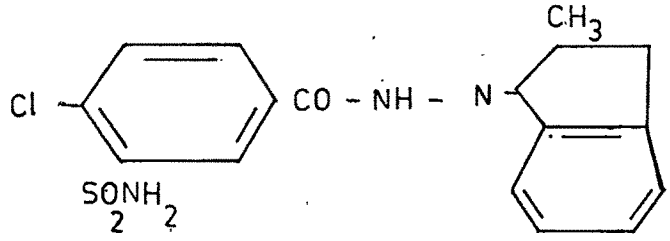
# CHAPTER-II

# THE PHARMACOLOGY OF INDAPAMIDE

The pharmacology of indapamide

The diuretics have been used successfully for many years as the first line of treatment for the hypertensive patient but they can produce several unwanted side effects. Indapamide, an indoline derivative of chlorosulphonamide, was synthesized in an attempt to produce a molecule which would have minimum diuretic activity and side effects but would have a maximum antihypertensive effect.

Indapamide has been shown to be a potent long acting antihypertensive agent when used alone or in combination for all degrees of hypertension (Campbell and Moore, 1981).




It differs from benzothiadiazine diuretics in that it contains only one sulphonamide group and no thiazide ring system (Campbell et al., 1977; Choi et al., 1982; Grebow et al., 1982; Campbell, 1983).

Indapamide is a new antihypertensive drug which has been shown to exert effective control of hypertension in animals (Kyncl et al.,1975) and in man (Royer, 1976). Its mechanism of action has not been fully elucidated although antihypertensive activity in man is associated with a

reduced vascular resistance (Canicave and Lesbre,1977). It decreases in vitro the contraction of vascular strips elicited by ANG and catecholamines (Gargouil and Mironneau, 1977).

1. Antihypertensive action

(a) Normal animals

Indapamide does not have significant cardiovascular activity in normotensive animals. In normal rats, cats and dogs intravenous administration of 30 ug to 30 mg/kg failed to change blood pressure or heart rate and in rats oral doses of up to 100 mg/kg did not change blood pressure over 96 hour measurement period (Moore et al., 1977). At high doses, 16 times the therapeutic level, blood pressure was lowered in normal volunteers but this was probably due to hypovolaemia (Campbell and Phillips, 1974).

(b) Hypertensive animals

At low oral doses, 1-10 mg/kg indapamide is a potent and long lasting hypotensive agent in several animal models of hypertension. In deoxycorticosterone acetate (DOCA)/saline hypertensive rats with unilateral nephrectomy a single dose of 10 mg/kg indapamide produced a maximal fall in systolic blood pressure after 24 hours of 25 mmHg, and the antihypertensive action lasted for 72 hours(Moore et al.,1977). Similar results were observed in DOCA/saline

rats without nephrectomy (Kyncl et al.,1975). Higher doses upto 100 mg/kg produced only small increases in activity but the blood pressure reduction continued for longer than 4 days. Falls of upto 48 mmHg in systolic blood pressure have been recorded following repeated administration of indapamide 10 mg/kg orally in DOCA/saline hypertensive rats with unilateral nephrectomy (Finch et al.,1977a, b).

Following repeated oral administration of lower doses of indapamide (1 mg/kg) or trichloromethiazide (3 mg/kg) to DOCA/saline nephrectomized rats for 14 days, mean systolic blood pressure fell more with indapamide (33 mmHg) than with trichloromethiazide (23 mmHg) (Moore et al.,1977). One week after indapamide treatment had ended, the blood pressure had only partially returned towards pre-treatment values. This long lasting hypotensive action of the drug cannot be related to retention of the drug in the body since the half-life of total radioactivity in the rat is 20 hours and all drug and metabolites have been eliminated within 2-5 days (Campbell et al.,1977).

This persistent activity of the drug has been observed in other experimental animal models. In the renal hypertensive dog indapamide, 5 mg/kg p.o. produced a maximal reduction (37 mmHg) in systolic blood pressure after 48 hours and an antihypertensive effect was still evident after 4 days

(Kyncl et al.,1975). In renal hypertensive cats, oral administration of 6-16 mg/kg p.o. over 14 days produced falls in mean arterial blood pressure of 9-26 mmHg which lasted for 5-7 hours and were not accompanied by reflex tachycardia (Finch et al.,1977b). The antihypertensive response to clonidine (20 ug i.c.v.) was significantly enhanced one week after cessation of indapamide treatment, but had returned to the pre-treatment value after a further 2 weeks.

Indapamide, 3 mg/kg p.o. appears to be more potent in spontaneously hypertensive rats than frusemide, spironolactone and chlorthalidone by factors of approximately 30, 100 and 300 respectively, and its duration of activity is longer. The dose-response curve was however less steep for indapamide than for the other compounds (Moore et al., 1977).

(c) Development of hypertension

The administration of DOCA and salt to uninephrectomized rats produces an irreversible hypertensive state after approximately 6 weeks (Selye et al.,1943). Administration of indapamide 0.5 or 10 mg/kg or propranolol 60 mg/kg to rats in the diet for 10 weeks together with the DOCA/saline prevented the onset of hypertension and there were no significant intergroup differences in 24 hour urine output, serum and urinary sodium or potassium concentrations (Hicks, 1979).

Heart weight was significantly reduced 22% by indapamide at 10 mg/kg suggesting that the preventive effect on the development of hypertension was associated with a decrease in cardiac hypertrophy. When all groups were subjected to an increased salt load 4 weeks after cessation of drug treatment, only in high dose indapamide treated animals did blood pressure fail to increase as much as in the controls indicating a continuation of indapamide's protective action.

(d) Dose-response in hypertensive patients

The antihypertensive activity of indapamide was studied at doses of 0.5, 1.0, 2.5 and 5.0 mg administered daily for 8 weeks in a double-blind placebo controlled study in mild to moderate hypertensive patients and showed that the drug has a comparatively flat dose-response curve. Maximal antihypertensive response was observed at 2.5 mg and no increase in activity was seen when the dose was doubled to 5.0 mg. However, at this higher dose, the serum potassium levels did drop significantly.

Other unpublished studies have confirmed these results although studies in Japan suggest that the maximum effect may be seen at 2.0 mg (Hashida, 1977) but this may be a consequence of a lower average body weight and the distribution of the drug in the body. These results would suggest that in the majority of patients 2.5 mg per day is an

effective dose and increasing the dose is unlikely to significantly reduce the blood pressure further.

On the contrary, increasing the dose is only likely to increase side effects such as diuresis, hypokalaemia, etc.

(e) Antihypertensive action in man

In man, the antihypertensive activity of the drug appears at a much lower dose than in animals. Clinical trials have been conducted in over 6,000 patients. The results indicate that a single daily dose of 2.5 mg (0.04 mg/kg) produces a blood pressure fall of 25-35 mmHg systolic and approximately 20 mmHg diastolic in mild to moderate hypertensive patients (Andries et al., 1977; Turner et al., 1977; Dunn et al., 1981; American and U.K. Multicentre Studies, unpublished; Bhalla, 1981). There was an initial decrease in blood pressure over the first 1-2 weeks of treatment but maximal effects were not seen for 6-8 weeks. After cessation of therapy blood pressure did not return to baseline values for upto 8 weeks (Turner et al., 1977; Kelly and Hamilton, 1977; Lenzi and Di Perri, 1977). This prolonged activity again cannot be due to prolonged elimination since the biological half-life of indapamide in man is 18 hours (Campbell et al.,1976).

2. Action on the kidney

(a) Diuretic effect

The mechanisms responsible for the antihypertensive activity of the diuretics are still not clearly understood. The known diuretic action suggests that lowering of the blood pressure may be related to extracellular fluid and blood volume reduction. Prolonged treatment with diuretics probably lowers plasma volume by about 7% and increasing the blood volume with dextran and salt can reverse the antihypertensive activity. Winer (1961) and Shah et al.(1978) have therefore hypothesized that the activity of the diuretics on peripheral vascular resistance may be due to a reverse autoregulation secondary to this extra-vascular volume depletion. This would suggest that there is some relation between water loss, natriuresis and the action on the smooth muscle.

Kraetz et al.(1978) compared the natriuretic activity and the effect on vascular reactivity of eight diuretics including indapamide in rats. They found no correlation between these parameters and concluded that it was possible to dissociate the natriuretic and vascular effects. Certainly at high single doses of indapamide, 30-40 mg, the drug is a potent diuretic (Onesti et al.,1977b; Campbell and Phillips, 1974) acting predominantly on the proximal segment of the distal tubule. However, it appears

to have natriuretic properties with less effect on kaliureis of uric acid excretion whilst glomerular filtration rate, renal blood flow, urine flow, urinary acid and potassium remain unaffected (Pitone et al.,1978). At low doses, however there appears to be only a minimal effect on urinary volume in rats at 0.1 mg/kg p.o. (Moore et al.,1977) and no significant natriuretic effect at 0.5 mg in man (Fernandes et al.,1977). Only at doses greater than 2.5 mg per day is an appreciable increase in urinary volume observed in man (Schlesinger et al.,1977). Plasma volume in patients treated with 2.5 mg indapamide for 6 weeks remains unaltered (Weidmann et al.,1980) and body weight, an index of volume loss, was not significantly altered in some studies (Anavekar et al.,1980; Astacio et al.,1980; Isaac et al.,1977) but was reduced in others (Horgan et al.,1981). Kelly and Hamilton (1977) found that body weight dropped after the first week of treatment but did not show any significant change thereafter.

Apparently, urinary volume per unit time in man is not significantly or consistently increased until dosages of indapamide exceed 2.5 mg daily (Goldberg and Furman, 1974; Schlesinger and Benchimol, 1980; Schlesinger et al.,1977). When administered in moderate to large dosages (5 to 30 mg) indapamide is a potent diuretic and results in substantial water and electrolyte loss (Leary et al.,1973).

Onset of diuresis occurs 1 to 3 hours after oral administration (Goldberg and Furman,1974). Although the peak urinary excretion rate of indapamide occurs approximately 3 hours following administration, maximum urinary flow does not occur for 6 hours (Campbell and Phillips,1974). The major diuretic response seen with moderate (10 mg) dosages persists for upto 12 hours following indapamide administration(Goldberg and Furman,1974). In healthy volunteers, urine output following indapamide 0.5 to 30 mg was shown to be dose related (Onesti et al.,1977a; Caruso et al.,1983).

