The Effect of Low to Medium Dose Inhaled Beclomethasone Dipropionate on Blood Glucose Level in patients with Bronchial Asthma

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ABSTRACT:

BACKGROUND:

Although inhaled corticosteroids (ICSs) are the mainstay of therapy in asthma, their use raises certain safety concerns.

OBJECTIVE:

This study aimed to evaluate the effect of inhaled Beclomethasone dipropionate on glucose level in patients with bronchial asthma .

PATIENT AND METHOD:

Ninety patient with new diagnosis of bronchial asthma were included in this study. Patients divided into two groups: 1st group includes those who are controlled with inhaled salbutamol only (30 patients). The 2nd group includes those who required also regular beclomethasone (60 patients). Fasting blood glucose and HbA1c was measured for all patients in both groups before and after three months of starting treatment.

RESULTS:

There was significant elevation of both FBS and HbA1c in group 2 patients after starting inhaled beclomethasone dipropionate in comparison to their baseline levels and the levels in group 1.

CONCLUSION:

The findings indicate that inhaled beclomethasone dipropionate in asthmatic patients may disturb blood glucose level.

KEY WORDS :asthma ,beclomethasone, blood glucose level.

INTRODUCTION:

Since their introduction to clinical practice in the early 1970s, inhaled corticosteroids have become the mainstay of treatment for persistent asthma. This is because of their proven efficacy, which is better than that of any other class of antiasthma therapy. Also, they have a much lower potential for unwanted systemic effects than oral corticosteroids. [1,2]

However, long term treatment of asthma with inhaled corticosteroids is associated with a significant risk of dose related systemic adverse events.3 This risk is particularly worrying in patients with moderate to severe asthma who require continuous treatment with high dose inhaled steroids to keep the disease under control and to prevent exacerbations, and who also require recurrent cycles of systemic glucocorticosteroids to treat exacerbations.4 The biomarkers most frequently used to assess systemic availability of glucocorticosteroids are serum cortisol, urinary cortisol and its metabolites, and serum osteocalcin. The most worrying potential systemic effects are osteoporosis, growth suppression, adrenal insufficiency, cataracts, and glaucoma.5../../gulf/Desktop/New folder/165.full.htm - ref-8

Although inhaled GCSs have a much lower potential for systemic effects than oral GCSs, there remains the possibility of complications from a low level of systemic effects in patients receiving long term therapy. The systemic effect potential of inhaled therapy is, therefore, still an issue of concern, and great efforts have been made to develop new GCSs with even less systemic activity for a given clinical effect. 6

Inhaled corticosteroids are highly effective and widely prescribed for asthma. When given in low doses, systemic effects are not apparent but the use of higher doses has been associated with skin bruising, cataracts, loss of glycaemic control and a reduction in bone mineral density. The currently available inhaled corticosteroids have

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very different pharmacokinetic properties and this may lead to important differences in the balance between efficacy and systemic activity.There are currently 5 inhaled corticosteroids available for the treatment of asthma. These are beclomethasone dipropionate (BDP), triamcinolone acetonide (TAA), flunisolide, budesonide, and fluticasone propionate (FP) 7

Beclomethasone dipropionate (BDP) is a prodrug for beclomethasone monopropionate (BMP),which has a higher receptor affinity than BDP 8. The transformation from BDP to BMP has been shown to occur in lung tissue. There is no information on the hydrolysis rate of BDP within airway cells. However, BDP has a low water solubility, and crystals of BDP dissolve very slowly in mucosal fluid . This low solubility is probably the determining factor in the rate of activation **of** BMP from BDP in the lungs. The limiting step in the inactivation of BDP and BMP is the hepatic metabolism of BMP, which has been shown to occur 2-4 times more slowly than the inactivation of second generation airway-selective **GCSs** such as BUD . The hepatic metabolism of BMP also results in the production of another active metabolite (beclomethasone), which has a receptor binding affinity approximately one third that of BDP, and one tenth that of BMP or BUD.9,10

PATIENTS AND METHODS:

