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The Role of Serotonin Modulators in the Treatment of Irritable Bowel Syndrome

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Introduction

Irritable bowel syndrome (IBS) is a chronic dysfunctional disorder of the gastrointestinal tract exhibiting varying symptoms, including abdominal pain, bloating, constipation, diarrhea, and/or altered bowel function. Approximately 20% of the US adult population report symptoms consistent with IBS, and it ranks second only to the common cold as the most common cause for work absence.[1-3] IBS predominantly affects females, with a 2:1 ratio as compared to males.[2] In 1995, the annual costs directly associated with IBS were estimated to be 8 billion dollars.[1]

Although the exact pathophysiology is unknown, postulated mechanisms include: GI tract dysmotility, psychological disturbances, inflammatory processes, and altered visceral sensitivity. Also, there is mounting evidence that IBS can occur after a patient has had infectious gastroenteritis. It is thought that up to 25% of those admitted for such diagnosis develop IBS-like symptoms.[4] IBS as a function of a neurological bowel disease has recently come to the forefront of research.

Irritable bowel syndrome can be divided into 3 main categories: diarrhea predominant, constipation predominant, or mixed constipation-diarrhea symptoms.[4] The criteria for diagnosis, outlined in 1999, state that if a patient experiences abdominal pain for 12 or more weeks in a 1 year time period and has features of two or more of the following: a) Pain relieved upon defecation, b) Onset associated with a change in frequency of stool, or c) Onset associated with a change in form (appearance) of stool, the patient can be diagnosed with IBS.[5]

Fortunately, most irritable bowel syndrome patients require no pharmacotherapy to correct their symptoms, since diet modification and lifestyle changes are usually enough to curb effects of IBS. Current pharmacotherapeutic modalities of therapy for IBS include fiber intake of 25-30g/day and mild osmotic laxatives for constipation predominant; anticholinergics, opioids including loperamide for diarrhea predominant; and antidepressants or antispasmodics to treat the pain associated with IBS. Although these treatments are effective in the majority of patients, there remains a small subgroup of patients that fail to respond to these therapeutic interventions.

Lotronex® (alosetron hydrochloride) and Zelnorm® (tegaserod maleate) are serotonin receptor modulators that are used in the treatment of resistant IBS symptoms. Serotonin's role in the GI tract has been well described.[4] Roughly 95% of all of the body's serotonin (5-HT) is located in the gut, with 10% of that in enteric neurons and the remaining 90% located in the enterochromaffin cells. Mainly 5-HT_3 and 5-HT_4 receptor subtypes populate the gut, both of which seem to exert the most clinically relevant effects of 5-HT. It is these 2 receptor subtypes that alosetron and tegaserod modulate to exert their clinical effect. This article will discuss the pharmacology, clinical trials, adverse effects, monitoring parameters, special prescribing restrictions, dosing and cost associated with each medication.

Lotronex® (alosetron)

Alosetron is a selective 5-HT_3 receptor antagonist made by GlaxoSmithKline (GSK). The Food and Drug Administration (FDA) originally approved it on February 9, 2000.[6] After approval, while in post marketing surveillance, cases of ischemic colitis that resulted in hospitalizations, surgery, and deaths were found to occur as a result of alosetron therapy. Due to these reports, GSK issued a voluntary recall on November 29, 2000. During the 2 years alosetron was off the market many women continued to inquire about obtaining the medication, as alosetron was the only medication that brought them relief.[7] Fortunately, after new research supported its continued use, GSK submitted an sNDA, which the FDA approved for alosetron's reintroduction to the market with restrictions on June 7, 2002.[7,8] These restrictions are described in a later section. Alosetron is available as a 1 mg oral tablet, and is indicated for women only with severe diarrhea predominant irritable bowel syndrome that is resistant to other treatment modalities. Alosetron should not be prescribed to men.

Pharmacology

5-HT_3 receptors in the enteric neurons of the GI tract mediate visceral pain, colonic transit and GI secretions. Activation of these receptors results in depolarization of myenteric neurons, which in turn release acetylcholine and induce fast excitatory postsynaptic action potentials. Inhibition of these receptor sites increases colonic transit time without increasing orocecal transit time, increases basal jejunal water and sodium resorption, and increases colonic compliance. This results in a decrease of diarrhea associated with irritable bowel syndrome.

