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Research Article

Methodology for determining the correlation of the clinical efficacy of therapy with the addition of a drug (for example, anti-asthma therapy in children)

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Abstract

Introduction: In the recent years, much attention has been paid to the use of leukotriene receptor antagonists (LTRA) in the treatment of bronchial asthma (BA). It has been even proposed to use them as alternatives to hormone therapy. Yet, there are studies demonstrating the advantage of montelukast as similar to placebo. The objective was to create a methodology for determining the correlation of the clinical efficacy of therapy with the addition of a drug (on example, clinical efficacy of montelukast in an anti-asthmatic therapy in pediatric patients).

Materials and methods: The data on prescribed regimens was retrospectively extracted from the inpatient records of 608 BA patients admitted to hospital in 2014–2015. Mathematical evaluation was based on the risk factor concept.

Results and discussion: The absolute efficacies (AEs) was estimated to be 91.85% (95% CI 90.15–93.55%) in the exposed group; the attributable efficacy (AtE) was found to be 17.00% (95% CI 10.91–23.09%); the relative efficacy (RE) was found to be 1.23 (95% CI 0.21–2.24); and the population attributable efficacy (PAtE) was found to be 7.55% (95% CI 2.49–12.61%).

Conclusions: The AtE, RE, and PAtE were statistically significant. The RE was found to be 1.23. However, the lower limit of its 95% CI (0.21–2.24) was less than 1, indicating that the increase in clinical efficacy was not found to be statistically significant. In the studied sample positive outcome rates were 91.85% (95% CI 90.15–93.55%) in the exposed group and 74.85% (95% CI 72.49–77.21%) in the comparator group. He presented methodology for determining the correlation of the clinical efficacy of the pharmacotherapy regimen with the addition of a drug can be successfully applied in the future.

Keywords

bronchial asthma, drug therapy, anti-asthmatic regimen, clinical efficacy, mathematical correlation, attributable efficacy, relative efficacy, population attributable efficacy

Introduction

Bronchial asthma (BA) is a common inflammatory disease of respiratory tract in children. Recent years have shown a worldwide increasing trend in incidence rates and severity of BA, as well as its earlier manifestation.

Substantial progress in treating BA was achieved when background therapy was introduced, which reduced chro-

nic allergic inflammation in bronchi and thus decreased a risk of bronchial obstruction and irreversible structural changes in the bronchial wall. The BA background therapy include inhaled glucocorticosteroids (IGCSs), systemic glucocorticosteroids (GCSs), leukotriene receptor antagonists (LTRAs), long-acting β2-agonists (LABAs) in combination with IGCSs, cromones (cromoglicic acid and sodium nedocromil), sustained-release theophyllines, and anti-IgE antibodies (GLOBAL INITIATIVE FOR ASTHMA 2016).

Treatment of severe refractory BA is a pressing problem. Patients with severe BA need high doses of combined drugs (IGCSs and LABAs) or, in case of their inefficacy, systemic GCSs.

Recently, the use of LTRAs in BA has taken a lot of attention. They have been suggested to be used as an alternative to hormonal agents (Ciółkowski et al. 2016, Hon et al. 2014). Studies show a high degree of clinical efficacy of LTRAs in pediatric BA patients (Stelmach et al. 2015). However, some studies have shown that montelukast is as effective as placebo (Joos et al. 2008). No study has shown statistical superiority of montelukast over IGCS (Castro-Rodriguez and Rodrigo 2010). A guideline on the management of acute BA attacks in children by the Italian Society of Pediatricians does not recommend the use of montelukast as a standard therapy for BA attacks (Indinnimeo et al. 2018). The recommendation is based on a Cochrane Library review that did not demonstrate a statistically significant difference in hospitalization risks after using oral montelukast in addition to the standard regimen (Watts and Chavasse 2012). Recent studies have supported this conclusion (Wang et al. 2018).

The objective of this study was to analyze the mathematical correlation between the addition of montelukast to an anti-asthmatic therapy in children and its clinical efficacy.

Materials and methods

The data on prescribed regimens was retrospectively extracted from case records of 608 BA patients, undergoing inpatient treatment in a Nizhniy Novgorod healthcare facility from 2014 to 2015.

