Kuwait Pharmacy Bulletin
DRUG INFORMATION FOR THE HEALTH PROFESSIONAL
Vol 20 No 2 Summer 2016 ISSN 1028-0480

Current and future treatment options for isolated systolic hypertension

Introduction

Systemic hypertension or systolic/diastolic hypertension is defined as having systolic blood pressure (SBP) ≥ 140 mm Hg and diastolic blood pressure (DBP) ≥ 90 mm Hg [1].

Isolated systolic hypertension (ISH) is defined as having SBP ≥ 140 mm Hg but DBP < 90 mm Hg. ISH has 3 different grades (1: SBP <160 mmHg/ subgroup SBP<150 mmHg; 2: SBP <180 mmHg; 3: SBP >/= 180 mmHg) [2].

According to the Framingham study, ISH incidence is high in both men and women aged 65 and above, (418/1000) and (533/1000), respectively [2]. For normotensive individuals aged 65, it is also expected that 90% will develop ISH if they live for 20- 25 y more [3]. It is believed that as the individual gets older, there will be several functional and structural changes in the arteries that adversely affect arterial compliance leading finally to increased SBP[4]. ISH has specific parameters, which include increased pulse pressure (PP), elevated pulse wave velocity (PWV), and early reflection of ejected blood from the heart. Pulse pressure is the difference between systolic and diastolic blood pressure. PWV is the velocity by which the ejected blood moves from the aorta toward the peripheral arteries. With aging, SBP increases and DBP decreases leading to an increased PP [5].

One of the important ISH treatment goals is to reduce SBP but not DBP. Reduced DBP leads to hypo-perfusion and severe cardiovascular events [3].

Pathophysiology

Functional changes

Aging is associated with several structural and functional changes in the arterial wall that adversely affect arterial compliance [4]. Increased sympathetic activity with aging was believed to be due to baroreceptor dysfunction or reduced sensitivity of beta-receptors. This may be due to aortic or carotid structural changes leading to increased sympathetic activity and increased noradrenaline (NA) levels. [4] At the same time, the function of alpha-receptors located in the arterial wall remains intact. As a result, arterial vasoconstriction is observed, leading to reduced heart rate, low plasma renin activity, reduced relaxation of aorta after isoproterenol administration, and increased smooth muscle tone [4] [6] leading to arterial stiffness (AS) [7].

Several studies show that the elderly population have endothelial dysfunction. This is demonstrated as reduced NO production, and increased vasoconstriction through endothelin activity on ETA receptors of vascular smooth muscles cells [7]. Angiotensin II (Ang II), another potent vasoconstrictor appears to increase with aging, stimulating collagen formation, vascular hypertrophy, matrix remodeling and oxidative stress as well as increased ET production. Moreover, it reduces the synthesis of elastin and depresses NO dependent signaling pathways. ANG II also contributes to vascular inflammation through the stimulation of cytokine and growth factor production [3]. Deficiency of natriuretic peptide (NP) an important vasodilator is another age-related functional change resulting in arterial wall stiffness.

Structural changes

AS increases systolic blood pressure by two mechanisms. Firstly it increases the speed of blood wave generated by ventricular ejection, leading to increased PWV. Secondly, it makes the blood reflect earlier from the peripheral to the central arteries leading to high pressure of the initial ejected wave[8]. Elas-

In this issue

tocalcinosis or medial arterial calcification, and elastic network fragmentation (high level of elastase activity) which are age-dependent physiological processes have a significant association with high PWV and high SBP as well[7].

Out of all elastases, it has been found that matrix metalloproteinases (MMPs), demonstrate a significant correlation between elasto-calcinosis, elastic network fragmentation, high PWV and ISH deterioration [7]. TGF-B release is also enhanced by MMP activity, enhancing the release of soluble elastin peptides, which act on elastin-laminin receptor (ELR) found on both VSMC and endothelial cells[7]. Several studies showed that in elasto-calcification, both TGF-B and elastin peptides have the ability to induce osteogenic phenotypic change in VSMCs through their activity on their receptors. This means that VSMCs will gain bone characteristics, such as the expression of osteopontin, which is a protein normally expressed in osteoblasts. On the other hand, they will lose some of their own muscular characteristics, such as smooth muscle alpha-actin and their lineage markers [7] leading to further increase in vascular wall stiffness.

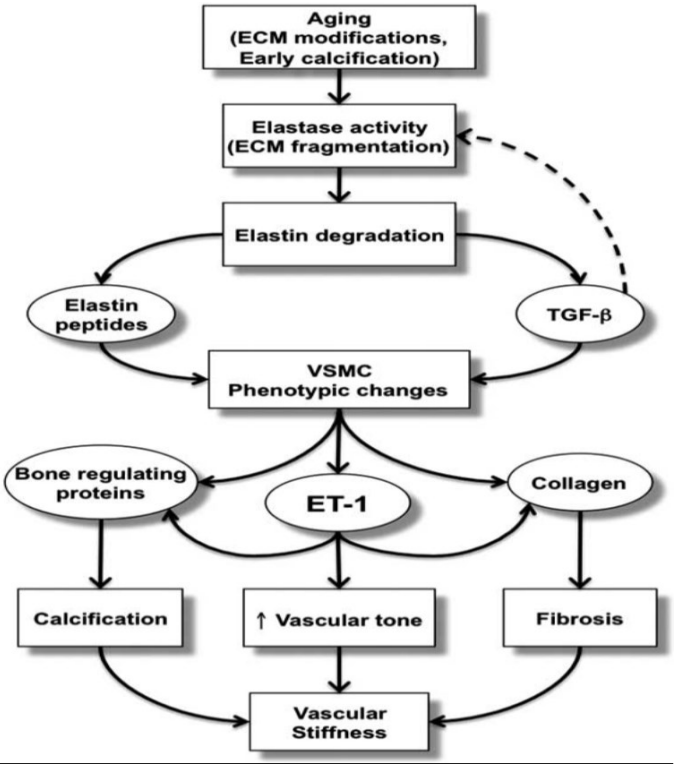


Figure 1
Scheme showing how aging can result in arterial wall stiffness through a sequence of different pathophysiological changes. (adapted from Bouvet et al)

Fibrosis is another mechanism that increases arterial wall stiffness through TGF-B, fibronectin, and collagen Ia [7]. Through TGF-B activity, collagen fibers will increase in number leading to increased vascular stiffness and deterioration of ISH. TGF-B also triggers connective tissue growth factor (CTGF). Several studies showed that CTGF plays a significant role in fibrosis and calcification through different mechanisms [7].

Conditions that accelerate ISH

Disease states

Some diseases and genetic polymorphisms have the ability to accelerate ISH. Atherosclerosis (dyslipidemia), hypertension, diabetes, and renal failure have the ability to cause early vascular aging [3]. It is believed that under such conditions, arterial wall stiffness is increased through endothelial dysfunction and vascular wall changes. In case of renal failure or end stage renal disease (ESRD), the calcification process is increased leading to increased arterial wall stiffness and PWV [7].

Patients who are diabetics, were shown to have a high risk to develop ISH [8]. For instance, chronic hyper-insulinemia and hyperglycemia increase the activity of RAAS and expression of angiotensin type 2 receptors in vascular tissues. This will ultimately lead to arterial wall hypertrophy and fibrosis. Impaired glucose tolerance (IGT) also enhances glycation of collagen fibers, adversely altering arterial wall elasticity [9].

High dietary sodium affects central blood pressure, which is more involved in the arterial wall stiffness than peripheral (brachial) blood pressure.

Obesity and overweight are two risk factors found to have an important role in ISH exacerbation. It has been shown that increased body mass index (BMI) and waist circumference in Asian individuals leads to increased SBP [1].

Genetic predisposition

Patients who carry MMP-3 genotype with the 5A allele have increased risk to develop age-related arterial wall stiffening. Large artery stiffening was found to be increased in patients who have MMP-9 polymorphism, especially those who carry the T allele. Polymorphism of angiotensin converting enzyme (ACE) genes, especially allele D, is found to adversely affect the mechanisms of ISH in older patients resulting in increased PP [7] [10]. It is also found that patients who are non-carriers of 192-bp (wild-type allele) in the promotor region of the anti-

atherogenic insulin growth factor I (IGF-I) mRNA, have high PWV readings and intima-media thickness (IMT) measurement. This leads to the development of atherosclerosis and subsequent ISH worsening[11].