Pharmacokinetics

Alosetron is rapidly absorbed after oral administration, with absolute bioavailability around 50%. Although absorption is decreased by 25% when administered with food, it may be given with or without food. Alosetron is extensively metabolized by the body, primarily by CYP 2C9 (30%), 3A4 (18%), and 1A2 (10%); and roughly 7% is recovered unchanged in the urine.[6] Alosetron does not affect the CYP isoenzyme's ability to metabolize other drugs in vivo, and because no one CYP enzyme is responsible for metabolism, drug interactions involving the CYP system are not clinically significant.[9] Alosetron is rapidly eliminated, with an estimated half-life of 1.5 hours. Pharmacokinetic parameters are not clinically affected by hepatic or renal dysfunction.[6] However, in some studies, alosetron concentrations were elevated 40% in women over 65 years compared to younger adults. Alosetron has not been studied in the pediatric population.

New Restrictions on Prescribing

As part of the agreement to allow alosetron to be remarketed GlaxoSmithKline had to develop a risk management program and a prescribing program to enroll physicians who wish to prescribe alosetron.[8] To enroll in the prescribing program, physicians must attest that they are willing and able to diagnose and treat IBS, diagnose and manage ischemic colitis, diagnose and manage constipation, understand the information presented in the package insert, the Medication Guide, and Patient-Physician Agreement. The physician must also educate the patient on the risks and benefits of alosetron and obtain the patient's signature on the Patient-Physician Agreement form, sign it, place the original in the patient's medical record and give a copy to the patient. The physician must report all adverse events to Medwatch, and affix the prescribing program stickers to all prescriptions. All forms for enrollment and education may be obtained from GSK or www.lotronex.com or by calling 1-888-825-5249.[10-12]

Alosetron may only be prescribed to women with severe diarrhea-predominant IBS who have failed to respond to conventional IBS therapy. In addition, the IBS symptoms must have lasted for a minimum of 6 months.

Clinical Trials

In a randomized, placebo-controlled trial, the efficacy and safety of alosetron was tested in 647 female patients with diarrhea predominant IBS. Male patients were not studied, as earlier clinical trials demonstrated less efficacy for male patients. Patients were randomly assigned to either alosetron 1 mg twice daily (n=324) or placebo (n=323) for 12 weeks, followed by a 4-week post-treatment period. Adequate relief of abdominal pain and discomfort

were the primary endpoints, while stool consistency, stool frequency, and urgency were secondary endpoints. As compared to the placebo group, a greater percentage of patients on alosetron reported adequate relief for all 3 months of treatment (41% vs. 29%). Alosetron also significantly reduced urgency and stool frequency, and increased stool firmness. Constipation was the most commonly reported side effect in the alosetron group as compared to the placebo group (30% vs. 3%).[13] The authors concluded that alosetron was efficacious and well tolerated in alleviating pain and bowel related symptoms in this population of women with IBS.

Furthermore, in a subset analysis of the quality of life scores from the above study population, alosetron showed a significant improvement on all 9 IBSQOL scales compared to placebo ($p<0.05$).[14] The authors concluded that, in addition to alleviating bowel related symptoms, alosetron improved quality of life scores for women with diarrhea predominant IBS.

In another randomized, double blind, placebo controlled trial; alosetron 1mg bid (n=72) was compared to placebo (n=80) in a 12 week trial in both men and women. Improvement in adequate relief was the primary endpoint of this study. Alosetron significantly increased the proportion of females, but not males, reporting adequate relief ($p<0.05$). Stool frequency, consistency, and percentage of days with urgency improved over placebo ($p<0.05$).[15] It is not known why male patients do not have an adequate response to alosetron.

Dosing

Because of new restrictions set forth by the FDA, patients should be initially prescribed alosetron 1mg daily. Upon reevaluation at 4 weeks, if the patient is still experiencing severe IBS symptoms with no evidence of intolerability (constipation, colitis), the dose may be increased to 1 mg twice daily.