In healthy subjects, indapamide, 2.5 or 10 mg resulted in mean increases in 24 hour urinary volume of 0.78 and 0.61 respectively (Goldberg and Furman,1974; Reyes et al.,1983b) and a 40 mg dose more than doubled the rate of urine production (from 1.8 to 4.3 ml/min) (Campbell and Phillips,1974). In patients with hypertension and associated congestive heart failure, indapamide 0.5 to 5.0 mg daily for 21 days resulted in a mean daily urine volume increase of 792 ml (57%) (La Corte et al.,1980b). Symptoms of intravascular volume depletion were noted in healthy volunteers administered indapamide 20 or 30 mg daily for 5 days (Onesti et al., 1977a). The diuresis resulting from indapamide 40 or 50 mg daily administered to healthy subjects (Leary et al.,1973) or oedematous patients (Leary et al.,1974) were comparable with that with frusemide 40 mg once or twice daily,

respectively. Urinary output in the 24 hours following the administration of indapamide 40 mg was greater ($P < 0.05$) than that with cyclopenthiazide 5 mg (Leary et al., 1973).

The assessment of changes in body weight is a useful although indirect, method of gauging the magnitude of urinary volume loss with a diuretic agent. In at least one-half of the studies reported indapamide 2.5 or 5 mg daily produced significant body weight reduction both in healthy volunteers and in patients with hypertension (Campbell, 1983). At these dosages, mean individual weight losses appear to range from 0.5 to 2.4 kg (Grimm et al.,1983). In unblinded (Bing et al., 1981) or double-blind comparative studies (Witchitz et al., 1975; Slotkoff,1983), weight loss with indapamide 2.5 or 5 mg daily equalled that with bendrofluazide 5 mg (Bing et al., 1981), hydrochlorothiazide 100 mg (Slotkoff,1983) or frusemide 40 mg (Witchitz et al., 1975) daily.

In short term studies (4 to 6 weeks) indapamide 1.0, 2.5, 5.0 mg daily did not significantly decrease plasma volume in patients with hypertension (Grimm et al., 1981; Brooks et al.,1983; Leenen et al.,1983). Neither indapamide 2.5 mg nor tienilic acid 250 mg daily decreased plasma volume in healthy volunteers or hypertensive patients when administered for 6 week periods (Weidmann et al.,1981). In contrast, plasma volume was decreased by 8% (360 ml; $P < 0.005$) in patients with hypertension treated with

hydrochlorothiazide 50 mg twice daily, but returned to pre-treatment level (Shah et al.,1978). As 24 hour urine volume and body weight are most often increased and decreased, respectively, during indapamide administration, its lack of effect on plasma volume suggests that redistribution of fluid from interstitial to the intravascular spaces may occur during treatment (Leenen et al.,1983).

In maximally hydrated healthy subjects or patients with hypertension, indapamide increased osmolar clearance and decreased free water clearance, whereas it increased both osmolar clearance and tubular reabsorption of free water under conditions of maximal dehydration. These data suggest that the proximal segment of the distal renal tubule (cortical diluting segment) is the primary site of the diuretic action of indapamide (Goldberg and Furman, 1974; Onesti et al.,1977b; Pitone et al.,1978). Studies in animals (Burke et al.,1983) and humans (Villarreal et al.,1983) have indicated that indapamide also exerts some diuretic activity in the proximal tubule.

In dogs, indapamide 0.1 mg/kg intravenously did not influence effective renal plasma flow or glomerular filtration rate, although a higher dose (1.0 mg/kg) temporarily increased both parameters. Similar responses occurred when hydrochlorothiazide (1.0 mg/kg) or trichlormethazide (0.3 mg/kg) were administered intravenously to dogs

(Suzuki et al.,1977). However, in other studies, glomerular filtration rate in dogs was not altered by the intravenous administration of indapamide 1 mg/kg (Laubie and Schmitt, 1977) or 3 mg/kg (Burke et al.,1983). Effective renal plasma flow was increased (15% $P < 0.05$) only at the higher dosage.

In several studies, glomerular filtration rate following indapamide administration has been estimated by measuring endogenous creatinine clearance (Brennan et al.,1982; Lemieux and L'Homme, 1983; Waal-Manning and Doesburg,1982). In healthy volunteers receiving indapamide 10 mg daily for 4 days creatinine clearance was decreased (from 107 to 97 ml/min) (Goldberg and Furman, 1974); however, creatinine clearance was unchanged following long term administration of a lower dose (2.5 mg every other day) to the patients of Waal-Manning and Doesburg. After indapamide 2.5 mg daily for 4 months creatinine clearance was increased ($P < 0.05$) compared with daily treatment with placebo or hydrochlorothiazide 50 mg (Lemieux and L'Homme, 1983). Creatinine clearance was also increased (50.9 to 63.4 ml/min; $P < 0.01$) in 8 patients with hypertension and renal insufficiency given indapamide 2.5 mg daily for 6 weeks (Brennan et al.,1982).

Although serum creatinine and blood urea nitrogen concentration are less reliable indicators of glomerular filtration rate (Brooks and Mallick, 1982), they have

nevertheless been used to monitor renal function in many of the clinical studies of indapamide. Alterations in serum creatinine attributable to indapamide treatment have been reported only rarely, and have not been clinically significant (Santoro et al., 1982). Similarly, most studies have not shown indapamide to affect blood urea nitrogen concentrations (Bing et al., 1981; Brennan et al., 1982) although there have been a few exceptions where statistically significant elevations were noted (Hashida, 1977; Chalmers et al., 1982; Santoro et al., 1982). Indapamide 1 to 2.5 mg daily, alone or in combination with other hypertensive agents for 6 weeks to 4 months increased blood urea nitrogen by a mean of 0.46 to 1.54 mmol/L ($P < 0.05$) (Hashida, 1977; Lemieux and L'Homme, 1983), while indapamide 2.5 mg daily for 8 weeks resulted in a smaller but significant increase (0.33 to 0.40 mmol/L; $P < 0.001$) (Chalmers et al.,1982). In 18 patients with hypertension and renal insufficiency (creatinine clearance from 13 to 61 ml/min), serum concentrations of blood urea nitrogen and creatinine were not elevated following indapamide 2.5 mg daily for 6 weeks (Acchiardo and Skoutakis, 1983). The small elevations seen in blood urea nitrogen concentrations following indapamide therapy have been attributed to mild dehydration (Lemieux and L'Homme, 1983).

Exchangeable sodium and potassium did not appear to be influenced by indapamide following treatment for 6 weeks to 10 months (Isaac et al., 1977, Weidmann et al., 1980); neither were there changes in whole body sodium or potassium. There were no significant changes in plasma sodium levels in any of the clinical studies. Various changes in plasma potassium levels have been observed with some investigators reporting a reduction (Demanet et al.,1977; Royer,1977; Weidmann et al., 1980; Bowker and Murphy, 1981; Horgan et al., 1981) and others reporting no significant change (Fernandes et al.,1977; Kelly and Hamilton, 1977; Schlesinger et al.,1977; Turner et al.,1977; Anavekar et al., 1980; Jorge and Perello, 1980) and one investigator finding a non-significant rise (Astacio et al., 1980). It has been suggested that any tendency for hypokalaemia during indapamide like the diuretics and vasodilators, increases plasma renin levels in men and animals approximately two-fold (Moore et al.,1977; Anavekar et al., 1980 ; Weidmann et al., 1980) although this effect may be less than that of combined hydrochlorothiazide/amiloride (Anavekar et al.,1980). Uric acid rose significantly with indapamide in some clinical studies (Demanet et al.,

1977; Kelly and Hamilton, 1977; Royer, 1977; Astacio et al., 1980; Horgan et al., 1981), but no significant difference was seen in others (Fernandes et al., 1977; Anavekar et al., 1980; Bowker and Murphy, 1981). These rises do not appear to be clinical significant since acute precipitation of gout has not been a problem with the use of the drug.

One can hypothesizes that if diuresis plays a major part in the mode of action of indapamide then the drug is unlikely to have a significant hypotensive activity in patients with severe renal impairment. In a recent single-blind placebo controlled study, indapamide 2.5 mg daily, has been administered for 4 weeks to nine anuric or oliguric patients undergoing chronic haemodialysis (Campbell and Moore, 1981). Blood pressure was reduced (Mean 10/7 mmHg) in all patients compared to placebo treatment. This reduction did not however appear to be related to the degree of insufficiency since a mean fall of 25/15 mmHg was found in the two patients who were functionally anephric. The diuretics, hydrochlorothiazide and metazolone however, do not have hypotensive activity in functionally anephric patients who are undergoing dialysis (Bennett et al.,1977) although others (Jones and Naura, 1979) have shown some lowering of blood pressure with chlorothiazide in patients with analgesic nephropathy

when a small degree of renal function (creatinine clearance 14 ml/min) remains.

(b) Effect on urinary pH and specific gravity

Urinary pH was unchanged 20 to 40 minutes following the intravenous administration of indapamide 1 mg/kg to dogs (Laubie and Schmitt, 1977) and a single 40 mg dose of indapamide given orally to 6 healthy volunteers only transiently increased urinary pH (Campbell and Phillips, 1974). In 13 patients with hypertension administered indapamide 2.5 mg daily, urine specific gravity was increased (average of 0.005 $P < 0.05$) after 4 to 6 weeks of treatment (Brennan et al., 1982).

(c) Influence on renin and aldosterone

Most diuretic agents can alter plasma renin activity (Young and Riddiough, 1978). Diuretics probably stimulate renin release via alteration of sodium (or possibly chloride) concentrations in the tubular fluid at the macular densa (specialised tubular cells within the juxtaglomerular apparatus, believed to act as 'chemoreceptors' controlling renin release) and/or by reduction of blood pressure or plasma volume (thereby altering renal perfusion pressure and stimulating intra-renal baroreceptors controlling renin release) (Nies, 1978; Young and Riddiough, 1978 Gilmore, 1983).

Indapamide 2.5 or 5 mg daily for 2 to 6 weeks consistently increased plasma renin activity 2 to 3-fold when used as a single agent in healthy subjects (Grimm et al., 1981; LeBel et al.,1983). In other studies, plasma renin activity was increased 2 to 5-fold following the administration of indapamide 2.5 mg daily alone (Anavekar et al.,1979; Chalmers et al.,1982; Santoro et al., 1982; de Ortiz et al.,1983) or in combination with benedrofluazide 5 mg (Bing et al.,1981) for upto 16 weeks. The increases which occur in plasma renin activity with indapamide are similar to those with other diuretics (Witchitz et al., 1974) and vasodilator agents (Campbell and Moore, 1981). However, the rise in plasma renin activity was prevented when indapamide 2.5 mg was administered with the beta-adrenergic blocker, pindolol 10 to 40 mg daily (Chalmers et al., 1982; LeBel et al., 1983).

