A literature review of Indapamide (SR) preparations

A research paper submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

Submitted by
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Acknowledgements:

This was a complete study of literature review of Indapamide, to do this study I had to work lots of on it through computer but this was almost impossible to get ideas about this work if I did not get help from my research fellow Mr. Atiqul Haque Pathan, Lecturer East West University. He supervised my research work continuously and always helped me to get the solution each and every time. His creative thinking and willingness to help me performing my research work smoothly has made his a big part in my work and core. After him I would like to thank Mr. Muniruddin Ahmed, Pro Vice Chancellor, East West University, because of his special supervision and helping so much in the work. My heartiest thanks to Mr. Dr. Chowdhury Faiz Hossain, The chairperson of East West University, Department of Pharmacy, to give me the chance to work on such topic and to provide me the environment. My special thanks to Mr. Apurba Sarker Apu, lecturer East West University, because his useful advices and direction for work which helped me a lot to do this work. I am really thankful to the Laboratory Officer of Pharmacy Laboratory because of their cordial collaboration with me while I worked on this research and also the Computer Laboratory of East West University and its technicians. I am really grateful to S.M. Tahsin Hassan, Ashraful Islam, C. M. Sayeem Sadly, Md. Maidul Islam and A.T.M. Faiz Ullah. For their advices and for sharing their thinking with me. I am so much happy to get continious support of my parents and family members. And finally I am so much thankful to Almighty Allah for everything of this.

ABSTRACT

The theoretical results of almost 970 published papers which were collected from different journals are reported in this work. The analysis was carried out at the research laboratory of East West University, Dhaka and data were represented to get the vital idea about the previous work and the possibilities of further work on this matter and different evaluations were performed in this research. A lot of study was done about indapamide sustained release form and collected information about the pharmacology, release profile, action of drugs, side effects and also about another important parameters.

The main intension of literature review of indapamide was to set the work pattern for the research. It was tried to get some ideas about the work from different journals and the websites. The work schedule was made after the evaluations of the literatures and the experiences were implemented on the further research process. The data of the research helped a lot to get the general information's and wok. From the study I got the relationship between the increase in blood pressure and the incidence of cardiovascular disease is well recognized today. Studies have shown that more attention should be paid to systolic blood pressure (SBP) in relation to cardiovascular risk and that therapeutic interventions should preferably focus on reducing SBP. The antihypertensive efficacy of indapamide 1.5 mg sustained release (indapamide SR), a low-dose thiazide-type diuretic, is assessed on SBP. The treatment with indapamide SR resulted in a better or equivalent control of SBP than treatment with a standard dose of a true thiazide diuretic (hydrochlorothiazide), a calcium channel blocker (amlodipine), and an angiotensin-converting enzyme inhibitor (enalapril). In conclusion, indapamide SR is very effective in lowering SBP—a major independent cardiovascular risk factor—notably in hypertensive high-risk patients with LVH, the elderly and diabetics, when compared to major antihypertensive treatments. This SBP-lowering effect is maintained over the long term.

Table of content:

Introduction:

It was a study of a literature review to see the previous study done on indapamide release pattern. To get the idea about the research and to get the massive knowledge this literature review was done. There was another purpose of this review to have some different idea of work on Indapamide. In that case some parameters were kept in front to review the literatures and the parameters were

- The release profile
- The kinetic release pattern
- Sustained release of Indapamide
- Combination products of indapamide
- The previous records of Indapamide's action

Basically the target of this research paper was set to get better knowledge about Indapamide and its previous works and to implement the data come out from the research for further laboratory works in future. It was studied a lot of about indapamide and collected information about the pharmacology, release profile, action of drugs, side effects and also about another important parameters.

Though the main intension of literature review of indapamide was to set the work pattern for the research so we tried to get some ideas about the work from different journals and the websites.

General information and concerns

General information and concerns were needed before literature review of Indapamide was as given below:

Indapamide:

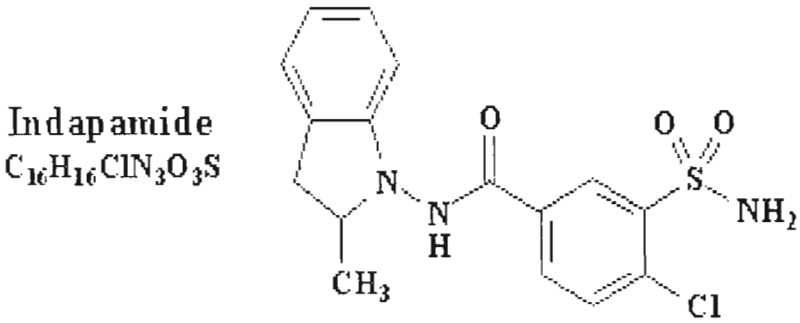
Indapamide is a Thiazide type diuretic which increases the amount of urine passed, which causes the body to lose water and salt. Indapamide helps to treat high blood pressure (hypertension). It also reduces the swelling and water retention caused by various medical conditions, such as heart, liver, or kidney disease. Indapamide is a prescription drug that is used for treating fluid retention and high blood pressure.

Chemical formula:

Systematic (IUPAC) name

4-chloro-N-(2-methyl-2,3-dihydroindol-1-yl)- 3-sulfamoyl-benzamide

The chemical formula of Indapamide is given below.



Pharmacokinetics and clinical pharmacology of indapamide:

Indapamide is a new antihypertensive diuretic agent indicated for the treatment of hypertension and edema. Indapamide shows an alteration in vascular reactivity to calcium and other agonists, suggesting the possibility of a direct vascular effect. The drug is recommended in doses of 2.5 to 5 mg once a day. It is rapidly and completely absorbed from the gastrointestinal tract, resulting in maximal blood levels in approximately 2.3 hours. Co administration of indapamide with food or antacids does not reduce bioavailability. Linear proportionality of blood concentration with increasing doses is evident following both single and multiple doses. Other pharmacokinetic parameters are not dose related. Indapamide is widely distributed in the body with extensive binding to erythrocytes. Binding to plasma proteins is approximately 76%. Disappearance of indapamide from the blood is biphasic, with a terminal half-life of approximately 16 hours. Renal clearance represents less than 10% of the total systemic clearance of the parent drug, showing the dominant role of hepatic clearance. Studies of 14C-labeled indapamide in humans demonstrate that 70% of the radioactivity is excreted in urine and 23% in feces. Indapamide is extensively metabolized; less than 7% of the dose is excreted in urine as unchanged compound. Studies of patients with renal impairment showed little or no accumulation of indapamide in the blood in comparison to patients

with normal renal function. Clinical studies demonstrate that indapamide has diuretic properties. Free water clearance studies indicate a site of action in the cortical diluting segment of the distal tubules. No adverse effect of indapamide on renal function is evident in normal volunteers, hypertensive patients, or geriatric hypertensive patients, as determined by glomerular filtration rate or effective renal plasma flow. Hemodynamic studies of indapamide in patients with mild to moderate hypertension show a significant (p less than 0.05) decrease in mean blood pressure (16%) and total peripheral resistance (15%). No other significant Hemodynamic effects are evident. The data suggest that indapamide may produce antihypertensive activity through a dual mechanism of action--diuretic and direct vascular. Additionally, it appears to be safe even for patients with impaired renal function.

The pharmacology of the Indapamide:

At low doses indapamide is a potent and long acting antihypertensive agent in various hypertensive animals and in man, but is without activity in normotensive subjects. A daily dose of 2.5 mg produces a minimal diuresis but at higher doses this increases without any significant augmentation of hypotensive activity. It appears to have no effect on most blood biochemical parameters, including glucose, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, nor adrenaline, adrenaline, but potassium levels may decrease and uric acid and renin increase. Indapamide had no effect on renal function nor does it alter left ventricular function, electrocardiograph (ECG) or heart rate, although cardiac output may marginally increase. Total peripheral resistance is significantly decreased and it may exert its antihypertensive effect by reducing vascular reactivity to various pressure stimuli by inhibiting the net inward flow of calcium and resultant phasic contractions in vascular smooth muscle. Indapamide differs from the diuretics in that it has comparatively high lipid solubility; it is also bound to blood proteins and elastin in vascular smooth muscle and little is eliminated in the urine. It may be for these reasons that the drug has less diuretic activity but more pronounced effect on vascular smooth muscle than compounds of similar structure.

Conditions while indapamide can be taken:

Indapamide can be taken if patients have any of these conditions:

- Diabetes
- Gout
- Kidney disease, small amounts of urine, or difficulty passing urine
- Liver disease
- Low blood levels of potassium, chloride, or sodium
- Thyroid disease
- An unusual or allergic reaction to indapamide, sulfa drugs, other medicines, foods, dyes, or preservatives
- Pregnant or trying to get pregnant
- Breast-feeding

Prescription:

Indapamide tablets should be taken orally according to prescription and should swallow the tablets with a drink of water. Doses should be taken at regular intervals Dose should not be taken as wish and at bedtime. In case of children the direction of the physicians should be followed.

If a dose is missed in any case, it should be taken as soon as it is possible. If it is almost time for the next dose, only that dose should be taken not the extra doses.

Indapamide Dosing

Most people start with an indapamide dosage of 1.25 mg once a day for high blood pressure control. Normally dose can be given 1.5 am to 5 mg in a day.

Medicines interact with indapamide:

- Amiodarone
- Dofetilide
- Heart medicines such as digoxin
- Lithium
- Medicines for diabetes
- Medicines for high blood pressure
- Medicines that relax muscles for surgery
- Medicine for colds and breathing difficulties

It's always better to consult with the physicians about the medicines given above before taking the indapamides.

Concerns before taking indapamide:

Blood pressure of the patient

Dehydration

Diet of the patients

Potassium and sodium intake in the body.

Reduce the risk of dizzy or fainting spells

Avoiding the alcohol intake

Keep out of the sun

Side effects of indapamides:

Side effects that may be seen after taking the indapamides are:

- blurred vision
- Change in the amount or frequency of urination
- Dry mouth
- increased thirst
- Irregular heartbeat (palpitations)
- Mood changes
- Muscle cramps or spasm
- Nausea, vomiting
- Seizures (convulsions)
- Skin rash, itching, or hives
- Unusual tiredness or weakness
- yellowing of the eyes or skin

And other side effects that can be seen are:

- Diarrhea
- Difficulty sleeping
- Dizziness or lightheadedness
- Headache
- increased sensitivity to the sun

- Loss of appetite
- Sexual difficulties (impotence)
- Stomach upset

The available preparations or brands:

The available preparations or brands present to interact with the diseases can be treated by Indapamides:

Angiotensin Converting Enzyme (ACE) Inhibitors

Captopril

Enalapril

Lisinopril

Perindopril

Ramipril

Benazepril

Fosinopril

Moexipril

Quinapril

Trandolapril

Bosentan

Calcium Channel Blockers

Verapamil

Diltiazem

Nifedipine

Felodipine

Amlodipine

Nitrendipine

Isradipine

Nicradipine

Nisoldipine

Lacidipine

Angiotensin receptor blockers (ARB)

Losartan

Candesartan

Irbesartan

Telmisartan

Valsartan

High-Ceiling or Loop Diuretics

Furosemide

Bumetanide

Thiazide and Thiazide-Like Diuretics

Chlorothiazide

Benzthiazide

Hydrochlorothiazide

Metolazone

Chlorthalidone

Indapamide

Xipamide

Clopamide

Potassium-Sparing Diuretics

Spironolactone

Triamterene

Amiloride

Diuretics

Carbonic Anhydrase Inhibitors

Acetazolamide

Methazolamide

Dichlorphenamide

5.β Adrenergic Blockers

Propranolol

Nadolol
Pindolol
Carteolol
Timolol
Levobunolol
Sotalol
Metipranolol
Metoprolol
Atenolol
Acebutolol
Betaxolol
Bisoprolol
Esmolol

β + α Adrenergic Blockers:

Labetelol
Carvedilol

Central Sympatholytics:

Clonidine
Methyldopa

Vasodilators:

Hydralazine
Minoxidil
Diazoxide
Sodium Nitroprusside

α Adrenergic Blockers:

Prazosin
Terazosin
Doxazosin
Phentolamine

After reviewing the literatures from publication it was seen that following work was done previously on Indapamide:

The findings after the literature review were as follows:

Among 970 journals we got the results like that:

Release kinetics of indapamides- 12 journal

Release pattern of Indapamides- 11 journal

Pharmacology and pharmacokinetics of Indapamide- 667 journal

Formulations of Indapamide- 68 journals

Preparations of Indapamide- 59 journals

Dosage form of indapamide- 54 journals

Sustained release of indapamide- 45 journals

Physical properties of indapamide- 10 journals

Chemical properties of indapamide- 113 journals

Side effects of Indapamide- 282 journals

Combined drugs of indapamide- 26 journals

Combined preparations of indapamide- 02 journals.

All the data was taken from the internationally published journals.

The Available publications of Indapamide SR release:

From pub med we got following works done on Indapamide SR preparations and the publications are as follows

1: Curr Med Res Opin. 2009 Jul 21.

Treating hypertension by rational use of diuretics: results of the Russian ARGUS-2 study.

Kobalava ZD, Kotovskaya YV, Villevalde SV, Moiseev VS.

