Acute Salbutamol Exposures in Children
Retrospective five - year study

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Salbutamol (Albuterol) is a sympathomimetic drug which is indicated as first therapeutic line in the treatment of bronchial asthma. In this study we've analyzed the cases with exposure to Salbutamol hospitalized and treated in the Department of Toxicology and Intensive Care of Clinical Emergency Hospital for Children Grigore Alexandrescu, from Bucharest. This is a retrospective and descriptive study, which lasted 5 years, from January 2012, until December 2016. The results showed that the administration of Salbutamol orally or inhalatory by nebulization in pediatric population is easy but frequently associated with accidental or iatrogenic overdoses.

Keywords: Salbutamol, intoxication, children

Salbutamol (Albuterol) is a sympathomimetic drug which is indicated as first therapeutic line in the treatment of bronchial asthma and, also in various pathologies with a broncho-obtructive component.

It is a member of phenylethanolamines, a secondary amino compound and a member of phenols having the molecular formula C13-H21-NO3 (Figure no.1)[(1].

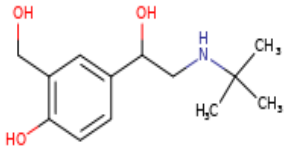

Fig. 1. Salbutamol chemical structure

Salbutamol is formulated as a racemic mixture of the R- and S-isomers. The R-isomer (levalbuterol) has 150 times greater affinity for the beta2-receptor than the S-isomer and the S-isomer has been associated with toxicity, increasing bronchial reactivity and inflamation [2].

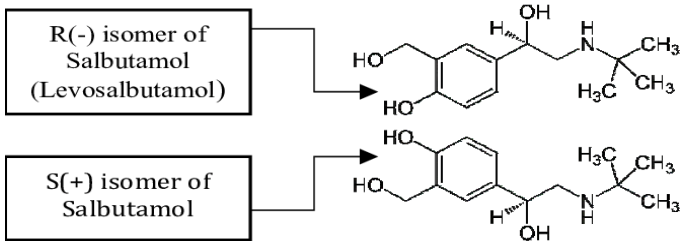

Fig. 2- Salbutamol isomers chemical structure

After oral administration it is rapidly and well absorbed, the peak concentration beeing reached within 2 to 3 hours . Following inhalation the drug is initially undetectable in the blood and the low concentration detected after 2 to 3 hours may be due to the portion of the dose which is swallowed and absorbed in the gut. The maximum clinical effect are achievede after 1 hour with the inhaled drug and approximately 2 to 3 hours with the oral one [3].

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After absorbtion it is metabolized in the liver through sulfate conjugationby to its inactive 4'-O-sulfate ester by phenol sulphotransferase 1A3 (SULT1A3), the (R)-enantiomer beeing preferentially metabolized by these enzyme compared to the (S)-enantiomer [4] .

Regardless of the route of exposure, the elimination half-life of salbutamol is between 3 and 5 hours. The elimination route is mainly renal (70-90%) via the organic cation transport pathway [4] and only a very small amound is excreted in the feces. Both metabolization and elimination of albuterol are processes influenced by the isome type, beeing 2 to 3 times lower for S enantiomer, thus resulting in acumulation and decreased clearance of this form [4].

Used in therapeutically doses, it has specificity for beta 2 adrenergic receptors , which are found in the smooth bronchial muscles (short-acting adrenergic beta 2 receptor agonist- SABAs). Activation of beta2-adrenergic receptors leads to the activation of adenylcyclase, the enzyme responsible for the conversion of adenosine triphosphate (ATP) to cyclic-3',5'-adenosine monophosphate (cAMP). The increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle due to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations. Increased cyclic AMP concentrations are also associated with reduce inflammatory cell mediator release from mast cells in the airway [1].

The beta-2 adrenergic agonists Salbutamol acts mainly on the smooth muscle of the bronchial tree but it can also act on the beta 2 receptor from the heart, blood vessels, digestive tract, bladder, uterus, and striated muscles. Consequently, apart from the bronchodilatory effect, the use of Salbutamol is associated with increased cardiac frequency, contractility and automaticity, urine retention, smooth abdominal muscles relaxation, smooth uterine muscles relaxation, or sphincters contraction.

Even if a therapeutic dosage is used, many factors influenced the pharmacokinetics and pharmaco-dinamics of salbutamol: type of drug (racemic or levalbuterol), state of the disease (decreased pulmonary deposition and absorption and altered clearance in asthmatic lungs), inhalation tehnique or delivery devices, genetic polymorphism of the β2-adrenoceptor (some of these beeing associated with a reduced bronchodilator response to albuterol in both asthmatic and nonasthmatic children) [3]. All of this characteristics can influence the amount of absorbed albuterol and the body response to this amount, beeing responsable for the occurance of side effects .

