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REVIEW PAPER

Forensic aspects of salbutamol overdose – doping, abuse, and suicide

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ABSTRACT

Introduction and aim. Salbutamol is a popular drug used in respiratory diseases. With the increasing prevalence of the use of this substance for therapeutic purposes and its availability on the market, the frequency of its use for other purposes has also risen due to its effects outside the respiratory system. The aim of the study was to investigate the medico-legal aspects of salbutamol.

Material and methods. Medical literature databases such as PubMed, Scopus, Web of Science and Google Scholar were searched. The search was carried out in accordance with the specified purpose of the keyword research using Boolean operators.

Analysis of the literature. In sports, the use of salbutamol is strictly regulated by anti-doping regulations. Recreational substance abuse and accidental overdoses, mainly among children and the elderly, are also important. Rare cases of suicide attempts associated with the use of salbutamol have also been reported.

Conclusion. Salbutamol overdoses are usually not life threatening. However, one should remember about the possibility of accidental overdose, especially among the elderly and children taking the drug chronically. Currently, the use of salbutamol for recreational purposes is rare. In sports, the status of salbutamol use, especially among athletes who do not require its use for therapeutic reasons, is still a controversial issue.

Keywords. abuse, doping, forensic toxicology, overdose, salbutamol, suicide

Introduction

Salbutamol was first synthesized in 1968. It is a substance worth careful analysis from various perspectives because, despite more than half a century passing, it remains one of the primary drugs used in the treatment of respiratory diseases such as asthma and chronic obstructive pulmonary diseases (COPD).[1,2] Despite the fact that this drug has been used for a long time, there are few available publications focusing on the risks associated with its use and on the diagnostics in cases of overdose, which can even result in the death of the patient. Salbutamol is a selective and short-acting agonist of β2 adrenergic receptors that can be found, for example, in bronchi, blood vessels and the uterus, particularly on the membranes of smooth muscle cells.[3] When ingested, nebulized or taken via an inhaler, salbutamol binds to β2 adrenergic receptors on the surface of smooth muscle cells. This interaction in the respiratory system triggers a series of events that lead to the relaxation of the muscles surrounding the airways. This bronchodilation effect helps to alleviate symptoms like wheezing, shortness of breath, and chest tightness.[4] In patients with asthma, it is used to stop an asthma attack and as a preventive measure against exercise-induced bronchoconstriction in people with exercise-induced asthma.[5] While, in COPD it is used to treat periods of exacerbation of the disease.[6] Due to the β receptors being located in areas other than the smooth muscles, sal-

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butamol can be associated with certain undesirable side effects. In the heart, there are 4 times more β1 adrenergic receptors than β2 adrenergic receptors, so impact of salbutamol on the heart should be minor. Based on an *in vitro* study that compared the effects of a non-selective agonists of β adrenergic receptors with salbutamol, it can be concluded that β2 receptor stimulation alone is not sufficient for the early induction of diastolic dysfunction. However, salbutamol in higher doses also acts on β1 adrenergic receptors.[7–9] After administration of salbutamol, the most common cardiovascular symptom is tachycardia. Cases of arrhythmia and angina pectoris have also been reported.[4,5] Effects on the musculoskeletal system may manifest themselves as tremors, however studies also suggest that high doses may cause myopathy.[5] Salbutamol can have metabolic effects: hypokalemia, as well as an increase in glucose, pyruvate and free fatty acids. There is also an observed elevation in insulin levels, which is a consequence of hyperglycemia. For this reason, it should be used with extreme caution in people with diabetes.[10–18] Also, through research conducted on humans, the influence of this substance on adipose tissue has been demonstrated, where stimulation of β2 adrenergic receptors leads to increased glucose uptake by brown adipose tissue (BAT).[19] According to research conducted on rodents, it appears that β3 adrenergic receptors are responsible for the activation of BAT, but the presence of the same mechanism in humans has not been confirmed.[20–22] In terms of the nervous system, salbutamol can cause hallucinations and trigger or prevent anxiety depending on the dose taken. However, it's important to emphasize that salbutamol's impact on the nervous system is generally mild. The central nervous system effects of salbutamol, such as increased alertness, are usually more noticeable when the medication is taken in higher doses. However, due to its bronchodilatory effect, it may help manage stress during an asthma attack. On the other hand, patients with epilepsy who received salbutamol showed a reduction in the frequency of seizures. Some studies have explored the idea that salbutamol's effects on these receptors might influence neuronal excitability and neurotransmitter release, potentially contributing to a decrease in seizure activity.[5] Although salbutamol is a bronchodilator, rare cases of paradoxical bronchospasm have been reported, the mechanism of which is not fully understood.[23] After inhalation, salbutamol is quickly absorbed and transported through the bloodstream. The primary route of metabolism occurs in the liver, where cytochrome P450 enzymes facilitate its transformation into inactive metabolites. These metabolites are then eliminated primarily through the kidneys.[24] Due to the prevalence and high availability of salbutamol, it is also necessary to take into account its medico-legal aspects. The effects caused in the body resulting from its properties and mechanism of action may be used for purposes that are not in line with the accepted principles, for example to improve sport performance. In addition, salbutamol overdose, intentional or accidental, is associated with life-threatening consequences, especially among children and elders.

