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Discussion

Dr. Lloyd M. Nyhus (Chicago, Illinois): The use of antibiotics in the treatment of pancreatitis, as has been said, has remained controversial, even though it has been widely recommended as recently as this past year. Prospective randomized studies dealing with this subject indicate that antibiotics are of no value in the treatment of pancreatitis. These studies, however, have been criticized because only patients with relatively mild alcoholic pancreatitis were included, and the argument remains unsettled.

Parenthetically, Dr. Schenk, the pancreatitis, acute, focal, produced in the animals in your experiments, seem rather mild. What would be the excretion of Tobramycin in fulminating hemorrhagic pancreatitis in your animals? It seems to me it's in this area that we have most interest.

The theoretical prerequisites for the effectiveness of an antibiotic are that the antibiotic reach the area of infection and that the bacteria involved are sensitive to it. The first prerequisite has been proven in the paper given today, at least as far as Tobramycin is concerned.

The second prerequisite, however, remains somewhat in doubt. Even though most studies, including our own, of pancreatic abscesses have not shown any anaerobic bacteria, it seems hard to conceive that this would be the only intra-abdominal infection without participation of this organism.

Before the antibiotic protocol for the treatment of pancreatitis is designed, we should have better microbiologic studies of the infectious complications of this disease.

It is of interest that in our patients with pancreatic abscess, treated preoperatively with aminoglycoside and clindamycin, not a single anaerobic culture was positive. This certainly suggests that clindamycin was at an effective level in the pancreatic tissues and secretions of these patients, thus lending credence to the observations of our essayists, at least as seen in their dog model.

In this context, what is the possible role of anaerobes in pancreatic abscesses, and do you know if antibiotics effective against these organisms are also excreted in the pancreatic juice?

Second, concerning the recommendations—they are only recommendations—for the clinical use of Cephamandole, in addition to Tobramycin, what is the rationale for recommending a combination of Cephamandole and Tobramycin, since Cephamandole does not increase the spectrum of bacteria covered by Tobramycin significantly, and especially as it has very limited activity against anaerobic bacteria?

Dr. William A. Altemeier (Cincinnati, Ohio): The type of experimental pancreatitis produced in their animals allows the excretion of Tobramycin in the pancreatic fluid, but I too raise the question of what will happen in the case of apoplexy of the pancreas, or the hemorrhagic, diffuse, severe type of pancreatitis? Will these glands secrete Tobramycin in the same degree?

Some of the older members of this Association will recall the experiences we had before 1940, before we had serum amylase determinations to help us in the diagnosis of acute pancreatitis and, in particular, hemorrhagic pancreatitis. At that time, it was not uncommon to operate upon patients with severe hemorrhagic pancreatitis. The pancreas would be diffusely and completely involved, and there were several operations which were done, one of which included gridironing the peritoneum over the surface of the pancreas and draining this fluid through flank incisions. At the same time, we took cultures.

I was impressed at that time with the frequency of the hemolytic Streptococcus being present in the fluid about the pancreas, and this has been the basis for my use of aqueous penicillin G for treatment in the early course of the disease.

There is increasing evidence that some cases of pancreatitis may be due to viral infection. This brings into focus the question of the value of Tobramycin in the early stages of this type of pancreatitis. We must conclude, however, that it will be of value in the patients who have survived the acute stage, and who have developed pancreatic abscesses.

Dr. Alexander and I reported 32 cases of pancreatic abscess in 1963, and we studied very carefully the bacteriology of the pus in those instances. Since then, this study has been continued and anaerobes do participate in the development and progress of pancreatic abscesses, particularly the anaerobic Streptococcus and Bacteroides fragilis.

In conclusion, I would echo some of the comments which have been made, that we need additional and detailed bacteriologic studies of the acute phase of pancreatitis (particularly the severe acute case), as well as of established cases with abscess.

Dr. H. Harlan Stone (Atlanta, Georgia): In the prevention or treatment of any type of infection, the use of a specific antibiotic is determined according to three factors: first, safety of drug; second, the appropriate antibacterial spectrum for the bacteria present in the infection; and third, which Dr. Schenk and his coworkers have addressed themselves to, the delivery of antibiotic to the site, whether

such is at risk of becoming infected or has already been involved in the infectious process. This latter is something that we must constantly keep in mind. For example, antibiotic delivery is exceedingly important with respect to patients who have meningitis, where there is no response if antibiotic does not cross the blood/brain barrier.

(slide) In a series of patients—and these represent five of 11 patients who were deemed to have fulminant, acute pancreatitis out of 373 admitted in the last 12 months to my service at Grady Memorial Hospital—we created thoracic duct fistulas. Lymph was collected, and then determinations of antibiotic concentration were made. For most aminoglycosides as well as for most of the cephalosporins, blood levels far exceeded the lymph concentrations.

(slide) However, when cefamandole was administered, lymph levels were significantly greater than were those in the blood. In fact, such averaged 280% greater. We have no good explanation, but it does appear that cefamandole has this unique ability either to be secreted actively or somehow transported in the peripancreatic lymph in far greater concentrations than occur in the blood. It appears to be an active, not a passive mechanism.

Thus, the selection of cefamandole as the antibiotic in this setting was indeed a very fortuitous choice.

DR. JOHN G. N. STUDLEY (Closing discussion): This paper, I think, was bound to cause controversy in the choice of antibiotics, as evidenced by suggestions of clindamycin and penicillin, neither of which we mentioned in our study.

We found that the concentration of Tobramycin in the pancreatic fluid would be high enough for bactericidal activity against most of its sensitive bacteria. However, we feel that combination therapy with an antibiotic which acts in synergy with Tobramycin is indicated, as lower concentrations of both drugs would then be needed for bactericidal activity.

Such an antibiotic would be Cephamandole, which, if it were excreted in the pancreatic juice, would not only act in synergy with Tobramycin, but also cover many of the bacteria isolated in pancreatic abscesses, as shown here.

(slide) As you can see, Tobramycin with Cephamandole would probably provide bactericidal activity against all of these bacteria. I would also like to mention that the streptococcus would be covered by Cephamandole and penicillin would therefore not be necessary.

Other evidence concerning Cephamandole is that we have repeated this study using this antibiotic, and found that it is excreted in the pancreatic juice in reasonable concentrations. Finally, Dr. Harlan Stone has mentioned that the lymph concentration of Cephamandole is greatly increased when this antibiotic is administered to patients with severe pancreatitis.

As regards the question about what's going to happen in serious forms of the disease, the answer to that is: I really don't know. This study was designed to elucidate which antibiotics were excreted in the pancreatic fluid in the milder forms of pancreatitis, in the hope that they could be used to prevent progression to serious forms of disease.