The Development of $\beta$-Stimulant Drugs for the Treatment of Heart Failure

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Introduction

Heart failure is a progressive disease of mixed aetiology which affects a large number of people in the Western World. In the U.S.A., for example, 250,000 new cases occur each year, with 200,000 deaths. Prognosis is poor, the survival rate being only 50% five years after initial diagnosis.

Heart failure may be caused by congenital defects or rheumatic fever, and these lesions may often be cured by surgery. More commonly the condition is caused by ischaemia or hypertension, and is often developed after a myocardial infarction. Though the patient presents with dyspnoea, fatigue, oedema, and often chest pain it is important to realise that these symptoms are caused by the failure of the heart to provide an adequate supply of blood to the tissues, and two types of treatment have been used to improve matters; vasodilators to reduce the resistance to blood flow, and cardiotonics to support the heart. The third type of treatment, diuretics, does not address the disease directly but will alleviate the symptoms. Only adrenergic cardiotonics will be considered in this paper.

Adrenergic Cardiotonics

Adrenergic agonists have many effects which were very confusing until
Ahquist\(^1\), and later Lands\(^2\), proposed the classification \(\alpha\), \(\beta_1\), \(\beta_2\) as shown in fig. 1. This explained, very adequately, why noradrenaline (predominately \(\alpha\) with some \(\beta_1\)) increases heart rate while causing vasoconstriction, adrenaline (\(\alpha\) plus \(\beta_1\) plus \(\beta_2\)) increases heart rate and causes some vasodilation, and isoprenaline (pure \(\beta_1/\beta_2\) agonist) increases heart rate and causes profound vasodilation.

![Diagram](image)

**Fig. 1**

**Chemical Structures**

- Noradrenaline: \(R = H\)
- Adrenaline: \(R = Me\)
- Isoprenaline: \(R = Pr^t\)

Pure beta agonists could help heart failure patients either by their \(\beta_1\) cardiotonic action, or \(\beta_2\) vasodilation, and both have been investigated. The catecholamines themselves are rapidly and extensively metabolised, hence having a short duration of action after parenteral administration, and no oral bioavailability. Replacement of the catechol hydroxyl groups by chlorine atoms gave dichloroisoprenaline (DCI) which was an orally active partial agonist, and demonstrated the feasibility of producing a beta stimulant drug. Several groups tried to modify the catecholamine structure in order to reduce the most troublesome aspect of metabolism, the enzyme catechol-\(\alpha\)-methyltransferase (COMT) which selectively methylates the meta hydroxyl group.
Mead Johnson workers mimicked the meta phenol group with methane sulphonamide, soterenol being a long lasting $\beta_1/\beta_2$ agonist$^3$. The main reason for the research at this time was to produce a selective $\beta_2$-agonist as a bronchodilator for the treatment of asthma, and when orciprenaline ($\beta_1 + \beta_2$) was found to be resistant to COMT$^4$ further work was carried out to obtain terbutaline ($\beta_2$)$^5$ and then fenoterol (very $\beta_2$-selective)$^6$. At Allen and Hanbury's laboratory modification of the meta phenol by insertion of a methylene group gave the $\beta_2$-selective agonist salbutamol (albuterol in USA)$^7$.

\[
\begin{align*}
\text{oerciprenaline} & \quad R = \text{Pr}^1 \\
\text{terbutaline} & \quad R = \text{Bu}^t \\
\text{fenoterol} & \quad R = \text{CH}_3 \\
\text{soterenol} & \quad X = \text{NHSO}_2 \text{Me}, R = \text{Pr}^i \\
\text{salbutamol} & \quad X = \text{CH}_2\text{OH}, R = \text{Bu}^t
\end{align*}
\]

These early structures led to speculation about how catecholamines bind to $\beta$-receptors. Certain features were rapidly established, as illustrated in
fig. 2, but the purpose of the catechol was not known. Subsequent synthesis of analogues replacing the methanol unit of salbutamol showed that acidic, basic, H-bond donating or accepting groups were all active, and probably the most likely common factor is that all could act as metal chelating groups. This role is also supported by the activity of compounds such as quinolene, which contains the powerful chelating system of 8-hydroxy quinoline (oxine). The 3-hydroxy-4-hydroxymethyl analogue of salbutamol is inactive, as is its soterenol counterpart.

