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Establishing Therapeutic Bioequivalence of a Generic Salbutamol (Butalin®) Metered Dose Inhaler to Ventolin®

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Abstract

Inhaled beta-adrenergic receptor agonist plays an important role in the management of bronchial asthma especially in the acute setting and still salbutamol (albuterol, USAN) is the most widely prescribed drug in this class.

In a randomized, open label, crossover, multicenter study, one and two actuations (100, 200µg) of Ventolin and Butalin inhaler were administered in 4 alternative different consequences for patients suffering from mild to moderate asthma for 4 days trial compares forced expiratory volume in the first second (FEV1) at (0, 15, 30, 45 and 60 minutes) and peak expiratory flow (PEF) at (0, 15, 30, 45, 60, 120, 240, 360 minutes) to prove equivalent pharmacodynamics, equipotency and safety.

Eighty-nine patients completed the study of which 61.8% were male. There was no significant difference between Ventolin and Butalin concerning the average of Ln transformed records for the FEV1 and PEF, and the $AUFC_{0\text{-}1h}$ for the 100 and 200 µg were (96.89-101.07) and (92.69-104.77) respectively, same for the PEF $AUC_{0\text{-}4h}$ that came with the ranges of (99.20-104.24) and (90.25-100.49) respectively. No significant difference was noted between the two products in regard of onset and duration of action, and the same was true when assessing products potency.

Concluding that both products are clearly equivalent and equipotent with similar safety profile.

Introduction

Bronchodilator drugs used alone or in conjunction with inhaled corticosteroid or other anti-inflammatory drugs are essential for the management of asthma [1,2]. β_2-adrenoceptor agonist considered one of the main effective categories and the short-acting salbutamol has been for long the most widely used bronchodilator. Most international guidelines recommend the use of beta-adrenergic agonist in the form of metered dose inhaler (MDI) for quick symptomatic relief [3].

Metered dose inhalers (MDIs) containing chlorofluorocarbon propellants are the dominant delivery system for bronchodilators. Concerns about the depletion of the ozone layer by the catalytic action of the free chlorine radicals from the chlorofluorocarbons had led to legislation calling for the elimination of the chlorofluorocarbon production [4].

Hydrofluoroalkanes, as hydrofluoroalkane-134a, do not contain chlorine and are therefore environmentally friendly alternative for use as propellants in the MDIs. They are known to be safe and efficacious as substitute for chlorofluorocarbon 11/12 with $\beta_2$agonists like salbutamol and have already been licensed for clinical use (Proventil, Airomir).

The incessant increase in the incidence of asthma and the requirement for new products phasing out chlorofluoro-

carbon (CFC) propellants, added to the need for cost effective medication in relation to the existing treatment, were the key factors for pharmaceutical industries to respond to a decade of off-patent availability of effective asthma drugs including salbutamol and encourage the development of novel generic bronchodilator/ inhaler device combinations [5].

Hence, the emergence of generic substitute has led to a pressing need to develop a precise and economical method to evaluate its potency and equivalence to current alternative in order to satisfy both clinician and regulatory authorities. The US Food and Drug Administration considered two inhaled formulations as bioequivalent if the 90% confidence interval (CI) of the relative potency is between 0.67 and 1.50.

Although *in vitro* comparisons between inhaled products are useful, still they do not reflect or can predict *in vivo* drug delivery to the site of action. The three principal *in vivo* methods currently available to study the bioequivalence of inhaled medications are radioaerosol drug deposition studies, pharmacokinetic studies and comparative pharmacodynamic clinical efficacy studies [6,7].

Radioaerosol studies that used gamma scintigraphy provide useful information about lung deposition but their predictive ability for clinical efficacy of β agonist is proven to be variable [8]. Pharmacokinetic studies on the other hand are of limited value for inhaled medications because the dose administrated is small and the resulting serum concentrations are often too low to assay accurately. Furthermore, serum concentrations may not correlate with the dose delivered to the lung. A urine assay of the salbutamol has been described as example of pharmacokinetic studies [9], however, there is no enough credibility of the bioequivalence data in subjects with asthma.

