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Therapeutic Drug Monitoring of Doxophylline at steady state in Indian Bronchial Asthma Patients

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ABSTRACT

Therapeutic drug monitoring (TDM) unit is a vital component of every clinical set up to provide the best patient care. To reach and achieve the complete therapeutic response the attainment of the desired therapeutic drug concentration is obligatory. This TDM prospective study intended to evaluate the possible link between the serum drug concentration and clinical response of doxophylline (DOXO) in treating bronchial asthma patients. Forty four (44) patients were recruited based on the inclusion and exclusion criteria for this study. Trough doxophylline steady state serum concentration was determined by reverse-phase high performance liquid chromatography (RP-HPLC) technique. The union between the expected therapeutic response and DOXO serum concentration was analyzed. Mean drug dose was 15.83±4.02 mg/Kg/day and mean total serum DOXO concentration was 21.3±9.84 µg/ml correspondingly. Mean doxophylline drug clearance was 30.26±7.67 (ml/Kg/h). Serum DOXO levels were in therapeutic range for 71% and sub-therapeutic range for 29% of asthma patients. Amongst the patients with sub-therapeutic DOXO serum levels, 62% patients arrived at complete response and 23% of asthmatics achieved partial response. The success of treatment was also analyzed based on the smoking habit and gender of patients. Smokers group had more number of patients who had no response when compared to the non-smokers group. The correlation between the serum DOXO levels and therapeutic response was very poor. Hence this study shows that therapeutic drug monitoring of doxophylline will add value only in non-responsive bronchial asthma patients and in patients vulnerable to adverse events with standard doses of doxophylline.

KEYWORDS

Therapeutic drug monitoring (TDM), doxophylline, bronchial asthma

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INTRODUCTION

In spite of the wide classes of drugs employed in treatment, 1 in 250 deaths occur worldwide due to asthma. Most of these deaths could be prevented as they are caused either due to suboptimal long-term medical care or delayed help during final attack. The report suggest to pursue further research in the areas of asthma cause and the current primary and secondary intervention strategies used in asthma treatment.(1)

Even though there are established treatment guidelines and therapy advancements, there is still lag in the effective asthma control achievement. This has been out veiled by a large cross sectional study which assessed using the Asthma Control Test (ACT) scores and another one named Gaining Optimal Asthma Control (GOAL) study. In the latter study 30% of 3500 asthma patients failed to achieve optimal asthma control. One other study revealed a 59% of treatment failure even though they had received primary care.(2-5) Hence there is a need for research to help in providing successful asthma care. The use of traditional xanthines is restricted in asthma treatment highly due to its increased occurrence of adverse events and narrow therapeutic index. The evolution of newer xanthines thus resulted. Among the newer xanthines, the present literature depicts very scanty evidence in the research carried out worldwide with respect to the drug Doxophylline. The previous authors have also commented that Doxophylline's complete potential has not been fully explored. Therapeutic drug monitoring of Doxophylline could be a positive step in treating asthma patients with optimal care. This study is further a step in asthma management towards effective utilization of Doxophylline.

MATERIALS AND METHODS

Patients

This prospective research was carried out at the in-patient unit of Chest and TB ward of Sri Ramachandra Hospital (Chennai, India) during March and November, 2014. Bronchial asthma patients who were on treatment with oral doxophylline tablets (400 mg, twice daily) and had attained steady state concentrations were admitted to the study based on the below inclusion and exclusion criteria. Ethics approval was obtained from Sri Ramachandra University ethics committee. The inclusion criteria for this study were: a) Bronchial asthma patients aged 18-65 years b) Bronchial asthma patients who were treated with doxophylline as mono-therapy or in combination with other medications c) Patients who were willing to give consent and participate in the study. The patients with the following criteria were excluded from the study. Exclusion criteria: a) Patients aged below 18 and above 65 years of age b) Critically ill patients who are clinically unstable c) Pregnant and lactating women. The patient's demographic data (age, sex, body weight, etc) and treatment details (time of administration, treatment duration, concurrent medication and adverse drug reaction) were noted at the time of sampling. Therapeutic response was evaluated based on the changes in spirometric parameters such as FEV1 (L), FVC (L), FEV1/FVC ratio and PEFR (L/sec). Statistical significance in all the 4 parameters was considered as complete response, in 2 or 3 parameters was termed as partial response and 1 or 0 parameters was taken as no response in patients.

Sample collection and drug estimation

Serum samples at trough level were taken from patients before the successive dose was administered when steady state has reached. Reverse-phase high performance liquid chromatography (RP-HPLC) was practically used for the determination of serum DOXO concentrations.(6) The peak area ratio of the samples were plotted in the calibration curve and the drug concentrations were derived . Analysis of the data set was performed using SPSS software version 11.5.