![Diagram]

H-bond donor?
H-bond acceptor?
acidic binding?
metal chelation?

\[ X = \begin{align*}
NHSO_2Me \\
CH_2SO_2Me \\
CH_2OH \text{ but not } CH_2OMe \\
NHCONHMe
\end{align*} \]

\[ \text{dopamine} \quad X = H, R = \begin{align*}
& \quad \\
& \quad \begin{align*}
& \quad OCH_3 \\
& \quad OCH_3
\end{align*}
\]
Removal of the meta group altogether gives part—or full agonists such as
denopamine, which has a longer duration than the catecholamines. Denopamine
has been used successfully in the treatment of heart failure acutely, but no
trials relating to chronic dosing have been published\textsuperscript{10,11}.

Salbutamol\textsuperscript{12} and its pyridine analogue pirbuterol\textsuperscript{13} have been studied in heart
failure, and had a beneficial effect acutely, which was probably largely due
to vasodilation, leading to a reduction of afterload on the heart. Chronic
dosing, however, failed to maintain this effect.

\textbf{Arvloxypropanolamines}

In the early 1960's J.W. Black, at the ICI laboratories, began the search for
\(\beta\)-receptor antagonists as anti-ischaemic agents, and the group rapidly
produced pronethalol, an analogue of DCI which possessed only a little of the
agonist properties, but was a moderately potent \(\beta\)-antagonist. Pronethalol
was effective in the treatment of angina pectoris\textsuperscript{14} and hypertension, and this
initiated widespread research activity throughout the World.

The first breakthrough came with the discovery of propranolol, a potent \(\beta\)–
antagonist with no agonist properties\textsuperscript{15}. The synthesis of monocyclic ring
analouges followed, and this has lead to pure antagonists, partial agonists,
and full agonists. During this period the possibilities for \(\beta_1/\beta_2\) selectivity
have also been discovered and exploited, and almost all combinations of
agonism, antagonism, and selectivity have now been realised\textsuperscript{8,16,17}. 

95
\[ \text{DCI} \rightarrow \text{pronethalol} \rightarrow \text{propranolol} \]

\[ \text{NHPr}^\dagger \]

\[ \text{X} \]

\[ \text{OH} \]

\[ \text{OH} \]

\[ \text{NHR} \]

\[ \text{HO} \]

\[ \text{HO} \]

\[ \text{NHR} \]

\[ \text{X} = 2 \quad \text{oxprenolol} \]

\[ \text{X} = 4 - \text{NHAc} \quad \text{practolol} \]

\[ \text{X} = 4 - \text{CH}_2\text{CONH}_2 \quad \text{atenolol} \]

\[ \text{X} = 4 - \text{CH}_2\text{CH}_2\text{OMe} \quad \text{metoprolol} \]

catechols are full agonists
phenols are partial agonists

\[ \beta\text{-antagonists, oxprenolol and practolol show a little agonism, all except oxprenolol are } \beta_1\text{-selective.} \]

There is insufficient space here to discuss the S.A.R. of \( \beta\)-antagonists in detail, but results are shown schematically in fig. 3. This is also a convenient point at which to define precisely the S.A.R. parameters which will be used in the subsequent discussion, which will centre on aryloxy-propanolamine partial agonists. As an example, the results from a denervated anaesthetised dog model are shown in fig. 4.
The benzene ring may be replaced by a variety of (aromatic) heterocycles.

in both cases \% agonism = \( \frac{x}{y} \times 100 \)

Selectivity = \( \frac{\beta_2 \text{ ED}_{50}}{\beta_1 \text{ ED}_{50}} \)

The difference between percentage agonism demonstrated in the above test and that observed in the biochemical situation where cAMP production is measured cannot be overemphasised. Thus (fig. 5) while isoprenaline is a full agonist in both systems other compounds which are, perhaps, 50\% agonists in vivo will
only show 5% in vitro, because, by definition, partial agonists need to occupy ALL receptors to achieve their maximum response while full agonists may only need to occupy 5 - 10% of the receptors to produce enough cAMP to achieve a full biological response. Compounds such as practolol are thus very weak agonists indeed. Some work in man with an ICI drug ICI 89406 suggests that drugs with around 30% agonism in the above test show neither a rise or fall in cardiac rate/force, and only compounds with more agonism than this will be cardiotonic in normal daily life\textsuperscript{10}.