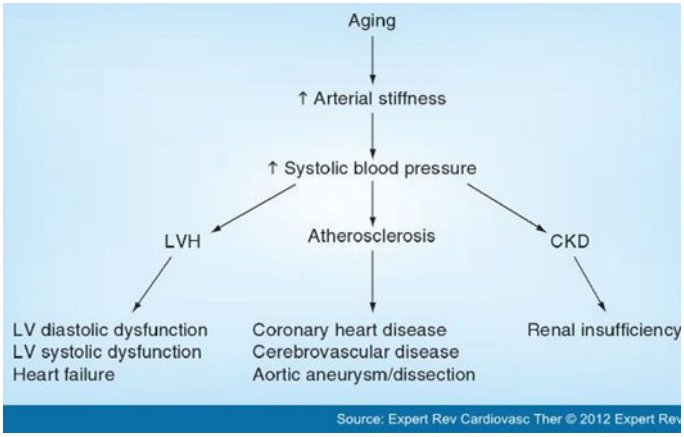


Figure 2. *Aging and cardiovascular events*

Cardiovascular risks

Individuals with SBP > 160 mmHg and DBP between 75-79 mmHg have 2.6 fold higher risk of mortality in comparison to those who have SBP between 110-119 mmHg. The Framingham study demonstrated that ISH increases both the risk of mortality and morbidity. For instance, the risk of myocardial infraction and non-fatal stroke is increased by two to three-fold respectively [4]. Two big cohort studies showed that SBP is a strong independent predictor of stroke and cardiovascular disease in comparison with DBP. Elevated SBP also is the strongest risk factor of renal-related death since it leads to renal impairment [1].

Treatment strategies

Mechanism of action of anti-hypertensive drugs

Angiotensin converting enzyme inhibitors and Angiotensin receptor blockers

ACEIs, such as lisinopril and ramipril, have the ability to inhibit the conversion of Ang I to Ang II. They also prevent the degradation of bradykinin, which plays a role in vasodilatation, regression of fibrosis and myocyte hypertrophy and increased levels of tissue plasminogen activator [12]. In addition, ACEIs stimulate the production of vasodilator substances such as prostaglandin E2 and prostacyclin. On the other hand, ARBs such as valsartan and telmisartan, will block AT1 receptors, so Ang II will not be able to work on its receptors. Fig 3 explains RAAS, the mechanisms through which the blood pressure increases, and the possible site of actions where anti-hypertensive drugs could work. Number (1) is where ACEIs work and (2) is where ARBs work [12].

Calcium channel blockers (CCBs)

CCBs (number (4) in RAAS figure) decrease vessel contractility. There are two types of voltage gated Ca channels, which are high voltage channel (L-Type) and low voltage channel (T-Type). CCBs in-

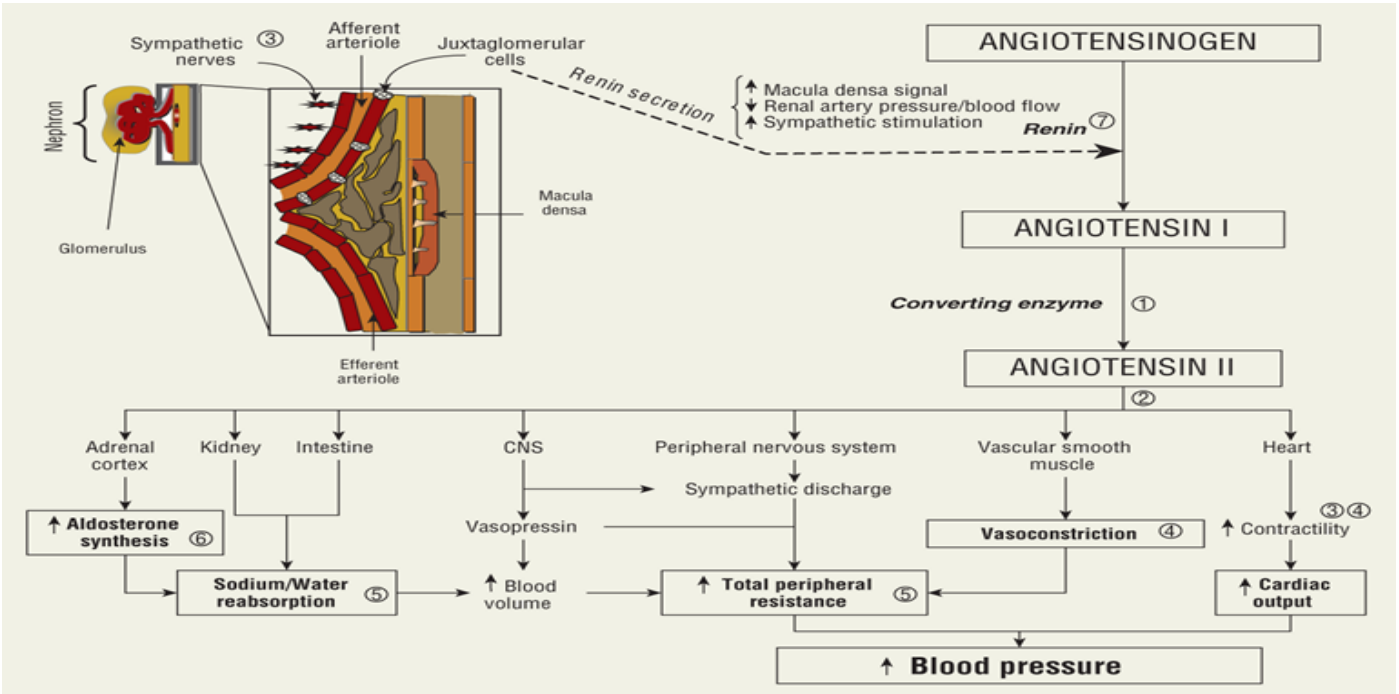


Figure 3. *RAAS and the site of actions of anti-hypertensive drugs. (adapted from Dipiro et al)*

hibit the influx of Ca into the cells by blocking L-type channels. This will lead to peripheral vasodilation and reduce cardiac contractility. There are two types of CCBs: dihydropyridines such as amlodipine and felodipine, and nondihydropyridines which are diltiazem and verapamil. Dihydropyridines mainly work on Ca channels located in the peripheral vessels, leading to peripheral vasodilatation. Non-dihydropyridines mainly work on

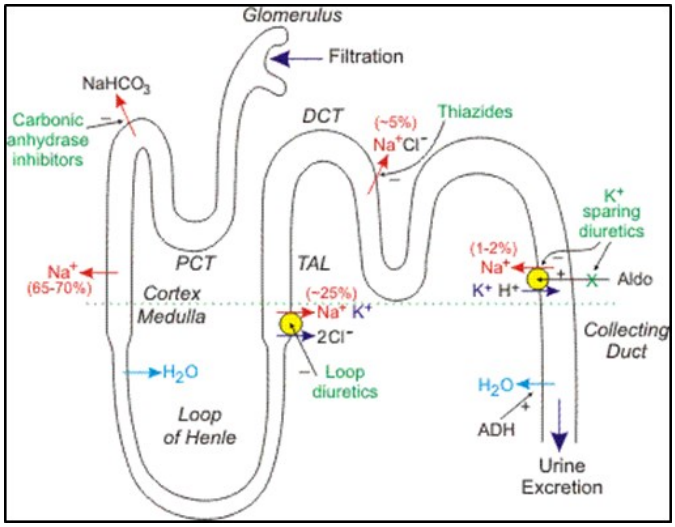


***Figure 4**. Action of diuretics in the nephron (adapted from http://cvpharmacology.com/diuretic/diuretics)*

Ca channels located within the heart smooth muscles, leading to negative inotropic and chronotropic effects [12]. At the end, cardiac contractility is reduced through reduction of heart rate and atrioventricular nodal conduction.

Beta blockers (BBs)

Number (3) in RAAS figure indicates the site of BB action. There are three types of BBs, cardio-selective (BB1), non-cardio-selective and intrinsic sympathomimetic (INS) BBs. Cardio-selective BBs block β-1 receptors, reducing cardiac contractility and renin release from juxtaglomerular cells in the kidney, ultimately reducing BP [12]. In comparison to BB1s, non-selective BBs also block B2 receptors, leading to vasoconstriction, bronchoconstriction and hyperglycemia. Therefore, cardio-selective agents such as atenolol, bisoprolol, nebivolol and metoprolol are preferred over non-selective agents such as nadolol, propranolol and timolol. INS agents, i.e. acebutolol and pindolol, act as partial β-receptor agonists. This means that they do not reduce cardiac output, resting heart rate or peripheral blood flow. However, they do partially stimulate β-receptors, leading to increased sympathetic tone. INS agents are rarely used in management of hypertension but mainly in treatment of heart failure or sinus bradycardia [12].

Diuretics

There are three different types of diuretics; loops, thiazides and potassium sparing agents [17]. Number (5) in RAAS figure indicates their site of action. Diuretics increase Na and water excretion by either a direct action on different parts of the nephron or an indirect action, by modifying the content of the urinary filtrate [13].

i. Loop diuretics

Loop diuretics such as furosemide and bumetanide inhibit Na+/K+/2Cl- co-transporters leading to prevention of the reabsorption of these ions into the body [13]. This type of diuretics has a vasodilator effect through different mechanisms. This includes decreased vascular responsiveness to some vasoconstrictors such as Ag II and NA; increased formation of some vasodilators, for example prostaglandins (PG), which are PGE2 from the medulla and (PGI2) from the glomeruli; and decreased production of endogenous ouabain-like natriuretic hormone, which also has vasoconstrictor properties. Loop diuretics have K-channel-opening effects within resistance arteries [13].

ii. Thiazide diuretics

Thiazide diuretics work on the distal tubule of the nephron where Na/Cl co-transporters are found. They inhibit Na^+ and Cl^- reabsorption. This leads to a natriuretic effect and Cl^- loss in the urine [13]. This is responsible for the initial fall in the blood pressure. There is a late fall in the BP caused by the vasodilatory effect of thiazides. This effect is achieved through the activity of thiazides on Ca channels that are located on the VSMCs.

iii. Potassium sparing agents

These agents, which are aldosterone antagonists and Na channel blockers, work on the collecting duct of the nephron. Aldosterone antagonists such as spironolactone and eplerenone compete with aldosterone on its receptors preventing both Na retention and K secretion. Triamterene and amiloride act by blocking luminal Na^+ channels found in the collecting tubules preventing both Na^+ absorption and K^+ loss [13].

