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Surgery

Maximum volume of nasal administration using a mucosal atomization device without aspiration in Japanese White rabbits

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ABSTRACT. Recently, a mucosal atomization device (MAD) has been applied in veterinary medicine. In the present study, the maximum volume of nasal atomization without aspiration using MAD was examined in eight healthy female Japanese White (JW) rabbits. Each rabbit had their head and neck examined by computed tomography before and after nasal atomization with four different doses (0.15, 0.3, 0.45, and 0.6 ml per nostril) of diluted contrast medium (1:2 mixture of iohexol and saline). This was done under general anesthesia by an intramuscular administration of alfaxalone 2.5 mg/kg, medetomidine 40 µg/kg, and butorphanol 0.4 mg/kg, with a 7-day washout period between each treatment. The diluted contrast medium was distributed in the nasal cavity, external nares, and/or oral cavity in all rabbits receiving each treatment. The intranasal distribution volumes of the contrast medium were 287 (250–333) mm^3 [median (interquartile range)] for 0.15 ml, 433 (243–555) mm^3 for 0.3 ml, 552 (356–797) mm^3 for 0.45 ml, and 529 (356–722) mm^3 for 0.6 ml of treatment. The intranasal distribution volume for 0.15 ml treatment tended to be lower than that for 0.6 ml treatment (P=0.083). The contrast medium was deposited in the trachea in one rabbit (12.5%) and four rabbits (50%) receiving treatments of 0.45 and 0.6 ml per nostril, respectively. The maximum volume of nasal atomization without aspiration into the trachea was 0.3 ml per nostril for the JW rabbits.

KEYWORDS: intranasal administration, mucosal atomization device (MAD), nasal atomization volume, rabbit

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Over the past 10 years, the interest in intranasal (IN) drug delivery within pharmaceutical research and development has increased [10, 12, 16, 17]. IN delivery, compared with oral administration, is a simple and convenient method of application and reduces the likelihood of first-pass metabolism [8]. The respiratory mucosa, which constitutes the main site for drug deposition and absorption, is highly vascularized; therefore, the time to effect can be as rapid as intravenous administration. Importantly, IN administration can allow direct delivery of drugs into the brain through the anatomical connection between the nasal cavity and brain without crossing the blood-brain barrier [14]. Therefore, IN administration may be advantageous for patients who require analgesia, sedation, induction of anesthesia, anxiolysis, termination of seizures, hypoglycemia management, narcotic reversal, and benzodiazepine reversal in clinical settings [6].

Intranasal administration of sedative and/or anesthetic drugs has been documented for therapeutic and experimental purposes in a number of different species, including rabbits [1, 9–11, 13, 18–20, 22, 24]. Some previous studies in rabbits have administered sedative and anesthetic drug combinations with a total volume of 0.15–0.64 ml/kg using a catheter-tipped syringe into the nostril [18–20, 22, 24]. Santangelo *et al*. [19, 20] reported that an IN combination of dexmedetomidine (0.1 mg/kg), midazolam (2 mg/kg), and butorphanol (0.4 mg/kg) (about 2.2 ml into one nostril) produced a deep sedation and analgesia within 5 min, corresponding with the peak plasma concentration of each drug, in eight healthy New Zealand White (NZW) rabbits, however, respiratory depression ensued, requiring oxygen supplementation during the anesthetic procedure. In addition, Yanmaz *et al*. [24] reported that an IN combination of dexmedetomidine (0.1 mg/kg) and midazolam (2 mg/kg) (about 1.0 ml into each nostril) produced sedation within 2 min in eight healthy NZW rabbits. However, percutaneous peripheral hemoglobin oxygen saturation (SpO_2) progressively decreased over time and continued to show less than 90% despite oxygen delivery (≥2 l/min) in front of the animal's nares. In these studies [19, 20, 24], it is speculated that a part of IN administered drug solution might flow into the trachea

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due to its large volume, causing rapid sedation and hypoxemia in rabbits. Weiland *et al*. [22] reported that an IN combination of medetomidine (0.2 mg/kg) with ketamine (10 mg/kg) or S(+)-ketamine (5 mg/kg) and butorphanol (0.4 mg/kg) (about 0.6 ml per nostril) provided effective induction of anesthesia for isoflurane anesthesia in 83 healthy young adult NZW rabbits but led to two fatalities. Since the overall fatality rate of 2.4% in this study [22] was higher than the reported rate of 1.39% [3], Weiland *et al.* [22] suggested that the potential causes of death may include the drugs themselves, preservatives, the volume of fluid, catheter-induced injury of the nasal mucosa, and the position of the animal during application. Therefore, it is considered that the development of safe technique and volume for IN administration are urgent issues for its clinical application in rabbits.

