs produced a marked increase in right ventricular contraction with little effect on heart rate.[74] The cardiac stimulant from aconite root, long used in Chinese medicine, has been identified as the β-agonist, higenamine (10)



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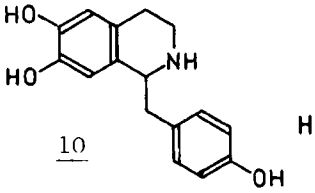

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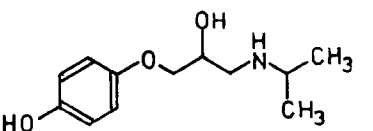

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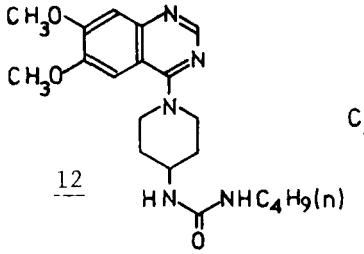
and the crystal structure has been determined.[75,76] H 80/62 (11) is said to produce inotropic stimulation in man with only little change in heart rate and peripheral vascular resistance[77] while oxyfedrine, a weak β-receptor agonist, also showed a positive inotropic action in volunteers.

Phosphodiesterase Inhibitors (PDEIs) - Although there are numerous examples of potent PDEIs, little success has been achieved in the past in developing a useful inotropic agent. Both theophylline and papaverine have cardiac stimulant activity but their use is limited by a range of additional pharmacological properties resulting probably from poor tissue and iso-enzyme selectivity.[79] Additionally, other mechanistic effects not related to PDEI often intrude.[80-82] In view of the opposing effects of cAMP and cGMP on myocardial contractility,[83,84] a basic requirement for a useful cardiac stimulant from this mechanistic class would be marked selectivity for cAMP- rather than cGMP-PDE.



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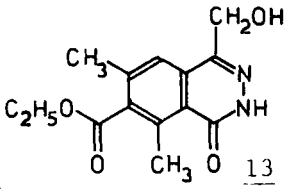

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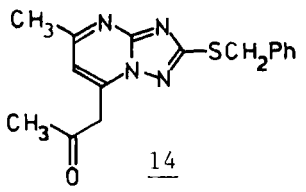
phthalazinol



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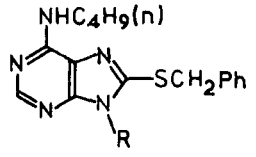
Interest in this area may be stimulated by UK-14,275 (12) which is some twenty times more potent than theophylline as an inhibitor of cAMP-PDE and which is an orally active, selective inotropic agent.[85] Infusion into normal volunteers[86] or patients with coronary heart disease[87] resulted in increased myocardial contractility without hypotension, tachycardia or subjective side effects being observed. Phthalazinol (EG 626) (13) is a potent selective inhibitor of human platelet cAMP-PDE.[88] Administration (300mg p.o.) to patients with ischaemic heart disease resulted in an increase in cardiac output but this could not be attributed unambiguously to a positive inotropic effect.[89] The s-triazolo(1,5a) pyrimidine derivative (14) is one of a related series of PDEIs which increased cardiac output in the dog with little effect on heart rate.[90]

Cyclic Nucleotide Analogues - SQ 80,122 (15) is superior to dibutyryl-cAMP as an inotropic agent, possibly acting by stimulation of a cAMP-dependent protein kinase.[91] In the dog, SQ 80,122 produced a positive inotropic effect not attenuated by β-blockade, with little effect on blood pressure and heart rate.



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SQ 80,122

R=β-D-ribofuranosyl-3',5'-cyclicphosphate

Ionophores - The investigation of ionophores as cardiac stimulants has proved attractive over the past few years due to the availability of a range of compounds which transport mono- and di-valent cations across

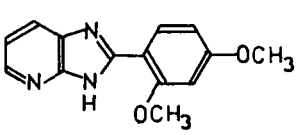
biological membranes.[92] Various ionophores have shown marked inotropic activity both in vitro and in vivo but these effects are reduced after β-blockade,[93,94] suggesting an indirect mechanism heavily dependent on catecholamine release.[95] This mode of action, together with the wide range of biological activities these compounds possess, may well limit clinical usefulness.