Adverse Events

The FDA has placed a black box warning on alosetron explaining the risk of ischemic colitis and serious complications of constipation that have resulted in hospitalizations, blood transfusions, surgery, and death. Alosetron should be discontinued in patients who develop constipation or symptoms of ischemic colitis. In all clinical trials of alosetron, the most commonly described adverse event was constipation, and was the most common reason for early exit of the clinical trial. Table 1 summarizes the adverse events experienced by patients in clinical trials.[6,16] Constipation was the only adverse event that was significantly higher in the alosetron group compared to placebo.

Table 1. Commonly described adverse events

Adverse Event	Placebo	Alosetron
Constipation	5%	32%*
Diarrhea	11%	9%
Abdominal Pain	7%	10%
Nausea	5%	6%
Headaches	8%	10%
Urinary Tract infection	4%	5%
Malaise and fatigue	6%	3%
Musculoskeletal pain	8%	7%
Cardiovascular (any event)	4%	6%

* Significantly different than placebo ($p<0.001$)

Additional reported adverse events include tachyarrhythmias, breathing disorders, hypnagogic effects, anxiety, sweating, and urticaria. However, none of these were significantly different than placebo.

Drug Interactions

Although the CYP system is heavily involved in the metabolism of alosetron, in vitro and in vivo metabolic probe studies have shown that alosetron does not inhibit CYP enzymes 2C9, 2C19, 3A4, or 2D6 at normal doses. However, In an in vivo metabolic probe study, alosetron produced a 30% inhibition of both N-acetyltransferase and CYP1A2. Although this has not been studied yet, this could affect concentrations of isoniazid, procainamide and hydralazine. No effect on the metabolism of theophylline, alprazolam, or ethinyl estradiol has been observed.[6,9] Also, the effects of inducers or inhibitors on the CYP system and alosetron pharmacokinetics has not been studied. Agents that affect GI motility, such as antidiarrheals and laxatives, could alter the efficacy of alosetron in patients and should be avoided.

Cost of therapy

The retail cost of alosetron for one month of therapy (30 tablets) ranged from $76.98 to $77.69.

Zelnorm® (tegaserod)

Tegaserod is a partial 5-HT_4 agonist made by Novartis Pharmaceuticals Corporation. Tegaserod was approved by the FDA on July 24, 2002 for the short-term treatment of women with constipation predominant IBS. Efficacy has not been established in men to date. Tegaserod is an aminoguanidine indole derivative of serotonin, and is available as tegaserod maleate in 2 mg or 6 mg tablets. Tegaserod, in pre-approval clinical trials, was shown to be effective in treating abdominal pain, altered bowel habit (consisting of decreased stool frequency, hardened stool consistency, straining) and bloating associated with constipation predominant IBS in women.[17]

Pharmacology

Tegaserod is a 5-HT_4 partial agonist that has high affinity for the 5-HT_4 receptor subtype, and moderate affinity for the 5-HT_1 receptor. Intestinal $5HT_4$ receptors are involved in motor, sensory and secretory functions. It has no appreciable affinity for the 5-HT_3 or the dopamine receptor.[18] Tegaserod, upon binding and activation of the 5-HT_4 receptor, triggers the release of other neurotransmitters from sensory neurons, primarily calcitonin gene-related peptide. These actions result in stimulation of the peristaltic reflex and intestinal secretion, and inhibition of visceral sensitivity. In vivo studies also showed that tegaserod normalized impaired motility throughout the gastrointestinal tract. As a partial agonist, tegaserod has a lower likelihood of inducing receptor desensitization compared to full agonists, theoretically lowering the likelihood for tachyphylaxis or tolerance.[19]

Pharmacokinetics

The pharmacokinetics of tegaserod are dose proportional over the 2 to 12 mg dose range. Tegaserod's absolute oral bioavailability is approximately 10% when administered to fasting subjects. Administration with food decreases oral absorption by approximately 50%, therefore it is recommended for administration before meals. While gender does not affect the area under the plasma concentration versus time curve (AUC), the AUC in elderly female subjects was 40% larger than young female subjects ($p<0.002$).[20] However, this effect was not judged to be clinically significant because this was within the variability of tegaserod's pharmacokinetic parameters and because of the shallow dose-response curve of tegaserod.

