Beta-2 agonist discussions in asthma and a review of current data

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ÖZET

Astımda beta-2 agonist tartışmaları ve mevcut verilere bakış

Güncel kılavuzlar doğrultusunda astım tedavisinde kontrol edici olarak ilk seçenek inhale steroidlerdir. Bununla birlikte özellikle hava yolu obstrüksiyonu bulunan pek çok hastada gerek semptom giderici olarak, gerekse ek kontrol edici ilaç olarak hava yolu düz kaslarında relaksasyona yol açan bronkodilatörlere ihtiyaç duyulmaktadır. Hem kısa etkili hem de uzun etkili beta-2 agonistler (SABA ve LABA) astımda kullanılan bronkodilatörler arasında ayrı bir öneme sahiptir. İyi bilinen yararlarına rağmen, son yıllarda LABA'ların güvenliliği üzerine artan sayıda makale yayınlanmıştır. Bununla beraber, LABA monoterapisi ile ilişkili olduğu bildirilen risk artışı, standart tedavi olarak LABA ile kombine inhale kortikosteroid alan hastalarda gözlenmemiştir. Astım mortalitesi dahil olmak üzere, riskler ile ilgili tartışma sürerken, inhale kortikosteroide LABA eklenmesinin yararları geniş şekilde dokümante edilmiştir. Farmakogenetik gelişmeler sayesinde, birçok çalışmada etkinlik ve güvenliliği gösterilmiş olan bu ilaçların bazı istenmeyen yan etkilerinin potansiyel genetik temeli olabileceğine de dikkat çekilmiştir. Sonuç olarak; LABA'lar inhale kortikosteroidler ile birlikte kullanıldığında, astımda semptomların giderilmesi ve akciğer fonksiyonlarının iyileştirilmesinde etkili ve güvenlidir; ancak, inhale kortikosteroid tedavisi yokluğunda LABA monoterapisi hiçbir şekilde uygulanmamalıdır. Uygun dozlarda inhale kortikosteroid kullanımına rağmen kurtarma tedavisine gereksinim duyan astım hastalarının tedavi rejimlerine düzenli bronkodilatör eklenmelidir.

Anahtar Kelimeler: *Astım, kısa etkili beta-2 agonist, uzun etkili beta-2 agonist, inhale steroid.*

SUMMARY

Beta-2 agonist discussions in asthma and a review of current data

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Current guidelines recommend inhaled steroids as the first line control medication in the treatment of asthma. However, many patients particularly with airway obstruction need bronchodilators either as a symptom reliever or control medicati-

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on to provide relaxation of bronchiolar smooth muscles. Both short acting and long acting beta-2 agonists (SABA and LABA) are of particular importance among the bronchodilators used in asthma. Despite their well-known benefits, in the recent years, a growing body of publications has been published on the safety of LABAs. However, the increased risk reported to be related to LABA monotherapy was not observed in patients receiving inhaled corticosteroid as the standard treatment in combination with LABA. The benefits of adding LABAs to inhaled corticosteroid have been thoroughly documented, while the risks, including asthma mortality, are currently under debate. Pharmacogenetic advancements drew attention to a potential genetic explanation for certain side effects of these medications whose efficacy and safety have been proven in several studies. In conclusion, LABAs are effective in relieving symptoms and improving lung functions and safe when combined with inhaled corticosteroid in asthma; however, LABA monotherapy should never be administered in the absence of inhaled corticosteroid treatment. Asthma patients that lack control of disease despite adequate doses of inhaled corticosteroids need addition of a regular bronchodilator to their treatment regimen.

Key Words: *Asthma, short acting beta-2 agonist, long acting beta-2 agonist, inhaled steroid.*

Current guidelines recommend inhaler steroids as the first line control medication in the treatment of asthma. However, many patients particularly with airway obstruction need bronchodilators either as symptom reliever or control medication to provide relaxation of bronchiolar smooth muscles (1). Beta-2 agonists are of particular importance among the bronchodilators used in asthma.

