Pharmacotherapy Of Hypertension

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Abstract*— large variety of drugs is available for treatment of hypertension. Moreover, many randomised controlled trials with clinically relevant endpoints (morbidity, mortality, quality of life) do exist in the cardiovascular field, providing for sufficient evidence to choose the appropriate agent in most circumstances. For diuretics and betablockers a large body of evidence in terms of beneficial effects on outcome does exist, for ACE-inhibitors in some special indications only. These drugs are therefore recommended as first-line treatments. For calcium-channel blockers (with the exception of isolated systolic hypertension in the elderly) and AT1-receptor-antagonists the results of endpoint-studies are still awaited. These results will have to be considered for revised versions of currently available guidelines. Pulmonary arterial hypertension (PAH) is a progressive and debilitating disease characterized by a pathological increase in the resistance of the pulmonary circulation . The increased pulmonary vascular resistance (PVR) leads to right ventricular dysfunction, exertional impairment, and premature death . The United States national prospective registry for primary pulmonary hypertension reported the median survival for the idiopathic form of PAH to be only 2.8 years without treatment .

Two meta-analyses have reviewed the treatments of PAH . A meta-analysis by Macchia et al in 2007 included some patients with non-PAH pulmonary hypertension and the results of several trials have been reported since this publication . A meta-analysis by Galiè et al published in 2009 concluded that PAH treatment improved mortality, however this conclusion is limited by the pooling of all three classes of PAH treatment and the inclusion of multiple doses of medication, some of which are not approved for clinical use due to either increased adverse effects or lack of efficacy. The failure to include unpublished data in this meta-analysis may have also introduced a publication bias. We sought to improve upon these previous meta-analyses by addressing these issues. By pooling the available literature, we sought to determine the effect of these classes of medication on total mortality and secondarily to assess their impact on other clinical endpoints, including dyspnea, exercise tolerance, hemodynamics, and adverse effects.

I. INTRODUCTION

Hypertension (HTN) and other related complications are recognized as emerging clinical and public health problems in 1 Saudi Arabia. The global economic burden of increased blood pressure was estimated to consume US$370 billion 2 worldwide and 10% of healthcare expenditures. It is the 3-leading cause of cardiovascular disease worldwide. Although the condition is common, readily detectable, and easily treatable, it is usually asymptomatic and often leads to 4 lethal complications if left untreated. Poorly controlled 5 hypertension is a common finding in the outpatient setting. The reasons for poor control have not been clearly delineated, but attention has focused primarily on patient factors such as 6 poor compliance with treatment and lack of access to care. Poor control of hypertension is associated with higher drug 7 costs and more physician visits. Therefore the purpose of

this study was to evaluate and compare therapeutic plan in outpatients with hypertension at Ballasmer General Hospital and Muhail General Hospital and determine the prevalence in both the genders between the age of 30 to 90 Years in the Asir Province.

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Hypertension is necessary to support gas exchange in the fetus, but if pulmonary arterial pressure is elevated after birth or during infancy or childhood, then pulmonary hypertension becomes a serious medical problem with substantial mortality and morbidity. Pulmonary hypertension is classically defined as a mean pulmonary artery pressure of ≥25 mmHg at rest, with a pulmonary capillary wedge pressure of ≤ 15 mmHg. Numerous disease processes can produce pulmonary hypertension in both adults and children, but these two populations are quite different when considering classification, genetic causes, and in some cases, treatment. This is largely because the exposure of the developing lung to pathological and/or environmental insults affects lung adaptation, development, and growth, leading to far greater complexity of phenotypes . The classifications of pulmonary hypertension introduced at the WHO Symposium in 1998 and subsequently modified at the Venice and Dana Point Symposia were primarily designed for use in adult diseases, and have been difficult to apply to pediatric populations. A new pediatric classification scheme was developed by an expert panel in Panama City in 2011 to better address the developmental underpinnings of pulmonary vascular disease in children . For instance, while idiopathic pulmonary arterial hypertension occurs in children, pulmonary hypertension very commonly occurs in association with congenital heart disease, or other lung diseases such as lung hypoplasia or bronchopulmonary dysplasia (BPD). The latter group appears to be growing, and represents a significant proportion of patients followed by pediatric pulmonary hypertension programs. Pulmonary hypertension affects roughly one-third of infants with moderate to severe BPD and results in greater morbidity and mortality, poor growth and neurodevelopmental outcome, long term mechanical ventilation support, and death due to right heart dysfunction and multi-organ failure . Pulmonary vascular disease also contributes to the morbidity and mortality of other pediatric diseases such as sickle cell disease, interstitial lung diseases, and cystic fibrosis . Relatively little is known about the epidemiology of pediatric pulmonary hypertension, and comprehensive registries to support phenotyping and clinical research are needed.

