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Author information

Tolerance of essential oils exposure in patients with allergic asthma

Jean Levy M.D.^a, Catherine Neukirch M.D.^a, Isabelle Larfi,^a Pascal Demoly M.D., Ph.D.^c,
Gabriel Thabut M.D., Ph.D.^{a,b,*}

^a Departments of Pneumology A and Pneumology B, Bichat-Claude Bernard University Hospital, Paris, France;

^b Paris Diderot University, Faculty of Medicine, Bichat campus, Paris, France;

^c Department of Pneumology and Allergology, Arnaud de Villeneuve Hospital, University Montpellier, and Sorbonne University, INSERM, IPLESP, Paris France;

***Corresponding author:** Prof. Gabriel Thabut, M.D., Ph.D. Service de Pneumologie B, Hôpital Bichat-Claude Bernard, 46 rue Henri Huchard, 75018 Paris, France

E-mail: gabriel.thabut@aphp.fr

Author contributions:

Conception and design: JL, CN, IL, PD, GT

Acquisition of data: JL, IL, GT

Analysis and interpretation of data: JL, CN, IL, PD, GT

Drafting or revising the manuscript for important intellectual content JL, CN, IL, PD, GT

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Agreement to be accountable for all aspects of the work: JL, CN, IL, PD, GT

Tolerance to exposure to essential oils exposure in patients with allergic asthma

Running head: Tolerance of essential oils in asthmatics

List of abbreviations

ACT : asthma control test

AHR : airway hyperresponsiveness

FeNO : fractional exhaled nitric oxide

FEV₁: forced expiratory volume in 1-second

FVC : forced vital capacity

ICS : inhaled corticosteroids

PD20 : methacholine provocative dose causing a 20% decrease in FEV₁

PPAS : purifying air spray with 41essential oils

SABA : short-acting beta-2 agonists

VOC : volatile organic compounds

Abstract

Background

Essential oils are volatile compounds of plant origin increasingly used by allergic and/or asthmatic subjects to purify indoor air. The active compounds of essential oils belong to terpenes, the most widespread biogenic volatile organic compounds (VOC). Although there is substantial literature showing associations between exposure to chemical VOCs and asthmatic symptoms and impaired respiratory function, the impact of essential oils in patients with asthma has never been studied.

Objectives

To evaluate the safety of a purifying air spray containing 41 essential oils (PPAS) in patients with mild or moderate allergic asthma.

Methods

This was a prospective open study in which 25 mild (19) and moderate (6) asthmatics were exposed to PPAS, one spray twice a day at 8 am and 8 pm in two different corners of a given subjects bedroom for 4 weeks. Before and after 4 weeks of exposure, fractional exhaled nitric oxide (FeNO), lung function, and methacholine challenge (PD₂₀) were performed and asthma control was assessed by the 5 questions of the Asthma Control Test (ACT). The spray was weighed after the 4-week exposure to assess compliance.

Results

FeNO was the primary endpoint and was thus analyzed in all (N=25) subjects irrespective of the level of airflow obstruction. The results apply to all (N=25) subjects in which FeNO could be measured at D1 and D30 (17 subjects). Mean (SD) FeNO amounted to 37.4 (16.6) and to 33.1 (18.7) ppm before and after PPAS exposure, respectively ($p=0.09$). No significant change in lung function and methacholine responsiveness was noted after PPAS exposure, the mean PD₂₀ amounting to 1179 (1124.42) μ g (range 100-3200) before and to 1226 (1189.8) μ g ($p=0.06$) after. The mean ACT before and after PPAS exposure amounted to 20.9 (4.2) and 21 (5.15), respectively ($p=0.80$). The mean weight of the PPAS bottles was 211.4 g (DS:0) before the first use and 171.41g (DS: 29.8) at the end of the study. The average amount of PPAS used was 40.0 gr (29.8). In the subgroup of subjects who used the highest quantities of essential oils (>40 gr), as assessed by the mean weight of the bottle at the end of the study, FeNO after 30 days of exposure decreased more than in the entire group: 7.9 ppm vs 4.2ppm ($p=0.07$).

Conclusion

No difference was noted on airway inflammation, lung function or asthma control in mild and moderate allergic asthmatics after exposure twice a day for one month, to a spray containing a mixture of 41 essential oils.

