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The utility of drug reaction assessment trials for inhaled therapies in patients with chronic lung diseases

Brittany B. Dennis[a], Giulia Rinaldi[a,1], Georgie Housley[b], Anand Shah[b,c], Owais A. Shah[a], Michael R. Loebinger[b,c,*]

[a] St. George's Hospital Medical School, University of London, London, UK
[b] Royal Brompton and Harefield NHS Foundation Trust, London, UK
[c] National Heart and Lung Institute, Imperial College London, London, UK

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ABSTRACT

Background: Current guidelines recommend a Drug Reaction Assessment (DRA) before beginning inhaled therapies to assess for bronchoconstriction and tolerability. There is limited evidence to support this recommendation.

Methods: In this study we aimed to establish the predictors of successful DRAs in different patient groups using a cohort of all DRAs performed in adults between 2011 and 2016 at the Royal Brompton Hospital. Spirometry, age, gender, height, and underlying lung disease were recorded. A multivariable logistic regression model was constructed to ascertain variables associated with successful DRAs.

Results: There were 1492 DRA trials using hypertonic saline (32%), antimicrobials (63%), or rhDNase (5%). The majority of patients (94%, n = 1408) passed the DRA. Mean FEV_1% predicted was 58.03 (SD 23.36). Female sex, type of inhaled product, and FEV_1% predicted were established as significant predictors for DRA success. An FEV_1% predicted > 55% was associated with greater probability of DRA success (Odds Ratio [OR]: 2.96 (1.80,4.86) $p < 0.0001$). Those receiving dry powder, inhaled antibiotics were more likely to pass the DRA compared to nebulised antibiotics (OR: 3.99 (1.38,11.51) $p = 0.01$)).

Conclusion: This study classifies distinct patient groups with varying baseline risks which can be used to predict tolerability when adding an inhaled product to their management plan. Some "low risk" patients may in future be able to self-assess their tolerability for inhaled therapies at home to avoid unneeded hospital monitoring.

1. Introduction

Patients with chronic lung diseases are often prescribed inhaled agents as part of long term management plans. These include mucoactive products to improve airway clearance, and inhaled antibiotics to reduce microbial burden. The most commonly used inhaled mucoactive agents include hypertonic saline (HTS) and recombinant human DNase (rhDNase). The latter is used almost exclusively in cystic fibrosis (CF). There are an increasing number of available antibiotics via the inhaled or nebuliser route. There is a significant evidence base for their clinical value in cystic fibrosis with reduced exacerbation rates and improved spirometry, and they are commonly used and recommended in international guidelines in other chronic lung conditions, such as bronchiectasis.

These inhaled therapies present a small risk of bronchoconstriction. A systematic review demonstrated that inhaled antimicrobials caused bronchoconstriction in 10% of adult bronchiectasis patients compared to 2.3% of those taking placebo [1]. Similarly, HTS has been reported to cause bronchoconstriction in 12% of asthma [2] and 39% of severe COPD [3] in the context of an induced sputum protocol and 6% of bronchiectasis [4] and 1–30% of CF patients in other cohort studies [4–6]. In view of this risk of bronchoconstriction, guidelines advise drug reaction assessments for all patients prior to starting treatment with inhaled mucoactive products or antimicrobials [7–9]. Due to the methodologies, small sample sizes and different tolerability thresholds of the previous studies, the evidence base is poor and it is a Grade D recommendation [7–9].

This study utilised a large cohort of patients with chronic respiratory disease to assess the rate of trial failure and variables related to these outcomes, in order to help inform clinical practice as to the

* Corresponding author. Royal Brompton and Harefield NHS Foundation Trust, Sydney Street, London, SW3 6NP, UK.
E-mail addresses: m1400041@sgul.ac.uk (B.B. Dennis), m1401237@sgul.ac.uk (G. Rinaldi), g.housley@rbht.nhs.uk (G. Housley), A.Shah2@rbht.nhs.uk (A. Shah), syedowaisalishah@gmail.com (O.A. Shah), M.Loebinger@rbht.nhs.uk (M.R. Loebinger).
[1] Indicated shared first author.

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value of these assessments and the identification of patient groups that may benefit most from this resource intensive assessment.

2. Materials and methods

2.1. Overview of study

DRAs were conducted in patients with chronic lung diseases, aged 18 years and older, according to a standard protocol. Demographic data including assessment outcome was recorded. This study recruited patients with a range of underlying conditions including ABPA, asthma, CF, non-CF bronchiectasis, COPD, sarcoidosis and "other diseases", including lung carcinoma, interstitial lung diseases and mucous-hypersecretion disorders. The DRAs took place at the Royal Brompton Hospital between April 2011 and March 2016. The inhaled therapies included hyperosmolar agents (e.g. HTS), mucolytics (e.g. rhDNase) and several antimicrobials. The antimicrobials were subdivided into nine subgroups: 1) colistin/Promixin, 2) Colobreathe DPI, 3) tobramycin 4) TOBI podhaler, 5) amikacin, 6) gentamicin, 7) meropenem, 8) aztreonam and 9) the small remainder of other antimicrobials. Bronchodilators were administered before and/or after the DRA according to medical needs confirmed by the medical team and physiotherapists.

A standard protocol for DRAs of inhaled therapies was used for all patients in this study. The height, age, sex, forced expiratory volume in 1 s (FEV_1), FEV_1% predicted pre-trial and post-trial, oxygen saturation (SpO2) via pulse oximeter, and subjective symptoms reported during the DRA were collected at the time of the trial. This study was locally registered and determined to be service evaluation and not requiring a formal research ethics committee review.