Fig. 5

Relationship between in vivo and in vitro effects

Partial agonism is exhibited by a number of different aryloxypropanolamine structures, which may be classified as phenols, non-phenols, or heterocycles. Prenalterol was the first partial agonist to be used for treating heart failure. It has around 50% agonism on both $\beta_1$ and $\beta_2$ receptors and shows marked haemodynamic benefit when dosed acutely to patients with moderate

\[ \text{prenalterol} \quad \text{Tazolol} \]
or severe degrees of failure\textsuperscript{19}. Over medium-term treatment these effects are maintained, and subjective improvement is noted\textsuperscript{20}, but beyond one month benefit is not maintained\textsuperscript{21}. In some trials ventricular tachyarrhythmias were noted, and some toxic effects were also found in animal studies; the oral dosage form of penalterol has been withdrawn. Some heterocyclic analogues of penalterol e.g. tazolol, have very similar animal pharmacology to penalterol, but none have progressed beyond initial volunteer studies.

Non-phenolic aryloxypropanolamines show varying degrees of agonism. The nature of an ortho substituent, in particular, has a considerable effect on the amount of agonism, with large groups destroying it altogether. Two attempts have been made to quantify this effect; in the first\textsuperscript{22}, calculation of the energy of various conformations of the oxypropanolamine chain of the simple series shown (A) suggested the presence of two low energy states. The major state was the expected all-trans conformation, with a minor gauche conformer present in some cases. Correlation of the prevalence of this gauche conformer with the degree of agonism gave a straight line plot, suggesting that it was this isomer which was responsible for agonism.

Unfortunately when this work was extended to the corresponding arylethanolamine series (B) there was no evidence for a minor conformer.

\[
\begin{align*}
\text{A; } n & = 1 \\
\text{B; } n & = 0
\end{align*}
\]
The second attempt at quantifying the effect was to correlate Taft's steric parameter $E_s$ with degree of agonism. Again, in series A a straight line was obtained, and this carried through to series B, and also to a number of other aryl-oxypropanolamine series. This result suggests that bulky ortho substituents prevent the molecule adopting the mode of receptor binding necessary for agonism.

**Effect of $\delta$ Subst. on Degree of Agonism**

![Diagram of effect of $\delta$ subst. on degree of agonism]

All the early work on $\beta$-(ant)agonists supported the view that the nature of the aryl ring determined most of the properties of the molecule — potency, selectivity, and degree of agonism. The demonstration of $\beta_1$-selective antagonism in bevantolo124 and tolamolo123, both of which contained aryl substituents which are not normally associated with cardioselectivity, prompted ICI workers to investigate the nature of the side-chain more thoroughly126,127. Ethers, thioethers, and more particularly amides and ureas...
were found to be markedly selective for $\beta_1$-receptors or, more accurately, to be selective against $\beta_2$-receptors as $\beta_1$-potency is no greater than with non-selective analogues.

With the above background the ICI group decided to develop a partial agonist for the treatment of heart failure. The profile aimed for was a long acting $\beta_1$-selective partial agonist having about 50% of the agonism of isoprenaline. The reasons for this profile were two fold; partial agonism would mean that at times when sympathetic tone is low, i.e. resting, walking, the drug would act as an agonist, providing cardiac support, while during exercise it would be an antagonist, preventing overstimulation of the heart. A partial agonist would, therefore, have a stabilising effect.

Cardioselectivity was seen to be essential, for the reasons shown in fig. 6. $\beta_2$ vasodilator effects cause reflex tachycardia which exacerbates the direct tachycardia caused by $\beta_1$-stimulation. The reflex effect of the blood pressure rise due to $\beta_1$-myocardial stimulation is vagally mediated bradycardia, which counteracts the direct tachycardia, thus providing a drug which will stimulate cardiac force with little effect on heart rate.

\[ \text{bevantolol} \]

\[ \text{tolmetin} \]

\[ \text{O} \]

\[ \text{N} \]

\[ \text{CONH}_2 \]

\[ \text{O} - \text{Me} \]

\[ \text{NHCOR} \]

\[ \text{NHCONHR} \]
The acylaminoalkyl series provided a versatile means of achieving the target profile. Variation of the amide group provided compounds with agonism ranging from 30–90% (see table) and this effect was so notable in the phenol series that non-phenols were also examined. With an unsubstituted benzene