The following drugs and their combinations were used as asthma control medications in the facility during the time-frame of the study: (1) IGCSs alone; (2) a combination of IGCS and short-acting β2-agonists (SABA); (3) a combination of IGCS and LABA; (4) a combination of IGCS and LTRA; (5) a combination of IGCS, SABA, and LTRA; (6) a combination of SABA and LTRA; (7)) a combination of IGCS, LABA, and LTRA.

To determine the mathematical correlation between the clinical efficacy of an anti-asthmatic therapy and adding montelukast to it, absolute numbers of positive and negative outcomes were determined for each treatment. The numbers were, respectively, 122 and 60 for IGCS, 54 and 15 for IGCS + SABA, 77 and 10 for IGCS + LABA, 35 and 4 for SABA + LTRA, 85 and 7 for IGCS + LTRA, 64 and 5 for IGCS + SABA + LTRA, and 64 and 6 for IGCS + LABA + LTRA.

A positive outcome was defined as improvement in a patient's health at the time of discharge from hospital achieved by using the initially prescribed regimen without an increase in doses and without adding any new medication. An outcome was defined as negative if a new medication, such as Euphylline, systemic GCS, etc., was added to the initially prescribed regimen or if the initial dosage or frequency was increased.

To study the correlation between the clinical efficacy of the addition of montelukast to an anti-asthmatic regimen in children, the absolute efficacies in exposed and unexposed groups, attributable efficacy, relative efficacy, and population attributable efficacy were determined along with standard errors and confidence intervals for each efficacy estimate. The concept of determining clinical efficacy was based on the concept of risk factors. This concept successfully used in health care (Maksimov et al. 2010, Zhukova et al. 2015, Zhukova et al. 2017).

Results and discussion

Statistical correlation between the clinical efficacy of an anti-asthmatic regimen and addition of montelukast to it was analyzed by estimating the absolute efficacies in patients receiving or by estimating the attributable efficacy, the relative efficacy, and the population attributive efficacy in patients not receiving montelukast as a component of anti-asthmatic therapy, as well as by determining standard errors and confidence intervals for each type of efficacy.

At the first step in the analysis of statistical correlation between the presence of montelukast in the regimen and its efficacy, a contingency table (Table 1) was constructed. Rows and columns are arranged in a way to make sure the calculated parameters could be correctly interpreted.

The first row shows the group of patients that received montelukast-containing regimen. The second row shows the group of patients that did not receive montelukast. Thus, the first group was a test group, which received the drug of interest. The second group was a reference group to be used for efficacy comparisons. Likewise, the first column shows the number of cases where the event in question (positive clinical outcome) was recorded in the first and second groups, and the second column shows the number of cases where the event did not occur.

After constructing the contingency table, a statistical hypothesis was formulated on the assumption that montelukast added to an anti-asthmatic regimen increased the rate of positive outcomes in BA, obviating the need to change treatment, to increase the dose, or to add new drugs. The first parameter, absolute efficacy (AE), was

Table 1. Contingency Table

Montelukast in anti-asthmatic therapy	Positive clinical outcome		Total
	Yes	No	
Yes	248 (a)	22 (b)	270 (A)
No	253 (c)	85 (d)	338 (B)
Total	501 (C)	107 (D)	608 (Q)

calculated as a proportion of cases with positive outcomes out of the total number of outcomes in patients taking regimen with montelukast. In other words, AE was the rate of positive clinical outcomes in the groups of patient receiving or not receiving montelukast as a component of the anti-asthmatic regimen. Equation (1) was used to calculate the rate of positive clinical outcomes in the exposed group (patients receiving montelukast in the regimen), AE was estimated to be 91.85%.

$$AEe = \frac{a}{A} \quad (1)$$

Thus, 0.9185 (91.85%) of the exposed group had positive clinical outcomes. Likewise, Eq. (2) was used to estimate the rate of positive clinical outcomes in the unexposed group (patients not receiving montelukast) at 74.85% (absolute efficacy in the comparator group (AEu)).

$$AEu = \frac{c}{B} \quad (2)$$

Point estimates were thus obtained for the favorable clinical outcome rate as dependent on whether montelukast was added to the anti-asthmatic regimen (exposed and comparator patient groups). The rates were not estimated for the total populations, but only for their representative samples, which approximately reflected the population properties. Such point estimates are prone to statistical errors. Standard errors were therefore calculated for the AE estimates to characterize the estimation accuracy. The standard error of the AE of the exposed group calculated from Eq. (3) was 0.017.

$$S_{AE} = \sqrt{\frac{AE \times (1 - AE)}{n}}, \quad (3)$$

where n is the size of the exposed or unexposed group, that is, A or B.