Aim

The aim of the study was to investigate the medico-legal aspects of salbutamol, with particular emphasis on overdoses and illegal or criminal uses, including doping and poisoning.

Material and methods

This narrative review was developed on the basis of a literature reviews available in recognized medical literature databases and libraries such as PubMed, Scopus, Web of Science and Google Scholar. The search was carried out using Boolean operators and keywords reflecting the purpose of the work e.g. "salbutamol", "abuse", "doping", "poisoning", "overdose", "intoxication", "suicide", "diagnostics" and "post-mortem." Then, on the basis of the selected literature, an analysis of the state of knowledge was made, specifying the most important aspects defined by the purpose of the work. Due to the limited access to full versions of scientific papers, "gray literature" containing only abstracts of conference presentations was excluded from the study. In order to properly ensure the legal context, the applicable legal provisions, in particular regarding doping in sport, were additionally analyzed.

Analysis of the literature

Substances affecting adrenergic receptors were already used 5000 years ago in China. During that time, *Ephedra sinica* was utilized. It contains ephedrine, which, among other effects, non-selectively stimulates α and β adrenergic receptors. In Chinese medicine, it was used to alleviate respiratory system diseases and as a stimulant.[3, 25]

However, earliest publications on adrenergic receptors appeared much later in 1948. Raymond P. Ahlquist proposed the classification of these receptors into α and β types, and the final, currently known classification and structure of receptors were described in 1993.[26,27] The next step in popularizing substances affecting adrenergic receptors was the introduction of isoprenaline in 1947. It has a non-selective impact on β adrenergic receptors. Initially, isoprenaline gained significant popularity among asthmatic patients. However, cases of fatal outcomes were recorded due to the use of this medication in high doses. This led to a decline in sales.[28,29] In response to the demand for a bronchodilator with fewer side effects, the synthesis of salbutamol in 1968 by a team led by David Jack proved significant. It was the world's first selective β2 receptor agonist and was in-

troduced under the trade name Ventolin. Compared to its predecessor, isoprenaline, salbutamol exhibits fewer side effects and has a longer duration of action after administration.[1,2] Following the synthesis of salbutamol, the next step was to obtain a substance with a longer duration of action. The first drug in the class of long-acting beta-2 receptor agonists obtained was salmeterol (trade name Serevent).

