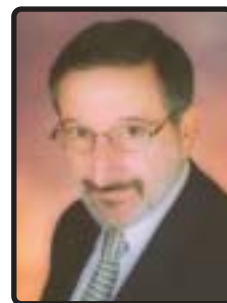


## EFFICACY AND SAFETY OF BUDESONIDE AND FORMOTEROL IN ASTHMA PATIENTS *by Herb Patrick MD*



Starting with this issue of Focus, there will be a change in the format of the research article. In each issue, there will be a review of a published research project related to Respiratory Care. This month's original article is: Michael Noonan, Lanny J. Rosenwasser, Paula Martin, Christopher D. O'Brien and Lisa O'Dowd, Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in adults and adolescents with moderate to severe asthma: a randomized clinical trial. *Drugs* 2006, 66(17):2235-2254

The Background or Introduction of the research project explains interest in the topic and why the topic is significant. Asthma affects more than 15 million people in the United States. Although attacks of bronchospasm are often triggered by known allergens, medications have been developed to decrease bronchospasm. Two such medications are beta agonists and corticosteroids. The addition of an inhaled long acting beta agonist (LABA) to inhaled corticosteroid therapy (ICS) is recommended by the Global Initiative for Asthma (GINA, 2005) for patients with moderate or severe persistent asthma. Combining these two controller medications in one inhaler simplifies treatment. For this project, a new combination product with formoterol (LABA) and budesonide (ICS) had been approved by the Food and Drug Administration as a pressurized metered dose inhaler (pMDI) named Symbicort' by the manufacturer,

AstraZeneca LP, Wilmington DE. (Note: The use of the trade name is for product identification purposes only and does not imply endorsement.) This study compared the combination of formoterol/budesonide in one inhaler versus individual formoterol and individual budesonide inhalers. A placebo inhaler was also included for comparison.

The Questions for the research project are: Does the efficacy of the combination medications when compared to the component medications remain unchanged? Does the safety of the combination medications when compared to the component medications remain unchanged? (Note: The Question asked in every research project always has the possible answers: "yes" and "no.") The preconceived answer by researchers to the Question is called the Hypothesis. For this project, the Hypotheses were: Yes, the efficacy remains unchanged. Yes, the safety remains unchanged.

The Methods for the research project describe the design and steps to answer the Questions. For this project, males and females, aged equal to 12 years or older, with moderate to severe asthma were recruited. This was a 12 week, 84 center (multicenter) study that was randomized (subjects assigned to drug without any deliberate pattern), double-blind (neither the subject nor the investigator knew the drug or placebo being given), double-dummy (the combination inhaler was disguised through the use of two inhalers; one with the combination drugs and one "dummy" inhaler to avoid identification), placebo-controlled (drug efficacy and safety would be compared to subjects receiving no drugs). For this project, subjects would be randomized into 5 groups: 1. budesonide/formoterol combination inhaler and a dummy inhaler, 2. budesonide + formoterol each separately and no dummy inhaler, 3. budesonide alone and a dummy inhaler, 4. formoterol alone and a dummy inhaler, and, 5. placebo inhaler and a dummy inhaler. Every subject used a peak flow meter, a hand-held electronic diary and a paper diary for their record keeping. The study protocol was approved by the Institutional Review Board (IRB) at each clinical site and conducted in accordance with guidelines for the ethical treatment of human subjects, good clinical practice and local regulations. Written informed consent and, where appropriate, assent (approval by a parent or guardian for a subject under the legal age for consent) were obtained before study procedures were initiated. Efficacy was evaluated as FEV-1 by spirometry 12 hours after a prior dose. Safety was evaluated as adverse events, vital signs, physical examinations, laboratory tests, electrocardiograms, and 24 hour Holter electrocardiograms. Statistical analyses determined that the number of subjects (sample size) within each of the 5 groups would need to be 112, for a total sample size of 560 subjects. Statistical comparisons for the differences between the groups would be performed using the ANCOVA (ANalysis of COVariance) test with p equal to or less than 0.05 defined as a statistically significant difference between the groups (p < 0.05 means a one in twenty likelihood that the difference between the groups is only due to chance and is not a real clinical difference). The Results disclose both the raw and the analyzed data, using

