Introduction

Herbal Medicine

Many of today's synthetic drugs originated from plant kingdom, and only about 2000 years ago our pharmacopoeia was dominated by herbal medicines.

Medical herbalism(i.e. the medicinal use of preparations that contain exclusively plant material)went into rapid decline when pharmacology established itself as a leading branch in therapeutics. In much of English speaking world, herbalism virtually vanished from the therapeutic map a century ago. In contrast, many of developing countries never abandoned medical herbalism(e.g. Chinese herbalism in china)and in other countries, e.g Germany and France, medical herbalism continued to co-exist with modern pharmacology, albeit at an increasingly lower level***(Ernst ,2000)***.

A recent United States survey suggested that 16.4% of all patients attending an internal medicine clinics were current users of herbal medicines***(Rhee et al.,2004)***.

According to these and other survey data, medical herbalism was most commonly employed for allergies, insomnia, respiratory problems, and digestive problems***(Eisenberg et al.,1998).***

Herbal medicines usually contains a range of pharmacologically active compounds; in some cases it is not known which ingredients are

important for therapeutic effect. Many herbalists believe that isolated ingredients have weaker clinical effect than whole plant extracts(***Schulz et al.,2001).***

Clinical trials of herbal medicines are feasible much in the same way for other drugs***(Ernst ,2000).***

Hypertension

Hypertension is defined conventionally as blood pressure >140/90 mmHg. This serves to characterize group of patients who carry a risk of hypertension-related cardiovascular disease that is high enough to merit medical attention ***(Kaplan, 2001)***. However, the risk of fatal and non fatal cardiovascular disease in adults is lowest with systolic blood pressure of less than 120 mmHg and diastolic of less than 80 mmHg***(Black, 1999).***

Hypertension is considered to be present when systolic blood pressure is consistently 140 mmHg or greater, and/or diastolic blood pressure is consistently 90 mmHg or greater. Recently, The Seventh Report of the Joint National Committee on prevention, detection, evaluation, and treatment of high blood pressure has defined blood pressure 120/80 mmHg to 139/89mmHg as "prehypertension". Prehypertension is not a disease category; rather, it is a designation chosen to identify individuals at high risk of developing

hypertension(***Chobanian , 2003).***

Etiology

1. ***Essential(primary) hypertension*:** has no identifiable cause. It may be caused by genetics, environmental factors, or even diet, such as how much salt you use.
2. ***Secondary hypertension:*** It indicates that the high blood pressure is caused by another disorder such as:

-Adrenal gland tumors.

-Cushing's syndrome (hypersecretion of cortisol).

-Kidney disorders: e.g glomerulonephritis, renal vascular obstruction and renal failure.

-Haemlytic-uraemic syndrome.

-Henoch-Schonlein purpura.

-Retroperitoneal fibrosis.

-Wilm's tumor ***(Wang and Wang, 2004)***.

-Spinal misalignment: may be due to misalignment of atlas vertebra ***(Bakris et al., 2007)***.

-As a result of usage of some drugs such as NSAIDS and oral contraceptives.

Table (1): Classification of hypertension according to WHO/ISH:

Category	Systolic	Diastolic
Optimal	<120	<80
Normal	<130	<85
High normal	130-139	85-95
Subgroup(borderline)	140-149	<90
Grade 1(mild HTN)	140-159	90-99
Grade 2 (moderate HTN)	160-179	100-109
Grade 3 (severe HTN)	≥180	>110
Isolated systolic HTN (ISH)	≥140	<90

(Joint British Societies, 2005)

Complications

While elevated blood pressure alone is not an illness, it often requires treatment due to its short and long-term effects on many organs. These effects include:

-Cerebrovascular accidents.

- Myocardial infarction.
- Hypertensive cardiomyopathy.
- Hypertensive retinopathy.
- Hypertensive nephropathy.