Dosage and route of administration

The most popular form of administering salbutamol is through inhalation. The oldest among the currently available inhalation methods is the use of a nebulizer. Several types of these devices are available on the market. Their common feature is turning liquid medicine into a mist. The aerosol is inhaled by the patient using a face mask or mouthpiece. Nebulizers can be pneumatic (jet nebulizers), meaning they use compressed air or oxygen. They can be divided into two subcategories: breath-enhanced and breath-actuated. These devices have large sizes and generate significant noise. A newer generation includes nebulizers with a mesh containing multiple holes (vibrating mesh technology). Aerosol is produced through vibration. During use, they generate less noise, are more efficient, and more portable. Currently, they are more expensive than jet nebulizers.[30–33] In the case of adults, the nebulization solution is prepared by diluting 2.5 to 5 mg of salbutamol in 2-5 ml of 0.9% sodium chloride, while for children aged 5–12 years, the dose of salbutamol is half as much.[10] A Metered-dose inhaler (MDI) is a device that delivers a specific amount of medication to the lungs in the form of an aerosol. The aerosol is released from the inhaler by pressing the top of the canister containing the drug. MDIs can be used with or without a spacer. Taking medications with an attached spacer to the MDI yields better results and reduces errors in drug administration. This is a very convenient way to take salbutamol because the inhaler itself is portable, the administration time is short, and it can be used in any conditions. However, patient training is required, especially regarding the correct coordination of inhalation.[34–36] MDIs are available, delivering 100 μg of salbutamol in a single inhalation dose. The dosage for adults is 100–200 μg for the relief of acute episodes of bronchospasm and for the prevention of bronchospasm. The prevention of exercise-induced bronchospasm requires a dosage of 200 μg. The maximum daily dose is 800 μg. The dosage for children aged 6-12 is similar, but the maximum dose is 400 μg.[16] Another method of inhaling salbutamol is using a dry-powder inhaler (DPI). Similar to MDIs, the medication is delivered directly to the lungs, but in the form of powder rather than an aerosol. The initiation of medication release from the inhaler is also different. The powder is drawn into the lungs during the patient's inhalation, requiring at least a minimum inspiratory effort. This method does not require synchronizing inhalation with the pressing of the top of the canister, as in MDIs. However, with higher doses, dry powder may cause coughing. Studies have shown that the use of spacers with MDIs decreases the risk of incorrect application by patients.[35,37–39] The DPI is available in doses of 100 or 200 μg per inhalation, and the dosage is the same as in the case of MDI.[14,15] Salbutamol is less commonly administered orally. It is available in the form of tablets or syrup. It can also be used in this form for treating asthma, but it is less effective compared to the inhalation form. Its onset of action is slower, and it has more side effects.[40] For adults, the recommended dose of salbutamol is 2-4 mg three to four times a day, with a maximum daily dose ranging from 16 to 32 mg depending on the manufacturer. In children aged 6–12, the suggested dose is 2 mg three to four times a day, with a maximum daily dose of 8 or 24 mg, depending on the manufacturer.[12,13] The syrup contains 2 mg of salbutamol in 5 mL and it is administered 3-4 times a day. The recommended dose is 4 mg for adults, 2 mg for children aged 6-12, and 1–2 mg for children aged 2–6.[11] Salbutamol is also available in the form of an injectable solution. This allows the administration of the medication subcutaneously, intramuscularly and intravenously. Indications for administering salbutamol in this form include asthmatic conditions and severe bronchospasm. Intravenous administration of salbutamol may be less effective and cause more side effects than its inhaled counterpart. For subcutaneous or intramuscular administration, the dosage is 8 μg/kg. On the other hand, intravenous administration requires dilution in sodium chloride with or without dextrose and administration at a rate of 3–20 μg per minute (dosage varies depending on the manufacturer).[17,18]

Pharmacokinetics and metabolism

The pharmacokinetics of salbutamol depends primarily on the route of administration. The most common method of administering salbutamol is through inhalation using an MDI with a spacer. Following this method, the onset of action is observed approximately 5 minutes after ingestion. The bioavailability of salbutamol is low, mainly due to local administration, limiting the amount of the substance entering the bloodstream. The bronchodilatory effect of salbutamol does not correlate with its serum concentration. The highest serum concentration is observed after 3–4 hours, and the average half-life of plasma activity is 4–6 hours. Clinically, it is observed that the average duration of action of salbutamol is around 6 hours.[3,41–44] Clinically used preparations containing salbutamol are a racemic mixture of the R- and S-enantiomers. The metabolism of salbutamol primarily occurs in the liver and gastrointestinal tract, where it undergoes conjugation with sulfate through sulfo-

transferase, leading to the formation of the metabolite – salbutamol – 4'-O-sulphate. Salbutamol partially unchanged and its metabolites are then excreted from the body primarily through urine.[45,46]

Table 1. Characteristics of salbutamol administration routes[10–18,31,40]