Introduction

Asthma is a chronic inflammatory airway disorder that leads to symptoms such as coughing, wheezing, and chest tightness. Alterations of the airways in asthma are the result of complex interactions between inflammation, airflow obstruction, and bronchial hyperresponsiveness (1). The dominant event leading to clinical symptoms in asthma is bronchoconstriction. The latter runs a variable course, with symptom-free periods interrupted by periods of exacerbations, often caused by viral infection, exposure to allergens, for allergic asthma, or fungi and indoor or outdoor pollutants (2). Allergic sensitization to inhaled allergens such as house dust mites, animal dander, pollen or molds is found in a large proportion of patients (50 to 85%), and this is due to atopy, which is a predisposition to develop allergic hypersensitivity reactions and to produce IgE in response to allergens (1). The international guidelines emphasize the importance of eliminating airborne allergens, notably those found indoors, such as dust mites, animal dander and molds, as the first step in the management of asthma (3).

Essential oils are mixtures of volatile compounds of plant origin. Recently, they have raised interest among scientists and physicians due to their acaricidal, antifungal, antiviral and bactericidal properties, which have been reported *in vitro* (4). Essential oils have become popular for ecological reasons, and are increasingly used and valued in the general population and allergic and/or asthmatic patients to purify indoor air. Several sprays of essential oils have been launched on the market over the last decade. The active compounds of essential oils belong to the monoterpenes and sesquiterpenes, which are the most common reactive biogenic volatile organic compounds (VOCs). Although there is a substantial literature showing associations between exposure to chemical VOCs and asthma, asthmatic symptoms and impaired respiratory function (5), to our knowledge, the impact of essential oils in patients with asthma has never been reported. The aim of the present study was to evaluate the safety of a purifying spray containing 41 essential oils in patients with mild or moderate allergic asthma. To this end, the effects of one-month exposure on airway inflammation, lung function and asthma control were studied.

Methods

Subjects

Twenty-five subjects (18 women and seven men) with mild or moderate controlled asthma were recruited during a follow-up visit to the Bichat hospital outpatient clinic and participated in the study (Table 1). All subjects had an established diagnosis of asthma with a disease

duration of at least 2 years. All were between 22 and 74 years of age, (mean 46.1 (14.6) years and had been diagnosed with mild (n= 19) or moderate asthma (n= 6), according to the GINA guidelines (3). All subjects had a positive medical history of recurrent dry coughing especially at night, ronchus, wheezing, chest tightness, or shortness of breath. All subjects, in the past year before inclusion in the study, had at least one episode documented of reversible airway obstruction (increase FEV₁ >12% and 200ml).

All were atopic, as defined by a positive skin prick test (wheal ≥3mm compared with control) to common aeroallergens of our area (house dust mites, cat and dog dander, grass, tree and weed pollens and moulds). Among the 25 subjects, 5 had a positive prick to house dust mites alone, 15 to house dust mite and grass pollen, 5 to house dust mite, grass pollen and *Alternaria*. All subjects used short-acting inhaled β₂-agonist (SABA) as needed, and those with moderate asthma, a low dose (≤500 µg/day equivalent beclomethasone) of inhaled corticosteroids (ICS). All subjects were non-smokers and were free of upper respiratory infections for at least 4 weeks prior to the study. Subjects with severe asthma according to the GINA guidelines (>500 µg/day equivalent beclomethasone) were excluded. Before enrollment in the study, all subjects signed a written informed consent.

Ethics, consent and permissions

The study was approved by the ethics committee of Ile de France 1 (registration number 14493).

All participants signed an informed consent document.

Study protocol

This was a monocentric, prospective open study. All subjects were exposed to Puressentiel purifying air spray 41 essential oils (PPAS), a mixture of 41 essential oils (Puressentiel laboratory, Brussels, Belgium). According to the manufacturer, the array of essential oils selected for this spray ensures effective destruction of dust mites, fungi, bacteria and viruses. Conformity tests according to current standards (EU N°528/2012 : <http://eur-lex.europa.eu/legal-content/fr/TXT/PDF/?uri=CELEX:32012R0528>) have been performed for this spray, which is classified as a biocide. All the ingredients contained in the spray are natural and comply with the BBDEO quality charter (Biochemically and Botanically Defined Essential Oils). The alcohol used is from plant sources not denaturated by phthalates, and the spray contains no propellant gas.

