

Deposition of intranasal glucocorticoids – preliminary study

Depozycja donosowych preparatów glikokortykosteroidowych – badania wstępne

Authors' Contribution:

A – Study Design
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C – Statistical Analysis
D – Data Interpretation
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Piotr Rapiejko^{1ABCEFG}, Tomasz R. Sosnowski^{2ABCEFG}, Jarosław Sova^{3ADF}, Dariusz Jurkiewicz^{1ADF}

¹Department of Otolaryngology with Division of Cranio-Maxillo-Facial Surgery, Military Institute of Medicine, Warsaw, Poland

²Chair of Integrated Process Engineering, Faculty of Chemical and Process Engineering, Warsaw University of Technology, Warsaw, Poland

³Department of Otolaryngology 7th Navy Hospital in Gdansk, Poland

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ABSTRACT:

Introduction. Intranasal glucocorticoids are the treatment of choice in the therapy of rhinitis. The differences in efficiency of particular medications proven by therapeutic index may result from differences in composition of particular formulations as well as from diverse deposition in nasal cavities. Intranasal formulations of glucocorticoids differ in volume of a single dose in addition to variety in density, viscosity and dispenser nozzle structure. The aim of this report was to analyze the deposition of most often used intranasal glucocorticoids in the nasal cavity and assessment of the usefulness of a nose model from a 3D printer reflecting anatomical features of a concrete patient.

Material and methods. Three newest and most often used in Poland intranasal glucocorticoids were chosen to analysis; mometasone furoate (MF), fluticasone propionate (FP) and fluticasone furoate (FF). Droplet size distribution obtained from the tested formulations was determined by use of a laser aerosol spectrometer Spraytec (Malvern Instruments, UK). The model of the nasal cavity was obtained using a 3D printer. The printout was based upon a tridimensional reconstruction of nasal cavity created on the basis of digital processing of computed tomography of paranasal sinuses. The deposition of examined medications was established by a method of visualization combined with image analysis using commercial substance which colored itself intensively under the influence of water being the dominant ingredient of all tested preparations. On the basis of obtained results regions of dominating deposition of droplets of intranasal medication on the wall and septum of the nasal cavity were compared.

Results. Droplet size of aerosol of tested intranasal medications typically lies within the range of 25-150 µm. All tested medications deposited mainly on the anterior part of inferior turbinate. FP preparation deposited also on the anterior part of the middle nasal turbinate, marginally embracing a fragment of the central part of this turbinate as well together with deposition in the middle and superior nasal meatus reaching the region of nasal ceiling and olfactory field. MF preparation deposited on the anterior part of the inferior turbinate and central part of this turbinate alike. The area of mucous membrane of lateral wall of nasal cavity on which MF deposited was similar to the area achieved after the application of FP preparation but much greater than in the case of FF preparation. FF drug deposition concentrates only on the anterior part of the inferior turbinate. Despite directing the drug to the lateral wall of the nasal cavity a great proportion of examined preparations deposit also on the nasal septum.

Conclusions The practical application of tridimensional representation (3D printout) of actual geometry of nasal cavity to establish the deposition of inGCS was proven. Droplet size and the geometry of the aerosol cloud introduced into the nostril determine the significant deposition of medication droplets in the anterior part of the nasal cavity. Both physical properties of the drug as well as spraying system applied influence spatial distribution of the drug. The interaction of the air flow with the layer of deposited fluid plays a major role in the deposition of the drug in the nasal cavity, therefore it is so important that the drug does not drain by gravity but remains at the site of deposition which may be reinforced by thixotropic properties of the preparation.

KEYWORDS:

nasal deposition, nose, turbinate, intranasal glucocorticosteroids

STRESZCZENIE:

Wprowadzenie: W leczeniu nieżytów nosa lekami z wyboru są glikokortykosteroidy donosowe. Różnice w skuteczności poszczególnych preparatów (wykazane indeksem terapeutycznym) mogą wynikać zarówno z różnic w składzie poszczególnych preparatów, jak również ze zróżnicowanej ich depozycji w jamach nosa. Preparaty donosowych glikokortykosteroidów różnią się bowiem objętością pojedynczej dawki, jej gęstością i lepkością, a także konstrukcją dyszy dozownika, dzięki któremu aplikowany jest preparat.

