International Scientific Association for Probiotics and Prebiotics

An international non-profit association of scientists dedicated to advancing the fundamental and applied science of probiotics and prebiotics

ISAPP Responds to Report of Increased Mortality with Probiotic Preparation in Pancreatitis study

Davis, Calif. – February 21, 2008 – With the publication of the PROPATRIA study[1] which reports higher mortality among subjects with acute pancreatitis treated with a combination of 6 strains of live *Lactobacillus* and *Bifidobacterium* species ("Ecologic 641"), the safety of "probiotics" in general has been called into question. But several issues should be considered before "probiotics" are accused of causing mortality.

Was the product used a probiotic?

By definition, a probiotic is a "live microorganism which when administered in adequate amounts confers a health benefit on the host."[2] Guidelines for applying this definition were issued in 2002 by working group convened by the FAO/WHO.[3] The guidelines stipulate that after proper definition of the strain or strains being used and assessment of safety for the target host, at least one (and preferably a confirmatory), appropriately designed study must be conducted to determine if the strain or product is efficacious. Only microbes meeting these criteria should be called "probiotic." In the case of Ecologic 641, human safety and efficacy data, especially for use in this acutely ill study population, are not published. Therefore it is not apparent that this product meets minimum criteria to properly be called a "probiotic." In addition, the publication of this paper does not properly define the blend of microbes: no strain designations are provided so it is impossible to know what the true composition of the product is.

Misuse of the term "probiotic" is rampant commercially; it is incumbent upon the research community to adhere to the scientific definition of this term.

Overgeneralized conclusions made in publication of study

It is therefore especially unfortunate that general conclusions about "probiotics" were made in this paper and several related press releases. Probiotics draw from a diverse group of live microbial genera, species and strains. Strains of yeast, *Esherichia coli, Bifidobacterium, Lactobacillus, Streptococcus, Lactococcus* and *Bacillus* species have been tested as probiotic microbes. In fact, there may be few physiological similarities among different probiotic strains. Scientific precision demands that in referring to the observations from this study, the specific test product, method of administration and treatment population are included.

Foods vs. drugs

It is important to recognize that safety is a function of the product (dose and composition), the intended user and the route of administration. In the case of the PROPATRIA study, the intended subjects were acutely ill with a condition that has been associated with a 10-30% mortality rate (as referenced[1]). The primary study aim was to determine if this product could reduce the number of infectious complications during hospital stays. The result failed to show any effect on this outcome. Furthermore, the product was administered via a nasojejunal tube twice daily delivering 10^{10} live bacteria per day. This is a higher dose to the normal intestine than what would be delivered in most probiotic foods. The intended use of the lactobacilli and bifidobacteria in this study was as a drug, not as a food. The results of this study should not be construed to imply that foods containing probiotics are unsafe for consumption by the generally healthy population.

It is clear from the FAO definition that the term "probiotic" is a broad term which describes live microbes used for a variety of products, including foods, supplements, drugs and medical foods.[4] The term "biotherapeutic" or "pharmabiotic" should perhaps be used more specifically to apply to probiotics that are intended to be used as drugs. This would provide differentiation between products safe for general consumption and products which can be evaluated from a "risk/benefit" perspective.

Was the test product, Ecologic 641, responsible for the increased mortality observed?

It is important to recognize that the mortalities recorded in the Besselink paper[1] were not due to infections of blood or organs by any of the strains of bacteria included in the Ecologic 641 product (Table 3). Mortality was due to organ failure, including ischemia of the small bowel in some cases.