PPAS with essential oils was sprayed twice a day (0.6 ml per spray) in the subject's bedroom (at two corners of the bedroom), according to the instructions indicated by the manufacturer: one spray in the morning and one spray in the evening (before bedtime) for 4 weeks. The subjects were asked to spray their room each day at 8 am and 8 pm. The procedures (listed

below) at baseline (D0) were conducted at 10 am. The procedures after exposure (D30) were conducted also at 10 am, 2 hours after the last spray. At baseline and 4 weeks after PPAS exposure, the control of asthma was assessed by a self-administered questionnaire, the Asthma Control Test (ACT). All procedures were standardized and conducted in the same following order. The control of asthma was first assessed by the Asthma Control Test (ACT). FeNO measurements were then performed before spirometry, followed by methacholine challenge.

Subjects were instructed to hold their medications (SABA and ICS) 12 hours prior the procedures.

A spray (200 ml) of essential oils (PPAS) was provided to each subject. After the 4-week exposure, the patient brought back the spray, which was weighed to assess compliance.

Exhaled nitric oxide measurement

At baseline and 4 weeks after PPAS exposure, a measurement of fractional exhaled nitric oxide (FeNO) was performed using a hand-held electrochemical device NIOX MINO (Aerocrine, Solna, Sweden). FeNO concentration in the exhaled air is a non-invasive method, which is an indirect marker of the extent of airway eosinophilic/T2 inflammation (6). Measurements of FeNO were performed according to the American Thoracic Society (ATS), European Respiratory Society (ERS) guidelines during an exhalation ≥ 6 s using $50\text{ mL}\cdot\text{s}^{-1}$ flow rates (7). FeNO was systematically measured before spirometry and methacholine challenge.

Pulmonary function

Before and after the 4-week PPAS exposure period, all subjects underwent assessment of forced expiratory volume in 1-second (FEV_1) and forced vital capacity (FVC). Flow-volume curves were obtained with a Biomedin spirometer (Biomedin Srl, Padova, Italy) in order to determine FEV_1 , and forced vital capacity (FVC). The spirometry technique met international standards, and reference values were those of the European Respiratory Society (8).

Bronchial hyperresponsiveness

Airway responsiveness was assessed by methacholine challenge testing, using an automatic inhalation-synchronized Mefar MB3 dosimeter jet nebulizer (Mefar SpA., Bovezzo, Italy), as previously described (9). After inhalation of isotonic saline as a control, subjects were administered methacholine until the FEV_1 had dropped by $\geq 20\%$ of the post-saline value, or until the maximal cumulative dose of $3.200\text{ }\mu\text{g}$ had been given; the cumulative doses administered were 100, 200, 400, 800, 1600 and $3200\text{ }\mu\text{g}$. A 3-min interval was allowed

before each dose increment. FEV₁ was measured 1 min after each dose; the best of 3 acceptable measurements was used. The methacholine provocative dose causing a 20% decrease in FEV₁ from control FEV₁ (PD₂₀ methacholine) was determined by interpolation from the dose-response curve (10). The higher the PD₂₀, the lower the bronchial responsiveness. A methacholine challenge test result was considered positive if the PD₂₀ was <1600 µg.

Asthma control and symptoms

. The ACT contains 5 questions that are related to the frequency of both asthma symptoms and required rescue medication use during the previous 4 weeks. The scores in the ACT range from 5 (worst control) to 25 (total control). The threshold ACT determining good asthma control is 20, a lower score indicating uncontrolled asthma (11).

Each subject also filled in a daily diary, at the same time as when they sprayed their room, and asked 7 questions concerning respiratory symptoms and perception of discomfort (i.e. perception of an odor, eye irritation, nose obstruction and irritation, chest tightness, coughing, wheezing). Any change in asthma medications was also recorded.

Statistical analysis.

Continuous variables are described by mean, standard deviation and range, whereas categorical variables are described by counts and percentages. Paired t-tests were used to analyze the evolution of continuous variables between baseline and study completion, whereas McNemar's test was used to test the change in categorical variables. All test are two-sided with a p-value < 0.05 indicating statistical significance.