II. CAUSES OF HYPERTENSION

- Primary hypertension

Hypertension results from a complex interaction of genes and environmental factors. Numerous common genetic variants with small effects on blood pressure have been identified as well as some rare genetic variants with large effects on blood pressure. Also, genome-wide association studies (GWAS) have identified 35 genetic loci related to blood pressure; 12 of these genetic loci influencing blood pressure were newly found. Sentinel SNP for each new genetic locus identified has shown an association with DNA methylation at multiple nearby CpG sites. These sentinel SNP are located within genes related to vascular smooth muscle and renal function. DNA methylation might affect in some way linking common genetic variation to multiple phenotypes even though mechanisms underlying these associations are not understood. Single variant test performed in this study for the 35 sentinel SNP (known and new) showed that genetic variants singly

or in aggregate contribute to risk of clinical phenotypes related to high blood pressure.

Blood pressure rises with aging when associated with a western diet and lifestyle and the risk of becoming hypertensive in later life is significant. Several environmental factors influence blood pressure. High salt intake raises the blood pressure in salt sensitive individuals; lack of exercise, central obesity can play a role in individual cases. The possible roles of other factors such as caffeine consumption, and vitamin D deficiency are less clear. Insulin resistance, which is common in obesity and is a component of syndrome X (or the metabolic syndrome), also contributes to hypertension.

Events in early life, such as low birth weight, maternal smoking, and lack of breastfeeding may be risk factors for adult essential hypertension, although the mechanisms linking these exposures to adult hypertension remain unclear. An increased rate of high blood uric acid has been found in untreated people with hypertension in comparison with people with normal blood pressure, although it is uncertain whether the former plays a causal role or is subsidiary to poor kidney function. Average blood pressure may be higher in the winter than in the summer. Periodontal disease is also associated with high blood pressure.

- Secondary hypertension

Secondary hypertension results from an identifiable cause. Kidney disease is the most common secondary cause of hypertension. Hypertension can also be caused by endocrine conditions, suchas , Cushing'ssyndrome, hyperthyroidism, hypothyroidis m, acromegaly, Conn's syndrome or hyperaldosteronism, renal artery stenosis (from atherosclerosis or fibromuscular dysplasia), hyperparathyroidism, and pheochromocytoma. Other causes of secondary hypertension include obesity, sleep apnea, pregnancy, coarctation of the aorta, excessive eating of liquorice, excessive drinking of alcohol, certain prescription medicines, herbal remedies, and stimulants such as cocaine and methamphetamine. Arsenic exposure through drinking water has been shown to correlate with elevated bloodpressure. Depression was also linked to hypertension. Loneliness is also a risk factor.

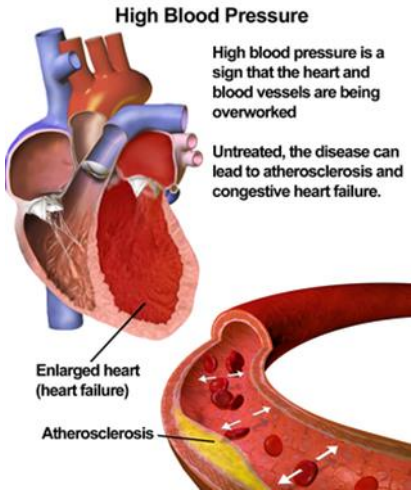

Illustration depicting the effects of high blood pressure

- Pathophysiology

In most people with established essential hypertension, increased resistance to blood flow (total peripheral resistance) accounts for the high pressure while cardiac output remains normal. There is evidence that some younger people with prehypertension or 'borderline hypertension' have high cardiac output, an elevated heart rate and normal peripheral resistance, termed hyperkinetic borderline hypertension. These individuals develop the typical features of established essential hypertension in later life as their cardiac output falls and peripheral resistance rises with age. Whether this pattern is typical of all people who ultimately develop hypertension is disputed. The increased peripheral resistance in established hypertension is mainly attributable to structural narrowing of small arteries and arterioles, although a reduction in the number or density of capillaries may also contribute.

It is not clear whether or not vasoconstriction of arteriolar blood vessels plays a role in hypertension. Hypertension is also associated with decreased peripheral venous compliance which may increase venous return, increase cardiac preload and, ultimately, cause diastolic dysfunction.