Treatment

***a)Lifestyle modification*:**

-Weight reduction and regular aerobic exercise are recommended as the first steps in treating mild to moderate hypertension.

-Reducing dietary salt is proven to be very effective : it decreases blood pressure in about 60% of people.

-Additional dietary changes beneficial for reducing blood pressure includes DASH diet (Dietary Approaches to Stop Hypertension), which is rich in fruits and vegetables and low fat or fat-free dairy foods.

-Discontinue tobacco use and alcohol consumption has been shown to lower blood pressure.

-Relaxation therapy, such as meditation, that reduces environmental stress, and reducing high sound levels can be an additional method of ameliorating hypertension ***(Chobanian, 2003).***

***b)Medications*:**

Commonly used drugs include:

1-ACE inhibitors such as captopril, enalapril, lisinpril.

2-Angiotensin II receptor antagonists: e.g, telmisartan, valsartan, candesartan.

3-Alpha blockers such as doxazosin, prazosin.

4-Beta blockers such as atenolol, propranolol, metoprolol.

5-Calcium channel blockers such as nifidipine, verapamil and dilitiazem.

6-Direct renin inhibitors such as aliskiren.

7-Diuretics e.g hydrochlorothiazide(HCTZ)

8-Combination products (which usually contain HCTZ and one other drug)***(Kragten & Dunselman, 2007)*** **.**

Hyperlipidaemia

Hyperlipidaemia is the term used to denote raised serum level of one or more of total cholesterol, low-density lipoprotein cholesterol, triglycerides, or both of them. Dislipidaemia is a wider term that also includes high level of low-density lipoprotein cholesterol ***(Joint British Societies, 2005)***

Secondary causes of hyperlipidaemia include:

1-High cholesterol: hypothyroidism, obstructive jaundice, anorexia nervosa, nephritic syndrome.

2-High triglycerides: diabetes mellitus, hepatitis, pregnancy, obesity, renal failiure.

3-Raised cholesterol and triglycerides: oral contraceptives, steroids, high doses of thiazides, pregnancy, multiple myeloma ***(Joint British societies, 2005).***

Classification:

*The Friedrickson Classification lists five types of hyperlipidaemia **(NCEP, 2001)**:*

1-Type I: Normal or slightly raised cholesterol with very high triglycerides, xanthoma, hepatosplenomegaly & pancereatitis. It is not usually associated with cardiovascular disease.

2-Type IIa: High cholesterol with normal triglyceride levels, xanthoma,

and corneal arcus. It is hereditary and carries a very high risk of cardiovascular disease.

3-Type IIb: Similar to type IIa, raised cholesterol and triglycerides. It is also associated with premature development of arterial disease.

4-Type III: Raised cholesterol and triglycerides, xanthomas, often associated with obesity, hyperuricaemia and an impaired GIT. There is an increased risk of coronary artery and peripheral vascular disease.

5-TypeIV: Raised triglycrides, atheroma, raised uric acid, xanthoma, liver and spleen enlargement and often an impaired GIT. It is associated with gout and nephritic syndrome. It may be familial but more often is seen secondary to diabetes, obesity, pancereatitis, alcoholism and hypothyroidism.

6-Type V: Raised triglycrides, xanthoma, and often abnormal glucose tolerance test. It is induced by high fat/carbohydrate diet and may accompany diabetes mellitus, panceritiitis and alcoholism. It is not usually associated with premature cardiovascular disease.

Complications

1-About 46% of deaths due to coronary heart disease (CHD) may be attributable to raised serum cholesterol ***(Clinical knowledge Summaries, 2006).***

2-people with heterozygous familial hypercholesterolemia have a four-fold increased risk of CHD.

3-People with familial combined hyperlipidaemia also have an increased

risk of CHD, but usually CHD presents after the age of 60.

4-Very sever hypertriglyceridaemia is a risk for pancreatitis.

5-Decreased levels of high density lipoprotein cholesterol are also an independent risk factor for CHD.