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Tables and Figures. For this project, 596 subjects were randomized into the 5 groups with 371 completing the 12 week study. The placebo group had the largest number of subjects discontinuing the study with  $75/125 = 60\%$  discontinued. For efficacy, the improvements in FEV-1 for subjects treated with the combination budesonide/formoterol (group 1) was similar to those treated with budesonide + formoterol (group 4) and significantly greater than those treated with budesonide alone (group 2), formoterol alone (group 3) or placebo (group 5). All treatments were well tolerated with no statistically significant differences between the 5 groups.

The Discussion/Reflections/Future Research offers a comparison with similar research projects and a critique of the research project, suggesting possible modifications that would improve the quality of the research. In this study, formoterol (for use in group 4) was only available as a dry powder inhaler (DPI) in the United States versus the combination budesonide/formoterol (for use in group 1) as a pressurized metered dose inhaler (pMDI). Therefore, subjects in group 1 and group 4 allowed a comparison of efficacy of combination pMDI therapy versus pMDI + DPI monocomponents. There was similar efficacy between these groups.

The Conclusion is the final summary of the research project. This project demonstrated that twice daily budesonide/formoterol as a combination inhaler has similar efficacy and safety compared to the components inhaled separately in adolescents and adults with moderate to severe persistent asthma. Therefore, in this project, the Hypotheses were supported, corresponding to a "yes" answer to both Questions. (Note: When writing the Conclusion, the Hypothesis must be addressed whether supported or not.)

Acknowledgements credit those who assisted the research project, both by time/effort and by financial support. For this research, the acknowledgement included those who assisted in writing and reviewing the manuscript and the investigators at all 81 centers in the United States. The Acknowledgement also included AstraZeneca as the study sponsor, who designed the study, managed the study, analyzed data, interpreted data, reviewed and approved the manuscript.

Conflicts of Interest are listed for all participating in authorship of the project. Conflicts include advisory board membership, ownership of stock, receipt of services, honoraria or gifts from companies related to the project. For this project, Dr. Noonan has served on an advisory board for and received honoraria from AstraZeneca. Dr. Rosenwasser has served as a consultant for and received honoraria from AstraZeneca. Drs. Noonan and Rosenwasser have both received funding from AstraZeneca as investigators in the study. Ms. Martin, Drs. O'Brien and O'Dowd are AstraZeneca employees and own stock in AstraZeneca.

The Bibliography section includes references to support the research as included in the manuscript by reference number. For this project, there were 32 references.

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*Clarification Statement:*

Articles written by Dr. Herbert Patrick from 2004 to date in 2007 and in the future, were, and will be, presented for educational and training purposes with the emphasis on teaching the scientific method used in clinical research. Actual patient data were not included, nor analyzed. The results and conclusions in each article, as with any educational training scenario, require the reader's clinical judgment to determine actual patient relevance.

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infection which causes unanticipated death or major permanent loss of function is to be treated as a sentinel event. Sentinel events require immediate action including investigating and response from the home care organization. One of the goals of sentinel event reporting is to aid in changing the health care providers' systems and processes so as to reduce the possibility of other future events. Failure on the part of a JCAHO accredited home care provider to report or cooperate in an investigation of a reviewable sentinel event can result in loss of accreditation.

While hand washing and cleaning of home care equipment may seem simple on the surface it can have deadly consequences for patients if not implemented as part of the care plan. An immunosuppressed patient, for example, can be at risk if the appropriate infection control measures are not in place in the residence. The same mentality that has made specific infection control measures common place in health care facilities needs to be applied to home care settings. A positive outcome is the goal of all respiratory care services in the home. Instituting appropriate infection control practices is an essential element towards that goal.

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