Tegaserod is roughly 98% protein bound, primarily to alpha1-acid glycoprotein. The estimated terminal half-life is 11 hours. Tegaserod is metabolized via 2 pathways. The first is presystemic acid catalyzed hydrolysis in the stomach, which is followed by subsequent oxidation and conjugation producing an inactive metabolite. The second pathway is direct glucuronidation. Approximately two-thirds is excreted unchanged in the feces, and the remainder is excreted as the glucuronide metabolite in the urine.[19] Mild and moderate renal and hepatic impairment did not significantly affect the pharmacokinetic parameters of tegaserod.[21] Tegaserod has not been studied for use in severe renal or hepatic impairment, and therefore should not be used in this population.

Clinical Trials

Three phase III clinical trials were conducted to assess the efficacy and safety of tegaserod. Two of the studies had a fixed dose regimen of 6 mg twice daily, while the third study used a dose titration design. Efficacy was determined based upon patient response to a specific test called the Subject's Global Assessment of Relief and the Subject's Global Assessment of Abdominal Pain and Discomfort. A patient was considered a responder if they were assessed as being completely relieved of symptoms for at least 2 of the 4 weeks at each assessment, or if they were at least somewhat relieved for each of the previous 4 weeks. The results are summarized in table 2. The differences in response rates vs. placebo were greater at the end of 4 weeks than at the end of 12 weeks. Tegaserod produced a clinically effective means of reducing constipation due to IBS.[18,19]

In another randomized, double blind, placebo-controlled trial, tegaserod was evaluated against placebo for 12 weeks. Two hundred ninety nine patients were randomized to 2 mg twice daily, 294 to 6 mg twice daily, and 288 to placebo. The Subject's Global Assessment of Relief and the Subject's Global Assessment of Abdominal Pain and Discomfort were used to determine efficacy. In females, the responder rates for the Subject's Global Assessment of Relief at the end of 12 weeks were 37.7%, 38.9%, and 27.5% for the 2 mg, 6 mg, and

Table 2. Percentage of patients responding to therapy, defined as symptoms completely relieved for 2 of 4 weeks, or somewhat relieved for 4 weeks [18,19]

Study	End of 4 weeks (portion of responders)			End of 12 weeks (portion of responders)		
	Tegaserod 6mg bid	Placebo	Difference (95% CI)	Tegaserod 6mg bid	Placebo	Difference (95% CI)
1	31%	17%	14%(6-21%)	39%	28%	11% (3-20%)
2	35%	22%	13% (8-17%)	44%	39%	5% (0-10%)
3	34%	20%	14% (6-22%)	43%	38%	5% (-4-14%)

placebo groups respectively. The differences between the each group and placebo were statistically significant (p=0.017 for the 2 mg and p=0.008 for 6 mg group after correcting for center effect). Similar statistically significant results were seen in the Subjetc's Global Assessment of Abdominal Pain and Discomfort.[22]

In the premarketing clinical trials for tegaserod, Novartis was unable to enroll enough male patients to obtain the power to detect a statistically significant difference, hence the indication for women only. Currently, Novartis is studying tegaserod's efficacy in male patients.

Dosing

The recommended dosage for tegaserod is 6 mg twice daily before meals for 4 to 6 weeks. If the patient responds to therapy at 4-6 weeks, an additional 4-6 weeks can be added. Tegaserod's efficacy has not been studied in males, or in patients for use longer than 12 weeks.

Adverse Events

Diarrhea, abdominal pain, headache, flatulence, and fatigue were the most commonly reported adverse events in phase III clinical trials.[23] However, the only adverse events reported that were statistically more significant than placebo were diarrhea and headache.[24] Table 3 summarizes the percent of patients who experienced adverse events compared to placebo in phase III clinical trials.[18]

Other adverse events reported in phase III clinical trials include increase in abdominal surgery, primarily cholecystectomies, hypotension, angina pectoris, increased liver enzymes, and facial edema. However, none of these were attributed to tegaserod use.