Clinical pharmacodynamics efficacy studies are ultimately the most clinically useful measure of the effectiveness of inhaled β agonist. As it is well known that β_2 agonists have two distinct pharmacodynamic effects of clinical importance in asthma: bronchodilation which is the most trend adapted in "*in vivo*" bioequivalence studies [10-13] and prevention of bronchoconstriction caused by direct agent like methacoline [14] or indirect agent like histamine [15] or exercise, cold air or allergen.

Both of these responses are clinically and physiologically distinct and important but demonstration of the bioequivalence of bronchoprotective effect is particularly important in patients with mild asthma who have minimal or no air flow obstruction and in whom it might be difficult to compare FEV1 values. Furthermore, there is some recommendation by the British Association of Lung Research as to how bronchodilator studies should be conducted [6] but none for conducting or analyzing the relative potencies of the bronchoprotective effects.
Since long, measures of bronchodilator drug efficacy have relied on direct measurement of the induced bronchodilatation by lung function testing, even though that this method does not allow potency discrimination between drug products, as single dose can result in maximal bronchodilatation [16].

The forced expiratory volume in the first second (FEV1), which like other spirometeric indices is affected by airway obstruction, is generally accepted as the most useful measure of airway potency since it is considered to be repeatable index. Peak expiratory flow (PEF) measurement is a convenient way of monitoring longer-term drug effects on lung function during clinical trials but still more effort dependent than the relatively prolonged FEV1 and although average changes in FEV1 and PEF are similar during bronchodilatation or constriction, the variability of PEF is greater.

In this study rigorous adherence to standardized spirometry techniques according to the American Thoracic Society [17] was fundamental to the accurate use of the above end points and both values were made more reliable by taking the best of at least three attempts, but accuracy was better assured during spirometry where a low forced vital capacity (FVC) reading, if this was inconsistent, indicates a poor effort which can validly discounted.

Butalin® Inhaler (Julphar`s Salbutamol) contains 200 actuations of 100µg Salbutamol Micronized (as sulfate) being the active ingredient, and oleic acid with norflurane as excipients, and contains (HFA 134a) Hydrofluroalkane as propellant, it is Chlorofluorocarbons (CFC) Free.

Material and Methods:

The main purpose of the study was to assure the clinical equivalence (effectiveness and safety), equipotence and parallel pharmacodynamics (onset and duration of action) of Butalin Inhaler and Ventolin Inhaler (GlaxoWellcome`s Salbutamol) on asthmatic patients classified according to the Global Initiative Guidelines (GINA) under step 1, 2 and 3, with both 100 and 200µg dosages.

The study corresponds to clinical study phase 4, designed as open, randomized, crossover with 4 sequences, 4 treatments and last for 4 days, multicenter performed at 5 centers in 3 Middle Eastern countries. The treatment was administrated on each of the four separate study visits. At least 24 hours and not more than 3 days were permitted between study visits. The random distribution to assign each patient to a specific therapeutic regime was carried out centrally by Proc Scheme (SAS, version 8.0).

The dose was delivered via a spacer device (Optichamber, Respironics, USA) that was distributed to all patients following the criteria of the European Respiratory Society [18]. Spirometry was done at baseline and repeated every 15 minutes for the first hour of the test using Microlab3500 (Micromedical, UK) in all study centers. Similarly PEF was also recorded during the first hour of the test and then the subject had to measure it hourly for another 5 hours duration using hand held peak flow meter (Personal Best, Respironics, USA) that was supplied as study material to all subjects.

Asthmatic patients as defined by the American Thoracic Society and those who could consistently perform reproducible spirometry from both sexes, aged 15 to 60 years, with FEV1 ranged between 60-90% of the theoretic value and FEV1/FVC <70% were enrolled after showing a bronchodilatory effect as FEV1 increased by ≥12% fifteen minutes post 200µg salbutamol dose, fulfilling all selection criteria, considering not to include patients treated with systemic corticosteroid or ß-adrenergic antagonist or been recently on inhaled corticosteroid therapy.