Russian Peoples' Friendship University, Moscow, Russian Federation.

ABSTRACT Objective: Insufficient use of diuretics in combination antihypertensive therapy is a main cause of poor blood pressure (BP) control in Russia. The objective of the ARGUS-2 study was to demonstrate that a rational use of a thiazide-like diuretic, indapamide sustained release (SR), alone or in combination, improves BP control in patients with arterial hypertension difficult to control due to isolated systolic hypertension (ISH), diabetes mellitus (DM), chronic nephropathy, or metabolic syndrome. Methods: The open-label, non-comparative, 3-month study without preliminary washout included 1438 hypertensive patients (mean age: 57.3 +/- 10.7 years, mean BP: 158.8 +/- 14.2/93.4 +/- 10.0 mmHg), with difficult-to-control arterial hypertension and who had never been treated with diuretics previously. Throughout the study, patients received indapamide SR 1.5 mg OD. BP control was defined as <140/90 mmHg for all patients and <130/80 mmHg for those with diabetes mellitus or chronic nephropathy. Results: Indapamide SR was given as initiation monotherapy to 13.7% of the patients, as substitutive monotherapy to 6.8% of the patients uncontrolled by a previous monotherapy, as additive therapy to 31.9% of the patients uncontrolled by previous monotherapy, and as additive therapy to 47.6% uncontrolled by previous combination therapy without a diuretic. Among included patients 75.7% received also an ACE inhibitor or an angiotensin II receptors blocker, 43.9% a calcium channel blocker, and 32.8% a beta-blocker. In 3 months

after indapamide SR administration, average BP level decreased to 131.8 +/- 9.7/80.5 +/- 6.9 mmHg and 84.5% of the study population achieved BP control. BP was controlled in 91.9% of patients with ISH (n = 477), 74.8% of those with diabetes (n = 214), 75.6% of those with chronic nephropathy (n = 82), and 85.1% of patients with metabolic syndrome (n = 745). No case of hypokalemia was reported. Conclusion: The study demonstrates the value of including the thiazide-like diuretic indapamide SR in a combined antihypertensive regimen to control BP in hypertensive patients with added cardiovascular risk factors whose hypertension is difficult to treat. Methodological limitations of this study are its open-label design and the possibility of a change in concomitant antihypertensive treatment during the study.

PMID: 19622008 [PubMed - as supplied by publisher]

2: Blood Press. 2009;18(1-2):17-22.

Baseline characteristics of participants in the Hypertension in the Very Elderly Trial (HYVET).

Bulpitt CJ, Beckett NS, Peters R, Banya W, Liu L, Wang JG, Stoyanovsky V, Dumitrascu D, Nikitin Y, Staessen JA, Burch L, Fletcher AE.

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The Hypertension in the Very Elderly Trial (HYVET) is a randomized double-blind trial of active antihypertensive treatment (indapamide 1.5 mg sustained release +/-2-4 mg perindopril) vs placebo in participants over the age of 80 years with a systolic blood pressure (SBP) of 160-199 mmHg during a placebo run-in period plus a diastolic blood pressure (DBP) of<110 mmHg. The trial has completed with 3845 subjects randomized and we report the baseline characteristics. The participants were a healthy group. The numbers smoking, drinking alcohol and having previous cardiovascular events were low, and their

hypertensive status was not usually associated with the metabolic syndrome; 1.0% of the whole group had a total cholesterol over 8.0 mmol/l, 1.1% a blood sugar over 11.1 mmol/l (irrespective of anti-diabetic treatment) and 1.7% a serum urate over 460 micromol/l (women) and 0.6% over 520 micromol/l (men). A serum creatinine over 150 micromol/l excluded participants from the trial. The gender differences and age comparisons were as expected but the women had higher average total and high-density-lipoprotein-cholesterol blood concentrations. Those with prior cardiovascular disease had an excess of the known cardiovascular risk factors. The baseline characteristics provide a basis for further understanding of the HYVET results, which have been published recently.

PMID: 19353407 [PubMed - indexed for MEDLINE]

3: Int J Pharm. 2009 Mar 31;370(1-2):129-35. Epub 2008 Dec 7.

Design and in vivo evaluation of an indapamide transdermal patch.

Ren C, Fang L, Ling L, Wang Q, Liu S, Zhao L, He Z.

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The aim of the present study was to develop and evaluate a novel drug-in-adhesive transdermal patch system for indapamide. Initial in vitro experiments were conducted to optimize formulation parameters prior to transdermal delivery in rats. The effects of the type of adhesive and the content of permeation enhancers on indapamide transport across excised rat skin were evaluated. The results indicated that DURO-TAK adhesive 87-2852 is a suitable and compatible polymer for the development of transdermal drug delivery systems for indapamide. The final formulation contained 4% N-dodecylazepan-2-one, 6% l-menthol and 3% isopropyl myristate. For in vivo studies patch systems were administered transdermally to rats while orally administered indapamide in suspension was used as a control. The PK parameters, such as the maximum

blood concentration (C(max)), time to reach the peak blood concentration (T(max)), mean residence time (MRT), area under the curve (AUC(0-t)) and terminal elimination half-life (T(1/2)) were significantly ($p<0.05$) different following transdermal administration compared with oral administration. In contrast to oral delivery, a sustained activity was observed over a period of 48h after transdermal administration. This sustained activity was due to the controlled release of drug into the systemic circulation following transdermal administration.

PMID: 19114099 [PubMed - indexed for MEDLINE]

4: N Engl J Med. 2008 May 1;358(18):1887-98. Epub 2008 Mar 31.

Comment in:

ACP J Club. 2008 Aug 19;149(2):10.

Curr Cardiol Rep. 2008 Nov;10(6):437-9.

Curr Hypertens Rep. 2008 Aug;10(4):258-60.

Curr Hypertens Rep. 2008 Aug;10(4):301-2.

Evid Based Med. 2008 Oct;13(5):136.

J Fam Pract. 2008 Aug;57(8):506-7.

N Engl J Med. 2008 Aug 28;359(9):971-2; author reply 973-4.

N Engl J Med. 2008 Aug 28;359(9):972-3; author reply 973-4.

N Engl J Med. 2008 Aug 28;359(9):973; author reply 973-4.

N Engl J Med. 2008 Aug 28;359(9):973; author reply 973-4.

N Engl J Med. 2008 May 1;358(18):1958-60.

N Engl J Med. 2009 Jul 23;361(4):424-5.

Nat Clin Pract Nephrol. 2008 Oct;4(10):526-7.

Treatment of hypertension in patients 80 years of age or older.

Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D, Stoyanovsky V, Antikainen RL, Nikitin Y, Anderson C, Belhani A, Forette F, Rajkumar C, Thijs L, Banya W, Bulpitt CJ; HYVET Study Group.

Collaborators (232)

Bulpitt CJ, Fletcher AE, Beckett NS, Peters R, McCormack T, Potter T, Extremera BG, Sever P, Forette F, Dumitrascu D, Swift C, Tuomilehto J, Coope J, Nachev C, Staessen J, Thijs L, Clarke R, Narkiewicz K, Davidson C, Duggan J, Leonetti G, Gainsborough N, De Vernejoul MC, Wang J, Stoyanovsky V, Tuomilehto J, Clarke R, Waldman A, Walton I, Ritchie C, Fagard R, Evans JG, Williams B, Warne R, Puddey I, Woodward M, Penhall R, Inderjeeth C, Roger S, Scholes R, Johnson C, Celis H, Adriaens G, Onsea W, Cornelli K, Vantroyen D, Cleen P, de Voogt P, Nachev C, Stoyanovsky V, Solakov P, Prokopova R, Mantova E, Smilkova D, Mantov S, Yankulova K, Kermova R, Popov D, Sirakova V, Gergova V, Kamenova D, Grigorov F, Vassileva R, Alahverdian R, Tzekova M, Liu L, Ge H, Wang S, Wang J, Zhang W, Jin S, Ge L, Lu YF, Ma S, Shen L, Guo J, Lv Z, Huang R, Li X, Guo B, Zhang T, Zhang L, Feng J, He Z, Wang J, Deng L, Liu L, Yuan Q, Zhang F, Li H, Wang D, Yang K, Sun M, Liu H, Yan X, Ren F, Tang J, Antikainen R, Strandberg T, Konttila T, Hynninen A, Jääskivi M, Airas J, Jääskeläinen T, Tuomilehto J, Litmanen H, Forette F, Doucet J, Belmin J, Benetos A, Berrut G, Boge T, Bonnefoy M, Carre A, Charasz N, Covillard J, Dantoine T, Escande M, Frances Y, Joire R, Jeandel C, Legrain S, Lion A, Maillet-Vioud M, Escaillas JP, Meaume S, Pfitzenmeyer P, Puisieux F, Quercy E, Rodat O, Soubeyrand J, de Wazieres B, Hindennach H, Lugassy L, Rossi J, Martel M, Paladel JM, Ravier C, Visconti A, Gallet JP, Zygouritsas D, Charles D, Flamand F, Grandmottet G, Grandmottetegermann M, Gevrey C, Mesnier PL, Robert G, Besset-Prat C, Brousse A, Lafont P, Morelli J, Vernede P, Volkmann A, Bodin X, Destrube B, Eoche R, Boye A, Seropian F, Gernigon P, Meker D, Thomere J, Thual Y, Volny F, Grassart E, Herent M, Lejay D, Lopez JP, Mannessier B, Pruvost G, Urbina JC, Duggan J, Anderson C, Lillis S, Gommans J, Grodzicki T, Chodorowski Z, Gaciong Z, Dumitrascu D, Comsa M, Sandru V, Prada G, Dunca-Moisin M, Jianu D, Jinga-Lazar, Enachescu V, Zaharia C, Nikitin Y, Kirichenko A, Olbinskaya L, Olbinskaya L, Martynov A, Zadionchenko V, Moiseev V, Storohzakov G, Nedogoda S, Karpov RS, Barbarash O,

Efremushkin G, Kostenko V, Boyarkin M, Churina S, Tyurina T, Ballyuzek M, Ermoshkina L, Timofeev A, Yakusheva S, Shilkina N, Barbarich V, Belhani A, Boughzela E, Soraya S, Youssef-Zouari B, Khalfallah AB, Houman MH, Abida AK, Rajkumar C, Wilkins M, Pandita-Gunawardena ND, Potter J, Ekpo E, Price M, de Kare-Silver N, Starczewski A, Chandran S, Nasar N, Datta-Chaudhuri M, McCormack T, Majmudar N, Gordon A, Brawn L, Solanki T.

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BACKGROUND: Whether the treatment of patients with hypertension who are 80 years of age or older is beneficial is unclear. It has been suggested that antihypertensive therapy may reduce the risk of stroke, despite possibly increasing the risk of death. METHODS: We randomly assigned 3845 patients from Europe, China, Australasia, and Tunisia who were 80 years of age or older and had a sustained systolic blood pressure of 160 mm Hg or more to receive either the diuretic indapamide (sustained release, 1.5 mg) or matching placebo. The angiotensin-converting-enzyme inhibitor perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mm Hg. The primary end point was fatal or nonfatal stroke. RESULTS: The active-treatment group (1933 patients) and the placebo group (1912 patients) were well matched (mean age, 83.6 years; mean blood pressure while sitting, 173.0/90.8 mm Hg); 11.8% had a history of cardiovascular disease. Median follow-up was 1.8 years. At 2 years, the mean blood pressure while sitting was 15.0/6.1 mm Hg lower in the active-treatment group than in the placebo group. In an intention-to-treat analysis, active treatment was associated with a 30% reduction in the rate of fatal or nonfatal stroke (95% confidence interval [CI], -1 to 51; P=0.06), a 39% reduction in the rate of death from stroke (95% CI, 1 to 62; P=0.05), a 21% reduction in the rate of death from any cause (95% CI, 4 to 35; P=0.02), a 23% reduction in the rate of death from cardiovascular causes (95% CI, -1 to 40; P=0.06), and a 64% reduction in the rate of heart failure (95% CI, 42

to 78; P<0.001). Fewer serious adverse events were reported in the active-treatment group (358, vs. 448 in the placebo group; P=0.001). CONCLUSIONS: The results provide evidence that antihypertensive treatment with indapamide (sustained release), with or without perindopril, in persons 80 years of age or older is beneficial. (ClinicalTrials.gov number, NCT00122811 [ClinicalTrials.gov].). Copyright 2008 Massachusetts Medical Society.

PMID: 18378519 [PubMed - indexed for MEDLINE]

5: Curr Med Res Opin. 2007 Dec;23(12):2929-36.

Antihypertensive efficacy of indapamide SR in hypertensive patients uncontrolled with a background therapy: the NATIVE study.

