DIR&D-EN 007 Version A

Annex 1: Effect of the presence of inspiratory valve and holding facemask duration on performance of an inhalation chamber for cats.

Study 1	
Place	Laboratoire OptimHal-ProtecSom (Valognes)
Date	31/08/2021
Author	A. Bardin
Tests date	29/07 – 05/08/2021
Tests author	A. Bardin
Study 2	
Place	Laboratoire OptimHal-ProtecSom (Valognes)
Date	28/01/2021
Author	M. Eckes
Tests date	Weeks 43, 44 et 47, 2020
Tests author	L. Fontaine et B. Hervieu

1. Introduction

Neonates and cats have very low tidal volumes [1,2], smaller than dead space of commercially valved holding chambers (VHCs). Removing the inspiratory valve of the VHC permits to eliminate the dead space and permits to improve the efficiency of inhaled treatments. Two studies were performed to evaluate the effect of the presence of the inspiratory valve on the inhalation chamber AnimHal® cat and the holding facemask duration on the cat's face for an optimal inhaled drug delivery. Indeed, if the cat is taking its medication quickly and efficiently, it permits to avoid its resistance for the next inhaled drug delivery.

2. Materials and methods

In the first *in vitro* study, the performance of inhalation chambers AnimHal® Cat with or without the inspiratory valve are evaluated with the salbutamol administration of a pressurized metered dose inhaler. In the second *in vitro* study, drug delivery as a function of the number of breathing cycles is evaluated with the inhalation chamber AnimHal® Cat without its inspiratory valve with the same inhaled drug.

The inhalation chambers are dismantled as indicated in the instructions for use and then washed in a soapy solution for 15 minutes, then dried at room temperature.

In the first study, a breathing simulator is used to create the respiratory pattern of a cat (tidal volume: 26.7 mL, inspiratory time: 0.47 s, expiration time: 0.72 s)[11]. The drug that would be inhaled by the cat is collected by an absolute filter. To maintain the facemask on the face model and ensure a sealing while keeping its shape, a 0.8 kg force is applied.

For the second study, this same bench model was used with the respiratory pattern of a neonate (which is close to the respiratory pattern of a cat). This study aimed to evaluate the number of breathing cycles after each pMDI administration for an ideal drug delivery. Different facemask holding durations are tested, to 2.6 seconds from 51.2 seconds, representing 2 to 40 breathing cycles after each pMDI administration.

Drug deposited in all components of the bench model (actuator, inhalation chamber, filter, face model and mask) is quantified with the appropriate solvents. Quantification is performed with UV spectrophotometry. Results are expressed as percent of the delivered dose and as means ± standards deviations.

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[1] Lin and al., "Simultaneous Visual Inspection for Barometric Whole-Body Plethysmography Waveforms during Pulmonary Functions Testing in Client-Owned Cats".

[2] B. Hervieu and al., "Inhalation Chamber in Neonatology: Benefit of a Device without dead space and Facemask Holding Duration for optimal Corticosteroid Inhalation."

3. Effect of the removal of the inspiratory valve

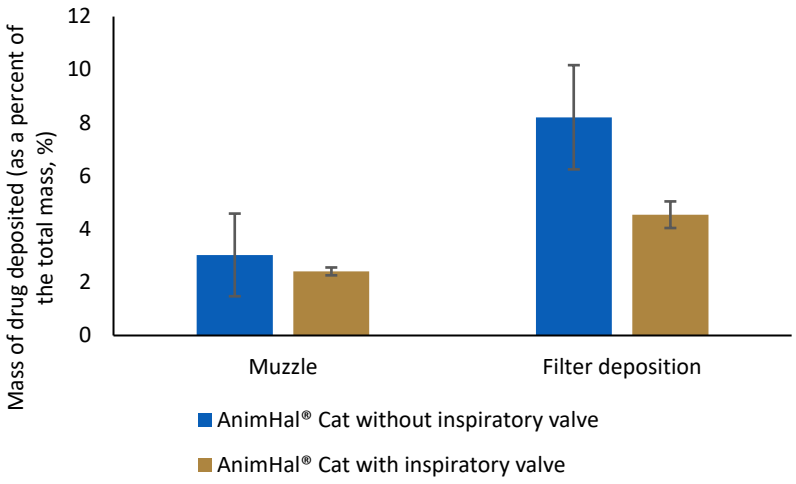

Figure 1: In vitro aerosol delivery when using AnimHal® Cat with or without the inspiratory valve