Renin reacts with an $alpha_2$-globulin substrate to form ANG I. Converting-enzyme (predominantly in the lung) converts ANG I to ANG II, the latter being not only a potent vasoconstricting substance but also partially responsible for aldosterone release from the adrenal cortex (Nies, 1978; Gilmore, 1983). Circulating concentrations of potassium and sodium also regulate the quantity of aldosterone released (Gilmore, 1983). Indapamide, 2.5 mg daily for 6 to 8 weeks consistently elevated plasma

aldosterone concentrations by 45% or more ($P < 0.01$ or less) in healthy volunteers and patients with hypertension (Weidmann et al.,1980; Chalmers et al.,1982; LeBel et al.,1983). Urinary aldosterone excretion was increased from 3.7 to 8.4 ug/24 hours ($P < 0.05$) in 6 healthy subjects administered indapamide 5 mg daily for 14 days (Noveck et al.,1983). There appears to be no correlation between urinary prostaglandin (PG) excretion (reflecting increased secretion of PGs by the kidney) and degree of increase in plasma renin activity and plasma aldosterone during indapamide therapy (LeBel et al., 1983). Pindolol 10 to 40 mg daily did not influence the increased aldosterone secretion induced by indapamide (Chalmers et al., 1982; LeBel et al., 1983).

3. Cardiovascular responses

(a) Effects on the heart

In an attempt to gain an insight into the mechanism of action of any new hypotensive agent, it is necessary to investigate its action on cardiovascular haemodynamics such as cardiac output, heart rate and peripheral resistance. However, interpretation of these results can often be made difficult by reflex homeostatic mechanisms and multiple actions of drugs. In normotensive cats,rats and dogs, with doses of indapamide upto 30 mg/kg, there was no change in cardiac output, heart rate, peripheral

or pulmonary resistance but neither was there an alteration in blood pressure (Moore et al., 1977). In renal hypertensive dogs, Laubie and Schmitt (1977) found that blood pressure reduced at a dose of 1 mg/kg i.v. and cardiac output showed an increase after 2 hours and a slight decrease over 24 hours; the latter effect was probably due to volume depletion. In contrast, frusemide showed a marked decrease in cardiac output with concurrent increases in sodium and water excretion.

A non-invasive cardiovascular assessment of indapamide has been made in hypertensive patients (Dunn et al., 1981). These workers have shown that after 8 weeks' treatment there was a significant rise in heart rate in both supine and erect positions as measured by pulse rate. Cardiac output measured indirectly by echo-cardiography, also rose significantly but this may in part be due to the increase in heart rate. Haiat et al.(1981) however, have shown from 24 hour monitoring of ECG after 1 month's treatment that heart rate remains unchanged. Other workers have shown no significant change in pulse rate (Fernandes et al.,1977; Andries et al., 1980; Velasco et al., 1980; Bowker and Murphy, 1981; Burgess et al.,1981) or a non-significant increase (Anavekar et al.,1980; Weidmann et al., 1980).

Heart rate during long term treatment with indapamide has generally remained unchanged, although some clinical reports have revealed significant decreases (Hamilton and Kelly, 1977; Turner et al., 1977; Dean, 1981; Guidi et al., 1982) or increases (Brennan et al., 1982; Houde and Carrier, 1983). Heart rate did not change from baseline measurement or vary with treatment group in parallel studies where indapamide 2.5 mg daily was compared with cyclopenthiazide 0.5 mg (Khan, 1981), or hydrochlorothiazide 50 mg alone (Ogilvie et al., 1983; Plante and Robillard, 1983) or in combination with amiloride 5 mg (Anavekar et al., 1979) each administered daily. The bradycardia response to the Valsalva manoeuvre was intact in healthy volunteers administered indapamide 5 mg daily for 14 days (Noveck et al., 1983).

The variable response observed with heart rate may be indicative of indapamide exerting an action on both arteries and veins.

In patients with hypertension, indapamide 1.0, 2.5 and 5 mg daily for 4 to 8 weeks had no effect on left ventricular end-diastolic or end-systolic volumes (Dunn et al., 1981; Gensini et al., 1983; Leenen et al., 1983). Ejection fractions as measured by echo-cardiography, were unchanged following long term treatment with indapamide in some patients (Gensini et al., 1983; Leenen et al., 1983).

While those assessed by Dunn et al.(1981) had increased ejection fractions (increased from 63 to 69%; $P < 0.05$). Stroke volumes were unchanged following indapamide 2.5 mg daily for 6 to 8 weeks (Dunn et al., 1981; Gensini et al., 1983).

Cardiac output, as assessed by echo-cardiography, was increased in the patients of Gensini et al., 1983 (increased from 5.92 to 6.63 L/min, $P < 0.05$) after indapamide 2.5 mg daily for 6 to 8 weeks; however, the same dosage administered for 6 weeks did not alter cardiac output in another study (Velasco et al., 1982). Cardiac index was unchanged in patients administered indapamide 1 to 5 mg daily for 4 to 8 weeks whether assessed by echo-cardiography (Leenen et al., 1983) or via a more precise technique utilising thermodilution catheters (Villarreal et al., 1983).

(b) Effect on cardiac function

Left ventricular function has been investigated non-invasively after treatment with indapamide for 24 weeks by measurement of the mean velocity of circumferential fibre shortening using standard echo-cardiographic techniques (Horgan et al., 1981). No significant changes were seen after either 12 weeks or 24 weeks treatment. Another study (Haiat et al., 1981) showed that there were no significant changes in ECG measurements in patients who were

monitored continually for an average of 24 hours following month's treatment with indapamide. Indapamide does not therefore appear to have any detrimental effect on the heart or cardiac performance.

Regression of left ventricular hypertrophy and cardiomegaly (as assessed by unspecified methods) occurred in 50 to 53% respectively, of the patients with these conditions treated with indapamide 2.5 mg daily for 1 to 18 months (Froment et al., 1975; Naegel et al., 1975; Rodat, 1975; Royer, 1976). Reduction of heart and chamber size was presumably due to improved blood pressure control.

In healthy volunteers and patients with hypertension, indapamide 2.5 or 5 mg daily for 14 to 90 days did not induce electrocardiographic alterations of the P-R or QRS intervals (Haiat et al., 1981; Noveck et al., 1983) or the QT intervals and T wave amplitude (Noveck et al., 1983).

(c) Effects on peripheral vascular resistance

Peripheral arterial resistance index was significantly reduced following 2 months treatment with indapamide as measured by carotid pulse wave recording (Canicave and Lesbre, 1977). Burgess et al.(1981) found that indapamide increased skeletal muscle blood flow by 25% (as measured by tracer disappearance metered to determine blood flow) after 1 week of indapamide treatment and 40% after 6 weeks.

Ogilvie et al.(1983) and Velasco et al.(1982) reported that in patients with hypertension, indapamide 2.5 mg daily for 6 to 12 weeks increased muscle or limb blood flow. Decrease in limb vascular resistance, total peripheral resistance was reported by Gensini et al.(1983); Velasco et al.(1982) and Villarreal et al.(1983). These results are interesting when compared to the hypotensive activity where there was little effect after one week but a significant reduction in blood pressure by the end of the study. This could suggest that after the first week indapamide may alter muscle blood flow and only after more prolonged dosing is there a direct effect in reducing peripheral arterial resistance. These results would imply that at least part of the hypotensive response to indapamide is due to an action on vascular smooth muscle whether by vasodilatation or by some other mechanism.

(d) <u>In vivo effects on vascular reactivity (Table-1)</u>

Several groups of investigators have studied the changes in vascular reactivity (assessed as pressor responsiveness) which occurs in association with indapamide administration in laboratory animals (Finch et al., 1977a,b; Moore et al., 1977; Hicks, 1979) and man (Weidmann et al., 1980; Grimm et al., 1981a; Noveck et al., 1982; Boer et al., 1983).

Pressor response to oxotremorine following blockade of peripheral muscarinic receptors with atropine was decreased more than 50% from control values in normotensive rats administered indapamide 10 mg/kg/day or reserpine 0.5 mg/kg/day orally for 6 days (Moore et al.,1977). The same dose of indapamide administered to pithed DOCA/saline-hypertensive rats for 10 days resulted in significant decreases in vasoconstriction when the rats were administered NA ($P < 0.03$) or TYR ($P < 0.05$) intravenously (Finch et al., 1977a,b). Pre-treatment of other DOCA/saline-hypertensive rats with hydrochlorothiazide 5 mg/kg intraperitoneally resulted in a similar hypotensive response noted in the indapamide-treated rats, but pressor responses to pharmacological or electrical stimuli were not altered when compared with controls. However, indapamide (10 mg/kg p.o.) orally reduced from approximately 175 to 125 mmHg ($P < 0.01$), the pressor response to electrical stimulus (Hicks, 1979). After 4 days dosing at 100 mg/kg p.o. of indapamide pressor responses to ANG II were significantly diminished by 25% in pithed rat preparations (Kraetz et al., 1978).

In studies in man, Weidmann et al.(1980) administered indapamide 2.5 mg daily to 12 patients for 6 weeks to evaluate response to vasoconstrictive agents following long term therapy. The pressor dose was defined as the quantity of vasoconstrictor substance necessary to increase

mean (NA) or diastolic (ANG II) blood pressure by 20 mmHg. Cardiovascular reactivity to NA was significantly decreased in patients with borderline hypertension only (pressor dose was increased from 99 to 156 ng/kg/min; $P < 0.02$). The pressor dose of ANG II was also increased following indapamide treatment, but only achieved statistical significance when normo- and hypertensive patients were analysed together (12 to 21 ng/kg/min; $P < 0.05$). Similar findings were reported by Grimm et al.(1981a) in patients with mild to moderate hypertension. Indapamide-induced changes in NA pressor dose and mean blood pressure were found to be inversely correlated.

Vascular reactivity was also assessed by Noveck et al. (1982), who administered indapamide 5 mg daily to healthy volunteers for 14 days prior to administering increasing doses of PE or ANG II. A pressor response was defined as increases of 25 to 35 mmHg and 20 to 30 mmHg in systolic and diastolic blood pressures, respectively. Pressor doses of PE were increased from 5.03 to 10.72 ug/kg, and pressor doses of ANG II increased from 16.7 to 31.7 ng/kg after indapamide treatment.

In these studies (Weidmann et al.,1980;Grimm et al., 1981a; Noveck et al., 1982), significant changes in plasma

catecholamine concentrations did not occur during indapamide treatment. However, plasma renin activity was increased ($P < 0.05$ or less) in all three studies, and increases ($P < 0.05$) in plasma (Weidmann et al., 1980) and urinary (Noveck et al., 1982) aldosterone concentrations were also noted.