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OBJECTIVES: Antihypertensive monotherapy rarely achieves blood pressure (BP) control. NATIVE (NATrilix SR use in combInation antihypertensiVe thErapy) evaluated indapamide sustained release (SR) in hypertensive patients receiving background therapy. RESEARCH DESIGN AND METHODS: Patients remaining hypertensive (systolic BP [SBP], 145-180 mmHg; diastolic BP [DBP], 95-105 mmHg) while receiving an angiotensin-converting enzyme (ACE) inhibitor (n = 709), beta-blocker (n = 629), calcium-channel blocker (CCB; n = 493), angiotensin II type 1 receptor blocker (ARB; n = 75), alpha-blocker (n = 29) or other therapy (n = 6) were enrolled, recruited by physicians from 228 centres in Pakistan. Indapamide SR 1.5 mg was administered daily for 3 months with background therapy. BP was assessed every 2 weeks, and blood glucose and total cholesterol were evaluated at baseline and study end in a patient subgroup. Adverse events were also recorded. MAIN OUTCOME MEASURES AND RESULTS: Of 2073 enrolled patients (49% males; mean age 51 years), 1941 received indapamide SR and background therapy. SBP and DBP decreased

significantly (SBP, 166 +/- 16 mmHg at baseline vs. 132 +/- 12 mmHg at 3 months; DBP, 102 +/- 8 mmHg vs. 83 +/- 6 mmHg; both $p < 0.0001$ vs. baseline). Patients uncontrolled with an ACE inhibitor, beta-blocker, CCB or ARB achieved an SBP/DBP decrease of 34 +/- 15/19 +/- 9, 33 +/- 17/19 +/- 10, 33 +/- 15/18 +/- 8 or 35 +/- 16/20 +/- 12 mmHg, respectively (all $p < 0.0001$). In all, 84% of patients achieved target SBP (< or = 140 mmHg) and 61% achieved BP normalisation (SBP < 140, DBP < 90 mmHg). The absence of placebo control may lead to an overestimation of the extent of the BP reduction achieved. Glucose and cholesterol levels were unaffected by indapamide SR. Four percent of patients experienced side-effects, which were mild-to-moderate in severity. CONCLUSIONS: In patients with hypertension despite antihypertensive therapy, indapamide SR significantly reduced BP with a good acceptability profile. Indapamide SR may represent an effective additional therapy for patients who do not achieve BP goals with other antihypertensive agents.

PMID: 17931463 [PubMed - indexed for MEDLINE]

6: Clin Drug Investig. 2007;27(11):735-53

Updated meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure.

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BACKGROUND AND OBJECTIVE: Despite advances in the treatment of hypertension, control rates continue to be suboptimal in both Europe and the US. Strategies that improve hypertension control are therefore urgently needed. This study aimed to assess the relative efficacies of various antihypertensive drugs commonly used in France in reducing systolic and diastolic blood pressure (SBP and DBP) by using a meta-analytical approach. This update of a previously

published meta-analytical approach extends the number of drugs evaluated from 13 to 19. METHODS: A total of 80 randomised, controlled trials published between 1973 and 2007 involving 10 818 patients were selected for inclusion in the meta-analytical approach. Data were examined for 19 drugs, and 16 drugs were included in the analysis: hydrochlorothiazide, indapamide sustained-release (SR), atenolol, amlodipine, lercanidipine, manidipine, enalapril, ramipril, trandolapril, candesartan cilexetil, irbesartan, losartan, olmesartan medoxomil, telmisartan, valsartan and aliskiren. Weighted average reductions in SBP and DBP over a period of 8-12 weeks were calculated for each drug from information on both the mean and the variability in BP reduction. No trials evaluating furosemide, spironolactone or cicletanine satisfied the inclusion criteria for this analysis. RESULTS: The average weighted reductions in SBP over 8-12 weeks were most marked with diuretics, and in particular indapamide SR 1.5 mg/day (mean change from baseline -22.2mm Hg), which reduced SBP to a greater extent than any of the other drugs evaluated (at any dosage considered). Average weighted reductions in DBP were generally similar with all classes of antihypertensives and ranged from -11.4mm Hg with the beta-adrenoceptor blocker atenolol and calcium channel antagonists to -10.3mm Hg with the angiotensin II type 1 receptor antagonists. CONCLUSION: This new analysis supports the results of the earlier investigation, in that indapamide SR 1.5 mg/day appeared to be the most effective drug for producing significant reductions in SBP within 8-12 weeks, which is an essential element in optimising cardiovascular prevention among hypertensive patients. The clinical application of these results should take into consideration all the limitations discussed in this analysis.

PMID: 17914893 [PubMed - indexed for MEDLINE]

: Am J Hypertens. 2007 Jan;20(1):90-7.

Efficacy of indapamide SR compared with enalapril in elderly hypertensive patients with type 2 diabetes.

Puig JG, Marre M, Kokot F, Fernandez M, Jermendy G, Opie L, Moyseev V, Scheen A, Ionescu-Tirgoviste C, Saldanha MH, Halabe A, Williams B, Mion D Jr. Ruiz M, Hermansen K, Tuomilehto J, Finizola B, Gallois Y, Amouyel P, Ollivier JP, Asmar R.

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BACKGROUND: Blood pressure control is the main influential variable in reducing microalbuminuria in patients with type 2 diabetes. In this subanalysis of the Natrilix SR versus Enalapril Study in hypertensive Type 2 diabetics with micrOalbuminuRia (NESTOR) study, we have compared the effectiveness of indapamide sustained release (SR) and enalapril in reducing blood pressure and microalbuminuria in patients > or =65 years of age. METHODS: Of the 570 hypertensive patients with type 2 diabetes and persistent microalbuminuria in the NESTOR study, 187 (33%) individuals > or =65 years of age were included in this analysis. Of these, 95 patients received indapamide SR 1.5 mg and 92 patients received enalapril 10 mg, taken once daily in both cases. Adjunctive amlodipine and/or atenolol was added if required. RESULTS: The urinary albumin-to-creatinine ratio decreased by 46% in the indapamide SR group and 47% in the enalapril group. Noninferiority of indapamide SR over enalapril was demonstrated (P = .0236; 35% limit of noninferiority) with a ratio of 0.95 (95% CI: 0.68, 1.34). Mean arterial pressure decreased by 18 mm Hg and 15 mm Hg in the indapamide SR and the enalapril groups, respectively (P = .1136). The effects of both treatments seen in these elderly patients were similar to those observed in the main population, although the extent of the reduction in microalbuminuria was slightly higher. Both treatments were well tolerated, and no difference between groups was observed regarding glucose or lipid profiles. CONCLUSION: Indapamide SR is not less effective than enalapril in reducing microalbuminuria

and blood pressure in patients aged >65 years of age with type 2 diabetes and hypertension.

PMID: 17198918 [PubMed - indexed for MEDLINE]

8: J Chromatogr B Analyt Technol Biomed Life Sci. 2006 Apr 13;834(1-2):149-54. Epub 2006 Mar 10.

Liquid chromatography-tandem mass spectrometry validated method for the estimation of indapamide in human whole blood.

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A highly precise and sensitive method for the estimation of indapamide in human whole blood using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) is described. The method developed is validated in human whole-blood matrix, with a sensitivity of 0.5 ng/ml as lower limit of quantification. The procedure for the extraction of indapamide and glimepiride as internal standard (IS) involves haemolysis and deprotienation of whole blood using ZnSO(4) followed by liquid-liquid extraction using ethyl acetate. The sample extracts after drying were reconstituted and analysed by LC-MS/MS, equipped with turbo ion spray (TIS) source, operating in the positive ion and selective reaction monitoring (SRM) acquisition mode to quantify indapamide in human whole blood. The mean recovery for indapamide was 82.40 and 93.23% for IS. The total run time was 2.5 min to monitor both indapamide and the IS. The response of the LC-MS/MS method for indapamide was linear over the range of 0.5-80.0 ng/ml with correlation coefficient, r>or=0.9991. The coefficient of variance (% CV) at 0.5 ng/ml was 4.02% and the accuracy was well within the accepted limit of +/-20% at 0.5 ng/ml and +/-15% at all other concentrations in the linear range. This method is fully validated for the accuracy, precision and

stability studies and also applied to subject-sample analysis of bioequivalence study for 1.5mg sustained-release (SR) formulations.

PMID: 16531130 [PubMed - indexed for MEDLINE]

Am J Hypertens. 2006 Jan;19(1):113-21.
Comment in:
Am J Hypertens. 2006 Jan;19(1):8-9.

Indapamide SR versus candesartan and amlodipine in hypertension: the X-CELLENT Study.

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BACKGROUND: Reducing systolic blood pressure (BP) is of major benefit to patients with isolated systolic hypertension, but lowering normal diastolic BP may be harmful in terms of cardiovascular risk. Effects of different drugs on systolic BP, diastolic BP, and pulse pressure are therefore of interest. METHODS: The NatriliX SR versus CandEsartan and amLodipine in the reduction of systoLic blood prEssure in hyperteNsive patienTs study (X-CELLENT) was a randomized, double-blind, placebo-controlled study comparing the effects of three drugs on these BP components. Patients with systolic-diastolic or isolated systolic hypertension (n = 1758) received indapamide (1.5 mg) sustained release (SR), candesartan (8 mg), amlodipine (5 mg), or placebo once daily for 12 weeks. RESULTS: Compared to placebo all active treatments reduced all BP components significantly (P < .001). For the patients with isolated systolic hypertension (n = 368), the three treatments significantly reduced systolic BP, but only indapamide SR did not change diastolic BP and thus reduced pulse pressure significantly relative to placebo (P = .005). In an ancillary study using ambulatory BP

monitoring (n = 576), all three treatments significantly reduced BP components during 24 h relative to placebo. Changes in systolic BP and pulse pressure were similar with the three treatments, but the reduction in diastolic BP was significantly smaller, and therefore more favorable, with indapamide SR compared with candesartan (P = .039). In patients with isolated systolic hypertension (n = 106), indapamide SR reduced 24-h systolic BP significantly more than amlodipine (P = .037), and only indapamide SR reduced 24-h pulse pressure significantly relative to placebo (P = .03). All three drugs were well tolerated. CONCLUSIONS: This distinctive BP-lowering profile of indapamide SR seems highly beneficial when compared to the either of candesartan or amlodipine.

PMID: 16461202 [PubMed - indexed for MEDLINE]

10: Drugs. 2006;66(2):257-71.

Indapamide sustained release: a review of its use in the treatment of hypertension.

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A low-dose sustained-release (SR) formulation of the thiazide-type diuretic indapamide, indapamide SR (Natrilix SR), retains the antihypertensive activity of the immediate-release (IR) formulation, with a smoother pharmacokinetic profile. In well controlled 12- to 52-week clinical trials, indapamide SR 1.5 mg/day was well tolerated and reduced blood pressure as effectively as therapeutic dosages of amlodipine, candesartan, enalapril, hydrochlorothiazide or indapamide IR. Indapamide SR was also more effective than enalapril in reducing left ventricular hypertrophy (LVH), and similar reductions in renal end-organ damage, assessed by microalbuminuria, were seen with indapamide SR- and enalapril-based antihypertensive strategies. Indapamide SR provides an effective option for initial

antihypertensive monotherapy and a basis for multidrug antihypertensive strategies.

PMID: 16451099 [PubMed - indexed for MEDLINE]

11: Pharmacoepidemiol Drug Saf. 2006 Oct;15(10):741-8.

Pharmacoepidemiology of antihypertensive drugs in primary care setting of Bahrain between 1998 and 2000.

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PURPOSE: To compare pattern of antihypertensive drug utilization in 1998 with 2000 following the: (a) publication of 1999 World Health Organization/International Society of Hypertension (WHO/ISH) guidelines for drug management of hypertension; and (b) introducing new antihypertensives to the essential drug list, in primary care, Bahrain. METHODS: Retrospective prescription-based survey carried out in seven out of 20 primary care health centers in Bahrain. A total of 9272 patients comprising 6543 with uncomplicated hypertension and 2729 with diabetic hypertension were studied. RESULTS: Between 1998 and 2000, the prescription rate of beta-blockers and methyldopa significantly declined ($p < 0.0001$) while the rate of angiotensin converting enzyme (ACE) inhibitors and calcium channel blockers (CCBs) increased ($p < 0.0001$) in uncomplicated hypertension. However, in diabetic hypertension there was a non-significant decline in utilization of beta-blockers, CCBs, methyldopa, and diuretics whereas a significant increase in prescribing of ACE inhibitors ($p < 0.0001$). Inclusion of Perindopril into the essential drug list resulted in an overall increase in utilization of ACE inhibitors: use of captopril and enalapril declined while lisinopril and perindopril increased. Substitution of immediate-release (IR) indapamide by sustained-release (SR) formulation did not change the overall

utilization of diuretics; however, intra-class changes were evident with a significant decline in use of thiazide diuretics and concomitant increase in use of SR indapamide by 2000. CONCLUSIONS: The antihypertensive prescribing pattern is influenced by WHO/ISH guidelines as well as by introduction of new antihypertensives to primary care essential drug list in primary care. The choice of a drug is also influenced by presence of co-morbidity with diabetes mellitus.

PMID: 16342299 [PubMed - indexed for MEDLINE]

12: Pharmazie. 2005 Nov;60(11):819-22.

Rapid and sensitive determination of indapamide in human blood by liquid chromatography with electrospray ionization mass spectrometric detection: application to a bioequivalence study.

