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Risk of exposure for the caregivers during aminoglycoside nebulization: an observational study

Risk of exposure for the caregivers during aminoglycoside nebulization: an observational study

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According to estimates from 2019, more than one million of deaths and economic costs around the world are annually attributable to antibiotics-resistant infections[1]. Thus, the antimicrobial resistance is challenging for the public health, even if the risk assessment is not frequent and the real exposure risk is difficult to evaluate[2].

Despite, the advent of CFTR modulators, the infections treatment with antibiotics remains a cornerstone of the treatment for many patients with CF (PwCF). For many years, they have been delivered by inhalation with the advantage to bypass the alveolar-capillary barrier and to favour the lung penetration[3].

The risk related to the occupational exposure to the antibiotics has scarcely been studied, even if some side-effects were demonstrated in nurses[4-6]. The exposure of proxy related to the nebulization of antibiotics has never been investigated. However, fugitive aerosol is emitted from the nebulizer, during both inspiration and expiration in the environment (medical aerosol), and by the patient during expiration (bioaerosol). The people circulating around the patient could be occupationally exposed to this fugitive aerosol. Our hypothesis was that the urine of caregivers would contain a detectable amount of the nebulized antibiotics in such conditions. The aim of this study was to observe the risk of exposure to the nebulized antibiotics by measuring the aminoglycosides concentration in the urine of parents of PwCF performing nebulization of aminoglycosides.

This prospective observational study was conducted in the caregivers of the children with CF in accordance with the Declaration of Helsinki and the current guidelines for Clinical Good

Practice. The study was approved by the local ethics committee (B4032023000087). All caregivers accompanying a pediatric PwCF for a routine visit in the CF center were eligible and prospectively assessed. To be included, the caregiver had to be an adult circulating at less than 5 meters of the PwCF for at least 3 minutes during the last nebulization before the visit. The PwCF had to nebulize an aminoglycoside at home in the last 6 hours before the time of the visit. The caregivers were excluded if they used aminoglycosides in the last week and if they are known to have a renal insufficiency.

The endpoint was the concentration of the nebulized antibiotic in the urinary excretion of the caregivers. All the measurements were carried out in the morning. The caregivers were requested to provide a urine sample (at least 20mL) which was immediately frozen at -80°C and stored. Urinary aminoglycoside concentration was assessed by the fluorescence polarization immunoassay method in replicate. The threshold detection was 0.8 and 0.33µg/dL for amikacin (AMIK2 insert, ROCHE diagnostics) and tobramycin (TOBR2 insert, ROCHE diagnostics), respectively.

Fifty-five PwCF were eligible during the recruitment period. Twenty-three caregivers (10 fathers and 13 mothers) for 23 PwCFmet the inclusion criteria and the others did not perform the last nebulization session. Five caregivers refused to participate because of lack of time. The characteristics of the PwCF and proxy are highlighted in table 1. The FEV1 of the 10 PwCF who were able to perform a lung function test in routine was in the normal range. A potential relationship between the lung function and the exposure was not possible to be verified. Four PwCF were doing all the nebulization session on the knees of the caregivers. All the PwCF older than 3 years (n = 14) were performing the nebulization with a mouthpiece as recommended in our center and the others were using a facemask. The PwCF were using a jet (Sidestream and PortaNeb, Philips Respironics)(n = 8) or a vibrating mesh nebulizer (eFlow, Pari)(n = 10).

The duration of the session was approximately 15 minutes and 8 minutes for the jet and the mesh nebulizer, respectively, and the minimal use duration of nebulized aminoglycosides was 6 months. Four of the recruited caregivers were preparing the drug to be nebulized. No room were ventilated by opening the window.

The median delay from the last exposure was 190 minutes (40-300min) and the median distance from the nebulizer was 2 meters (0.5-5m). The nebulized aminoglycosides were tobramycin (40mg/4mL and 80mg/4mL for <5years and 5-10years, respectively)(n = 15) and amikacin (250mg/4mL)(n = 3). Eight samples out of the 18 were positive for aminoglycosides, none of them for amikacin. Fifty percent of the caregivers staying the full nebulization session close to the PwCF were positive for aminoglycoside. None of the caregivers reported any adverse effects related to the session (bronchospasm, cough…).

The exposure to the fugitive aerosol from the nebulization was not surprising because an exposure to airborne particles has been previously documented in the firefighters at the World trade Center[7] and the vessel crew[8]. Health care workers are also occupationally exposed to airborne particles[9]. Occupational exposure was demonstrated during the delivery of nebulized pentacarinat[10,11]. Even if data were not available concerning environmental contamination through use of other aerosolized antibiotics, a potential environmental contamination inherent in the usual aerosol technique was suggested[12].