The variables that determine the clinical equivalence are the 90% confidence interval for area under curve (AUC) of the effect on 15 minutes interval measured FEV1 versus time between baseline time and 1 hour ($AUC_{0\text{-}1h}$) and the effect on one hour measured PEF between baseline and 6 hours ($AUPEC_{0\text{-}6h}$), and were determined by the liner trapezoid rule, as well as the percentile of the maximum FEV1 and PEF change from baseline (FEV1 and $PEF_{max\%}$). Pharmacodynamics including onset and duration of action were determined by liner interpolation, considering a 10% change of FEV1 from baseline as onset point and duration of action end when PEF less than 10% from baseline.

Adverse events were illnesses or signs or symptoms that appeared or worsen during of the study. All adverse events, including observed elicited, or volunteered problems, complaints or symptoms, were recorded on the Adverse Events Case Report Form. Each adverse event is to be evaluated for date/time of onset, duration, intensity, seriousness and casual relationship with the clinical study material or other factors according to Karch & Casagna. Tolerability was assessed by measuring blood pressure, heart rate and ECG (lead II).

The study was carried out in accordance with Good Clinical Practice and the Declaration of Helsinki. All patients gave informed consent. The Ethics Committee of the Ministry of Health, UAE as well as the Ethics Committees of participating centers approved the protocol.

Results

Demographic data

Eighty-nine non-smoking patients (55 males/ 34 females) were enrolled between July 2004 and March 2006 from 5 centers in 3 Middle Eastern countries, with an average age of 35.7 ± 8.6 years and 26.8 ± 5.7 kg/m^2 for BMI (Table 1.1).

Patients suffered from asthma since 8.7 ± 8.3 years (1 - 37). Average ideal FEV1 for male was 3.7 ± 0.5 (2.3 – 4.7) and for females 2.8 ± 0.4 (1.9 – 3.5), while average ideal FVC for males was 4.3 ± 0.6 (2.7 – 5.7) and females 3.5 ± 0.5 (2.1 – 3.7) using Knudson et al. **19** The FEV1 change percent from the predicted ideal value varies between 54 to 92 with average of 68.2 ± 13.3 after taking into consideration the patient's sex, age and height.

The bronchodilator sensitivity test calculated as percent of change of the FEV1 fifteen minutes post inhalation of 200 µg Salbutamol revealed sensitivity average percentile of 31 ± 14.9 and range of (12 - 35). 45.3% (n=34) of the patients had other allergic conditions (Table 1.2).

Salbutamol dose was fixed during the study and balanced across visits using the Latin square method. 16.9% of the patients (n=15) were on Mometasone furoate nasal spray **(Table 1.3),** and compliance for study medications reached 100% with no violations to the study protocol or withdrawal.

The area under FEV1 and PEF curves versus time for both the 100 and 200µg of Butalin MDI were comparable to the same recorded with Ventolin MDI. Similarly, no significant difference was detected between the two MDIs in concern of the maximum percentile of change for both FEV1 and PEF rate (Table 2.1).

Pharmacodynamic results

Mean baseline of FEV1 natural logarithmic (Ln) transformed values were 0.75 ± 0.39 for 100µg Butalin day vs. 0.74 ± 0.38 for 100µg Ventolin day, while for the 200µg dosage was 0.73 ± 0.35 for Butalin day vs. 0.71 ± 0.31 for Ventolin day.

Dose response graphs of Ln FEV1 over the first hour between the two inhalers were superimposed (Fig.1), and the same was demonstrated with six hours Ln PEF (Fig.2) to prove therapeutic equivalency.