Celem pracy: jest analiza depozycji najczęściej stosowanych w Polsce donosowych glikokortykosteroidów w obrębie jamy nosa oraz ocena przydatności modelu nosa uzyskanego z drukarki 3D, który odwzorowuje strukturę anatomiczną jamy nosowej konkretnego pacjenta.

Materiał i metody: Do analizy wybrano 3 najnowocześniejsze i najczęściej stosowane w Polsce glikokortykosteroidy donosowe: furoinian mometazonu (MF), propionian flutikazonu (PF) i furoinian flutikazonu (FF). Rozkład wielkości kropeł uzyskiwanych z badanych preparatów wyznaczono za pomocą laserowego spektrometru aerozolowego Spraytec (Malvern Instruments, UK). Model jamy nosa uzyskano, wykorzystując możliwości drukarki 3D. Wydruk oparto o trójwymiarową rekonstrukcję jamy nosa stworzoną po cyfrowej obróbce obrazu tomografii komputerowej zatok. Depozycję badanych leków w jamie nosa określano metodą wizualizacyjną. Obraz analizowano, stosując komercyjną substancję ulegającą intensywnemu zabarwieniu pod wpływem wody (która jest głównym składnikiem wszystkich badanych preparatów). W oparciu o dane uzyskane z analizy obrazu porównano następnie obszary dominującej depozycji kropeł leku donosowego – tak na ścianie bocznej jamy nosowej, jak i na przegrodzie.

Wyniki: Wielkość kropeł aerozolu przebadanych leków donosowych najczęściej mieści się w zakresie od 25 do 150 μm . Wszystkie badane preparaty osadzały się przede wszystkim w przedniej części małżowiny nosowej dolnej. Preparat PF deponował się także na przedniej części małżowiny nosowej środkowej, w nieznacznym stopniu obejmując również fragment jej części centralnej. Osadzał się także w przewodzie nosowym środkowym i górnym, dochodząc do rejonu strępu nosa i okolic pola węchowego. Preparat MF deponował się zarówno na przedniej części małżowiny nosowej dolnej, jak i w centralnej jej części. Powierzchnia błony śluzowej bocznej ściany nosa, na której osadził się preparat MF była zbliżona do uzyskanej po aplikacji preparatu PF, ale znacznie większa niż w przypadku preparatu FF. Depozycja leku FF koncentrowała się jedynie w przedniej części małżowiny dolnej. Pomimo kierowania leku na boczną ścianę nosa, znaczna część badanych preparatów deponowała się również na powierzchni przegrody nosa.

Wnioski: Wykazano możliwość zastosowania trójwymiarowego odwzorowania rzeczywistej geometrii jamy nosa (wydruk 3D) do określenia depozycji donosowych glikokortykosteroidów. Potwierdzono, że wielkość kropeł i geometria chmury rozprzeczanej w jamie nosowej aerozolu, decydują o depozycji leku w przedniej części jamy nosa. Na przestrzenny jej rozkład mają wpływ i właściwości fizyczne leku, i zastosowany układ rozpylania. W przemieszczaniu się leku w obszarze jamy nosa dużą rolę odgrywa oddziaływanie przepływającego powietrza z warstwą zdeponowanego preparatu. Dlatego istotne jest, aby nie spływał on grawitacyjnie, lecz pozostawał w miejscu depozycji. Sprzyjają temu właściwości tiksotropowe preparatu.

SŁOWA KLUCZOWE: depozycja nosowa, nos, małżowina nosowa, sterydy donosowe

INTRODUCTION

A characteristic feature of rhinitis is the presence of inflammation in the lining of the nose and paranasal sinuses [1]. Taking into account the etiology of rhinitis in its therapy, intranasal glucocorticoids (inGCS) are recommended as a treatment of choice. Both ARIA (Allergic Rhinitis and its Impact on Asthma) [2] as well as European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS 2012) [3] and Polish Standards of Rhinitis Treatment (PoSLeNN) [4] recommend intranasal glucocorticoids as a basic treatment. Among currently recommended substances are: mometasone furoate, fluticasone furoate and fluticasone propionate which due to low bioavailability and due to this feature - high safety - are advocated in allergic rhinitis treatment [5]. Research by Schäfer et al. [6] revealed significant differences in therapeutic index (TIX) to which both effectiveness and safety of the inGCS contribute. TIX of mo-

