New therapeutic agents for hypertension

JOHN L. REID

Department of Medicine and Therapeutics, University of Glasgow, Glasgow, UK

- 1 Over the last 40 years a range of therapeutic strategies has been introduced for the long term treatment of hypertension.
- 2 Although safe effective agents are available a significant number of patients are unable or unwilling to take these drugs as long term treatment.
- 3 Both insufficient efficacy and adverse effects justify the search for new antihypertensive strategies.
- 4 Recent developments include orally active angiotensin (AT_1) receptor antagonists (ARA) which appear to offer the benefits of prevention of angiotensin II effects without the adverse effects of bradykinin potentiation, such as cough, which limit the usefulness of angiotensin converting enzyme (ACE) inhibitors.
- 5 Imidazoline receptor agonists offer the potential of centrally active antihypertensives without the adverse effects of sedation and dry mouth. Further clinical experience is necessary to confirm whether the clinical efficacy and good tolerability are confirmed with long term use.
- 6 Both ARA and imidazoline preferring substances offer the bonus of a desirable haemodynamic profile in patients with heart failure and may open new therapeutic avenues in the management of cardiac failure.

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Hypotensive drugs or antihypertensive drugs?

The first effective drugs for the management of hypertension were introduced into clinical practice in the 1950s. Colin Dollery's professional career at Hammersmith Hospital spans the era from the first introduction of ganglion blockers, reserpine and hydralazine to the wide range of effective medicines available in the late 1990s. Colin Dollery has made a substantial personal contribution to the assessment and evaluation in man of many of the classes of drugs introduced over the last 45–50 years. These range from intravenous or intramuscular ganglion blockers to specific and selective receptor antagonists or competitive enzyme inhibitors which are precisely targeted to modify biochemical mechanisms and physiological function [1–4]. He has contributed many novel observations [5] and introduced original concepts [6] though not all of these were subsequently confirmed by others [7]. In addition to major contributions to clinical pharmacology, Colin Dollery has been actively involved in introducing novel approaches to hypertension management and patient care such as the Department of Health and Social Services (DHSS)

Computing Project [8] as well as long term evaluations of the response to treatment in malignant hypertension [9] and milder degrees of hypertension. In the early years of drug treatment only those with very high blood pressure were considered for treatment. Side effects were universal and often disabling. Through the years Colin Dollery has had a special interest in evaluating side effects, where possible applying innovative quantitative approaches [10]. Where they were not feasible he pioneered the use of self rating analogue scales and self administered questionnaires in hypertension research [11].

Now in 1996 when Sir Colin Dollery is retiring from Hammersmith Hospital it is pertinent to ask—'Do we need new therapeutic agents for hypertension?' We have diuretics, α -adrenoceptor blockers, β -adrenoceptor blockers, ACE inhibitors and calcium antagonists which provide a plethora of safe and effective medicines alone or in combination. Of course we have plenty of such drugs but we do still need new drugs for hypertension. A substantial number of patients are not optimally controlled on existing agents even in combination. Others experience treatment limiting side-effects with

Correspondence: Professor J. L. Reid, Department of Medicine and Therapeutics, Gardiner Institute, Western Infirmary, Glasgow, G11 6NT, UK

several drug classes. In addition, although there is evidence from epidemiological survey and prospective clinical trials of benefit of treatment with some drug classes, in terms of reduction in stroke risk and cardiovascular events [12, 13], hypertensive patients remain at increased risk of atherosclerosis and particularly from the cardiac complications of myocardial infarction and sudden death [14].

Current strategies of antihypertensive drug development

In view of the availability of a range of safe effective drugs, what are the requirements of a new antihypertension drug class in the late 1990s (Table 1). There is little doubt that a new agent would be expected to show at least comparable efficacy in reducing blood pressure when compared with existing agents. Better tolerability with few if any side-effects and no long term tissue toxicity would be another requirement. It would be advantageous if new agents did not adversely affect other cardiovascular risk factors such as lipids or glucose tolerance or be contraindicated in the presence of other common diseases of older age groups. Finally, in view of the continuing burden of atherosclerosis and cardiac disease it would be highly desirable if any antihypertensive agent possessed additional anti-atherogenic actions. At the present time we are uncertain whether this last goal can be achieved. This is in part because of incomplete understanding of the details of the links between hypertension, atherosclerosis and the clinical significance associated with ischaemic heart disease and stroke.