Recently, a mucosal atomization device (MAD) has been widely used in human emergency medicine [14] and has been applied in veterinary medicine as well [4, 21]. The MAD can atomize drugs into a mist of particles 30–100 microns in size [7]. The benefits of the nasal atomized release include less drug loss in the oropharynx, higher cerebrospinal fluid levels, better patient acceptability, and better sedative and analgesic effects [15]. In rabbits, IN administration with the MAD is expected to be less invasive and safer than using a catheter-tipped syringe. However, the maximum nasal atomizing volume without aspiration is unknown, and the permissible volume of drug solution for IN administration is relatively low [8, 16, 18, 23].

The aim of the present study was to determine the maximum volume of fluid that could be atomized into the nasal cavity using the MAD without aspiration into the trachea in rabbits.

MATERIALS AND METHODS

Experiment animals

Eight healthy female Japanese White (JW) rabbits (12 to 24 months of age, body weight 2.99 to 4.28 kg) were used. All rabbits were in good to excellent health conditions, based on a physical examination, and were cared for according to the principles of the "Guide for the Care and Use of Laboratory Animals" prepared by Rakuno Gakuen University. The Animal Care and Use Committee of Rakuno Gakuen University approved the present study (Approval No. VH20A23).

Experiment protocol

Each rabbit was assigned four occasions by a computer-generated randomized table and their head and neck were examined by computed tomography (CT) following nasal atomization of four different doses of diluted contrast medium under general anesthesia with a 7-day washout period between each treatment. For anesthesia, each rabbit was provided supplemental flow-by oxygen (2 l/min) at the nose and was slowly injected with a drug mixture of alfaxalone (2.5 mg/kg) (Alfaxan®; Meiji Seika Pharma Ltd., Tokyo, Japan), medetomidine (40 µg/kg) (Medetomin®; Meiji Seika Pharma Ltd.), and butorphanol (0.4 mg/kg) (Vetorphal®; Meiji Seika Pharma Ltd.), into the dorsal lumbar muscle with a 24-gauge, 1-inch needle (TOP injection needle; TOP Co., Ltd., Tokyo, Japan). Following the rabbit losing the righting reflex, CT scanning of the head and neck was performed in the sternal recumbency (Plain-CT image). Then, the rabbit received one of the four IN atomizing (INA) treatments: 0.15 ml per nostril (INA0.15 treatment, n=8), 0.3 ml per nostril (INA0.3 treatment, n=8), 0.45 ml per nostril (INA0.45 treatment, n=8), or 0.6 ml per nostril (INA0.6 treatment, n=8) of 1:2 mixture of iohexol (Omnipaque® 300; Daiichi Sankyo Co., Ltd., Tokyo, Japan) and saline (Isotonic Sodium Chloride Solution; Terumo Co., Ltd., Tokyo, Japan) into the left nostril with the MAD (MAD Nasal™ Intranasal Mucosal Atomization Device; Teleflex Medical Japan, Ltd., Tokyo, Japan). The tip of the MAD, with a soft conical plug removed, was inserted into the nostril and the diluted contrast medium was sprayed quickly into the nasal cavity (Fig. 1). Within 5 min following the INA treatment, CT scanning was performed again in the sternal recumbency (MAD-CT image). The rabbit was oxygenated with the flow-by oxygen at the nose during the CT scan and until the rabbit recovered from anesthesia.

Computerized tomographic scanning

Multidetector-row CT of the head and neck was performed using a 16-slice CT scanner (Bright Speed Elite 16ch®; GE Healthcare, Milwaukee, WI, USA). All rabbits were placed in sternal recumbency with the head on pillows for the CT scanning. The imaging conditions were 120 kV, 80–300 mA, thickness of 0.625 mm, and field of view (FOV) of 250 × 250 mm^2. The images were analyzed using a software (AZE Virtual Place Liberty Lite®; Cannon Medical Systems Co., Ltd., Otawara, Japan). The scanning was performed and measured randomly and blindly by a veterinarian with diagnostic imaging experience (A.H.). All images were reviewed by the two authors (Y.W. and A.H.).