In hypertension, increased blood pressure results from constriction of the small arteries and arterioles, which leads to increased resistance to flow. This increase in peripheral resistance may theoretically result from the presence of increased stimuli leading to excess vasoconstriction or from intrinsic abnormalities within the resistance vessels leading to an increased response to normal stimuli, or a combination of the two mechanisms. There is fairly general agreement that hypertension is accompanied by evidence of increased vascular reactivity to constrictor stimuli, and this change may be responsible in part, if not mainly, for the increased peripheral resistance which characterises this disorder. The mechanism(s) responsible for increased vascular activity are unclear, although structural medial hypertrophy in resistance vessels, abnormalities in vascular smooth muscle calcium-sodium exchange processes and local intravascular release of vasoactive substances (particularly PGs) have been suggested as possible contributing events (Doyle, 1982).

Table-I : Effect of indapamide on vascular reactivity

| Reference | Population | Indapamide regimen | Vaso-constrictor, stimulus | Effect on vasoconstrictor response |
|---|---|---|---|---|
| Boer et al., (1983) | Hypertensive | 1.25 mg or 5 mg daily 28 days | NA i.v. | Decrease in pressor reactivity occurred in responding (8 of 10) patients. Post-treatment appeared to be dose related |
| Carretta et al. (1983) | Hypertensive | 2.5 mg daily 42 days | NA i.v. | Decrease ($P < 0.05$) in pressor reactivity in 8 of 10 patients. |
| Grimm et al. (1981a) | Normotensive | 2.5 mg daily 42 days | NA i.v. | No significant change in pressor dose of either agent following indapamide treatment |
| | Hypertensive | 2.5 mg | NA i.v. | Increase ($P < 0.001$) in pressor dose |

Contd...

Table-I : Effect of indapamide on vascular reactivity (Contd.)

| Reference | Population | Indapamide regimen | Vaso-constrictor, stimulus | Effect on vasoconstrictor response |
|---|---|---|---|---|
| | | | ANG I.v. | Increase($P < 0.05$) in pressor dose required |
| Noveck et al, (1982) | Normotensive | 5.0 mg/day 14 days | PE i.v.<br>ANG i.v. | Increase ($P < 0.05$) in pressor dose required |
| Weidmann et al, (1980) | Normotensive and hypertensive | 2.5 mg daily 42 days | NA i.v. (15-30 mg/L) | Increase($P < 0.02$) in pressor dose required for borderline hypertensives ($P \leq 0.02$) and all subjects together but not in normotensives. |
| | | | ANG II (1.5-3.0 ug/L) | Pressor dose in indapamide treatment patients approximately doubled, but significant only when all patient groups analysed together ($P < 0.05$) |

Pressor response measured indirectly using standard cuff and sphygmomanometer or automatic blood pressur recorder.

(e) In vitro effects on vascular reactivity

Indapamide has been shown to inhibit vascular smooth muscle contractile response to various agonist drugs and electrical stimulation in a wide variety of in vitro preparations from rats (Kyncl et al.,1975; Finch et al., 1977a; Uhlich et al., 1977; Kraetz et al.,1978; Borkowski et al.,1981) and rabbits (Kyncl et al.,1975; Usui et al., 1978). ANG, ADR, TYR, $PGF_2$ and nicotine resulted in decreased vasoconstriction in the presence of indapamide, while its effects on NA induced smooth muscle contraction have been inconsistent. Resting tone in arterial and venous smooth muscle is usually not affected by indapamide (Campbell and Moore, 1981) (Table-II). In the perfused mesentery preparation, indapamide was slightly more potent than frusemide and considerably more active than either chlorthalidone or hydrochlorothiazide (Kraetz et al.,1978). In the portal vein preparation, responses to electrical stimulation and NA were antagonized after incubation for 1 hour with indapamide but not hydrochlorothiazide 0.1 mmol/l (Borkowski et al.,1981). The vascular activity of these various agents does not correlate with their natriuretic potency.

Rat diaphragmatic twitch in response to constant phrenic nerve stimulation was not antagonized by indapamide, suggesting that it may have little effect on skeletal muscle innervation (Borkowski et al., 1981).

Indapamide had a relaxing effect on contraction in various rabbit arterial preparations which had been stimulated by $PGF_2$, this relaxation was not inhibited by atropine propranolol or aminophylline (Usui et al.,1978). Hydrochlorothiazide produced a lower frequency of relaxation than indapamide. In these $PGF_2$ stimulated vessels, although the statistical significance of this difference was not stated. Interestingly, Usui et al.(1978) reported that indapamide potentiated pulmonary arterial contractile response to transmural electrical stimulation. Interference with neuronal amine uptake was the apparent cause of the inhibition of nicotine and TYR induced vasoconstriction. Usui and co-workers indicated that indapamide did not appear to relax vascular smooth muscle through ganglionic blockade or decreased NA from adrenergic nerve terminals, but suggested as have Burgess et al.(1981) and Campbell and Moore (1981) that the effect of indapamide on contraction may be due to a direct action on vascular smooth muscle.

Decreased contractile response was not seen in mesenteric arteries or portal veins removed from indapamide-treated DOCA-hypertensive rats and exposed in vitro to NA, 5-HT or adenosine-5'triphosphate (Finch et al., 1977a,b).

Table-II: Effects of indapamide on vascular reactivity in vitro

| Preparation | Vasoconstrictor stimulus | Change in response | Indapamide concentration (mmol/L) | Reference |
|---|---|---|---|---|
| Aortic strip | ANG | 44% | 0.3 | Kyncl et al.(1975) |
| | ANG | 15% | 0.15 | Uhlich et al. (1975) |
| | NA | 70% | 0.6 | |
| Vena cava* | NA | 52% | 3.0 | |
| | ANG | 59% | 0.03 | Kyncl et al.(1975) |
| | ADR | 86% | 0.3 | |
| Portal vein | NA | 48% | 0.5 | |
| | Transmural electrical stimulation | 39% | 0.5 | Borkowski et al. (1981) |
| Krebs-perfused mesentery | NA | 50% | 0.12 | Kraetz et al.(1978) |
| Krebs-perfused kidney | Periarterial renal nerve stimulation (10 Hz) | 30% | 0.01 | |
| | | 77% | 0.1 | Borkowski et al. (1981) |
| | NA | 50% | 8.1 | |

Contd...

Table-II: Effects of indapamide on vascular reactivity in vitro (contd.)

| Prepara- | Vasocons-trictor stimulus | Change in res-ponse | Indapa-mide concen-tration (mmol/L) | Reference |
|---|---|---|---|---|
| Vas deferens | Transmural electrical stimulation (3-12 Hz) | 0% twitch | 0.1 | |
| | | 40% | 0.1 | Borkowski et al. (1981) |
| | NA | 0% | 0.1 | |
| Super-fused anococcy-geus muscle | Transmural electrical stimulation (2 Hz) | 63% | 0.05 | |
| | | 76% | 0.1 | |
| | NA | 10% | 0.1 | |
| | Tyramine | 67% | 0.1 | Borkowski et al. (1981) |
| Phrenic nerve diaphragm | Phrenic nerve stimulation (0.25 Hz) | 0% | 0.1 | |

* All preparations from normotensive rats (except rabbit vena cava).

Dick and Feddo (1984) reported comparative study on the effects of indapamide with those of chlorthalidone and of drugs potentially interfering with calcium transport, e.g. verapamil, papaverine, phentolamine and diazoxide using isolated rabbit aorta in order to detect calcium antagonistic properties. Drugs were introduced into medium and left in contact with the tissue for 20 minutes. Indapamide and chlorthalidone failed to show any relaxation effect towards either NA or high $K^+$ pre-contracted aorta strips, whereas verapamil and papaverine reduced the $K^+$ contraction dose dependently and phentolamine, verapamil, papaverine and diazoxide induced a significant relaxation of the NA contraction. Pre-incubation with indapamide or chlorthalidone did not affect the dose-response curve of NA-induced contractions. Phentolamine antagonized the NA contraction strongly whereas verapamil and papaverine shifted the dose-response curve to the right only at the highest concentration. In a $Ca^{2+}$ depleted and high $K^+$ depolarized aorta pre-incubation with verapamil was able to antagonize $Ca^{2+}$-induced contraction effectively in a dose-dependent fashion whereas papaverine only showed partial inhibition at the highest concentration. The effects of the drugs on responses to NA in a $Ca^{2+}$ free medium were also investigated. This type of contraction is likely to be due to mobilization of internally located $Ca^{2+}$. The results demonstrate that phentolamine was able to counteract this type of

contraction effectively whereas only a high concentration of verapamil, papaverine and diazoxide was effective in reducing the NA contraction in $Ca^{+2}$-free medium. Both indapamide and chlorthalidone failed to affect this type of contraction. In conclusion, neither indapamide nor chlorthalidone possess calcium entry and or intracellular calcium antagonistic properties under different conditions as measured in a conduit vessel of rabbits. It remains to be seen that same holds true for resistance vessels in e.g. mesenteric vascular bed or intra-renal resistance vessels.

(f) Electrophysiological measurements

The electrophysiological and mechanical properties of vascular and cardiac muscle have been studied to elucidate the mechanism of action of indapamide at the level of the muscle cell membrane. Mironneau and Gargouil (1979) studied action potentials, transmembrane currents and muscle contraction in longitudinal strips of rat or rabbit portal vein. Short-lasting depolarizations (50 msec) caused an inward flow of calcium ions which triggered the phasic component of muscle contraction in the portal vein. This calcium current was unaffected by NA but was increased by ANG. Incubation with indapamide 0.3 mmol/l for only 3-5 minutes reduced the action potential amplitude (50%), the inward (27%) and outward (19%) transmembrane currents and the phasic contraction (29%). Recent work has shown that contractions of this tissue are

reduced even at 3 umol/l (Krikorian, 1980). The increase in calcium current and the phasic contraction to ANG were abolished in the presence of 0.3 mmol/l indapamide. Recent work (Campbell and Moore, 1981) has shown that indapamide is 10-200 times more potent in abolishing the ANG-induced increase in calcium current and the outward potassium current but hydrochlorothiazide and chlorthalidone at the same concentration were without significant effect. Longer-lasting depolarizations (100-400 msec) produced a tonic contraction which was independent of the inward calcium current and consistent with calcium release from intracellular stores. NA increased both this tonic contraction and the outward current. Indapamide could only reduce the NA-induced increase in contraction after incubation for 20-30 minutes; brief exposure being ineffective. Indapamide could affect intracellular calcium stores secondary to inhibition of inward calcium transport. Further confirmation of the action of indapamide on calcium flux has been reported (Schleiffer et al., 1980). Incubation of rat thoracic aorta with indapamide 2.75 umol/l for only 2-10 minutes significantly enhanced the ANG stimulated increase in Ca influx and efflux.

