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ADVERSE EFFECTS OF NASAL DECONGESTANTS (REVIEW OF LITERATURE)

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Summary

Nasal decongestants are ones of the most popular and widespread medicines due to high frequency of respiratory infections. But on the other hand they are characterized by significant abuse potential for users seeking such effects as euphoria, psychostimulation, less of appetite and lose the weight.

The affections of the cardio-circulation and nervous systems are the most frequent complications after overdosing of the nasal decongestants. The development of the strikes in the young age was associated with the nasal decongestants abuse in every tenth patient.

The cases of the malignant arterial hypertension, cerebral hemorrhages, ischemic strokes, heart decompensation after the nasal decongestants abuse is known as nasal decongestants poisoning. And although the side effects more often develop when nasal decongestants are used orally, intranasal way could not be considered as absolutely safe, especially in cases of overdosing.

The development of the psychotic disorders is one of the most frequent nasal decongestants adverse effects. The elderly people with organic brain damage, drug addiction, mental illness are in the risk group for the development of psychotic complications.

Misuse of the nasal decongestants in children is especially dangerous because of the high risk of the development of the life-threatening toxic poisoning. Fatal cases of poisoning were associated with small age of a child, using several medicines with the same ingredient, using decongestants in a daycare setting, mistakes in measuring and identification the medicine, the absence of the doctor's prescription, use of the product for adult age.

Using nasal decongestants in supine position of the patient may lead to the significantly dose increase inside the nasal cavity and may cause toxic poisoning.

Adolescents are quite sensitive to the development of nasal decongestants side effects with such risk factors as age, gender, family income, physical and mental health, use of other medicines and alcohol.

The special type of the adverse effects of the long-term using of the nasal decongestants is the rhinitis medicamentosa taking place in adult persons with predisposition to the nasal hyperreactivity. The diagnosis of the rhinitis medicamentosa is based on the nasal hyperactivity and swelling of the nasal mucous membrane in combination with poor response on treatment caused or exaggerated by long-term use of topical nasal decongestants.

The development of the rhinitis medicamentosa depends on a number of factors such as the type of nasal decongestants, the type of preservative, the presence of risk factors that determine the patient's predisposition to the development of nasal hyperreactivity.

Here we review the existing literature concerning the adverse effects of the nasal decongestants including the development of the rhinitis medicamentosa.

Key words: *Nasal Decongestants; Adverse Effect; Poisoning; Rhinitis Medicamentosa.*

Nasal decongestants (NDs) are ones of the most popular and widespread medicines due to the high frequency of respiratory infections [1]. The peculiarities of the NDs using by the population are their wide range in each pharmacy shop, over-the-counter sales, lack of awareness of possible complications in case of misuse or abuse [2]. That's the reason why NDs are ones of the leaders of the adverse effects [3].

According to the classification of the adverse effects by M.D. Rawlins and J.W. Thomson (1997), modified by J. Rene Royen, NDs are able to cause adverse reactions of the type A (dose-dependent) and the type C (addiction in cases of long-term therapy) [4].

The systemic NDs comprise one of the five groups of the over-the-counter medicines with the most frequent association with overdosing, misusing and adverse effects [5]. These groups are codein-containing medicines (especially in combination with pain-killers), medicines for cough treatment (in particular dextromethorphan), sedative

antihistamines, NDs, laxatives [6]. Regarding to the NDs the toxic effect of the NDs is more typical in case of the systemic orally overdosing.

The affections of the cardio-circulation and nervous systems are the most frequent complications after overdosing of the NDs [7].

Pseudoephedrine hydrochloride is the first in the list of the abusing NDs. This is because of the peculiarities of the chemical formula of the molecule - it is extremely close to methamphetamine, a well-known narcotic substance [8].

Pseudoephedrine has quite long history of the using in medicine, it is effective in treatment of the infections of the upper and lower respiratory airways, bronchial asthma [9]. Pseudoephedrine and ephedrine are the ordinary components of the cough-mixtures and it should be taken into account in therapy prescription. It has been reported about the adverse effects after using such cough-mixtures up to the development of the psychotic disorders. The psychotic disorders were recorded after

pseudoephedrine (67%) and ephedrine (57%) using [10].