In case of toxic doses, besides the increasing of the beta 2 adrenergic effects, the beta 2- selectivity is lost, becoming also the effect of the beta 1 receptor stimulation [5].

Because of the continuous increase of the broncho-obstructive pathology (bronchial asthma, bronchitis, obstructive sleep apnea, bronchiectasis, pulmonary emphysema) and the use of beta 2 agonists as the first therapeutical line in these diseases, the cases that associate unwanted effects following exposure to therapeutic or toxic doses of Salbutamol, will increase at the same time [6- 9].

The existence of various pharmaceutical pediatric forms (syrup, nebulization, inhalation) , increases the accessibility of children to this drug, and represents another risk factor for overdose, most frequently through misadventures (dose or route of administration) from parents.

We intend to make a study to outline the demographic, clinical, and evolutionary characteristics of pediatric patients who are exposed to therapeutic or toxic doses of Salbutamol and also, to evaluate the type of Salbutamol products and the route of exposure, to determine the suitable administration for the least risk of side-effects.

Experimental part

In this study we've analyzed the cases with exposure to Salbutamol hospitalized and treated in the Department of Toxicology and Intensive Care of Clinical Emergency Hospital for Children Grigore Alexandrescu, from Bucharest. This is a retrospective and descriptive study, which lasted 5 years, from January 2012, until December 2016.

For each hospitalized patient, with Salbutamol exposure (intoxication or side-effects), we have analyzed the demographic issues (age, sex, environment), the exposure circumstances (accidentally, voluntarily, the type of preparation, the route of exposure and dose), clinical manifestations and the evolution during the treatment. Changes in vital parameters (heart rate, respiratory rate and blood pressure) were reported at normal values by age groups [10].

All of these data were obtained from the patient medical documents, with the approval of the Ethics Committee and were entered into a Microsoft Excel database.

Results and discussions

During the study (January 2012-December 2016), 4984 cases of acute intoxication have been hospitalized and treated within the Pediatric Antitoxic Center. Of these, 59 cases were accidental or voluntary exposures to Salbutamol, the incidence of this type of exposure being 1.2%. The patients were aged between 0 to 14 years, with an average age of 4.67 years.

Most cases were registered in the small child, between the ages of 1-4 years (38/59). This finding can be explained both by the increased incidence of respiratory pathology, especially in the first years of collectivity, but also by the behavioral particularities of this age, the small children having a pronounced "exploratory" character, this being realized, with predilection, by ingestion. The data from the specialized literature identifies as the main risk group, regarding the acute accidental intoxications, the group of children between the ages of 1-5 years [11]. In the age group 5-10 years, 17 cases were registered, and in the age group 10-14 years, only 4 cases (Figure 3).

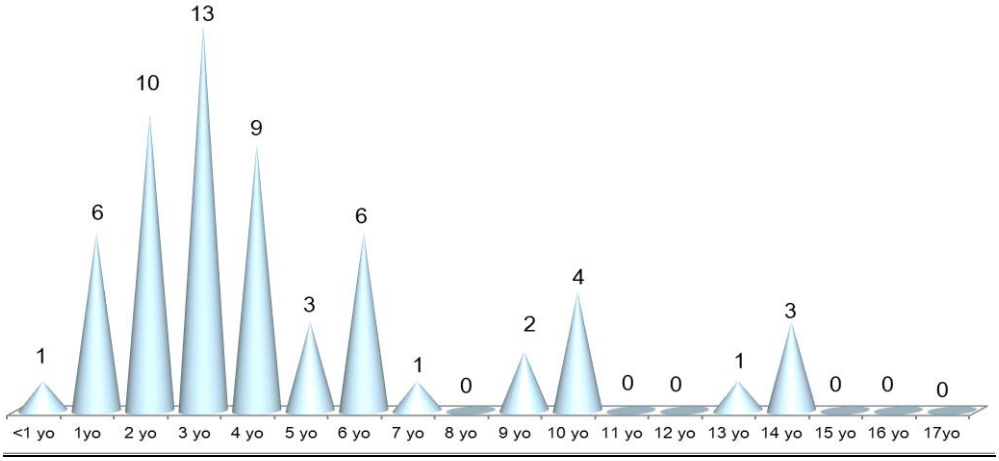

Fig.3. Lot distribution by age

The studied group consisted of 31 girls, representing 52.6% of the total cases analyzed, and 28 boys, respectively, 47.4%, finding a ratio of girls / boys of 1.1 / 1. Regarding the patients environment, the number of cases from the rural area (n = 4.68%) is significantly lower, compared to the one from the urban area (n = 55, 93.2%). The large number of patients in the urban area could be explaind by increased incidence of respiratory tract infections secondary to urban aglomeration and air pollution but also the increased accessibility to specialized medical services and treatment [12].