4. Effect on prostaglandin (PG) synthesis

Many studies have demonstrated the ability of renal tissues to generate PGs. Although the exact interrelationships between PG metabolism (primarily that of $PGE_2$ and $PGI_2$) and blood pressure have not been elucidated, it is likely that some PGs play some part in the overall regulation of blood pressure (Lant, 1981; Campbell, 1983).

The in vitro effects of indapamide, frusemide, spironolactone and hydrochlorothiazide (all in concentrations ranging from 0.1 to 5000 nmol/L) on PG and thromboxane biosynthesis were studied in sheep seminal vesicles and human platelet microsomal fractions, respectively (Gbeassor et al., 1982). While indapamide was the most potent inhibitor of thromboxane synthesis, hydrochlorothiazide showed no activity at all. Similarly indapamide was the most potent stimulator of the vasodepressor $PGI_2$, with hydrochlorothiazide again showing little activity.

In 11 of 19 patients with essential hypertension, indapamide 2.5 mg daily for 6 weeks increased ($P < 0.025$) urinary $PGE_2$ excretion probably via stimulation of renal production (LeBel et al., 1983). Urinary $PGF_2$ excretion was not significantly altered and there was no correlation between the percentage difference in $PGE_2$ excretion

(43% increase) and the mean changes in blood pressure, plasma renin activity or plasma aldosterone concentrations. Renal production of $PGE_2$ is suppressed in a certain percentage of patients with essential hypertension, and alteration of concentrations during treatment with indapamide could result in intra-renal haemodynamic changes which might contribute to a decrease in blood pressure (LeBel et al., 1983).

5. Mechanism of antihypertensive action

It has been proposed that indapamide decreases blood pressure via 2 major mechanisms: through relaxation of vascular smooth muscle, and diuretic effect (Issac et al., 1977; Campbell, 1983; Caruso et al., 1983; Rutsaert and Fernandes, 1983). Evidence for a direct effect on vascular smooth muscle consists of in vitro and in vivo data which demonstrate the ability of indapamide to decrease calcium inward currents, vascular reactivity and peripheral arterial resistance.

Indeed, indapamide appears capable of decreasing inward calcium currents and clonic (phasic) contractions in vitro smooth muscle preparations; it has therefore gained a provisional classification as a calcium

antagonist (Opie, 1980). However, the effect of indapamide on calcium influx has not been shown to be dose-dependent, as has been demonstrated with calcium antagonists such as verapamil and nifedipine, and it has not been possible to demonstrate any calcium antagonist effect on the heart with indapamide (Mironneau and Gargouil,1979). Comparison of indapamide with calcium channel blocking agents (e.g. papaverine, verapamil) did not demonstrate any significant direct interference by indapamide with trans-cellular or intra-cellular calcium mobilization (de Wildt and Hillen, 1983). Also, the effects on calcium current are elicited only when concentrations of indapamide are used which exceed by a factor of 50 to 100 the concentration in human serum required to induce a blood pressure-lowering response. It is not clear whether indapamide interferes directly with potential-dependent or receptor-operated channels responsible for smooth muscle contraction, or whether it alters some other process such as the sodium/calcium exchange proposed to control smooth muscle relaxation (Murphy and Mras, 1983). It could also be argued that the concentrations used in some of these in vitro studies (0.1-30 ug/ml) were higher than steady state blood levels (0.3 ug/ml) found in patients, however, it has been shown that the concentrations of indapamide are approximately 9 times higher in vascular smooth muscle than in the perfusate (Campbell et al.,1977), also there does

appear to be a ten-fold difference in the hypotensive dosage between the rat (0.3-1 mg/kg) and man (0.04 mg/kg), although it is difficult to be precise because of the absence of animal data on effective hypotensive doses during long-term treatment.

Studies in man have shown treatment with indapamide to be associated with decreased vascular reactivity. In patients with hypertension, limb vascular resistance, total peripheral resistance and peripheral resistance index were decreased and muscle blood flow was increased following the administration of indapamide. Although, these changes were of statistical significance, their clinical importance remains uncertain, particularly since changes in calculated resistance values are notoriously difficult to attribute solely to vasodilation or vasoconstriction (Safar et al., 1983; Schlant et al., 1982).

Indapamide has demonstrated considerable efficacy as an antihypertensive agent in patients with renal insufficiency and in a small group of patients with renal failure of sufficient severity as to warrant frequent haemodialysis. This has been suggested as being supportive of a primarily vascular mechanism of action (Caruso et al., 1983; Santoro et al., 1982) on the premise that a diuretic antihypertensive agent would be ineffective in this patient

population. Excepting the patients requiring haemodialysis (a procedure capable of lowering blood pressure through removal of sodium), the mean creatinine clearance in the patients with renal insufficiency receiving indapamide was approximately 50 ml/min. However, thiazide diuretics may also lower blood pressure in patients with creatinine clearances as low as 25 ml/min (Acchiardo and Skoutakis, 1983); in other studies, chlorothiazide significantly decreased blood pressure in patients with a mean creatinine clearance of 14 ml/min (Jones and Naura,1979); and the quinazolinone diuretic metolazone was effective in the treatment of hypertensive patients with creatinine clearance as low as 15 ml/min (Bennett and Porter, 1973).

Although there are some notable differences, the renal and metabolic effects exerted by indapamide are similar to many available diuretic agents and their blood pressure-lowering abilities are almost identical. Such biochemical changes are generally not observed with vasodilating drugs which decrease blood pressure solely due to their direct effect on vascular smooth muscle, through inhibition of peripheral or central nervous system activity, or through inhibition of inward calcium current in vascular smooth muscle (Mimran et al., 1983). In addition, the reflex increase in sympathetic activity and heart rate usually seen with direct-acting vasodilating agents

(Gunnels, 1982) does not occur during indapamide treatment. However, there is recent evidence (Caretta et al., 1983) which shows that indapamide interferes with the baroreceptor reflex and this may account for the lack of tachycardia at rest seen following treatment with this agent. Thus whether the vascular effects of indapamide make an important contribution to its clinical efficacy or only ancillary properties, is not yet clear, and requires further careful study (Chaffman et al., 1984).

6. Metabolic effects

(a) Effects on sodium balance

In healthy volunteers and patients with hypertension, single doses of indapamide increased the percentage of filtered sodium excreted to 3.4% ($P < 0.001$) (Onesti et al., 1977b; Pitone et al., 1978) whereas non-parallel studies have shown the percentage of filtered sodium excreted following usual doses of thiazide compounds and frusemide to be 8 and 23%; respectively (Brater and Thier, 1978; Franscisco and Ferris, 1982). Low doses of indapamide (less than 1 mg) have not resulted in statistically significant episodes of natriuresis, but larger doses ranging from 2.5 to 30 mg have increased urinary sodium excretion by 72 to 127 umol/min (Onesti et al., 1977b; Caruso et al., 1983; Reyes et al., 1983b). In most studies,

indapamide (usually 2.5 mg daily) has not altered total exchangeable sodium. Serum sodium concentrations following long term administration of indapamide have generally not been altered (Witchitz et al., 1974; Isaac et al., 1977; Santoro et al., 1982; Grimm et al., 1981a, 1983).

(b) Effects on potassium balance

As indapamide increases the activity of the renin-angiotensin-aldosterone system and increases sodium delivery to the renal distal tubules (Pitone et al.,1978), it is not surprising that its administration should result in a dose-related increase in urinary potassium excretion and in decreased serum potassium concentrations.

Indapamide decreases estimated total body potassium, but these changes have been statistically insignificant ($\approx$ 125 mmol). Single doses of indapamide 2.5 to 40 mg have consistently increased the rate and quantity of urinary potassium loss in healthy subjects (Leary et al., 1973; Villarreal et al., 1983) and statistically significant decreases in mean serum potassium concentrations have occurred in approximately 75% of reported clinical trials of indapamide (Hamilton and Kelly, 1977; Santoro et al., 1982; Grimm et al., 1983; Houde and Carriere, 1983;Noble et al.,1983).Although these decreases have usually not exceeded the normal lower physiological limit for serum

potassium concentration. Some patients have required potassium supplements (Wallach, 1978a; Campbell ,1983). In parallel controlled studies, decreases in serum potassium concentrations following indapamide 2.5 mg daily were equal in magnitude compared with those with hydrochlorothiazide 50 or 100 mg daily (Laubie and Schmitt, 1977; Coutinho et al.,1980; Burke et al., 1983; Morledge,1983; Noble et al.,1983; Ogilvie et al.,1983; Plante and Robillard, 1983).

(c) Other electrolyte studies

Urinary chloride excretion is significantly increased by indapamide in a dose-related manner (Caruso et al.,1983). A single dose of 40 mg increased chloride excretion from 7.5 to 25 mmol/hour ($P < 0.01$) and this increase in urinary excretion was prolonged (upto 72 hours). The single dose administration of indapamide 2.5 mg increased 24 hour urinary chloride loss upto 106.3%, whereas 40 mg of the relatively short-acting ($\approx$ 6 hours) agent frusemide increased excretion by 40%. However, serum chloride concentrations seen with indapamide have not resulted in concentrations below the normal range (Froment et al.,1975;Royer, 1976; Hamilton and Kelly, 1977; Freitag and Miller,1980; Capone et al.,1983; Noveck et al.,1983; O'Brien et al.,1984).

Bicarbonate ion excretion and serum bicarbonate concentrations appear to be minimally affected by indapamide (Milliez and Tcherdakoff, 1975; Witchitz et al.,1975; Turner et al.,1977; Anavekar et al.,1979; Chalmers et al., 1982; Lemmieux and L'Homme, 1983).

Most studies have shown indapamide to have a hypocalciuric effect approximately equal to that of hydrochlorothiazide in patients with hypertension with normal or elevated serum calcium concentrations (Campbell and Phillips, 1974; Andries et al.,1980; Santoro et al., 1982; Waal-Manning and Doesburg, 1982; Reyes et al., 1983b). Serum calcium concentrations have not been altered during treatment with indapamide and urinary phosphate excretion and serum phosphate concentrations have not been appreciably altered (Kubik and Coote, 1981; Waal-Manning and Doesburg, 1982; Lemmieux and L'Homme, 1983).

The single dose administration of small dose of indapamide (2.5 mg) to 7 healthy subjects did not alter 24 hour urinary magnesium excretion inspite of sodium, potassium and chloride loss (Reyes et al., 1983b). The serum magnesium concentrations were not altered by indapamide 2.5 mg daily (Acchiardo and Skoutakis,1983). Indapamide 40 mg increased ($0.05 > P > 0.02$) urinary magnesium excretion and decreased serum magnesium concentrations

($P < 0.01$), and serum concentrations remained decreased for 10 days following this single dose (Campbell and Phillips, 1974; Acchiardo and Skoutakis, 1983; Reyes et al., 1983b).

