

Comparative Pulmonary Function & Pharmacokinetics of Fluticasone Propionate and Salmeterol Xinafoate in Asthmatics Using 3M Conix™ and Advair Diskus®

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Introduction

Previous work demonstrated that the 3M Conix DPI system was capable of efficiently delivering a harvested salbutamol sulfate formulation via in vitro testing (1). The purpose of this study was to take the 3M Conix technology, in the form of an injection moulded device, into a clinical environment and demonstrate its capability of effectively and safely delivering a combination therapy (fluticasone propionate and salmeterol xinafoate) to asthmatic patients. Response to both 3M Conix™ and Advair Diskus® was assessed via FEV1 and blood plasma measures.

The in vitro fine particle dose (FPD) performance of the Conix device was matched to that of Advair Diskus 100/50 (Advair) using Next Generation Impactor (NGI) testing. Whilst particles of 5 µm are likely to be respirable, there is not a good correlation with lung deposition of the drug (2). The optimum size for deposition into the smaller spaces of the lung and clinical efficacy appears to be in the region of 3 µm (3); hence this size range was selected for in vitro matching of drug delivery from the study devices. This approach of matching FPD at <3µm was also driven by the desire to assure safety, matching FPD at <5µm would have required a greater amount of each medication from Conix to be administered, particularly in the <3µm region that we considered to be the most critical for systemic absorption.

Study Outline

The study was a single-centre, open label, trial in subjects with mild-to-moderate asthma who had been stable for at least 6 months. Subjects had to demonstrate 12% reversibility of bronchoconstriction with two inhalations of albuterol sulfate.

After abstaining from their current maintenance asthma medication for at least 24 hr and food for 12 hr, subjects received two treatments separated by 7-16 days, according to a randomized, two-period crossover design. Between treatment days, subjects resumed prescribed asthma medication. Pulmonary function was followed at 30 min and hourly intervals for 12 hr, and 15 blood samples were collected for pharmacokinetics over 12.5 hr. All drug plasma analyses were done using validated LC/MS/MS methods. Safety was assessed by the occurrence of adverse events, including the need for rescue medication.

Treatments

The reference treatment was one inhalation from an Advair Diskus labelled to deliver 100 µg fluticasone propionate (fluticasone) and 50 µg salmeterol base equivalent (salmeterol), i.e., 100/50 Advair, which was sourced in the USA. The test treatment was developed to be comparable to this in vitro FPD (<3 µm) of each drug in the reference, and was one inhalation from the Conix device which contained approximately 10% less of each drug per pre-metered dose relative to Advair due to the better in vitro efficiency of Conix. The Conix device contained a proprietary drug / lactose blend made using standard commercially available materials and was sourced from Loughborough UK. The two formulations are compared in Table 1.

Table 1 – Comparison of 3M Conix and Advair formulations

	Fluticasone			Salmeterol		
	Drug Lactose (% w/w)	Fil Mass per Dose (mg)	Drug Content (% w/w)	Drug Lactose (% w/w)	Fil Mass per Dose (mg)	Drug Content (% w/w)
3M Conix (n=10)	0.734	12.7	95.1	0.358	12.7	46.0
Advair (n=30)	0.792	13.1	104.0	0.393	13.1	51.6

The FPD of each drug delivered from the Conix device was successfully matched (targeted to be within ± 15%) to that from Advair using NGI testing (Table 2).

Table 2: Comparison of Conix and Advair Diskus In Vitro Data

	Fluticasone				Salmeterol			
	Delivered Dose, µg	F10-3µm, µg	%	MMAD µm	Delivered Dose, µg	F10-3µm, µg	%	MMAD µm
3M Conix (n=10)	31.1	12.9	41.8	2.04	14.7	5.9	40.5	2.03
Advair (n=30)	101.1	14.2	14.0	3.31	50.3	6.2	12.3	3.47

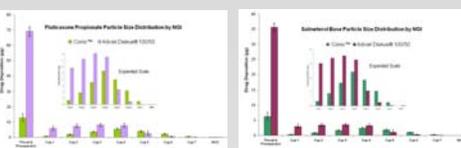
Note 1: Delivered dose derived from the total mass of drug on the impactor data (i.e., amount delivered vs. Mouthpiece Note 2: Testing performed at 40% RH, three total volume (flow rate adjusted to achieve 40% approximately 63 L/min for Conix and 79 L/min for Advair)

Whilst the primary metric of matching FPD <3µm was met, the in vitro testing revealed several differences between the test (Conix) and reference (Advair) products (e.g., MMAD and total delivered dose). The large decrease in the delivered dose with Conix was a result of the cyclone technology of this device that produces far fewer large particles, i.e. larger particles, typically lactose, are preferentially retained within the device. Such particles would, if not retained by Conix, typically impact in the throat and pre-separator regions of the NGI, thus any drug still bound to the surface of lactose would otherwise form part of the delivered dose but would not be respirable. This effect can be seen in the NGI profiles as less pre-separator and throat deposition from Conix for each of the drugs (Figure 1).

Advair Diskus® is a registered trademark of GlaxoSmithKline.

Treatments (Continued)

Figure 1: Comparison of NGI Profiles for Fluticasone and Salmeterol from Conix and Advair Devices



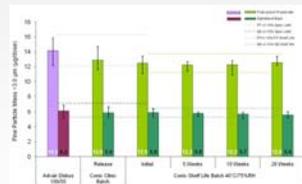
The decrease in delivered dose was also partly due to the fact that the Conix device contained approximately 10% less drug in each pre-metered dose (Table 1), however the reduction in large particles was clearly the dominant contributing factor.