Cardiac Stimulant Peptides - The exciting development in this area, which may have a profound impact on our understanding of the mechanisms of cardiac contraction, has been the isolation and identification of a cardiac stimulant polypeptide from the sea anemone Anthopleura xanthogrammica.[96,97] The compound, anthopleurin A (AP-A), a fortynine unit polypeptide, is some thirty times more potent than digoxin as a cardiac stimulant in the anaesthetised dog and has a better therapeutic ratio.[98] Interestingly, the amino acid sequence is remarkably similar to the so-called toxin II isolated from Anemonia sulcata but the latter is a less effective cardiac stimulant, possibly having a different mode of action.[99] The cardiac stimulant potency of AP-A, coupled with a mode of action which is different from other known inotropic agents, will no doubt stimulate speculation on the possibility of a natural inotropic peptide receptor/transmitter system, particularly in light of recent developments in the morphine/enkephalin area.

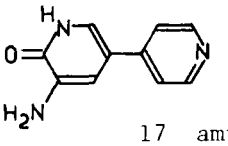
Alpha-Adrenergic and Histamine Agonists - The predominant role of myocardial β-receptors is well established but evidence is now accumulating for the additional presence, in some species, of α, H-1 and H-2 receptors although their physiological significance still awaits clarification. The α-agonists methoxamine and phenylephrine produce positive inotropic effects in cat papillary muscle[100] and rat heart[101] respectively without activation of the adenyl cyclase/cAMP system. Indeed, it has been suggested that stimulation of α-receptors in rat heart leads to a decrease in cAMP[102] and an increase in cGMP.[103] The suggestion that cardiac α- and β-receptors are interconvertible under certain conditions[104,105] has been questioned.[106]

Histamine has been known since Dale's work to produce an inotropic effect but it is only recently that cardiac histamine receptors have been classified.[107,108] The situation is complex, however, as in guinea-pig heart, H-1 receptors are present in the left atrium and right ventricle with H-2 receptors in the right atrium and ventricle. Stimulation of either receptor can produce a positive inotropic effect but only H-2 activation is associated with an increase in cAMP.[109] The cardiac effects of both clonidine and tolazoline in isolated guinea-pig heart appear to involve histamine receptors[110,111] but the relevance of this data to other species is not clear.[112] Histamine receptors have been identified in human heart.[113]

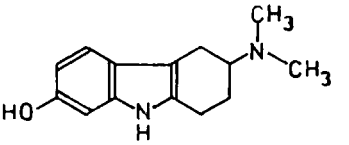
Miscellaneous - In volunteers, the imidazo(4,5-b)pyridine derivative[114] AR-L57CL (16) produced a positive inotropic effect of short duration accompanied by subjective side effects.[115,116] Both amrinone (Win 40,680) (17) and Win 35,020 (18) produced a long-lasting inotropic effect after oral administration in the dog.[117,118] 9-Hydroxyellipticine (19)



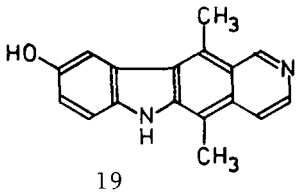
16 AR-L57CL



17 amrinone



18 Win 35,020



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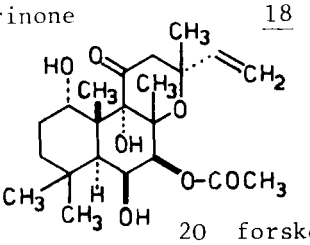

20 forskolin

increased contractile force in anaesthetised dogs but like (18), relies heavily on catecholamine release.[119] Forskolin (20), a diterpene derivative from the Indian plant Coleus forskohli,has dose-dependent positive inotropic and blood pressure lowering activity in animals. The mechanism of action has not been elucidated as yet but does not depend on either catecholamines or inhibition of cAMP-PDE or Na^+-K^+ATPase.[120] Interestingly, inosine produces a positive inotropic effect in the dog and may also exert a modulatory action on β-adrenoceptors.[121]

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