	Nebulizer	Metered-dose inhaler (MDI)	Dry-powder inhaler (DPI)	Salbutamol p.o.	Salbutamol i.v, i.m, s.c.
Drug form	Solution for oral inhalation	Liquefied gas propellant	Dry powder	Tablets or syrup	Solution
Method of use	Inhalation via face mask or mouthpiece, breath-enhanced or breath-actuated	Inhalation by pressing the top of the canister containing drug	Inhalation the powder into the lungs	Orally	Subcutaneously, intramuscularly, intravenously
Dosage	Adults: 2.5-5 mg dissolved in 0.9% sodium chloride Children 5-12 years old: 1.25-2.5 mg dissolved in 0.9% sodium chloride	Adults: 100 or 200 µg, daily max dose 800 µg Children 5-12 years old: 100 or 200 µg, daily max dose 400 µg	Adults: 100 or 200 µg, daily max dose 800 µg Children 5-12 years old: 100 or 200 µg, daily max dose 400 µg	Adults: 2 to 4 mg 3–4 times a day Children 5-12 years old: 2 mg 3-4 times a day	s.c and i.m – 8 µg/kg i.v – 3–20 µg per minute
Advantages	No coordination of inhalation required	Portable	Portable, no coordination of inhalation required	Portable, no coordination of inhalation required	No patient cooperation required
Disadvantages	Non-portable, noisy, long drug administration time	Most MDIs do not have dose counter (difficult to determine how many doses left), correct coordination of inhalation required	At least minimum inspiratory effort required, cough in case of higher doses	Later effect than after inhalation, more side effects	Risks associated with administration subcutaneously, intramuscularly, intravenously

Interactions

Interactions between salbutamol and other drugs are a significant aspect that requires attention when treating patients with respiratory conditions alongside other medical conditions. Salbutamol, as a bronchodilator, can interact with certain substances, potentially affecting treatment efficacy or increasing the risk of side effects. If salbutamol is used concurrently with other drugs affecting adrenergic receptors and exerting similar effects, there may be a potential intensification of side effects, such as increased heart rate, elevated blood pressure, and the risk of cardiac arrhythmias.[16] Additionally, the use of formoterol (a long-acting agonist of β2 adrenergic receptors) may lead to an increased tolerance to the bronchodilation effect of salbutamol.[47] Salbutamol should not be combined with non-cardioselective beta-blockers like propranolol as they block its effects on beta2-receptors and hence its bronchodilatory effects.[48–50] Interactions also occur between salbutamol and methylxanthine derivatives such as theophylline. There are studies showing improvement in spirometric parameters with the use of a combination of salbutamol and theophylline.[51,52] On the other hand, it has been demonstrated that the combination of these two drugs can lead to more pronounced tachycardia and supraventricular extrasystoles. Additionally, the effectiveness of theophylline was found to be higher when not used in conjunction with salbutamol.[53,54] Studies have shown that salbutamol binds to monoamine oxidases (MAO) and inhibits their activity. Monoamine oxidases are enzymes that catalyze the oxidation reaction of monoamines. Salbutamol exhibits a greater preference for binding to MAO-B than to MAO-A [55,56]. In a situation where a patient is taking both salbutamol and drugs from the group of MAO inhibitors, there may be a synergistic effect. The result of such a combination could be an intensification of adverse effects, particularly related to the cardiovascular system (increase in blood pressure).[16,57] Also, tricyclic antidepressants (TCAs) are used in the treatment of depression, and they too can intensify adverse effects on the cardiovascular system such as prolonged the QTc interval.[58] One of the adverse effects of salbutamol can be hypokalemia. Therefore, it is risky to use it with other drugs that cause a decrease in blood potassium levels. Examples of such drugs include non-potassium sparing diuretics, which encompass carbonic anhydrase inhibitors, loop diuretics, and thiazides.[3] Caution should also be exercised when using salbutamol and digoxin. A study conducted on healthy volunteers indicates that salbutamol lowers the serum concentration of digoxin. However, the concentration in skeletal muscles remains unchanged.[59] Using desflurane in patients taking salbutamol is also risky, as it is associated with the potential for hypotension.[58]

Detection and interpretation

In recent years, there has been a significant development in methods for detecting salbutamol in body fluids. The methods used allow to find substances in concentrations at the level of femtograms per milliliter.[60] In general, methods of detection and determination of concentrations can be divided into physico-chemical and immunoassays.[61,62] Physico-chemical detection methods include, for example, mass spectrometry with gas or liquid chromatography. They are characterized by high hardware requirements, are time-consuming and have higher cost.[62,63] Their advantage, however, is that they can be used for micro-volume probes for analysis.[64] Immunoassays are faster, less expensive and more accessible.[61] They use specific antibodies labelled with enzymes, chemiluminescent molecules, metal particles or DNA molecules to detect substances.[60,62,65] When using

