A Review of 10 Years of Experience with Indapamide as an Antihypertensive Agent

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SUMMARY  Indapamide is an effective antihypertensive agent for which a dual mechanism of action has been put forward: a limited diuretic activity combined with antivasoconstrictive effects, resulting in decreased peripheral vascular resistance. Results from clinical trials show that 2.5 mg indapamide once daily effectively reduces arterial blood pressure in about two-thirds of patients with mild to moderate hypertension and that this reduction is related to the severity of the hypertension. As a rule, indapamide’s blood pressure-reducing effect is rapid in onset (within 1 or 2 weeks) and by 1 month reaches 65% of its maximum, which occurs after 3 to 4 months of treatment. No tachyphylaxis has been observed during long-term treatment, nor has withdrawal syndrome at discontinuation of therapy. Indapamide has been successfully combined with beta blockers, methyldopa, and other antihypertensive agents, adding considerable effectiveness without noticeable increase in adverse reactions. In general, the drug is well tolerated and side effects are mild and rare. Possibly in relation to its limited diuretic activity at 2.5 mg daily, long-term treatment seldom elicits significant changes in electrolyte balance. In addition, indapamide does not induce deleterious effects on carbohydrate and lipid metabolism. Indapamide is an effective, well-tolerated, first-line antihypertensive agent. The fact that long-term administration does not induce biochemical abnormalities that constitute cardiovascular risk factors indicates another advantage of the drug.

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KEY WORDS • diuretics • antihypertensive drugs • blood pressure reduction

INDAPAMIDE, a newly developed sulfonamide diuretic, has been used in Europe in the treatment of essential arterial hypertension since 1974 and has been introduced recently in Australia, Canada, the United States, and Japan. This paper reviews 10 years of experience with the drug as an antihypertensive agent.

Pharmacological Profile
Antihypertensive Effect

Indapamide, 4-chloro-N-(2-methyl-1-indoline-)3-sulfamoylbenzamide, was selected from a series of indoline and isoindoline derivatives of chlorosulfamoylbenzamide, as an agent with minimal natriuretic and substantial antihypertensive properties. As is the case with other diuretics, indapamide has no hypotensive effect in normotensive animals or healthy humans.1–2 In several animal models of hypertension, including deoxycorticosterone acetate (DOCA)-saline hypertensive rat and dog; the renal hypertensive rat, dog, and cat; and the spontaneously hypertensive rat, indapamide was a potent, long-acting antihypertensive agent.3

In a placebo-controlled dose-response study in patients with mild to moderate hypertension, after 40 weeks, maximal antihypertensive activity was observed at 2.5 mg indapamide daily (mean fall in standing diastolic blood pressure [DBP] 16 mm Hg) and no further increase was noted at 5 mg daily (mean fall in standing DBP 16 mm Hg).4 In contrast, the mean reduction in serum potassium concentration was 0.4 mmol/L at 2.5 mg daily versus 0.6 mmol/L at 5 mg daily. These results show that indapamide has a relatively flat dose-effect curve for blood pressure reduction, whereas its dose-effect curve for diuretic activity is steeper, as judged from the fall in serum potassium. The results with 2.5 mg daily were confirmed in a similar study with patients in the supine position, indicating no influence of posture on indapamide’s antihypertensive effect.5

In addition, 24-hour intraarterial blood pressure monitoring showed that the standard dosage of indapamide, 2.5 mg once daily, provided blood pressure control over 24 hours, thus facilitating good patient com-
pliance.\(^4\) Taken together, these results indicate that in hypertensive patients, indapamide, 2.5 mg once daily, lowers blood pressure effectively with only limited effects on diuresis.

**Dual Mode of Action**

**Diuretic Activity**

Indapamide has dose-related diuretic properties in both animals and humans.\(^3\) Short-term studies in hypertensive patients indicated that indapamide 2.5 mg daily had only mild diuretic activity, whereas this effect became manifest at 5 mg daily.\(^2,8,9\) These results were confirmed in medium-term studies over 10 months.\(^4\) Overall, the results of these studies showed that at 2.5 mg daily no significant effect on total body sodium or potassium pool and plasma volume was apparent, while weight loss, hypokalemia, and hyperuricemia were only mild. In contrast, plasma renin activity and plasma aldosterone increased more markedly.

In both dogs and humans, the site of action of indapamide's diuretic effect appears to be predominantly localized in the proximal segment of the distal tubule of the nephron.\(^10,11\) Results from an acute study in healthy volunteers as well as from short-term studies in hypertensive patients showed that indapamide has no significant effect on glomerular filtration rate (GFR) and renal blood flow. Several other studies suggested that indapamide may well have an additional mode of action compared to other diuretics used as antihypertensive agents. First, from comparative studies in hypertensive animals it appeared that indapamide, at equivalent diuretic activity, has a more potent antihypertensive action than other diuretics. Second, in a small group of hypertensive patients with severe renal failure who were functionally anephric and receiving long-term hemodialysis, 4 weeks of indapamide treatment at 2.5 mg daily induced a significant antihypertensive effect that could not be associated with diuresis.\(^12\)