Evaluation of the distribution of nasal atomized contrast medium

According to a previous report that determined lung volumes in CT scanning images [2], a total volume of the nasal cavity was determined by adding up the fractional volumes of low-density regions calculated by multiplying the area of low-density within the nasal cavity and the slice thickness (0.625 mm) in each CT slice of the Plain-CT image. Depositions of nasal atomized contrast medium were detected as high-density regions in the MAD-CT image comparing with the corresponding Plain-CT image. A fractional volume of high-density region in each slice of the MAD-CT image was calculated by multiplying the area of high-density within the nasal cavity and the slice thickness. Then, an intranasal distribution volume of the contrast medium was calculated as the sum of fractional volumes in each rabbit.

In addition, the total diffusion of nasal atomized contrast medium in the MAD-CT image was evaluated by a scoring system. The scoring system consists of five scales categorizing the range of deposition of the contrast medium depending on the distance from the nasal cavity. These scales were rated with scale 1 for the deposition of atomized contrast medium within the nasal cavity (the

Fig. 1. The rabbit received intranasal administration of diluted contrast medium into the left nostril with a mucosal atomization device (MAD). The tip of the MAD, with a soft conical plug removed, was inserted into the nostril and the diluted contrast medium was sprayed quickly into the nasal cavity.

dorsal nasal meatus, the middle nasal meatus, the ventral nasal meatus, the dorsal nasal concha, the middle nasal concha, and the ethmoidal conchae), scale 2 for the deposition in the oral cavity and/or external nares, scale 3 for the deposition in the nasopharynx and/or the larynx, scale 4 for the deposition in the esophagus, and scale 5 for the deposition in the trachea. The entire diffusion score was calculated as the sum of these scales in each rabbit.

Statistical analysis

Data were expressed as median (interquartile range) and statistically analyzed using Excel for Macintosh (Microsoft Office 2016; Microsoft Corp., Redmond, WA, USA) and SPSS (IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY, USA: IBM Corp.). Differences in the intranasal distribution volume of the contrast medium and the entire diffusion score were analyzed among INA treatments by using the Friedman test, followed by the Scheffe test as a post-hoc multiple comparisons test. In addition, linear regression between the administration volume of the contrast medium and its intranasal distribution volume by using simple linear regression. The level of significance was set at $P<0.05$.

RESULTS

Figure 2 shows typical CT slices posterior to the incisors (Level-I), at the first palatal ridge (Level-II), anterior to the first upper premolar teeth (Level-III), and anterior to the first upper molar (Level-IV). The levels of CT slices were determined with reference to a previous anatomical study on the rabbit nasal cavity [16]. In the CT slices of each INA treatment, the contrast medium was detected in the left nasal cavity at Level-I and II. Larger amounts of contrast medium were deposited in the left ventral meatus with the anterior part of the left middle nasal concha, and around the left side of the vomeronasal organ in the CT slices of INA0.3, INA0.45, and INA0.6 treatments. At Level-III and IV, the contrast medium was not detected except for in one rabbit receiving INA0.6 treatment, where a small amount of contrast medium was deposited in the ethmoidal conchae. The total volume of the nasal cavity measured from the Plain-CT image was 5,082 (4,843–5,275) mm^3. The intranasal distribution volumes of the contrast medium were 287 (250–333) mm^3 for INA0.15 treatment, 433 (243–555) mm^3 for INA0.3 treatment, 552 (356–797) mm^3 for INA0.45 treatment, and 529 (405–722) mm^3 for INA0.6 treatment. The intranasal distribution volume for INA0.15 treatment tended to be lower than that for INA0.6 treatment ($P=0.083$). Simple linear regression analysis showed a significant increase in the intranasal distribution volume with the administration volume of the contrast medium ($P=0.004$).