The presence of other effects of the pseudoephedrine such as decreasing an appetite, increasing the concentration, reduced weakness and insomnia has made it one of the most well-known doping agents. And the peculiarities of the chemical structure of pseudoephedrine led to its use as a substrate in the synthesis of illegal amphetamine and methamphetamine [11].

The other popular ND with high frequency of the side-effects is propylhexedrine. Together with the action on the nasal mucosa propylhexedrine decreases the appetite and that's why it is widely used in the treatment of obesity and it also has psychostimulant properties. The misuse of the propylhexedrine can lead to the serious and sometimes even fatal outcomes [12, 13, 14, and 15].

The negative effect of NDs on the functioning of the nervous and cardio-vascular systems with development of the malignant arterial hypertension, cerebral hemorrhages, ischemic strokes, heart decompensation is described in literature as NDs poisoning [16]. And although the side effects more often develop when NDs is used orally, intranasal way could not be considered as absolutely safe, especially in cases of NDs overdosing.

The clinical case of the acute heart failure and malignant hypertensive crisis due to the naphazoline abuse by the 40-years old male patient was described [17] as well as the development of the Takotsubo syndrome in young female patient with allergic rhinitis because of the abusing of the NDs and topical steroids [18]. And young male patient presented an acute ischemic infarction localized in the posterior cranial fossa of the brain following the abuse of xylometazoline-containing nasal decongestant for 10 years was reported by D.Leupold and K.E.Wartenberg [19]. The development of the strikes in the young age was associated with the NDs abuse in every tenth patient [20].

In most cases the development of NDs' adverse effect is caused by exceeding the ND dose and/or duration of administration. Therefore, Musshoff F. et al [21] described the xylometazoline intoxication in the three boys (triplets) delivered to the hospital unconscious presented sinus bradycardia and supraventricular extrasystoles. Recovery and bounce-back in two of the triplets took place after 11 hours since instillation of nasal drops, the third boy woke up 20 hours after. The cause of the complications was a pharmacist error, as a result of which each of the triplets received an amount of the drug that was 40 times the therapeutic age dose.

But the side effects may take place with an appropriate dose of NDs also. Pilszczek F.H. et al [22] described a case of myocardial infarction in a young woman due to the use of phenylpropanolamine at a therapeutic dose for weight reduction.

Separately, we should consider the cases of adverse events and side effects caused by improper administration of the drug. For example, the literature describes a case of pulmonary edema when naphazoline is taken orally [23]. Anand J.S. et al [24] reported a case of psychoactive effects in six prisoners when xylometazoline was inhaled. The inmates simulated a runny nose, sinusitis, and allergic rhinitis to accumulate an appropriate dose of ND. They described the result of the overdose as

a "feeling of strength," "stimulation," "excitement".

The development of psychotic disorders is one of the most frequent manifestations of adverse effects of NDs. At the same time, the occurrence of psychoactive effects was observed not only with the systemic use of nasal decongestants, but also with the use of nasal aerosols. In 2020, two cases of the emergence of euphoria in response to the use of naphazoline were described [25]. The publication of Blackwood G.W. is informative in this respect. [26], which described the development of paranoid psychosis in a woman as a result of long-term use of oxymetazoline and camphor, eucalyptus, and menthol oil ointments. Of interest is that the psychiatric disorders proved to be reversible after withdrawal of the drugs.

Sometimes the relationship between the development of a psychotic disorder and the use of NDs may not be obvious due to atypical manifestations of the adverse effect. ENT-doctors should remember that the risk of adverse effects of NDs increases when they are combined with antihistamines, adrenocorticoids, antisecretory agents, i.e. drugs that may cause the same effects. The risk group for the development of psychotic complications includes elderly people with organic brain damage, drug addiction, and mental illnesses [27].

The data of Marshall R.D. and Douglas C.J. are somewhat similar (28), who cite as risk factors for psychotic complications when using phenylpropanolamine: 1) symptoms or anamnestic evidence of bipolar disorder; 2) a history of psychosis; 3) female gender; and 4) a psychiatric family history.

Children are the most sensitive to the toxic effects of NDs. Fatal cases of NDs poisoning in children have been described in the literature. Dart R.C. et al. [29] describe 118 deaths among children due to the use of drugs for colds and coughs. Of them only in 15 cases the drug was prescribed by the doctor, in 103 parents themselves prescribed the treatment to the child with an excessive dose in 88 cases. Factors contributing to the development of fatal poisonings in children were: age under 2 years, simultaneous use of sedatives, use of drugs in preschools, simultaneous use of two medications with similar ingredients, improper use of dosers (measuring spoons, etc.), and incorrect identification of the drug (use of a drug intended for adults).