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A rapid and sensitive method using liquid chromatography with electrospray ionization mass spectrometric detection was developed and validated for the determination of indapamide in human blood. Blood samples were extracted with n-hexane-dichloromethane (1:1, v/v) and separation was performed on a Symmetry C18 column (150 x 3.9 mm i.d., 5 microm) with the mobile phase consisting of acetonitrile-water (60:40, v/v). Indapamide and internal standard (propylparaben) were detected by negative electrospray ionization and selected ion recording (SIR) at m/z 364 for indapamide and m/z 179 for propylparaben. This method has a lower limit of quantification (LLOQ) 2.0 microg/L with a linear calibration range of 2.0 microg/L to 120 microg/L. The method showed excellent reproducibility with an inter- and intra-assay precision of < 9.4% (% RSD), as well as excellent accuracy with an inter- and intra-assay accuracy of

between 98.0 and 102%. Furthermore, the method was successfully applied to a bioequivalence study in which 20 healthy volunteers received a single oral dose of 3 mg reference and test sustained-release indapamide formulations, in an open, two-period, randomized crossover protocol. The maximum blood concentrations (C(max)) were 60.3 +/- 22.6 microg/L and 57.6 +/- 18.7 microg/L at 13.1 +/- 6.9 h and 18.3 +/- 7.4 h, the times to reach the peak concentration (T(max)), for the test and reference tablets, respectively. The relative bioavailability of the test tablets was 110.1 +/- 34.5%, compared with the reference tablets. There were no statistically significant differences in the main pharmacokinetic parameters, and the two formulations were judged to be bioequivalent.

PMID: 16320942 [PubMed - indexed for MEDLINE]

13: Fundam Clin Pharmacol. 2005 Dec;19(6):637-45.

An overview of the pharmacology and clinical efficacy of indapamide sustained release.

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The relationship between blood pressure (BP) and cardiovascular risk is clearly established; hypertension increases the rate of cardiovascular. High systolic blood pressure (SBP) may be the main parameter involved in cardiovascular morbidity and mortality. The benefit of lowering BP, particularly with diuretics has been proven in many outcome studies. Indapamide, a thiazide-type diuretic, was available for many years at a dosage of 2.5 mg in an immediate release formulation. A new sustained release (SR) formulation has been developed in order to allow the same antihypertensive efficacy with a better acceptability profile. This paper reviews the pharmacology of indapamide 1.5 mg SR from the bench to the bedside. Indapamide has a dual mechanism of action: diuretic effect

at the level of the distal tubule in the kidney and a direct vascular effect, both of which contribute to the antihypertensive efficacy of the drug. The SR formulation contains a hydrophilic matrix, which delivers a smoother pharmacokinetic profile. This avoids unnecessary plasma peak concentrations, which may be associated with side effects. Indapamide SR has now been extensively used in hypertensive patients, including those at increased risk, for example elderly or diabetic patients. It has been shown to decrease BP, particularly SBP, with 24-h efficacy, allowing a once-daily dosage. Studies have demonstrated BP lowering to be at least as effective as all major therapeutic classes including the more recent antihypertensive drugs. Beyond BP decrease, indapamide SR has also been shown to protect against hypertensive target-organ damage in the heart and the kidney and to have a favorable metabolic profile. A broad evidence-base has accumulated to support the benefit of indapamide 1.5 mg SR in hypertensive patients, alone or as part of combination therapy, as recommended by the majority of guidelines.

PMID: 16313275 [PubMed - indexed for MEDLINE]

14: Am J Cardiovasc Drugs. 2005;5(2):131-40.

A meta-analytical approach to the efficacy of antihypertensive drugs in reducing blood pressure.

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INTRODUCTION: Hypertension constitutes a veritable public health issue. Several classes of drugs are available for the treatment of hypertension. The objective of this meta-analytical approach was to assess the efficacy of antihypertensive drugs most commonly used in France in reducing clinical SBP and DBP. METHODS: The antihypertensive drugs selected were hydrochlorothiazide, indapamide sustained release (SR), furosemide and

spironolactone for diuretics; amlodipine and lercanidipine for calcium channel antagonists; atenolol for beta-adrenoceptor antagonists (beta-blockers); enalapril and ramipril for ACE inhibitors; and candesartan cilexetil, irbesartan, losartan, and valsartan for angiotensin II receptor antagonists. The trials selected were published between 1973 and 2004, evaluated monotherapy with trial drugs as fixed-dosage or with dosage increase, and assessed blood pressure reduction between 2 and 3 months. The analysis method used was based on the calculation of the sum weighted for the trial size. RESULTS: A total of 72 trials (comprising 9094 patients) were selected and analyzed. No trial evaluating furosemide or spironolactone satisfied the inclusion criteria for this analysis. For SBP, the reduction was more marked with diuretics, calcium channel antagonists, and ACE inhibitors. Of all the drugs studied, indapamide SR gave the greatest SBP reduction (-22.2 mm Hg). Evaluated therapeutic classes had a similar magnitude of effect on DBP, i.e. reduction between -11.4 mm Hg with beta-adrenoceptor antagonists and -10.3 mm Hg with angiotensin II type 1 receptor antagonists. CONCLUSION: Indapamide SR 1.5 mg appeared to be the most effective drug for a significant reduction in SBP within 2-3 months, which is an essential element in optimizing cardiovascular prevention among hypertensive patients. The clinical application of these results should take into consideration all the limitations discussed in this analysis.

PMID: 15725044 [PubMed - indexed for MEDLINE]

15: J Chromatogr B Analyt Technol Biomed Life Sci. 2005 Feb 25;816(1-2):35-40.

Liquid chromatography-electrospray tandem mass spectrometry method for determination of indapamide in serum for single/multiple dose bioequivalence studies of sustained release formulations.

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Indapamide and internal standard (5-chloro-2-methoxy-N-[2-(4-sulphamoylphenyl)ethyl]benzamide) were isolated from plasma by a single step liquid-liquid extraction in t-butyl methyl ether. The chromatographic separation was achieved on a reversed-phase C(18) monolithic column with a mobile phase consisting in a methanol/aqueous 0.1% formic acid mixture and a flow rate of 0.8 ml/min, in isocratic conditions, within 11 min. Target compounds were transferred in an ion trap analyzer via an atmospheric pressure electrospray interface (AP-ESI). The mass analyzer was used in a selected reaction monitoring (SRM) mode, in order to enhance on detection selectivity. Whole method produces quantitation limit for indapamide of 1 ng/ml. Method was successfully applied to assess bioequivalence of two sustained release marketed pharmaceutical formulations of indapamide 1.5 mg coated tablets, carried-out in a single/multiple doses, randomized design.

PMID: 15664331 [PubMed - indexed for MEDLINE]

16: J Hum Hypertens. 2004 Dec;18 Suppl 2:S9-S14.
Comment in:
J Hum Hypertens. 2004 Dec;18 Suppl 2:S1.

Efficacy of indapamide 1.5 mg, sustained release, in the lowering of systolic blood pressure.

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The relationship between the increase in blood pressure and the incidence of cardiovascular disease is well recognized today. Studies have shown that more attention should be paid to systolic blood pressure (SBP) in relation to

cardiovascular risk and that therapeutic interventions should preferably focus on reducing SBP. The antihypertensive efficacy of indapamide 1.5 mg sustained release (indapamide SR), a low-dose thiazide-type diuretic, was assessed on SBP. Three randomized, double-blind, controlled studies were conducted with indapamide SR, over a period of 3 to 12 months. Elderly patients or patients with target-organ damage, hypertension and left ventricular hypertrophy (LVH) (LIVE study) or with type II diabetes with microalbuminuria (NESTOR study) showed a decrease in SBP varying from 22.7 to 31.8 mmHg. The treatment with indapamide SR resulted in a better or equivalent control of SBP than treatment with a standard dose of a true thiazide diuretic (hydrochlorothiazide), a calcium channel blocker (amlodipine), and an angiotensin-converting enzyme inhibitor (enalapril). No therapeutic escape was observed. All treatments showed good acceptability with no unexpected adverse event. In conclusion, indapamide SR is very effective in lowering SBP-a major independent cardiovascular risk factor-notably in hypertensive high-risk patients with LVH, the elderly and diabetics, when compared to major antihypertensive treatments. This SBP-lowering effect is maintained over the long term.

PMID: 15592572 [PubMed - indexed for MEDLINE]

17: Am J Cardiovasc Drugs. 2004;4(6):369-78.

Reversal of left ventricular hypertrophy: what have recent trials taught us?

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Regression of left ventricular hypertrophy (LVH) is an important intermediate target for antihypertensive therapy. Thus, several trials and meta-analyses have attempted to compare the effects of different antihypertensive agents on LVH, but flawed study designs and methodologic problems have limited the utility of these

studies. PRESERVE (Prospective Randomized Enalapril Study Evaluating Regression of Ventricular Enlargement), LIVE (LVH: Indapamide Sustained Release Versus Enalapril) and LIFE (Losartan Intervention For Endpoint reduction in hypertension) represent a new generation of large well designed trials with the power to compare different antihypertensive drugs. These studies have shown that treatment regimens based on enalapril and a nifedipine gastrointestinal therapeutic system are of similar efficacy (PRESERVE), that indapamide sustained release (SR) is superior to enalapril (LIVE), and that a regimen based on losartan is superior to a regimen based on atenolol (LIFE) in reversing hypertensive LVH. LIVE incorporated on-treatment echocardiographic quality control, with centralized readers blinded for both treatment and sequence of recording. The findings of these rigorous studies, to some extent in disagreement with results of previous meta-analyses, support the notion that antihypertensive drugs need to be judged on their individual effects on important intermediate endpoints such as LVH in well designed and adequately sized studies. However, extrapolation of the results of these studies in terms of class effects could be misleading and should be made with caution.

PMID: 15554722 [PubMed - indexed for MEDLINE]

18: J Hypertens. 2004 Aug;22(8):1613-22.

Equivalence of indapamide SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: the NESTOR Study.

Marre M, Puig JG, Kokot F, Fernandez M, Jermendy G, Opie L, Moyseev V, Scheen A, Ionescu-Tirgoviste C, Saldanha MH, Halabe A, Williams B, Mion Júnior D, Ruiz M, Hermansen K, Tuomilehto J, Finizola B, Gallois Y, Amouyel P, Ollivier JP, Asmar R.

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OBJECTIVES: To test whether microalbuminuria in patients with type 2 diabetes and hypertension is primarily dependent on the severity of hypertension, and to compare the effectiveness of two antihypertensive drugs with opposite effects on the renin-angiotensin system [the diuretic, indapamide sustained release (SR), and an angiotensin-converting enzyme inhibitor, enalapril] in reducing microalbuminuria. DESIGN: A multinational, multicentre, controlled, double-blind, double-dummy, randomized, two-parallel-groups study over 1 year. METHODS: After a 4-week placebo run-in period, 570 patients (ages 60.0 +/- 9.9 years, 64% men) with type 2 diabetes, essential hypertension [systolic blood pressure (SBP) 140-180 mmHg, and diastolic blood pressure (DBP) < 110 mmHg], and persistent microalbuminuria (20-200 microg/min) were allocated randomly to groups to receive indapamide SR 1.5 mg (n = 284) or enalapril 10 mg (n = 286) once a day. Amlodipine, atenolol, or both were added, if necessary, to achieve the target blood pressure of 140/85 mmHg. RESULTS: There was a significant reduction in the urinary albumin : creatinine ratio. Mean reductions were 35% [95% confidence interval (CI) 24 to 43] and 39% (95% CI 30 to 47%) in the indapamide SR and enalapril groups, respectively. Equivalence was demonstrated between the two groups [1.08 (95% CI 0.89 to 1.31%); P = 0.01]. The reductions in mean arterial pressure (MAP) were 16.6 +/- 9.0 mmHg for the indapamide SR group and 15.0 +/- 9.1 mmHg for the enalapril group (NS); the reduction in SBP was significantly greater (P = 0.0245) with indapamide SR. More than 50% of patients in each group required additional antihypertensive therapy, with no differences between groups. Both treatments were well tolerated. CONCLUSIONS: Indapamide-SR-based therapy is equivalent to enalapril-based therapy in reducing microalbuminuria with effective blood pressure reduction in patients with hypertension and type 2 diabetes.

PMID: 15257186 [PubMed - indexed for MEDLINE

19: Curr Med Res Opin. 2004 May;20(5):639-44.

Left ventricular hypertrophy in hypertensive patients in Indian primary care: prevalence and effect of treatment with sustained release indapamide.

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OBJECTIVE: Epidemiologic studies indicate an ethnic determinant of left ventricular hypertrophy (LVH), but its prevalence in hypertensive Asian Indians at diagnosis is not known. The observation that LVH regression reduces cardiovascular risk independent of blood pressure, suggests that initial antihypertensive treatment, which also regresses LVH is a desirable goal. This study investigates the prevalence of LVH and its regression with indapamide sustained release (Natrilix SR) in untreated Indian hypertensive patients managed in the primary care setting. DESIGN AND METHODS: Randomly selected physicians serving a defined population recruited untreated hypertensive patients to determine prevalence of LVH. All patients then received indapamide SR treatment for 6 months. LVH was assessed by echocardiography. All measurements were centralized and interpreted by a single blinded observer. MAIN OUTCOME MEASURES: The primary treatment outcomes were the percentage of patients whose LVH regressed with treatment and the number of patients who achieved a blood pressure below 140/90 mmHg. RESULTS: Of the 86 patients recruited, 21 (24.4%, 95% confidence interval (CI) 15.3-33.8) had LVH. There were 11 cases (26.2%) in men, 10 (22.7%) in women, and 15 (32.6%) in those above 50 years. Treatment regressed LVH in 16 (76.2%, 95%CI, 58.0-94.4) by a mean of 25.4 g/m2 (95%CI, 2.8-47.7, $p < 0.05$). Blood pressure was controlled in 71 (82.6%, 95%CI, 74.5-90.6) patients. CONCLUSION: Prevalence of LVH in untreated Indian hypertensive patients is similar to that in white western populations. Initial indapamide SR treatment is effective in both controlling blood pressure and regressing LVH in the primary care setting.