(d) Effect on uric acid

35 to 50% of patients with primary gout have hypertension and 26 to 33% patients with mild hypertension (untreated) are hyperuricaemic (Ogilvie, 1983). The incidence of hyperuricaemia may increase to 50 to 70% when diuretic therapy is instituted. Diuretic-induced hyperuricaemia is mainly due to extracellular fluid volume contraction (Mangini and Young, 1978; Plante and Robillard, 1983), but decreased urate excretion and/or post-secretory reabsorption may also play roles (Mangini and Young, 1978; Lant, 1981).

It is difficult to assess the exact potential of indapamide to increase serum uric acid concentrations. Several well-designed trials have shown that indapamide (1 to 5 mg daily; 3 to 108 week treatment periods) could increase serum uric acid concentrations by 0.035 to 0.083 mmol/L (Royer, 1976; La Corte et al., 1980b; Weidmann et al., 1981; Santoro et al., 1982; Houde and Carriere, 1983; O'Brien et al., 1984) while other similarly conducted studies demonstrated no significant effect (Hatt and Leblond, 1975; Witchitz et al., 1975; Anavekar et al.,1979;

Andries et al., 1980). The ranging results may be due to exclusion of patients with histories of gout or hyperuricaemia from many of clinical trials (Hashida, 1977; Andries et al., 1980; Charoenlarp and Jarvoonvesama,1981; Horgan et al., 1981) or the administration of allopurinol or uricosuric agents during others (Rodat, 1975; Demanet et al.,1977; Goto et al., 1982; Beling et al., 1983). However, uncommon acute gouty arthritis has occurred during treatment with indapamide.

(e) Effects on glucose tolerance

In isolated perfused rat pancreas, high concentrations of indapamide (10 or 100 mg/L) have reduced total insulin secretory response to glucose infusions (Foy and Furman, 1972; Furman, 1977; Furman and Razak, 1981). Although indapamide 2.5 or 5 mg daily for 12 weeks increased blood glucose concentrations similarly to hydrochlorothiazide 50 mg twice daily (8.3, 15.8 and 11.6% respectively) in non-diabetic hypertensive patients (Slotkoff, 1980; Wheeley et al.,1982; Beling et al., 1983), most studies in diabetic and non-diabetic patients with hypertension have not revealed a significant decrease in glucose tolerance with indapamide (Coutinho et al.,1980; Greco et al., 1983). Similarly, indapamide has not significantly altered blood

glucose concentrations or insulin secretion in hypertensive diabetics who have received it for upto 1 year (Roux and Courtois, 1981; Baba et al., 1982; Bam and Bouwer, 1983). As decreased glucose tolerance with thiazide diuretics in non-diabetic patients with hypertension may take upto 2 years to develop, long term studies are required to determine the exact potential indapamide has in inducing this metabolic abnormality.

(f) Influence on lipid metabolism

Several sulphonamide diuretics in common use (hydrochlorothiazide, chlorthalidone and frusemide) are known to have a blood lipid-lipoprotein elevating effect both in healthy and hypertensive men (Joos et al., 1980; Grimm et al., 1981b) and in post-menopausal women (Boehringer et al., 1982). The specific mechanism of diuretic-induced increases in serum lipid concentrations is unknown (Grimm et al., 1981b; Perez-Stable and Caralis, 1983; Weidmann et al., 1983), but studies with chlorthalidone have indicated that it occurs most frequently in patients with low initial total cholesterol concentrations (4.8 mmol/l) (Perry, 1983). Although some investigators regard this phenomenon as a 'biochemical' side effect of uncertain clinical relevance (Boehringer et al., 1982; Ogilvie, 1982, 1983), it has been proposed that increased serum low

density lipoprotein, triglyceride and total cholesterol concentrations during antihypertensive therapy with diuretics may favour an increased risk of coronary artery disease (Grimm et al., 1981b) and counteract the benefits of reduction of mild and moderate hypertension (Perez-Stable and Caralis, 1983).

Long term data are limited, but the administration of indapamide 1 to 4 mg daily to healthy and hypertensive patients over 1 to 24 months has not been associated with increases in total serum cholesterol (Hatt and Leblond, 1975; Weidmann et al., 1981; Baba et al., 1982; Goto et al., 1982; Waal-Manning and Doesburg, 1982; Beling et al., 1983; Scalabrino et al., 1984) or low density lipoprotein concentrations (Baba et al., 1982; Goto et al., 1982; Waal-Manning and Doesburg, 1982; Meyer-Sabellek et al., 1984; Scalabrino et al., 1984).

7. Other activities :

Indapamide produces no significant effect on the central autonomic or somatic nervous systems, respiration, gastro-intestinal function and blood coagulation. Also, it does not appear to have any antipyretic, analgesic or anti-inflammatory activity.

8. Toxicology studies

Acute toxicity

Indapamide has a low order of toxicity. Median lethal doses ($LD_{50}$) were 410 to 557 mg/kg intraperitoneally and 577 to 635 mg/kg intravenously in mice; 393 to 421 mg/kg intraperitoneally and 394 to 440 mg/kg intravenously in rats; and 347 to 416 mg/kg intraperitoneally and 272 to 358 mg/kg intravenously in guinea-pigs. The oral $LD_{50}$ for all 3 species of rodent is 3000 mg/kg, whereas in dogs it was determined to be 2000 mg/kg (Kyncl et al., 1975; Moore et al., 1977; Pruss and Wolf, 1983).

Subacute and chronic toxicity

Indapamide 25 to 150 mg/kg administered orally to mice for 2 months and 100 to 300 mg/kg administered orally to rats for 3 months was found to be well tolerated in these laboratory animals. Although no abnormal organ histology occurred which was attributable to indapamide, the higher dosage levels did result in excerbation of spontaneously occurring renal and cardiac lesions (Moore et al., 1977; Pruss and Wolf, 1983).

Studies in mice and rats lasting 21 and 24 months, respectively failed to demonstrate any carcinogenic effects from the administration of indapamide 10 to 100 mg/kg/daily (Pruss and Wolf, 1983).

9. Effects on reproduction

Indapamide 0.5 to 18 mg/kg/daily neither affected male or female reproductive capacity nor induced teratogenic effects in mice, rats or rabbits (Moore et al.,1977; Pruss and Wolf, 1983). Maternal treatment with indapamide during gestation did not affect post-natal development in rat or mouse offspring (Moore et al., 1977).

10. Pharmacokinetic studies

In healthy volunteers bioavailability of indapamide after 5 mg dose was estimated to be 93% (Caruso et al., 1983). Peak concentrations of indapamide occurred approximately 0.5 to 2 hours after oral administration and remained relatively constant upto 8 hours. Mean steady state blood concentrations of 89 and 158.5 ug/L occurred after 4 daily doses of indapamide 2.5 and 5 mg respectively (Klunk et al., 1983).

In vitro, indapamide accumulated in vascular smooth muscle and the red cell binding of indapamide was found to be high. The red cell to plasma ratio of radioactivity after in vitro incubation of whole blood with $^{14}C$-indapamide ranged upto 9:1 and in vivo ratios obtained in man following treatment with indapamide was similar (5.7:1). Indapamide binds predominantly (98%) to the carbonic anhydrase fraction of the red cell, but the activity of this enzyme

remains intact (Campbell, 1977; Lettieri and Portelli, 1983). In man, indapamide is 76 to 79% protein bound.

The indapamide volume of distribution is large and has been estimated from blood concentrations to be 25 to 27 L (Grebow et al., 1982; Klunk et al., 1983). The volume of distribution estimated from plasma concentrations was 110 L (Campbell et al., 1976, 1977).

Human studies have shown indapamide to be excreted 60 to 70% renally, with about 7% as unchanged drug and the remainder as metabolic products. Upto 19 metabolites of indapamide have been detected in urine (Taylor et al., 1976; Campbell et al.,1977; Grebow et al.,1982). The renal clearance of indapamide has been estimated to be 1.71 ml/min; therefore, hepatic clearance is responsible for the greatest portion of the total systemic clearance (20 to 23.4 ml/min). Faecal elimination accounts for 16 to 23% of an orally administered dose. The elimination half-life of indapamide has been estimated to range from 13.9 to 17.8 hours in healthy subjects.

Indapamide does not significantly accumulate in patients with renal insufficiency or failure following long term treatment (Klunk et al.,1982). Pharmacokinetics data in patients with hepatic dysfunction are lacking. Indapamide is not dialysable.

11. Use in hypertension

The terms 'mild', 'moderate' and 'severe' hypertension respectively refer to diastolic blood pressure ranges of 90 to 104, 105 to 129 and 130 mmHg, unless otherwise specified.

(a) Open studies

In hypertensive patients (usually with mild to moderate hypertension) treated in published reports of open studies, indapamide 2.5 mg daily for 1 to 12 months reduced resting systolic and diastolic pressures by about 15 to 18%. In 2 studies (Naegel et al.,1975; Rodat, 1975), effort systolic and diastolic pressures were decreased by approximately 10 to 16%.

In these uncontrolled studies, the patient groups were predominantly (55 to 60%) female, and mean patient age generally ranged from 52 to 61 years. In several of the studies (Naegel et al.,1975; Brun and Grunwald,1976; Reyes et al., 1983a) patient dietary sodium intake was restricted to some degree whereas the patients of Issac et al.(1977) were allowed ad lib sodium intake. Several studies (Naegel et al., 1975; Rodat, 1975; Issac et al.,1977) permitted patients with severe or resistant hypertension to continue previous antihypertensive medications, including alpha-methyldopa, guanethidine or dihydrallazine. Following indapamide 2.5 mg daily for 1 month, Mimran et al.(1981, 1983) added a beta-adrenergic blocking agent to the drug regimen of

patients who had not achieved blood pressure 'control' with indapamide alone (approximately 10% of total patient group). When combined treatment was administered to these patients, mean diastolic blood pressure was decreased by 18 mmHg. In the study reported by Marais (1981) 264 of the 387 patients achieved normalisation of blood pressure on indapamide alone; approximately 69% of the patients with mild to moderate hypertension, and 40% of those with severe hypertension.

In the trial with the largest patient population (2184; Mimran et al., 1981, 1983), normalisation of blood pressure occurred most frequently between the first and second month of indapamide treatment. In this study, the antihypertensive efficacy and the tolerability of indapamide did not appear to be influenced by the age or sex of the patients, although the higher the untreated blood pressure before the initiation of indapamide, the greater the blood pressure reduction.