Table 1: percent of the total mass collected on the filter (means ± standards deviations).

inhalation chamber	AnimHal® Cat without valve	AnimHal® Cat with valve
Filter	8.21 ± 1.96 *	4.54 ± 0.50 *

Results obtained (figure 1, table 1) are tested with student T test (Excel, version 2108). Drug deposition obtained on the filter is statistically different between the two devices. The removal of the inspiratory valve is associated with a drug delivery twice higher that those obtained with the inspiratory valve.

4. Effect of the holding facemask duration on the drug delivery

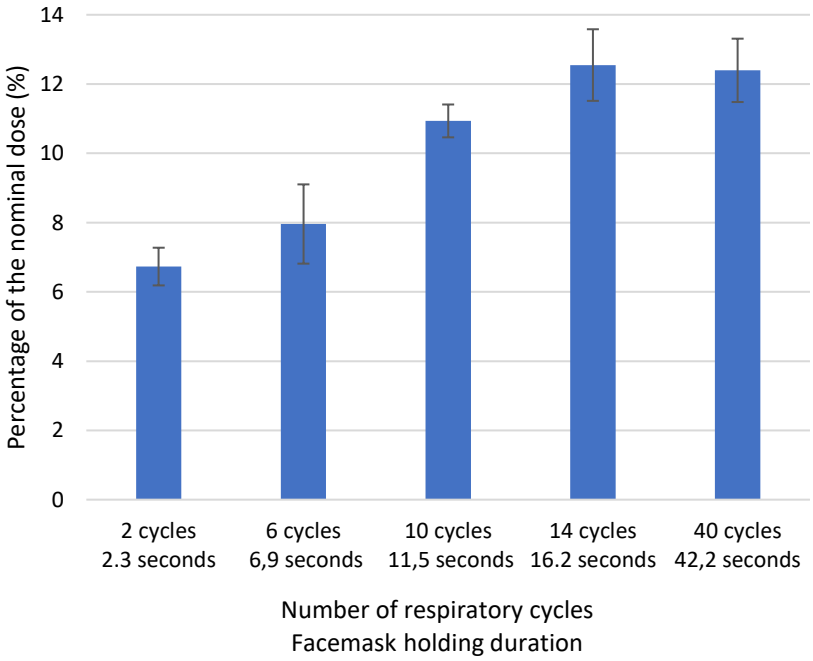

Figure 2 : Effect of number of breathing cycles (to 2 from 40 cycles, which corresponds to 2.6 from 51.2 seconds) after each pMDI dose release on in vitro drug delivery obtained.

Figure 2 represents drug dose delivery obtained on the filter with the variation of number of breathing cycles after each pMDI dose release. Drug dose delivered increases up to 14 cycles with AnimHal® Cat without inspiratory valve, which corresponds to a facemask holding duration of 16.2 seconds. Drug dose delivered after 2 breathing cycles corresponds to a facemask holding duration of 2.3 seconds, is equivalent to 50% of the maximal drug dose delivered after 14 breathing cycles.

Conclusion

Results obtained are suggesting that the removal of the inspiratory valve permits to significatively increase the drug dose delivered on the filter, suggesting a significatively increase of the drug dose deposited in the lungs. That is why it is recommended to use AnimHal® Cat without inspiratory valve, except of cats whose weight is higher than 9 kg.

Results obtained with the second study showed that with AnimHal® Cat without inspiratory valve, it would be a possible solution to administer 2 pMDI drug doses in 2.3 seconds instead of administering one dose then holding the facemask on the cat's face for 16.2 seconds.

Results obtained raises the question of what is more beneficial for the cats and their owners?

- Administering two pMDI drug doses and maintain the mask 2.3 seconds on the cat's face?

Or

- Administering one pMDI drug dose then maintain 16.2 seconds the mask on the cat's face with the risk of a lower drug dose deposited because of the cat's agitation?

Isn't it easier for the cat's owner to maintain the cat twice 2.3 seconds and make it breathe into the inhalation chamber instead of one time for 16.2 seconds?