An oral charcoal pre-treatment of 10g two minutes prior to dosing was therefore included in the study to reduce the contributions of swallowed drugs to the clinical assessments.

Figure 1 shows that whilst FPD was matched at <3µm (approximately around cup 4 and below) Advair consistently produces more particles on each cup above this cut-off. Thus in selecting to match FPD at a cut-off of <3µm, Advair was found to deliver approximately 20% more of each drug by mass in the 0-5µm range than Conix. This was due to the greater mass of particles produced by Advair in the 3-5µm range (approximately between cups 2 and 3). Therefore electing to match the in vitro FPD cut-offs at <3µm did not disadvantage Advair compared with the 'more traditional' <5µm cut-off point, Advair was actually delivering significantly more of each drug than Conix in the <5µm region as a consequence.

As the Conix formulation was a development material, it was important that the formulation be shown to be stable. Stability was demonstrated after storage at 45°C / 75% RH for six months (Figure 2) and after transportation (data not presented).

Figure 2: Summary of 3M Conix FPD (<3µm) Stability Data



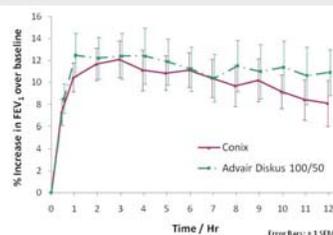
In summary, the stability and in vitro performance matching of 3M Conix to Advair demonstrate that the test treatment was suitable for the intended use and was not unfairly biasing the clinical study in favour of Conix.

Results

Nineteen subjects entered the study and one subject withdrew for personal reasons. Subject No. 5 did not have a stable baseline for both study days, so the data from 17 remaining subjects were evaluated for FEV1. Subject No. 2 had contaminated pre-dose values for both analyses, so the data from 17 subjects were evaluated for pharmacokinetics.

FEV1 was the primary measure of bronchodilator efficacy. The increases in FEV1 profiles over baseline were found to be comparable for both devices in both peak increase and duration (Figure 3). There were no statistically significant differences in these values between the devices.

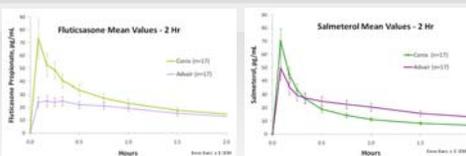
Figure 3: Comparison of FEV1 profiles for 3M Conix and Advair Diskus devices



Results (Continued)

Figure 4 shows the plasma profiles for fluticasone and salmeterol for the first 2 hours following inhalation. After 2 hours, plasma concentrations of fluticasone were comparable from the two devices while plasma concentrations of salmeterol remained slightly higher through the final sampling time (12.5 hr) from Advair Diskus.

Figure 4: Comparison of Plasma Profiles of Fluticasone and Salmeterol from the 3M Conix and Advair Diskus Devices



C_{max} of both fluticasone and salmeterol were higher from the 3M Conix device. The mean extent of absorption (AUC) of fluticasone was ~30% greater with 3M Conix, whereas the extent of absorption of salmeterol was ~41% greater with Advair Diskus.

Examination of the variability shown in Figures 3 and 4 illustrates that both DPI devices were equally reliable. Subjects found the 3M Conix device easy to use.

Inhalation of the formulations from both 3M Conix and Advair Diskus were safe and well tolerated during the study. No adverse events were reported and no rescue medication was required.

Conclusions

The 3M Conix technology provided comparable improvement in pulmonary function compared with Advair Diskus while starting with less drug in each pre-metered dose. These pulmonary function results suggest that both DPI devices can give similar efficacy but the salmeterol pharmacokinetic results help to underscore the fundamental differences between the devices, namely that the NGI data predicted a greater amount of swallowed particles with Advair Diskus. About 30% of the systemic activity of inhaled salmeterol from Advair Diskus comes from oral absorption of swallowed drug (4). Our study results show a greater initial absorption with 3M Conix, which we attribute to increased pulmonary absorption; but greater continued absorption at later times, leading to a 41% greater extent of absorption on average with Advair Diskus, which we attribute to slower but more extensive oral absorption because of the greater mass of large particles of salmeterol generated with Advair Diskus. It appears that a single charcoal pre-treatment was not sufficient to block this amount of swallowed drug.

An alternative interpretation of the salmeterol pharmacokinetic data, without the need for an oral absorption component, can be considered. It was noted in the NGI test data that Advair Diskus delivered appreciably more particles of each drug in the range of 3-5 µm as did 3M Conix (Figure 1). The observed pharmacokinetics could be explained by a more rapid absorption of smaller particles (e.g., 0.5-1 µm) from the alveolar spaces with 3M Conix, and a slower and continued absorption of larger particles (3-5 µm) from the bronchial spaces with Advair Diskus. However, one would also have to discount the large differences between products observed in the NGI apparatus in throat deposition and accept the supposition that the single charcoal pre-treatment was able to completely prevent the oral absorption of swallowed drug. An additional clinical study with a more extensive charcoal block treatment is needed to test this hypothesis. It is our opinion that the salmeterol pharmacokinetics are more likely explained by a combination of pulmonary and oral absorption mechanisms.

In summary, 3M Conix is a new DPI that can safely deliver efficacious quantities of a combination formulation containing fluticasone and salmeterol with the added benefit of low throat deposition.

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