PMID: 15140328 [PubMed - indexed for MEDLINE]

20: Am J Hypertens. 2003 Aug;16(8):623-8.

Effect of indapamide SR in the treatment of hypertensive patients with type 2 diabetes.

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BACKGROUND: To evaluate the effect of the sustained-release formulation of indapamide (indapamide SR) in type 2 diabetic patients with mild-to-moderate hypertension and its possible side effects, particularly on glucose metabolism and lipid profiles. METHODS: A total of 64 patients randomly received 1.5 mg of indapamide SR or placebo once daily for 3 months. The effects were evaluated by 24-h ambulatory blood pressure monitor, fasting blood sampling for biochemistry, lipid profiles, and frequently sampled intravenous glucose tolerance test. RESULTS: The changes in standing and supine blood pressure (BP) were significant (154.7 +/- 9.4/94 +/- 2.9 mm Hg v 134.4 +/- 5.1/82.4 +/- 5 mm Hg and 155 +/- 9.8/94.6 +/- 3.6 mm Hg v 135.1 +/- 4.9/82.1 +/- 4.7 mm Hg) in the indapamide group, but not in the placebo group. According to the 24-h ambulatory blood pressure monitor reading, a significant reduction was observed in not only in the whole-day mean BP (mean systolic BP/mean diastolic BP, 149 +/- 19.3/87.6 +/- 11.3 mm Hg v 135.7 +/- 12.6/79.6 +/- 9 mm Hg) but also the whole-day mean median arterial pressure (109 +/- 12.7 mm Hg v 98.7 +/- 8.2 mm Hg) for the indapamide group, but not the placebo group. There were no changes in biochemical data including serum sodium, potassium, chloride, uric acid, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen,

creatinine, lipid profiles, fasting blood glucose, insulin, hemoglobin Alc, and glucose metabolism parameters (insulin sensitivity, glucose effectiveness, and acute insulin response) from frequently sampled intravenous glucose tolerance test after indapamide or placebo therapy. CONCLUSIONS: Indapamide SR can significantly lower the whole-day BP in hypertensive patients with type 2 diabetes. Also, it did not alter or aggravate patients' lipid profiles, glucose metabolism, and did not exert possible side effects of hypokalemia and hyperuricemia. Therefore, monotherapy with indapamide SR should be suggested in type 2 diabetic patients with mild-to-moderate hypertension.

PMID: 12878366 [PubMed - indexed for MEDLINE]

21: J Hypertens Suppl. 2003 Mar;21(1):S25-30.

New treatment guidelines for a patient with diabetes and hypertension.

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Guidelines for medical treatment are becoming increasingly popular and many guidelines have been produced by various societies in diabetes, hypertension, and renal disease as well as general medicine. By their nature, they are outdated considering the rapid and efficient publication of many papers related to the treatment of hypertension in diabetes. Increased blood glucose causes vascular damage and abnormal vascular structure all over the body, an abnormal structure that is especially vulnerable to high blood pressure, even within the so-called normal range. There is now more and more evidence, especially in diabetics, that blood pressure should be as low as possible. In this context, it is important to stress that the so-called J-shaped relationship between blood pressure and mortality may not be so relevant. Major epidemiological studies came from the Framingham and the Multiple Risk Factor Intervention Trial (MRFIT) Diabetic

Cohort. The MRFIT Cohort showed that cardiovascular mortality was increased by a factor of 2-4 in diabetic patients, and there was a clear association between systolic blood pressure and complications without any threshold value. It could be suggested that since diabetes is an important cardiovascular risk factor, a lower value (130/85 mmHg) than for non-diabetics (140/90 mmHg) should be proposed. The tight blood pressure control arm of the United Kingdom Prospective Diabetes Study was <150/85 mmHg (achieved 144/82 mmHg) and the aim in the less tight control arm was <180/105 mmHg (achieved 154/87 mmHg). In the tight control group, 29% needed three or more antihypertensive drugs. In the Hypertension Optimal Treatment study, the frequency of major cardiovascular disease events in the group with target <80 mmHg (achieved 144/81 mmHg) was 11.9/1000 patients/year, which was significantly lower than the event rate (24.4/1000 patients/year) in the group with target <90 mmHg (achieved 148/85 mmHg). A reduction in the frequency of diabetic nephropathy by angiotensin-converting enzyme (ACE) inhibitor treatment in normotensive lean microalbuminuric type 2 diabetic patients has been shown. However, it is impossible from the present data to draw any conclusions with respect to effect on the main composite endpoint of ACE inhibition in microalbuminuric type 2 diabetic patients without previous cardiovascular events or without hypertension. Recent published studies have also demonstrated beneficial effects with angiotensin receptor blockers (ARBs) in hypertensive patients with type 2 diabetes and nephropathy. Diuretics form a very important basis for antihypertensive treatment, also often in combination with agents that inhibit the renin-angiotensin system. Several studies show that treatment with the diuretic indapamide reduces the level of microalbuminuria in patients with type 2 diabetes. Diuretics were used as an adjunctive to reduce blood pressure in all studies; it is therefore understandable that many guidelines suggest that diuretics form part of the treatment of hypertension in diabetics. Many studies of an epidemiological nature and follow-up studies in diabetic patients show that blood pressure control is of vital concern in the prevention of diabetic complications, and indeed the usual criteria for good blood pressure control may not be stringent enough in diabetic patients. Many classes of antihypertensives

may be used, but it appears that diuretics, such as indapamide sustained release (SR), constitute an important proposal in all treatment strategies.

PMID: 12769164 [PubMed - indexed for MEDLINE]

22: J Hypertens Suppl. 2003 Mar;21(1):S19-24.

Effect of indapamide SR on microalbuminuria--the NESTOR study (Natrilix SR versus Enalapril Study in Type 2 diabetic hypertensives with micrOalbuminuRia)--rationale and protocol for the main trial.

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In type 2 diabetic hypertensive patients, microalbuminuria can be due to hypertension and/or diabetic nephropathy. Angiotensin-converting enzyme (ACE) inhibitors act preferentially on microalbuminuria due to diabetic nephropathy. The objective is to demonstrate the efficacy of a thiazide-like diuretic, indapamide sustained release (SR), at reducing microalbuminuria in hypertensive type 2 diabetic patients in comparison with an ACE inhibitor, enalapril. The study is an international multicentre, 12-month, randomized, double-blind, controlled, two parallel group study of type 2 diabetic patients with hypertension (140 mmHg < or = systolic blood pressure <180 mmHg and diastolic blood pressure <110 mmHg) and microalbuminuria. Intervention is after a 4-week placebo period, patients with microalbuminuria > or = 20 and < or = 200 microg/min are randomized to indapamide SR 1.5 mg or to enalapril 10 mg once a day for a one-year treatment period. An additional label treatment by amlodipine 5-10 mg (1st step) and atenolol 50-100 mg (2nd step) a day is permitted after 6 weeks of treatment based upon blood pressure response. The main outcome measures are

microalbuminuria expressed as urinary albumin to creatinine ratio, albumin fractional clearance, and albumin excretion rate evaluated on overnight urine collections. Secondary criteria are supine and standing systolic, diastolic and mean blood pressure; and biological and clinical safety. This study will complete the knowledge of the efficacy of indapamide SR in hypertension and target organ damage and will provide valuable information on the management of type 2 diabetic hypertensives with microalbuminuria.

PMID: 12769163 [PubMed - indexed for MEDLINE]

23: J Hypertens Suppl. 2003 Mar;21(1):S13-7.

Clinical role of Natrilix SR in the treatment of at-risk hypertensive patients.

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Although recent trials have shown that antihypertensive treatment can bring about a reduction in stroke, coronary heart disease, heart failure and renal disease, the situation is no longer improving. This is due to the fact that the percentage of hypertensive patients with satisfactory blood pressure is still very poor. International guidelines on hypertension indicate the importance of assessing the absolute risk of patients and the use of a lower dose of drugs to improve the efficacy-tolerability profile. Diuretics used at lower dosage than in the past are effective in reducing morbidity and mortality and continue to be drugs of first choice in the treatment of hypertension. Indapamide sustained release (Natrilix SR) 1.5 mg has an antihypertensive effect equivalent to indapamide immediate release 2.5 mg with a 50% reduction in incidence of serum potassium levels <3.4 mmol/l. Natrilix SR has proved to have a neutral effect both on lipid and glucose profiles and to reduce microalbuminuria in diabetic hypertensive patients. Recent multicentre European clinical trials have shown that Natrilix SR decreases

diastolic blood pressure to <90 mmHg in about 75% of patients treated for 1 year. In elderly patients with isolated systolic hypertension, Natrilix SR has been proven to be as effective as amlodipine 5 mg and significantly more effective than hydrochlorothiazide 25 mg. Natrilix SR produces regression of left ventricular hypertrophy which, in the Left ventricular hypertrophy: Indapamide Versus Enalapril study was greater than that induced by enalapril. Natrilix SR represents an appropriate choice not only as a first-line drug in many hypertensive patients but also in at-risk patients like the elderly, subjects with other cardiovascular risk factors, target organ damage, diabetes, or impaired renal function.

PMID: 12769162 [PubMed - indexed for MEDLINE]

24: Cardiovasc J S Afr. 2001 Feb-Mar;12(1):52-3.

Significant hypertrophy regression with indapamide sustained release 1.5 mg.

[No authors listed]

PMID: 11474686 [PubMed - indexed for MEDLINE]

25: J Hypertens. 2001 Feb;19(2):343-50.

A comparison of indapamide SR 1.5 mg with both amlodipine 5 mg and hydrochlorothiazide 25 mg in elderly hypertensive patients: a randomized double-blind controlled study.

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OBJECTIVE: To analyse the efficacy of indapamide sustained-release (SR) 1.5 mg in reducing blood pressure versus amlodipine 5 mg and hydrochlorothiazide 25 mg, in elderly hypertensive patients. DESIGN: Double-blind, randomized, 12 week study using three parallel groups. SETTING: European teaching hospitals and general practices. PATIENTS: Randomized patients, (n = 524) including 128 patients with isolated systolic hypertension (ISH); mean age: 72.4 years; mean systolic/diastolic blood pressures (SBP/DBP): 174.5/97.9 mmHg. MAIN OUTCOME MEASURES: Clinic systolic and diastolic blood pressure variations. RESULTS: Indapamide SR 1.5 mg demonstrates a similar efficacy to that of amlodipine 5 mg, as well as to that of hydrochlorothiazide 25 mg (equivalence P < 0.001); the mean decreases in SBP/DBP were -22.7/-11.8 mmHg, -22.2/-10.7 mmHg and -19.4/-10.8 mmHg, respectively. In the ISH subgroup, indapamide SR 1.5 mg tends to have greater efficacy than hydrochlorothiazide 25 mg in reducing the SBP (-24.7 versus -18.5 mmHg, respectively; equivalence P = 0.117), while similar results are obtained with amlodipine 5 mg (-23 mmHg, equivalence P < 0.001). The normalization rate was relatively high for indapamide SR 1.5 mg (75.3%), when compared with amlodipine (66.9%) and hydrochlorothiazide (67.3%), especially in the subgroup of isolated systolic hypertensive patients: 84.2 versus 80.0% for amlodipine, and versus 71.4% for hydrochlorothiazide. CONCLUSIONS: Indapamide SR 1.5 mg shows similar antihypertensive efficacy to amlodipine 5 mg and hydrochlorothiazide 25 mg in elderly hypertensive patients, while in patients with isolated systolic hypertension, indapamide SR 1.5 mg shows a similar efficacy to amlodipine 5 mg but a greater efficacy than hydrochlorothiazide 25 mg.

PMID: 11212979 [PubMed - indexed for MEDLINE]

26: Drug Saf. 2001;24(15):1155-65.

Metabolic profile of indapamide sustained-release in patients with hypertension: data from three randomised double-blind studies.