Overall, effectiveness ratings were generally based upon the ability of indapamide to reduce diastolic blood pressure to 90 to 95 mmHg or less, although ocular changes or functional symptoms were considered in some studies (Brun and Grunwald, 1976). In the multicentre trial reported by Marais (1981) indapamide was approximately 82% effective in the treatment of 189 patients with mild (diastolic 90 to 110 mmHg) hypertension; a single daily

dose of 2.5 mg was the sole agent used in 154 of these patients. This degree of effectiveness was similar to that noted in other open studies (Baba et al., 1982; Mimran et al., 1981, 1983; Naegel et al., 1975; Rodat, 1975) where effective ratings ranged from approximately 70 to 80%.

Of the 60 patients of Baba et al.(1982) with diabetes mellitus, only 4 exhibited decreased glucose tolerance while taking indapamide, and none of the 467 patients of Mimran et al.(1981, 1983) with elevated (6.05 mmol/L) pretreatment fasting blood sugars appeared to be affected when fasting blood glucose concentrations were repeated at 3 months.

(b) Comparisons with placebo

Unblinded comparisons: Indapamide has been compared with placebo treatment in a large number of short to long term (1 to 24 months) studies which have usually involved small (10 to 30) numbers of patients with mild to moderate essential hypertension. In such studies, indapamide (usually 2.5 mg daily) was clearly more effective than placebo treatment, most often lowering systolic and diastolic pressures or mean blood pressure by 10 to 20% more than placebo.

Of the 644 patients in the large multicentre trial of Passeron et al.(1981), the percentage of responders (in whom diastolic blood pressure normalised or fell at least 30 mmHg) was 64% following 3 months of treatment with indapamide 2.5 mg daily. This response rate was in general agreement with those of other placebo comparisons, which ranged from 70 to 90% (Jorge and Perello, 1980; Charoenlarp and Jarvoonvesama, 1981; Goto et al.,1982; Guidi et al., 1982; Santoro et al., 1982; de Ortiz et al., 1983); a notable exception was the response rate (2/13; 15%) of the patients studied by Fernandes et al.(1977), where the low (0.5 or 1.0 mg) daily doses of indapamide probably prevented optimum blood pressure responses.

The patients of Passeron et al.(1981) were divided into 3 groups according to pre-treatment blood pressures, and were monitored at monthly intervals over the 3-month course of indapamide treatment. In the 307 patients with mild hypertension mean blood pressures normalised following 1 month of therapy with indapamide 2.5 mg daily, while the patients with moderate and severe hypertension showed their largest declines in systolic and diastolic pressures after 2 and 3 months of treatment. Similarly, in the studies of Dunn et al.(1981) and Bam and Bouwer (1983), the antihypertensive effect of indapamide appeared

during the first month, increased during the second, and stabilized during the third month of treatment. In contrast to these findings, the patients of Bhalla (1981) exhibited their maximum antihypertensive response to indapamide during their first month of treatment. The antihypertensive effect of indapamide was sustained during upto 24 months of continuous treatment in a recent placebo comparison (Scalabrino et al., 1984).

(c) Single and double blind comparisons

In blinded, parallel group and cross-over comparisons of indapamide and placebo, the antihypertensive response to indapamide has been consistently better than that with placebo. Systolic and diastolic blood pressures (erect and supine) were generally reduced 10 to 20% from placebo levels, with response rates usually falling within the 50 to 70% range. The dose of indapamide was most often 2.5 mg daily, but Capone et al.(1983) also used 1 and 5 mg daily doses and 18 of the 24 patients of Van Hee et al.(1981) maintained excellent blood pressure control (decreases in supine systolic and diastolic pressures of 19 and 15% respectively) on indapamide 2.5 mg every other day following 2 months of daily administration.

Although the antihypertensive effect of indapamide was fully manifest in 4 to 6 weeks in several of the blinded placebo comparisons (Capone et al., 1983; Lenzi

and Di Perri, 1977; O'Brien et al., 1984) one group of patients had blood pressure reductions which stabilized only after 4 months of treatment, regardless of the pre-treatment severity of hypertension (Andries et al.,1980). Most of these studies were relatively short term (8 to 12 weeks) however, the long term trials of Andries et al. (1980) and Beling et al.(1983) further demonstrate that indapamide is capable of inducing a sustained blood pressure reduction in most patients treated.

12. Comparisons with hydrochlorothiazide

In parallel group and cross-over comparisons, indapamide 2.5 mg daily demonstrated antihypertensive efficacy essentially equal to that of hydrochlorothiazide 50 mg daily (Morledge, 1983; Noble et al., 1983; Ogilvie et al., 1983; Plante and Robillard, 1983) or 100 mg daily (Coutinho et al., 1980). In one partially retrospective study (Lemieux and L'Homme, 1983), indapamide induced a statistically greater decrease in blood pressure although the difference was not necessarily clinically important. Similarly, indapamide 2.5 mg daily showed statistically significant superiority over hydrochlorothiazide 50 mg daily in the study of Feldstein et al.(1981); however, randomisation of patients (re: placebo blood pressures) did not appear to be satisfactory. The patients in these studies had mild to moderate hypertension, with the

exception of the majority of those studied by Lemieux and L'Homme (1983) and Noble et al.(1983) where mean pre-treatment diastolic pressures were 129 and 111 mmHg, respectively. Following the administration of indapamide 2.5 mg hydrochlorothiazide 50 mg daily for 1 month, the patients of Noble et al.(1983) not responding (diastolic 90 mmHg) were placed on methyldopa as a second line medication (starting at 250 mg twice daily, and titrated to a dose not exceeding 3000 mg daily). Amongst the patients who required the addition of methyldopa to achieve adequate blood pressure control (n = 10, both group), those receiving indapamide 2.5 mg daily required a significantly smaller average dose than those receiving hydrochlorothiazide 50 mg (1100 vs 1575 mg, $P < 0.05$). In the study of Lemieux and L'Homme (1983), 11 patients also took reserpine and 9 patients took methyldopa, a beta-blocker or guanethidine in addition to indapamide or hydrochlorothiazide. Antihypertensive agents other than the study drugs were not used in the other trials.

13. Comparisons with bendrofluazide (bendroflumethiazide)

Single daily doses of indapamide 2.5 mg or bendrofluazide 5 mg produced similar reductions in blood pressure in 2 studies conducted in patients with mild or moderate essential hypertension (Bing et al.,1981; Zacharias,1981).

The two diuretic agents were the sole antihypertensive agents administered to the patients of Bing and co-workers whereas the patients of Zacharias were administered 100 or 200 mg daily in addition to the trial drugs. Indapamide and bendrofluazide induced a mean decrease in body weight of approximately 2.5 kg and significantly ($P < 0.05$) decreased serum potassium concentrations in the patients of Bing et al.(1981), while these parameters were not changed in the patients of Zacharias (1981).

In the study of Bing et al.(1981), 12 patients were continued on a combination of indapamide 2.5 mg and bendrofluazide 5 mg daily for an additional 16 weeks. This combination resulted in a further fall in diastolic pressure (from approximately 92 to 87 mmHg (erect), but not in systolic or mean arterial pressure.

14. Comparisons with other diuretic agents

In controlled studies, generally of brief duration, indapamide 2.0 to 5.0 mg daily was shown to have equal antihypertensive efficacy compared with daily administration of hydrochlorothiazide/amiloride combination (Anavekar et al., 1979), chlorthalidone 100 mg (Hatt and Leblond, 1975), meticrane 300 mg (Ikeda et al., 1982), or chlorothiazide 500 mg (Milliez and Tcherdakoff, 1975). Pre-treatment and placebo systolic and diastolic pressures

were usually decreased 10 to 20% by indapamide and the other diuretics tested. Two of the studies compared indapamide with other diuretics when each was used as the sole antihypertensive agent, but patients in the other 2 studies (Hatt and Leblond, 1975; Anavekar et al., 1979) continued previous non-diuretic therapy (including methyldopa, beta-blockers guanethidine clonidine, prazosin and reserpine) throughout the comparisons.

15. Comparisons with beta-adrenergic blocking agents and their use in combination

In double-blind randomised placebo-controlled studies, the antihypertensive effectiveness of indapamide 2.5 mg daily was shown to equal that of pindolol 10 or 15 mg (Chalmers et al., 1982; Rumboldt et al., 1984), atenolol 100 mg daily (De Divitiis et al., 1983), or metoprolol 200 mg daily (Kubik and Coote, 1981). In these 4 studies, indapamide generally decreased diastolic pressures 6 to 14%, while beta-adrenergic blockade resulted in diastolic pressures 7 to 16% below placebo values. The combination of indapamide with a beta-adrenergic blocker was always more effective in decreasing diastolic pressures than either agent used alone, with 10 to 20% decreases being most common. A factorial analysis following the study of Chalmers et al.(1982) revealed that the hypotensive effects seen in the combination therapy phase represented

simple addition of the separate effects of the two drugs. A 'response' rate of 67% with combined therapy with indapamide and atenolol, compared with 47% with either drug alone, was reported by De Divitiis et al. (1983) when response was defined as a lowering of diastolic pressure to 95 mmHg.

As might be expected, each of the beta-antagonists compared with indapamide induced a decrease in heart rate (usually 5 to 10 beats/min) when used alone or in combination. When indapamide was used as the sole antihypertensive agent, significant decreases in heart rate were not reported.

Indapamide 2.5 mg daily for 8 weeks further decreased mean systolic and diastolic blood pressures by approximately 10% in 24 patients who had an inadequate antihypertensive response (diastolic pressure remaining 95 mmHg) to oxeprenolol 160 to 480 mg daily (O'Brien et al., 1984).

16. Comparison with methyldopa and their use in combination

In a single published report in 71 patients with mild (diastolic pressure 95 to 109 mmHg, 52 patients) or moderate (diastolic pressure 110 to 120 mmHg, 19 patients) essential hypertension, indapamide, 2.5 mg daily was essentially equal to methyldopa 500 mg daily in blood

pressure-lowering effect (Meine, 1981). After 8 weeks of active treatment with either agent, indapamide decreased systolic and diastolic pressures about 18% compared with placebo levels, whereas methyldopa induced an approximate 14% decrease. In addition, the rate of blood pressure response was faster with indapamide (2 vs 4 weeks for normalisation of blood pressure to 160/90 or less). Following 8 weeks of treatment, 50% of the patients on indapamide had 'normal blood pressure, while only 22% of the methyldopa patients had achieved this level of antihypertensive control.

The antihypertensive efficacy of indapamide in combination with methyldopa was studied by La Corte et al.(1980a). Seventeen patients with hypertension who had been stabilized on methyldopa 500 to 1000 mg daily were randomly placed on indapamide 2.5 mg daily or placebo for 6 weeks. The mean decreases in systolic and diastolic blood pressures following the addition of indapamide to methyldopa treatment were 19/8 mmHg indicating the efficacy of the combination. The agents were well tolerated during their co-administration.