Self-prescription of medications by parents to infants has a high risk of toxic poisoning, since most cold medications are not used during the first year of life. However, parents often self-prescribe them at their own discretion. In 2006, there were three cases of infant deaths due to taking flu medications [30].

Overdose of NDs even in the form of nasal drops in children can lead to severe central nervous system depression and development of cardiovascular side effects. Thus, Goldhammer J.E. et al. [31] gave an example of toxic ND poisoning with the development of hypertensive crisis in a 4-year-old child during surgery on the upper respiratory tract.

In this case, overdose was caused by improper use of the container with ND: in the lying position of the patient, the bottle-applicator was not placed vertically upwards, which led to an uncontrolled increase in the amount of the drug that entered the

child's nasal ducts [31]. The authors of the study proved that when the container is not positioned correctly and the force of compression is significant, the amount of drug injected increases by 16-50 times and can cause toxic poisoning [32].

Adolescents were highly susceptible to the development of adverse effects from the use of combination cold medications [33]. Age, sex, family income, physical and mental health, use of other drugs and alcohol were of importance.

One of the no less frequent, though not so threatening, undesirable effects of long-term ND use is rhinitis medicamentosa [34]. The latter is more typical for adult patients, while children are more susceptible to the development of toxic poisoning. The presence of hyperreactivity and nasal mucosal edema in a patient combined with poor response to treatment caused or enhanced by long-term use of topical NPs makes it possible to diagnose drug-induced rhinitis [35].

The development of the rhinitis medicamentosa depends on a number of factors and on the type of the selected topical NDs. The undisputed leader among the substances causing the rhinitis medicamentosa is naphazoline. More modern NDs are associated with a much lower percentage of adverse effects. Although, one of the most widely used topical NDs, oxymetazoline, is the cause of rhinitis medicamentosa in 85% [36].

The development of rhinitis medicamentosa is influenced not only by the decongestant, but also by the preservative contained in the bottle of drops or aerosols. The most dangerous in this regard is benzalkonium hydrochloride, which itself can cause the development of rhinitis medicamentosa in thirty days of use [37].

The development of drug-induced rhinitis in a patient depends not only on the type of topical ND, but also on the presence of risk factors that lead to the patient's propensity to develop nasal hyperresponsiveness. It has been found that medication-induced rhinitis develops more frequently in smokers, people with a history of psychiatric complications, and individuals with a higher level of anxiety [38].

Serbian otolaryngologists conducted a study to identify the reason that led patients to use topical NDs with the subsequent development of rhinitis medicamentosa. Such factors were: acute infections of the upper respiratory tract (29.3%), vasomotor rhinitis (21.7%), allergic rhinitis (16.3%), deflected septum (13%), nasal polyposis (12%). Rhinitis due to trauma (4.4%) and hormonal disorders (3.3%) were slightly less common [39].

The publication of Patel A., Levi J.R. and Brook C.D. [36] about a higher propensity to develop opioid dependence among patients with drug-induced rhinitis is interesting in this respect, which should be kept in mind when performing surgical interventions and postoperative analgesia.

A big problem of managing a patient with

medication-induced rhinitis is the high risk of relapse of the disease during the next episode of use of topical nasal decongestants. Thus, according to De Corso E. et al. [40], every third patient with drug-induced rhinitis returns to continuous use of topical NDs one year after withdrawal.

Even short-term use of topical NDs can result in the recurrence of medication-induced rhinitis in prone individuals. For example, in patients with medication-induced rhinitis, seven-day use of topical NDs showed a high rate of nasal hyperresponsiveness a year after drug withdrawal [41]. Patients with medication-induced rhinitis should be aware of the possibility of recurrence of dependence and prohibition of ND prescribing [37].

Promising in this respect is the experience of Australia, where pharmaceutical control over the sale of decongestant-containing drugs was started. The analysis showed that although the number of requests practically did not change in comparison with the period of free and uncontrolled sale, the number of refusals by pharmacists to purchase the drug significantly increased [42].