**Antivasoconstrictor Activity**

A growing body of evidence indicates that, apart from its diuretic effect, indapamide displays certain vascular effects contributing per se to a significant decrease in total peripheral resistance. In vivo, it reduced the increased vascular reactivity to vasopressive amines, electrical stimulation, and angiotensin II in hypertensive rats,\(^3\) and corrected the abnormally elevated cardiovascular reactivity to norepinephrine (and to a lesser extent angiotensin II) in hypertensive patients without concomitant increase in adrenergic nervous system activity.\(^1,2\) In vitro, vascular reactivity to various vasopressive agents was reduced by indapamide in a dose-dependent manner, an activity that was suggested to be due to reduced transmembrane calcium transport in vascular smooth muscle.\(^13,14\)

Recently, the putative role of interference of indapamide with the synthesis of vasoactive prostanoids was put forward.\(^15\) The authors found a significant increase in urinary excretion of the vasodilator and hypotensive prostaglandin PGE\(_i\) in hypertensive patients after 6 weeks of indapamide 2.5 mg daily. In line with these findings, the same group showed that indapamide had a more potent activity than hydrochlorothiazide (HCT), furosemide, or spironolactone in inhibiting thromboxane A\(_2\) synthesis and in stimulating prostacyclin synthesis in vitro. These findings are at present difficult to evaluate and certainly need further investigation.

Finally, several studies suggested that 1 to 2 months of treatment with indapamide 2.5 mg daily induces hemodynamic changes similar to those caused by venoarteriolar vasodilatation. In these studies, evaluating cardiovascular hemodynamics either with invasive (thermodilution catheter) or noninvasive techniques (echocardiography or impedance cardiography), cardiac output and heart rate remained virtually unchanged, while total peripheral vascular resistance was significantly reduced by about 15\%.\(^10,17\)

**Pharmacokinetics**

This review only summarizes the most relevant pharmacokinetic properties.\(^8,18\)

Possibly related to its high lipid solubility, absorption of indapamide from the gastrointestinal tract is extremely rapid (within 0.5-1 hour after an oral dose) and complete. Bioavailability of the tablet formulation is 100\% and is virtually unchanged with food or antacids.

Indapamide is widely distributed throughout the body, with extensive binding to some specific sites. In blood, it is highly bound to red blood cells (80\%) and, more specifically, to carbonic acid anhydrase (98\%) without having any significant inhibiting activity on this enzyme. In plasma, it is relatively highly bound to plasma proteins (79\%). It is also taken up to a significant degree in the vascular wall with specific binding to elastin. Because of this high binding capacity in the vascular compartment, the drug has a relatively low apparent volume of distribution (± 60 L) and 40\% of the dose is located in the blood 1 hour after administration.

After single oral doses of 2.5, 5, and 10 mg, as well as after repeated administration of 2.5 mg daily for 15 days, plasma elimination half-life of unchanged indapamide is about 16 to 18 hours, indicating that once-daily dosing is possible and that no change in kinetics occurs after repeated dosing. Both single- and multiple-dose data indicate that indapamide's kinetics are linear. Steady-state plasma levels are reached within 3 to 4 days after starting treatment, and the drug does not accumulate in hypertensive patients with various degrees of renal insufficiency.

Indapamide is extensively metabolized in the liver. The main route of elimination is the urine (60-70\% of total administered radioactivity), but only 5 to 7% of the dose is excreted into the urine as unchanged drug; 20 to 23% of total radioactivity is eliminated into the feces. Renal clearance of indapamide is approximately 5 ml/min, representing less than 10\% of systemic clearance. These data are in sharp contrast to those of
reference diuretics, in which urinary excretion as unchanged drug generally represents over 50% of the administered dose and renal clearance may reach 300 ml/min.

It is speculated that the high lipid solubility of the indoline moiety confers to indapamide its highly localized binding to structures in the cardiovascular system. This, in contrast to diuretics, that mainly concentrate in the urine, may account for some of the observed differences in pharmacological activity between indapamide and other diuretics.

Therapeutic Efficacy and Safety

Single First-line Agent

Several single- and double-blind comparisons with placebo or other antihypertensive agents have shown indapamide's efficacy as sole therapeutic agent, as judged by a return to normal blood pressure in 58 to 71% of treated hypertensive patients. When the time-course of indapamide's antihypertensive effect at 2.5 mg daily is analyzed, it is clear from the results of the noted medium-term studies that its blood pressure-reducing effect is rapid in onset (within 1 or 2 weeks) and becomes progressively more pronounced. As a rule, after 1 month its effect reached 65% of maximum, which was attained after 3 to 4 months of treatment and was maintained over the whole study period. When active treatment was interrupted and patients were further studied during a placebo run-out of 2 to 4 weeks, blood pressure progressively returned to pretreatment values without producing an overshoot or rebound phenomenon.

In comparative studies with other first-line antihypertensive agents, indapamide's efficacy at 2.5 mg daily proved to be equivalent to that of various diuretics (HCT, 50 mg/day; HCT, 50 mg/day plus amiloride, 5 mg/day; chlorothalidone, 50 mg/day; metolazone, 2.5 mg/day; bendroflauzide, 5 mg/day) and beta blockers (atenolol, metoprolol, nadolol, oxprenolol, pindolol, or propranolol), the antihypertensive effects of the two drugs were consistently additive. In general, this combination was well tolerated because side effects were not additive.