R 3.2 software was used for all analyses.

FeNO was the primary endpoint and was thus analyzed in all subjects irrespective of the level of airflow obstruction. The results apply to all subjects in which FeNO could be measured at D1 and D30. The data were pooled as a single sample regardless the degree of asthma severity, mild and moderate.

Assuming a baseline FeNO of 40 ppm (SD=25), an estimated 25 patients were needed to detect an 8-ppm difference in FeNO between inclusion and study completion, with alpha=0.05, power = 0.8, and SD of the difference = 15.

Results

All 25 subjects completed the 30 days of exposure.

Exhaled nitric oxide measurement

FeNO was the primary clinical outcome and was measured the day before the first exposure (D1) and the day after the last exposure (D30). Among the 25 subjects, the measurement of FeNO was not interpretable on day 1 in 5 subjects and on day 30 in 4 subjects, due to their inability to sustain a constant flow rate (50 ml.s^{-1}) throughout the measurement period. The measurement of FeNO was therefore collected before and after the PPAS exposure in 17 subjects. For the 20 subjects who had a measurement at D1, FeNO amounted to 34.1 ± 17.3 ppm (Table 1). For the 17 subjects who had a measurement of FeNO at D1 and D30, FeNO amounted to 37.4 (16.6) and to 33.1 (18.7) ppm before and after PPAS exposure, respectively (Table 2), a difference of -4.24 (9.69) ppm, which was not significant ($p=0.09$ paired t-test) (Table 2). Using a non-parametric test (Wilcoxon paired test) led to a similar result ($p=0.11$). Individual values before and after PPAS exposure are shown in Fig1.

Lung function and methacholine bronchial challenge

Baseline lung function was measured in all subjects and was in the normal range (Table 1). After PPAS exposure, no significant change in lung function was noted, the mean FEV_1 ranged from 3.03 (0.97) L to 2.97 (0.86) L ($p=0.27$), before and after exposure, respectively (Table 2, Fig.2).

Methacholine responsiveness at inclusion (D1) was measured in 24 subjects, one being unable to perform repetitive expiratory maneuvers throughout the test. As shown in Table 1, a wide range of PD_{20} was noted at D1, indicating that some subjects exhibited a strong bronchial hyperresponsiveness before PPAS exposure, the mean PD_{20} amounting to 1179 (1124.42) μg (range 100-3200). A small, but non-significant, increase in PD_{20} was observed after PPAS exposure (D30) as compared to D1, PD_{20} amounting to 1226 (1189.8) μg ($p=0.06$) (Table 2, Fig. 2 panel C). The proportion of subjects having a negative bronchial methacholine challenge ($\text{PD}_{20} > 1600 \mu\text{g}$) did not differ between D1 and D30 ($p=0.32$).

Asthma control and symptoms

The mean ACT before (D1) and after (D30) PPAS exposure was 20.9 (4.2) and 21 (5.15), respectively, a non-significant difference ($p=0.80$). Individual ACT values before and after PPAS exposure are shown in Fig.2 (panel D).

Presence of any of seven symptoms, as listed in the method section, was noted daily at the same time as when they spray their room (8 am and 8 pm). by each subject (Table 3). No significant differences were observed for 5 symptoms (nose irritation and obstruction, chest tightness, cough, wheezing) between D1 and D30, whereas odor increased and eye irritation decreased significantly ($p=0.025$). It should be noted, however, that the percentage of subjects who reported one of the 7 symptoms at least once, one day during the PPAS exposure period, increased as compared to the percentage at D1 (Table 3).

Observance

To assess compliance, the weight of the PPAS bottles was measured prior the first use and at the end of the study. The mean baseline weight was 211.4 g (DS:0) and post study weights 171.41g (DS: 29.8). The average amount of PPAS used was 40.0 gr (29.8), with variations from 9.5 to 121.5 gr.