Analyzing the circumstances of the exposure, we found the following aspects:

-8 (13%) of the 59 cases in the study group were secondary to the use of Salbutamol syrup, in 50 of the cases (85%) the pharmaceutical form was the solution for inhalation, and in a single case, pressurized inhalation suspension (2%) (Figure 4).

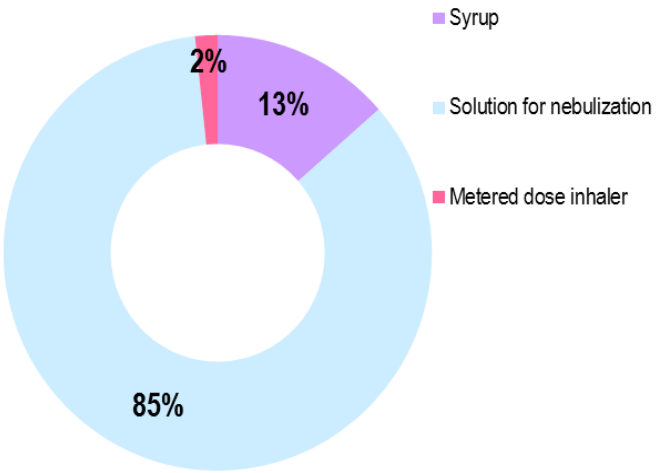

Fig. 4. The pharmaceutical forms of Salbutamol

- In 37% of cases (22/59) the route of exposure was the digestive route, by ingesting a toxic dose, either of syrup (6 cases), or inhalation solution (14 cases: 8 accidental ingestion, and 6 cases of wrong administration , orally, of the inhalation solution), and in 37 of the cases, the exposure was by inhalation.

-Accidental exposure through administration errors or accidental ingestion, in neglected children, was the most common cause (58 cases vs. a case of voluntary intoxication)

In children, therapeutic doses in case of Salbutamol inhalation are 0.15-0.3mg / kg, up to a maximum of 10mg every 1-4 hours, if necessary, or 0.5mg / kg per hour, in continuous nebulization [13]. Oral administration is controversial.

For the analyzed patients the doses of Salbutamol were 0.6-3.8mg / kg per dose.

51 of the patients in the study group were exposed to doses more than 0.8mg / kg of Salbutamol, this being considered the maximum of the therapeutic interval, being labeled with acute intoxication [14]. Among these, 17 (33.3%) were the effect of digestive exposure: 6 cases of accidental ingestion of syrup, 8 cases of accidental ingestion of inhalation solution, and 3 cases of mistaken administration, on the digestive route of the inhalation solution. The inhalation route was involved in overdosage in 34 (66.6%) of the patients: 33 overdosages of the inhalation solution and a voluntary intoxication, with metered dose inhaler

Table 1
TYPES OF EXPOURE DEPENDING ON THE PHARMACEUTICAL FORM

Pharmaceutical form	Overdose through administration mistakes	Overdose by accidental ingestion	Side Effect
Salbutamol Syrup	0 cases	6 cases	2 cases
Nebulization solution	33 cases	8 cases	6 cases

In the study group, the inhalation route by nebulization was the most frequent identified mode of overdosage, most probably secondary to the type of the used product, with a concentration of 5mg / ml, corresponding to doses of 0.03-0.06 ml / kg. These small quantities are often misinterpreted by parents.

In 8 of the analyzed patients, the clinical manifestations appeared as a result of administration of therapeutic doses of Salbutamol (Figure 5).These side-effects occurred after syrup administration in two of the cases and after the inhalation solution in 6 of the cases.

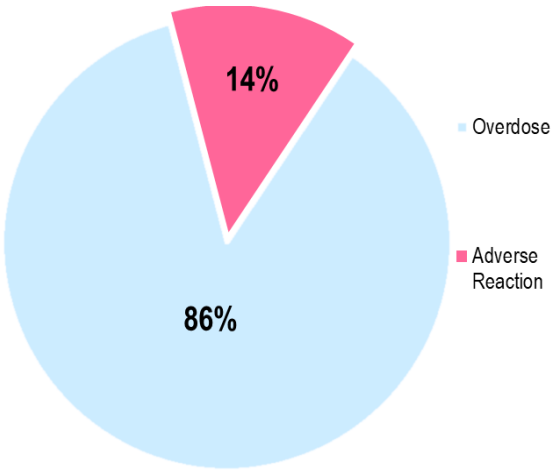

Fig. 5. Dose-related type of Salbutamol exposure

Although in literature, oral administration of Salbutamol is considered a spare method (low efficiency and many adverse effects) , in the analyzed group, the administration of inhalatory solution for nebulization was more often associated with the occurrence of undesirable effects, not only in toxic doses - overdoses by mistaken, but also at therapeutic doses [15].