Management

Conservative treatment

1-Diet can decrease both cholesterol and triglycerides levels. This can be achieved by replacing butter with olive oil and mono-unsaturated margarine, eating less red meat and more poultry, more fish, more bread, more vegetables and green vegetables and more fruits.

2-Weight reduction, regular physical exercise, smoking cessation and control of both blood pressure and blood glucose ***(Clinical knowledge Summarries, 2006)***

Drugs

In patient without two or more risk factors drug therapy should be considered if the LDL remains above 190 mmol/dl and dietary schedule for at least six months has failed. In patients without evidence of atherosclerosis and with two or more risk factors drug therapy should be considered if the LDL cholesterol remains greater than 160 mmol/dl. Patients with atherosclerosis disease should be considered candidates for therapy if the LDL is greater than 100 mg/dl***(Stein, 2002).***

Cholesterol lowering medication when applied to patients with atherosclerosis not only decrease coronary events, but can prolong

survival as well***(Sander and Giles, 2002).***

HMG CoA Reductase inhibitors and bile acid sequestrans are good combination therapy in patients with resistant hypercholesterolemia. By having different mechanism of action these compound work synergistically and are the preferred agents for combination therapy. Niacin alone or in combination with bile acid sequestrans or HMG CoA Reductase inhibitors can be used. When using either reductase inhibitors or niacin, liver function tests should be checked initially for the first several months and then again with any increase in dose.

Dietary soluble fiber enhancement, with commercial dietary supplementation is proven to be very effective natural approach to cholesterol lowering***(Stein, 2002).***

Hypertension and hyperlipidaemia

Hypertension and hyperlipidaemia often coexist. Each is an independent risk factor for cardiovascular events. The likelihood of coronary events appears to be compounded when the two occur together ***(Scannpieco et al., 1988 and Neutel et al., 1992).***

The presence of high blood pressure and hyperlipidaemia is so common in patients with hypertension that may have argued that the high blood pressure itself may play a role in altering lipid metabolism, resulting in lipid abnormalities. However recent data have demonstrated that hypertension and hyperlipidaemia are genetically inherited and probably genetically linked, but are separate variables that frequently

may present independently of one another. In a study comparing age, and body mass index-matched patients with normotension with and without a family history of hypertension, the patient with a family history has significantly greater total cholesterol concentrations than those without a family history ***(Samuelsson et al., 1987 and Glasser, 2001)***. The authors also reported that this may have important therapeutic implications, as studies using occurrence of coronary events to judge the success of treatment of patients with hypertension have shown the treatment of hypertension alone or of hypercholesterolaemia alone produced modest results; only when both conditions were controlled there was a marked reduction in coronary artery disease ***(Samuelsson et al., 1987 and Glasser, 2001).***

Hibiscus sabdariffa

Hibiscus sabdariffa L.(family malvaceae),commonly known in English as Roselle or red sorrel and in Arabic as karkade, is widely grown in Central and West Africa, South East Asia, and elsewhere. The plant is an erect annual herb. The thick ,red and fleshy, cup-shaped calyces of the flower are consumed worldwide as a cold beverage and as a hot drink(sour tea).These extracts are also used in folk medicine against many complaints that include high blood pressure, liver diseases and fever***(Dalziel, 1973; Wang et al.,2000;Ross, 2003)***.The red anthocyanin pigments in the calyces are used as food coloring agents***(Esselen and Sammy,1975).***

Constituents

There are many published reports on the constituents of different plant parts of H.sabdariffa***(Ross, 2003)***. Citric and malic acid have been reported as the major organic acid in aqueous extract of the flower, but tartaric acid was found only as a trace component(***Indovina and Capotummino,1938)***,although it was detected, along with citric and organic acid, by paper chromatography in flower extracts from Taiwan***(Lin,1975)***.High concentrations of organic acids in the calyx, with citric acid predominating, but with malic and organic acid also

present***(Kerharo, 1971)***.Citric, hibiscus, malic and tartaric acids were detected in the calyces of 5 strains of H.sabdariffa.In all strains, the concentration of acids increased during the development of calyces, but declined after they reached ripeness***(Khafaga and Koch, 1980)***.Ascorbic acid was reported in aqueous extract***(Buogo and Picchinenna, 1937).***