Current treatments of ISH

Non-pharmacological approaches include life style modifications such as increased physical activity, healthy diet rich in fruits and vegetables and low in fat and sodium, reduced alcohol intake, weight reduc-

tion for obese patients and smoking cessation. If these approaches fail to reduce blood pressure, drug therapy should be initiated, especially in patients who have SBP >160 mmHg, since the cardiovascular risk is high in this situation [4]. Pharmacological agents should also be considered in patients with SBP of 140-160 mmHg and have one of the following conditions: diabetes, left ventricular hypertrophy and angina pectoris [4].

Anti-hypertensive drug therapy should be carefully prescribed for elderly patients, since they have impaired baroreceptor sensitivity and mostly deteriorated renal function, all of which may lead to orthostatic hypotension and volume depletion [14]. The aim is to gradually reduce SBP to < 140 mmHg while maintaining DBP to avoid subsequent hypo-perfusion, or reducing it to < 80 mmHg [4]. Diuretics, especially thiazide and thiazide like diuretics, are the first line and most suitable agents in elderly patients. They may be contraindicated in patients with hyperuricemia, gout, diabetes, or those with renal impairment. In such conditions, alternatives are available, for example CCB, ACEI, or ARB. Long acting dihydropyridine CCBs such as amlodipine and nifedipine (long-acting formulation) are also considered as first line options for ISH patients who cannot tolerate thiazide diuretics or have severe hypertension [15]. On the other hand, non-dihydropyridine such as diltiazem or verapamil are good if the patient has a family or personal history of ischemic attack. ACEIs or ARBs are also given for elderly patients with ISH and signs of heart failure or left ventricular hypertrophy, diabetes mellitus or chronic kidney disease [15] [16].

BBs have very limited effect on SBP and do not decrease arterial wave reflection and arterial wall stiffness. Nevertheless, these negative findings do not eliminate the use of BBs as a secondary prevention for hypertensive patients who have a history of heart attack or myocardial infarction [15].

Combination therapy of two or more antihypertensive drugs is usually needed, such as in the case of treatment failure with a single agent. The available guidelines for the management of ISH in elderly patients suggest that ACEIs could be used in combination with diuretics or CCBs (dihydropyridine) or ARBs with diuretics.

In the ACCOMPLISH trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) combining ACEIs with CCBs was shown to be better than combining ACEIs with diuretics. Benzopril and amlodipine combination were superior to benzopril and hydrochlorothiazide in reducing cardiovascular morbidity such as non-fatal stroke and non-fatal myocardial infarction, and mortality [16]. Sometimes triple therapy is used, including a diuretic, ACEI and CCB. Later on, if the ISH is persistent, nitrates are a good option but still under investigation [15].

How do anti-hypertensives affect ISH markers?

Increased PWV is reduced by ACEI and CBBs. Nitrates reduce ISH through peripheral arterial rather than thoracic aorta vasodilatation. High smooth muscle tone within large arteries is also reduced by the activity of vasoactive drugs such as CCBs, ACEI, ARBs, BBs with intrinsic sympathomimetic activity (e.g. pindolol) and nitrates. This will enhance arterial compliance and improve its elasticity as well as reduce the early wave reflection. ISH is also reduced through plasma volume reduction by diuretics. ACEIs, ARBs, and CCBs can also improve endothelial function leading to increased NO levels and subsequent vasodilatation. ACEIs or ARBs, by their activity on the RAAS system, can minimize Ang II influence on fibrosis and inflammation[4]. ARBs such as valsartan and ACEIs such as perindopril have been shown to reduce fibrosis by reduction of chronic collagen accumulation [5] [17]. Perindopril is able to reduce the collagen component of the arteries even at non-anti-hypertensive doses. ACEIs increase the diameter and compliance and dispensability of peripheral muscular arteries [17].

Novel ISH therapy

Endothelial antagonists

A study in which warfarin and vitamin K1 were administered to rats models for 4 weeks showed that arterial calcium deposition, PP and collagen to elastin ratio were increased. Following administration of a selective endothelin receptor antagonist (ETA), which is darusentan, an ARB, which is irbesartan and a thiazide diuretic, which is hydrochlorothiazide [7] it was found that all the three drugs reduced the PP by almost the same ratio, but the only drugs that were able to induce mineral loss (Ca loss) were darusentan and irbesartan, with darusentan the most effective. This suggests that ETA receptor antagonists could be a potential option for the treatment of ISH since they have the ability to reduce PP and induce Ca loss, which reduces arterial wall stiffness [7].

Vasopeptidase inhibitors

Vasopeptidase inhibitors have the ability to work on

ACE and neutral endopeptidase. They reduce Ang II and increase natriuretic peptide levels. There are several agents developed in this class including omopatrilate, sampatrilat and gemopatrilat [18]. Omopatrilate is the only one confirmed and intensively investigated agent for hypertension treatment, especially for ISH. Once daily dosing of omopatrilate 80 mg/day is able to reduce SBP by 20-26 mmHg and DBP by 14-17 mmHg [18]. It was found that omopatrilate reduces SPB in different hypertensive patients, including ISH patients, more than ACE inhibitors [19].

Nitrates

For patients with refractory ISH, it has been shown that adding oral extended-release isosorbide mononitrate to the current anti-hypertensive drugs can reduce SBP. Isosorbide mononitrate is considered as a NO donor, which has the ability to enhance vasodilatation leading to BP reduction. They directly affect vascular smooth muscle through activating guanylyl cyclase to form c-GMP, which inhibits Ca entry into the cell. This will inhibit VSMC contraction resulting in vasodilatation and BP reduction. In addition, nitrates can reduce central blood pressure, augmentation index (AIx) and PWV [6].

Vitamin D supplementation

Vitamin D deficiency was found to adversely affect the cardiovascular system, contributing to the pathogenesis of cardiac hypertrophy and elevated blood pressure. Furthermore, vitamin D has anti-atherosclerotic properties and it is found that low serum levels of the active form 25-hydroxy-vitamine D, is proportionally correlated with higher level of peripheral arterial diseases. High doses of vitamin D supplementation can be an option to reduce SBP through reducing arterial wall stiffness and its normal physiological activity [20].

Aldosterone antagonists

Adding aldosterone antagonists such as spironolactone and eleprenone to the existing anti-hypertensive medications could be a new approach for ISH treatment [21]. They are able to inhibit myocardial and vascular fibrosis through the inhibition of collagen synthesis induced by aldosterone. This will counteract arterial wall stiffness leading to reduced SBP. Eleprenone is a new agent with a better safety profile than spironolactone [21] .

Conclusion

ISH is the most common type of hypertension in the elderly population whose most common etiology is arterial wall stiffness. There are some disease conditions and genetic predispositions that accelerate ISH development leading to cardiovascular morbidity and mortality.

ACEIs, ARBs, diuretics, and CCBs are used for ISH treatment with thiazide diuretics and CCBs being the first line agents. The other anti-hypertensive drugs are used if the patients have concomitant conditions or treatment failure with one agent.

New approaches focus on lowering arterial wall stiffness. These include endothelial antagonists, nitrates, vitamin D supplementation, vasopeptidase inhibitors and aldosterone antagonists. Endothelial antagonists are still in basic research and need clinical investigation in this disease state [7]. Omopatrilate is the only vasopeptidase inhibitor that completed all clinical trials but its side effects currently limit its use [19]. Nitrates are clinically approved, and they are good choice as add on therapy on the existing anti-hypertensive drugs [6]. For vitamin D supplementation, the need for further randomized controlled trials is important in order to ensure strong correlation between vitamin D deficiency and arterial wall stiffness in the elderly [20]. Aldosterone antagonists are used but still need further investigation [21].

In conclusion, ISH is a challenging disease where the goal is to reduce SBP without affecting DBP to avoid the hypo-perfusion risk.

