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Abstract

There has been an evolution in the understanding of the treatment of hypertension in children and adolescents over the past decade. This has been fueled in part by the increased attention paid to the clinical problem, given the increasing numbers of children and adolescents being diagnosed with this condition. There has also been a growing number of clinical trials performed and completed that demonstrate the blood pressure (BP)-lowering effects of antihypertensives and the side effect profiles of these medications, and that has led to FDA-labeling of many antihypertensive medications for use in children and adolescents. However, none of these trials has provided definitive data on the optimal first line agent for this patient population. Clinical experience and other approaches discussed in this review are still necessary to guide treatment of hypertension in the young. The quest for the optimal antihypertensive agent is just beginning, and it is going to take some extraordinary effort to reach that goal.

Keywords

Hypertension; Blood pressure; Pediatric; Children; Adolescents; Antihypertensive medication; Treatment

Introduction

There are a number of comprehensive guidelines that discuss not only treatment of high blood pressure (BP), but also the evaluation of the pediatric patient with this condition. In the US, the most recent guidelines that are available that review and discuss matters related to blood pressure in children and adolescents are in the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. The 4th Report was published in August 2004 by the National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents [1]. The intent of the report was to update clinicians about high blood pressure in children and adolescents, to provide recommendations based on available evidence, and to use consensus expert opinion when the evidence was lacking. In that published report, which was comprised of over 20 pages, about five pages were devoted to pharmacologic management of hypertension. Within those five pages were two pages of tables related to antihypertensive medications; however, it should be noted that no one class of antihypertensive agent was recommended as optimal initial therapy.

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Another comprehensive report on the management of high blood pressure in children and adolescents came from the European Society of Hypertension in 2009 [2]. Similar to the Fourth report, this document provides another set of guidelines that represent consensus among a number of specialists interested in the detection and control of high blood pressure in the pediatric population. In a more recent published review of the proceedings of another large working group, the Pediatric Cardiovascular Risk Reduction Initiative (PCVRRI) added a bit more insight to the discussion on treatment. That working group reported that between the publication of the 4th Report and the publication of the PCVRRI Report, there was only a modest amount of new data relative to the issue of blood pressure as a cardiovascular risk factor [3••]. Most of the new data related to results of clinical trials of antihypertensive agents in the pediatric age group.

While none of the recently published guidelines promotes a specific first line agent, they all point out the myriad of choices among the available agents. The primary question posed in this paper, of which first-line antihypertensive agent is optimal, is one for which there is a simple answer: an optimal agent is not yet available. Despite that, there will be an attempt to promote further discussion about the quest for an optimal agent.

Importance of Understanding Blood Pressure Measurements

Blood pressure is one of the vital signs assessed in a variety of clinical settings that range from primary care offices and clinics, to large scale screening and survey projects, to urgent care centers, and emergency departments. There are several things to consider when assessing the actual values obtained. The context in which the readings were obtained needs to be considered, and the method employed to measure/obtain the readings is also extremely important. An indirect measurement of blood pressure is most often obtained in an outpatient care setting (not an intensive care unit or cardiac catheterization laboratory), whether in the primary care office or the emergency department. The methods for measuring blood pressure indirectly include auscultatory methods (using aneroid manometry methods, or rarely mercury sphygmomanometry) and oscillometry. While these medical procedures seem rather simplistic in this high-tech world of 21st century medicine, the impact of improperly measuring blood pressure, or improper interpretation of the results, is not always appreciated. There are many sources that may be used to refresh a clinician's knowledge of the proper blood pressure measurement techniques, and they will not be reviewed here [1, 4]. It is important, however, to point out three key points:

1. properly functioning and well-calibrated equipment is the key to obtaining reliable blood pressure readings;
2. while oscillometry is readily available presently, in that method of indirect blood pressure measurement, mean arterial pressure (MAP) is directly measured, while systolic and diastolic blood pressure values are calculated; and
3. the 4th Report guidelines clearly state: "auscultation remains the recommended method of blood pressure measurement in children under most circumstances" [1].