Albeit there was no significant difference between the 100 and 200µg FEV1 readings for any of the two MDIs, equipotency was assessed via comparing the difference of

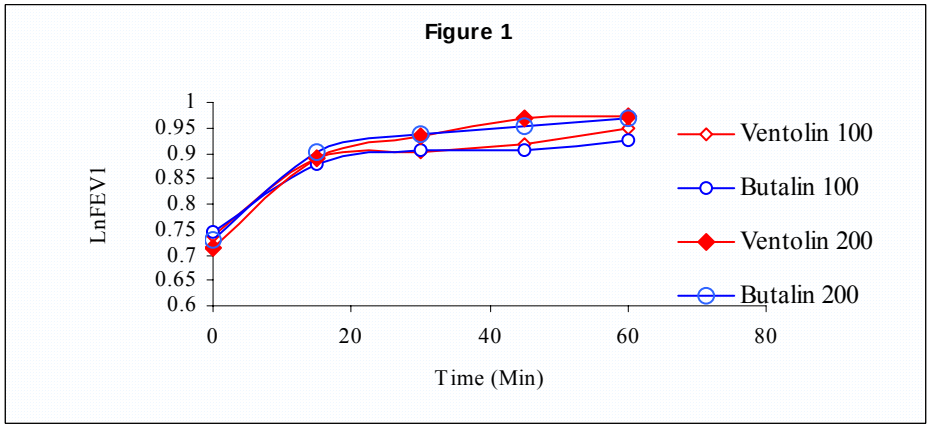

Fig. 1: *Mean of LnFEV1 after inhalation of 100 and 200µg of the two-salbutamol products (Ventolin and Butalin).*

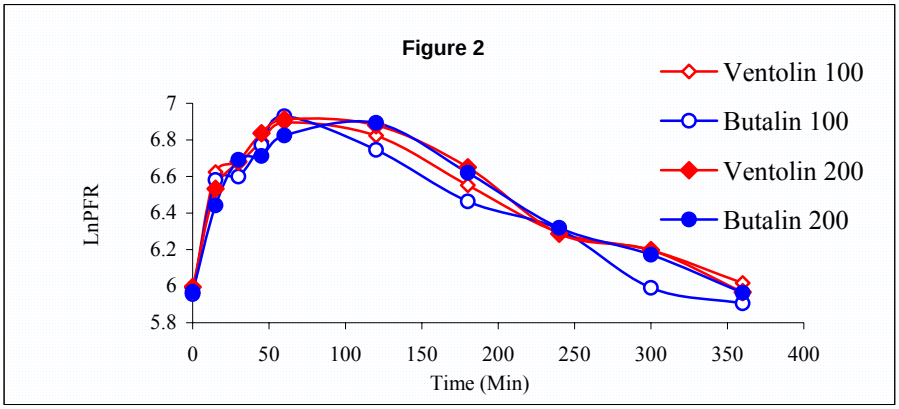

Fig. 2: *Mean of LnPEF after inhalation of 100 and 200µg of the two-salbutamol products (Ventolin and Butalin).*

between the two dosages of each over the first hour of the test and the results came insignificant ($P > 0.05$).

All patients showed significant response (more that 10% change at the FEV1) defined as onset of the bronchodilator effect to both Salbutamol MDIs and for each the 100 and 200µg dosage at almost the same time point ($p > 0.05$), and the bronchodilatation continue for a like duration between similar dosages of both MDIs (Table 2.2).