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OBJECTIVE: To evaluate the influence of indapamide sustained-release (SR) 1.5 mg/day, a thiazide-related sulfonamide diuretic, on serum levels of lipids (total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol and triglycerides), glucose and uric acid, and renal function (serum urea and creatinine levels). METHODS: Pooled data from three randomised, double-blind, controlled studies are analysed. Two of these studies were of short duration (2 and 3 months), one of which included a 9-month nonblind extension phase, and the third was a 12-month prospective study. Short- and long-term metabolic effects of the treatment could thus be analysed. All studies were conducted in patients with mild-to-moderate hypertension; the total population randomised in these studies comprised 1195 patients, of whom 505 had left ventricular hypertrophy (LVH). RESULTS: After 2 to 3 months' treatment with indapamide SR 1.5 mg/day, there was no significant change from baseline in serum lipid levels and glucose levels. This neutral effect was maintained after 9 and 12 months of treatment. Renal function was not affected by short- or long-term indapamide SR 1.5 mg/day therapy. Serum uric acid level was slightly increased after short-term therapy, but was restored to baseline values during long-term therapy with indapamide SR 1.5 mg/day. CONCLUSIONS: Indapamide SR 1.5 mg/day has no deleterious effect on glucose metabolism, serum levels of lipids and uric acid, or renal function. This antihypertensive agent can be considered to be an attractive therapeutic choice for all patients with mild-to-moderate hypertension, including the elderly and patients with increased cardiovascular risks, i.e. those with LVH.

PMID: 11772148 [PubMed - indexed for MEDLINE]

27: Drugs Aging. 2001;18(3):151-64.

Hypertension in the Very Elderly Trial (HYVET): protocol for the main trial.

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A number of trials and meta-analyses have demonstrated clear benefits of blood pressure (BP) reduction in patients aged <80 years with regard to the reduction in stroke and cardiovascular events. However, a variety of studies have suggested that the positive relationship between BP and cardiovascular mortality is weakened or indeed reversed in the very elderly. Most intervention trials to date have either excluded or not recruited sufficient patients aged > or =80 years to determine whether there is a significant benefit from treatment in this age group. A meta-analysis of intervention trials that recruited patients aged > or =80 years has suggested a benefit in terms of stroke reduction but has also raised the possibility of an increase in total mortality. The benefit to risk ratio therefore needs to be clearly established before recommendations can be made for treating very elderly patients with hypertension. The Hypertension in the Very Elderly Trial (HYVET) pilot recruited 1283 patients aged > or =80 years and showed the feasibility of performing such a trial in this age group. It was a Prospective Randomised Open Blinded End-Points (PROBE) design but the main trial has additional pharmaceutical sponsorship to run a double-blind trial. Therefore, the main trial is a randomised, double-blind, placebo-controlled trial designed to assess the benefits of treating very elderly patients with hypertension. It compares placebo with a low dose diuretic (indapamide sustained release 1.5mg daily) and additional ACE inhibitor (perindopril) therapy if required. As in the pilot trial, the primary end-point is stroke events (fatal and non-fatal) and the trial is designed to

determine whether or not a 35% difference occurs between placebo and active treatment. The main objective will be achieved with 90% power at the 1% level of significance. Secondary outcome measures will include total mortality, cardiovascular mortality, cardiac mortality, stroke mortality and skeletal fracture. 2100 patients aged > or =80 years are to be recruited and followed up for an average of 5 years. Entry BP criteria after 2 months of a single-blind placebo run-in period are a sustained sitting systolic BP (SBP) of 160 to 199mm Hg and a diastolic BP of 90 to 109mm Hg. The standing SBP must be >140mm Hg. The trial will be carried out in accordance with the principles of Good Clinical Practice. We describe in detail the protocol for the main trial and discuss the reasons for the changes from the pilot, the use of the drug regimen, and the BP criteria to be used in the trial.

PMID: 11302283 [PubMed - indexed for MEDLINE]

28: J Hypertens. 2000 Oct;18(10):1465-75.

Regression of left ventricular hypertrophy in hypertensive patients treated with indapamide SR 1.5 mg versus enalapril 20 mg: the LIVE study.

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OBJECTIVE: To compare the efficacy of indapamide sustained release (SR) 1.5 mg and enalapril 20 mg at reducing left ventricular mass index (LVMI) in hypertensive patients with left ventricular hypertrophy (LVH). DESIGN: The LIVE study (left ventricular hypertrophy regression, indapamide versus enalapril) was a 1 year, prospective, randomized, double-blind study. For the first time, a committee validated LVH before inclusion, provided on-going quality control during the study, and performed an end-study reading of all echocardiograms

blinded to sequence. SETTING: European hospitals, general practitioners and cardiologists. PATIENTS: Hypertensive patients aged > or = 20 years with LVH (LVMI in men > 120 g/m2; LVMI in women > 100 g/m2). Data were obtained from 411 of 505 randomized patients. INTERVENTIONS: Indapamide SR 1.5 mg, or enalapril 20 mg, daily for 48 weeks. MAIN OUTCOME MEASURES: LVMI variation in the perprotocol population. RESULTS: Indapamide SR 1.5 mg significantly reduced LVMI (-8.4 +/- 30.5 g/m2 from baseline; P< 0.001), but enalapril 20 mg did not (-1.9 +/- 28.3 g/m2). Indapamide SR 1.5 mg reduced LVMI significantly more than enalapril 20 mg: -6.5 g/m2, P = 0.013 (-4.3 g/m2 when adjusted for baseline values; P = 0.049). Both drugs equally and significantly reduced blood pressures (P< 0.001), without correlation with LVMI changes. Indapamide SR progressively reduced wall thicknesses throughout the 1-year treatment period. In contrast, the effect of enalapril observed at 6 months was not maintained at 12 months. CONCLUSIONS: Indapamide SR 1.5 mg was significantly more effective than enalapril 20 mg at reducing LVMI in hypertensive patients with LVH.

PMID: 11057435 [PubMed - indexed for MEDLINE]

29: Fundam Clin Pharmacol. 2000 Mar-Apr;14(2):139-46.

Pharmacokinetics of sustained and immediate release formulations of indapamide after single and repeated oral administration in healthy volunteers.

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The pharmacokinetics of a 2.5 mg immediate release (IR) formulation of indapamide was compared to a 1.5 mg sustained release (SR) formulation of indapamide after single and repeated oral administration dose using double blind

randomised cross-over studies. In the first study, 12 subjects received a single dose of each treatment: IR fasted, SR fasted or with food. In the second study one tablet of either formulation was administered daily for one week at breakfast. In each study, blood samples were collected pre dose (Cmin) and up to 120 h after the last dose. Urine was collected over the dosing interval (24 h). Following a single oral administration the SR formulation had a lower dose-normalised Cmax compared to the IR formulation (17.6 +/- 6.3 vs. 39.3 +/- 11.0 ng x mL(-1), respectively), a much longer t(max) (12.3 +/- 0.4 vs. 0.8 +/- 0.3 h) and a greater t75 (15.3 +/- 6.1 vs. 1.8 +/- 1.4 h) but there were no differences in dose-normalised AUC (559 +/- 125 and 564 +/- 146 ng x h x mL(-1)) nor in t(1/2z) values (14.8 +/- 2.8 vs. 18.4 +/- 13.4 h). The SR formulation clearly demonstrated sustained release characteristics as compared to the IR formulation. Food co-administration had no effect on dose-normalised AUC for the SR formulation. After repeated administration, steady-state was achieved by day 5. The absorption rate of the SR formulation was lower and the 24 h peak-to-trough fluctuation was 4-fold lower compared to the IR formulation. After dose correction there wasno change in AUC, (726 +/- 207 and 690 +/- 183 ng x mL(-1) x h for SR and IR, respectively). The elimination parameters (t(1,2z), Ae(tau), and CLr) remained unchanged. The SR formulation showed sustained release of indapamide with a reduction in peak concentration, while steady-state level was not affected by formulations. The two formulations have the same bioavailability.

PMID: 10796061 [PubMed - indexed for MEDLINE]

30: Drugs. 2000;59 Suppl 2:27-38; discussion 39-40.

Clinical positioning of indapamide sustained release 1.5mg in management protocols for hypertension.

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Indapamide sustained release (SR) 1.5mg is a new galenic formulation that is characterised by a relatively constant plasma concentration at steady state, with only minor fluctuations during the 24-hour period. A dose-titration study of 3 doses of indapamide SR (1.5, 2 and 2.5mg) given once daily has shown that the 3

dosages are equipotent in lowering blood pressure, and have an effect similar to that of indapamide immediate-release (IR) 2.5mg; all were statistically more effective than placebo. The percentage of hypertensive patients whose serum potassium was less than 3.4 mmol/L was significantly lower after indapamide SR 1.5mg than after indapamide IR 2.5mg. Neither indapamide formulation had any significant effects on lipid profile, glucose, urea and serum creatinine; only uric acid was slightly raised during the 2-month study. In an equivalence study, indapamide SR 1.5mg and IR 2.5mg produced similar blood pressure reductions (within the equivalence limit of +/-5mm Hg), whereas the percentage of patients whose serum potassium fell to less than 3.4 mmol/L was lower in the IR 1.5mg group than in the SR 2.5mg group. Antihypertensive treatment with indapamide SR 1.5mg once daily produced reductions in blood pressure in elderly patients with systolic/diastolic or isolated systolic hypertension that were similar to reductions with amlodipine 5 mg/day. The incidence of adverse effects was very low in all studies with indapamide SR 1.5mg and very similar to that in the placebo group, confirming thereby the improvement in the efficacy: tolerance ratio with the new indapamide compound.

PMID: 10678595 [PubMed - indexed for MEDLINE]

31: Drugs. 2000;59 Suppl 2:21-25; discussion 39-40.

Diuretics as a basis of antihypertensive therapy. An overview.

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Diuretics have been, except for during a few recent years, the most commonly used therapy for hypertension. Although use of these agents fell significantly in the early 1990s, since then it has begun to increase again. Their recent return to popularity reflects 3 major factors: (i) recognition of the effectiveness of much

lower dosages than previously used, thereby providing good antihypertensive activity with fewer adverse effects; (ii) the excellent reductions in morbidity and mortality achieved by low dosage diuretic-based therapy in multiple randomised controlled trials in elderly patients with hypertension; and (iii) the increasing recognition that some diuretic-induced shrinkage of effective blood volume is essential for the adequate treatment of many, if not most, patients with hypertension. Therefore, diuretics will probably continue to be the basis for antihypertensive therapy, and the indapamide sustained release 1.5 mg formulation provides all the essential characteristics of diuretic therapy.

PMID: 10678594 [PubMed - indexed for MEDLINE]

32: Wien Klin Wochenschr. 1999 Nov 12;111(21):903-7.

[Renaissance of diuretics in the treatment of hypertension]

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Diuretics and beta-blockers are the only antihypertensives known for their significant reduction of cardiovascular morbidity and mortality, particularly in the elderly. The use of low-dose diuretics can improve the efficacy-safety ratio. Hypokalemia, hypomagnesemia as well as disturbances of carbohydrate and lipid metabolism are dose-dependent side effects of diuretics but only minimal during the low-dose therapy. A novel low-dose formulation of indapamide was developed as a sustained-release (SR) coated tablet (1.5 mg/day) and compared to the immediate release (IR) formulation of indapamide (2.5 mg/day). A > 50% reduction in the number of patients with serum potassium levels < 3.4 mmol/l among hypertensive patients treated with indapamide SR as compared to IR was observed. Indapamide SR has also been shown to be effective (more than 20 mg enalapril) in the reduction of left ventricular mass index (LVMI) in hypertensive

patients treated for one year (LIVE study). Therefore, low-dose diuretics are, in accordance with international recommendations for the low-dose antihypertensive drugs, a first line therapy of hypertension.

PMID: 10599155 [PubMed - indexed for MEDLINE]

33: Am J Hypertens. 1999 Jul;12(7):673-81.

Effect of hypertension and its treatment on lipid, lipoprotein(a), fibrinogen, and bilirubin levels in patients referred for dyslipidemia.

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We measured the serum lipid profile, together with plasma fibrinogen and serum lipoprotein(a) (Lp[a]), glucose, bilirubin, and albumin levels in 491 patients (310 men) who were referred for the management of primary dyslipidemia. All these variables have been shown to predict vascular events. The patients were not taking lipid-lowering drugs; hypertension was present in 156 (31.7%) of them. Of the hypertensive patients, 52 (33%) were not receiving any treatment to control their blood pressure. This omission was not due to a lower prevalence of established vascular disease. The treated hypertensives were divided into three groups according to their treatment: 62 were taking lipid-hostile antihypertensives (beta-blockers, thiazides), 37 were taking lipid-neutral antihypertensives (angiotensin converting enzyme inhibitors, Ca-channel blockers, angiotensin II receptor blockers, indapamide sustained release), and five were taking lipid-friendly antihypertensives (doxazosin). Lipid-hostile antihypertensive drugs were associated with a significantly higher fibrinogen concentration when compared with untreated hypertensives or those taking lipid-neutral/lipid-friendly drugs (median values: 383, 353, and 336 mg/dL, respectively; $P < .01$). Lipid-neutral/lipid-friendly antihypertensive drugs were associated with lower Lp(a)

levels when compared with untreated hypertensives (median values: 22 and 45 mg/dL, respectively; P < .05). The serum bilirubin level was significantly lower in the untreated hypertensives when compared with normotensives or the treated hypertensives. There were no significant differences in lipids, glucose, or albumin among the groups of hypertensives or normotensives. The influence of antihypertensive drugs on additional cardiovascular risk factors should be considered when selecting medication to reduce blood pressure.