In the recent years, a growing body of publications has been published on the safety of long acting beta-2 agonists (LABA). This article will provide a brief definition of LABA and short acting beta-2 agonist (SABA) followed by an assessment of the process with LABAs and a discussion of most recent data (2).

HISTORY of BETA-2 AGONISTS

Epinephrine used to be given for asthma treatment for a long period of time until its replacement by inhaler isoproterenol in Europe in 1940s followed by more selective beta-2 agonists including salbutamol and terbutalin in 1960s. Products with longer duration of action were developed through the end of 1980s.

Isoprotenol entered clinical practice in 1940s particularly in countries with high asthma prevalence including New Zealand, Australia, England, Scotland, Ireland and Norway; however an increase in asthma mortality was noted in these six countries in 1960s. Deaths due to asthma increased 3 fold in subjects aged 5-34 years in England, Australia and New Zealand between the years of 1959-1966. "Isoproterenol forte" that was 2-8 fold stronger than the standard form of isoproterenol was particularly blamed.

Salbutamol has been the most widely used SABAs since 1970s (3). It has been followed by the discovery of other short acting agents, including terbutalin and phenoterol. A second peak in asthma mortality was noted during the use of phenoterol, a complete agonist, in New Zealand in 1976. Although the risk was higher with phenoterol, albuterol also posed a similar risk of mortality with regular use of beta-2 agonists at dosages above the recommended range, i.e. 1.4 canisters per month (4). Case-control studies performed in the following years have demonstrated that phenoterol use was associated with mortality independent of the severity of asthma. Mortality reduced as a result of warnings against using phenoterol at high dosages and the issue was suggested to be related with overdosage (5-10).

Other studies have also suggested that using phenoterol at high dosages was associated with an increased risk of mortality and that this drug should be used when needed, rather than regularly in order to prevent any problems in asthma control (11-13). Suissa et al. suggested that SABAs did not increase the risk of fatal or nonfatal myocardial infarction in patients with chronic obstructive pulmonary disease (COPD) based on 12.090 subjects followed-up between the years of 1980-1997 and (14).

HISTORY of LABAs

LABAs include two bronchodilators with similar pharmacological mechanisms though they also have significantly different features: formoterol and salmeterol. Both molecules have been developed to interact specifically with beta-2 receptors. Best way to understand the profile of these molecules is to determine various physicochemical features of beta-2 receptor in its micro environment including the cellular membrane. Formoterol and salmeterol belong to different chemical classes.

Formoterol is a phenyletanolamine substituted formanilid and has been synthesized among a series of molecules developed systematically to increase beta-2 receptor selectivity and bronchodilator effect (15). Although it was originally designed for oral administ-

ration, studies have shown that inhalation increased its duration of effect (16).

Salmeterol is a saligen derivative of phenyletanolamin, developed in the early 1980s and in use in clinical practice since 1990s. The head group of salbutamol was used in the design of this molecule. Its aliphatic side chain was extended to interact with a theoretical exocyte inside or outside the beta-2 receptor; this chain prolongs the duration of effect of salmeterol molecule (15).

Formoterol binds reversibly to the receptor with high affinity and receptors remain in a state of high affinity (17). However, salmeterol binds to its receptor less reversibly and hence acts as a partial agonist (18). Although certain studies have indicated that salmeterol use did not influence the response to rescue medication, clinical significance of this in not clear.

Formoterol has been suggested to cause beta-2 receptor down-regulation following long term exposure due to its potent agonistic activity. It was noted that initial down-regulation observed at the beginning of the treatment was followed by complete beta-2 receptor restoration. There is no clinical evidence suggesting that high agonistic activity results in down-regulation or development of tolerance, since human bronchiolar smooth muscles have quite an extensive beta-2 receptor reserve.

A comparative study performed by Palmquist et al. has compared salmeterol and formoterol and showed that bronchodilator effect of both drugs lasted longer than 12 hours (19). Formoterol has a faster onset of effect compared to salmeterol. Although salmeterol has certain intrinsic activities at the receptor level, it is not capable of improving severe smooth muscle contractions contrary to more effective beta-agonists. Formoterol is a complete agonist; it is more effective than salmeterol in vivo and has a higher maximal effect. In clinical practice, however, there is no evidence suggesting that formoterol is more effective than salmeterol. A randomized double blind study performed in patients with asthma has shown that high dose formoterol provided better protection against metacholine-induced bronchoconstriction compared to salmeterol (20,21).

