Indoramin in the treatment of hypertension

A mini-review and update

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Summary

The origins, preclinical development and clinical pharmacology of a new antihypertensive agent, indoramin (Baratol; Wyeth), are briefly reviewed. Indoramin is a competitive postsynaptic α-adrenoceptor antagonist with a myocardial membrane-stabilizing component of action. These features are believed to be responsible for its antihypertensive efficacy. They may also explain the absence of problems common to older α-blockers such as reflex tachycardia and postural hypotension. Clinical evaluation of a new agent such as indoramin in the management of hypertension is discussed in terms of efficacy, dosage regimen, tolerance, adverse effects, interactions, withdrawal syndrome, and long-term influence on the complications of high blood pressure.

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Following the introduction of indoramin (Baratol; Wyeth) for the treatment of essential hypertension in South Africa, it is appropriate to provide a brief review and update encompassing the origins, preclinical development, mode of action and therapeutic use of the agent.

Background and origins

Increased peripheral vascular resistance is a major feature of essential hypertension, and since α-adrenoceptor-blocking drugs reduce peripheral resistance it would theoretically be ideal to use them for antihypertensive therapy.[1] In practice, older α-blockers were little used for this purpose. They tended to be poorly absorbed after oral administration and to provoke gastrointestinal disturbances, reflex tachycardia and postural hypotension. Alpha-blocker-induced reflex compensatory cardio-acceleration also increased cardiac output and therefore tended to offset any lowering of blood pressure in response to vasodilatation. If these drawbacks could be overcome, antihypertensive efficacy would be increased and limiting side-effects avoided. One possible way to accomplish this would be to incorporate a component of action into an α-blocker that would counteract or prevent this reflex response; the mode of action of indoramin reflects this approach.[2]

In the synthesis of indoramin,[3] features of two types of molecule were combined. A series of so-called *bis*-indoles[4] had shown good antihypertensive activity in which α-blockade was believed to have played an important part. Replacement of one indolylethyl moiety of the *bis*-indole by a benzamido group gave rise to indoramin, in which a resemblance to procainamide had been incorporated.[5] The extent to which an α-blocking action (as in the *bis*-indole) and membrane-stabilizing action (as in procainamide) had been combined in the new molecule can perhaps be judged from the following section.

Preclinical development

Indoramin lowered blood pressure effectively in all species studied.[6,7] It also showed competitive α-adrenoceptor antagonism in a wide variety of *in vitro* and *in vivo* experiments, with for instance a pA_2 value against noradrenaline of 7,4 in the guinea-pig aorta.[8] The hypotensive or antihypertensive activity was not accompanied by tachycardia, which suggested that the α-blockade might indeed be accompanied by some action preventing reflex stimulation of heart rate. Many experiments indicated that this was a direct cardioregulatory property involving myocardial membrane stabilization. For example, indoramin was shown to be a potent local anaesthetic agent[9] and electrophysiological studies on canine myocardial strips showed that at therapeutic plasma concentrations there was a significant decrease in the rate of depolarization.[10] *In vivo* evidence of this direct effect on the heart fully supported the results in isolated tissue,[11] and indoramin has shown good antidysrhythmic activity in a variety of experimental situations.[9]

Another factor contributing to the lack of tachycardia can now be understood in terms of knowledge not available at the time indoramin was conceived. The discovery of presynaptic α-receptors and negative feedback control of noradrenaline release enabled us to appreciate that unselective α-blockers will interfere with this negative feedback control and thus allow greater stimulation of postsynaptic ß-receptors in the heart and α-receptors in the blood vessels. This will contribute to both an increase in heart rate and the relative ineffectiveness of unselective α-blockers in lowering blood pressure. Indoramin avoids both of these drawbacks by acting specifically at postsynaptic α_1-receptors. Typically the ratio of post- to presynaptic potencies is about 1 000:1.[12,13]