PMID: 10411364 [PubMed - indexed for MEDLINE]

34: Clin Pharmacokinet. 1999;37 Suppl 1:33-8.

Concluding remarks. Pursuit of the optimal outcome in hypertension.

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Achieving the optimal outcome in hypertensive patients requires the selection and use of appropriate strategies to lower the blood pressure and reduce the patient's risk of cardiovascular events such as stroke and coronary heart disease. It also requires ongoing monitoring of the patient to ensure that the desirable end-points of treatment are being met, and that the heart, kidneys and other sites are being effectively protected from potential complications. Current guidelines on the treatment of hypertension continue to emphasise the use of low dose diuretics as appropriate first-line therapy whenever pharmacological intervention is indicated, except where there are positive indications (e.g. coexisting congestive heart failure or diabetic nephropathy) for other classes of drugs. Diuretics have repeatedly been shown to reduce the morbidity and mortality associated with hypertension, both in the elderly and in younger adults, and their combination with other antihypertensive agents (when clinically indicated) permits the use of lower total dosages. The thiazide-related diuretic indapamide has been reported to have a number of advantages over the thiazides, including minimal or no adverse

influence on plasma lipids and glucose metabolism, or on kidney function in patients with renal insufficiency. It has also been found to produce regression of left ventricular hypertrophy, which is now accepted as an important objective of antihypertensive therapy. The recently developed sustained release (SR) formulation of indapamide allows use of a lower daily dosage of the drug, thereby improving its efficacy:safety ratio in comparison with immediate release formulations. Clinical studies have confirmed the efficacy of indapamide SR 1.5 mg daily in lowering elevated blood pressure, and this formulation can be considered an appropriate choice whenever a diuretic is indicated for the treatment of hypertension, including elderly hypertensives and, because of its metabolic 'neutrality', hypertensive patients with diabetes.

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35: Clin Pharmacokinet. 1999;37 Suppl 1:21-32.

Clinical implications of indapamide sustained release 1.5 mg in hypertension.

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Recent international guidelines on the detection, clinical assessment and management of patients with hypertension have highlighted a number of themes that should be incorporated into routine clinical practice. First, although antihypertensive therapy is having a major impact on reducing the incidence of coronary heart disease, cerebrovascular disease and heart failure, community surveys show that most hypertensive patients remain untreated or have suboptimal blood pressure control. Second, the guidelines have emphasised the importance of making an overall assessment of individual patients to gauge their absolute risk of a cardiovascular event; risk factors include not only blood pressure but also target

organ damage, the presence of coexisting symptomatic vascular disease and the number of associated cardiovascular risk factors. Patients at the highest risk, especially those with diabetes, the elderly and patients with target organ damage, merit vigorous antihypertensive therapy, and such patients often require treatment with more than one drug to achieve target levels of blood pressure (< 135/80 mm Hg). An additional important theme in recent guidelines has been a move towards using lower dosages and therapies that provide 24-hour blood pressure control with once-daily administration. Since diuretics have been reaffirmed as evidence-based first-line therapy in a broad spectrum of patients with hypertension, especially the elderly, a new lower dosage sustained release formulation of indapamide has been developed (indapamide SR 1.5 mg). Recent multicentre European clinical trials have defined the efficacy and tolerability of indapamide SR 1.5 mg, both relative to other antihypertensive drugs and in key subgroups of patients. Indapamide SR 1.5 mg has an antihypertensive effect, maintained throughout the 24-hour administration interval, equivalent to that of immediate release indapamide 2.5 mg, but the new formulation has even less effect on circulating K+ levels. Indapamide SR 1.5 mg is at least as effective as amlodipine or hydrochlorothiazide. In patients with left ventricular hypertrophy (LVH), a comparative study of indapamide SR 1.5 mg and enalapril (the LIVE study) used a rigorous unique study design with blinded reading of echocardiograms to show that after 1 year the ACE inhibitor had no significant effect on LVH regression, whereas indapamide SR 1.5 mg produced significant reductions in left ventricular mass index. Diuretic-based therapy for hypertension has been reaffirmed in international guidelines as effective first-line therapy, especially in the elderly and patients with LVH. Indapamide SR 1.5 mg shows an improved efficacy-tolerability profile, with impressive 24-hour effects on blood pressure, important ancillary properties with regard to LVH and cardiovascular protection.

PMID: 10491730 [PubMed - indexed for MEDLINE]

36: Clin Pharmacokinet. 1999;37 Suppl 1:13-9.

Galenic development and pharmacokinetic profile of indapamide sustained release 1.5 mg.

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In accordance with international guidelines recommending the use of low doses of antihypertensive agents, a new formulation of indapamide--indapamide sustained release (SR)--has been developed. Indapamide has been used worldwide for many years as an immediate release (IR) formulation at a dose of 2.5 mg. The IR formulation leads to plasma peaks of indapamide immediately after administration of the tablet. These peaks are responsible for possible unfavourable electrolyte or metabolic effects relating to indapamide blood concentrations. The SR formulation, by eliminating plasma peaks, allows a smoothing of the pharmacokinetic profile of indapamide. This new galenic formulation is based on a hydrophilic matrix tablet composed of a cellulose derivative, methylhydroxypropylcellulose (MHPC), and a binder, polyvinylpyrrolidone (povidone). The originality of the matrix lies in the percentages of MHPC and povidone, which permit a linear release in vitro of indapamide. After optimisation, the chosen ratio of these 2 constituents allowed the release of more than 70% of the dosage over 16 hours in a very reproducible manner. The 2 tested formulations (SR and IR) have the same bioavailability; however, the main pharmacokinetic parameters of the new SR 1.5 mg formulation, calculated after single and repeated administration, show a profile typical of an SR formulation, i.e. a lower maximum concentration (Cmax), a longer time to Cmax, and the same minimum concentration as the IR formulation. This new SR formulation, which allows a reduction in the daily dose of indapamide from 2.5 to 1.5 mg, leads to an improvement in its efficacy/tolerability ratio, thereby meeting the

recommendations of the international guidelines for the treatment of essential hypertension.

PMID: 10491729 [PubMed - indexed for MEDLINE]

37: J Hypertens. 1998 Nov;16(11):1677-84.

Low-dose antihypertensive therapy with 1.5 mg sustained-release indapamide: results of randomised double-blind controlled studies. European study group.

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OBJECTIVE: In accordance with international recommendations on the need to decrease doses of antihypertensive drugs, a low-dose (1.5 mg) sustained-release (SR) formulation of indapamide was developed to optimize the drug's efficacy : safety ratio. The aim of this work was to evaluate the benefit of a low-dose diuretic by consolidating the efficacy and safety results of two clinical trials with a similar design. PATIENTS AND METHODS: Clinical data were obtained in two European randomized double-blind studies with 690 mild to moderate hypertensive patients (95 mmHg < or = supine diastolic blood pressure < or = 114 mmHg using a mercury sphygmomanometer) treated respectively for 2 and 3 months, with a mean age of 53 and 57 years, 44 and 57% males, mean supine diastolic blood pressure of 100.6 and 102.5 mmHg and mean supine systolic blood pressure of 161.0 and 164.5 mmHg. RESULTS: The first study, a dose-finding study with indapamide SR at 1.5, 2 and 2.5 mg versus placebo and the immediate-release (IR) formulation of indapamide, showed that the 1.5 mg dosage of the new indapamide formulation had an improved antihypertensive efficacy : safety ratio. The second study confirmed the equivalence of blood

pressure reductions with 1.5 mg indapamide SR and 2.5 mg indapamide IR, and better acceptability with 1.5 mg indapamide SR, particularly in the number of patients with serum potassium levels < 3.4 mmol/l, which was reduced by more than 50%. The long-term efficacy of 1.5 mg indapamide SR was observed through a 9-month open-treatment follow-up to the second study.
CONCLUSION: The 1.5 mg SR formulation of indapamide has an improved antihypertensive efficacy : safety ratio, which is in accordance with international recommendations for the use of low-dose antihypertensive drugs and diuretics in first-line therapy of hypertension.

PMID: 9856369 [PubMed - indexed for MEDLINE]

38: J Cardiovasc Pharmacol. 1998 Oct;32(4):673-8.

Twenty-four hour antihypertensive efficacy of indapamide, 1.5-mg sustained release: results of two randomized double-blind controlled studies.

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The antihypertensive efficacy of a 1.5-mg sustained-release formulation (SR 1.5) of indapamide, a diuretic related to thiazide, has been pointed out by using conventional sphygmomanometric measurement 24 h after dosing in clinic, in two large European randomized, double-blind, controlled studies (2 and 3 months). One of these studies was then extended to 12 months, as a complementary open study. Quality-controlled ambulatory blood pressure monitoring (ABPM) data for a total of 216 patients from these studies are presented, including subgroups of hypertensives and responders. Indapamide SR 1.5 achieves an adequate 24-h blood pressure control by significantly reducing the 24-h, diurnal, and nocturnal blood pressures versus baseline, confirming the sphygmomanometric data. The benefit at 2 and 3 months is maintained at 1 year, which confirms the long-term efficacy of SR 1.5 mg. The trough-to-peak ratio--not previously calculated for a

diuretic according to international guidelines--meets Food and Drug Administration requirements and confirms the 24-h efficacy of indapamide SR 1.5.

PMID: 9781939 [PubMed - indexed for MEDLINE]

39: J Hypertens. 1998 Apr;16(4):531-5.

Centralized echocardiogram quality control in a multicenter study of regression of left ventricular hypertrophy in hypertension.

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OBJECTIVE: To test the feasibility and utility of instituting centralized echocardiographic quality control during a multicenter study of regression of left ventricular hypertrophy in hypertension. DESIGN AND METHODS: The LIVE (Left Ventricular Hypertrophy: Indapamide Versus Enalapril) study is an ongoing multicenter, double-blind, controlled study of regression of echocardiographic left ventricular mass index in hypertensive patients with left ventricular hypertrophy (left ventricular mass indexes > 100 g/m2 for women and > 120 g/m2 for men) treated for 1 year with 1.5 mg indapamide sustained-release coated tablets versus 20 mg enalapril. A centralized evaluation committee has validated a prestudy sample echocardiogram from each center, and is now reviewing all videotapes recorded during this study for quality control; final results will be based on a further randomized blinded analysis by this centralized evaluation committee. RESULTS: Since December 1994, 878 patients have been preselected (videoechocardiographic recordings sent for assessment), 645 selected (videoechocardiographic recordings validated), and 576 randomly allocated to treatment. After preliminary quality control, 27% (233) of baseline echocardiograms were rejected by our centralized evaluation committee, and 22%

(142) of postinclusion echocardiographic measurements had to be repeated, mainly because they were of poor echogenic quality. Analysis of approved baseline echocardiograms for the first 274 randomly allocated patients with digitized data showed that there was a significant correlation between centralized evaluation committee and investigator calculations of left ventricular mass index ($r = 0.76$, $P < 0.001$), with consistently higher values for investigator calculations, independently of level of left ventricular mass index (correlation between difference and mean of investigator and centralized evaluation committee measurements, $r = 0.08$, $P = 0.28$). The mean difference was 8 +/- 20 g/m2 ($P < 0.001$). CONCLUSION: Early results of the LIVE study quality control showed that real-time 'live', centralized echocardiographic reading was not only feasible, but also useful for avoiding unquantifiable echocardiograms and overestimation of left ventricular mass index. Thus, real-time, centralized echocardiographic quality control should be recommended for multicenter studies of regression of left ventricular hypertrophy.

PMID: 9797199 [PubMed - indexed for MEDLINE]

40: Ann Cardiol Angeiol (Paris). 1998 Feb;47(2):94-104.

[Efficacy and safety of indapamide 1.5 mg sustained release coated tablets in the therapy of arterial hypertension]

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OBJECTIVE: In line with international recommendations concerning the need to decrease the doses of antihypertensives, a low dose form (1.5 mg) of indapamide, sustained release coated tablet (SR), has been developed in order to optimize the efficacy-safety ratio while maintaining a once daily dosage. The objective of this study was to evaluate the benefit obtained by reviewing the results of two clinical trials conducted according to a similar methodology. PATIENTS AND

METHODS: European randomized double-blind trials were conducted in a total of 690 hypertensive patients. The first trial was conducted in 285 patients treated for 2 months and the second trial was conducted in 405 patients treated for 3 months. The second study was extended to 9 months under open-label conditions in order to obtain a follow-up of one year with clinical and ambulatory blood pressure monitoring. The average patient characteristics on inclusion were, in the two studies: age: 53 and 57 years, 44% and 57% of men, diastolic blood pressure (DRP): 100.6 and 102.5 mmHg, systolic blood pressure (SBP): 161.0 and 164.5 mmHg. RESULTS: The first dose-ranging study demonstrated the antihypertensive efficacy of indapamide 1.5 mg SR; the study second confirmed the equivalent efficacy with the 2.5 mg immediate release form of indapamide and a greater than 50% reduction of the number of patients presenting a serum potassium less than 3.4 mmol/l. The long-term study verified the absence of therapeutic escape. Clinical safety data assessed the absence of effects of indapamide on carbohydrate and lipid metabolism. CONCLUSION: Indapamide 1.5 mg sustained release coated tablet presents an optimized antihypertensive efficacy/safety ratio in line with international recommendations concerning the use of low-dose antihypertensives and diuretics as first-line treatment for hypertension.