Bronchoprotective effect of salmeterol is not dose-dependent. Its maximal bronchoprotective effect was not maintained when the dose was increased from 250 µg to 500 µg, and no additional benefit was observed. Formoterol, however, demonstrated maximum bronchoprotective effect (4.5 fold) at the highest dosages (120 µg). A bronchoprotective effect directly proportional with dosage is observed, however, tremor may also increase slightly. It is not certain whether this has any clinical importance. Although the use of LABAs as partial or complete agonists is controversial, it has been suggested that a complete agonist should be more effective, in cases of extensive airway obstruction such as COPD (22,23).

SAFETY of LABAs

Guidelines define clearly beta-2 agonist use in the treatment of asthma; however, debates on the use and safety of these drugs has been continuing since quite a long period of time. This debate was first ignited in 1968 when higher asthma mortality was determined with the more potent formulation of isoproterenol in England, Australia and New Zealand. This increased asthma mortality was not observed in countries where this empowered formulation was not found (24). Case-control studies performed after a more recent epidemic in 1976 supported a relationship between the use of phenoterol and increased risk of fatal asthma; increase in odds ratio by 2.6 for each additional canister was found. Beta agonists with longer duration of action (LABAs) entered clinical practice in England in 1990s with the expectation of increased compliance and thus a decline in mortality and morbidity. The recommendation of regular use of these drugs raised some concerns. Therefore, the first randomized, 16-week study SNS (Serevent Nationwide Surveillance Study) performed in 1993, compared salmeterol and salbutamol in 25.180 patients randomized in a 2/1 manner and was full of surprises (25).

In this study, one group of patients was given salmeterol (50 µg, 2 puffs morning and bedtime) and the other group was given salbutamol (200 µg, 2 puffs four times a day). Asthma related deaths were 3 fold higher in the salmeterol arm (0.07-0.02%), however this finding was not statistically significant. Study protocol has shown that 17% of the study patients had severe asthma, though the initial intention was to recruit patients with mild asthma, only 69% of the patients were receiving inhaled steroid, number of control subjects did not match that of patients, there was no run-in period and that 9.5% of the subjects received more than 3 canisters of rescue medication monthly. Although statistically insignificant, as a result, FDA demanded further studies from the manufacturer and thus Salmeterol Multicenter Asthma Research Trial was planned (26).

SMART Study (Salmeterol Multicenter Asthma Research Trial)

Debates on the safety of LABAs were much more exacerbated after the study of Nelson et al., which com-

pared the safety of salmeterol and placebo added to regular treatment (26). This randomized, double blind, placebo-controlled and observational study (SMART Study) was designed to compare respiratory-related and asthma-related outcomes in subjects receiving usual asthma pharmacotherapy alone or usual asthma pharmacotherapy plus salmeterol. Two methods of recruitment were utilized during the study. Initially, subjects were recruited via print, radio, and television advertising and were assigned to a study investigator by geographic location during 1996 to 1999 (phase 1). However, when recruitment waned, the large-scale advertising campaign was stopped and study investigators were added to facilitate enrollment during from 2000 to 2003 (phase 2). During phase 2, subjects were recruited directly by the study investigators. Drugs to last for 28 weeks were given in Visit 1, and basal values for SABA usage were recorded, however were not followed throughout the study. Patients were controlled at every four weeks by a telephone call after the first visit.

The primary end point was the occurrence of combined respiratory-related deaths or respiratory-related life-threatening events (defined as intubation and mechanical ventilation). Secondary end points included all-cause deaths, combined asthma-related deaths or life-threatening events, asthma-related deaths, respiratory-related deaths, combined all-cause deaths or life-threatening events, and all-cause hospitalizations. Other end points included the relative frequency of all-cause serious adverse events.