Postural hypotension was another major drawback preventing widespread acceptance of older α-blockers for the treatment of hypertension. In contrast, the incidence of postural hypotension with indoramin is minimal. Probable reasons for this include the competitive nature of the antagonism, the apparently greater potency in resistance than in capacitance vessels,[8] and the lack of antagonism of postsynaptic α_2-receptors. Animal experiments involving additional falls in blood pressure on 90° head-up tilt were fully in accord with clinical experience in this respect. Unlike most other antihypertensive agents studied, indoramin

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caused no such additional falls in blood pressure on head-up tilt, except at the highest dose tested, which was many times the maximum human therapeutic dose.[2]

Indoramin is well absorbed when orally administered, does not cause gastro-intestinal disturbances and does not provoke tolerance. In addition, its vasodilator and bronchodilator properties will allow it to be used on patients for whom some other antihypertensive treatments are contraindicated, as discussed in the clinical part of this review.

Clinical pharmacology of indoramin

The following factors should be considered when evaluating a new drug such as indoramin in the management of hypertension: (*i*) efficacy; (*ii*) dosage regimen; (*iii*) tolerance; (*iv*) short- and long-term adverse effects; (*v*) interactions; (*vi*) withdrawal syndrome; and (*vii*) long-term influence on the complications of high blood pressure.

Efficacy of indoramin

Although in preliminary single-dose studies in normal subjects indoramin produced an increase in heart rate in association with a fall in systolic and diastolic blood pressures,[14] long-term studies in hypertensive patients have demonstrated clinically important falls in blood pressure without any increase in heart rate,[15,16] so confirming the results of animal studies already described.

Twenty-four-hour records of intra-arterial ambulatory blood pressure[17] after 6 weeks' treatment of hypertensive patients with twice-daily indoramin demonstrated significant reduction in blood pressure throughout the whole 24-hour period, including the early-morning phase of rising blood pressure just prior to awakening.

Comparative studies of indoramin against other antihypertensive drugs are generally lacking, but Yajnik *et al.*[18] found no significant difference between indoramin and methyldopa in 89 patients in a controlled trial.

Dosage regimen

Patient compliance is assisted by once- or twice-daily rather than more frequent administration of a drug. The studies of Gould *et al.*[17] already referred to have shown that twice-daily administration of indoramin provides satisfactory 24-hour control of blood pressure. Treatment should begin with 25 mg twice daily, increasing by 25 mg increments at not less than 2-week intervals to a maximum of 75-100 mg/d.

Tolerance

Tolerance may develop to some antihypertensive drugs, but long-term treatment with indoramin for 1 year or longer[16,17] has shown no reduction in antihypertensive effectiveness or need for increased doses. Rather there appears to be a sustained gradual fall in blood pressure which may make it possible to reduce the dose of indoramin required to maintain satisfactory control.

Adverse effects

The most frequently reported adverse effects associated with the use of indoramin are sedation, dry mouth, dizziness and failure of ejaculation.[19] Their incidence varies between different studies and depends on the method by which they are elicited. Sedation is the most common adverse effect; it is usually mild and dose-related, and appears to occur less frequently than with methyldopa.[18] A small reduction in dose may lead to its disappearance without reduction in blood pressure control.

Other less frequent adverse effects include weight gain and fluid retention, headache and depression.

No other significant adverse effects have appeared with prolonged use of indoramin. In particular it does not appear to produce an increase in antinuclear factor or a systemic lupus erythematosus-type syndrome. Nevertheless, as with all drug treatment vigilance is required to identify previously unrecognized adverse effects associated with long-term use, particularly if they are limited to certain groups of patients at special risk.

Interactions with other drugs

Several important interactions between antihypertensive and other drugs are recognized. Drugs that inhibit monoamine reuptake can antagonize the hypotensive effects of those blocking adrenergic neurons and of clonidine, but do not appear to influence the action of indoramin.[20] The efficacy of ß-adrenergic blocking drugs and of diuretics can be reduced by non-steroidal anti-inflammatory drugs,[21] but this has not yet been studied with indoramin. The systemic clearance of some ß-adrenoceptor-blocking drugs is reduced by treatment with cimetidine,[22] but it is not yet known whether a similar interaction occurs between indoramin and cimetidine.