Ninety patients who are diagnosed for the 1st time as Bronchial Asthma were enrolled in this study. The diagnosis of Bronchial Asthma was suspected clinically and confirmed by spirometer and reversibility test using Vitalograph limited spirometer (S model) at Pulmonary Function Unit of Baghdad Teaching Hospital .ALL patients are nonsmokers have no history of diabetes mellitus and not using corticosteroids (systemic or inhaled) or hormonal therapy for any reason . Fasting blood glucose(measured using standard methods by Autoanalyser Abboute) and HbA1c (using High Frequency Liquid Chromatography by D-10 (BioRed) were measured for all patients at Teaching Laboratory of Medical City .So 90 patient were included in this study(50 male and 40 female, Age range 17-48) .Patients divided to two groups: 1st group includes those who are controlled with inhaled salbutamol only taken on as required bases(30 patients ,15 male and 15 female) . The 2nd group includes those who required regular low to medium dose(400-800 µg/day) of beclomethasone inhaler to be added to salbutamol inhaler taken on an as required bases because their symptoms not controlled on occasional use of inhaled salbutamol alone(60 patient ,35 male and 25 female). Fasting blood glucose and HbA1c was measured for all patients in both groups after at least 3 months of starting treatment.

All data were coded and entered to the computer by using Statistical Package for Social Signs (SPSS 17) .Summarizing of data done by using number, percentage and (mean± SD). Comparison between continuous variables measured by using t-test. Chi Square test used to measure the association between both groups according to the gender. P-value $\leq$ 0.05 considered to be significant.

RESULTS:

Ninety patients(50 male and 40 female, Age range 17-48) were included in this study. Group 1 includes those patients whose their symptoms were controlled with inhaled salbutamol only (30 patients ,15 male and 15 female) while group 2 group includes those who required regular beclomethasone inhaler to be added to salbutamol (60 patient ,35 male and 25 female).

Table 1 shows that the baseline fasting blood sugar(FBS) was (84.50±9.70) in group 1 and (84.08± 11.15) in group 2 while the baseline HbA1c was (4.68±0.56) in group 1 and (4.85±0.59) in group 2

Table 2 shows that the mean age in group 1 was (31.77±9.50) while in group 2 was (31.03±9.79) There is no statistically significant difference in age between the two groups(p=0.76).There is no significant difference between the two groups regarding baseline fasting blood sugar (p=0.963) and baseline HbA1c.

In group 1,the study shows no significant difference in FBS(p= 0.95)and HbA1c (p=0.89)before and after using salbutamole. while in group 2, although no significant difference in HbA1c exist after starting beclomethasone inhaler(p=0.72),a statistically significant difference in FBS occur (p=0.009).(table 3)

Study of biochemical tests of both group shows that FBS found to elevated in group 2 after using inhaled beclomethasone in comparison to group 1(91.73±12.08) and (84.40±9.38) respectively and this elevation in group 2 found to be statistically significant(P=0.011) .Similarly ,HbA1c found to elevated in group 2 after using

inhaled beclomethasone in comparison to group 1(5.09±0.79) and (4.69±.55) respectively and this elevation in group 2 found to be statistically significant(P=0.02) .(table 4)

Table 1 : Baseline fasting blood sugar and HbA1c of group 1 and group 2.

	N	Minimum	Maximum	Mean	Std. Deviation
Group 1					
FBS before	30	69	105	84.50	9.709
HbA1c before	30	4.0	5.8	4.680	.5567
Group 2					
FBS before	60	65	106	84.08	11.151
HbA1c before	60	4.0	6.4	4.847	0.5927

Table 2: Comparison between group 1 and group 2 according to their baseline characters.

	group						
	group1			group2			
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	P value
Age	30	31.77	9.500	60	31.03	9.789	.769
FBS before	30	84.50	9.709	60	84.63	12.056	.963
HbA1c before	30	4.680	.5567	60	4.853	.6252	.261

Table 3 : Comparison of fasting blood sugar and HbA1c before and after using salbutamole inhaler in group 1 and using both salbutamole and beclomethasone inhalers in group 2

		Mean	N	Std. Deviation	P value
Group 1					
Pair 1	FBS before	84.50	30	9.709	
	FBS after	84.40	30	9.387	.958
Pair 2	HbA1c before	4.680	30	.5567	
	HbA1c after	4.690	30	.5536	.8990
Group 2					
Pair 1	FBS before	84.08	60	11.151	
	FBS after	88.25	60	11.638	.009
Pair 2	HbA1c before	4.847	60	.5927	
	HbA1c after	4.868	60	.7264	0.723