Upon an interim analysis performed in 26.355 patients, the occurrence of primary outcome, respiratory-related deaths or life-threatening events was low and was not significantly different for salmeterol and placebo (50 vs. 36; RR= 1.40; 95% CI, 9.91 to 2.14) in this study. However, there was a small, significant increase in respiratory-related deaths (RR= 2.16; 95% CI, 1.06 to 4.41) and asthma-related deaths (RR= 4.37; 95% CI, 1.25 to 15.34) in subjects receiveing salmeterol vs placebo which boosted concerns. This increased risk in patients receiving salmeterol was more marked in African-Americans with higher rates of asthma-related deaths in people of this race. An NNT analysis performed to compare Caucasian patients with African-American patients underlines this risk more clearly. The study had to be early terminated due to adverse events in African-American patients and difficulties in patient recruitment.

There was no difference in the treatment modalities of patients died due to respiratory causes and patients with life-threatening conditions in the total study population. Subgroup analyses revealed that lower PEF values, less inhaled corticosteroid (ICS) usage, higher rates of hospitalization and more admissions to the emergency ward among African-Americans. Drug compliance was poor and poor healthcare conditions were prevalent among these patients.

Although the study was not performed to evaluate the efficacy of ICS, the role and importance of ICS became clearer at the end of the subgroup analyses. It was not surprising that patients who did not receive ICS, ended up with poor prognosis. When ICS was used, salmeterol resulted in 16/6.127 and placebo resulted in 13/6.138 deaths, and the difference was not statistically significant. In African Americans, when no ICS was used, death rates were 21/7.049 and 9/7.041 with salmeterol and placebo, respectively.

In conclusion, it was understood that SMART study was not designed safely; subjects were recruited without checking their status of ICS usage. The study was active between the years 1996 and 2003; however, most of the deaths due to respiratory causes took place in the year 1998. The interim results were obtained after recruiting 26.000 patients rather than in the early period (26).

In the light of these results, it has been suggested that salmeterol might be even dangerous to use in African Americans due to greater beta-receptor polymorphism, which probably is a class effect not to be associated with salmeterol alone. It has also been suggested that formoterol might also lead to an increased risk of mortality (27). These debates on safety affected other LABAs too, finally the warnings valid for salmeterol-alone in 2003, became valid for all LABAs in 2006.

Possibly, the most interesting point of these analyses was noted when the relationship between this increased risk and use of ICS prior to the study was investigated. No increased risk was observed with the use of salmeterol in patients receiving ICS as the standard treatment prior to the study. However, FDA that LABA containing medications should not be the first line treatment in asthma, that they can only be used at low or moderate dosages when response to ICS is not adequate.

In addition to all of these, Mclvor et al. suggested in 1998 that salmeterol masked airway inflammation and increased the risks of severe exacerbations and deaths due to exacerbations (28). Details of the study has shown that better improvement was ac-

complished in morning PEF and FEV_1 values, use of rescue beta-2 agonists was reduced and thus ICS use was decreased quickly and early in the course of the disease. The dose of ICS was 277 µg in salmeterol group and 612 µg in placebo group. This reduction resulted in an increase in eosinophils in sputum in the LABA group compared to the placebo group. This has been suggested to be a consequence of premature dose reduction before adequate control of the inflammation.

SALPETER META-ANALYSIS

A meta-analysis performed by Salpeter et al. in 2005 re-triggered the debate (29). This meta-analysis that included 19 studies and 33.000 subjects reported that LABAs increased severe and life-threatening asthma episodes and asthma-related deaths. Pooled data of the nineteen studies indicated that long acting beta-2 agonists increased episodes requiring hospitalization [OR 2.6 (95% CI 1.6-4.3)] and life threatening episodes [OR 1.8 (95% CI 1.1-2.7)] statistically significantly compared to placebo. Rates of hospitalization in children [OR 3.9 (95% CI 1.7-8.8)] and adults [OR 2.0 (95% CI 1.1-3.9)] were found to significantly increase with both salmeterol [OR 1.7 (95% CI 1.1-2.7)] and formoterol [OR 3.2 (95% CI 1.7-6.0)] compared to placebo.