Withdrawal syndrome

The abrupt withdrawal of some drugs may be associated with the appearance of a characteristic syndrome, the most important among antihypertensive drugs being that following sudden withdrawal of clonidine. Several investigators have abruptly discontinued treatment with indoramin[16,20,23] without evidence of withdrawal hypertension or any other adverse clinical effects.

Long-term influence on complications of hypertension

There is now good evidence that long-term control of moderate and severe hypertension, and probably of mild hypertension, is associated with a fall in morbidity and mortality caused by high blood pressure,[24] and it is probable that indoramin will have a similar beneficial effect, although this will have to be demonstrated in prospective studies. It is hoped that its membrane-stabilizing antidysrhythmic properties may exert a cardioprotective action. Recent studies (R. Verma, L. Abrams, P. Turner —personal communication, 1982), using a new technique for assessing membrane-stabilizing activity in man which depends on inhibition of human sperm motility *in vitro*,[25] have shown that indoramin is considerably more potent than lignocaine and procaine in this respect (Table I). Clinical studies of the antidysrhythmic properties of indoramin in patients with different types of dysrhythmia are now in progress, and should provide important information on this question.

TABLE I. CONCENTRATIONS WHICH DECREASE HUMAN SPERM MOTILITY TO 50% OF CONTROL VALUES (EC_{50})

Drug	EC_{50} (mM)
d-1 propranolol	**0,8**
Indoramin	**4,0**
Lignocaine	**16,0**
Procaine	**18,0**

Indoramin in the stepwise management of hypertension

At present a stepwise approach is generally recommended in the management of essential hypertension. One drug is used initially, followed by the addition of a second if necessary and a third in those few cases in which control is still not adequate. It is too early to define with certainty the true place of indoramin in such therapy, since management is to some extent determined by recommendation and experience, as well as changing prescribing habits. Experience to date with indoramin has been greatest in second-step therapy. Here it is likely to find a useful place in association with a diuretic, especially in patients in whom ß-receptor-blocking drugs are contraindicated because of increased airways resistance or concurrent vasospastic conditions, or with a ß-blocking drug in patients in whom a thiazide diuretic is contraindicated, for example because of gout or diabetes. Such combined treatment will be associated with smaller doses of indoramin than in monotherapy, and so with a lower incidence of sedation and other dose-related adverse effects.

Although evidence for the use of indoramin as sole therapy is so far less thoroughly substantiated, there are no contraindications to the latter, provided the dose is not increased too much or too rapidly. Indoramin may also have a valuable role as third-line treatment in that relatively small proportion of patients who have not responded satisfactorily to a ß-blocking drug plus a diuretic and in whom a vasodilator would now be considered appropriate.