Podoll et al. [5] compared differences in blood pressure measurements that were obtained in a standard practice vital sign station using oscillometry with those measured by trained personnel using the 4th Report recommendations and aneroid manometry, and they found some interesting results. Readings obtained in the vital sign station were predominantly higher, and only 12 % differed by < 5 mmHg. The mean differences they found in that group of 390 children at 580 visits were 13.2 ± 8.9 mmHg for systolic BP readings and 9.6 ± 7.6 mmHg for diastolic readings. Another study of triage BP readings obtained in an emergency department showed that such readings are rarely predictive of the actual presence of hypertension [6]. These findings underscore what is commonly seen in clinical practice and

the need to carefully reevaluate the patient's blood pressure readings when a diagnosis of hypertension is being entertained.

There is also some variability in measurement techniques and BP readings in specialty settings. A survey of pediatric nephrologists in the United States and Canada about the evaluation and management of hypertension found that techniques for measuring casual blood pressure by the respondents to the survey varied widely. The most common technique reported was oscillometry, but they did report the use of mercury column and aneroid sphygmomanometers as well [7]. More recently, data from the Chronic Kidney Disease in Children Study has shown that oscillometric devices may overestimate both systolic and diastolic BP compared to the auscultatory technique, potentially affecting the classification of children as hypertensive or normotensive [8].

These studies highlight that understanding the factors that can affect blood pressure measurements and ensuring that reliable, accurate measurements are obtained is the first step in accurately diagnosing and treating hypertension. Keeping in mind that the primary focus of this article is treatment of hypertension, the reader is referred to several recent comprehensive reviews of the evaluation of elevated blood pressure in children and adolescents [1, 2, 9, 10, 11].

Treatment of Hypertension

Generally, there is a two-pronged approach to the management or treatment of hypertension in all patients. These include non-pharmacologic measures, often referred to as therapeutic lifestyles changes (TLC), and pharmacologic measures [1, 9, 12]. There are a number of reviews focusing on the non-pharmacologic measures and treatment of hypertension, and current guidelines make the case that every child and adolescent with hypertension would benefit from non-pharmacologic measures of dietary guidance, enhanced physical activity, limitations in sedentary activities, stress reduction and avoidance of illicit drug and tobacco use. These components of a treatment program take a fair degree of motivation or 'buy-in' on the part of not only the patient, but often also the patient's family, yet can be effective in reducing blood pressure [9–14].

The second approach to treatment is use of antihypertensive medications. In general, most pediatric guidelines, such as those found in the 4th Report, are fairly conservative with respect to medication use, and therefore include a limited list of indications for the use of antihypertensive medications in children. The recommended indications from the 4th Report are listed in Table 1 [1]. The final indication is a bit vague, especially as it relates to the issue of 'persistence", i.e. six months? One year? This may depend upon the insights gleaned from interactions with the patient and family, and the level of motivation of the patient and family should also be taken into account. Some families become very motivated to implement improved dietary habits and exercise when medication use is considered, thus making the discussion of potential drug therapy a wake-up 'call to action.' Given the familial nature of hypertension, to a great degree, the suggestions made for the child or adolescent patient with hypertension may have spin-off effects of improved habits for adults in the household, yet there is no data and only anecdotal experience to support that. Others see it as just a matter of time to have the need for antihypertensive medications for a child or adolescent, based on experiences within that patient's family.