Table 4: Comparison between group 1 and group 2 regarding their fasting blood sugar and HbA1c after using salbutamole inhaler in group 1 and both salbutamole and beclomethasone inhalers in group 2.

	group						
	group1			group2			
	N	Mean	Std. Deviation	N	Mean	Std. Deviation	P value
FBS AFTER	30	84.40	9.387	30	91.73	12.083	.011
HbA1cAFT	30	4.690	.5536	30	5.093	.7952	.026

DISCUSSION:

An inhaled corticosteroid is now the main agent used for prophylaxis in adult asthma and increasingly so in children. Administration of large doses of inhaled corticosteroids, aided by more concentrated aerosol preparations and improved delivery devices, has allowed further reductions in the use of oral corticosteroids. Although inhaled corticosteroid have a much lower potential for systemic effects than oral corticosteroid**,** there remains the possibility of complications from a low level of systemic effects in patients receiving long term therapy. . So it has to be asked what is the balance of advantages and disadvantages of these agents. Both the desired and the unwanted effects of inhaled GCS therapy can be measured in many different ways, but the results of different measurements are not always in agreement. This makes the whole issue complex and confusing for many clinicians.

In Iraq, still Beclomethasone dipropionate (BDP) is the most commonly used inhaled corticosteroid and usually delivered from a pMDI. However, BDP has a low water solubility, and slow hepatic metabolism which has been shown to occur 2-4 times more slowly than the inactivation of second generation airway-selective **GCSs** such as BUD (9,10)

As BDP is partially transformed into the more active BMP in lung tissue and because of its low inactivation by first-pass metabolism so it may have a greater systemic effects than budesonide (BUD).

In this study we compare the effects of inhaled Beclomethasone dipropionate on carbohydrate metabolism in adults with asthma .However , we not compare these effects with that of inhaled BDP in normal subjects because Harrison *et al* [(11)]concluded that systemic bioavailability of steroids should not be assessed in normal subjects but rather in subjects with asthma of different severity as they found that baseline values of urinary total cortisol metabolites were lower in asthmatic patients than in normal subjects .

In this study, there was no statistically significant difference between the two groups regarding age and baseline FBS and Ha1c.

The study showed that after using inhaled beclomethasone dipropionate for 3 month in 60 asthmatic patients in group 2 ,a statistically significant increase in FBS occured (from 84.08 ±11.151 to88.25±11.638) (p=0.009) however, no significant difference in HbA1c occurs and none of the patients develop diabetes mellitus .

Statistically significant (P=0.011) elevation in FBS in group 2 observed after using inhaled beclomethasone in comparison to group 1 (91.73±12.08) and (84.40±9.38) respectively . Similarly , HbA1c found to be elevated significantly in group 2 (P=0.02) after using inhaled beclomethasone in comparison to group 1 (5.09±0.79) and (4.69±.55) respectively .

These findings agreed with that of Kruszynska et al who found that high dose inhaled BDP may disturb both carbohydrate and lipid metabolism [(12)].Also these results agreed with a conclusion made by Ernst et al published in Current Opinion in Pulmonary Medicine after they review the articles appearing in the last year which have addressed the safety of ICSs when used in the treatment of asthma. In this review they conclude that ICSs have systemic effects and one result appears to be an increase in the risk of diabetes onset and progression, especially at high doses of inhaled corticosteroids [(13)].

However ,the result in this study are incompatible with that of Faul et al [(14)] when study shows that the absence of a clinically significant within-subject difference in the changes in %HbA1c associated with fluticasone versus oral montelukast therapy, or between either therapy or baseline does not warrant recommending changes in therapy for asthma or

diabetes in patients with these co-morbid conditions. However, they suggest that clinicians carefully monitor blood glucose control when diabetic patients initiate ICS, especially with higher dosages.

Another study by Turpeinen showed that only high dose inhaled corticosteroids can affect carbohydrate metabolism in children with asthma [15].

While inhaled glucocorticoids have greatly reduced the morbidity of chronic severe asthma, often allowing a reduction in oral steroid dosage, continuing surveillance of the long term consequences of such treatment appears to be indicated.

CONCLUSION:

The findings indicate that inhaled beclomethasone dipropionate even in moderate doses may disturb carbohydrate metabolism.

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