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REFERENCES

1. Brownlee G. Drugs which lower blood pressure. *Trans Med Soc Lond* 1966; **82:** 103-110.
2. Archibald JL. Indoramin. *In*: Scriabine A, ed. *Pharmacology of Antihypertensive Drugs*. New York: Raven Press, 1980: 161-177.
3. Archibald JL, Alps BJ, Cavalla JF, Jackson JL. Synthesis and hypotensive activity of benzamidopiperidylethylindoles. *J Med Chem* 1971; **14:** 1054-1059.
4. Archibald JL, Baum T, Childress SJ. 1,4-Bis(2-indol-3-ylethyl)piperidines. *J Med Chem* 1970; **13:** 138-140.
5. Archibald JL. Medicinal chemistry and animal pharmacology of indoramin. *Br J Clin Pharmacol* 1981; **12:** suppl 1, 45S-47S.
6. Alps BJ, Borrows ET, Johnson ES, Staniforth MW, Wilson AB. A comparison of the cardiovascular actions of indoramin, propranolol, lignocaine, and quinidine. *Cardiovasc Res* 1972; **6:** 226-234.
7. Baum T, Shropshire AT, Eckfeld DK *et al.* Studies relating to the antihypertensive and antidysrhythmic action of indoramin. *Arch Int Pharmacodyn Ther* 1973; **204:** 390-406.
8. Collis MG, Alps BJ. The evaluation of the α-adrenoceptor blocking action of indoramin, phentolamine and thymoxamine on the rat and guinea-pig isolated mesenteric vasculature and aortic spiral preparations. *J Pharm Pharmacol* 1973; **25:** 621-628.
9. Alps BJ, Hill M, Fidler K, Johnson ES, Wilson AB. The reversal of experimental arrhythmias by indoramin. *J Pharm Pharmacol* 1971; **23:** 678-686.
10. Coltart DJ, Meldrum JJ, Royds RB. Myocardial effects of indoramin, a new hypotensive agent. *Br J Pharmacol* 1971; **42:** 664-665P.
11. Algate DR, Rashid S, Waterfall JF. Cardioregulatory properties of indoramin in the rat. *J Pharm Pharmacol* 1981; **33:** 236-239.
12. Rhodes KF, Waterfall JF. Pre- and postsynaptic α-adrenoceptor antagonism by indoramin in isolated tissues of the rat. *J Pharm Pharmacol* 1978; **30:** 516-517.
13. Algate DR, Waterfall JF. Action of indoramin on pre- and postsynaptic α-adrenoceptors in pithed rats. *J Pharm Pharmacol* 1978; **30:** 651-652.
14. Coltart J. Clinical pharmacological studies on indoramin in man. *Br J Clin Pharmacol* 1981; **12:** suppl 1, 495-605.
15. Fitzgerald MVJ. A long-term open evaluation of indoramin in hypertension. *Br J Clin Pharmacol* 1981; **12:** suppl 1, 117S-124S.
16. Yajnik VH, Patel SC. Long-term efficacy of indoramin in hypertension. *Br J Clin Pharmacol* 1981; **12:** suppl 1, 125S-130S.
17. Gould BA, Mann S, Davies A, Altman DG, Raftery EB. Indoramin: 24 hour profile of intra-arterial ambulatory blood pressure, a double-blind placebo-controlled crossover study. *Br J Clin Pharmacol* 1981; **12:** suppl 1, 67S-73S.
18. Yajnik VH, Chaubey BS, Thiruvengadam KV, Bhatia ML. A comparison of indoramin and methyldopa in patients pretreated with a thiazide diuretic. *Br J Clin Pharmacol* 1981; **12:** suppl 1, 95S-100S.
19. Johnson ES. Indoramin in essential hypertension: a survey of the patient records from long-term clinical trials. *Br J Clin Pharmacol* 1981; **12:** suppl 1, 131S-138S.
20. White C de B, Royds RB, Turner P. Some clinical pharmacological studies with indoramin, with observations on its therapeutic usefulness. *Postgrad Med J* 1974; **50:** 729-733.
21. Watkins J, Abbott EC, Hensby CN, Welster J, Dollergy CT. Attenuation of hypotensive effect of propranolol and thiazide diuretics by indomethacin. *Br Med J* 1980; **281:** 702-705.
22. Reimann IW, Klotz V, Siems B, Frolich JC. Cimetidine increases steady state plasma levels of propranolol. *Br J Clin Pharmacol* 1981; **12:** 785-790.
23. Shah KD. Open assessment of the long-term efficacy and tolerance of indoramin in hypertension. *Br J Clin Pharmacol* 1981; **12:** suppl 1, 101S-104S.
24. Report of the Management Committee. The Australian therapeutic trial in mild hypertension. *Lancet* 1980; **i:** 1261-1267.
25. Hong CY, Chaput de Saintonge DM, Turner P. The inhibitory action of procaine, (+) propranolol and (±) propranolol on human sperm motility: antagonism by caffeine. *Br J Clin Pharmacol* 1981; **12:** 751-752.