While the 4th Report does provide some guidance to clinicians for the use of antihypertensive medications, the guidelines are a bit vague and non-directive with respect to selection of an initial agent. This is much different than adult guidelines such as the JNC-7, which provides clear clinical practice recommendations for the treatment of hypertensive adults that is based upon clinical trial evidence conducted in large numbers of

patients [15]. An evidence base like that does not exist for children and adolescents, and what works for adults may not necessarily work as well for younger patients. Since mechanisms of blood pressure elevation and pharmacokinetic differences can vary with age, different classes of antihypertensive medications might be chosen for children and adolescents. Until such time as clinical trial data are available to compare amongst the various classes of antihypertensive agents, several of them may potentially be first-line agents. Those include angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers, beta blockers, calcium channel blockers, and diuretics. Thus, the tables of antihypertensive medications that are available in the Report generally provide the clinician with helpful information such as starting dose, dosing interval, information about whether or not a medication has Federal Drug Administration (FDA) labeling and some other comments; but do not recommend when to select a specific agent. Instead, the general advice provided is to choose a medication from the number of different classes of antihypertensive agents, titrate the dose against blood pressure and monitor for side effects [1]. Use of combination therapy is recommended if blood pressure control cannot be achieved with a single agent.

As stated in the 4th Report and in the report of the PCVRRI, there are now a number of medications that have been studied in children and adolescents from a pharmacokinetic and pharmacodynamic perspective and also for safety and efficacy, most often compared against placebo. Yet, these trials have been conducted using single agents in isolation, looking to show a blood pressure-lowering effect without testing amongst agents or between classes of medications for comparative effectiveness or safety [1, 3••]. The one exception to this rule is a recent trial comparing valsartan to enalapril, which showed similar efficacy of the two agents [16]. The results of this trial may help to inform future pediatric guidelines.

As hypertensive pediatric patients are evaluated, there may be underlying renal, cardiac or endocrine disease discovered as leading to or contributing to the elevated blood pressure. Those underlying diseases may help to guide the choice of antihypertensive agent. This is similar to the ‘compelling indications’ approach in the JNC-7 guidelines [15••]. Alternatively, there may be a good reason to avoid certain agents. With underlying chronic kidney disease, an agent that affects the RAAS axis (such as an ACE-inhibitor or ARB) would be appropriate. A patient with either type 1 or type 2 diabetes may also benefit from an ACE-I or ARB to prevent the progression of diabetic renal disease. Beta-blockers seem to be an appropriate choice when hypertension persists following repair of coarctation of the aorta. On the other hand, one should avoid the use of beta-blockers in the child or adolescent with asthma or diabetes.

While using a pathophysiologic approach to guide the choice of antihypertensive medication is advocated by some authors, it would require some investigation to determine the mechanism of hypertension in the individual patient. Newer noninvasive techniques to assess hemodynamic parameters are not readily available in most outpatient settings [17]. Another approach to guide initial therapy is based on renin levels. This approach has been used more extensively in adults, but it has not been studied in children; its general guidelines would support the use of an anti-renin agent in those with a high measured plasma renin level. Those with low measured renin level would be considered to have volume overload, and a diuretic would be prescribed [18, 19].

With now well over a decade of clinical trial experiences with a number of antihypertensive agents over a relatively large group of children with hypertension, some key concepts have emerged. One is that antihypertensive medications are effective at lowering blood pressure in children and adolescents. Flynn recently reviewed the currently available pediatric data from clinical trials that have been done since the passage of the Food and Drug

Administration Modernization Act (FDAMA) [20]. In that paper, not only does he describe the results of these studies, which have resulted in a dramatic increase in the availability of pediatric-labeled antihypertensive medications, but he also points out their shortfalls. Not all of the studies resulted in pediatric labeling, and these studies were generally of short duration and not designed to assess clinical outcomes. An updated table with dosing guidelines for various classes of antihypertensive agents is also included [20].

Another key point is that children and adolescents seem to tolerate these medications quite well, and the profiles of side effects are either similar to, or possibly better than, those seen in adult populations. An interesting example of this was noted in the PATH-1 clinical trial that studied amlodipine, in which there was less peripheral edema reported than what has been seen in adults using that agent [21, 22••].