Discussion

Several epidemiologic studies have suggested possible associations between chemical VOCs linked to human activity, such as petrochemical derivatives, and risk of asthma and allergy (5,12). Among the available studies, to our best knowledge, none was designed to examine specifically the impact of essential oils in patients with asthma. Terpenes are active substances found in essential oils which are usually considered to be harmless products. They may also be emitted from paint, cleaners and other consumer products. However, in a case-control study (12) in which possible relations between symptoms of asthma and indoor concentrations of VOCs in dwellings were studied, exposure to a terpene (limonene), was related to bronchial hyperresponsiveness, and exposure to α -pinene and carenes ($\delta 2$, $\delta 3$), to a reduction in peak expiratory flow.

The present prospective experimental study was specifically designed to investigate the impact of exposure to essential oils in asthmatics. The latter should be among the most sensitive subjects to these compounds, because VOCs have been shown to influence the airways by induction of inflammatory responses and asthmatic symptoms (13). We therefore examined in asthmatics, the effect of essential oils on bronchial inflammation and reactivity, as well as asthma control and symptoms.

After 30 days of exposure (2 activations per day) to a spray containing 41 essential oils, no differences were noted for FeNO, airway hyperresponsiveness (AHR) and asthma control in psubjects with mild or moderate controlled allergic asthma.

To assess airway inflammation, bronchial biopsy remains the gold standard. However, the process is invasive, and FeNO concentration in exhaled air is a non-invasive method which

is used to estimate eosinophilic / T2 inflammatory processes in the lung (6). Nitric oxide (NO) is an important cellular signaling molecule that regulates pulmonary blood flow, mucus production, ciliary activity and inflammation. Under normal circumstances, NO is produced at very low concentrations by constitutive NO synthases (endothelial NOS and neuronal NOS). In case of airway inflammation, pro-inflammatory cytokines upregulate inducible NOS, producing higher levels of NO (14). Patients with asthma, even at milder stages of the disease, have been shown to exhale FeNO in higher concentrations than normal subjects, FeNO being associated particularly with eosinophilic airway inflammation (15).

The cut-off level used for FeNO to assess airway inflammation in asthma is usually set at 30 ppb (25th and 75th percentile, 20 and 40 ppb) (6). This is in line with the mean FeNO value (37.4 ppm) found in our subjects (Table 2). After one month of daily PPAS exposure, no significant change in FeNO was noted (Table 2, Fig.1), indicating that the essential oils contained in the spray did not enhance airway inflammation. Interestingly, this was also observed in the subjects with a high level of FeNO (>40 ppb) at inclusion, indicating the presence of bronchial inflammation, as well as in those with low FeNO values (≤ 25 ppb), and therefore, a low level of airway inflammation.

Airway hyperresponsiveness (AHR) can also be considered as a surrogate marker of airway inflammation and is recognized as an important characteristic finding in asthma (16). As for FeNO, no significant changes in airway responsiveness to methacholine were noted in our subjects after PPAS exposure (Table 4, Fig.2 panel C). Of note, as previously described (17, 18), we found in our subjects a relationship, although non-significant, between FeNO and AHR: 60% of subjects with an FeNO between 0-25 ppm exhibiting AHR as assessed by PD₂₀, 75% between 25-50 ppm and 100% above 50 ppm.

In summary, these data demonstrate that, in our setting, exposure to a spray containing 41 essential oils did not enhance airway inflammation in subjects with mild and moderate controlled allergic asthma.

Airway inflammation is related to asthma symptoms and exacerbations (19), patients with FeNO > 28 ppb being the most likely to develop an exacerbation (20).

Clinical control has been shown to be associated with a lower degree of eosinophilic inflammation as assessed by indirect markers like FeNO and PD₂₀ (21). As a result of its absence of effect on airway inflammation, we found that exposure to PPAS did not significantly impact asthma control as assessed in the present study by the ACT score (Fig 2, panel D).

The effect of PPAS exposure was further assessed by recording 7 symptoms (Table 3) that could be related to a possible irritating effect of the essential oils. Although appearance of one symptom among the 7 recorded was reported at least once throughout the period of

exposure, no significant difference, except for odor and eye irritation (which significantly decreased) was noted between D1 and D30.

Study limitations

The first limitation of this study is that the subjects could have sprayed the PPAS in other areas of their living space instead of their bedroom. A characteristic odor of the PPAS spray allows indirectly to ensure that the subject has been exposed. The questionnaire that the subjects filled each day included a question “odor”. As shown in table 3, 3.4% of the subjects reported an odor at baseline compared to almost 50% during the exposure period, the perception of this odor being in all likelihood related to the use of PPAS.