metasone furoate is 7.0 and for fluticasone furoate just 0.33 [6]. The inGCS preparations differ according to the volume of a single dose as well as viscosity or dispenser (the dispenser nozzle in particular). The authors proposed a working thesis that therapeutic effect of intranasal glucocorticoids depends not only on the effectiveness of active substance itself but also the deposition in the nasal cavity contributes significantly. Even though multiple research teams have been attempting to assess the deposition of intranasal drugs, due to numerous methodological limitations the results of previously published studies are inconclusive. The *In vivo* studies usually conducted with use of radiolabelled aerosols require modifications of the drugs produced. Additionally, these are usually conducted on very small samples. The *In vitro* studies conducted so far were based on nose models only partially reflecting anatomical relationships within the nasal cavity. Technological progress associated with the introduction of the widespread use of 3D

Tab.I. Comparison of the investigated drugs.

TYPE OF ACTIVE INGREDIENT	MARKING IN THE STUDY	VOLUME AND MASS OF A SINGLE DOSE OF ACTIVE INGREDIENT	SHAPE OF THE TIP OF THE DISPENSER AND OTHER FEATURES
fluticasone furoate	FF	approx. 50 ml / 27.5 mg	- 
mometasone furoate	MF tix	approx. 100 ml / 50 mg	Thixotropic drug 
fluticasone propionate	PF	approx. 100 ml / 50 mg	-

printers has brought new research capabilities and the possibility of preparing models of nasal cavities of a particular patient based on digital processing of computed tomography of these patients. The aim of this report was to analyze the deposition of most popular inGCS within the nasal cavity with use of a nasal cavity model obtained from a 3D printer.

MATERIAL AND METHODS

The research was divided into two stages: during the first stage the properties of atomized drugs were established, in the second the deposition of drugs in the anatomically appropriate model of nasal cavity was examined. The tests were conducted with use of original packages of most often sold inGCS preparations in September and October 2015 in Poland. Three most modern substances were selected for analysis: mometasone furoate, fluticasone furoate and fluticasone propionate which due to low bioavailability and high safety are recommended in allergic rhinitis treatment [2]. As many preparations containing abovementioned substances are available on the Polish market it was decided to conduct the research using the most commonly prescribed preparations in Poland. According to IMS DataView 10/2015 report concerning sales of inGCS packages in September and October 2015, most often sold preparation containing mometasone furoate (MF) was Pronasal, most often sold preparation containing fluticasone furoate (FF) was Avamys and most often sold preparation containing fluticasone propionate (FP) was Fanipos. Table 1 provides characteristics of the investigated drugs.

STAGE I – ANALYSIS OF PHYSICAL PROPERTIES OF TESTED PREPARATIONS

Measurement of droplet size distribution

Measurement of droplet size distribution obtained from the tested formulations was determined by use of a laser aerosol spectrometer Spraytec (Malvern Instruments, UK) which enables to measure particles/aerosol droplets within the range

of 0.1-900 μm with high sampling frequency (1 kHz). All the atomizers were placed at the same distance (15 cm) from the axis of the course of the laser beam and the position of the optical receiver. Aerosol was triggered manually. The schema of droplet size measurement layout is depicted in Fig. 1. Each measurement of size distribution was repeated three times.

STAGE II – ANALYSIS OF DRUG DEPOSITION IN THE NASAL CAVITY

Preparation of tridimensional anatomical model of the nasal cavity

The model of the nasal cavity was obtained using a 3D printer. The printout was based on tridimensional reconstruction of the nasal cavity created after digital processing of computed tomography of paranasal sinuses. The precision of mapping of the model was determined by precision (thickness) of layers obtained in CT scan. Mapping of real-life objects by 3D printers, due to technology employed, is more precise compared to images obtained in computed tomography.

Computed tomography was performed using Siemens Emotion VI scanner – thickness of layer with reconstruction 0.63 mm kernel H 31. To obtain the printout a CT scan of size close to average size of the nasal cavity was chosen by analyzing the sizes of the inferior and middle turbinate. The greatest distance between the posterior and anterior end of these turbinates was taken into account. A vertical dimension of the inferior turbinate was also taken into consideration measured from its attachment point to the lower margin at height of the anterior point of attachment of the middle turbinate [8]. One hundred nasal cavities were assessed (50 computed tomographies): 50 left and 50 right sides. Excluded from the analysis were CT scans containing inflammatory changes, benign and malignant tumors filling nasal cavity and anatomical abnormalities. The following abnormalities were excluded: significant curvature of the nasal septum, pneumatized middle turbinates and large asymmetry of sinuses. A total of 78 CT scans belonging to patients aged 25-63 were finally evaluated.