Pharmacological properties

The LD50 of H.sabdariffa calyx extract in rats was found to be above 5000 mg/kg ***(Onyenekwe et al., 1999),*** suggesting that the extract is virtually non-toxic. In spontaneously hypertensive rats, treatment with the extract at doses 500-1000 mg/kg decreased blood pressure, and also significantly decreased serum creatinine, cholesterol and glucose levels, but significantly decreased the serum content of uric acid. The treatment caused no significant effect on either water intake or urine output

Effect on smooth muscle

The aqueous extract of H.sabdariffa calyces rhythmically contracted rat uterus, guinea-pig tracheal chain and rat diaphragm. The same extract stimulated quiescent rat uterus and frog rectus abdominis muscle***(Sharaf,1962; Ali et al., 1991)***.This extract also inhibited the tone of various isolated muscle preparations that included rabbit aortic strip(***Obiefuna et al., 1994)***and rat ileal strip***(Salah et al.,2002).*** However, the presence of stimulatory substance(s) in the extract has been also demonstrated using the frog rectus abdominis preparation ***(Ali***

et al., 1991). The mechanism of action of H.sabdariffa aqueous extract on smooth muscles is not certain. However, as the extract contains organic acids and minerals, the effect of the extract on different smooth muscle preparations would be expected to be variable. The overall effect is a direct relaxation of smooth muscles, which may explain, at least partially, the hypotensive action of the extract.It was suggested that the relaxant response was related to endothelium- dependent and endothelium- independent mechanisms***(Obiefuna et al., 1994)*** , or mediated through calcium channels, possibly generated by constituents such as quercetin and eugenol***(Salah et al., 2002).*** Further studies of the mechanistic aspects of the extract on smooth muscles are warranted.

Effect on blood pressure

Intravenous injection of aqueous extracts of H.sabdariffa calyx to anaesthetized cat ***(Ali et al., 1991)*** and anaesthetized rats (***Adegunloye et al.,1996)***lowered blood pressure in a dose dependent manner. This effect was resistant to a number of receptor blocking agents, but the hypotensive effect was partially blocked by atropine ***(Ali et al., 1991),*** and antihistamine (H1 blockers). Therefore, the hypotensive action may be mediated, at least partially, by a cholinergic and\or histaminergic mechanism. Sectioning of the left and right vagi nerves did not have a significant effect on the fall of mean arterial blood pressure**.**

It was postulated that the hypotensive action of H. sabdariffa could

be ascribed to a direct vasorelaxant effect ***(Adegunloye et al., 1996).***Another possible mechanism for the hypotensive activity may be inhibition of Angiotensine1 converting enzyme (ACE).The later action has been demonstrated in vitro with a crude hydroethanol extract of H.sabdariffa calyces, and was ascribed to flavones present in the extract. In addition, a beneficial cardioprotective effect of this extract was shown in vivo, and was attributed to flavonoids and anthcyanines***(Jonadet et al.,1990)***.

More recently the antihypertensive action of H.sabdariffa has been confirmed in spontaneously hypertensive rats***(Onyenekwe et al., 1999)*** and in rats with experimental hypertension***(Odigie et al., 2003)***and given the aqueous extract at doses 250-1000 mg/kg for up to 14 weeks.