methods based on immumoassays, it is also necessary to take into account the possibility of cross-reactions, especially with other low molecular weight molecules with a similar structure, such as clenbuterol.[60,65,66] Blood or urine may be used as biological material to detect salbutamol in the body and to determine its concentrations.[67–70] Some of the dose taken is also metabolized in the liver.[67] However, when inhaled, the drug has a predominantly local effect and is partially absorbed into the bloodstream, bypassing the liver and the first pass effect. A portion of the inhaled dose can also be swallowed and absorbed into the digestive system.[70] In the blood, salbutamol may be measured both in serum and plasma.[61] The concentration of salbutamol in urine may vary depending on the urine density, which is influenced by hydration levels during exercise. In order to reduce the number of false negative results, it is postulated to adjust the urine specific gravity to a standardized level.[71] When interpreting the results, especially trace concentrations, the possibility of environmental contamination should be taken into account.[60] Salbutamol is sometimes used to increase muscle mass gain in farm animals such as pigs.[62,72] Moreover, ultra-sensitive methods detect the presence of trace amounts of salbutamol in water.[66] In addition, the metabolism of the medicine in the human body differs between people who use the medicine chronically (e.g. asthma) and those who use it occasionally (e.g. to improve performance) or individuals not using the drug.[73]

Doping

Doping in sports is an unethical practice involving the use of substances or methods that enhance an athlete's physical performance beyond their natural abilities. The primary goal of doping is to achieve better sports results by increasing strength, endurance, speed, or the body's ability to recover. Sports organizations such as the World Anti-Doping Agency (WADA) undertake comprehensive efforts to detect and eliminate doping from sports, ensuring the integrity of competition and safeguarding athletes' health.[74,75] Salbutamol has also found application in sports, as athletes are at higher risk experiencing of exercise-induced asthma (EIA) and exercise-induced bronchospasm (EIB) compared to the general population. EIA refers to the narrowing of airways triggered by exercise, leading to symptoms such as wheezing, coughing, shortness of breath, and chest tightness in individuals with a history of asthma. EIB, on the other hand, is a similar condition that can also occur in individuals without a previous asthma diagnosis. Both EIA and EIB are caused by the exposure of airways to cold, dry air during exercise, leading to inflammation and constriction. For athletes, these conditions can be challenging to manage, as they can significantly impact performance and overall well-being. However, it's important to note that athletes with EIA or EIB should not be discouraged from participating in sports. Proper management, including pre-exercise use of bronchodilators like salbutamol (with adherence to anti-doping regulations), warm-up routines, and appropriate medical guidance, can help individuals with these conditions continue to engage in physical activities safely and effectively.[74,76,77] The second aspect is taking the drug by non-asthmatic athletes to improve results. Striking a balance between legitimate medical needs and preventing its misuse for a doping purpose poses a challenge in the ongoing fight against doping in sports. As it is a controversial subject, the position of the WADA on such use of salbutamol has been changing over the years. Currently, all selective and non-selective substances acting on β2 adrenergic receptors are only allowed in strictly defined cases. The use of inhaled salbutamol is permitted only at a maximum dose of 1600 μg over 24 hours in divided doses not to exceed 600 μg over 8 hours starting from any dose. The acceptable concentration in urine (1000 ng/mL) was also established, the exceeding of which indicates taking the drug in unacceptable doses (Table 1). In the event of a positive doping control result, the athlete may undergo a pharmacokinetic test in order to prove that they have been taking the drug in doses complying with the anti-doping rules. This is aimed at ruling out the possibility that the athlete's body metabolizes the drug in an atypical manner.[78] Despite the relationship between the dose taken and the concentration achieved in urine, studies suggest that it is not possible to determine the exact dose of the drug taken based on the concentration in a urine sample.[79–82] Literature on this subject shows discrepancies regarding the desired effects of salbutamol in terms of doping. An *in vitro* study suggests that this substance may have androgenic activity and exhibit an anabolic effect.[83] There are studies conducted on people suggesting that taking salbutamol increases muscle strength and contractility. The effect varies depending on the muscle group and better results were achieved when the drug was administered orally rather than inhaled.[84–86] One meta-analysis ruled out positive effects of salbutamol on aerobic and anaerobic performance and strength in healthy athletes. Additionally, it has been suggested that due to the lack of strong evidence that taking salbutamol can lead to improved athletic performance, salbutamol should be removed from WADA's list of banned substances.[87] According to another meta-analysis, the intake of salbutamol by healthy athletes improves their anaerobic capacity, however, it is not clear whether such effects are achievable at therapeutic doses approved by WADA.[86] Due to the above unclear or even contradictory reports, determining the objectives of anti-doping regulation regarding salbutamol is impossible.