Figure 3 shows the typical depositions of the contrast medium in multiplanar reconstruction CT images after each INA treatment. Table 1 shows the entire diffusion scores and the number of rabbits showing each scale after each INA treatment. The contrast medium was distributed in the nasal cavity and external nares and/or oral cavity in all rabbits receiving each INA treatment. Overflows of the contrast medium from the nasal cavity to the nasopharynx and the trachea were detected in rabbits receiving INA0.45 and INA0.6 treatments. The contrast medium deposited in the trachea was detected in one rabbit (12.5%) and four rabbits (50%) receiving INA0.45 and INA0.6 treatments, respectively. The entire diffusion score was score 3 in all rabbits receiving INA0.15 and INA0.3 treatments. The entire diffusion score was score 3 in seven rabbits and score 11 in one rabbit

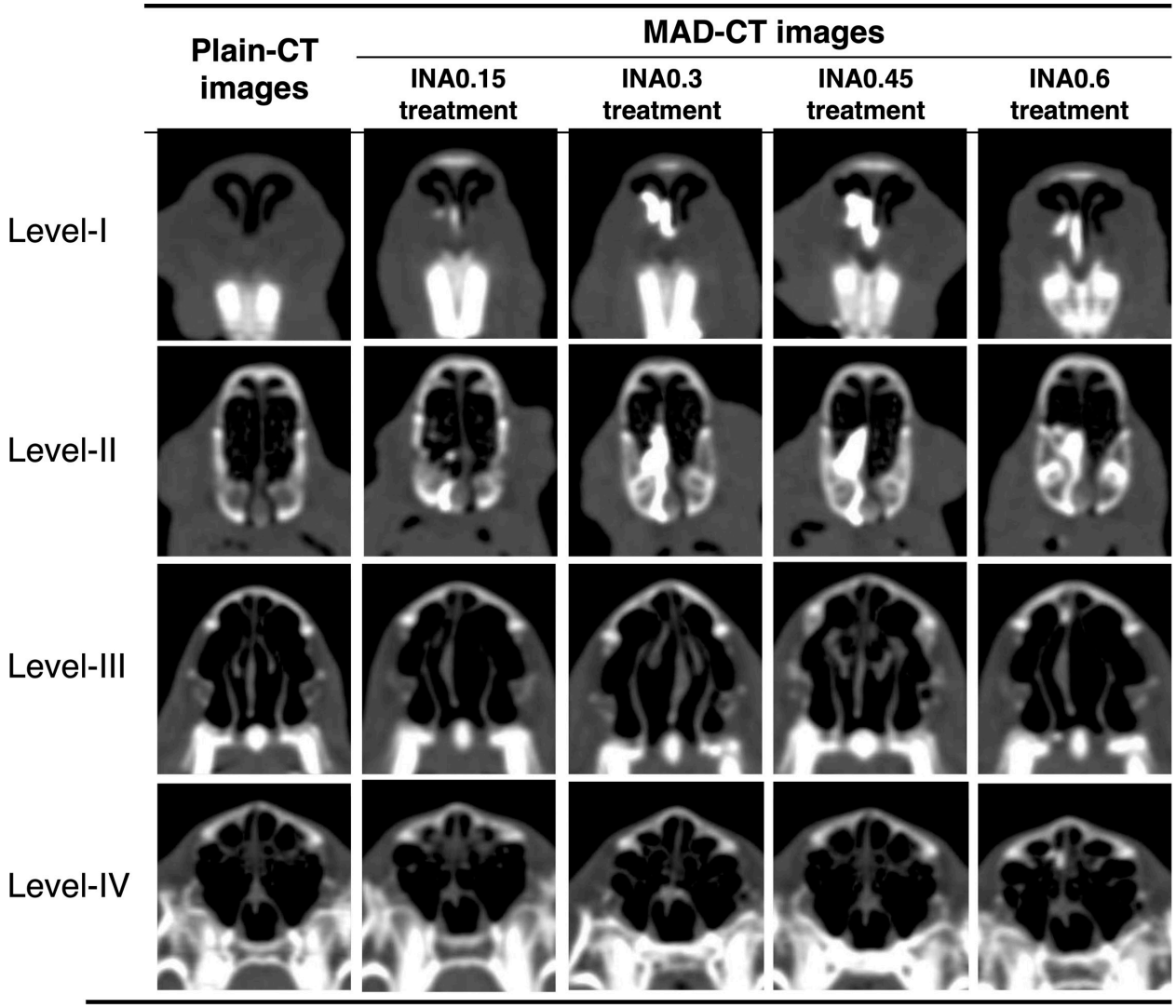

Fig. 2. Computed tomography (CT) images of the nasal cavity in Japanese White rabbits receiving an atomization of 1:2 mixture of iohexol and saline into the left nasal cavity. Typical CT slices at posterior to the incisors (Level-I), at the first palatal ridge (Level-II), anterior to the first upper premolar teeth (Level-III), and anterior to the first upper molar (Level-IV). In the CT slices of each intranasal atomizing (INA) treatment, the contrast medium was detected in the left nasal cavity at Level-I and II. At Level-III and IV, the contrast medium was not detected except for one rabbit receiving INA0.6 treatment, where a small amount of contrast medium was deposited in the ethmoidal conchae. Larger