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Effective treatment of the malabsorption which results from pancreatic exocrine deficiency (e. g., cystic fibrosis; chronic pancreatitis; status post pancreatectomy; etc.) requires that active pancreatic enzymes (including protease and lipase) are present high (proximal) enough in the small intestine to ensure adequate digestion and absorption before the ingested food passes the ileocecal valve and enters the colon. Protective coating of enzyme to prevent inactivation by gastric acid was a critical advance in this treatment.

It is obvious that sufficient enzyme must be taken orally by these patients for digestion to occur. However, it is also essential that these enzymes "survive" transit through the stomach (where gastric acid can inactivate them) and that the enzymes then become "active" (i. e., freed from protective coating) as soon as possible after entering the small bowel. Different enzyme preparations (i. e., different FDA approved brands such as Creon, Ultrase, and Pancrease) have different physical and chemical characteristics which result in substantial efficacy variation in different patients.¹ Thus, while some patients do well regardless of brand, many rapidly discover that one brand is noticeably more effective (than others with the same enzyme content) in controlling malabsorption symptoms. These differences no doubt result from variation in their pH requirement for lysing the protective enteric coating and in their physical characteristics (e. g., how tightly the enzyme and its coating are "packed"). Physicians and patients usually discover the optimal brand and dose by a series of trials. Once the patient has settled on the best brand, (s)he is usually stable on that preparation for many years (although growing children may need some increase in dose).

When patients complain that "enzymes don't work", physicians run through a mental check-list of possibilities (e. g., "a bad batch", non-compliance, change in diet, increased gastric acidity, new onset of a second gastrointestinal disorder, etc.)

The recent advent of generic "equivalents" which are substituted by pharmacists for the brand named by physicians, but written without the DAW (dispense as written) request, has greatly complicated this differential diagnosis. It is now a frequent cause of puzzling "treatment failure". Often, neither the doctor nor his/her patient is even aware of the substitution. Furthermore, generic "equivalents" are not only not "equivalent" to the brand the physician thought he had ordered, they are also not equivalent to each other. The result can be

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therapeutic chaos. In the extreme case, the patient may become non-compliant (a situation we used to see commonly before the advent of modern enzymes when many adult patients stopped taking enzymes, saying "they don't work"). This was a frequent occurrence when CF patients began surviving into adulthood, and had more gastric acid (and/or less pancreatic bicarbonate).

In addition to the therapeutic failure problems noted above, there is another less obvious, but equally worrisome problem with generic substitution. Enzyme preparations which are not activated until they have traversed most of the small bowel, are likely to remain active as they enter the large bowel (especially if treatment failure has led the physician or patient to increase the dose). Unopposed enzyme in the colon is almost certainly responsible for very serious problems (including an obstructing colonopathy requiring surgery, including, in some cases, partial colectomy) in young children who were taking very high enzyme doses.² Whether this will become a problem in older patients as a result of generic substitutions remains to be seen.

Finally, in recent years there has been fairly convincing evidence that gastrointestinal cancer is slightly more common in young adults with cystic fibrosis than in control populations. The reasons for this are not completely defined, but it is not unreasonable to presume that it is a consequence of unopposed enzyme and/or undigested food, particularly fat, in the colon. Both of these potential problems can result when generic substitutions interfere with carefully crafted therapeutic recommendations arrived at after weeks or months of trial and error.

In summary, "generic equivalence" is simply not a valid concept when applied to exogenous pancreatic enzymes used to treat exocrine pancreatic deficiency. Generic substitution result in patients incurring unnecessary and unjustifiable compromise of treatment and increased risk of complications. I recommend that, when a specific brand of pancreatic enzyme is prescribed, either: 1) the designation "dispense as written [DAW]" or its equivalent be assumed by the pharmacist even if not expressly written by the physician; or 2) the pharmacist contact the physician prior to "generic substitution", and inform him/her that the substitute being proposed may not have the same physicochemical properties (and therefore therapeutic effect) as the brand-name drug the physician had ordered.

Sincerely,

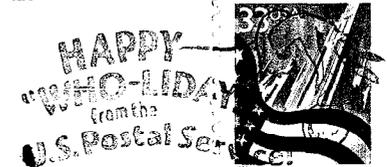


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