The prognostically unfavorable factors for recurrence of the rhinitis medicamentosa were high levels of anxiety and signs of chronic inflammatory process of the mucous membrane [38].

The basis of treatment of drug-induced rhinitis is NDs withdrawal. Surgical measures in the nasal cavity, in particular resection of the nasal turbinates, are also widely used. Although the efficacy of nasal cavity resection in various rhinological pathologies remains very debatable, in half of cases unsatisfactory results of surgery occur in patients with medication-induced rhinitis, which makes this category of patients challenging for rhinosurgeons [43].

Conclusions

Thus, although HCs have been and remain one of the most popular drugs for treating the common cold, numerous adverse effects do not allow them to be considered completely safe. Over-the-counter sales and uncontrolled use of NDs increase the risk of unwanted effects. For greater patient safety, it is advisable to introduce control over the prescription and sale of NDs, raise public awareness about the proper use of NDs, their possible side effects and negative consequences, and identify a risk group for the occurrence of rhinitis medicamentosa.

Perspectives for further research. The identification of the main pathogenetic factors, the investigation of the effectiveness of different methods of treatment, strict adherence to the nasal decongestants instructions will improve the quality of medical care and prevent of the development of the rhinitis medicamentosa.

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НЕБАЖАНІ ЕФЕКТИ НАЗАЛЬНИХ ДЕКОНГЕСТАНТІВ (ОГЛЯД ЛІТЕРАТУРИ)

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Резюме

Назальні деконгестанти є одними з найпопулярніших і поширених ліків через високу частоту респіраторних інфекцій. Але, з іншого боку, вони характеризуються значним потенціалом зловживання для користувачів, котрі шукають таких ефектів як ейфорія, психостимуляція, зниження апетиту та схуднення.

Враження серцево-судинної і нервової систем є найчастішими ускладненнями передозування назальних деконгестантів. Виникнення інсульту в молодому віці пов'язано із зловживанням назальними деконгестантами у кожного десятого пацієнта.

Випадки зляканої артеріальної гіпертензії, геморагічних та ішемічних інсультів, серцевої недостатності після надмірного використання назальних деконгестантів відомі як отруєння назальними деконгестантами. І хоча небажані ефекти частіше розвиваються після перорального використання назальних деконгестантів, інтраназальний шлях введення не можна вважати абсолютно безпечним, особливо у випадках передозування препарату.

Розвиток психотичних розладів - один з найчастіших небажаних ефектів назальних деконгестантів. Групою ризику розвитку психотичних ускладнень є старечий вік, органічне враження головного мозку, психічні хвороби і медикаментозна залежність.

Особливо небезпечне зловживання назальними деконгестантами у дітей через високий ризик розвитку токсичного загрозового для життя отруєння. Летальні випадки отруєнь асоціювали з малим віком дитини, використанням декількох ліків з тим самим інгредієнтом, використанням ліків в дитячих дошкільних установах, помилками у вимірюванні дози та ідентифікацією ліку, відсутністю лікарського призначення, використанням ліків для дорослих.

Використання назальних деконгестантів в лежачому положенні пацієнта може призвести до суттєвого збільшення дози

препарату в носовій порожнині і може спричинити токсичне отруєння.

Підлітки досить чутливі щодо розвитку небажаних ефектів назальних деконгестантів. Поява останніх залежить від віку, статі, сімейного доходу, фізичного і психічного здоров'я, вживання інших препаратів і алкоголю.

Особливим видом небажаних ефектів тривалого застосування назальних деконгестантів є медикаментозний риніт, що виникає у дорослих людей зі схильністю до розвитку назальної гіперреактивності. Діагноз медикаментозного риніту виставляють на підставі наявності назальної гіперреактивності і набряку слизової оболонки в комбінації з поганою відповіддю на лікування, спричинених чи підсилених тривалим використанням топічних назальних деконгестантів.

Розвиток медикаментозного риніту залежить від чисельних чинників, таких як тип назального деконгестанту, тип консерванту, наявності чинників ризику, котрі зумовлюють схильність пацієнта до розвитку назальної гіперреактивності.

В огляді наведені літературні дані щодо небажаних ефектів назальних деконгестантів, включаючи розвиток медикаментозного риніту.

Ключові слова: носові деконгестанти; небажаний ефект; отруєння; медикаментозний риніт.

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