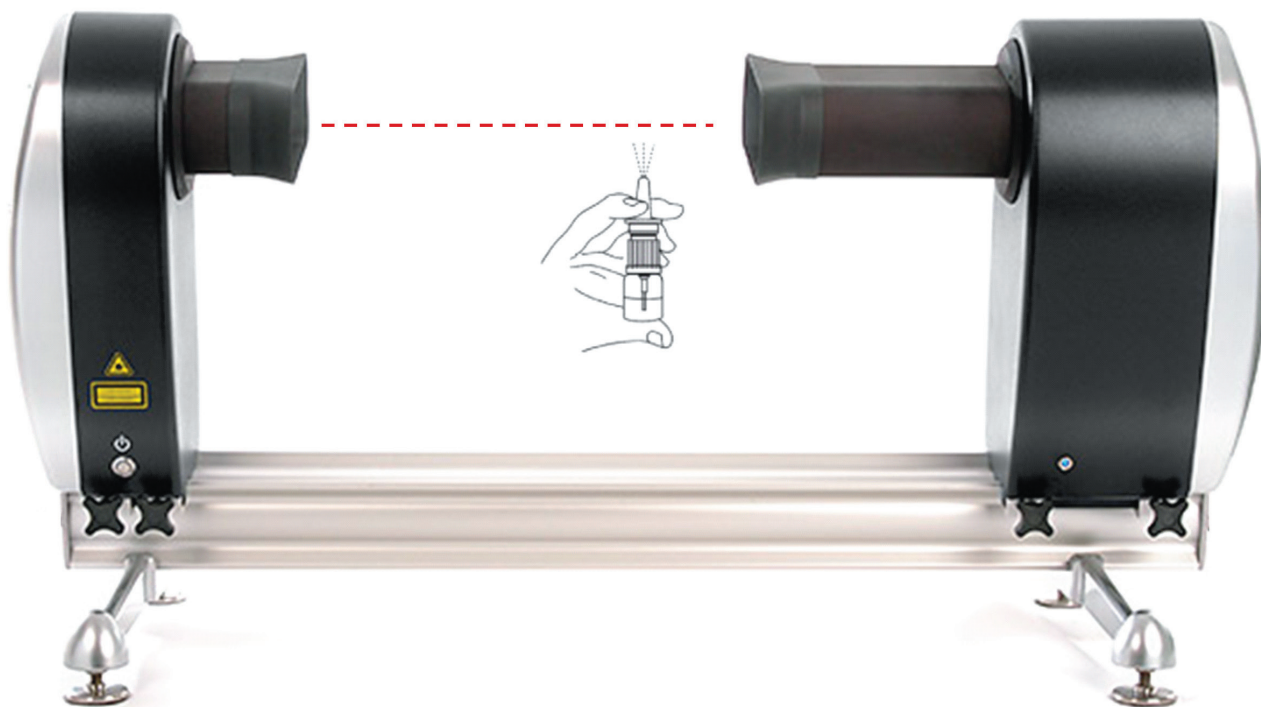


Fig. 1. Schematic principle of measuring the size distribution of aerosol droplets leaving the medicament dispenser using a spectrometer Spraytec

CT scan result closest to obtained average dimensions of examined anatomical structures was converted into files visible to the 3D printer. Program Mimics by the company Materialise was used to conversion and digital processing. Computed tomography files with the extension Dicom (Digital Imaging and Communications in Medicine) were converted into files used to prepare 3D printouts with the extension STL (Stereolithography). Reconstructions were created on the basis of the mask of soft tissues and model of the head retrieved was digitally processed obtaining the left half of the nasal cavity. Digital data were transferred to the 3D printer. Those files were then used to print out the final mockup on a printer by Stratasys company, model Objet30 Orthodesk. In printing technology polyjet acrylic was used (spraying technology UV-curable acrylic). Printout accuracy: in the Z axis – $28\ \mu\text{m} = 0.028\ \text{mm}$ in the X and Y axes – $0.1\ \text{mm}$. Nasal septum was replaced with a transparent plate to allow recording. Lateral view of the nasal cavity is shown in Fig. 2

Study of the deposition of inGCS in nasal cavity

Spatial distribution of droplet deposition of dispersed medications in the nasal cavity was determined by a method of visualization combined with image analysis with adaptation