In evaluating the details of the Besselink paper,[1] a serious question arises regarding the randomization of patients into the placebo and intervention groups. The authors indicate that "Groups were much the same at baseline in terms of patients' characteristics and disease severity." However, there appear to be differences in multiorgan failure between the 2 groups, with the test group having higher rate of multiorgan failure than the placebo group. Although it is true that "…there was no difference between the groups with regard to organ failure that started after the day of randomization (p=0.6)," the organ failure rate during admission, regardless of time of onset, was clearly statistically higher in the intervention group (27%) than the placebo

group (16%) (p=0.02) (Table 2). Since this fact speaks to a difference in severity of disease at admission and since most of the deaths were caused by multiorgan failure (20 of 24 deaths in the intervention group and 7 of 9 in the placebo group), it is very likely that the increased mortality in the intervention group was not due to the "probiotic" intervention but to the fact that more subjects with organ failure were included in the intervention group. This was possible because at entry patients were not stratified by severity of disease. In short, this paper does not provide convincing evidence that the live microbial preparation contributed to mortality.

Additional investigation into the cause of mortality is warranted for this study so that specific conclusions can be made. If on further analysis, a mechanism is revealed which suggests that Ecologic 641 contributed to mortality in this group of patients, it will be relevant to assess if the specific strains or blend of strains possessed any unique attributes, or if the mechanism could reasonably be extrapolated to other strains of these same species or microbes in general.

Conclusions

- This study must not be interpreted to imply that properly defined and studied probiotics used in foods or well-defined supplements are not safe for the generally healthy population. Probiotics have been consumed by millions of people on a regular basis for many years without reports of adverse effects.
- We call on the scientific community to only use the term "probiotic" when established criteria are met.[3] All components must be identified to the strain level and the blend must be shown to be safe and confer a health benefit.
- With regard to the specific report of mortality, the difference between the groups seems to be due to lack of homogeneity of the groups at time of randomization and not due to the "probiotic" intervention itself.
- This study did not find any difference between placebo and intervention groups with regard to risk of developing infectious complications (the primary outcome of the study).
- Of the infectious complications that occurred, none were caused by the lactobacilli or bifidobacteria used in this study (Table 3).
- The temptation is great, especially in situations where standard therapy is lacking, to determine if probiotics might have an impact in treatment of disease. But establishment of safety of the approach becomes critical when we seek to treat vulnerable patients. Unfortunately, we must recognize that validated models for safety of live microbes often do not exist.[5] Research to define proper animal models of safety must be a priority for this field.
- The authors conclude that "probiotics should not be administered routinely in patients with predicted severe acute pancreatitis." Although caution is a prudent recommendation, we cannot conclude from this study that probiotics are harmful, or that they should not be used in patients who are seriously ill. Such a general conclusion does not take into account differences in microbes that might be used for such applications, the particular pathology of the patients, the mode of delivery or the dose of the product. Rather, if a well documented probiotic is proposed to be used in such patients, care must be taken by the local ethics board and/or governmental health agency to review applicable details of the study and make the decision as to whether or not such a study should be performed.

About ISAPP

The International Scientific Association for Probiotics and Prebiotics (ISAPP) is an association of academic and industrial scientists involved in research on fundamental and applied aspects of probiotics and prebiotics. The scientists participating in ISAPP have a common interest in generating high quality scientific information for the probiotic and prebiotic fields and providing guidance for collaborative and multidisciplinary research. The organization hopes to raise the scientific credibility of the field by working with experts and conducting meetings on high quality research. Providing an objective, science-based voice also will benefit the end users of these products by helping them make informed choices. ISAPP is the only scientific organization dedicated specifically to probiotics and prebiotics, bringing together scientists from all pertinent disciplines, including food science, microbiology, immunology, biochemistry, nutrition and medicine. Board members include Gregor Reid, Ph.D., M.B.A., Canada, President; Glenn Gibson, Ph.D., England, Vice President; James Versalovic, MD, Ph.D., USA, Secretary; Karen Scott, Ph.D., Scotland, Treasurer; Mary Ellen Sanders, Ph.D., USA, Executive Director; Todd Klaenhammer, Ph.D., USA; Francisco Guarner, M.D., Ph.D., Spain; and Nathalie Delzenne Ph.D., Belgium. For more information, visit www.isapp.net.

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