Table 1.1. Demographic data *(n=89)*

Characteristic	
Sex Male/Female: n (%)	55/34 (62/38)
Age (yr) Mean ± SD (range)	35.7 ± 8.6 (14 - 58)
Height (cm) Mean ± SD (range)	169.2 ± 9.8 (140 - 190)
Weight (kg) Mean ± SD (range)	73.8 ± 13.7 (40 - 119)
BMI (kg/m^2) Mean ± SD (range)	26.8 ± 5.7 (16.7 - 41.3)

Table 1.2. Medical history *(n=89)*

Allergic conditions	**n =34 (38.2%)**	**Other medical**	**n (%)**
Rhinitis	22 (29.3)	Hypertension	11 (12.4)
Rhinitis + conjunctivitis	9 (19)	Diabetes Mellitus	3 (3.4)
Rhinitis + Dermatitis	1 (1.3)		
Conjunctivitis	1 (1.3)		
Dermatitis	1 (1.3)		

Table 1.3 Concomitant therapy *(n=89)*

Drugs	**n (%) patients**
Mometasone furoate nasal spray	12 (13.5)
Beclomethasone inhaler	8 (9.0)
Salmeterol and Fluticasone inhaler	6 (6.7)
Oxymetazoline nasal spray	5 (5.6)
Budesonide inhaler	5 (5.6)
Antileukotriene	3 (3.4)
Local antihistamine drops	2 (2.3)
Thyroxine	2 (2.3)

Table 2.1 Area under curve and maximum percentile of change

Para meters	100 µg							200 µg						
	Ventolin MDI		Butalin MDI		Ratio	90% CI	*P* value	Ventolin MDI		Butalin MDI		Ratio	90% CI	*P* value
	Mean	± SD	Mean	± SD				Mean	± SD	Mean	± SD			
AUFC $_{0\text{-}1h}$	2.48	0.88	2.46	0.81	0.99	96.9-101.1	0.63	2.53	0.83	2.49	0.87	0.98	92.7-104.8	0.58
FEV1 $_{max\%}$	2.53	0.88	2.56	0.82	1.0	96.2-100.4	0.88	2.61	0.89	2.6	0.86	1.0	96.9-101.8	0.78
AUPEC $_{0\text{-}6h}$	2558	747	2513	735	0.99	99.2-104.2	0.61	2567	712	2553	721	0.99	90.3-100.4	0.58
PEF $_{max\%}$	523.9	144	518.1	153	1.0	98.1-103.5	0.43	506.4	133	499.5	134	1.0	99.7-100.2	0.43

Table 2.2 Pharmacodynamic timings

Parameter	100 µg					200 µg				
	Ventolin MDI		Butalin MDI		*P* value	Ventolin MDI		Butalin MDI		*P* value
	Mean	± SD	Mean	± SD		Mean	± SD	Mean	± SD	
FEV1 Tmax (min)	39.6	16.2	38.8	20.4	0.49	37.2	19.8	37.6	17.4	0.63
PEF Tmax (hours)	1.1	1.2	1.2	1.1	0.47	1.0	1.3	1.0	1.3	0.86
Onset of action (min)	21.3	12.0	22.2	13.5	0.52	21.1	10.3	21.2	11.6	0.89
Duration of action (hours)	3.96	1.88	3.87	1.97	0.92	4.32	1.19	4.19	1.22	0.86

Table 2.3 Tolerability and adverse events

Parameter	100 µg					200 µg				
	Ventolin MDI		**Butalin MDI**		***P* value**	**Ventolin MDI**		**Butalin MDI**		***P* value**
	Mean	**± SD**	**Mean**	**± SD**		**Mean**	**± SD**	**Mean**	**± SD**	
Pulse rate/min	83.7	8.6	85.6	8.2	0.45	86.5	7.5	84.8	6.2	0.24
Diastolic Bp (mmHg)	73.5	6.3	75.7	9.7	0.5	73.8	7.2	75.9	8.5	0.41
Respiratory rate/min	20.7	2.5	19.6	2.1	0.55	22.8	3.4	21.2	2.4	0.41
ECG	Normal		Normal		-	Normal		Normal		-
Headache (%)	0		2.3		NS	2.3		3.4		NS
Cough (%)	1.1		1.1		NS	0		0		-
Nausea (%)	-		-		-	0		2.3		NS
	0		1		NS	1		0		NS

Safety results

No significant change (P> 0.05) was noticed between baseline and hour one readings concerning vital signs and ECG. Similar incidences of adverse events including headache, cough, nausea and palpitation were recorded for both formulations with similar severity and causal relation. No serious adverse events were reported (Table 2.3).