Fig. 2. Lateral view of tridimensional mapping of nasal cavity

of a technique proposed by Kundoor and Dalby [9] in which a commercial substance which colored itself intensively under the influence of water (water is the dominant ingredient of all tested medications). Based on obtained results of visualization areas of dominant droplet deposition of intranasal drug on the wall and septum of the nasal cavity were compared (its function in the examined model was taken by a transparent platelet). Digital image analysis was performed by generally

used software Image J (NIH, USA). Aerosol was administered to the left nostril, directing the tip of the dispenser towards the lateral wall of the nasal cavity, i.e. positioning the dispenser in such a position that the axis passing through the dispenser was directed towards the inner corner of the eye [10].

RESULTS

Obtained distributions of droplet size produced by examined intranasal medications are illustrated in Fig. 3. These show that every examined substance produces droplets larger than 20 μm , of average size (mass median aerodynamic diameter, MMAD) of about 60 μm ($58.8 \pm 4.6 \mu\text{m}$ in the case of FF, $64.8 \pm 8.3 \mu\text{m}$ in the case of MF tix and $62.3 \pm 4.5 \mu\text{m}$ in the case of FP). FF preparation emits aerosol of narrower distribution than two remaining preparations and administers fewer droplets larger than 100 μm . In case of MF tix and FP preparation, also the drop diameter of up to 150–200 μm was discovered. The similarity of dispersion of MF tix and FP reveals that the droplet size is determined by structure and the method of triggering the spray in greater extent than the composition and physicochemical properties of the drug.

Figures 4 and 5 depict results of visualization of deposition on the lateral wall of the nasal cavity, Figure 6 – on the surface of the septum.

For every tested preparation intensified deposition was observed on the anterior part of the inferior turbinate. In case of FP preparation this deposition spreads also to the anterior part of the middle turbinate embracing also a fragment of the central part of that turbinate to a small extent and the middle and superior nasal meatus reaching the region of the nasal cavity ceiling and olfactory field. The central part of the inferior turbinate is covered to greatest extent in case of using MF tix while the surface of the mucous membrane of the lateral wall of the nasal cavity on which MF tix preparation deposited is similar to the one achieved after FP preparation application but much larger than in the case of FF preparation. FF drug deposition focuses essentially solely on the anterior part of the inferior turbinate. Large proportion of the preparation, in spite of directing the dispenser to the lateral wall of the nasal cavity deposits also on the surface of the nasal septum, usually reaching deeper than deposition on turbinates which is visible in Figure 6.

DISCUSSION

Many studies have shown that the vast majority (about 50%) of formulations administered via nasal spray is deposited in

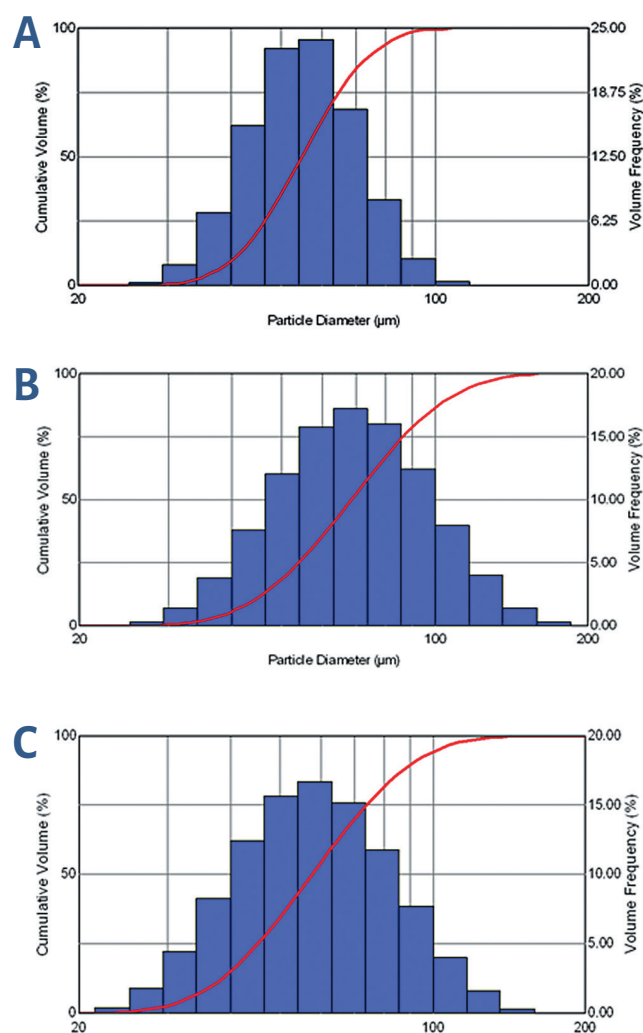


Fig. 3. Droplet size distribution in aerosol leaving dispensers with examined intranasal preparations: a) FF, b) MF tix, c) FP

