Predicting bronchodilator response of a short acting beta-2-agonist from aerodynamic particle size data using artificial neural networks

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INTRODUCTION

Opportunities exist to use *in-vitro* measurements of inhaled drug formulation quality as predictors of *in-vivo* performance.

Benefits of this approach include:

- Assurance of consistent clinical quality
- Remove/Reduce/Refine – *in-vivo* studies
  - Bridging
  - Bioequivalence
- Improved regulatory procedures
  - Expedited post-approval changes
- Maximised quality and efficiency
  - Define design space (**Figure 1**)
  - Facilitate continuous improvement
- Provision of robust supply chain with surety of supply

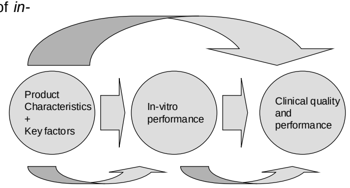


Figure 1. Process flow for application of IVIVC for definition of product design space

AIMS & OBJECTIVES

Artificial neural networks (ANNs) are computational systems able to mimic the mechanisms of human learning (**Figure 2**). These have been used to generate *in vitro in vivo correlation* (IVIVC) models for orally inhaled dosage forms, which predict measures of clinical quality from knowledge of aerodynamic drug particle size characteristics and subject demographics (**1, 2**). In order to predict clinical responses in individual subjects, knowledge of major causes of inter- and intra- subject variability is required.

The aim of this study was to further demonstrate the utility of ANNs for generating IVIVC models from clinical data for different drug formulations discriminated by aerodynamic particle size.

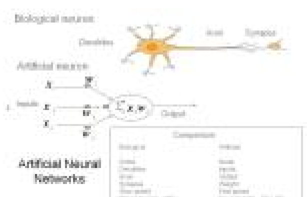


Figure 2 . Comparison of biological neuron and computer neuron

EXPERIMENTAL & MODELLING METHODS

ANNs were used to model clinical data from a study to assess the effects of β_2-agonist (albuterol sulfate) particle size on bronchodilator response (BDR) in mild to moderate asthmatics (**3**). Monodisperse aerosols of MMAD 1.5 µm, 3 µm and 6µm generated using a spinning top aerosol generator (STAG) were administered to 18 mild-moderate asthmatics as a cumulative dosing regimen in a randomised placebo controlled study.

Dose 1 – 10 µg	Dose 3 – 20 µg
Dose 2 – 10 µg	Dose 4 – 60 µg

- **Input data (independent variables)**
  - Aerodynamic Particle Size (PS) characteristics - Andersen Cascade Impactor (ACI) and Time of flight (ToF) analysis
  - Patient Characteristics – Age, Body Size, Disease Severity (FEV_1), Bronchodilator reversibility to a standard MDI, Forced Vital Capacity (FVC)
- **Output data (dependent variables)**
  - Bronchodilator response (BDR) – Increase in FEV_1 from pre-treatment baseline measured following each dose

RESULTS & DISCUSSION

ANNs were able to generate complex models which predicted the BDR of individual patients at different time points following the administration of the cumulative dosage regimen (**Tables 1 and 2**).

A number of factors were shown to influence the model and contribute to the variability in BDR.

- Aerodynamic PS – Largest MMAD (% of dose emitted in range 3.3 µm – 10 µm) gave greatest BDR (Figure 3)
- Bronchodilator reversibility to standard MDI – Greatest BDR for those responding better to MDI
- Body Size – Greatest response in largest patients
- Baseline FVC – Lowest response in patients with highest pre-treatment FVC
- Age - Older individuals showed slightly lower improvements in lung function compared to pre-treatment baseline
- Pre-treatment FEV_1 – Greater BDR for those with greatest disease severity

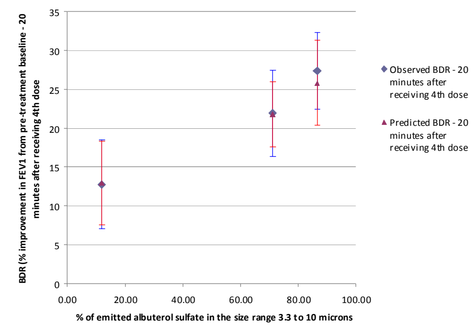
Table 1. Indices of predictability from ANN models for individual doses from the cumulative dosing regimen. Parameters calculated from comparisons of observed BDR versus predicted BDR for data not used in generating models (unseen data).

Dose	Validation R^2	Slope and intercept from line of best fit for validation plot (observed BDR vs predicted BDR) Target m = 1 Target c = 0	Comment
1st Dose	N/A	N/A	No notable difference in bronchodilator response between individual particle size variants
2nd Dose	0.97	m = 1.00 c = -0.9	For BDR measured at 10 minutes after receiving the dose
3rd Dose	0.85	m = 0.88 c = 1.4	For BDR measured at 10 minutes after receiving the dose
3rd Dose	0.80	m = 0.84 c = 5.8	For BDR measured at 20 minutes after receiving the dose
4th Dose	0.93	m = 1.05 c = -1.04	For BDR measured at 20 minutes after receiving the dose
4th Dose	0.85	m = 1.21 c = -1.27	For BDR measured at 30 minutes after receiving dose

Table 2. Comparison of observed and predicted BDR measured at 10 minutes after receiving the 2nd dose (high predictability – for unseen data)

Data record	Observed BDR (% improvement in FEV_1 at 10 minutes after Receiving the 2nd dose	ANN model prediction of BDR (% improvement in FEV_1 at 10 minutes after receiving the 2nd dose	Prediction error $\sqrt{(\text{predicted-observed})^2}$	% error
1	31.1	29.6	1.5	4.8
2	33.6	32.6	1.1	3.3
3	4.7	1.9	2.8	59.8
4	18.2	16.8	1.4	7.6
5	8.5	6.7	1.7	20.3
6	24.2	19.7	4.2	17.3
7	29.7	29.3	0.4	1.4
8	28.0	28.3	0.4	1.3
9	5.4	6.8	1.4	25.9
10	26.4	29.4	3.0	11.3
11	11.5	11.7	0.2	2.1
12	29.8	28.2	1.5	5.1
13	23.1	22.0	1.1	4.7
Mean	21.1	20.2	1.6	12.7
(SD)	10.3	10.5	1.1	16.2

Figure 3. Effect of particle size on the BDR in a selection of individuals (n=6) demonstrating greatest sensitivity to particle size differences – The ANN model is able to predict both BDR and variation in BDR amongst the selected patients from knowledge of Aerodynamic PS



CONCLUSIONS

- ANN models are able to predict BDR in individual subjects for monodisperse aerosols
- Models show that larger particles provide greatest clinical effect – MMAD alone is not able to discriminate predictably. Knowledge of particle size distribution is required.
- Patient characteristics influence the magnitude of clinical effect and contribute to overall variability and must be included in IVIVC models
- ACI is able to discriminate between formulation variants giving different clinical performance – potential use as a discriminatory tool

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