

## DOES THE COMBINATION OF ALBUTEROL & IPRATROPIUM BROMIDE HAVE THE SAME EFFECTIVENESS AS THE DRUGS SEPARATELY IN PATIENTS WITH COPD? *by Herbert Patrick MD*



In this issue of *Focus*, we will discuss a Respiratory Care research project funded by an outside agency. An outside agency includes pharmaceutical companies, equipment manufacturers and private or government grant sources. We will continue to discuss each research project using the traditional Scientific Method format: Background or Introduction, Question, Hypothesis, Methods, Results, Conclusions, Reflections, Future Research, Bibliography, Acknowledgements, and Conflicts of Interest.

Dey Laboratories, a pharmaceutical organization, sponsored this research project. Dey wanted to market DuoNeb™, a unit dose formulation combining albuterol and ipratropium bromide for patients with chronic obstructive pulmonary disease (COPD). The Food and Drug Administration (FDA) required efficacy studies on the combination as an inhalant (nebulizer) solution, despite the market presence of Combivent™ as an MDI combination of the same drugs.

The design for this research project was prospective, randomized, double blind, crossover and positive control. The prospective component was based on a tabulation of the future clinical course of patients. The randomized design was the unbiased selection of patients with COPD.

Let's examine each of these terms for the research project design. Prospective means looking ahead from the time of patient

enrollment. In this research project, patient PFT's would be tabulated prospectively. Randomized means that each patient in the research project would be selected from the population of patients at our institution with COPD without regard to any feature, such as attending physician, prior inhaled medication, or age, height, or weight. If randomization is successfully applied in a research project, then a single patient characteristic should not be a dominant component. Double blind means the identity of the drug given to each patient was not known by the researcher or by the patient. Crossover means there will be two groups of similar patients and two different treatments. Half of the patients start with one treatment and then crossover to the second treatment. Meanwhile, the other half of the patients starts with the second treatment and crossover to the first treatment. Positive control means that the patient will always receive drug and never placebo during the research project.

As we have noted for other research projects funded by an outside agency, the first step between the principal investigator of the research project and the sponsor is to arrange a Confidentiality Agreement. This Agreement assures the sponsor that the principal investigator and other members of the investigative team will not disclose any research project related information into the public domain unless first approved by the sponsor. The public domain includes speaking to colleagues, publication of journal articles and book chapters, and presenting poster or slides at local, national, or international conferences. Dey Laboratories provided their standard Confidentiality Agreement.

The second step for research projects funded by an outside agency is principal investigator submission of papers to the Institutional Review Board (IRB) describing details of the proposed research project. These papers describe the project design and include a consent form for each subject to sign before enrolling and participating in the research project. IRB approval is necessary before initiating the research project by gathering data or enrolling subjects in the project.

The third step for research projects funded by an outside agency is creating a funding account for handling salaries and supplies. A budget is needed for the project, either tallied by subject enrolled or by calendar year. This budget is also reviewed and approved by the outside agency and the financial officer at the site of the project. Now let's review the research project:

The **Background or Introduction** of the research project explains interest in the topic and why the topic is significant. For this project, combining two individual drug treatments for COPD could allow more efficiency when using nebulizer treatment. Instead of two sequential nebulizer treatments of 15 minutes each, only a single treatment would be necessary. This could improve patient compliance with medication and could possibly offer a total bronchodilator effect greater than the sum of the effects of the individual drugs. This additive characteristic is called synergy. Other patient clinical characteristics that might improve with this combination of medications include number of



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visits to the out-patient office, visits to the ER, and number of hospitalizations.

The **Question** proposed is: Does the combination of albuterol and ipratropium bromide have similar effects as the sum of each agent administered separately? (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 Hypothesis was: Yes, the combination will work similar to the individual components used together.

For the **Methods**, the Respiratory Care staff was involved in identifying patients with COPD who would be approached for enrollment in this research project. The goal enrollment was fifteen patients. Each patient had to sign an Informed Consent form in order to complete enrollment. The patient's out-patient chart was reviewed and patient characteristics recorded. The patient then had spirometry performed several times as part of an all day screening visit. For the first test, no inhaled medication was permitted for the previous 12 hours so that a baseline could be established. Next, nebulized albuterol was administered in the standard concentration of 2.5mg in 3mL and the spirometry was repeated every hour for 4 hours. Lastly, the nebulized ipratropium bromide was administered in the standard concentration of 0.5mg in 2.5mL and the spirometry was repeated every hour for 4 hours. Therefore, a total of 9 spirograms were performed to determine if the patient qualified to be in the study by having bronchodilator response to each drug. If

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this screening visit was successful, the patient was randomized into one of two groups receiving sequential nebulizer treatments: Group 1 was albuterol followed by ipratropium bromide; Group 2 was DuoNeb<sup>TM</sup> followed by saline. Each patient was given appropriate vials medication to continue their nebulized treatments at home. Monthly visits were needed for spirometry testing for a total of 6 months. At 6 months, the patients were crossed over from Group 1 to Group 2 and from Group 2 to Group 1 for the final 6 months of treatment. Patient interval history and physical examinations at the monthly visits were recorded in a customized notebook identified by the patient's initials only. Each patient continued their new medication at home and return monthly for spirometry. The duration of the project was one year for each patient. Screening and monthly spirometry values were forwarded electronically to a central tabulating agency. Improvement in spirometry in the first 6 months versus the second 6 months were compared with  $p < 0.05$  significant.

To formulate the **Results**, patient data were analyzed by the central tabulating agency for our fifteen patients and all patients enrolled across the country. Patient

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randomization was successful as no characteristic was significant between the two groups of patients. Effectiveness of DuoNeb™ was, in fact, better than the individual component medications, i.e., synergy was present.

The **Conclusions** were DuoNeb™ was equal to or better than separate use of albuterol and ipratropium bromide for patients with COPD. Therefore, in this project, the Hypothesis was supported, corresponding to a "yes" answer to the Question. (Note: When writing the Conclusion, the Hypothesis must be addressed whether it was supported or not.)

The **Reflections** offers an opportunity to critique the research project, suggesting possible modifications that would improve the quality of the research. For example, patients with COPD responsive to albuterol and ipratropium bromide were selectively recruited for this study. This research project did not address whether patients with spirometry unresponsive to bronchodilators should receive them. Reflections can also include a comparison with similar research projects.

**Future Research** is important because research should lead to more research. For example, this project could lead to a larger, multi-site project based on the same experimental design.

References from similar research and the reference for non-parametric statistics are included in the **Bibliography** section.

**Acknowledgement** offers credit to those who assisted in the research project, both by time/effort and by financial support. The acknowledgement included Respiratory Care practitioners who participated and the financial support from Dey Labs.

**Conflicts of Interest** are listed for all Respiratory Care Practitioners and others participating in authorship of the project. Conflicts include ownership of stock or receipt of services or gifts from companies related to the project.

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