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Effect of Drug-Targeting Nebulization on Lung Delivery☆

Efecto de la nebulización dirigida de fármacos en la administración pulmonar

To the Editor:

It has been difficult to develop more effective nebulizers for the improved delivery of drugs directly to the lungs. Adaptive nebulizers were designed for the administration of drugs at a specific time during inspiration, depending on the intended target (drug-targeting nebulization). Controlled inhalation nebulizers, such as AKITA®, have recently become another addition to adaptive aerosol delivery systems.[1] The aim of our study was to measure the inhaled dose and pulmonary bioavailability obtained from drug-targeting nebulization, compared to conventional continuous nebulization.

We used the AKITA® delivery device (Activaero; Germany) that provides individualized, controlled flow and inhalation volumes in several puffs. Aerosolized drug delivery was either continuous or targeted (Fig. 1) during each 4-s controlled inhalation. The number of inhalations was 43 or 86, respectively.

The inhaled dose of a solution of amikacin (125 mg/ml) was measured *in vitro* using a residual gravimetric method.[2] Five healthy non-smoking male volunteers (mean age 27.8 ± 4.7 years) were selected, and approval was obtained from the ethics committee.

Subjects were randomized to receive a solution of salbutamol (GlaxoSmithKline, Belgium) (625 mg/ml) *via* continuous or targeted nebulization.

Subjects swallowed 100 ml of activated charcoal before and after nebulization (Carbomix, Norit, Netherlands). Urine samples were obtained before nebulization and 30 min after (Cu-30), and then from each spontaneous micturition and 240 min (Cu-240) after the start of nebulization. The volume of each micturition was measured.

Salbutamol levels in urine were measured in triplicate by HPLC.[3] The amount of salbutamol excreted in urine (Cu) was calculated by multiplying the concentration by the volume of each sample. Pulmonary bioavailability was compared using the Cu-30 sample.

Mean anthropometric and spirometric values were as follows: height 177.6 ± 8.8 cm and weight 80.0 ± 19.6 kg, FVC 103.7% ± 16.8% of the predicted value and FEV1 100.3% ± 14.5% of the predicted value.

The inhaled dose was not significantly different (15.8% *versus* 16.5%, respectively, p=0.975) but the amount of drug delivered with the continuous nebulization method was twice that of the targeted method (p<0.001).

The excreted amounts of salbutamol are summarized in Table 1. Cu-30 was similar for both delivery systems (p=0.947). The accumulated amount of salbutamol excreted in urine was significantly higher with the targeted nebulization system (p<0.05).

Pulmonary bioavailability of nebulized salbutamol is a reproducible measurement for predicting drug deposition in the lung[4] and for determining the amount of drug that is provided to the body *via* the pulmonary route and rapidly excreted in the urine. Concentrations may be overestimated in healthy individuals,[5] but this does not affect the comparison of the delivery methods. Our results

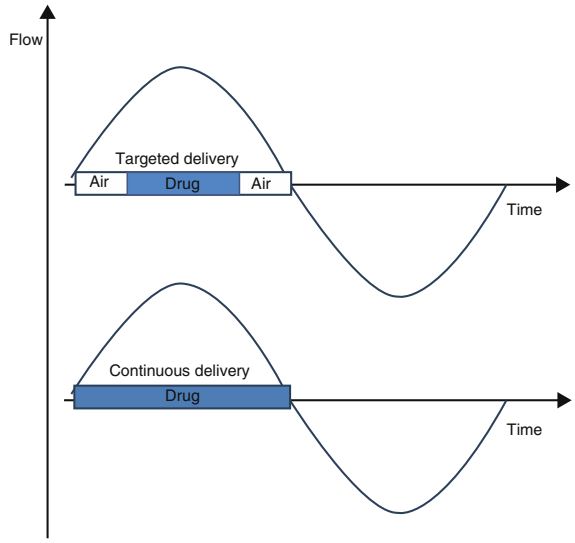

Fig. 1. Nebulization delivery modes during one inspiratory cycle.

Table 1
Excreted Salbutamol (mcg) Retrieved After Nebulization With the Continuous or Discontinuous Delivery System in 5 Healthy Individuals.

	Continuous	Discontinuous
Cu-30	36.69 ± 31.56	35.56 ± 28.39
Cu-60	30.59 ± 15.63	51.72 ± 37.24
Cu-240	51.08 ± 25.87	84.89 ± 36.47
Accumulative amount	118.36 ± 47.77	172.18 ± 46.82*

Results expressed as mean±standard deviation.
* p<0.05.

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confirm that the AKITA® device delivers a greater amount of drug than other devices, with a pulmonary bioavailability approximately twice that previously described with 8 conventional nebulizers with different flows.[4] However, drug-targeting nebulization did not affect pulmonary bioavailability compared to continuous administration. A significantly higher accumulated amount of excreted salbutamol was recovered from subjects using the targeted delivery device.

Further studies in radio-labelled aerosols will be needed to clarify the effect of targeted nebulization on drug deposition in the lungs. To conclude, drug-targeted nebulization does not change pulmonary bioavailability in healthy individuals but it does reduce the amount of drug delivered.

Clinical Trial: NCT01913184.

Authorship

a) Study concept and design or data collection, analysis or interpretation: Gregory Reychler, Anne-Sophie Aubriot, Julien Masquelier and G. Giulio Muccioli.
b) Preliminary draft of the article or critical review of significant intellectual content: Gregory Reychler, G. Giulio Muccioli and Giuseppe Liistro.
c) Final approval of version submitted for publication: Gregory Reychler, Anne-Sophie Aubriot, Julien Masquelier, G. Giulio Muccioli and Giuseppe Liistro.

Conflict of Interest

No conflict of interests.

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