Clinical manifestations of exposure to Salbutamol are secondary to adrenergic beta 2 receptor stimulation, and also, in the case of overdosage, to beta 1 effects, as a result of losing the selectivity for beta 2 receptors. Therefore, at cardiac level, beta hyperstimulation is responsible for increasing the discharge of impulses of the sinoatrial node, also for increasing of contractility and automaticity at the ventricular level, changes that are responsible for the appearance of sinus tachycardia, or other tachyarrhythmias, palpitations and even angina pectoris or myocardial infarction [16, 17]. In the study group, 45 of the patients (76.3%) had sinus tachycardia.

Among the neuromuscular manifestations, tremor is most commonly encountered, not only in therapeutic doses but also in the case of overdoses. Although the mechanism of action is not fully elucidated, it is assumed that Salbutamol-induced hypopotassemia plays an important role, but also the direct action of this drug on skeletal muscle can be involved [18]. Nervosity, agitation are other symptoms associated with Salbutamol exposure. In the analyzed group, 68% of the patients (40/59) reported during the hospitalization psychomotor agitation. Other clinical manifestations that occurred with variable frequency were: nausea, vomiting, facial hyperemia, drowsiness (figure 6).

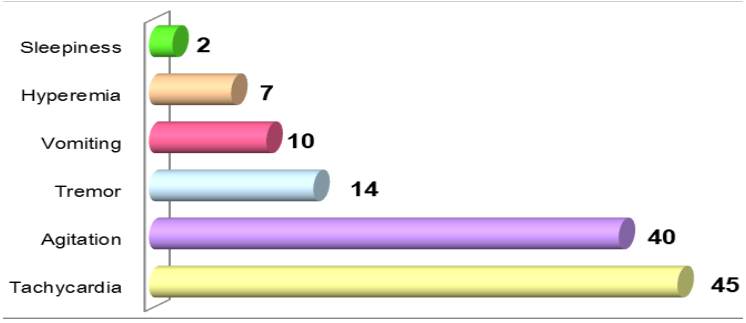

Figure no. 6- Clinical manifestations of Salbutmol exposure

Treatment of Salbutamol exposure is symptomatic. In case of psychomotor agitation, it may be necessary to sedate the patient with benzodiazepines. In the analyzed group, 20 of the patients required administration of Diazepam. In severe intoxications, which associate hypotension or arrhythmias, treatment with beta-blockers is required. By first intention, Esmolol 0.025-0.1mg / kg, or Propranolol 0.01-0.02mg / kg iv must be administrated, but in patients with asthma, the administration of beta-blockers should be carefully monitored. In the analyzed group, none of the patients had severe forms of intoxication.

In all patients the recovery was complete in 1-3 days (Figure 8), the average lenght of hospitalization was 1.3 days, the Salbutamol intoxications in children being generally mild and with a rapid resolution of symptoms.

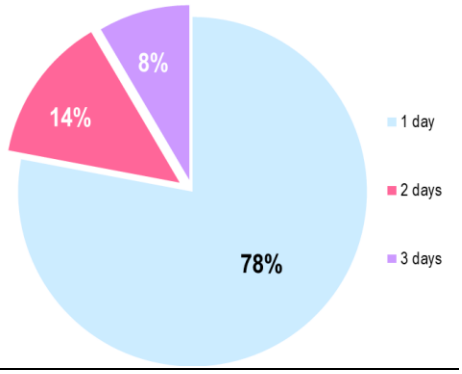

Fig. 8. Length of hospitalization for Salbutmol exposure

Conclusions

The administration of Salbutamol orally or inhalatory by nebulization in pediatric population is easy but frequently associated with accidental or iatrogenic overdoses. The metered doses inhaler is the safest route of administration. By using a spacer or an inhalation chamber, which allows an easy and complete administration of the drug and decreases the difficulties due to bad synchronization between breathing times and the puffs administration, this method can be used also in the young child.

Exposure to Salbutamol is mainly associated with cardiovascular effects (tachycardia, palpitations, chest pain) and neuromuscular effects (tremor, agitation), these occurring in both therapeutic and toxic doses. These effects are generally mild and of short term, the evolution of the recovery being complete with symptomatic treatment only.

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