However, we cannot ensure that all the subjects sprayed the PPAS in their bedroom, although they gave a positive answer to this question asked during the last visit at D30.

The second limitation is that we did not measure the concentrations of terpenes emitted by the spray in the subject’s bedroom, and therefore we do not know the levels to which each subject was exposed. It is possible that harmful effects might have occurred for higher concentrations, bronchial obstructive reactions having been reported for indoor concentration of 1.0 mg/m³ of terpenes, about two-thirds being limonene (12). To evaluate the tolerance to the PPAS spray, we selected the number of sprayings (2) recommended by the manufacturer. It is possible however, that exposure to a higher number of sprayings would have led to some deleterious effects. Although we cannot exclude this possibility, it is interesting to note that in the subgroup of subjects who used the highest quantities of essential oils, as assessed by the mean weight of the bottle at the end of the study, FeNO after 30 days of exposure decreased more than that in the whole group: 7.9 ppm vs 4.2 ppm. This could be due to an anti-inflammatory effect of some essential oils, as recently described (22, 23).

The particle size of the PPAS spray was not measured in our study. However, the manufacturer indicated a median particle size of 90 µm which may have impacted our findings, the latter not penetrating deep into the respiratory tract.

Finally, the subjects included in our study were well controlled mild and moderate asthmatics with a strong allergic component based on skin testing. Therefore the present results might not apply to subjects with more severe or less controlled non allergic asthma.

Conclusion

To the best of our knowledge, this is the first human prospective experimental study examining the possible adverse effects of essential oils in subjects with allergic asthma. Results presented herein demonstrate that there was no change in bronchial inflammation, lung function and control after exposure twice a day for one month to a spray containing a mixture of 41 essential oils in subjects with mild and moderate allergic asthma. Further

studies are needed to confirm the safety during longer exposure and in patients with more severe or less controlled asthma.

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Figure legends

Figure 1

Individual and median (red triangles) values of fractional exhaled nitric oxide (FeNO) before (D1) and after one month of exposure (D30) to Puressentiel Purifying Air Spray 41 essential oils.

Figure 2

Individual and median (red triangles) values of FEV₁ (% predicted) (panel A) and in liters (panel B), PD₂₀ (panel C) and Asthma control test (ACT) panel D, before (D1) and after one month of exposure (D30) to Puressentiel Purifying Air Spray 41 essential oils.

Table 1. Baseline characteristics of patients

Parameter	Missing (n)	Statistic	Range
Female sex – n (%)	0	18 (72%)	
Age – yrs	0	46.1±14.6	22.7 – 74.4
Weight – kg	0	79.96±17.13	47 – 117
Height – m	0	1.67±0.09	1.54 – 1.88
Body mass index – kg.m ⁻²	0	28.6±5.29	17.69 – 38.27
FEV ₁ – liters	0	3.03±0.97	1.61 – 5.24
FEV ₁ – % of predicted values	0	99.7±17.6	65.0 – 134.0
FVC – % of predicted value	0	105.6±15.1	77.0 – 134.0
FeNO – ppm	5	34.1±17.3	10 – 68
PD ₂₀ – µg	1	1179.2±1124.42	100 – 3200

Plus-minus values are means ± SD. BMI : body mass index, FEV₁ : forced expiratory volume in one second. FVC : forced expiratory capacity.

includes all patients n=20

Table 2. Changes in pulmonary function tests between baseline and day 30

Variable	Difference	p
FeNO – ppm [§]	-4.24±9.7	0.09
FEV ₁ – liters	-0.06±0.27	0.27
FEV ₁ – % predicted	-0.48±7.9	0.76
FCV – % predicted	-0.40±6.99	0.77
PD ₂₀ – µg *	93.75±237.0	0.06

*n=24 patients with available data at Day 1 and Day 30. §n=17 patients with available data at Day 1 and Day 30.
Analysis involved Student paired t-test.