References

1. Park JB et al, Hypertens Res, 2015. 38(4): p. 227-36.
2. Farsang C and Sleight P. J Hypertens, 2001. 19(12): p. 2279-81.
3. Mancia G et al. J Hypertens, 2015(33): p. 33-43.
4. Kocemba J et al. J Hum Hypertens, 1998. 12(9): p. 621-6.
5. Durprez D. American J Med 2008. 121: p. 179-184.
6. Abad-Perez D et al. Trials Journal, 2013 14(1): p. 388-396.
7. Bouvet C E et al. Curr Hypertens Rev, 2010(6): p. 20-31.
8. Esposito R et al. J Hum Hypertens, 2015 p. 1-5
9. Shirwany N et al. Acta Pharmacologica Sinca, 2010. 31: p. 1267-1276.
10. Safar ME et al. Stroke, 2000. 31 p. 782-790.
11. Schut A et al. Stroke, 2003 34 p. 1623-1627.
12. Dipiro J T et al. Hypertension in Pharmacotherapy: A Pathophysiologic Approach 2014 p. 49-84.
13. Rang H P et al. Kidney in Rang and Dale's pharmacology p. 347-359.
14. Roccella EJ. Hypertension, 1994. 23 p. 275-285.
15. Stokes G. Clinical interventions in aging, 2009. 4: p. 379-389.
16. Durpez D. Expert Rev Cardiovasc Ther, 2012. 10(11): p. 1367-1373.
17. Van Bortel L et al. Hypertension, 2001. 38: p. 914-921
18. Sagnella GS. J Renin Angiotensin Aldosterone System, 2002. 3: p. 90-95.
19. Worthley M et al. Brit J Clin Pharmacol, 2003. 57(1): p. 27-36
20. McGreevy C et al. J Am Soc Hypertens, 2015 9(3): p. 176-183
21. Zwieten PA, Netherlands Heart J, 2002. 10 (1): p. 19-22.

Fatimah Al Haddad

Final Year student, Faculty of Pharmacy, Kuwait University

TEST YOUR KNOWLEDGE

Answers on back page

1) ***Which of the following is a non-dihydropyridine calcium channel blocker?***

A. Amlodipine
B. Verapamil
C. Propranolol
D. Nifedipine
E. Ramipril

2) ***Which among the drugs is a vasopeptidase inhibitor that is investigated for hypertension treatment?***

A. Darusentan
B. Olmesartan
C. Omopatrilat
D. Valsartan
E. Diltiazem

3) ***Which of the following is a potassium sparing diuretic?***

A. Triamterene
B. Sampatrilat
C. Irbesartan
D. Chlorthalidone
E. Furosemide

Is there a problem?

A 52 year old male patient was given the following prescription for his newly diagnosed benign prostatic hyperplasia. He is going to take the drug for the first time. Is there any major error with the prescription?

Patient Name: Ahmad Rafi Age: 52 years
Address: Street No.13

Rx

Terazosin tablets
5mg once daily x bedtime
Send one pack

Dr. Ali
Signature Date: 18/06/16

Answer (Prescription Exercise)

The initial dose is incorrect. Should be initially 1 mg at bedtime and slowly titrated to maximum 10mg, depending on response, to avoid hypotension.

TOPICAL ISSUES AND CONTROVERSIES

Pain medication

Most people with chronic pain take analgesics for long periods.[1] Many take multiple analgesics as part of a multimodal treatment plan. It is not uncommon to admit a patient with chronic pain to the hospital setting who is taking an opioid, an anticonvulsant, an antidepressant and a muscle relaxant.[2]

A subset of individuals who live with chronic pain are admitted to the inpatient setting, experiencing acute pain following trauma or surgery. This unique population of patients presents major challenges.

Typically, by virtue of the patient's critical condition following major trauma, the medications taken for chronic pain treatment are automatically discontinued. Many of the analgesics taken for chronic pain treatment can be safely taken before surgery and should not be discontinued.[1,3] Exceptions are drugs such as ibuprofen and naproxen, as these can increase bleeding time. However, these agents can be replaced with alternative non-opioids such as acetaminophen, celecoxib and nabumetone that have no or minimal effect on bleeding time,.[4]

Patients who have not taken their pain medication for several days before surgery or who have not received them following trauma are behind, in terms of pain control, from the beginning of care. They now suffer often severe acute pain, on top of underlying out-of-control chronic pain. Managing all of their pain effectively and safely presents a major challenge to the entire healthcare team.[5] This is particularly true when the patient has been

taking an opioid for treatment of chronic pain.
Individuals who take regular daily doses of an opioid for several days develop physical dependence.[1] If the opioid is no longer needed or pain is reduced, dose tapering is recommended to prevent withdrawal symptoms (rhinitis, nausea, diarrhea, sweating). However, when the opioid is abruptly discontinued preoperatively or following trauma, the patient is exposed to this dangerous physiologic response.[1]

Most individuals who have been taking opioids for extended periods are considered opioid-tolerant, which is another normal physiologic response in which higher doses of an opioid may be needed to provide the same level of pain relief achieved previously with a lower dose.[1] Although it is impossible to predict the opioid requirement in the patient experiencing acute pain on top of chronic pain, one study showed that following knee arthroplasty, opioid-tolerant patients required 5-7 times the opioid dose required by opioid-naive patients during the first 48 postoperative hours.[6]

Under ideal circumstances, patients are told to take their pain medications on the morning of surgery.[5] However, if analgesics have been stopped preoperatively because of trauma or another condition that has resulted in missed doses, their long-term medications should be started as soon as possible after surgery. A growing practice in many institutions is to routinely administer an anticonvulsant, such as gabapentin or pregabalin, in the immediate preoperative period to patients with pre-existing chronic neuropathic pain.[1,7]

Ketamine for refractory pain

Another trend in the care of individuals admitted to the hospital setting with pre-existing chronic pain who have severe acute pain is to administer an IV ketamine infusion in sub-anesthetic doses to relieve pain that is refractory to first-line analgesics, such as non-opioids, opioids, local anesthetics and anticonvulsants. Ketamine is increasingly used on admission to the post-anesthesia care unit to prevent escalation of severe pain in patients with known underlying chronic pain. The drug is also administered for neuropathic pain, ischemic pain, regional pain syndromes and cancer pain.[8,9] It is listed by the WHO as an essential drug for the treatment of refractory pain in the palliative care setting.[9]
Ketamine is classified as a general anesthetic with dose-dependent analgesic, sedative and amnestic properties.[9,11] Its primary underlying mechanism of action is in the central nervous system, where it works as an *N*-methyl-D-aspartate antagonist to block the binding of glutamate, an excitatory neurochemical that facilitates pain transmission.[12] Enhancement of the descending inhibitory pain pathway and anti-inflammatory effects at central sites have also been proposed as mechanisms of action.[11]
At anesthetic doses, ketamine can produce dissociative (psychomimetic) effects, including hallucinations and "out-of-body" sensations, but at the low doses used for analgesia (referred to as "sub-anesthetic doses" e.g., 0.1-0.5 mg/kg),[12] ketamine produces effective pain relief with minimal psychomimetic adverse effects.[13] A benzodiazepine, such as midazolam, is frequently administered to reduce any psychomimetic effects that might occur. More common adverse effects include sedation, salivation, nausea and vomiting, tremors and increased intracranial pressure; however a major benefit is that the drug does not produce respiratory depression.
It is important to discuss the psychomimetic effects of ketamine with patients before administration and to tell them that they may experience "dreamlike feelings" during the infusion.

References

1. Pasero C, Quinn TE, Portenoy RK, et al. Opioid analgesics. In: Pasero C, McCaffery M, eds. Pain Assessment and Pharmacologic Manage ment. St. Louis: Mosby Elsevier; 2011:277-622.
2. Turk DC, Wilson HD, Cahana A. Lancet. 2011;377:2226-2235.
3. Ashraf W, Wong DT, Ronayne M, Williams D. J Perianesth Nurs. 2004; 19:228-233.
4. Pasero C, Portenoy RK, McCaffery M. Nonopioid analgesics. In: Pasero C, McCaffery M, eds. Pain Assessment and Pharmacologic Manage ment. St. Louis: Mosby Elsevier; 2011:177- 276.
5. Dykstra KM. J Perianesth Nurs. 2012;27:385-392.
6. Patanwala AE, Jarzyna DL, Miller MD, Erstad BL. Pharmacotherapy. 2008;28:1453-1460.
7. Davis MP. F1000 Med Rep. 2010;2:63.
8. Bell RF, Eccleston C, Kalso EA. Cochrane Database Syst Rev.2012;11: CD003351.
9. Prommer EE. J Palliat Med. 2012;15:474-483.
10. Bell RF, Dahl JB, Moore RA, Kalso E. Cochrane Database Syst Rev. 2009:CD004603.
11. Niesters M, Martini C, Dahan A. Br J Clin Pharmacol. 2013 Feb 21.
12. Motov SM. Medscape Emergency Medicine. http:// www.medscape.com/viewarticle/781463 2013.
13. Panzer O, Moitra V, Sladen RN. Crit Care Clin. 2009;25:451-469.

Source: http://www.medscape.com/viewarticle/782693_4

Why are there no low-priced generic versions of insulin?

Generic drugs account for more than 80% of prescriptions filled in the USA, saving the healthcare system billions of dollars a year. In contrast to about a $4/month out-of-pocket cost for some generic pills, monthly costs for brand-name insulins range from $120-400. The case of insulin, used by approximately six million people with type 1 and type 2 diabetes in America, differs from other drugs for a number of reasons. Insulin's Canadian discoverers sold the patent to their university for $1, stating that profit was not their goal. Since then, a series of incremental technological advances have maintained the patents, while older formulations have been removed from the market.