Combination Therapy

In placebo-controlled studies in which indapamide was associated with a beta blocker (atenolol, metoprolol, nadolol, oxprenolol, pindolol, or propranolol), the antihypertensive effects of the two drugs were consistently additive. In general, this combination was well tolerated because side effects were not additive.

Studies on Specific Topics

Safety

The acceptability of indapamide 2.5 mg once daily is good. Side effects have been rare and mild, the most frequently reported being asthenia, dizziness, headache, fatigue, muscle cramps, and gastrointestinal disturbances, usually occurring within the first month of treatment. Other adverse reactions were nonspecific and low in frequency. Cutaneous rash and impotence were occasionally reported.

Hypokalemia was the most common biochemical adverse effect. Approximately 10% of treated patients had decreased serum potassium values, but only 1% reached values below 3 mmol/L, irrespective of the pretreatment level (Canadian and U.S. prescribing information). After long-term treatment with indapamide 2.5 mg daily, the mean decrease in serum potassium concentration was limited (0.3–0.4 mmol/L); potassium supplementation was rarely required and only in patients with low initial values.

During long-term treatment, serum uric acid levels have been found to be increased by about 8%, but only in a few patients has gout been precipitated. Glucose and lipid metabolism do not seem to be influenced to a significant extent by indapamide, as judged from the stability of blood glucose and serum lipid concentration during long-term treatment.

Side effects are rarely severe enough to warrant withdrawal of the drug. Dropout rates because of poor acceptability are extremely low; for example, 1.3% of 1202 patients taking only indapamide for 3 months withdrew from a recent United Kingdom multicenter study. In this study, subjective well-being was assessed with a visual analogue scale. It was noted that 55% of the patients felt better taking indapamide alone than they had with previous therapy, and only 5% felt worse, results that are in line with the low withdrawal rate.

Elderly Hypertensive Patients

Treating hypertension in the elderly presents a problem for several reasons that cannot be dealt with in detail in this context. Drug treatment, if deemed necessary, should not be too aggressive and should be free of serious side effects. Therefore a modest reduction in blood pressure with relatively few side effects is an acceptable compromise.

Studies in elderly hypertensive patients confirmed that the clinical efficacy and safety of indapamide 2.5 mg daily in this subpopulation are similar to those in younger patients. As in younger adults, intraarterial 24-hour blood pressure monitoring in elderly hypertensives showed that overall blood pressure was reduced throughout the 24 hours with a once-daily dose. No adverse effects were observed on reflex cardiac control. From these and other studies it seems that because of its progressive antihypertensive effects, its favorable side effect profile, and its simple dosage
regimen, indapamide may be a valuable drug in the treatment of elderly hypertensive patients.

Hypertensive Patients with Renal Insufficiency

Thiazide diuretics are generally ineffective in hypertensive patients with GFR values below 25 ml/min, while loop diuretics (and other antihypertensive agents) conserve their antihypertensive effect in such patients. Because of its additional nonrenal mode of action, indapamide could theoretically be an alternative possibility.

In two different studies, a small number of hypertensive patients with mild to severe renal insufficiency were treated for 6 to 8 weeks with indapamide 2.5 mg daily. The drug lowered blood pressure significantly in all groups of patients irrespective of the degree of renal function impairment. In addition, in functionally anephric hypertensive patients receiving maintenance hemodialysis, indapamide 2.5 mg daily for 4 weeks produced a significant fall in blood pressure without adverse effects on biochemical indexes.

These encouraging results are interesting, but certainly need confirmation in a larger number of patients before any conclusion can be drawn regarding indapamide's effectiveness in this particularly vulnerable group of hypertensive patients.

Diabetic Hypertensive Patients

The "wrong way" effect of thiazide diuretics on glucose tolerance in nondiabetic and on glycemic control in diabetic hypertensive persons is now well acknowledged. As several studies showed no significant difference in fasting glycaemia in nondiabetic hypertensive patients after 1 to 3 years of indapamide treatment, it was interesting to look at persons who were already diabetic. These studies confirmed the absence of any significant change in mean fasting and 2-hour postprandial glycaemia.

Serum Lipids and Lipoproteins

It is well recognized that diuretics may adversely influence serum lipid and lipoprotein concentrations. More specifically, serum levels of total and low-density lipoprotein cholesterol as well as total and very low-density lipoprotein triglycerides increase. As some of these indexes are known atherogenic risk factors, the possible effect of indapamide on serum lipids and lipoproteins was studied. Weidmann et al. showed that 6 weeks of treatment with indapamide 2.5 mg daily had no significant influence on any of the investigated serum lipid or lipoprotein levels.

Conclusion

In reviewing 10 years of experience with indapamide as antihypertensive agent, it seems clear that the agent conforms to present-day criteria for an acceptable first-line antihypertensive agent, in that it combines satisfactory blood pressure reduction with low frequency of side effects and a simple once-daily dosage regimen.

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