Pulse pressure (the difference between systolic and diastolic blood pressure) is frequently increased in older people with hypertension. This can mean that systolic pressure is abnormally high, but diastolic pressure may be normal or low, a condition termed isolated systolic hypertension. The high pulse pressure in elderly people with hypertension or isolated systolic hypertension is explained by increased arterial stiffness, which typically accompanies aging and may be exacerbated by high blood pressure.

Many mechanisms have been proposed to account for the rise in peripheral resistance in hypertension. Most evidence implicates either disturbances in the kidneys' salt and water handling (particularly abnormalities in the intrarenal renin–angiotensin system) or abnormalities of the sympathetic nervous system. These mechanisms are not mutually exclusive and it is likely that both contribute to some extent in most cases of essential hypertension. It has also been suggested that endothelial dysfunction and vascular inflammation may also contribute to increased peripheral resistance and vascular damage in hypertension. Interleukin 17 has garnered interest for its role in increasing the production of several other immune system chemical signals thought to be involved in hypertension such as tumor necrosis factor alpha, interleukin 1, interleukin 6, and interleukin 8.

Excessive sodium or insufficient potassium in the diet leads to excessive intracellular sodium, which contracts vascular smooth muscle, restricting blood flow and so increases blood pressure.

III. PHARMACOTHERAPY OF PULMONARY HYPERTENSION

The aims of therapy for pulmonary arterial hypertension are selective pulmonary vasodilation, restoration of normal endothelial function, and reversal of remodeling of the pulmonary vasculature. All of these serve to reduce right ventricular afterload and prevent right ventricular failure. The choice of agents will often depend on the severity and acuity of illness – for instance, acute pulmonary vasodilation is needed for PPHN and acute pulmonary hypertensive crises after cardiopulmonary bypass, but long-term therapy may focus more on vascular remodeling. The main therapeutic avenues involve the nitric oxide (NO), prostacyclin, and endothelin pathways, which are summarized in excellent recent comprehensive reviews. It is also important to note that the scientific understanding and therapeutic management of pulmonary hypertension are changing rapidly.

- Nitric oxide

Nitric oxide (NO) is synthesized from the terminal nitrogen of L-arginine by the enzyme nitric oxide synthase (NOS). Three isoforms of NOS are present in the lung, although endothelial NOS is regarded as the most important regulator of NO production in the lung vasculature. NO is a gas molecule that diffuses freely from the endothelium to the vascular smooth muscle cell. The biologic effects of NO in vascular smooth muscle are mediated primarily through activation of soluble guanylate cyclase, which converts GTP to cGMP , cGMP serves as a second messenger that relaxes vascular smooth muscle through activation of cGMP-gated ion channels and activation of cGMP-dependent protein kinase. However, recent studies indicate that alternative NO signaling pathways may also exist through reaction of NO with protein thiols to form S-nitrosothiols (SNO), which may induce vasodilation or protein modification.

Nitric oxide is currently FDA approved only for treatment of PPHN in the neonatal period. Since eNOS is decreased or dysfunctional in PPHN, iNO is thought to provide specific replacement therapy that is inhaled directly to airspaces approximating the pulmonary vascular bed. While it is most commonly administered with mechanical ventilation, iNO can also be provided via CPAP or nasal cannula devices, although the concentration may need to be increased to account for the entrainment of room air.

- Sildenafil

Cyclic GMP is the second messenger that regulates contractility of smooth muscle through activation of cGMP-dependent kinases, phosphodiesterases and ion channels. In vascular smooth muscle cells, NO-mediated activation of soluble guanylate cyclase is a major source of cGMP production. Because cGMP is such a central mediator of vascular contractility, it is not surprising that its concentrations are regulated within a relatively narrow range to allow fine-tuning

of vascular responses to oxygen, nitric oxide, and other stimuli.

Phosphodiesterases are a large family of enzymes that hydrolyze and inactivate cGMP and cAMP, thus regulating their concentrations and effects, as well as facilitating "cross-talk" between the two cyclic nucleotides. The type 5 phosphodiesterase (PDE5) is especially highly expressed in the lung, and not only uses cGMP as a substrate but also contains a specific cGMP binding domain that serves to activate its catabolic activity. As the primary enzyme responsible for regulating cGMP, PDE5 may well represent the most important regulator of NO-mediated vascular relaxation in the normal pulmonary vascular transition after birth.