The recent move toward "biosimilars", so-called because the properties of large molecules don't allow for exact copies as do generic small-molecule drugs, isn't likely to dramatically affect the cost equation either. The authors state that the drugs that ultimately see extensive generic competition differ from those that attract few, if any, manufacturers.

The history of insulin highlights the limits of generic competition as a public-health framework. Nearly a century after its discovery, there is still no inexpensive supply of insulin for people living with diabetes in North America, and Americans are paying a steep price for the continued rejuvenation of this oldest of modern medicines.

Recombinant technology

Recombinant technology came along first from Genentech and Lilly in 1978, when they inserted cloned insulin genes into bacteria and created Humulin R (rapid) and Humulin N (NPH) in 1982. Novo Nordisk's chemical conversion of bovine into human insulin to create its own recombinant insulin reached the United States by 1988.

Next, researchers began moving around amino acids to create new insulin analogs with different properties: In 1996, lispro became the first fast-acting insulin analog to be approved, with the aim of better minimizing postprandial glucose excursions, followed by aspart in 2000 and glulisine in 2004.

Long-acting synthetic analogs were also developed to reduce hypoglycemia and improve overall

diabetes control. Glargine was the first of these, on the US market in 2000, followed by detemir in 2005. The first patents on these products expired in June 2014.

Biosimilar, but cheaper?

Now with those patents expired, "biosimilars" have entered the picture. Lilly and Boehringer Ingelheim's biosimilar version of glargine was recently approved in the European Union.

In the USA, the same product received tentative approval from the FDA, but final approval is being held up for 30 months, until mid-2016, because Sanofi has filed a lawsuit claiming patent infringement.

Meanwhile, unregulated biosimilar insulins have appeared in countries with less strict regulatory policies, including China, India, and Mexico. On 19 November 2015, the Committee for Medicinal Products for Human Use (CHMP) recommended the refusal of the marketing authorisation for the medicinal product Solumarv which was intended for the treatment of diabetes. This was expected to be used to treat patients with diabetes who require insulin to control their blood sugar levels. However, the CHMP was concerned that the company did not define the product's manufacturing process in sufficient detail to warrant a positive recommendation. The company had presented clinical studies in healthy people and in those with type 1 and type 2 diabetes, designed to show that Solumarv was similar in safety and effectiveness to the reference medicine Humulin

S (Eli Lilly). But the CHMP said that there was insufficient evidence showing that the product used in those studies was representative of the batches intended for market and that its quality was comparable to that of Humulin S. However, the CHMP concluded that Solumarv could not be approved as a biosimilar of Humulin S and recommended that it be refused marketing authorization," the EMA said in a statement.

Marvel Lifesciences may request a re-examination of the opinion within 15 days of receipt of notification of this negative opinion.

Even if biosimilar insulins do take hold in North America, they're not likely to produce the same cost saving as do generic drugs, given the additional data that will be required to prove their safety and efficacy, including immunogenicity studies. Economists estimate that the price reduction for biosimilar insulins might not exceed 20% to 40%, in contrast to the 80% or greater cost savings from most other generic drugs.

Moreover, biosimilars aren't going to change the fundamental difference between insulin and many other types of drugs that have been copied to various degrees.

Insulin is not a single entity but a family of related products that has evolved through incremental improvements. Subsequent iterations of insulin represented actual innovations, each one being safer, more effective, or more convenient than its predecessor.

Because of that, generic drug manufacturers are unlikely to invest in producing older versions of insulin that may already be obsolete.

And this is the case despite the fact that studies don't consistently show that analogs produce better outcomes than do the older NPH and regular insulins, and the advantages should be weighed against the costs, particularly for patients without adequate health insurance.

It's hard to say that contemporary patients who cannot afford their insulin (let alone the patent-protected glucometers and test strips required to adjust the dose) are well served by having as their only option an agent that is marginally more effective than those that could have been generically available 50 or 30 or 10 years ago, had generics manufacturers introduced cheaper versions when patents expired. The upshot, is that after years of incremental innovation, insulin may be no more affordable than it was when the original patent holders sold their stake for $1 to ensure access to this essential medicine.

Sources:

1) http://www.medscape.com/viewarticle/841669

NEWS from the FDA

FDA approves new insulin pump-sensor combination

The FDA has approved the Animas Vibe insulin pump and continuous glucose monitor (CGM) system for the management of insulin-requiring diabetes in adults aged 18 years and older.

The new product incorporates the Dexcom G4 Platinum CGM technology, allowing users to read glucose monitor data from the pump screen itself, rather than requiring a separate device.

Other features of the Animas Vibe will enable precise insulin dosing with a low basal increment, ranging from 0.025 to 25.0 units per h, and bolus increments starting at 0.05 and going up to 35.00 units per bolus.

Users can customize dosing, as the device allows for up to 12 personalized settings of insulin-to-carb ratios, insulin-sensitivity ("correction") factors, and blood glucose targets in 30-minute increments. It is waterproof up to 12 ft for 24h.

The Dexcom CGM is approved for up to 7 days of continuous wear, with a mean absolute relative

difference, the percentage of data points above or below a laboratory reference standard for blood glucose, of 13%. The transmitter is water resistant up to 8 ft for 24h.

The Animas Vibe system also allows for customizable alarms to indicate high or low glucose levels. However, it does not include the capability to suspend the pump based on a preset low glucose level detected by the CGM. That "low-glucose-suspend" feature is thus far available only in Medtronic's MiniMed 530G with Enlite system, approved by the FDA in September 2013.

Ramucirumab-Docetaxel approved for advanced NSCLC

The FDA has approved the combination of ramucirumab (Cyramza) and docetaxel for the treatment of patients with metastatic non-small-cell lung cancer (NSCLC), specifically after disease progression on or after platinum-based chemotherapy. Patients with *EGFR* or *ALK* mutations should have progression while on approved therapy for those aberrations. This follows earlier approvals of ramucirumab for the treatment of advanced gastric or gastroesophageal junction cancer as well.

The approval of ramucirumab in NSCLC is based upon results of a large phase III trial known as REVEL, results of which were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago. That trial included 1,253 patients randomized to either docetaxel and ramucirumab or docetaxel and placebo.

The median overall survival in the ramucirumab arm was 10.5 months, compared with 9.1 months in the placebo arm. This resulted in a hazard ratio for death of 0.86 (95% CI, 0.75-0.98; $P = .024$). Progression-free survival was also significantly improved with ramucirumab, with an HR of 0.76 (95% CI, 0.68-0.86; $P < .001$).

Safety was evaluated in 1,245 of the patients in the study, and the drug had an acceptable toxicity profile. The most frequently report adverse events included neutropenia, fatigue, and stomatitis.

The FDA's new approval is for a recommended dose and schedule of 10 mg/kg IV ramucirumab and 75 mg/m^2 IV docetaxel, administered once every 3 weeks. Ramucirumab is a fully human monoclonal antibody against the VEGF Receptor 2, which inhibits angiogenesis.

Ramucirumab has been and continues to undergo testing in a variety of malignancies. The drug showed promise in combination with paclitaxel in a phase III trial of metastatic gastric cancer, and is in various stages of phase III trials in colorectal cancer, hepatocellular carcinoma, and breast cancer as well.

FDA approves first oncolytic virus with new melanoma therapy

The FDA has approved its first oncolytic virus therapy, talimogene laherparepvec (Imlygic), a drug for the treatment of patients with melanoma lesions in the skin and lymph nodes.

Talimogene laherparepvec is a genetically modified live oncolytic herpes virus therapy that is injected directly into melanoma lesions where it replicates inside the cancer cells producing granulocyte-macrophage colony-stimulating factor (GM-CSF). The drug causes cell death and then rupture, which releases tumor-derived antigens and GM-CSF, which may promote an antitumor response.