amounts of contrast medium deposited in the left ventral meatus, the anterior part of the left middle nasal concha, and around the left side of the vomeronasal organ in the CT slices of INA0.3, INA0.45, and INA0.6 treatments. Plain-CT images: CT scanning image before the nasal atomization. Mucosal atomization device (MAD)-CT images: CT scanning image after the nasal atomization. INA0.15 treatment: INA treatments with a 0.15 ml per nostril. INA0.3 treatment: INA treatments with a 0.3 ml per nostril. INA0.45 treatment: INA treatments with a 0.45 ml per nostril. INA0.6 treatment: INA treatments with a 0.6 ml per nostril.

receiving INA0.45 treatments. The entire diffusion score for INA0.6 treatment was significantly higher than those for INA0.15 and 0.3 treatments (P=0.013 and P=0.013, respectively).

DISCUSSION

The aim of the present study was to determine the maximum volume of fluid that could be atomized into the nasal cavity using the MAD without aspiration into the trachea in rabbits. In this study, we show that the diluted contrast medium, nasally atomized by the MAD, distributed into the nasal cavity and overflowed into the nasopharynx and the trachea in a dose-dependent manner. The contrast medium was aspirated into the trachea in one rabbit and four rabbits receiving treatments with 0.45 ml and 0.6 ml per nostril, respectively. It was concluded that the maximum nasal atomizing volume to prevent aspiration into the trachea was 0.3 ml per nostril in JW rabbits.

In the present study, the median intranasal distribution volumes of the contrast medium were 287 mm^3 for INA0.15, 433 mm^3