PMID: 9772936 [PubMed - indexed for MEDLINE]

41: Arch Mal Coeur Vaiss. 1996 Sep;89 Spec No 4:27-38.

[Evaluation of trough/peak ratio of indapamide 1.5 mg sustained-release form assessed by ambulatory blood pressure monitoring]

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Because of the high variability of casual blood pressure measurements. ABPM has become a complementary clinical tool for evaluating antihypertensive treatment. Nevertheless, there is still a lack of practical guidelines to interpret the data. A review of the literature shows that ABPM efficacy data are analyzed differently, especially the trough-to-peak ratio proposed by the Food and Drug Administration. Published trough-to-peak ratios are widely disparate due to the diversity of the calculation methods which are most often not justified. Thus inappropriate comparisons of these results can easily produce incorrect conclusions. The aim of this review is to select, through the literature, basic methodological requirements commonly agreed on for accurate assessment of trough-to-peak ratio, and to apply them to the ABPM data on indapamide, a diuretic related to the thiazides. Six methodological requirements commonly agreed on at this time are the following: 1. study design: placebo-controlled study with a placebo run-in period; 2. patients selection: compliance with the study protocol, record obtained before and after treatment for each patient; 3. population analysis: whole and responder population: 4. quality control of the records: 5. placebo effect subtraction; 6. global and individual calculation with the indication of median values. Given that, no T/P ratio, especially for a diuretic, has yet been calculated according to these requirements, the above methodological points were taken into account for the T/P calculation of indapamide, from a placebo-controlled dose-finding study involving 285 patients.

PMID: 8952811 [PubMed - indexed for MEDLINE]

42: Arch Mal Coeur Vaiss. 1996 Sep;89 Spec No 4:17-25.

[Treatment of hypertension with indapamide 1.5 mg sustained-release form: synthesis of results]

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In accordance with international recommendations on the need to decrease doses of antihypertensive drugs, a low-dose (1.5 mg) sustained-release form of indapamide was developed so as to optimize the safety/efficacy ratio, while maintaining a once-daily administration. The new formulation ensures that the active ingredient release occurs in a sustained manner over 24 hours, with mean concentrations close to the maximal concentration over a prolonged period, while avoiding peak plasma concentrations. Clinical data were obtained mainly through two European multicenter, randomized, double-blind trials, totalling 690 patients. Firstly, the antihypertensive efficacy' of the new indapamide 1.5 mg form was demonstrated by measuring blood pressure 24 hours after the last drug intake, using a mercury sphygmomanometer; the equivalence of its antihypertensive efficacy with the immediate-release form of indapamide 2.5 mg was then verified. Biochemical safety data showed better acceptability with indapamide 1.5 mg with in particular a reduction of more than 50% of the number of patients with kalemia < 3.4 mmol/l; clinical safety data confirmed the good acceptability observed with the 2.5 mg immediate-release form of indapamide since many years, especially regarding glucose and lipid neutrality. In conclusion, the 1.5 mg sustained-release form of indapamide has an improved antihypertensive efficacy/safety ratio which is in accordance with international recommendations for the usage of low doses of antihypertensive drugs and diuretics in the first-line treatment of hypertension.

PMID: 8952810 [PubMed - indexed for MEDLINE]

43: Am J Ther. 1996 Jul;3(7):506-514.

Combination Treatment with Sustained-Release Verapamil and Indapamide in the Treatment of Mild-to-Moderate Hypertension.

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A multicenter study of the treatment of mild and moderate hypertension compared three once-daily regimens for efficacy and safety: Group I, verapamil sustained release (SR) 240 mg; Group II, verapamil SR 480 mg; and Group III, combination therapy of verapamil SR 240 mg plus indapamide 2.5 mg. After a 3-week placebo washout period and a 2-week preliminary treatment period with verapamil SR 240 mg daily, those patients with diastolic blood pressures of <95 mm Hg were excluded from further study; 137 remaining patients with sitting diastolic blood pressure of 95--115 mm Hg, representing "incomplete" responders to verapamil SR 240 mg, were randomized in a double-blind fashion to one of the three treatment groups for a duration of 16 weeks. Efficacy was assessed after 16 weeks of double-blind therapy or at end point. All three treatments significantly reduced sitting diastolic and systolic blood pressure from baseline levels. Compared with Group I (verapamil SR 240 mg daily), there was a significant reduction ($p < 0.05$) in Group II combination therapy of 8.6 mm Hg systolic and 3.0 mm Hg diastolic and a significant reduction ($p < 0.05$) in Group II (verapamil SR 480 mg daily) of 7.6 mm Hg systolic and 3.9 mm Hg diastolic BP. Patients who had the least change in blood pressure (diastolic blood pressure decreases of <5 mm Hg) to lead-in verapamil SR 240 mg daily, prior to randomization, tended to have a greater response to combination therapy than to verapamil SR 480 mg. Adverse

experiences leading to withdrawal from the study occurred in 21% of patients receiving verapamil SR 480 mg daily (Group II). There was a significantly greater withdrawal from Group II than the other two treatment groups (8.5% from Group III and 4% from Group I). This trial demonstrated that adding indapamide 2.5 mg to the incomplete responders of verapamil SR 240 mg enhances efficacy and was well tolerated.

PMID: 11862282 [PubMed - as supplied by publisher]

44: Am J Ther. 1996 Mar;3(3):229-236.

Combination Treatment with Sustained-Release Verapamil and Indapamide in the Treatment of Mild-to-Moderate Hypertension.

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A multicenter study of the treatment of mild and moderate hypertension compared three once-daily regimens for efficacy and safety: Group I, verapamil sustained release (SR) 240 mg; Group II, verapamil SR 480 mg; and Group III, verapamil SR 240 mg plus indapamide 2.5. mg. After a 3-week placebo washout period and a 2-week preliminary treatment period with verapamil SR 240 mg, patients with sitting diastolic blood pressures of 95--115 mm Hg were randomized in a double-blind fashion to one of the three treatment groups for a duration of 16 weeks. (Patients with diastolic BP < 95 mm Hg on this initial treatment were excluded from further study.) Efficacy assessed after 16 weeks or at the end point showed all three treatments significantly reduced sitting diastolic blood pressure from baseline levels. Compared with Group I (low-dose) verapamil SR treatment, there was a reduction in Group III combination therapy of 8.6 mm Hg systolic and 3.0 mm Hg diastolic and a significant reduction in Group II high-dose verapamil SR therapy of 7.6 mm Hg systolic and 3.9 mm Hg diastolic BP. Efficacy results were

independent of age or body weight. Patients who were poor responders to lead-in verapamil SR 240 mg daily prior to randomization tended to have a greater response to combination therapy than to high-dose verapamil SR. Adverse experiences leading to withdrawal from the study occurred in 21% of patients receiving high-dose verapamil (Group II), exceeding the withdrawal from the other two treatment groups (8.5% from Group II and 4% from Group I). The most frequent adverse experiences in Group II were constipation and peripheral edema; headache was most common in Groups I and III. This trial demonstrates that adding indapamide to low-dose verapamil SR enhances efficacy and is well tolerated.

PMID: 11862255 [PubMed - as supplied by publisher]

45: Arch Mal Coeur Vaiss. 1995 Aug;88(8):1083-7.

[Therapeutic benefit of a low dose of indapamide: results of a double-blind against placebo European controlled study]

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Indapamide is a diuretic prescribed in the treatment of hypertension at the dosage of 2.5 mg per day. In accordance with international recommendations concerning the need to use low doses of antihypertensives, a new lower-dose form of indapamide has been developed to achieve the best safety/efficacy ratio by decreasing the incidence of hypokalemia. A new pharmaceutical sustained-release (SR) form was developed to give a smooth pharmacokinetic profile in comparison with the indapamide instant release (IR) form. The aim of this study was to determine the lowest new dosage of the SR form producing similar hypertensive efficacy as the LR form, and decreasing the percentage of patients with a serum potassium concentration below 3.4 mmol/l. This multicenter study was designed as a single-blind, run-in, placebo period of 1 month, followed by a double-blind,

active treatment period of 2 months, using parallel groups: 285 patients with essential uncomplicated mild-to-moderate hypertension (95 mmHg < or = supine diastolic blood pressure (sDBP) < or = 114 mmHg) were included and randomly treated by either IR indapamide (2.5 mg) or SR indapamide (1.5, 2.0, 2.5 mg). After 2 months of active treatment, the one-way analysis of variance on the principal criterion (difference in sDBP between M2 and M0) revealed a significant treatment effect (p = 0.016). The mean drop in sDBP (+/- standard deviation) was 5.8 mmHg (+/- 8.6) after 2 months of placebo; 10.1 mmHg (+/- 7.0) after indapamide IR 2.5 mg; and 11.0 mmHg (+/- 9.4), 8.9 mmHg (+/- 9.4), and 10.5 mmHg (+/- 8.5) after indapamide SR 1.5 mg, 2 mg, and 2.5 mg, respectively. The difference between the placebo and indapamide treatment was significant (p < or = 0.05). No significant difference was detected between the various indapamide treatments, i.e., no difference between the IR and SR formulations, no difference between the various dosages of the SR form, and therefore no dose/effect relationship in the dose interval tested (SR 1.5, 2, and 2.5 mg). The incidence of patients with a serum potassium concentration less than 3.4 mmol/l was lower with indapamide SR 1.5 mg (11%) than with indapamide 2.5 mg, SR 2 mg, and SR 2.5 mg, respectively: 29%, 18% and 14%. These results show the interest of a low dose of indapamide in improving the safety while producing the same antihypertensive efficacy.

PMID: 8572850 [PubMed - indexed for MEDLINE]

Scopes of works on Indapamide:

There are several scopes were found to work on Indapamide for further studies and the scopes are like as below:

1 Preparation of sustained release Indapamide

2. Make more long acting preparations

3. Faster the kinetic release of Indapamide

4. Reduction of Blood pressure in a short time

5. To teat long term medication of Hypertension

6. To treat the Diabetes Mellitus.

Discussion

The study on research paper review was done to get the massive and clear Idea about the research works had been done on Indapamide. Indapamide is a Thiazide type diuretic which is used to control the Hypertension and Increased blood Pressure mainly. The target of the research was initially to set a parameter for further research on the Sustained release preparations of Indapamide Molecule. This literature review was so important for me because the total research plan was dependent upon on this literature review. And it was tried to get the best result on this topic through this review process.
Few parameters were set before the research and the work was based on that. Indapamide is available normally in combined preparation with another anti hypertensive drugs but when comes in individual or single dose preparation, in that case there are some problems which are faced normally , so why the work on Indapamide molecule is not so massive and also not very much clear. When I worked on the literatures the maximum publications I got was almost about the Pharmacology and the pharmacokinetics of this molecule, in that case it was so tough to match the parameters with the journals because The intension of finding literatures were to get the idea about the sustained release preparations and the release pattern of the molecules. In that case I tried to review almost every journal founded. It was found that the work on release pattern and sustained release was done in very few aspects and which was not enough sufficient to get the clear idea about the molecule. But it was tried to get the best output from the available information and documents. From the review I got the SR product of this material is so much important because of the following reasons:

Therefore, monotherapy with indapamide SR should be suggested in type 2 diabetic patients with mild-to-moderate hypertension and many classes of antihypertensive may be used, but it appears that diuretics, such as indapamide sustained release (SR), constitute an important proposal in all treatment strategies. It was seen the efficacy of indapamide SR in hypertension and target organ damage provide valuable information on the management of type 2 diabetic hypertensive with microalbuminuria. This antihypertensive agent can be considered to be an attractive therapeutic choice for all patients with mild-to-moderate hypertension, including the elderly and patients with

increased cardiovascular risks, i.e. those with LVH. Also Indapamide SR 1.5 mg was significantly more effective than enalapril 20 mg at reducing LVMI in hypertensive patients with LVH. The SR formulation showed sustained release of indapamide with a reduction in peak concentration, while steady-state level was not affected by formulations. The 1.5 mg SR formulation of indapamide has an improved antihypertensive efficacy/safety ratio, which is in accordance with international recommendations for the use of low-dose antihypertensive drugs and diuretics in first-line therapy of hypertension. Therefore it was see the indapamide sustained release 1.5 mg formulation provides all the essential characteristics of diuretic therapy. The half life of the Indapamide is 14 to 18 hours which itself is huge to release for a product. And also because of this the release of the drug is normally very slow. So the parameters were set in this research to work further on release after I have got the information from the journals.

In summary, more attention might be paid to the controlled clinical trials might shown on the basis of further studies indapamide SR to treat hypertension and cardio vascular risks by using these data found from the literature review.

Conclusion:

In conclusion, the literatures review of Indapamide showed that indapamide is a long acting Thiazide type diuretic which should be used to treat the Hypertension and cardio vascular diseases and for the long duration of period. And also from the work it was found that the further work might be effective if we take the data got from the literature review of Indapamide. And also it was so important to study more from the different sources and then go for the practical preparations and evaluations. But still the data was found from the literature review is enough to study for further more and get ideas about the work and start the work immediately.

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