There are currently a number of novel approaches to reduction of blood pressure with therapeutic potential which are being pursued in experimental animal models and in early clinical trials in man. These strategies are summarized in Table 2. This incomplete list includes agonists and antagonists of several established and putative vascular mediators. While hypertension remains a possible drug target for these agents other conditions including heart failure, angina, migraine, stroke and peripheral vascular disease are being considered by optimistic industrial pharmacologists and their advisers.

Of the different approaches identified in Table 2, only two classes have reached clinical practice. These classes are drugs interacting with imidazoline receptors and angiotensin receptor antagonists. While rilmenidine and moxonidine have been available for some time, the

Table 1 Desirable features of a new class of antihypertensive drugs

1	Reliable and predictable primary efficacy in reducing blood pressure
2	Superior safety and tolerability
3	Prevention (and reversal) of target organ damage in the kidney, heart and brain
4	Prevention of atherosclerosis and its complications in heart and brain

Table 2 Some current strategies to identify 'new' antihypertensive drugs

1	Angiotensin II (AT ₁) receptor antagonists losartan, candesartan, irbesartan
2	Imidazoline receptor preferring agents rilmenidine, moxonidine
3	Neutral endopeptidase (NEP) inhibitors (or combined NEP and ACE inhibitors)
4	Renin inhibitors
5	Endothelin receptor antagonists
6	Neuropeptide Y antagonists
7	Nitric oxide synthase (NOS) inducers

recognition that these centrally acting drugs might act not on central α -adrenoceptors but on an imidazoline preferring receptor is a recent development [15, 16].

In 1995 the orally active angiotensin II antagonist losartan was marketed in many countries. Although the concept of angiotensin receptor blockade was not new, losartan was the first agent in this class which was orally active and widely available for the long term treatment of hypertension. The remainder of this review will be devoted to these new classes of drugs.

Imidazoline preferring agents

The early antihypertensive drugs included several classes which owed their antihypertensive efficacy at least in part to an action on the central nervous system. They included reserpine in high doses and alpha methyl dopa [17, 18]. In the late 1960s clonidine, an α -adrenoceptor agonist, was found to have central effects on blood pressure which were attributed to atypical alpha agonist properties. These findings led to the identification of α -receptor heterogeneity and the recognition of α_2 sub-type receptors which in some circumstances are prejunctionally located. Clonidine at least in the high doses used in the 1970s was frequently accompanied by side-effects of sedation and dry mouth [19]. Colin Dollery took an active role in studying a number of clonidine analogues and α_2 -adrenoceptor agonists. Side-effects of dry mouth and sedation appeared to be directly related to the efficacy in lowering blood pressure [11, 20]. There were, however, some inconsistencies in classical pharmacological studies of phenylalkylamine and imidazolines [21–23]. Differences in binding affinity to membrane preparations in brain and kidney of several species led not only to further sub-classification of α_2 -adrenoceptors but to the finding of a new class of binding sites which preferred imidazoline structures [24]. Drugs varied in their relative potency for α_2 and imidazoline binding sites [15, 24]. It was suggested that blood pressure lowering and sedative properties could be separated and antihypertensive activity enhanced without serious sedation [25]. Some clinical trials with rilmenidine and moxonidine suggested blood pressure reduction could be achieved with less sedation than that with clonidine [26, 27]. There is, however, evidence

that in higher doses the newer agents lose their relative selectivity [28].

The distribution of imidazoline binding sites in brain and other tissues differs from that of α_2 -adrenoceptors [29]. Although there are still uncertainties about signal transduction pathways and effector coupling of imidazoline receptors, there is a putative endogenous ligand [30, 31]. Clinical experience with low doses of these drugs suggests good tolerability and efficacy compared with established classes [26, 27]. Although there is to date no evidence of any additional benefit on atherosclerosis and target organ damage, the efficacy of centrally acting drugs in reversing left ventricular hypertrophy is well documented. The central adrenergic effects of imidazolines could possibly be useful in the treatment of heart failure as a further strategy to reduce neurohumoral drive.

