

Inderal — a forerunner of a radically new generation of products

In the second article in a series on landmark drugs, Jenny Bryan discusses the development of Inderal (propranolol) and beta-blockers, and looks at how Inderal was a major advancement in the treatment of hypertension and why it has slowly been superseded by other, newer agents

When beta-blockers dropped off the first-line therapy list for hypertension in last year's National Institute for Health and Clinical Excellence and British Hypertension Society (BHS) guideline update, it was the end of an era for a group of drugs that were a major advance for blood pressure treatment. Starting with Inderal (propranolol), they were also the first real fruit of the receptor research that shaped pharmaceutical investigation during the second half of the 20th century.

In the years after Inderal's introduction, first for angina in 1965 and then for hypertension in 1969, conferences were full of demonstrations of the lock-and-key approach of receptor-targeted drug design, with beta-blockers and later histamine antagonists as examples.

Sir James Black, whose research led to the development of both beta-blockers and histamine antagonists, and won him a Nobel prize in 1988, was heavily influenced by the work of US pharmacologist, Raymond Ahlquist. It was Dr Ahlquist who developed the concept of two receptors, α and β , for the neurotransmitter noradrenaline while searching for a cure for dysmenorrhoea, although his original research paper was initially rejected because it did not fit with mid 20th century understanding of adrenergic transmission.¹

Inderal was the product that established beta-blockers as an essential part of blood pressure treatment, but it was not the first on the market. Pronethalol (Alderlin), an earlier product of cardiovascular research at ICI (now AstraZeneca), was launched in 1963.² But Inderal was 10–20 times more potent than pronethalol, with a better therapeutic ratio, and it was Inderal's tolerability that so impressed clinicians.

Gordon McInnes, president-elect of the BHS, can just remember the pre-beta-blocker days when it was possible to distinguish patients who were compliant with their blood pressure treatment, which included drugs such as methyl dopa, guanethidine and reserpine, because they felt so much worse than those who were not taking their medicine.

"Beta-blockers were undoubtedly a landmark in the treatment of hypertension because they replaced older drugs which were appallingly tolerated. Suddenly, we had a treatment which was well tolerated and blocked the sympathetic nervous system," he recalls.

Even today, however, the mechanism of action of beta-blockers is not fully under-



Inderal as it appeared in the 1980s

stood. "When they arrived it was thought that they worked by slowing heart rate and reducing cardiac output but, as different beta-blockers have different effects on heart rate, the cardiac mechanism has been questioned, and they probably work more through the renin-angiotensin system," Professor McInnes explains.

When Inderal was launched, diuretics were already established in the treatment of hypertension and continued to play an important role. But the successful marketing activity supporting beta-blockers, their novel mode of action, and their additional anti-anginal effects ensured their commercial success.

It was not all plain sailing for beta-blockers. Faced with intense competition from other companies developing them, ICI moved ahead to market with its third beta-blocker, practolol (Eraldin), launched in 1970. This drug was more cardioselective than propranolol and the reduced effects on the β_2 -receptors of bronchial smooth muscle suggested that it could be used to treat hypertension in asthma patients.

However, reports of systemic lupus erythematosus (SLE) syndrome, rash and ocular damage with practolol emerged during the early 1970s and the drug was withdrawn for the treatment of hypertension in 1975.³

Fortunately for ICI, it had another beta-blocker waiting in the wings that proved to be a world-beater. This was atenolol (Tenormin), launched in 1976. It was almost as potent as propranolol and as selective for the β_1 receptor as practolol, but was without the safety concerns that proved to be idiosyncratic of practolol.

Atenolol also had the advantage of a once-a-day formulation and, with its British heritage, it kept the lion's share of the hypertension market against the growing range of beta-blockers coming onto the market, some with intrinsic sympathomimetic activity (such as oxprenolol and pindolol) and others (such as labetalol and carvedilol) with mixed β_1 - and α_1 -agonist activity.

In 1986, results of the "International studies of infarct survival-1 (ISIS-1) trial" extended the role of beta-blockers into acute treatment of myocardial infarction.¹ Patients treated with intravenous atenolol followed by oral atenolol, five hours (mean time) after their event, showed a 15 per cent reduction in seven day mortality.⁴ Similar results were achieved with rival beta-blocker, metoprolol, in the "Metoprolol in acute myocardial infarction (MIAMI) trial".⁵ Those were pre-thrombolysis days, but beta-blockers have retained their place in the management of acute MI, despite the routine use of throm-

bolytic drugs as first-line treatment.⁶ However, they have subsequently fared less well against newer groups of antihypertensive agents and even their old rivals, the diuretics.

A turning point came with publication of the Medical Research Council's placebo-controlled comparison of atenolol and hydrochlorothiazide plus amiloride in older patients with hypertension.⁷ While the diuretic combination significantly reduced strokes by nearly a third and coronary events by nearly half, beta-blockers had no impact.

Subsequent meta analyses and, most recently, a Cochrane review⁸ have confirmed the lack of effect of beta-blockers on stroke and coronary disease when used as first-line therapy for hypertension.

This, combined with the diabetes-inducing effects of beta-blockers, resulted in their relegation to fourth-line treatment in the recent NICE and BHS guidelines update. The update recommends a calcium channel blocker or thiazide diuretic as first-line treatment of hypertension in patients over 55 and an ACE inhibitor for younger patients.⁹

"There were huge expectations for beta-blockers, especially after the post-MI studies, and it was assumed that they would be a breakthrough for reducing events and mortality. But the expectations were not soundly based and the results came as a surprise for a lot of people," says Professor McInnes. Some continue to argue that it is atenolol which is

inferior to other antihypertensive agents, rather than beta-blockers as a group, and a recent reanalysis of beta-blocker trial data has calculated a 13 per cent reduction in MI in hypertensive patients treated with non-atenolol beta-blockers.¹⁰

Professor McInnes supports the new NICE and BHS recommendations as "clear, unified, evidence-based advice". But he points out that beta-blockers do still have a significant role as add-on therapy in problem hypertensive patients and he estimates that they continue to be used by about one in five people with high blood pressure.

In heart failure, time and experience has looked more favourably on beta-blockers, though not on propranolol or atenolol. A number of beta-blockers have fallen in and out of favour in the treatment of heart failure, but the advantage currently lies with the β_1 -, β_2 - and α_1 -blocking agent, carvedilol, following its significantly greater reduction in cardiovascular death, stroke and MI compared with the β_1 -selective metoprolol.¹¹

As well as their core indications, beta-blockers do, of course, have a range of other uses, such as treating migraine and glaucoma. Inderal itself, although largely superseded by other, newer agents, still has a substantial following worldwide. And, as the forerunner of a radically new generation of products, it set the pace for blood pressure treatment for nearly four decades.

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