(Hajj-Farraji and Hajj Tarkhani, 1999) reported that in 54 patients with moderate essential hypertension, daily consumption of an aqueous H.sabdarifa extract (two spoonful of blended " sour tea "boiled in one glass of water for 20-30 min)resulted in about 11%decrease in systolic and diastolic blood pressure 12 days after beginning the treatment Three days after cessation the treatment, the blood pressure rose again by about 6-8%.The author did not investigate the possible mechanism(s) of action of plant extract, but a diuretic, vasodilator and/or an inhibitory effect on ACE was postulated**.**

The effectiveness of an aqueous extract of H.sabdariffa on mild to moderate hypertension was recently confirmed in a clinical trial involving 39 Mexican patients(***Herrera-Arellano et al., 2004)***. These authors also reported that the extract was made from 10 g dried calyx in 0.5 L water(9.6 mg anthocyanin content)and was given daily for 4 weeks before breakfast. For comparison, 36 hypertensive patients were given the ACE inhibitor, captopril(25 mg twice daily for 4 weeks).The extract treatment reduced the systolic pressure from 139 to 124 mm mercury, and the diastolic from 91 to 80 mm mercury. These results were not significantly different from those obtained by captopril treatment. No adverse effects were found with either treatment, confirming the effectiveness and safety of the extract.

Anticholesterol effects

H.sabdariffa calyx(5% or 10%)was fed to rats with hypercholesterolemia for 9 weeks**.**The treatment progressively lowered the different lipid fractions in plasma , heart, brain, kidney, and, liver; and also decreased the activities of several plasma enzymes used in the tests as markers of tissue function. This treatment, however, slightly raised the content of plasma phospholipids. Although the mechanism of action of H.sabdariffa as a cholesterol lowering agent was not elucidated in this work, it was hypothesized, albeit with no experimental evidence,

that the extract may contain some compounds that activate hormonal secretions, such as adrencortical hormones, which stimulate the metabolic pathway of cholesterol by conversion into other compounds (***El-Saadany et al., 1991)***.

The anticholesterol action of H.sabdariffa(0.5% or 1%)was confirmed in rabbits fed cholesterol for 10 weeks. This treatment was effective in reducing the serum concentration of triglycerides, total cholesterol and low density lipoprotein cholesterol, and in mitigating atherosclerosis in the aorta. Histopathologically, it was found that feeding H.sabdariffa has reduced foam cell formation and inhibited smooth muscle cell migration and calcification in the blood vessel of treated rabbits ***(Chen et al., 2003).***

Interaction with drugs

The interaction of three Sudanese beverages, including H.sabdariffa, with the kinetics of chloroquines was studied in human volunteers**.**H.sabdariffa was found not to have a significant effect on any pharmacokinetic parameter, indicating its safety when taken with drugs that may have the metabolic pathway of chloroquine ***(Mahmoud et al.,1994)***.

The administration of the extract by healthy men induced no significant changes in the major kinetic parameters on paracetamol, although very minor and probably biologically insignificant alterations

in some were observed***(Kolawole and Maduenyi, 2004).***In the view of the fact that H.sabdariffa drinks may be ingested with medicines, more studies to ascertain the presence or absence of interaction with drugs of different metabolic profiles are warranted.

Toxicological properties

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Workers from Nigeria have recently studied the effect of subchronic administration of aqueous extracts of H.sabdariffa on the testis, as the plant is often claimed in West African folk medicine to be an aphrodiasiac ***(Orisakwe et al., 2004)***.They reported that rats were given1.15, 2.3and 4.6 g/kg/day of an aqueous extract of H.sabdariffa calyx in the drinking water for up to 12 weeks. At the end of the treatment period there was a steady decrease in body weight, but no changes in relative or absolute body weights of the testis. However the higher two doses of the extract caused a significant decrease in the epididymal sperm count, histological distortion of the tubules, disruption of normal epithelial organization and disintegration of sperm cells. The authors postulated that these effects were related to interference by the extract with spermatogenesis that may have been caused by an oestrogenic action of the extract ***(Ali et al., 1991)*** It is however difficult to ascribe the above testicular effects to an oestrogenic action in the absence of any significant changes in testicular weight, as oestrogens are known to reduce the weight of male reproductive organs. The relevance of the testicular toxicity of H.sabdariffa in human is

not certain when the relatively high amount of extract given in the drinking water for 12 weeks is taken into consideration.