A third point is that these medications appear to attenuate some of the surrogate markers of cardiovascular disease and they also seem to improve the outcome of children with chronic kidney disease (CKD) [23]. Some examples of this include the report by Seeman et al., showing regression of left ventricular hypertrophy (LVH) over 6 months in a small group of children with hypertension and LVH using the ACE-I ramipril. The group studied had a preponderance of hypertension secondary to renal disease (76 % with secondary vs. 24 % with essential hypertension) [24]. The ESCAPE trial also used ramipril to study the renoprotective effects of ACE-inhibition and intensified blood pressure control on the progression of chronic kidney disease (CKD), using treatment goals based on ambulatory BP monitoring (ABPM). The authors concluded that intensive lowering of blood pressure reduced the rate of progression of renal function decline in children with CKD-associated hypertension. Additionally, they noted that the BP lowering and antiproteinuric effects of ramipril were greatest in more severely hypertensive and proteinuric children [25••].

Is there an optimal agent for use in hypertensive children?

When considering the optimal first-line agent antihypertensive medication for a child or adolescent with hypertension, many things need to be considered, and it is not clear that there could ever be only one ‘optimal’ agent. Considering the issue in general, aspects of the agent that might be considered ‘optimal’ are included in Table 2. Quite frankly, it seems unrealistic to expect that there will ever be just one ‘optimal’ agent for pediatric hypertension. What might be optimal for one patient may not be optimal for another. Many issues have to be taken into account when considering which agent to use as a first-line. Clinicians who care for children and adolescents with hypertension need to be familiar with a selection of agents, probably at least one from each major drug class, to be able to provide optimal treatment for their patients.

Selection of the optimal first-line agent for a given patient will generally be based on information obtained from the patient. Clearly, therapeutic lifestyle changes should be encouraged, but when the time comes to choose an antihypertensive medication, the patient’s individual circumstances need to be considered. For most children and adolescents, it seems prudent to choose a longer acting agent to attempt to enhance adherence. A medication that is used once daily can be incorporated into the patient’s daily routine, either in the morning or at bedtime. One might suggest taking the medicine after brushing one’s teeth or at the breakfast table. Another advantage to once-daily dosing is not having to take medication at school. Long-term adherence to medication, as well as the habits of increased activity and a healthier diet are challenging, and it takes a great degree of motivation to continue with these activities.

In a recent review, Blowey provides useful insights about where things need to go relative to this issue. The date that we currently have relative to available medications is a starting

point. From there, additional clinical trials need to be conducted that can compare among the available agents. The studies will not be easy to do, nor will they be inexpensive to conduct, as they will need to be sufficiently powered to detect differences in a variety of factors that impact response to these medications, such as demographics, genetic influences, and developmental differences [23]. Another recent report by the Lewin Group attempted to put the impact of efforts to improve FDA-approved pediatric labeling on the care for children and adolescents with hypertension, and they concluded that despite these efforts, there remain many drugs that do not have pediatric labeling, and that additional efforts are necessary to close the gap between the medications that are labeled and indicated for pediatric use and actual usage [26].

Conclusion

Relative to the care of the child or adolescent with hypertension, significant advances have been made in the establishment of pediatric labeling for guidance on the use of antihypertensive medications. The search for the optimal first-line agent has in many ways just begun. Now that some medications are FDA-approved for use in children and adolescents, it is time to take the next steps to compare among available agents and among classes of agents to get to the next level of evidence. That level will be one on which there is established guidance for safe, effective and tolerable antihypertensive medications that are affordable to those who need it. Then, and only then, might we find the answer to the question of which first-line antihypertensive agent is optimal.

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Table 1

Indications for using antihypertensive medications in children/adolescents

Patients with hypertensioHTNn who are symptomatic
Patients with secondary hypertensionHTN
Patients with findings of Target Organ Disease
Patients with Diabetes mellitus, type I or II
Patients with persistence of elevated BP blood pressure, despite efforts at therapeutic lifestyle change

Table 2

Characteristics of the optimal first-line antihypertensive medication for children/adolescents

Effectiveness: for lowering BP blood pressure and for preventing long term sequelae
Short-term safety
Long-term safety
Ease of administration
Palatability
Long-acting formulations
Availability
Affordable