Table 2. Concentrations of salbutamol related to effect[75,82,88,89]

Maximal level approved by WADA (urine)	Therapeutic level (blood)	Rescue level (blood)	Toxic level (blood)	Lethal level (blood)
1000 ng/mL	4–20 ng/mL	20–40 ng/mL	>30 ng/mL	>160 ng/mL
4.18 nmol/L	0.0167–0.0836 nmol/L	0.0836–0.1672 nmol/L	>0.1254 nmol/L	>0.6696 nmol/L

Abuse and accidents

The form of salbutamol abuse or overdose varies greatly. The misuse of salbutamol is a concerning issue that can have significant health implications. The therapeutic concentration of the drug and the toxic concentration in the serum differ by only 10 ng/mL. Meanwhile, the concentration considered lethal is approximately 8 times higher than the therapeutic dose (Table 2). In the literature, already in the 1980s, authors drew attention to the risk of salbutamol abuse among children. Lack of proper education of the patient or their caregiver on the dosage of the drug can lead to accidental or intentional intake of doses higher than recommended.[90] Children who do not fully comprehend the potential risks associated with misusing medication might engage in such behavior without realizing the potential harm. Especially in a stressful situation during an acute asthma attack when they administer large doses of medication to control the symptoms. Cases of symptomatic overdose of salbutamol in children have also been reported.[91–93] Determining poisoning in such cases due to the non-specific set of symptoms will pose significant diagnostic problems, therefore it is crucial to collect a thorough interview regarding the possibility of drug overdose. The main symptoms in such cases included cardiac arrhythmias in the form of tachycardia with QT prolongation, hypokalemia, glycemic disturbances and metabolic acidosis.[93,94] In cases of suspected overdoses, it is crucial to quickly collect blood for analysis due to the short half-life of salbutamol, which is 3-6 hours.[89] In addition, young children who are left unattended may accidentally take too much medicine by taking and ingesting a medicine that belongs to someone else.[95] In such cases, overdoses leading to life-threatening cardiac disorders have been reported.[96] Moreover the abuse of salbutamol by children can stem from different factors and take various forms. There have been reports of pediatric patients misusing salbutamol to relieve anxiety or induce euphoria.[97] The ease of access to inhalers, if other family members are using prescribed medication, can contribute to this phenomenon. When the drug is used for recreational purposes, it usually involves the inhaled form. Then, the gases used as a carrier of the substance in the inhaler also contribute to the intoxication effect combined with the action of salbutamol. There are also publications on adult patients addicted to this drug. In some cases, in addition to the anxiolytic effect, even hallucinations are said to have occurred. The off-label use of salbutamol as a means to alleviate anxiety is a topic that has gained attention. The mechanisms underlying this reported effect are not fully understood, and the potential risks and side effects of using salbutamol for anxiety relief have not been comprehensively studied.[98] Chronic abuse of salbutamol can result in a range of complications, including hypokalemia and acute overdose leads to sinus tachycardia, ventricular and supraventricular tachycardia and myocardial ischemia. Additionally, a case of diagnostic difficulties associated with recurrent supraventricular tachycardia resulting from chronic salbutamol abuse was also described.[99] Additionally, cases of chronic abuse have been reported in association with Munchausen syndrome.[100] Furthermore, relying on salbutamol inappropriately can lead to a diminished effectiveness of the medication over time. This means that when it is genuinely needed to manage asthma symptoms, it might be less effective due to tolerance development. Chronic misuse might also exacerbate underlying respiratory issues and increase the risk of respiratory infections, given that prolonged bronchodilation.[101] Furthermore the geriatric population is also important as it is particularly prone to overdose. In such cases, overdosing may be associated with progressive dementia changes resulting in an additional dose being taken due to memory problems or difficulties using the inhaler and the wrong way of drug administration. This is especially dangerous due to the widespread occurrence of polypharmacy and the possible interaction between the drugs used by the patient, reduced cognitive abilities, visual impairment, deterioration of liver, kidney and heart function in this population. The possibility of overlapping with pre-existing arrhythmias and those caused by drug overdose is also particularly important. An unusual example of misuse of inhaled salbutamol is multiple applications of the drug directly to the skin for self-injury and burns.[102,103] In the analysis of the abuse of this drug, it is important to also consider non-medicinal ingredients present in for example MDI. For instance, in the most well-known product containing salbutamol - Ventolin, besides the medication, there is 1,1,1,2-tetrafluoroethane (HFA-134a). Studies conducted on animals and healthy volunteers have shown that this is a relatively safe gas. This means that HFA-134a should not pose a threat even if a large dose of the medication is ingested. However, rapid emptying of containers containing this gas lowers their temperature, which in extreme cases can lead to frostbite.[104–107] In the case of a salbutamol overdose, substances with antagonistic effects, such as those that block β2 adrenergic receptors (e.g., propranolol), should be administered, and electrolyte imbalances such as hypokalemia should be corrected.[108,109]