the anterior part of the nasal cavity, and only 25% reaches the middle nasal meatus and middle turbinate [11–13].

In our research we observed deposition of examined preparations (MF, FP and FF) primarily on the anterior part of the inferior turbinate. The head of the inferior turbinate is the first (after the nasal valve) and at the same time the largest anatomical structure on which administered intranasal preparations deposit. In the majority of nasal diseases accompanied by an inflammatory process within the nasal mucosa (like allergic rhinitis, acute and chronic rhinitis and sinusitis) it comes to swelling and hyperplasia of the turbinate mucosa, which additionally complicates passive penetration of preparations administered intranasally. The deposition of fluticasone propionate (FP) preparation embraced apart from the anterior part

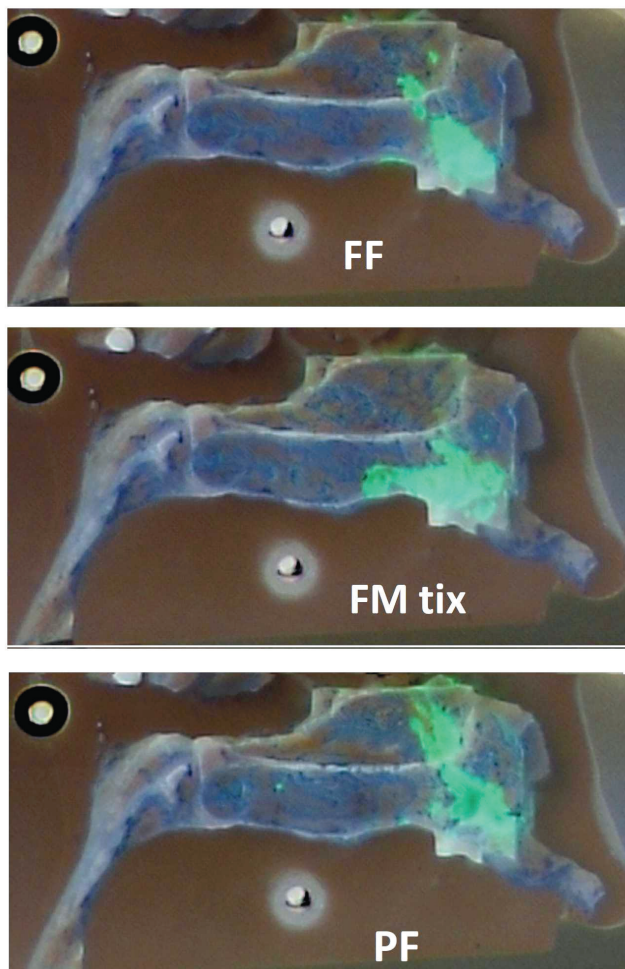
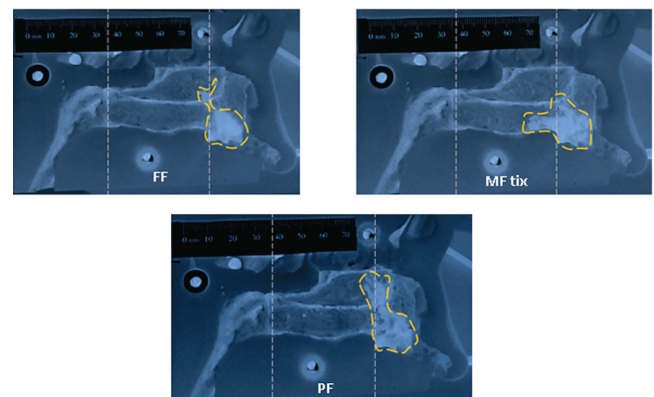


Fig. 4. Measured areas of deposition of examined drugs on the lateral wall of the nasal cavity.