In rats, the average consumption of 150-180 mg/kg/day of an aqueous ethanol extract of H.sabdariffa calyces appeared to be safe, although higher doses may elevate the activity of plasma enzymes indicative of tissue function(such as alanin tranaminase and aspartate aminotransferase).However the activity of some related plasma enzymes(alkaline phosohatase and lactate dehydrogenase)was not significantly affected, nor was there any evidence of histological damage to the heart and liver of treated rats***(Akindhunsi et al.,2003).***

Enalapril

Mechanism of action

It is an angiotensin converting enzyme (ACE) inhibitor. Its essential effect is to inhibit the conversion of relatively inactive angiotensin I to the active angiotensin II. Thus the ACE inhibitors attenuate responses to angiotensin I not to angiotensin II***(Peach, 1977).***

Chemical structure:

Nonsulfhydryl di-peptide angiotensin converting enzyme inhibitor**.** It is inactive till converted to their corresponding di-acids. The C2H5 in the box are removed by esterases and replaced with a hydrogen atom to form the active molecule**.**

Figure (1): Chemical structure of selected angiotensin converting enzyme inhibitors***(Cushman et al., 1977).***

Clinical pharmacology:

Enalapril maleate is the second ACE approved in the United States, it must be hydrolysed by esterases in the liver to produce the active parent di-carboxylic acid, enalaprolat. Enalapril is rapidly absorbed when given orally and has an oral bioavailability of about 60%.Enalapril half-life is only 1.3 hours. Nearly all the drug is eliminated by the kidney either as an intact enalapril or enalaprilat. The oral dosage of enalapril is 2.5-40 mg daily which is sufficient to start therapy of heart failure and hypertension, respectively***(Regoli et al., 1974)***.

Therapeutic uses

It plays a prominent role in the treatment of the major causes of mortality in modern societies (cardiovascular diseases)

1. Hypertension: inhibition of ACE lowers systemic vascular resistance mean, systolic, and diastolic blood pressure in various hypertensive states ***(Testa et al., 1993).***
2. Left ventricular systolic dysfunction: It is now clear that, unless contraindicated, ACE inhibitors should be given to all patients with impaired left ventricular systolic function regardless of whether the patient is experiencing symptoms of overt heart failure. ***(SOLVD investigators., 1991).***
3. Myocardial infarction: the use of ACE inhibitors in myocardial infarction is rapidly evolving ***(Cody*, *1994).***

- Progressive renal impairment: ACE inhibitors have been shown in numerous animal studies ***(Hoelscher et al.,1995)***and in several clinical trials ***(Keilani et al., 1995)*** to retard significantly the loss of kidney function associated with diabetic nephropathy. .
- Scleroderma renal crisis: a few small observational studies have suggested that ACE inhibitors markedly improved this otherwise grim prognosis.

Adverse effects:

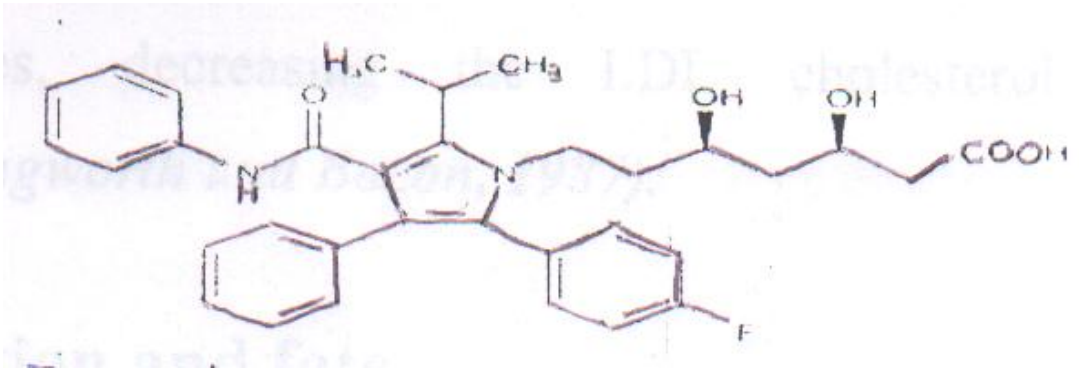
It was found that ACE inhibitors can cause many complications e.g hypotesion, angioneurotic oedema***(Israili & Hall, 1992)***, cough ***(Israili & Hall, 1992)***, dysphagia, hyperkalaemia, neutropenia, acute renal failiure, glycosuria(***Cressman et al.,1982).***