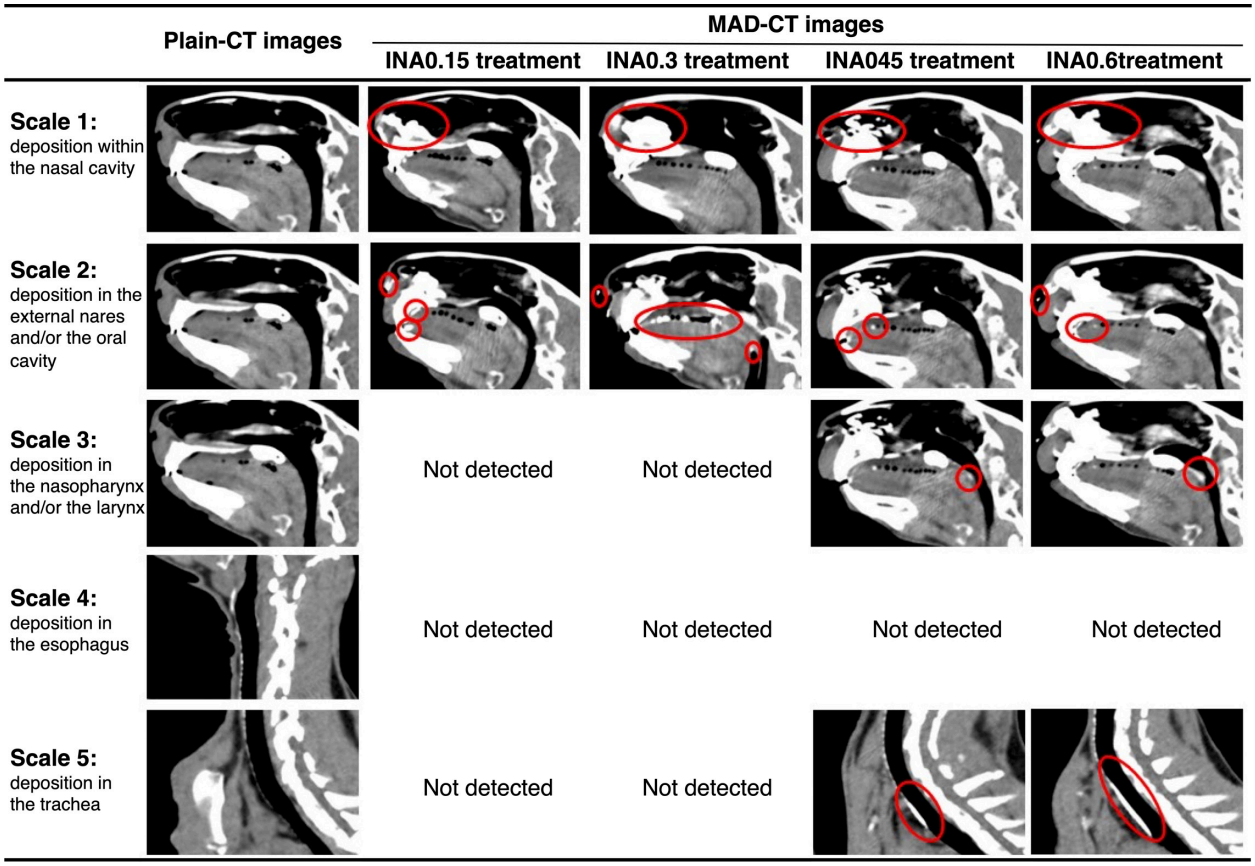

Fig. 3. Typical depositions of the contrast medium in multiplanar reconstruction computed tomography (CT) images in Japanese White rabbits receiving an atomization of 1:2 mixture of iohexol and saline into the left nasal cavity. The contrast medium was distributed in the nasal cavity, external nares, and/or oral cavity in all rabbits receiving each intranasal atomizing (INA) treatment. Overflows of the contrast medium from the nasal cavity to the nasopharynx and the trachea were detected in rabbits receiving INA0.45 and INA0.6 treatments. Plain-CT images: CT scanning image before the nasal atomization. Mucosal atomization device (MAD)-CT images: CT scanning image after the nasal atomization. INA0.15 treatment: INA treatments with a 0.15 ml per nostril. INA0.3 treatment: INA treatments with a 0.3 ml per nostril. INA0.45 treatment: INA treatments with a 0.45 ml per nostril. INA0.6 treatment: INA treatments with a 0.6 ml per nostril. Red mark: high-density area deposited by contrast medium.

Table 1. The entire diffusion scores after intranasal atomizing (INA) treatments and the numbers of rabbits showing each scale for deposition of contrast medium

	INA0.15 treatment	INA0.3 treatment	INA0.45 treatment	INA0.6 treatment
The entire diffusion score	3 (3–3)[a]	3 (3–3)[a]	3 (3–3)	8.5 (3–11)
Number of rabbits showing each scale				
Scale 1: deposition within the nasal cavity	8	8	8	8
Scale 2: deposition in the external nares and/or the oral cavity	8	8	8	8
Scale 3: deposition in the nasopharynx and/or larynx	0	0	1	5
Scale 4: deposition in the esophagus	0	0	0	0
Scale 5: deposition in the trachea	0	0	1	4

The entire diffusion scores are expressed as a median (interquartile range) from 8 rabbits. The rabbits received intranasal atomization (INA) with 1:2 mixture of iohexoland saline of 0.15 ml (INA0.15 treatment), 0.3 ml (INA0.3 treatment), 0.45 ml (INA0.45 treatment) and 0.6 ml (INA0.6 treatment). The scoring system consists of 5 scales categorized the range of deposition of the contrast medium depending on the distance from the nasal cavity. The entire diffusion score was calculated as the sum of scales (score 1–15). Significant difference from the INA0.6 treatment: [a] $P<0.05$.

for INA0.3, 552 mm^3 for INA0.45, and 529 mm^3 for INA0.6 treatments. These intranasal distribution volumes were large relative to their original liquid volumes of 0.15 ml for INA0.15, 0.3 ml for INA0.3, and 0.45 ml for INA0.45 treatments. The contrast medium diffused efficiently into the nasal cavity by spraying it as a mist of particles 30–100 microns in size, using the MAD [7], if the original liquid volume is up to 0.45 ml. However, the contrast medium leaked into the nasopharynx and the trachea in one

rabbit receiving INA0.45 treatment. Nasal atomization up to 0.3 ml per nostril is certainly safe for JW rabbits.