Angiotensin (AT_1) receptor antagonists

The octapeptide, angiotensin II, has been recognised since the 1940s to be responsible for a range of cardiovascular actions. Increased blood pressure results from direct arteriolar vasoconstriction as well as facilitation of sympathetic neurotransmission peripherally and in the brain. Increased aldosterone release results in increased sodium retention. In addition to these and other effects of circulating angiotensin II there is increasing support for locally generated angiotensin II with autocrine and paracrine actions [32].

Angiotensin II receptor antagonists have been available for over 20 years. However, these early peptide analogues were usually short acting, not suitable for oral dosing and possessed partial agonist (pressor) effects [33]. Losartan potassium is the first of a series of non peptide antagonists with high oral bioavailability [34, 35]. Losartan and close chemical analogues have aided in distinguishing a sub-type of angiotensin receptors (AT_1) which mediates all the classical (cardiovascular and endocrine) actions of angiotensin II and another sub-type— AT_2 which may have a role in foetal/early life and wound healing [36].

Losartan is an AT_1 selective antagonist [37]. In man it is consistently and well absorbed after oral administration. It is, however, rapidly and extensively metabolised to the carboxylic acid analogue—E3174 which is also a potent AT_1 antagonist [34]. Interestingly while the parent compound is a competitive antagonist with a short elimination half-life, E3174 has non-competitive or irreversible properties and a long duration of action. These observations and the differential species specific formation of E3174 explain some conflicting aspects of the preclinical *in vitro* and *in vivo* pharmacology in rats, who like man, can make E3174 *in vivo* compared with dogs and rabbits who do not. E3174 probably contributes substantially to the long duration of effect of oral losartan and to the lack of any rapid rebound at the end of the dose interval.

Losartan causes dose dependent inhibition of the pressor response to intravenous angiotensin II and a fall in blood pressure [38]. The effect on angiotensin is

selective with no actions on bradykinin effects [39]. Not surprisingly the fall in blood pressure is enhanced when sodium intake is low and/or diuretics are given [40, 41]. Otherwise the cardiovascular and endocrine effect of losartan in normal and hypertensives are entirely predictable [42].

Antihypertensive efficacy is comparable with other first line agents (β -adrenoceptor blockers, ACE inhibitors and calcium antagonists). The response is not influenced by age or gender but as noted above is enhanced by co-administration of a diuretic [43]. Blood pressure control is maintained over 24 h with once daily dosing [44].

Losartan has been well tolerated in the controlled trials performed for regulatory authorities. Only dizziness exceeded the placebo rate and then only by 1%. Drug-attributed side-effects and withdrawal rates were numerically less on losartan than placebo and considerably less than that observed after conventional drugs in comparable trials. There was a modest, predictable rise in serum potassium and a modest fall in uric acid related to non-angiotensin II mediated renal effects of losartan. Losartan appears to be free of the common side-effects of β -adrenoceptor blockers (tiredness) calcium antagonists (ankle swelling) and angiotensin converting enzyme (ACE) inhibitors (cough). The latter finding is especially relevant as 10–20% of patients on ACE inhibitors will develop a dry troublesome cough. Cough appears likely to be related to non-angiotensin II mechanisms specifically bradykinin potentiation. In patients who consistently developed a cough on an ACE inhibitor treatment with losartan led to cough no more frequently than after placebo or treatment with a thiazide diuretic used as an active control [46].

If the early reports of good tolerability are sustained, losartan could be widely used not only in patients with ACE induced cough but across the spectrum of hypertension. Prospective controlled trials are underway to examine long-term efficacy, safety and influence on cardiovascular morbidity and mortality.

In preliminary studies in heart failure losartan has shown symptomatic benefit and haemodynamic improvements [47]. The rationale for the use of angiotensin antagonists in heart failure includes the potential to block the effects of angiotensin II generated not only by the classical pathway but also any alternative non ACE pathways such as chymase [48].

Conclusions

Although there are a range of established antihypertensive drugs available, many patients are not adequately controlled by or experience unacceptable side effects on conventional therapy. Recently introduced antihypertensives such as imidazolines and angiotensin receptor antagonists appear to offer improvements over related existing drug classes such as centrally acting agents and ACE inhibitors by improving tolerability and reducing the side-effect burden.

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