Fetopathic potential, hepatotoxicity***(Hagley et al.,1993)***, skin rash and proteinurea also have been detected ***(Materson, 1992).***.

Atorvastatin

Chemistry

It is composed of a hexahydronaphthalene ring system with two appendages: a methylbutyrate ester and a hydroxyl acid that can form a six membered lactone ring**.**



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(Israili al., 1992).

Effects on plasma lipids and lipoproteins

(Symposium, 1988b) reported that Atorvastatin produces a dose-related decrease in the concentration of LDL- cholesterol in plasma. There is also slight decrease in the content of cholesterol of each LDL particle. The amount of cholesterol in VLDL also declines. Triglycrides concentration declines up to 25%. The concentration of HDL-cholesterol rises to 10% to 13%. The drug has similar effects in patients with familial hypercholesterolaemia aand in hypercholesterolaemia associated with diabetes mellitus or with nephritic syndrome***(Grundy, 1988).***

Mechanism of action:

Atorvastatin is a competitive inhibitor of HMG-CoA reductase enzyme which catalyze the reduction of 3-hydroxy-3-methylglutatyl-coenzym A to mevalonate, which is the rate limiting step in hepatic cholesterol biosynthesis. Inhibition of the enzyme decrease the de novo cholesterol synthesis, increasing the expression of low-density lipoprotein receptors on the hepatocytes. This increase the LDL uptake by the hepatocytes, decreasing the LDL cholesterol in the blood***(Illingworth and Bacon, 1987).***

Absorption and fate

Approximately 30% of an oral dose of atorvastatin is absorbed. Most of the drug is extracted from the blood during the first pass metabolism. The active and the inactive metabolites accumulate in plasma. More than 95% of the drug is protein-bound. Most of the degradation products are excreted in faeces, less than 10% appears in the urine***(Albert et al., 1989).***

Adverse effects and drug interaction

The drug has been generally well tolerated and no unexpected toxicity has been reported***(Symposium, 1988b and Albert et al., 1989)***. Less than 10% of patients developed gastrointestinal symptoms, headache, or rash, but these symptom rarely necessitates discontinuation of the drug. Asymptomatic

elevation of serum transaminases derived from liver occurs in

approximately 2% of patients***(Reavan and Witzum, 1988& Symposium, 1988b).***

Preparations, dosage, and therapeutic uses

Dosage begins at 20 to 40 mg per day given with food. If necessary the dose is increased at 4- weeks intervals to a maximum of 80 mg per day ***(Levy et al., 1972).***

Atorvastatin is indicated as first-line therapy for patients who are at high risk of myocardial infarction attributable to hypercholesterolaemia. This includes patients with total cholesterol concentrations in plasma >300 mg/dl or those with values >240 mg/dl who also have documented coronary artery disease or one of the other risk factors.

Atorvastatin is also effective in secondary hypercholesterolaemia associated with diabetes mellitus and nephritic syndrome. The drug has teratogenic effect in animals; it is contraindicated in pregnant women or women of child bearing age who may become pregnant***(Grundy, 1988).***