Negative results of this meta-analysis were quite interesting; however, several deficiencies were also notable when investigated closely. This meta-analysis was performed excluding significant amount of data by including the data of only 19 studies despite the fact that a large number of publications on LABAs are available. In addition, majority (78%) of the data were obtained from Salmeterol Multicenter Asthma Research Trial, the design of which is considered controversial. No patient receiving a fixed combination of ICS and LABA was included in the meta-analysis of Salpeter et al.

Later assessment by Cochrane suggested that there were no studies reporting increase in deaths due to asthma among patients receiving agonist in combination with ICS (30). LABAs were not found to be associated with increased episodes or hospitalizations.

In the large case-control study performed by Anderson et al. in England, no positive correlation was determined between LABA use and deaths due to asthma. Ninety five percent of patients in this study received inhaler steroids (31,32).

COMPARISON of SALPETER and FACET STUDIES

A total of 9 and 0 asthma related deaths were encountered in salmeterol and placebo arms of steroid naive patients in SMART, respectively. When assessed for patients receiving ICS at the beginning of the study, 4 deaths in salmeterol arm and 3 deaths in placebo arm were seen. Another important study, FACET study, on the other hand, showed 8 and 3 hospitalizations due to asthma, as a recognized marker of asthma mortality, in budesonid + placebo and budesonid + formoterol arm, respectively (33). Objective interpretation of these data dictates clearly that this risk is valid for patients not receiving ICS and no risk is valid in patients receiving ICS. The meta-analysis of Salpeter et al. (30) might be misleading since it does not include large studies on safety of LABAs and mandatory use of ICS and since most data are obtained from the problematic SMART.

EFFECTS of ICS USE on LABA SAFETY

Data regarding at least almost adequate use of ICSs as recommended in the guidelines is utterly important in case of the safety of LABAs. The meta-analysis of Sears et al. has investigated any changes in cardiac or other causes of mortality with use of formoterol in a population of asthma patients receiving inhaler steroids in more than 90% (34).

This meta-analysis was performed with the data of 49.906 subjects randomized to formoterol group and 18.098 subjects not randomized to long acting beta-agonist treatment in 117 controlled parallel group studies on formoterol use. Analyses were performed on the data of more than 68.000 patients and 8 asthma related deaths (0.34 events/1000 patients) were recorded in 49.906 patients randomized to the formoterol arm (92% using ICS). Two asthma-related deaths (0.22 events/1000 patients) were recorded in 18.098 patients 83% of whom received ICS receiving treatments other than long acting beta-agonists, and no statistically significant differences were determined between the groups. Asthma-related severe adverse events (90% of the hospitalizations) were significantly less in the formoterol arm (0.75% vs. 1.10%). No differences were determined between the two groups in terms of cardiac mortality and non-asthmatic non-cardiac mortality.

META-ANALYSIS JAESCHKE

Another meta-analysis evaluating the safety of LABAs in populations receiving ICS was performed by Jaeschke et al. in 2008 (35). A total of 62 randomized controlled studies with 29.401 LABA users followed-

up for more than 8200 patient-years were included. A common feature of these studies was that both LABA and control groups received ICS at similar or different dosages.

When the meta-analysis of Jaeschke et al. was compared with that of Salpeter et al., it was figured that only one article was common among the 62 and 19 articles used in the analyses, respectively. Results of this analysis indicated no increase in asthma-related hospitalizations or severe adverse events in patients receiving a combination of ICS and LABA. The effect of LABA on asthma-related deaths and asthma-related events or intubations could not be evaluated since there were few such cases.

This meta-analysis did not show any statistically significant differences in terms of hospitalizations and asthma-related severe adverse events between patients receiving ICS + LABA and ICS only. Fourteen deaths were recorded in the LABA group and 8 in the control group, and OR was 1.26. Consequently, this meta-analysis evaluated the safety of adding LABA to ICS treatment and failed to prove any opposing evidences.