Fetal and neonatal lung development, along with commonly used therapies, appears to regulate PDE expression and activity. In developing lambs and rats, PDE5 is expressed according to specific developmental trajectories that result in a peak of expression during late fetal life, followed by an acute fall around the time of birth .This drop in PDE5 activity would be expected to amplify the effects of nitric oxide produced by birth-related stimuli such as oxygen and shear stress . In contrast, when pulmonary vessels of fetal lambs undergo remodeling by chronic intrauterine pulmonary hypertension, PDE5 activity increases relative to controls . Even more striking is that after birth, PDE5 activity does not fall in this lamb model of PPHN, but rather increases dramatically to levels well over those observed in spontaneously breathing or ventilated control lambs. This abnormal increase in activity would be expected to diminish responses to both endogenous and exogenous NO, and could explain the incomplete clinical efficacy of iNO in some patients. It is also interesting to note that recent reports indicate that PDE5 is highly expressed in the remodeled human right ventricle, raising the possibility that sildenafil therapy may improve right ventricular function.

Sildenafil is also an attractive therapeutic option for infants with chronic pulmonary hypertension due to congenital diaphragmatic hernia or bronchopulmonary dysplasia because it can be given orally, and over longer periods of time with apparent low toxicity. In a rat model of hyperoxia-induced BPD, chronic use of sildenafil decreased medial wall thickness and RVH and improved lung alveolarization. A clinical case series examined the effect of oral sildenafil in 25 infants and children (<2 years of age) with pulmonary hypertension due to chronic lung disease (mostly BPD). Most patients showed some improvement after a median treatment interval of 40 days, and the majority of infants were able to wean off iNO. Five patients died after initiation of sildenafil treatment, but none died from refractory pulmonary hypertension or right heart failure. A similar approach might benefit some infants with chronic pulmonary hypertension associated with lung hypoplasia . These important pilot studies suggest that sildenafil is well tolerated in infants with pulmonary hypertension due to chronic lung disease, and paves the way to further studies in this especially challenging population.

An interesting recent study showed that in a rat model of congenital diaphragmatic hernia, antenatal administration of sildenafil to the dam reduced PDE5 activity and increased cGMP, and produced striking reductions in the vascular findings of persistent pulmonary hypertension . This is the first indication that pulmonary hypertension can be treated before birth, and will likely open up a productive line of investigation in antenatal diagnosis and treatment.

Tadalafil is a longer-acting selective phosphodiesterase type 5 inhibitor recently approved by the FDA for treatment of adult pulmonary hypertension. A recent retrospective report examined pediatric patients with pulmonary hypertension that were converted from sildenafil to tadalafil to achieve once-daily dosing at 1 mg/kg/day . Interestingly, in addition to the ease of administration, about half of the patients exhibited significant improvements in mean pulmonary arterial pressure and pulmonary vascular resistance index measured at heart catheterization. Side effect profiles were similar for the two agents. These results indicate that tadalafil may be safe for pediatric patients with PAH and has the advantages of only once-daily dosing.

Prostanoids

A complementary vasodilatory pathway in the fetal lung is mediated by prostacyclin (PGI_2) and cAMP (Figure 1). Prostacyclin is a metabolite of arachidonic acid that is endogenously produced by the vascular

endothelium. The vascular effects of PGI2 are mediated through its binding to a membrane IP receptor which activates adenylate cyclase and increases cAMP, which triggers smooth muscle cell relaxation through reducing intracellular calcium concentrations. Prostacyclin production appears to increase in late gestation and early postnatal life, indicating its importance in promoting the neonatal pulmonary vascular transition. Pulmonary hypertension in both neonates and older children is characterized by an decrease in the biosynthesis of prostacyclin accompanied by increased synthesis of the vasoconstrictor thromboxane A_2 . Furthermore, the PGI_2 receptor (IP) is decreased in adult and pediatric patients with pulmonary hypertension, and animal studies point to its contribution to altered vasodilation in PPHN . Prostacyclin is a potent vasodilator in both the systemic and pulmonary circulations and also has anti-platelet effects. Prostacyclin was one of the earliest pulmonary vasodilators used for clinical treatment of pulmonary hypertension, and was approved by the FDA in 1995 for the treatment of severe chronic pulmonary arterial hypertension.

PDE3 Inhibition - Milrinone

Similar to the NO–cGMP pathway, prostacyclin–cAMP signaling is regulated by cAMP-hydrolyzing PDE isoforms such as PDE3 and PDE4. We recently reported that PDE3A expression and activity in the resistance pulmonary arteries increase dramatically by 24 h after birth . These results were unexpected, as we would have predicted that PDE3 activity would decrease after birth to facilitate cAMP accumulation, similar to the patterns reported for PDE. We also observed that addition of inhaled nitric oxide dramatically increased PDE3 levels, which suggests that inhibition of PDE3 activity might enhance the vasodilatory effects of iNO/cGMP signaling in addition to its expected effects on the cAMP pathways .