Discussion

Salbutamol MDI is the most widely prescribed drug in its category [20]. Although the use of chlorofluorocarbons (CFCs) as propellants in MDIs have been permitted under a temporary essential use exemption from Montreal Protocol, **21** pharmaceutical companies have developed alternative CFC-free propellant.

Albeit that the patent for Salbutamol expired in 1989, the first generic metered dose inhaler (MDI) preparation of Salbutamol was not approved by the US FDA until late 1995 [22]. This delay resulted primarily from the lack of an acceptable and valid method for establishing *in vivo* bioequivalence of the generic salbutamol inhaler to the innovator preparation Ventolin.

A number of methodological approaches have been advocated for the assessment of generic MDI bioequivalence. The FDA did not consider the plasma pharmacokinetics [23-25] or Gamma scintigraphy methods as reliable reflection of the relative quantity of drug delivered to the site of action in the lung (the β_2 biophase) [26,27].

For this reason, still the clinical studies of inhaled β adrenergic preparation in subjects with asthma that rely on the measurement of the clinically relevant pharmacodynamic response of salbutamol are the most creditable to reflect the relative quantity of drug delivered to the effecter compartment in the lung by the generic and the innovator preparations.

In our study we used 2x2 considering two dosages for the two formulations in 4 different sequences in each two dosages of both formulations are administrated. This does not only provide a more powerful evaluation of the dose response relationship, but also provides an opportunity to prove whether the dose-response curves are parallel of the two formulations.

Results presented here provide assessment of the potency per actuation of the generic salbutamol (Butalin inhaler) relative to that of Ventolin inhaler. Each actuation of the Butalin inhaler is estimated to deliver a quantity of salbutamol to the β_2 receptors in lung that is equivalent to 1.01 actuations of the Ventolin MDI, with the 90% CI for this estimate 96.9 to 101.1. Stated in another way, this indicates that each actuation of Butalin inhaler delivers significantly >96.9% (p<0.05) and significantly <101.1% (p<0.05) as much salbutamol to the lung receptors as does one actuation of Ventolin. The fact that CI lies entirely within the range that the FDA currently accepted provides evidence that Butalin is bioequivalent to Ventolin. The same is true regarding the maximum percentile of bronchodilation changes, also the onset and total effect duration of one and two actuations of the generic salbutamol analogous to that resulted from Ventolin.

A number of factors may interfere with the delivery and effect of inhaled medications. One of such is the type of spacer device used. Barry and O'Callaghan have demonstrated that the use of two different devices was associated with different amounts of drugs delivered [28,29]. The use of a standard aero chamber in all patients in this study eliminates one such problem. The comparable results obtained may suggest that this factor plays no significant role since our patients had mild to moderate asthma.

A common problem with this kind of studies response is the failure to show a significant dose-response relationship,**12** as we found that in spite of the fact that the efficacy FEV1 average reading were almost a mirror image between both MDIs for the two dosages but no significant difference in response was recorded between the 100 and 200μg dosages (P>0.05).

The development of safe and comparable generic of innovator brand drugs is vital in containing healthcare costs. The cost of generic brands has been found to be much less than the innovator brands in a recent study from Kuwait. [30]. While a study like the current one is important in establishing the efficacy and safety of these brands.

Conclusion

In conclusion and according to FDA Guidance on Bioavailability and Bioequivalence "Bioavailability and

Bioequivalence Studies for inhaled Drug Products – General Considerations, U.S. Department of Health and Human Services, Food And Drug Administration, Center for Drug Evaluation and Research (CDER)", the results of the present study demonstrate that the Test product (Butalin Inhaler®, Gulf Pharmaceutical Industries/ Julphar) is clinically interchangeable with the Reference product (Ventolin Inhaler®, GlaxoWellcome) with similar pharmacodynamic profile.

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