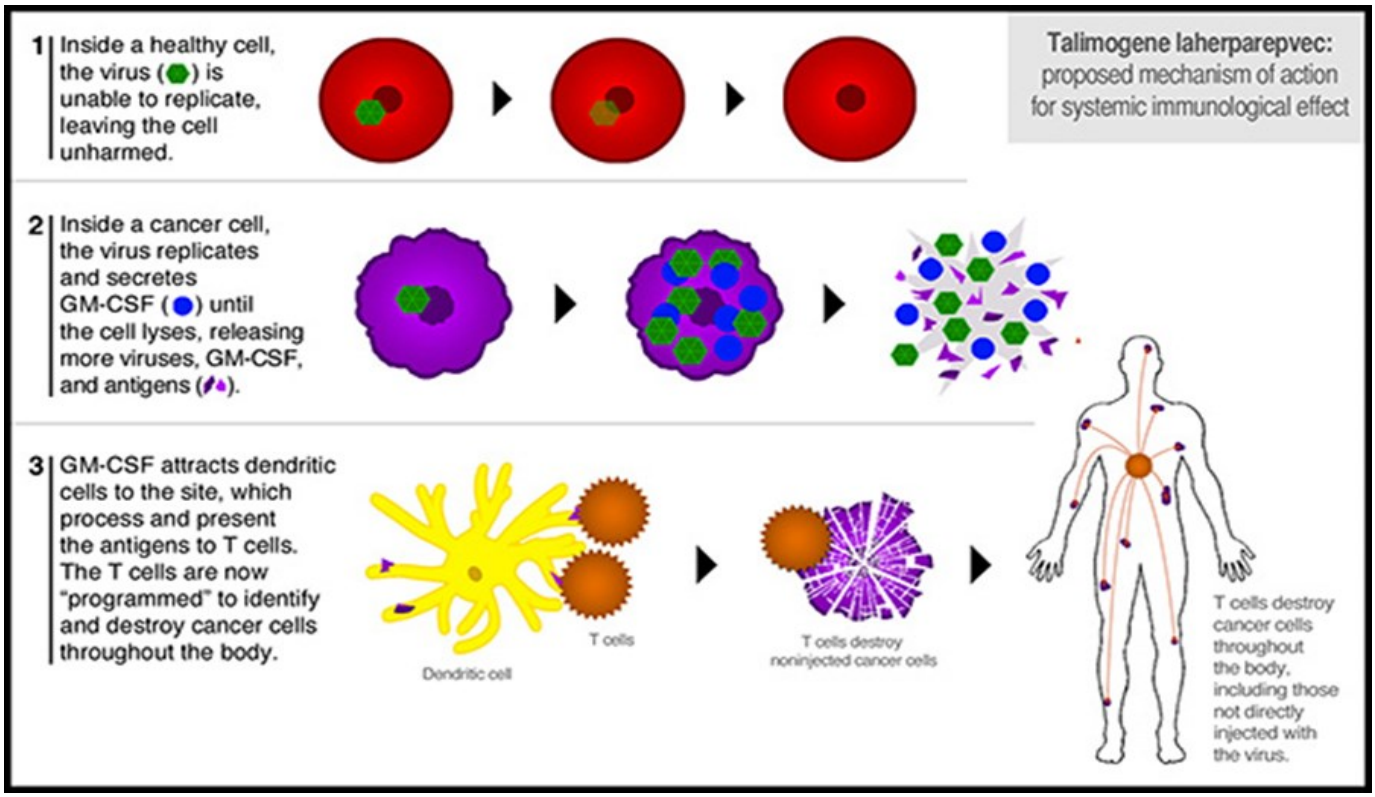
The FDA made the approval based on the efficacy results of the phase III OPTiM study, which included 436 patients with unresectable advanced melanoma. Patients were randomly assigned to talimogene laherparepvec intra-tumorally or GM-CSF every 14 days for 28 days. After the initial injection, talimogene laherparepvec was administered again 3 weeks later, followed by additional doses every 2 weeks for at least 6 months. The primary endpoint of the analysis was a durable response rate. More patients assigned to talimogene laherparepvec achieved a durable response, a decrease in size of their skin and lymph node lesions, compared with patients assigned GM-CSF (16.3% vs 2.1%). Patients assigned talimogene laherparepvec had a response that lasted a minimum of 6 months. Of the patients achieving a durable response, 29.1% had a durable complete response and 70.8% had a durable partial response. The median time to response among patients assigned talimogene laherparepvec was 4.1 months.

As an oncolytic viral therapy, Imlygic has a unique approach, and provides another option for treating eligible patients with unresectable disease that has recurred after initial surgery.

The most common adverse events seen in the OPTiM study were fatigue, chills, fever, nausea, flu-like symptoms, and pain at the injection site.

The FDA noted that talimogene laherparepvec was not associated with any improvement in overall

survival and has not been shown to have an effect on melanoma spreading to the brain, bone, liver, lungs, or other internal organs. In addition, because the injection includes a live herpes virus, herpes virus infection can also occur; therefore, the treatment should not be given to individuals with suppressed immune systems or who are pregnant.



Osimertinib granted accelerated approval for T790M+ve NSCLC

The FDA granted accelerated approval to osimertinib (Tagrisso, AstraZeneca), previously known as AZD9291, for the treatment of advanced non–small-cell lung cancer (NSCLC) with the *EGFR* mutation T790M. The drug is indicated for use in patients who have progressed on or after use of another tyrosine kinase inhibitor (TKI).

This approval provides a new treatment for patients who test positive for the *EGFR* resistance mutation, T790M, and is based on substantial evidence from clinical trials that shows Tagrisso had a significant effect on reducing tumor size in over half of patients who were treated.

The FDA also approved a companion diagnostic test, the cobas EGFR Mutation Test v2 (Roche). This is a new version of the test, that adds the T790M mutation to other known *EGFR* mutations. Osimertinib's approval is based on results from the AURA extension and AURA2 phase II trials, which collectively included 411 NSCLC patients who progressed after use of another TKI. In those trials together, the overall objective response rate (ORR) was 59%. In another phase I trial of the drug including 63 patients, the ORR was 51%, and the median duration of response was 12.4 months.

In the AURA and AURA2 trials, the most common adverse events (AEs) were generally mild or moderate and included diarrhea, rash, and dry skin. No grade 3 or higher AEs occurred in more than 3.5% of patients.

Though the FDA granted osimertinib accelerated approval, the drug is still being evaluated in a larger phase III trial (AURA3) comparing it to platinum-based doublet chemotherapy again in patients whose disease progressed with other TKI treatment and who harbor the T790M mutation. That study, which is active but not currently recruiting, has an estimated enrollment of 410 patients. This treatment has the potential to become the standard of care for patients living with EGFRm T790M non-small cell lung cancer.

Source
www.medscape.com/viewarticle/815349

ISLAMIC CONTRIBUTIONS TO MEDICINE

Islamic pharmacy (*Saydanah*), the art of preparing and dispensing drugs, separate from the profession of medicine, was recognised in the 8th century. It involved herbalists, collectors and sellers of medicinal herbs and spices, manufacturers, sellers of syrups, cosmetics, aromatic waters and pharmacist authors.

Drug stores were first established in Baghdad in 754, Market Inspectors (*Mohtasibs)* were responsible for checking the cleanliness of the containers, preparation of drugs and their dispensing. During the reign of Caliph Mamun al-Rashid (d.833) a licensing system was introduced. Druggists and physicians had to pass an examination to practice and licensed pharmacists were called *Sayadala*. Sinan ibn Sabit (d.943), director of Baghdad hospital, was the first administrator of a licensing department and founder of a public health system.

Islamic pharmacy introduced 2000 new substances including anise, cinnamon, cloves, senna, camphor, sandalwood, musk, myrrh, cassia, tamarind, nutmeg, cloves, aconite, ambergris, and mercury.. They were first to develop syrups and juleps, new pills, elixirs, confections, tinctures, and inhalants, and introduced hemp as an anaesthetic. Muslim pharmacists made scientific investigations of the composition, dosages, uses and therapeutic effects of drugs.

Umayyad period

The first figure associated with the development of Islamic pharmacy was Khalid bin Yazid (d.704). Under his direction translators were given stipends, and several Egyptian and Greek books of medicine, chemistry and astrology were translated into Arabic. He was the first to establish a library in the Islamic world.

Abbasid Period

Jabir ibn Hayyan (d. 815 Kufa) was a renowned chemist and alchemist, and considered to be the father of modern chemistry, freeing it from superstition and emphasising systematic experimentation. He is credited with the invention of over 22 types of basic laboratory equipment, such as the alembic and retort, as well as many commonplace chemical substances such as hydrochloric acid, nitric acid and processes such as sublimation, calcinations, crystallization, evaporation and dissolution.

The first medical formulary (*Aqrabadhin Kabir*) was written in Arabic by Sabur bin Sahl (d.869). This guidebook for pharmacists included recipes for compounding drugs, remedies for ailments, their pharmacological actions, dosage and the methods of administration. It was imitated by many during the Middle Ages. The Latin translation was used as a model for future Pharmacopeias.

Portion of the formulary (Aqrabadhin) by Ibn al-Tilmīdh (d. 1165/560). The copy was completed on 25 Rabi' I 902

Muhammad Ibn Zakaria al-Razi (d.925) introduced into pharmacy the use of mild purgatives, cupping for cases of apoplexy (sudden effusion of blood into an organ) and cold water for fevers. The director of Muqtadari hospital in Baghdad, he acted as a chemist to mix drugs for patients. His books *Qarabadain Kabir* (The Great Book of Krabadain), and *Qarabadain Saghir* introduced 829 novel drugs. He promoted the medical uses of chemical compounds with a book on home remedies, *Tibb al-Fuqara.*

Muhammad ibn Ahmad al-Maqdassi performed pharmaceutical experiments and wrote several books as guides to materia medica. Abu al-Qasim al-Zahrawi (936-1013) pioneered the preparation of drugs by sublimation and distillation. His *Kitab al-Tasrif* (*Liber servitoris)* provides the reader with recipes and explains how to prepare the `simples' from which were compounded the complex drugs then generally used.