Table 1. Study group characteristics

Demography	Values
No. of patients	44
Male	66%
Female	34%
Age (yr)	55.09±9.19*
Body weight (kg)	53.29±11.57
DOXO dose (mg/day)	400
DOXO dosage (mg/kg/day)	15.82±4.01
Serum DOXO concentration (µg/ml)	21.5±9.94
DOXO CL/F (L/h)	30.26±7.67
Coefficient of Variation	17.51%

* Mean±SD

RESULTS AND DISCUSSION

The total number of patients that comprised the study group was 44. A demographic data and treatment detail for the study subjects is collectively given in Table 1. The number of male participation was higher in the study with 66%. The mean trough level DOXO concentration was 30.26µg/ml. Mean DOXO dose for the study group was 15.82±4.01 mg/kg/day. There was a high inter-individual variability of 17.51% observed

from the TDM of this drug. Table 2 show the level of therapeutic response exhibited by the study subjects based on the attainment of therapeutic concentrations of doxophylline. In patients with DOXO levels within therapeutic range 10% of them showed no response. In contrast 62% of patients showcased complete response in sub-therapeutic DOXO level group. Both the groups had approximately 20% of patients with partial response. Fig 1. The percentage of non-responsive patients was slightly higher in the female sub group. Fig 2. However this rise in the percentage did not yield any significance. Analysis of the trough level concentrations based on the smoking habit of patients depicted statistical significance as shown in the Fig 3.

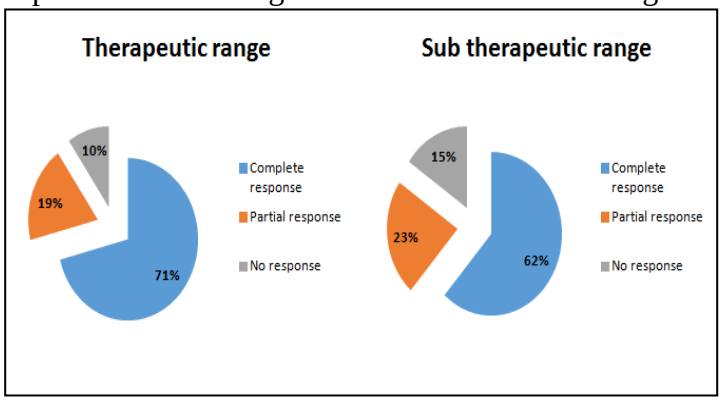

Figure 1. Pie chart showing the ratio of therapeutic response based on the Doxophylline drug status in patients.

Table 2. TDM of Doxophylline

Therapeutic range	**Percentage**
Complete response	71%
Partial response	19%
No response	10%
Sub-therapeutic range	
Complete response	62%
Partial response	23%
No response	15%

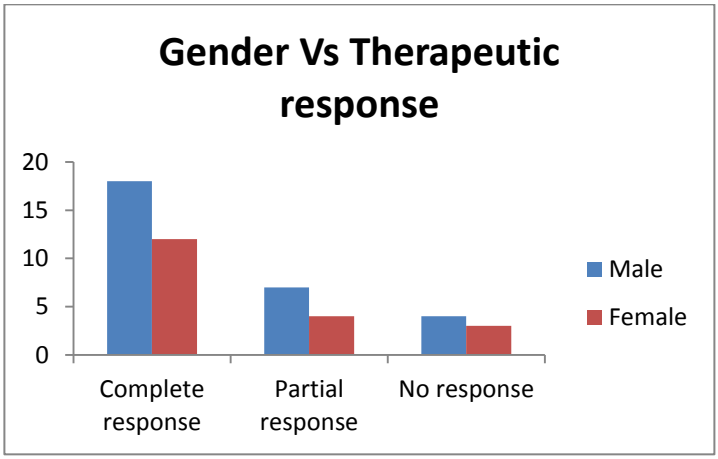

Figure 2. Comparison of therapeutic response of patients based on patient sex

Surprisingly no adverse events were recorded in this study. As an evidence to the said statement the drug levels of doxophylline also did not exceed the therapeutic range. There are few studies which have documented that doxophyline causes digestive system, nervous system and circulatory system related side effects but in a lesser proportion when compared to theophylline.(7-12) The reason for no observed adverse events in this study may be due to the use of 400mg twice daily.

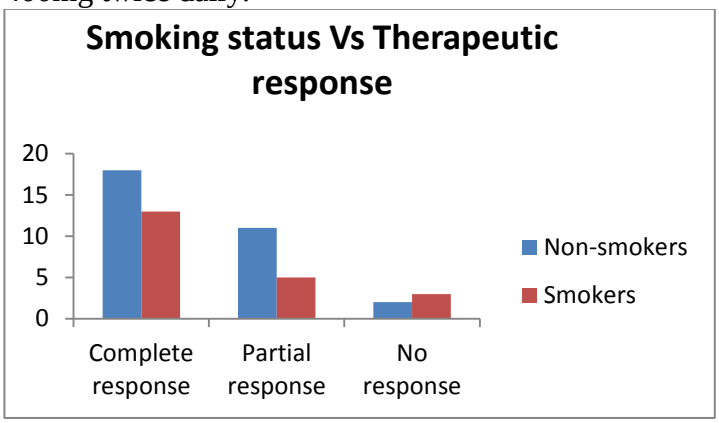

Fig 3. Comparison of therapeutic response of patients based on patient smoking status.

The correlation between the serum DOXO levels and therapeutic response was not up to the expectations. Hence this study shows that therapeutic drug monitoring of doxophylline will add value only in non-responsive bronchial asthma patients and in patients in whom adverse events may occur with standard doses of doxophylline.

CONCLUSION

Therapeutic drug monitoring of doxophylline is requisite primarily in situations when patients are non-responsive, elevated doses of doxophylline is essential for treatment, patients possess one or more co-morbid conditions, occurrence of adverse events and at times of concurrent medication. To conclude the results in a simple way, therapeutic drug monitoring of doxophylline is not crucial in normal situations.

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