The nasal atomization with the MAD produced a distribution of contrast medium in the nasal cavity, the oral cavity, and the external nares in JW rabbits. The contrast medium in the nasal cavity was mainly deposited in the ventral meatus and around the vomeronasal organ. Robertson and Eberhart [18] demonstrated that most of the contrast medium reached the vomeronasal organ and some was swallowed, when it was administered IN at 0.2 ml per nostril by using a catheter-tipped syringe into Flemish Giants and NZW rabbits. Xi *et al*. [23] reported that two needle structures were observed at the bottom of the ventral concha, which connect to the mouth and the vomeronasal organ in an anatomically accurate rabbit nasal airway model developed from high-resolution magnetic resonance imaging scans of a female NZW rabbit. In the present study, it is surmised that a part of the contrast medium, nasal atomized with the MAD, leaked from the nasal cavity into the oral cavity through the vomeronasal organ and the needle structures at the bottom of the ventral concha. In addition, the soft conical plug was removed to ensure that the tip of the MAD was inserted into the nostril, therefore, a small amount of contrast medium might leak and deposit around the external nares.

In the present study, the contrast medium nasally atomized by the MAD distributed into the nasal cavity and overflowed from the nasal cavity into the nasopharynx and the trachea in a liquid volume-dependent manner. Contrarily, the contrast medium was not distributed in the posterior nasal cavity, including the ethmoidal conchae, in most rabbits. The ethmoidal conchae are a dead zone with no outlet, where the airflow speed is extremely low compared with other regions inside of the nose of rabbits [16, 23]. Corley *et al*. [5] reported that approximately 1.1% of normally inhaled airflow entered the posterior ethmoidal conchae region. Xi *et al*. [23] reported the distribution of inhaled airflow was highly heterogeneous within the rabbit nasal cavity, with the inhaled airflow nearly evenly distributed at slow respirations (0.34 l/min), but starting to exhibit patterns of heterogeneity with the high-speed flow zone in the dorsal meatus at a normal respiration rate (0.68 l/min), which ventilated more inhaled air to the ethmoidal conchae. The high-speed flow zone shifted downward to the anterior and ventral parts of the middle nasal concha as the respiration rate increased to 1.36 l/min, and even further downward at a higher respiration rate of 2.04 l/min [23]. It was probable that the nasal atomized contrast medium quickly flowed from the left ventral meatus and the anterior part of the left middle nasal concha to the nasopharynx, while it did not distribute into the ethmoidal conchae in most rabbits. The total volume of the nasal cavities of an adult NZW rabbit was reported to be 6 ml [8], and similarly the total volume of the nasal cavity measured from the Plain-CT image was 5,082 mm^3 for JW rabbits in the present study. Although the volume of one side of the nasal cavity of NZW rabbits and JW rabbits is 2.5 to 3 ml, the airflow flowing into the ethmoidal conchae is extremely small [5], and the maximum volume of liquid that can be atomized into the nasal cavity using the MAD is about 0.3 ml in one nasal cavity. Therefore, it is considered that even a relatively small liquid volume of 0.45 to 0.6 ml can overflow from the nasal cavity into the nasopharynx and the trachea.

With the arguments above, we can come to the conclusion that the aspiration into the trachea was detected following the nasal atomization of 0.45 and 0.6 ml of diluted contrast medium per nostril in rabbits. In conclusion, the maximum nasal atomizing volume should be 0.3 ml per nostril to prevent aspiration into the trachea in rabbits.

There are some limitations of the present study. First, the diluted contrast medium was intranasally atomized into rabbits anesthetized with an intramuscular injection of a drug combination of alfaxalone, medetomidine, and butorphanol. It is undeniable that the anesthesia might suppress the laryngeal reflex in rabbits and promote aspiration of the contrast medium into the trachea. Second, the depositions of nasal atomized contrast medium might be underestimated if a portion of the atomized contrast medium particles is too small to be detected on CT scanning. Third, the results of the present study need more considerations when it is directly applicated since the physical properties of the diluted contrast medium may be different from the candidate drugs nasally atomized to rabbits using MAD. However, these limitations do not refute the notion that there is an upper volume limit for safe atomization of drug solution using MAD in order to prevent aspiration in the trachea.

CONFLICT OF INTEREST. The authors have nothing to disclose.

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