The first pharmacological book by a Muslim was

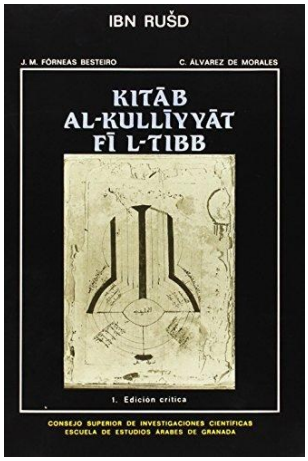
compiled by Abu Mansur Muwaffaq who lived in 10th century Herat. He wrote the *Kitab al-abniyia 'an Haqa'iq al-adwiya*, (*The foundations of the true properties of Remedies*) which is the oldest prose work in modern Persian. It deals with 585 remedies (466 derived from plants, 75 from minerals, 44 from animals), classified into four groups according to their action.

Ibn al-Quff was apparently the first Arab physician to call for a standard set of weights and measures in medicine and pharmacy. He is also known to have excelled in anatomical descriptions of the body, especially of the heart and the blood system.

Islamic Spain & Maghrib

Saeed ibn Abd Rabbihi (d.960) was a pharmacist-physician of Cordoba. His *Kitab al-Dukkan* (The Pharmacy Shop) consisted of 17 chapters on compound drugs and recipes. Ahmad Ibn al-Jazzar (d.984) practiced medicine in Qayrawan, Tunisia. In his apothecary he kept syrups, electuaries, and other preparations. His book *al-Bughiya* on compound drugs was written as a complimentary to *al-I'timad*. *Tibb al-Fuqara wal Masakin* was intended for poor people who could not afford a doctor and imported drugs. Anyone could cure common diseases by buying readily available herbs.

Abu Salt Umaiyah Andalusi (d. 1134) was a resourceful physician, astronomer, mathematician, and an eloquent poet. His brief compendium on materia medica al-*Adwiyah al-Mufradah* was in use in hospital pharmacies in Egypt. The *simples* were listed according to their therapeutic action on various organs. The book was translated into Latin by Arnold of Villanova in second half of the 13th century.



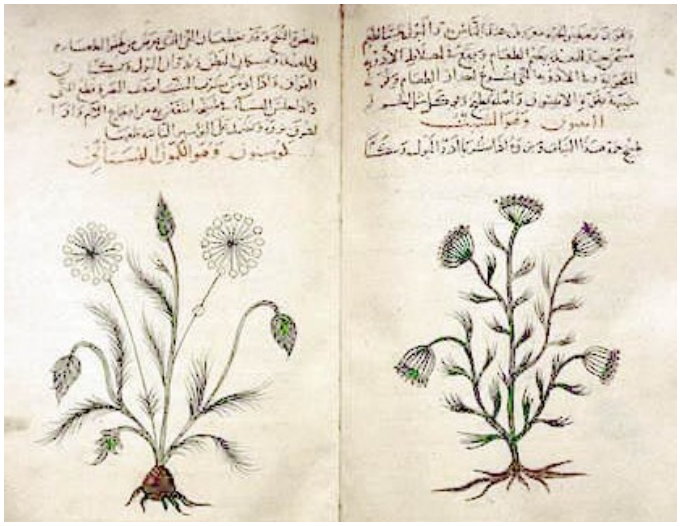
Abdul Malik Ibn Zuhr (d.1161) wrote *Kitab al-Aghziya* describing various types of foods and drugs and their effects on a person's health. In his *Kitab al-Iqtisad* he gave a summary of diseases, therapeutics and hygiene, written especially for the benefit of the layman. His pharmacopoeia was the first Arabic book to be printed with a movable type in 1491. He developed drug therapy and medicinal drugs for the treatment of specific diseases.

The seven volume medical encyclopedia *Kitab al-Kulliyat fil Tibb* by Qazi Ibn Rushd (1126-1198) includes two volumes on materia medica and general therapeutics.

Ibn Baytar (d.1248) described some 1400 drugs derived from various plants including some 200 new plants in his book "*Kitab al-Jamey fil Adwiya al-Mufrada*". It was based on 300 actual plants discovered by him along the Mediterranean coast between Syria and Spain. This was one of the greatest botanical compilations dealing with medicinal plants in Arabic. The book refers to works of some 150 previous Arabic authors, and also quotes 20 Greek scientists.

A book on pharmaceutical formulae, *Aqrabadain Kabir* by Sabur ibn Sahl, was imitated by many during the Middle Ages. The original in Arabic was lost, but the Latin translation was used as a model for future Pharmacopeias.

Manuscripts for books by the Iraqi scholar Ishaq ibn Imran on diet and drug therapy entitled, *Aqwil fee Taba'i al-Aghziyya wal 'adwiya* are preserved in libraries in Istanbul, Madrid, Munich and Paris.



Arabic herbal medicine guidebook De Materia Medca of Dioscorides. Cumin & dill. c. 1334; https://commons.wikimedia.org/w/index.php?curid=736179

Pharmacy in Asia

During the Moghul period several pharmacopoeias (Qarabadain Shifae'ee, Zakai, Qadri and Elaj-ul-Amraz) specified quantities of drugs in a given prescription, and indicated methods of preparation. The Unani medical system is still flourishing in Iran and the Indian sub-continent. Sometimes called Hikmat or Unani-Tibb, its practitioners were called Hakims.

Adapted with permission from an article by Zakaria Virk http://www.alislam.org/egazette/articles/Muslim-Contribution-to-Pharmacy-201009.pdf

STATE OF KUWAIT
Pharmaceutical & Herbal Medicines Control and Registration Administration

New Pharmaceutical products approved from May to October 2015

Adenorythm Soln. for Infn.30mg/10ml Vianex S.A. / France Adenosine-30mg
Adenorythm Solution for Injection 6mg/2ml Vianex S.A. / France Adenosine-6mg
Aremed Tablets 1mg Remedical Limited/Cyprus Anastrozole – 1mg
Atropine Sulphate Aguettant Soln. for Inj. 0.5mg/5ml in PFS Laboratoire Aguettant/France Atropine Sulphate – 0.5mg
Bendaplatin Powder for Solution for Infusion 50,100mg Bendalis GmbH/Germany Oxaliplatin – 50, 100mg
Brilinta Tablets 60mg Astrazeneca AB/Sweden Ticagrelor – 60mg
BSS Sterile Irrigating Solution, Plastic Bag Alcon Lab Inc./USA Sod. Chloride, USP -6.4mg Pot. Chloride, USP -0.75mg Cal. Chloride (Dihydrate), USP -0.48mg Mag. Chloride (Hexahydrate), USP – 0.3mg Sod. Acetate (Trihydrate), USP – 3.9mg Sod. Citrate (Dihydrate), USP – 1.7mg
Budesma Pressurised Inhalation 200mcg Glenmark Pharmaceuticals Limited/India Budesonide – 200mcg