During the nebulization, aerosolized droplets are three-dimensionally emitted in the air over variable angle and distance depending on the size of the particles[13], and on the speed of the airflow[14]. Depending on their size, the emitted particles leave (diameter higher than the respirable diameter) or remain within the vortex associated to the jet because the gravitational force[13]. The particle levels in the air decay with the particle mass, the distance from the nebulizer and the time after the nebulization[15,16]. Our results have to be nuanced

based on all these elements. The airflow was not possibly include in the interpretation because only 10 PwCF were able to perform a spirometry. The exposure was mainly a short-range airborne exposure because the small particles emitted in the air by the used nebulizers (respirable because mainly around 3-5 microns) and the short distance of the caregivers from the nebulizer during the session (lower than 5m).

Aminoglycosides are concentration-dependent antibiotics and their concentration in the urine of non-exposed subjects is expected to be undetectable. As the amikacin is excreted unchanged from the serum in the urine (more than 80%) in less than 9h[17], the concentration found in the urine should be close to or lower than its serum concentration. Then, it reflects the systemic exposure of the caregivers. The observed risks related to exposure are not benign. Even if it is expected to be associated to high serum concentrations, ototoxicity related to nebulized amikacin was demonstrated with a unpredictable genetic predisposition related to the MT-RNR1 gene[18]. Similarly, a nephrotoxicity has been observed[19]. Moreover, the repeated nebulizations of aminoglycoside and the resulting exposure of the caregivers could contribute to the modification of the airway resistome[20]. Finally, prior antibiotic caregiver's exposure to antibiotics could produce in the future a detrimental effect on response to immune checkpoint inhibitors because the gut microbial imbalance is mediated by antibiotics[21].

Some limits to the study have to be addressed. First, the time between nebulization and urine sampling was variable. However, due to the short half-life of the aminoglycosides and the aim of assessing the exposure, we hypothesized that if the caregivers were exposed to the fugitive aerosol, the maximal 6h-delay between the nebulization and the sampling was optimal to avoid the disappearance of the urine aminoglycoside before sampling and then demonstrated the exposure. The aminoglycosides air concentration related to the exposure of the caregivers

was evidently not similar for all of them due to the limits of the protocol (variable distance and duration of exposure, uncontrolled aeration of the room, participation to the preparation of the nominal dose) of this real-life study.

In conclusion, the caregivers are importantly exposed to the fugitive aerosol during a nebulization session even when they are not involved in the nebulization itself. In case of antibiotics nebulization, the importance of this risk has to be considered. This risk could justify modifying the routine related to the nebulization of antibiotics in the future by adding an expiratory filter to the nebulizer or by prioritizing other methods of administration (dry powder or pressurized-metered dose inhalers) even if further studies related to these changes are needed.

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Contribution

Gregory Reychler, Conception and realization of the study, analysis of the results, and writing of the manuscript

Zoé Verdereau, Conception and realization of the study, analysis of the results, and correction and approbation of the manuscript

Anne-Sophie Aubriot, Conception of the study, analysis of the results, and correction and approbation of the manuscript

Sophie Gohy, Conception of the study, analysis of the results, and correction and approbation of the manuscript

Silvia Berardis, Conception of the study, analysis of the results, and correction and approbation of the manuscript

Lidvine Boland, Conception of the study, analysis of the results, and correction and approbation of the manuscript

Vincent Haufroid, Conception of the study, analysis of the results, and correction and approbation of the manuscript

Jean-Christophe Dubus, Conception and realization of the study, analysis of the results, and writing of the manuscript

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Table 1: Descriptive data about the participants and the experimental conditions, and results related to the exposure

Subjects	Aminoglycoside	Last nebulization (hour)	Last miction (hour)	Distance of exposure from the nebulizer (m)	Age of the patient (year)	Age of the caregiver (year)	Creatinine (µg/dL)	Detection of aminoglycoside (µg/dL))
1	Tobramycin	4	1	3	6	30	239.1	-
2	Tobramycin	3	0.5	0.5	4	35	59.2	0.41
3	Tobramycin	2	0.5	1	2	29	323.2	-
4	Tobramycin	3	2	4	3	26	67.3	-
5	Tobramycin	1.5	2	5	8	34	27.2	0.34
6	Tobramycin	2	1	0.5	2	29	131.6	0.42
7	Tobramycin	2	0.25	4	3	27	188.5	0.52
8	Tobramycin	2	0.25	1	3	31	24.8	-
9	Tobramycin	3	0.5	2	8	42	165.1	-
10	Tobramycin	3	0.3	3	0.9	31	85.5	-
11	Tobramycin	3	1	3	1	29	120.7	0.51
12	Tobramycin	4	1	1	7	40	100.3	0.37
13	Tobramycin	5	0.5	2	10	42	178.6	-
14	Tobramycin	3	1	3	4	36	68.6	0.37
15	Tobramycin	5	2	4	3	32	102.1	0.41
16	Amikacin	0.6	2	1	16	35	85.1	-
17	Amikacin	0.6	3	2	15	47	130.1	-
18	Amikacin	1.5	3	2	16	23	102.9	-

Threshold detection for amikacin and tobramycin: 0.8 and 0.33µ/dL, respectively

Grey color: detected aminoglycoside in the urine of the caregiver