Drug Interactions

In vitro drug-drug interaction data indicated that tegaserod did not affect the CYP isoenzyme system. As of now, tegaserod does not influence the metabolism of other medications. Drugs that potentially could interact with tegaserod include pro-kinetic agents increasing the risk of diarrhea, and antimuscarinics antagonizing the affects of tegaserod. Tegaserod should not be used in combination with other GI motility altering medications without careful monitoring.

Cost of Therapy

The retail cost for one month of therapy (60 tablets) of tegaserod 2 mg ranged from $154.78 to $178.39, while a month supply of the 6 mg tablets ranged from $156.36 to $178.39.

Conclusions

Serotonin modulators represent a new class of medications that can be used to treat IBS symptoms. While these agents can be effective in the treatment of symptoms associated with IBS, they are not the first line agents, and should be considered once the patient has failed to respond to conventional therapy.

Alosetron, a 5-HT_3 receptor antagonist, has been shown to be very efficacious in the treatment of severe diarrhea predominant IBS in women that have failed other therapies, but it must be monitored diligently. Alosetron should be discontinued in patients at the first sign of constipation or ischemic colitis.

Tegaserod, a 5-HT_4 receptor partial agonist, has been shown to be efficacious in the treatment of severe constipation predominant IBS in women at a dose of 6 mg twice daily. Although efficacy has not been established in males due to patient enrollment

Table 3. Adverse events occurring in >1% of patients

Adverse Event	Tegaserod 6mg bid (n=1,327)	Placebo (n=1,305)
Diarrhea*	9%	4%
Abdominal pain	12%	11%
Nausea	8%	7%
Flatulence	6%	5%
Headache*	15%	12%
Dizziness	4%	3%
Migraine	2%	1%
Accidental Trauma	3%	2%
Leg Pain	1%	<1%
Back Pain	5%	4%
Arthropathy	2%	1%

* Statistically significant versus placebo

problems, no evidence exists to show that tegaserod would not work in male patients. While tegaserod has not yet been shown to cause such serious complications as alosetron, it should also be monitored carefully in all patients.

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25. Prices based on 4 community pharmacies in the Gainesville, FL area.

Hepsera® (adefovir dipivoxil) is an acyclic nucleotide analog recently approved for the treatment of chronic hepatitis B in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases or histologically active disease. The usual adult dose is 10mg once daily; however, dosage adjustment is necessary in patients with renal dysfunction.

Update on The Guidelines for the Diagnosis and Management of Asthma

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Introduction

The treatment of asthma is not stagnant and unchanging. New information is constantly evolving as studies are conducted, reinforcing or disproving previous ideas and treatment strategies. Results from additional research have become available since 1997 when the previous Guidelines for the Diagnosis and Management of Asthma were published.[1] The National Asthma Education and Prevention Program Expert Panel Report (NAEPP EPR) released the Update on Selected Topics 2002[2] in June of this year, which is an up-to-date report of recommendations on the diagnosis and management of asthma.

The objective of this article is to compare the differences between the 1997 guidelines and the 2002 update. Unfortunately, the complete guidelines, with references to the actual studies recommendations are based on, will not be available until 2003. For practical purposes, the update is divided into three categories: medication, monitoring and prevention.

Medication

Long-Term Management of Asthma in Children Under the Age of Five

The update discusses changes in the requirements for initiation of long-term therapy in the treatment of asthma in infants and children younger than five years of age. The following summarizes the differences between the 1997 guidelines and the 2002 update.

1997 Guidelines

Long-term treatment should be initiated in infants and young children requiring symptomatic treatment more than two times per week or in children experiencing severe exacerbations less than six weeks apart.

2002 Update

Initiation of long-term asthma treatment should be considered in infants and children with more than three episodes of wheezing in the past year lasting more than one day AND the child's sleep having been affected AND the child having a high risk of developing asthma (defined as parental history of asthma OR physician diagnosed atopic dermatitis OR any two of the following: physician diagnosed allergic rhinitis, wheezing apart from colds, or peripheral blood eosinophilia). It is still recommended to initiate long-term treatment in infants and young children requiring symptomatic treatment more than two times per week OR in children experiencing severe exacerbations less than six weeks apart.