Nevertheless, the benefits and necessity of LABAs should not be disregarded. Addition of LABAs to treatment with low or high dose steroids decreased the rate of asthma exacerbations significantly. It has been suggested that large, randomized-controlled studies showing the benefits of LABAs clearly were not included in these meta-analyses; and that meta-analysis analyzing only the side effects could lead to misinterpretations.

BALANCING the BENEFITS and RISKS of INHALED LABAs

In the light of all these data, FDA asked Pediatric Consensus Committee, Pulmonary Allergy Drugs Consulting Committee, Drug Safety and Risk Management Consulting Committee to assemble to discuss the risk and benefits of LABAs in December 2008 (36). A meta-analysis including 110 studies was performed prior to this assembly (37). Inclusion criterion used by FDA was the ability to encounter asthma-related death, intubation and hospitalization data in post-study analyses. A composite end point of asthma related death, intubation, or hospitalization was used, and there were 2.80 more such events per 1000 patients in the group that received LABAs than in the group that did not. These studies compared LABA and non-LABA treatment in the absence of any ICS treatments and a statistically significant difference in rates of 3.80 per 1000 subjects was found. However, studies evaluating LABA + ICS treatments with ICS treatment alone have shown that the difference decreased to 0.25 per 1000 patients though not statistically significantly. No serious adverse events were reported for the fixed-dose combinations (36-38).

In several published meta-analysis reports, LABAs were documented not to increase and even decrease the hospitalization risk when used in combination with ICSs. Hospitalization risk for formoterol and salmeterol groups treated with ICS was reported to be OR 0.74 (95% CI 0.53-1.03) by Jaeschke in a meta-analysis of 62 studies including 15.710 cases. Bateman reported hospitalization risk associated with salmeterol and ICS combination therapy to be OR 1.07 (95% CI 0.66-1.73) in 66 studies including 20.966 cases. A significant decrease in the hospitalization risk [OR 0.59 (95% CI 0.37-0.93)] associated with ICS and formoterol combination therapy was also reported by Jaeschke, in a meta-analysis of 16 studies including 5996 cases (38,39).

Consequently, the benefits as well as contribution to increased rates of mortality and morbidity of beta-2 agonists have been explained as follows:

- Bronchospasm due to propellants.
- Hypoxemia and cardiotoxicity due to hypoxemia.
- Increased antigen exposure of an unprotected airway.
- Accumulation of distomer to toxic amounts in the racemic mixture of sympathomimetics.
- Development of tolerance/tachiplaxis to the bronchoprotective effects of beta-2 agonists.
- Pharmacogenetic advancements drew attention to a potential genetic explanation for certain side effects of these medications whose efficacy and safety have been proven in several studies (27,40,41).

LABAs are quite effective in asthma; however, LABA monotherapy should never be administered in the absence of ICS treatment.

LABAs in COPD

These debates in the treatment of asthma have also influenced the use of beta-agonists in COPD. Despite Salpeter's meta-analysis suggesting beta-agonists should not be used because of their cardiac side effects, Aaron has suggested that meta-analyses performed in COPD indicate better lung function, less dyspnea and exacerbations and improvement in qu-

ality of life with beta-agonists. Aaron has also stated that beta-agonists were found to be safe in large clinical studies and that the meta-analysis of Salpeter was inadequate, contained duplications and did not reflect the truth (42). For instance, TORCH (Towards a Revolution in COPD Health) trial was interpreted differently by the two investigators. Aaron has strongly declared that long acting beta-agonists do not kill patients with COPD.

Rodrigo et al. performed a meta-analysis to evaluate the safety of LABAs in COPD and suggested that they decreased severe exacerbations by 21% compared to placebo, however did not give mortality rates any different than placebo. LABA usage was associated with less airway obstruction and reduced need for rescue medication. They also added that they agreed with Aaron on Salpeter's meta-analysis and that they did not agree with what Salpeter suggested (43).

CONCLUSION

In conclusion, LABAs are effective in relieving symptoms and improving lung functions and safe when combined with ICS in asthma; however, LABA monotherapy should never be administered in the absence of ICS treatment. Asthma patients that lack control of disease despite adequate doses of ICSs need addition of a regular bronchodilator to their treatment regimen.

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