2.2. Drug reaction assessment protocol

The DRA protocol requires that patients' spirometry (FEV_1) is monitored pre-trial. This may be preceded by a bronchodilator if used by a patient as part of their standard management or if directed by the medical team. The inhaled therapies' DRA was conducted under the supervision of a physiotherapist. Spirometry was repeated immediately after nebulising and the pre- and post-trial FEV_1 volumes were compared. If there was a $< 15\%$ decrease in FEV_1 and the drug was well tolerated the patient was deemed to have passed the DRA. If the FEV_1 decreased by $\geq 15\%$ an unsuccessful DRA was recorded and spirometry was repeated at 20 min. If at 20 min the FEV_1 was still 15% lower than pre-trial values they were offered nebulised salbutamol. After this, spirometry generally returned to pre-trial values, otherwise a review by the medical team was sought. Patients were also deemed to have an unsuccessful trial if they were unable to tolerate the therapy symptomatically, regardless of their FEV_1 values.

2.3. Statistical analysis

Baseline demographic characteristics including age, sex, and medical comorbidity are reported for total patient population as well as separately by trial outcome. Dichotomously measured variables are reported by percentage where continuous measures are summarized using means and standard deviations (SD). To establish the prognostically relevant differences in the clinical and demographic characteristics between groups based on trial performance we performed a univariate logistic regression with successful completion of DRA as the primary outcome. Findings from the univariate analysis were used to inform the construction of our multivariable model. Specifically, baseline demographic or clinical characteristics deemed significant in the univariate analysis were selected for inclusion into the multi-variable logistic regression model. The odds ratio and corresponding p-values are reported in the baseline demographic characteristics table. We generated a series of models to determine the optimal cut-off for FEV_1% predicted constructing the same model for each 5% change in FEV_1% predicted. Additionally, we constructed a model using FEV_1 as a continuous variable. A priori designed subgroup analyses were performed in the antibiotic cohort, whereby we evaluated 1) the individual effect of antibiotic class on DRA, 2) the direct comparison of inhaled dry power versus nebulised antibiotics, and 3) a comparison of nebulised antibiotics to all other classes. The outcome for each subgroup analysis was successful completion of the DRA.

The covariates included in the logistic regression models were assessed for multi-collinearity. During data cleaning, box-plots were constructed to identify outlier observations. Sensitivity analyses were performed removing outlier observations. All continuous variables were assessed for normal distribution, whereby proper transformations were applied when necessary. We determined the appropriateness of our sample size (n = 1492) to address our primary analysis, the multivariable logistic regression of the inhaled therapy DRAs. With DRA outcome (success or failure) as our primary independent variable, in addition to the four covariates identified for inclusion using univariate analysis, we determined our model could withstand the addition of 124 covariates under the assumption that model stability is maintained with 10–12 observations per covariate. Within this model we have allowed for 249 observations per covariate in our sample of 1492 [10].

3. Results

1492 patients with chronic lung disease underwent a DRA at the Royal Brompton Hospital between April 2011 and March 2016. A summary of the demographics and characteristics of the patient cohort can be found in Table 1. The patients consisted of 43% males with a mean (SD) age of 44 years (17.95), height 1.67 (0.09), FEV_1% predicted 58.03 (23.36). Bronchiectasis (33%) and cystic fibrosis (49%) accounted for the most common underlying lung conditions. Among those included in the study 35.76% (n = 534) were recruited as inpatient. Pre-test bronchodilators were used in the majority of the population (57.30%, n = 855).

The majority of DRAs were for antimicrobials (63%, n = 940), whilst 32% (n = 477) and 5% (n = 75) were for HTS and rhDNase, respectively. The antimicrobial cohort is subdivided by nine classes, of which the majority comprised colistin/Promixin (n = 271), tobramycin (n = 137), TOBI podhaler (n = 217), and aztreonam (n = 133).

The univariate analysis evaluated which patient demographics were associated with either passing or failing the DRA. Older age ($p = 0.001$) was significant for being less likely to pass the DRA, whilst, being female was associated with being 1.89 times ($p = 0.005$) more likely to pass the DRA. Bronchiectasis was the only underlying disease shown to be significantly associated with DRA failure (OR of 0.50, $p = 0.002$), suggesting that patients with bronchiectasis were 50% less likely to pass the trial. In contrast, CF was shown to be associated with a 2 times (OR: 2.15, $p = 0.001$) greater likelihood of passing the inhaled therapy DRA. Having a higher FEV_1 and FEV_1% predicted PT were also both significantly ($p < 0.001$) associated with passing the DRA. Fig. 1 demonstrates the failure rates of DRA trials across a range of FEV_1 percentage predicted cut-offs. The type of compound used was also significantly associated with DRA outcome whereby patients receiving inhaled antibiotics demonstrate a 2.20 times greater likelihood of passing than patients receiving hypertonic saline (OR:2.20, $p = 0.002$; 95% CI 1.34, 3.62). Those receiving rhDNase had the lowest DRA failure rates. The other underlying diagnoses and patient demographics did not demonstrate any significant association with passing or failing the inhaled therapy DRA, as shown in Table 1.

3.1. Findings from multi-variable logistic regression model

A multivariate analysis (Table 2) demonstrated that sex, FEV_1% predicted and type of inhaled product remained independently significantly associated with DRA outcome. The multi-variable logistic