The standard error of the AE was similarly estimated at 0.024 for the unexposed group.

Because different rates might be obtained using other samples, the extent of potential differences and the minimum intervals were estimated that cover actual point estimates, that is, the minimum intervals wherein the rate estimates fall with a probability of 95%. This interval is known as the 95% confidence interval (95% CI) in statistics. In practice, this means that 95% of potential samples have the rate estimates that fall within the 95% CI, while only 5% of all rate estimates are beyond the 95% CI. The 95 or 99% CI is commonly used in studies (Eq. (4)).

$$CI_{AE} = AE \pm t \times S, \quad (4)$$

where t is the critical value of statistical significance (t = 1.96 for 95% CI), and S is the standard error of AE.

So, 95% CI in the exposed group ranges from a lowest 88.59% to a highest 95.12% with the mean AEe being 91.85% and the standard error – 1.70%. Thus, a montelukast-containing anti-asthmatic regimen ensured positive outcomes in 91.85 ± 1.70% of cases in the exposed group.

Similar calculations with Eq. (4) yielded a 95% CI of 0.7485±0.0236 (or 74.85±2.36%) for AE of the comparator group.

The AE estimates obtained for the patient groups receiving or not receiving montelukast showed that montelukast increased the favorable clinical outcome rate. Next, in order to estimate how substantial was the contribution of montelukast to this increase, the attributable efficacy (AtE) was calculated, which characterizes the proportion of efficacy that is associated with and accounted for by the study drug. AtE was estimated from Eq. (5) to be 0.1700, or 17.00%.

$$AtE = AEe - AEu = \frac{a}{c} - \frac{c}{B} \quad (5)$$

Thus, the probability of positive clinical outcome was 91.85% in the montelukast-treated group and 74.85% in the group that had not received montelukast. The AtE was 17.00% in that case; i.e., montelukast increased the probability of the event in question (positive clinical outcome) by 17.00%.

To estimate the standard error of the difference, a pooled estimate of the proportion was obtained from Eq. (6) to be 0.8240.

$$F = \frac{C}{Q} \quad (6)$$

The standard error of AtE was estimated from Eq. (7) to be 0.0311 (or 3.11%).

$$S_{AtE} = \sqrt{F \times (1 - F) \times \left(\frac{1}{A} + \frac{1}{B}\right)} \quad (7)$$

After that, 95% CI of the AtE was estimated to be 10.91–23.09%.

Thus, montelukast as a component of an anti-asthmatic regimen increased the likelihood of a positive clinical outcome in children with BA by 17.00±6.09%. So, possible (true) AE values falling within 95% CI indicate that AEe > AEu; i.e., montelukast made favorable clinical outcomes of anti-asthmatic therapy more likely.

Clinical efficacy estimates are based on statistics (mean, error of the mean, and CI), which, in turn, are based on the probability theory. Like in the CI analysis of attributable efficacy, CIs are important to consider for all efficacy estimates. For instance, the CIs of AEe and AEu calculated earlier (88.59–95.12% and 70.23–79.48%, respectively) do not include 0 or negative values and can, therefore, be deemed statistically significant.

Basing on the AtE estimate, montelukast was shown to increase the likelihood of a favorable clinical outcome by 17.00% on average.

The relative efficacy (RE) was calculated to assess the strength of the association between drug exposure and outcome, characterizing how many times the efficacy of anti-asthmatic therapy increased due to adding monteluk-

ast. The AEe/AEu ratio is higher than 1 when the clinical efficacy is higher in the exposed group, it is lower than 1 if the clinical efficacy is lower in the exposed group, and it is equal to 1 when the clinical efficacy is the same in the two groups. Mathematical calculations showed that the clinical efficacy ratio in the two groups is higher than 1.