Recommendations for when to begin long-term asthma therapy have been broadened to include more conditions allowing for more children and infants to benefit from treatment.

Combination Therapy

Previously, when long-term therapy was initiated, inhaled corticosteroids were used as the treatment of choice. If asthma symptoms were not controlled, a long-acting beta-2 agonist was added. Initiating therapy with the combination of inhaled corticosteroids and a long-acting beta-2 agonist is now recognized as a more effective approach. One hundred thirty-six patients were enrolled in a randomized, double-blind, double-dummy, parallel group clinical trial comparing salmeterol 21 ug, fluticasone 44 ug, fluticasone 110 ug, salmeterol 21 ug PLUS fluticasone 44 ug, salmeterol 21 ug PLUS fluticasone 110 ug, and placebo. Results showed the greatest improvement in asthma signs and symptoms in the combination therapy groups. Forced expiratory volume (FEV) was significantly improved for the higher-dose fluticasone treatment group and for both of the combination treatment groups when compared to placebo. In addition, the FEV significantly improved more in the combination treatment groups when compared to the monotherapy group. A significant decrease in patient reported asthma symptoms and number of nighttime awakenings and a significant increase in the num-

ber of days without asthma symptoms was observed in the combination treatment groups compared to the monotherapy treatment groups. This study supports the recommendation of initiating long-term therapy with the combination of inhaled corticosteroids and long-acting beta-2 agonists.[3]

Combination Therapy in Infants and Children Under the Age of Five

The preferred combination therapy has been redefined for the treatment of moderate persistent asthma in infants and children under the age of five. Low dose inhaled corticosteroids used in conjunction with long-acting inhaled beta-2 agonists is now the treatment of choice.

1997 Guidelines

The options for treatment of moderate persistent asthma in this age group include either medium-dose inhaled corticosteroids OR medium-dose inhaled corticosteroids used concomitantly with either nedocromil or theophylline. No preference was given to any of the combinations of treatment.

2002 Update

The preferred treatment of moderate asthma in this age group is low-dose inhaled corticosteroids used with long-acting inhaled beta-2 agonists OR medium-dose inhaled corticosteroids alone.

Based on evidence from studies, the NAEPP EPR now recommends initiation of combination therapy in the treatment of moderate persistent asthma in infants and children under the age of five with low-dose inhaled corticosteroids and long-acting beta-2 agonists.

Combination Therapy in Adults and Children Over the Age of Five

The recommendation for combination therapy in the treatment of moderate persistent asthma in adults and children over the age of five has also been redefined. The options remain the same but the combination of inhaled corticosteroids used in conjunction with long-acting beta-2 agonists has now become the treatment of choice.

1997 Guidelines

The options for treatment of moderate persistent asthma include either medium dose inhaled corticosteroids OR low to medium dose inhaled corticosteroids combined with one of the following: a long-acting beta-2 agonist OR sustained release theophylline OR long-acting beta-2 agonist tablets. No preference of treatment was noted in the 1997 guidelines.

2002 Update

The preferred treatment for moderate persistent asthma is low to medium dose inhaled corticosteroids AND a long-acting inhaled beta-2 agonist. The second-line treatment option is either medium dose inhaled corticosteroids as monotherapy OR the combination of low to medium dose inhaled corticosteroids with either a leukotriene modifier OR theophylline.

Based on evidence from studies, the NAEPP EPR now recommends initiation of combination therapy in the treatment of moderate persistent asthma in adults and children over the age of five with low-dose inhaled corticosteroids and long-acting beta-2 agonists.