Endothelin Receptor Antagonists - Bosentan

Endothelin-1 (ET-1) is a 21 amino acid protein formed by serial enzymatic cleavage of a larger prepropeptide to the vasoactive form, and is one of the most potent vasoconstrictors described in the pulmonary vasculature . ET-1 is principally produced in endothelial cells in response to hypoxia, and is known to promote endothelial cell dysfunction, smooth muscle cell proliferation and remodeling, as well as inflammation and fibrosis . ET-1 binds to two receptor subtypes, ET receptors A and B, and the binding of ET-1 to the ETA receptor on smooth muscle cells produces vasoconstriction. Increased ET-1 production and altered ET receptor activity have been consistently reported in neonatal and adult animal models of pulmonary hypertension, and lung ET-1 expression and plasma ET levels were elevated in severe PAH in adults . In several animal and human studies, plasma endothelin-1 concentrations are consistently increased during and following cardiopulmonary bypass, suggesting a role for endothelin-1 in the pathophysiology of cardiopulmonary bypass-induced pulmonary hypertension . Endothelin-1 is believed to play a role in the pathogenesis of neonatal pulmonary hypertension, and endothelin blockade augments pulmonary vasodilation . A recent prospective examination of 40 newborns with congenital diaphragmatic hernia and poor outcome also indicated that plasma ET-1 levels were highly correlated with the severity of pulmonary hypertension.

CONCLUSION

The present robust meta-analysis suggests that prostanoids, ERAs, and PDE5 inhibitors all confer a therapeutic benefit. Of these, only intravenous prostacyclins has a proven survival benefit, particularly in patients with severe disease. Non-intravenous prostanoids, ERAs, and PDE5 inhibitors have not been shown to improve mortality, however these agents have not been adequately studied in patients with the most severe disease. Additional studies will be required to determine the optimal dose and duration of these therapies in exacting the best possible outcomes at the lowest cost and risk of adverse events for patients

REFERENCES

[1] Khaled MA*, AsifAnsari Md., Anwar HA Md., Analysis of Prevalence, Risk Factor and Pharmacotherapy of Hypertension in Outpatient, Page No: 64

[2] Christopher J Ryerson, Shalini Nayar, John R Swiston, and Don D Sin , Pharmacotherapy in

pulmonary arterial hypertension: a systematic review and meta-analysis

[3] Robin H. Steinhorn, MD, Pharmacotherapy of Pulmonary Hypertension

[4] Levin DL, Rudolph AM, Heymann MA, et al. Morphological development of the pulmonary vascular bed in fetal lambs. Circulation. 1976;53:144–151. [PubMed] [Google Scholar]

[5] Cerro MJ, Abman S, Diaz G, et al. A consensus approach to the classification of pediatric pulmonary hypertensive vascular disease: Report from the PVRI Pediatric Taskforce, Panama 2011. Pulm Circ. 2011;1:286–298. [PMC free article] [PubMed] [Google Scholar]

[6] Simonneau G, Galie N, Rubin LJ, et al. Clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2004;43:5S–12S. [PubMed] [Google Scholar]

[7] Simonneau G, Robbins IM, Beghetti M, et al. Updated clinical classification of pulmonary hypertension. J Am Coll Cardiol. 2009;54:S43–S54. [PubMed] [Google Scholar]

[8] Humbert M, McLaughlin VV. The 4th World Symposium on Pulmonary Hypertension. Introduction. J Am Coll Cardiol. 2009;54:S1–S2. [PubMed] [Google Scholar]

[9] Lammers AE, Adatia I, Cerro MJ, et al. Functional classification of pulmonary hypertension in children: Report from the PVRI pediatric taskforce, Panama 2011. Pulm Circ. 2011;1:280–285. [PMC free article] [PubMed] [Google Scholar]

[10] Slaughter JL, Pakrashi T, Jones DE, et al. Echocardiographic detection of pulmonary hypertension in extremely low birth weight infants with bronchopulmonary dysplasia requiring prolonged positive pressure ventilation. J Perinatol. 2011;31:635–640. [PubMed] [Google Scholar]

[11] An HS, Bae EJ, Kim GB, et al. Pulmonary hypertension in preterm infants with bronchopulmonary dysplasia. Korean Circ J. 2010;40:131–136. [PMC free article] [PubMed] [Google Scholar].