of the inferior turbinate also the anterior part of the middle turbinate and the middle and superior nasal meatus together with the olfactory region in the nasal cavity. In our measurements the preparation which penetrated to the central part of the nasal cavity to largest extent was mometasone furoate (MF). Both preparations, that is fluticasone propionate (FP) and mometasone furoate (MF) covered the largest area of mucosa of the lateral wall of the nasal cavity. Fluticasone furoate (FF) preparation deposited only in the anterior part of the inferior turbinate, at the same time covering the smallest (of examined preparations) area of mucosa of the lateral wall of the nasal cavity. It seems that the cause of such differences in deposition might be the volume of a single dose of fluticasone furoate (FF) half the size of doses of other preparations released from the dispenser, which according to the manufacturer is 50 micro-



Ryc. 5. Regional drug deposition analysis on the lateral wall of the nasal cavity (after image conversion).

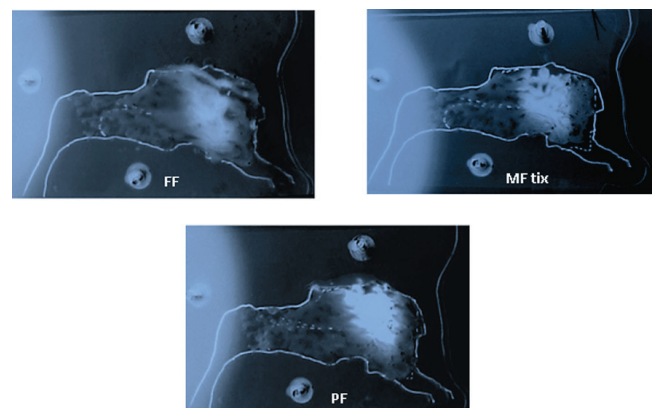


Fig. 6. Drug deposition on the surface of the nasal septum (after image conversion)

liters. At the same time a single dose of mometasone furoate (MF) as well as fluticasone propionate (FP) has twice the volume, i.e. 100 microliters. Thixotropic properties of mometasone furoate (MF) preparation slow down flowing of the liquid deposited to the inferior nasal meatus and throat, extending the residence time of the drug on the surface of the turbinates and middle nasal meatus.

Fig. 7 shows the areas of lateral wall covered with following preparations (data after digital image processing) whereas Fig. 8 compares the surface of these areas, taking the surface measured for FF preparation as 100%. In case of MF tix the surface area in which the drug deposited was greater by 32%, whereas in case of FP – by 60% compared to the area of FF deposition. What was already emphasized, only MF tix penetrates to the



Fig. 7. Areas of deposition of drug on the surface of the nasal wall.

central part of the nasal cavity to greater extent. Moreover, FP penetration to the upper regions of the anterior part of the nasal cavity may be evaluated as beneficial for a drug without thixotropic properties (therefore having a natural tendency to flow down).

COMPARISON OF THE LATERAL WALL COVERAGE BY DEPOSITED DRUGS

Some portion of each nasal formulation is also deposited in the nasal vestibule and nasal valve area but this area is invisible (covered) in given research model. From observations made in the course of measurements, however, it shows that this deposition was significant. Intensified deposition in these areas, such as the anterior part of the nasal cavity is determined by a huge momentum of drops resulting from giving them high speed (of up to 10 m/s [14]) while spraying. Additionally, a diverging shape of cone of sprayed aerosol interferes with converging geometry of nasal duct [15], resulting in a large proportion of aerosol depositing in the region of the nasal valve due to inertial effects. In each examined preparation this effect is similar even though triggered by different volume of liquid in a single dose.

Regional deposition distribution of the drug in the nasal cavity observed in our research is analogous to data reported in papers by other authors on drugs administered with atomizers, measured with e.g. radiotracer techniques (e.g. [16]). However, it should be emphasized at the same time that the situation analyzed by us was different from the case of inhaling aerosols administered from nebulizers wherein, first, the droplets are much smaller ($<10\ \mu\text{m}$), and second – are not introduced at high speed, but subject to natural inhalation. Droplet inhalation through the nose is another factor facili-

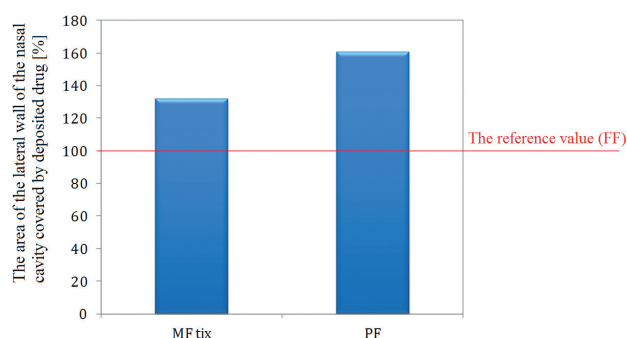


Fig. 8. Comparison of sizes of areas of lateral wall covered by deposited drugs.

tating their penetration in the nasal cavity compared to administration from atomizer with breath held.