Long-Term Effects of Inhaled Corticosteroids

The previous guideline's statement that "Inhaled corticosteroids improve health outcomes for children with mild or moderate persistent asthma, and the potential but small risk of delayed growth is well balanced by their effectiveness" has not changed in the 2002 guidelines but is now supported with more evidence. When the previous guideline was published, only short-term studies had been conducted. A multi-centered, double-blind, double-placebo, randomized controlled clinical trial followed 195 children for one year and found that beclomethasone (two puffs inhaled four times daily) did cause a decrease in growth. The slowed growth rate was found to affect pre-pubertal males more than females.[4] In a separate double-blind, placebo-controlled randomized clinical trial, 94 children between the ages of seven and nine were evaluated for the effect of beclomethasone on growth. This trial, which was conducted over 7 months, found a significant decrease in growth in

both males ($p<0.001$) and females ($p<0.008$) of one centimeter. This study concluded that the growth did not catch up following a four month wash-out period ($p=0.45$).[3] Two other studies did not find a detrimental effect on growth. The first study followed fifty-eight children for 4.9 years to evaluate the impact of beclomethasone and budesonide on growth. This study found a difference in growth based on asthma severity ($p=0.003$) and not based on treatment group (95% confidence interval of -4.2 to +2.9).[6] The second study was a meta-analysis of 21 trials comprising 810 patients. This analysis found "a significant tendency for beclomethasone to be associated with attaining normal stature" ($p=2.17$ E-13).[7] However, long-term effects of inhaled corticosteroids on growth rates were not established in any of these trials.

More long-term studies have now been conducted evaluating the effect of inhaled corticosteroids on growth in children. A prospective clinical trial followed 211 children over 9.2 years to determine the effects of budesonide on growth. This trial found a significant decrease in growth by one centimeter during the first year of treatment ($p<0.001$); however, final adult height was reached in most patients ($p<0.001$). Also, no association of decreased growth based on gender ($p=0.3$) was found.[8] In addition, studies show no harmful effects on bone density and no increase in the formation of cataracts or glaucoma.[9] Finally, inhaled corticosteroids were shown to have only a minor, if any, effect on the hypothalamic-pituitary-adrenal (HPA) axis function. (The studies these statements are based on will not be released until the official publication of the guidelines in 2003).

Use of Antibiotics

The 2002 guidelines are consistent with the 1997 guidelines stating that asthma is an inflammatory disease and antibiotics are not recommended as a treatment option. Antibiotics are only to be used in patients with other conditions such as fever or suspected underlying bacterial infection.

Monitoring

It is still encouraged to use written action plans in patients with moderate or severe persistent asthma and in patients with a history of severe asthma exacerbations. It is also still recommended to utilize peak flow monitoring as the basis for the written plan.

Prevention

The NAEPP EPR has reevaluated and updated the previous guideline's statements regarding the progression of asthma in children between the ages of five and twelve.

1997 Guidelines

Early treatment of mild persistent or moderate persistent asthma in children between the ages of five and twelve may help slow the progression of the disease process.

2002 Update

Treatment of mild persistent or moderate persistent asthma in children between the ages of five and twelve may provide asthma control but symptoms and airway hyperresponsiveness may return upon discontinuation of treatment.

NAEPP EPR now states that treatment of mild persistent and moderate persistent asthma in children between the ages of five and twelve does help control symptoms but does not cure the underlying disease. The symptoms of asthma will return upon stopping treatment.

Summary

The major updates to the 1997 Guidelines for the Diagnosis and Management of Asthma have been released. The primary categories of changes include medication usage, monitoring and prevention. Within the medication category the following changes were made: (1) when to initiate long-term treatment in infants and children, (2) use of low-dose inhaled corticosteroids in conjunction with long-acting beta-2 agonists as the combination therapy of choice in moderate persistent asthma, (3) increased evidence documenting the safety of inhaled corticosteroids, and (4) the inappropriateness of using antibiotics in the treatment of asthma. No changes were made in the category of monitoring; it is still recommended to utilize peak flow monitoring and written action plans in the treatment of moderate or severe persistent asthma. In the prevention category, it is now realized that early initia-

tion of treatment in mild to moderate persistent asthma in children aged five to twelve will not cure the disease, only maintain control of symptoms.

The publication of the complete 2002 Asthma Guidelines, including references to the studies the recommendations are based on, should be released sometime in 2003. Refer to www.nhlbi.nih.gov for further information.

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