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Table 3. Symptoms

Variable	Baseline	D2-D28*	D29	p§
Nasal irritation	4 (16.0%)	15 (60.0%)	6 (24%)	0.41
Nasal obstruction	4 (16.0%)	12 (48.0%)	6 (24%)	0.32
Chest tightness	4 (16.0%)	11 (44.0%)	3 (12%)	0.56
Cough	4 (16.0%)	12 (48.0%)	1 (4.0%)	0.18
Wheezing	2 (8.0%)	7 (28.0%)	0 (0%)	1
Odor	1 (4.0%)	11 (44.0%)	6 (24%)	0.025
eye irritation	8 (32.0%)	14 (56.0%)	3 (12%)	0.025

*Indicates the proportion of patients having this symptom at least once between D2 and D28. §McNemar test comparing the proportion of patients having the symptom between D 1 and D 29.

Declaration of interest

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Competing interests

Jean Levy and Gabriel Thabut received a grant from Puressentiel laboratory. The funding source had no role in the design, conduct, or analysis of the study or the decision to submit the manuscript for publication.

Figure 1

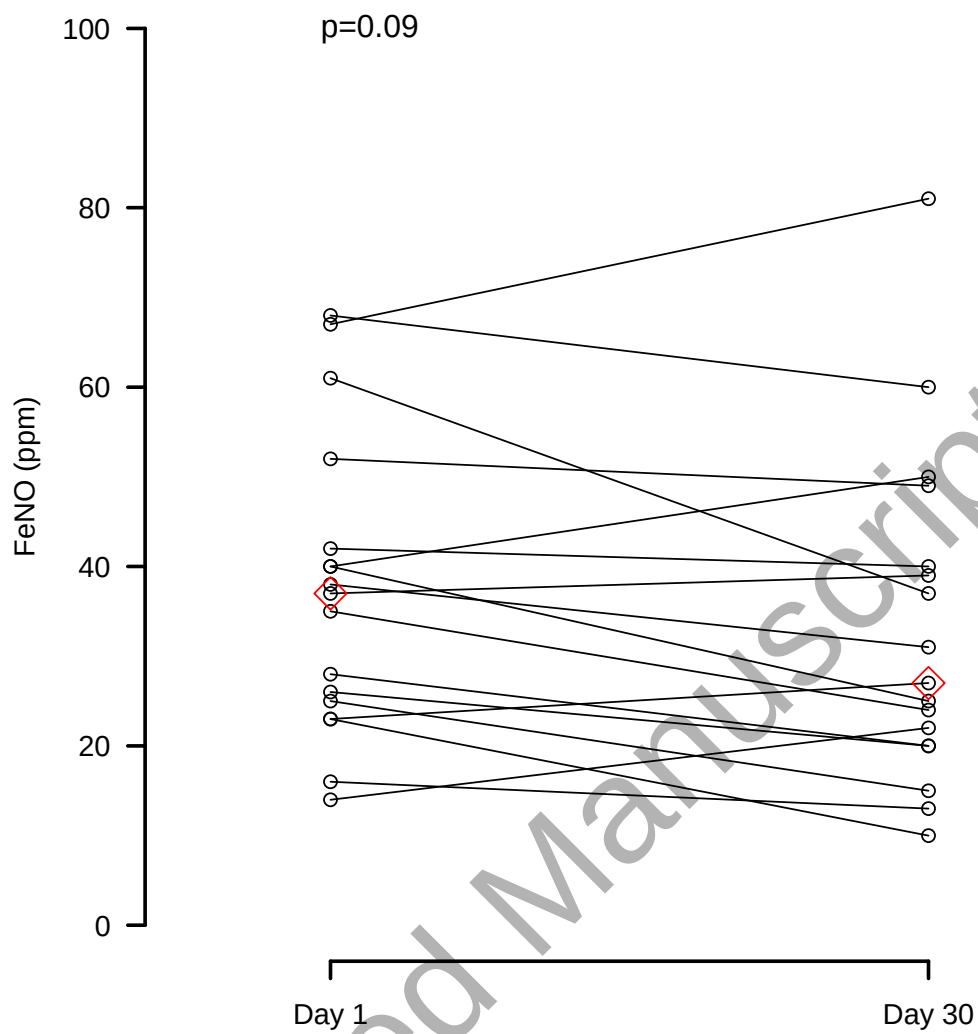


Figure 2