While analyzing the literature on drug coverage in the nasal cavity it is worth paying attention to specificity of particular research methods. For instance, in *in vivo* methods using isotopic labeling time of deposition measurement reaches few minutes from the time of drug administration. Therefore results obtained in research conducted with the help of radiolabelled intranasal preparations do not reflect their deposition but the site where the preparation resides a few minutes after its application (at time of detection with gamma camera). It causes consequences for observed regional distribution of the preparation in the nasal cavity where two effects are significant. First of them is the fact that after administration of tested preparation, the participant breathes through the nose, therefore air flow introduced to nostrils displaces the preparation deposited on the surface of mucous linen in the nasal cavity. Such an effect of moving the preparation towards the nasopharynx and pharynx is decid-

edly quicker than its dislocation resulting from mucociliary transport. The second significant effect might be involuntary “sniffle” causing a feeling of leakage of the drug from the nose [17]. This effect would bear a greater significance for drugs without thixotropic properties which might cause too quick transfer of these substances to the pharynx and a shorter time of contact between active ingredient and nasal mucosa. Therefore the deposition in the frontal and central region of the nasal cavity followed by transport with inspiration to deeper parts of the nasal cavity seems to have most benefits. Too deep penetration seems to be unfavorable due to too fast transport of the drug to the nasopharynx and therefore weaker therapeutic effect and potential adverse effects concerning mucous lining of the pharynx. Thixotropic properties of the drug prevent drainage by gravity consequently allowing more uniform distribution of the drug in the nasal cavity (in this situation intense retraction and displacement of the drug to the pharynx will not take place because the drug does not drip). It prolongs the time of staying of the preparation on the surface of the nasal mucosa and may influence the increase of effectiveness of a given medication.

In our opinion, using a model of nasal cavities from a 3D printer based on tridimensional reconstructions on nasal cavities obtained from digital computed tomography of the nose and paranasal sinuses allows to perform precise measurements of deposition of intranasal drugs. In a research planned in such a manner all advantages of *in vitro* studies can be used while being performed in nasal cavities equivalent to *in vivo* studies as far as anatomical details are concerned. We hope that in the future this method may contribute to personalization of rhinological treatment through *in vitro* testing (with the use of the model of the nose of a particular patient) of deposition of many intranasal medications and choice of a specific preparation

most appropriate for a particular patient (their nasal cavity).

Further research on the deposition of intranasal drugs conducted with the use of air flow through the nasal cavity simulating breathing and using anatomical models of nasal cavities with variable parameters (variable size of turbinates) seems to be reasonable. It would enable more detailed analysis of intranasal drugs deposition.

CONCLUSIONS

Conducted research shows that aerosol droplets of intranasal drugs, due to their size (25–150 μm) and shape of the cloud leaving the nozzle of the dispenser partly deposit within the area of the vestibule and nasal valve. Only MF preparation penetrates to the central part of the nasal cavity to a larger extent. Remaining two preparations (FF and FP) deposit mainly in the anterior part, while FP penetrates stronger to the middle and superior meatus reaching the region of the nasal ceiling and olfactory field.

The results of presented research suggest that the distribution of the drug on the surface of the nasal cavity is carried out to a large extent due to the interaction of the deposited layer of the drug with the air introduced while breathing. Therefore, it is important that the drug does not drip by gravitation and stays at site of deposition for as long as possible which enables its successive transfer to deeper regions of the nasal cavity. Thixotropic properties of the drug support achieving this goal.

The paper also proves that using tridimensional printouts of the nasal cavities based on medical imaging (CT) enables analysis of the deposition of intranasal drugs in real conditions of their usage.

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Corresponding author: Piotr Rapijko, Military Institute of Medicine, Szaserów Street 128, 04-141 Warsaw, E-mail: piotr@rapiejko.pl

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