17. Use in patients with renal insufficiency

In an open study by Brennan et al.(1982), indapamide 2.5 mg daily was substituted for the particular diuretic (frusemide, chlorthalidone, or a thiazide) which had

previously been administered to 13 patients. The hypertension and renal insufficiency of the patient group were both moderate in severity (mean pressure, 161/103 mmHg; mean creatinine clearance 50 ml/min, range 30 to 65 ml/min). The antihypertensive regimen of each patient included other agents (i.e. propranolol, methyldopa, guanethidine, hydrallazine, clonidine and prazosin) which were continued throughout the trial. After 6 weeks treatment with indapamide, diastolic blood pressure measurements were unchanged from those taken when the other diuretics had been administered. Although the blood urea nitrogen and serum creatinine values were changed, mean creatinine clearance increased to 64 ml/min ($P < 0.01$) indicating that the blood pressure control was not retained at the expense of renal function impairment.

In 6 patients with moderate hypertension and impaired renal function (creatinine clearance 60 ml/min), indapamide 2.5 mg daily for 8 weeks decreased systolic and diastolic blood pressures approximately 13.5% ($P < 0.01$), while mean serum concentrations of uric acid and potassium were altered from pre-treatment values from 0.42 to 0.45 mmol/L and from 4.7 to 4.4 mmol/L respectively ($P < 0.05$). Indapamide 2.5 mg daily was also used as the sole antihypertensive agent in 29 patients studied by Acchiardo and Skoutakis (1983) while 11 of these patients had normal renal function (creatinine

clearance 91 to 110 ml/min), 13 others had mild to moderate impairment (creatinine clearance 36 to 84 ml/min) and 4 had severely compromised renal function (creatinine clearance 8 to 27 ml/min). Regardless of the severity of the renal impairment; systolic and diastolic blood pressures were decreased 5 to 10% after 6 weeks administration. Renal function (as measured by creatinine clearance, blood urea nitrogen, and serum creatinine) was unchanged after treatment with indapamide. In a separate phase of this single-blind, placebo-controlled study, Acchiardo and Skoutakis (1983) also administered indapamide 2.5 mg daily to 9 functionally anephric and hypertensive patients (mean pre-dialysis pressures; systolic 150 mmHg and diastolic 90 mmHg) who required frequent haemodialysis. Over the 4-week treatment period, pre- and post-dialysis blood pressures were reduced 4 to 8% ($P < 0.05$). However, since the blood pressure of dialysis patients may be influenced by multiple factors and the patient groups were small, it is difficult to conclusively attribute this hypotensive effect solely to indapamide.

Heart rate and body weight were not significantly changed by indapamide in either study (Brennan et al., 1982; Acchiardo and Skoutakis, 1983).

18. Use in oedematous states

In patients with oedema due to unknown causes, congestive heart failure, or hepatic disease, indapamide 2.5 mg to 20 mg daily was an effective diuretic agent with both lower and moderately high doses (2.5, 5 and 10 mg) being approximately equal in effectiveness to hydrochlorothiazide 100 mg daily (Goldberg and Furman, 1974; Slotkoff, 1983). Further studies are required before the efficacy of indapamide in the treatment of oedema can be clearly stated.

19. Side effects

Approximately 25% of the clinical trial reports involving indapamide have stated that no side effects occurred during treatment, while an additional 25% have not addressed the subject of side effects at all. The incidence and severity of indapamide-induced hypokalaemia has been reasonably well documented, but little descriptive information regarding other side effects of indapamide has been reported. In comparative studies, the frequency or severity of side effects caused by indapamide was similar to or, in some cases, less than those of several benzothiadiazide diuretics, beta-adrenergic blockers and methyldopa. Most of the electrolyte and metabolic derangements indapamide can induce, occur only occasionally (Chaffman et al., 1984).

(a) Hypokalaemia

The administration of indapamide has resulted in statistically significant decreases in mean serum potassium concentrations in approximately 75% of published reports. Despite these decreases, most patient groups have maintained mean potassium concentrations within normal physiological limits. The clinical significance of such mild diuretic-induced changes in potassium balance is controversial (Perez-Stable and Caralis, 1983).However, some patients have had indapamide-induced decreases in serum potassium concentrations large enough to warrant supplemental potassium therapy (Horgan et al.,1981; Beling et al.,1983; Mimran et al., 1983). Clinical manifestations of hypokalaemia have occurred in 1.2 or 3% and 7% of patients treated with indapamide 2.5 or 5.0 mg, respectively.

(b) Other side effects

Central nervous system side effects reported after indapamide treatment, have included headache (Seedat and Reddy, 1974; Marais, 1981; Ikeda et al., 1982; Beling et al., 1983), dizziness and similar symptoms (Brun and Grunwald,1976; Andries et al.,1977; Turner et al., 1977; Bing et al.,1981; Bowker and Murphy, 1981; Brennan et al., 1982; de Ortiz et al., 1983; Slotkoff, 1983) and

nervousness and related complaints (Hashida, 1977; Brennan et al., 1982).

Fatigue and similar symptoms have been frequently reported (Hamilton and Kelly, 1977; Bowker and Murphy,1981; Horgan et al., 1981; Goto et al., 1982). Although fatigue with indapamide is usually not a serious problem, 4 of the 437 patients of Royer (1977) withdrew from therapy for this reason. Fatigue during indapamide treatment has been associated with a marked increase in sodium excretion (Milliez and Tcherdakoff, 1975). Muscular cramps or spasm (Anavekar et al., 1979; Astacio et al., 1980; Passeron et al., 1981) have also occurred occasionally, most frequently reported in the lower extremities (Noble et al., 1983; Vukovich et al., 1983).

Although orthostatic hypotension (Andries et al.,1977; Bowker and Murphy, 1981; Goto et al., 1982) and palpitations (Brennan et al.,1982; De Divitiis et al., 1983) have occasionally caused problems, the cardiovascular tolerability of indapamide has been good. A blood pressure rebound phenomenon does not occur following withdrawal of indapamide (Reyes and Leary, 1983).

Mucocutaneous or gastrointestinal disturbances (nausea, diarrhoea, indigestion, dry mouth, constipation) have been infrequently reported (Bowker and Murphy, 1981; Horgan et al.,1981; Passeron et al.,1981; Van Hee et al.,

1981). Butaeye et al.(1979) reported a single case of indapamide-induced hepatitis in a patient who had received 5 mg daily for 10 months. The diagnosis was confirmed by histology and a positive lymphoblast transformation test. Withdrawal of indapamide resulted in complete reversal of all abnormal laboratory and clinical findings.

Although rare, impotence and decreased libido have been reported in a few instances (Dunn et al.,1981; Capone et al., 1983; de Ortiz et al., 1983).

20. Dosage and administration

The recommended initial daily dose of indapamide for the treatment of hypertension or oedema is 2.5 mg administered orally. If after 1 or 2 months of therapy the antihypertensive response is found to be inadequate, the dosage may be increased to 5 mg daily or an additional antihypertensive agent may be added. Similarly, in the treatment of oedema, an inadequate diuretic response after 1 week of treatment is an indication for the higher dosage. If blood pressure is normalised within 1 to 2 months with indapamide 2.5 to 5 mg daily, the dose frequency may be reduced to alternate days in some patients without loss of control (Chaffman et al., 1984).

Indapamide is contraindicated in patients with anuria or those who have demonstrated hypersensitivity to the drug

or other sulphonamide-derived agents. It should be used with caution in patients with renal insufficiency or impaired hepatic function, as alterations in fluid and/or electrolyte balance induced by indapamide could exacerbate azotaemia or precipitate hepatic encephalopathy in these patients (Chaffman et al., 1984).

As with other diuretics, patients receiving indapamide should be observed for clinical signs of fluid or electrolyte disorders, and periodic laboratory determinations of serum electrolytes and organic substances (uric acid, creatinine, glucose, etc.) should be performed at appropriate intervals. Caution should be exercised when indapamide is administered to patients also receiving digitalis glycosides or lithium salts since hypokalaemia or hyponatraemia, both potential problems with indapamide therapy, may precipitate and/or worsen toxic reactions to these agents. Studies in diabetic patients with hypertension treated with indapamide have revealed alterations in glucose tolerance only rarely, but a clear statement on the effects of indapamide on glucose tolerance must await further long term well controlled trials (Chaffman et al., 1984).

21. Place of indapamide in therapy

Indapamide is an indoline derivative of chlorosulphonamide which shares many chemical, pharmacodynamic

and therapeutic similarities with the numerous sulphonamide diuretics currently available for therapeutic use. In addition to its diuretic activity indapamide has been shown to decrease vascular smooth muscle reactivity and peripheral resistance in various in vitro and in vivo models (Chaffman et al., 1984). Indapamide at low doses, has minimal diuretic activity and that it possibly exerts its hypotensive action by decreasing vascular reactivity to pressor agents, by inhibiting the net inward flow of calcium and thereby decreasing overall peripheral vascular resistance. Whether these peripheral effects make an important contribution to the antihypertensive activity of indapamide in man needs further clarification. The finding that indapamide retains its hypotensive activity in functionally anephric patients lends support to this hypothesis (Campbell and Moore, 1981). In usual dosages (2.5 mg) indapamide has demonstrated similar efficacy to the thiazide diuretics in lowering mild to moderately elevated blood pressure. Higher dosages (5 mg daily) have also been effective, but have been associated with significantly greater diuretic responses and tendencies toward biochemical aberrations (Chaffman et al., 1984).

Indapamide with its high lipid solubility is different from the diuretics since only small amounts are eliminated in the urine and it is preferentially taken up by the elastin of the vascular smooth muscle.

Indapamide may have a greater effect on vascular smooth muscle than the diuretics but does not have the pronounced activity of the vasodilators with their troublesome side effects such as orthostatic hypotension, flushing and tachycardia (Campbell and Moore, 1981).

Chaffman et al.(1984) reported that the primary advantage of indapamide over currently available diuretic agents is its apparent low side effect profile. Although more long term data from larger patient groups are needed to confirm the findings reported to date, some electrolyte and other metabolic abnormalities appear to occur with less frequency or severity with lower dosages of indapamide (2.5 mg) than with equipotent (re: blood pressure effect) dosages of some other diuretic agents. Indapamide also lacks significant effects upon the central nervous system and apparently does not inhibit normal cardiac or pulmonary function. Withdrawal of indapamide has not been associated with a 'rebound' effect on blood pressure.

Indapamide has also shown some efficacy in the reduction of salt and fluid retention in relatively small numbers of patients with oedema generally due to unknown causes or congestive heart failure.

Thus, indapamide appears to be a suitable alternative to more established drugs as a 'first-line' treatment for patients with mild to moderate hypertension.