The RE was estimated to be 1.23 from Eq. (8):

$$RE = \frac{AEe}{AEu} = \frac{a/A}{c/B} \quad (8)$$

Thus, montelukast added to the anti-asthmatic regimen resulted in a 1.23–time increase in clinical efficacy. The result was tested for significance because the calculations were performed for the sample. The standard error of RE was calculated for this purpose from Eq. (9) and was 0.0364.

$$S_{RE} = \sqrt{\frac{1-AEe}{a} + \frac{1-AEu}{c}} \quad (9)$$

The 95% CI of the RE was obtained from Eq. (10):

$$CI_{RE} = RE \pm Exp\left(\ln\frac{AEe}{AEu} \times t \times S\right) \quad (10)$$

The obtained range of RE with 95% CI was 0.21–2.24. Likewise AtE, possible (true) values falling within 95% CI are interpreted as follows. RE > 1 indicates that the drug improves clinical efficacy. When RE = 1, the drug does not affect clinical efficacy. When RE < 1, the drug decreases clinical efficacy.

The resulting 95% CI estimates do not support the hypothesis that there is a conclusive increase in clinical efficacy from a statistical point of view.

The population attributable efficacy (PAtE) was obtained as an absolute difference between the parameters across the total population and parameters of the unexposed group. The PAtE is similar to AtE, but, unlike the latter, characterizes the population component of efficacy and, therefore, depends on how broadly montelukast is used in the given population.

The PAtE was estimated at 0.0755 (7.55%) with Eq. (11):

$$PAtE = \frac{C}{Q} - \frac{c}{B} \quad (11)$$

Thus, montelukast increases clinical efficacy in the total population by 7.55% when used as a component of anti-asthmatic therapy.

To evaluate the standard error of PAtE, a pooled proportion estimate was obtained from Eq. (6) to be 0.8240.

Using Eq. (12), the standard error of PAtE was estimated to be 0.0258 (2.58%).

$$S_{PAtE} = \sqrt{F \times (1-F) \times \left(\frac{1}{Q} + \frac{1}{B}\right)} \quad (12)$$

The 95% CI of PAtE was obtained from Eq. (13) to be 2.49%-12.61%.

$$CI_{PAtE} = PAtE \pm t \times S \quad (13)$$

Thus, montelukast provides a 2.49–12.61%-time increase in clinical efficacy of the anti-asthmatic regimen (95% CI).

The χ2-square test was also determined by formula (14):

$$\chi^2 = \sum_{i=1}^{l}\sum_{j=1}^{c}\frac{(A_{ij} - E_{ij})^2}{E_{ij}} \quad (14),$$

where i – the row number (from 1 to l), j – the column number (from 1 to c), $\mathbf{E}_{ij}$ – the **actual** number of observations in cell ij, $\boldsymbol{A}_{ij}$ – the **expected** number of observations in cell ij.

χ^2 was obtained from Eq. (14) to be 29.91.

This method is most common for analyzing the contingency table. At a significance level (probability) of $p \leq 0.05$, the critical point of the Pearson distribution (χ2-square) was 3.84. The resulting value of 29.91 exceeds 3.84, therefore, there is a statistical relationship between the addition of montelukast to the anti-asthmatic regimen and positive clinical effects.

But the Pearson criterion (χ2-square) gives reason to speak about the presence or absence of a statistical relationship between the influencing factor and the upcoming event. The proposed concept of risk factors makes it possible to quantify statistical dependence.

Conclusions

The AtE, RE, and PAtE estimates were found to be statistically significant. RE was 1.23; i.e., there is a 1.23-time increase in clinical efficacy. However, the lower limit of its 95% CI (0.21–2.24) was less than 1, indicating that RE is not statistically significant and there may be no positive clinical effect of montelukast in other patient samples. In the studied sample, montelukast considerably improved efficacy of the anti-asthmatic therapy. The favorable outcome rates were 91.85% (95% CI 90.15–93.55%) in the exposed group and 74.85% (95% CI 72.49–77.21%) in the comparator group. Adding montelukast to an anti-asthmatic regimen was found to increase its clinical efficacy in the retrospective study, but the conclusion needs further verification. The presented methodology for determining the correlation of the clinical efficacy of the pharmacotherapy regimen with the addition of a drug can be successfully applied in the future.

Conflict of interest

There is no conflict of interest to declare.

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