**Effect of Acylaminoalkyl Substitution – on AGONISM**

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Agonism % in dog *</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-NHCOCH₃</td>
<td>Ph₁</td>
<td>15 (practolol)</td>
</tr>
<tr>
<td>2-CN</td>
<td>Ph₁</td>
<td>16 [k1 1313]</td>
</tr>
<tr>
<td>4-OH</td>
<td>Ph₁</td>
<td>56 (preseranol)</td>
</tr>
<tr>
<td>4-OH</td>
<td>CH₂CH₂NHCONM₂</td>
<td>22</td>
</tr>
<tr>
<td>4-OH</td>
<td>CH₂CH₂NHCOCH₂Ph</td>
<td>40</td>
</tr>
<tr>
<td>4-OH</td>
<td>CH₂CH₂NHCON:Ph</td>
<td>50</td>
</tr>
<tr>
<td>4-OH</td>
<td>CH₂CH₂NHSO₂Ph</td>
<td>65</td>
</tr>
<tr>
<td>4-OH</td>
<td>CH₂CH₂NHCONHΑOH</td>
<td>69</td>
</tr>
<tr>
<td>4-OH</td>
<td>CH₂CH₂NHCONHCH₂Ph</td>
<td>60</td>
</tr>
<tr>
<td>4-OH</td>
<td>CH₂CH₂NHSO₂NHPh</td>
<td>92</td>
</tr>
<tr>
<td>4-OH</td>
<td>CH₂CH₂NHCONH₂</td>
<td>92</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>X</th>
<th>R</th>
<th>Degree of agonism *</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>NHCONHPh</td>
<td>21%</td>
</tr>
<tr>
<td>H</td>
<td>NHCON</td>
<td>33%</td>
</tr>
<tr>
<td>H</td>
<td>NHSO₂NHPh</td>
<td>52%</td>
</tr>
<tr>
<td>H</td>
<td>NHCONH₂</td>
<td>61%</td>
</tr>
<tr>
<td>H</td>
<td>NHCONNHCH₂Ph</td>
<td>70%</td>
</tr>
<tr>
<td>F</td>
<td>NHCONNHCH₂Ph</td>
<td>60%</td>
</tr>
<tr>
<td>H</td>
<td>NHCONNHCH₂Ph</td>
<td>30%</td>
</tr>
</tbody>
</table>

* isoprenaline = 100%
ring agonism of up to 70% could still be realised. With these non-phenols bulky ortho substituents still had the same effect as that described earlier for series A, allowing for "fine tuning" of the degree of agonism, and with groups larger than Cl or CH₃ almost all agonism is lost.

Most of the compounds in the table are moderately β₁-selective, having a β₁/β₂ ratio of around 3–5 (prenalterol 0.9, isoprenaline 0.3); when a primary or secondary urea group is present this still applies, but further substitution causes complete loss of β₂-activity (as an agonist) and it was from this series that the development candidate was selected.

Xamoterol is a potent, long acting, 43% partial agonist with a selectivity of several hundred to one for β₁ vs β₂ receptors. This profile has been confirmed in healthy volunteers, the drug having an i.v. ED₅₀ of 5 µg/kg (4 µg/kg in dog) and 40–50% agonism. Effective treatment is achieved by dosing 200 mg b.d. The cardio-stabilising effect of partial agonism was also confirmed (fig. 7).

Effect of acylaminoalkyl substitution on selectivity

<table>
<thead>
<tr>
<th>R</th>
<th>Selectivity ratio β₁/β₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃SO₂Ph</td>
<td>0.7</td>
</tr>
<tr>
<td>CH₃COCH₂Ph</td>
<td>2.3</td>
</tr>
<tr>
<td>CH₃CONHCH₂Ph</td>
<td>4.3</td>
</tr>
<tr>
<td>CH₂CONHMe</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>CH₂CONHMeOMe</td>
<td>&gt; 250</td>
</tr>
<tr>
<td>CH₂CONHPh</td>
<td>&gt; 350</td>
</tr>
<tr>
<td>NHCONHMe</td>
<td>350</td>
</tr>
<tr>
<td>NHCONHMe</td>
<td>poorly active</td>
</tr>
</tbody>
</table>
In heart failure patients none of the theoretical problems which could occur due to β-stimulation have been seen. Thus there is minimal, or no, tachycardia, no increase (in fact a decrease) in arrhythmias, no worsening of ischaemia and, very importantly, no tolerance has been observed up to three years’ dosing. Xamoterol may be co-prescribed safely with diuretics, cardiac glycosides or ACE inhibitors.

On the positive side xamoterol increases cardiac output at rest, reduces exercise heart rate, and increases exercise workload and duration. It reduces angina of effort and is effective in postural hypotension. Perhaps most important, it improves clinical signs and symptoms and ‘quality of life’.

**Fig. 7 Xamoterol in Volunteers**

1. Cardiotonic at rest
2. No effect during moderate exercise
3. Beta antagonist during severe exercise

![Diagram](image)

**RL307** Cardiac performance

Control Xamoterol

Stimulus: sleep, walking, jogging, running
References