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Inhalation challenges with occupational agents: Threshold duration of exposure

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Summary
Objectives: The aim of this study was to characterize the threshold duration of exposure needed to elicit an asthmatic reaction during specific inhalation challenges (SIC) with various occupational agents and to determine the duration of exposure that should be completed before the test can be considered negative.
Methods: This retrospective study analysed the cumulative duration of challenge exposure that was required to elicit a $\geq$20% fall in forced expiratory volume in one second in 335 consecutive subjects with a positive SIC.
Results: The threshold duration of challenge exposure required to induce an asthmatic reaction was $\leq$60 min in 179 (53%) subjects, between 61 and 120 min in 74 (22%) subjects, and longer than 120 min in 82 (25%) subjects. The multivariate linear regression analysis showed that a longer duration of exposure was associated with exposure to low-molecular-weight agents ($p < 0.001$), a higher level of baseline non-specific bronchial hyperresponsiveness to histamine ($p = 0.015$), increasing age ($p = 0.011$), and a shorter duration of asthma symptoms at work ($p = 0.060$).
Conclusions: This study demonstrates that the sensitivity of SICs for diagnosing OA is highly dependent upon the duration of the challenge exposure. These data may provide useful guidance for improving the reliability of SICs performed with realistic methods of exposure.

Abbreviations: FEV1, forced expiratory volume in one second; HMW, high molecular weight; LMW, low molecular weight; OA, occupational asthma; PC_{20}, provocative concentration of histamine causing a 20% fall in FEV_1; SIC, specific inhalation challenge; $TD_{20\%FEV1}$, threshold duration of exposure inducing a $\geq$20% fall in FEV_1.

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Introduction

A specific inhalation challenge (SIC) with occupational agents is still regarded as the "reference" method to establish the diagnosis and aetiology of immunologically-mediated occupational asthma (OA).[1–3] A major limitation of SICs is their potential for inducing false-negative results when specific bronchial reactivity to the sensitizing agent has declined after cessation of workplace exposure.[4–9] Using a closed-circuit device that allows for generating quantified levels of various agents, Lemière and co-workers elegantly demonstrated that the specific bronchial reactivity to sensitizing occupational agents almost never completely disappear after cessation of exposure,[8,9] although the dose of the agent required for inducing a positive SIC response significantly increases.[8]

Since standardized preparations are not available for most occupational agents, SICs are still usually performed by exposing the subjects to the suspected occupational agent using the "realistic" approach originally described by Pepys and Hutchcroft in the early 1970s.[10] This methodology aims at reproducing as close as possible the conditions of exposure at the workplace in terms of the chemical and physical characteristics of the agent, for example, dust, aerosol, vapour, or fume.[10–13] The concentrations of the agents generated during these SICs are usually not measured due to the wide diversity of the tested agents and the high technical demands for controlling exposures. In these realistic SICs, the duration of the challenge exposure is used as a surrogate of the dose of the agent delivered to the subjects. However, the cumulative duration of exposure to the suspected agent, which should be completed before the test can be considered negative, has never been thoroughly evaluated.

The aim of this study was to characterize the threshold duration of exposure that was required to elicit a $\geq$20% fall in FEV1 ($TD_{20\%FEV1}$) in a large series of positive SICs induced by various occupational agents as well as to identify the factors that can affect this parameter.

Methods

Study design and population

In this retrospective study, the records of all subjects investigated for possible OA who showed a positive SIC, defined by a $\geq$20% fall in FEV_1, from January 1992 to December 2011 at our institution were reviewed. These tests are routinely performed in our centre in the investigation of work-related asthma. The protocol of the study was approved by the *Comité d'éthique médicale du Centre Hopitalier Universitaire de Mont-Godinne* (approval number 84-2012). A statement of informed consent was not required because the data were analysed retrospectively in an anonymous way.

Specific inhalation challenges

SICs were completed according to a previously described protocol[12,14,15] that remained unchanged over the reviewed period. Briefly, occupational agents were generated in five-cubic-meter cubicles using a realistic approach.[10,12] Asthma medications were withdrawn according to their duration of action,[11] while inhaled corticosteroids were halted 72 h prior to the tests. The level of exposure during SICs was continuously monitored only for isocyanates using an MDA 7100 monitor (MDA Scientific Inc., Glenview, IL) and was kept below the ceiling value of 20 ppb.

Spirometry[16,17] was obtained at baseline, immediately after each exposure, then every 15 min for the first hour, every 30 min for the second hour, and hourly thereafter for a total of at least six hours after the end of exposure. The baseline level of non-specific bronchial hyperresponsiveness to histamine[14] and, since 2006, sputum eosinophil counts[15] were assessed at the end of the control day and re-assessed 6 and 24 h after the active challenges. The degree of non-specific bronchial hyperresponsiveness was expressed as the provocative concentration of histamine causing a 20% fall in FEV_1 (PC_{20}).[18] A SIC was considered positive when a sustained $\geq$20% fall in FEV_1 was recorded on two consecutive assessments. The pattern of bronchial responses was characterized as immediate, late, dual, or atypical according to previously described criteria.[10,19]

On the first day, the subjects were exposed to a 'control' agent for 30 min to ensure that FEV_1 fluctuations were $\leq$12% of the baseline value. The 'control' substance was selected according to the nature of the occupational agent suspected of causing OA. For instance, lactose powder was used as the 'control' substance for SIC with agents in powder form (e.g. flour, drugs, persulphates), pine dust for SIC with wood dusts, vinyl gloves for SIC with latex gloves, and diluents for polyurethane products and other resins. On the following day, the subjects were challenged with the suspected occupational agent (s). The duration of exposure to both high-molecular-weight (HMW) and low-molecular-weight (LMW) agents was gradually increased (i.e. 1 min, 4 min, 10 min, 15 min, 30 min, and 60 min) until a $\geq$20% fall in FEV_1 occurred or a cumulative exposure of two hours was completed. Those subjects who did not demonstrate a $\geq$20% fall in FEV_1 during the first active test day underwent a repeated challenge in the same way for a maximum of 2–3 h on the next day. Accordingly, all subjects were challenged for at least 240 min before considering the SIC as being negative. In addition, further challenges were proposed when there was a significant (>3-fold) decrease in the post-challenge PC_{20} value[14] or an increase in sputum eosinophils >3%,[15] as compared to the control day values.

Data analysis

Quantitative data are presented as median with 25th and 75th percentiles. Comparison between subgroups of subjects was made using the Chi-square test for categorical variables and the Wilcoxon rank-sum test for numerical variables. A multivariate linear regression analysis was conducted to identify the factors that affected the $TD_{20\%FEV1}$. The independent variables incorporated into the regression model included the relevant demographic and clinical characteristics of the subjects (i.e. age, gender, and smoking status, atopy, duration of asthma symptoms at