Suicides and poisonings

Possibility of poisoning and death caused by intentional overdose or criminal administration of xenobiotics is one of the challenges in post-mortem diagnostics. A multi-threaded analysis is then required using post-mortem diagnostic tools, information obtained during the investigation conducted by the authorities and the medical data of the deceased. In such cases, the key issues are also deciding whether there was a homicide or a deliberate overdose of the drug with the intention of suicide. There have been cases of the use of salbutamol for suicidal purposes described in literature.[110] The dosage of salbutamol is usually related to its route of administration, but the lethal dose of the substance still requires clarification. Although in most cases the patients are saved without damage to their health, there have been cases of poisoning that resulted in death.[111,112] A particularly vulnerable group are patients with chronic respiratory diseases (e.g. asthma) due to easy access to the drug; moreover, the presence of a chronic disease increases the overall risk of suicide, it also applies to the pediatric population.[113] In addition, due to the scant symptoms resulting from small excess doses, many suicide attempts may go unnoticed and the symptoms ignored, which makes it difficult to provide the patient with appropriate psychological care. In addition, chronically ill patients often choose drugs they take on a daily basis for suicide attempts. The most common form of medication used in self-poisoning are oral form of salbutamol.[114,115] The key procedure in such cases is the analysis of the victim's environment, as in the case of suicide, multiple empty packages of the substance consumed can usually be found. In cases of salbutamol overdose, death is caused by cardiac arrhythmias (mainly ventricular and supraventricular arrhythmia) caused by sympathetic receptors stimulation and hypokalaemia.[93,111] This creates significant diagnostic problems during post-mortem examination, due to the possible lack of detectable changes during autopsy, which may suggest sudden cardiac death in a functional mechanism.[116,117] Under such circumstances, particularly in cases where there are no witnesses or if the individual is found deceased without any attempts at rescue, authorities may discontinue their investigation. Then toxicological and histopathological tests become crucial to confirm or exclude poisoning.[118,119] In similar cases, important information is provided by post-mortem examination of salbutamol concentrations in blood and urine, however, due to the frequent use of the drug in the population, its result should be interpreted in consideration of the patient's medical documentation regarding the drugs taken.[120–124] The differential diagnosis should also take into account a severe asthma attack as the cause of death in which salbutamol overdose occurred during life-saving procedures.[125–127] An attack may occur as a result of a stressful situation, e.g. during a robbery. Death can be a result of a bronchospasm, but also the bronchodilator overdose.[125] In such cases life-threatening overdose occurs as a result of unknowingly and unintentionally taking too much of the drug by the victim as a rescue in emergency situation. An important issue is also determining the criminal administration of salbutamol in cases of poisoning or the Munchausen by proxy syndrome, where the victim is often a child and the perpetrator is their parent.[115]

Conclusion

The growing popularity of salbutamol results in an increase in its use for non-therapeutic purposes. The uncommon substance overdoses typically end up with mild complications and a full recovery of patient. However, one should remember about abuse of substances for recreational and sports performance purposes, inconsistent with anti-doping regulations. In addition, special care should be taken of people regularly taking salbutamol for health purposes, especially children and elderly, due to possibility of accidental overdose, e.g. by taking an additional dose. Further research is needed to better define suicidal and criminal use, particularly in chronically ill population, including post-mortem procedures for suspected overdose. Additionally, future research should investigate the post-mortem concentrations of salbutamol to establish clearer thresholds that differentiate between therapeutic use and accidental or intentional misuse.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

Data availability

No datasets were generated or analyzed during the current study

Ethics approval

Not applicable.

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