Bypro Tablets 50mg Fresenius Kabi Oncology Ltd./India Bicalutamide – 50mg
Carbaglu Dispersible Tablets 200mg Orphan Europe SARL/ France Carglumic Acid-200mg 16
Cardoz Tablets 6.25, 12.5mg IPCA Laboratories Limited/India Carvedilol – 6.25, 12.5mg
Cholib Tablets 145/20mg Abbotte Laboratories/U.K. Fenofibrate – 145mg Simvastatin – 20mg
Clear Air Tablets 10mg Amoun Pharmaceutical Co./Egypt Montelukast (as sodium) – 10mg
Clidacin BA Free Soln. for Inj. /Infn. 600mg/4ml Vianex S.A./Greece Clindamycin-150mg
Colomycin Powder for Injection 1,000,000 IU/Vial Forest Laboratories UK Limited/UK Colistimethate Sodium-1,000,000 IU
Colpocin -T Solution for IV infusion 500mg/100ml Demo S.A Pharmaceutical Industry/Greece Metronidazole – 5mg
Dermamed Ointment 0.05% Medpharma Pharmaceuticals & Chemicals Ind. (L.L.C.)/U.A.E Clobetasol Propionate – 0.500mg
Dextrose 10% w/v & Sod. Chloride 0.9% w/v Inj. USP Qatar Pharma /Qatar Dextrose Monohydrate-100g Sodium Chloride-9g
Dormifor IV Emulsion 1000mg/100ml Vials Arwan Pharm. Ind. Lebanon s.a.l./Lebanon Propofol-1000mg 7338 MAR 16
Dormifor IV Emulsion 200mg/20ml Vials Arwan Pharm. Ind. Lebanon s.a.l./Lebanon Propofol-200mg 7336 MAR 16
Dormifor IV Emulsion 500mg/50ml Vials Arwan Pharm. Ind. Lebanon s.a.l./Lebanon Propofol-500mg 7337 MAR 16
Entapro Tablets 10,20mg Escitalopram (as Oxalate) – 10, 20mg Spimaco/Saudi Arabia
Erylik Gel Laboratoires Bailleut/France Erythromycin – 4mg Tretinoin – 0.025g
Fusitin Cream 2% KSPICO/Kuwait Fusidic acid – 20mg
Gadovist & Solution for Injection 1mmol/ml vials Bayer Pharma AG/Germany Gadobutrol – 604.72mg (Equivalent to 1.0mmol gadobutrol containing gadolinium 157.25mg)
Gaviscon Double Action Mint Oral Suspn. Liquid Bottles Reckitt Benckiser Healthcare (UK) Ltd./UK Calcium Carbonate – 325mg Sod. Alginate – 500mg Sod. Bicarbonate – 213mg
Gemcitabina Glenmark Lyophilized Powder for Injection 200mg, 1g Glenmark Pharmaceuticals Limited/India Gemcitabine (as hydrochloride) – 200mg, 1g
Glados Tablets 15, 30mg Tabuk Pharmaceutical Manufacturing Co./Saudi Arabia Pioglitazone (as HCl) – 15, 30mg
Glemont-CT 4 Glenmark Pharmaceuticals Limited/India Montelukast (as sodium) – 4, 5mg
Glencet Tablets 5mg Glenmark Pharm. Ltd./ India Levocetirizine Dihydrochloride-5mg
Glimitoid Tablets 2,4mg Eva Pharma for Pharm. & Medical Appliances SAE/Egypt Glimepiride – 2,4mg
Hisdine Syrup Medpharma Pharmaceuticals & Chemicals Ind. (L.L.C.)/UAE Desloratidine – 0.5mg Sutril Neo Prolonged-Release Tablets 5, 10mg Ferrer International S.A./Spain Torasemide – 5, 10mg
Hydroxyethyl Starch (200/0.5)10% w/v in Sod. Chloride 0.9%w/v Injn. Qatar Pharma /Qatar Hydroxyethyl Starch 200/0.5-100gm Sod. Chloride-9gm
Hysone Injection Quickmed Biotech & Research Pvt. Ltd./India Hydrocortisone (as sodium succinate) – 100mg
Ipoz Tablets 15, 30mg Global Pharma Co. LLC/ U.A.E. Pioglitazone-15, 30mg
Kapetral Talets 150, 500mg Remedica Ltd./Cyprus Capecitabine – 150, 500mg
Kucef Plus Injection Quickmed Biotech & Research Pvt. Ltd./India Ceftriaxone (as Sodium) 100mg Sulbactam sodium 500mg
Lemtrada Concentrate for Solution for Infusion 12mg Genzyme Therapeutics Ltd./UK Alemtuzumab (rDNA) – 12mg
Lenvima Capsules 4, 10g Eisai Europe Ltd./U.K. Lenavatinib (as mesilate) – 4, 10mg
Levafloxacin Lyomark Solution for Infusion 500mg/100ml Lyomark Pharma GmbH/Germany Levofloxacin (as Levofloxacin 0.5 H_20) – 500mg
Levanix Tablets 500mg Neopharma/U.A.E. Levofloxacin-500mg
Loxoprel Tablets 2.5mg Actavis Group PTC ehf/Ireland Letrozole-2.5mg
Maxigesic Tablets AFT Pharmaceutical Ltd./Newzeland Paracetamol – 500mg Ibuprofen – 150mg
Medsten Cream 1% Medpharma Pharmaceuticals & Chemicals Ind. (L.L.C.)/U.A.E Clotrimazole – 10mg
Mefex Tablets 500mg Neopharma/UAE Mefenamic Acid – 500mg
Montas Chewable Tablets 4, 5, 10mg Oman Pharmaceutical Products Co. L.L.C.

(ZYNOVA)/Oman Montelukast – 4, 5, 10mg
Negafen Cream Julphar Gulf Pharma Ind./U.A.E. Terbinafine HCl – 10mg
Neoclav Powder for Oral Suspension 228.5mg/5ml Neopharma/UAE Amoxicillin (as Trihydrate) – 200mg Clavulanic Acid (as potassium Clavulanate) – 28.5mg
Ofev Soft Capsules 100, 150mg Boehringer Ingelheim Int. GmbH/Germany Nintedanib – 100, 150mg
Olanole Tablets 5, 7.5, 10mg Laboratories Cinfa S.A. Pamplona/Spain Olanzap ine – 5, 7.5, 10mg
Omiz Plus Capsules 40mg/1100mg Tabuk Pharm. Mfg. Co. / KSA Omeprazole-40mg Sodium Bicarbonate-1100mg
Opdivo Injection 40 and 100mg/10ml Bristol-Myers Squibb Company/USA Nivolumab – 40 and 100mg
Oxaliplatin Bendalis Concentrate for Solution for Infusion 200mg Bendalis GmbH/Germany Oxaliplatin – 200mg
Pemetrexed Glenmark Lyophilized Powder for Injection 500mg Glenmark Generics S.A./Argentina Premetrexed (as sodium) – 500mg
Peridom Tablets 10mg Oman Pharmaceutical Products Co. L.L.C. (ZYNOVA)/ Sultanate of Oman Domperidone (as maleate) –10mg
Periotoneal Dialysis Soln. with 1.36 % Dextrose Qatar Pharma /Qatar Sod. Chloride -5.38g Sod. Lactate -4.48g Cal. Chloride Dihydrate-0.184g Mag. Chloride Hexahydrate-0.051gm Glucose Anhydrous – 13.6g
Periotoneal Dialysis Soln. with 2.27 % Dextrose Qatar Pharma /Qatar Sod. Chloride -5.38g Sod. Lactate -4.48g Cal. Chloride Dihydrate-0.184g Mag. Chloride Hexahydrate-0.051gm Glucose Anhydrous-22.70g
Periotoneal Dialysis Soln. with 3.86 % Dextrose Qatar Pharma /Qatar Sod. Chloride -5.38g Sod. Lactate -4.48g Cal. Chloride Dihydrate-0.184g Mag. Chloride Hexahydrate-0.051gm
Phenylephrine Aguettant Soln. for Injn. 50mcg/ml Laboratoire Aguettant/ France Phenylephrine-500mcg 7333 MAR 16
Potassium Chloride 1.5% w/v Injn. USP Qatar Pharma /Qatar Potassium Chloride-1.5g
Praluent Solution for Injection 75, 150mg in PFP Sanofi-Aventis Groupe/France Alirocumab (rDNA) – 75, 150mg
Pregadex Capsules 75, 150mg Spimaco/Saudi Arabia Pregabalin – 75, 150mg
Prof Cod & Flu Film Coated Caplets Tabuk Pharmaceutical Manufacturing Co./Saudi Arabia Ibuprofen – 200mg Pseudo-ephedrine HCl – 30mg Chlorpheniramine Maleate – 2mg
Prosterol Modified Release Tabs 10mg Eva Pharma for Pharm. & Medical Appliances SAE/Egypt Alfuzosin HCl – 10mg
Rocursonium Bromide Hospira Soln. for Injn./Infn.50mg/5ml Hospira UK Ltd. / U.K. Rocuronium Bromide-50mg
Rosatin Tablets 10mg Al-Taqaddom Pharm. Mfg. Co./ Jordan Rosuvastatin-10mg
Ryzodeg Flex Touch Son. for Inj. 100 IU/ml Novo Nordisk A/S/Denmark Insulin degludec 70% Insulin aspart 30% (rDNA) – 300U
Sutril Neo Prolonged-Release Tablets 10mg Ferrer International S.A./Spain Torasemide – 10mg
Synjardy Tablets 12.5/1000mg Boehringer Ingelheim International Empagliflozin – 12.5mg Metformin
Talgan Inhalation Susp. For Nebuliser 0.25. 0.5mg/ml Anfarm Hellas S.A./Greece Budesonide -0.25, 0.5mg
Tamiflu Powder for Oral Suspension 6mg/ml F. Hoffmann-La Roche Ltd. GmbH/Germany Oseltamivir (as phosphate) -6mg
Tivicay Tablets 50mg ViiV Healthcare UK Limited/UK Dolutegravir – 50mg
Tresiba FlexTouch Soln. for Inj. 100U/ml Novo Nordisk A/S/Denmark Insulin Degludec (rDNA0 – 300U

Answers to: Test your knowledge

Correct answers:
1-B; 2-C; 3-A

The *Kuwait Pharmacy Bulletin* (ISSN 1028-0480) is published quarterly by the Faculty of Pharmacy, Kuwait University, and includes a list of recently approved drugs from the MOH. It aims to provide instructive reviews and topical news items on a range of drug related issues. It is widely distributed free within the university, to hospitals, polyclinics & private pharmacies as well as to other universities within the Gulf & Middle East region.

The information in this bulletin does not necessarily reflect the views of the editorship, nor should it be taken as an endorsement of any product that is mentioned herein. Articles are generally adapted from literature sources and rewritten or occasionally reproduced with permission from the appropriate sources.

Readers wishing their own copy may ask to be added to the mailing list by contacting the Executive Editor.

***Executive Editor*: Yunus Luqmani. *Assistant Editors*: Leyla Hasan Sharaf, Samuel Koshy**

Editorial Office: Faculty of Pharmacy, Health Sciences Centre, Kuwait University, PO Box 24923 Safat, 13110 Kuwait, Fax:25342087; email: yunus@hsc.edu.kw