

Comparative Study of Bentiromide Test and Endoscopic Retrograde Pancreatography in Patients with Chronic Pancreatitis

Jae Bock Chung, Seung Woo Park, Si Young Song,
Young Myung Moon, Jin Kyung Kang, and In Suh Park

We performed a bentiromide test in 25 patients with chronic pancreatitis and 7 normal controls to evaluate pancreatic exocrine function, and compared the test results of patients with their endoscopic retrograde pancreatography(ERP) findings. The cumulative 6-hour recovery rate of para-aminobenzoic acid(PABA) in the urine was significantly lower in patients with chronic pancreatitis($55.8 \pm 24.2\%$) than in controls($82.0 \pm 10.0\%$). Among 25 patients with chronic pancreatitis, however, 7 patients showed normal recovery rates of PABA. Pancreatograms of the patients represented 4 mild changes, 5 moderate changes, and 16 marked changes. The average 6-hour recovery rates of PABA of the groups were $56.9 \pm 21.6\%$, $78.4 \pm 10.5\%$, and $47.2 \pm 23.7\%$, respectively. Urinary PABA recovery rates were found subnormal as follows: 3(75%) in the mild changes group; 1(20%) in the moderate changes group; and 14(87.5%) in the marked changes group. We found hardly any correlation between the degree of functional impairment and the changes noted by ERP. These findings suggest that both the pancreatic function test and morphologic study are required to evaluate the degree of functional impairment in patients with chronic pancreatitis.

Key Words: Bentiromide test, PABA, endoscopic retrograde pancreatography

Pancreatic exocrine function can be evaluated by various methods such as Lundh's meal test, the pancreozymin-secretin(P-S) test, and the bentiromide test. The P-S test has been known to be the most precise method of all(Nakano *et al.* 1974; Ronly *et al.* 1978; Braganza *et al.* 1982), but it needs duodenal intubation. However the bentiromide test, a pancreatic exocrine function test, does not require duodenal intubation(Kato *et al.* 1977; Imamura *et al.* 1978; Delchier and Soule, 1983; Tanner and Robin-

son, 1988), and thus inflicts little pain on patients.

A few researchers have reported that the results of the bentiromide test had a good correlation with the P-S test(Imamura *et al.* 1978; Hoek *et al.* 1981; Weizman *et al.* 1985; Berg *et al.* 1986). The advent of endoscopic retrograde pancreatography(ERP) provided the opportunity to analyze the secretory abnormalities of patients with chronic pancreatitis with reference to alterations in pancreatic ductal morphology. A precise relationship between exocrine functional impairment and pancreatic ductal morphology, obtained by ERP in chronic pancreatitis, has not hitherto been established. In order to demonstrate its clinical usefulness, we performed the bentiromide test in 25 patients with chronic pancreatitis and compared the results with the ERP findings.

Received November 4, 1997

Accepted December 8, 1997

Department of Internal Medicine, Institute of Gastroenterology, Yonsei University College of Medicine, Seoul, Korea

Address reprint request to Dr. J.B. Chung, Department of Internal Medicine, Yonsei University College of Medicine, C.P.O. Box 8044, Seoul 120-752, Korea

MATERIALS AND METHODS

Included subjects were 25 patients with chronic pancreatitis who showed definite pancreatic ductal morphologic changes by Cambridge classification (Axon *et al.* 1984) on ERP performed at Severance Hospital in Seoul, Korea from 1991 to 1993. Along with the patients, 7 controls underwent the identical test. The mean age of patients was 48.0 ± 12.4 years (ranging from 27 to 75) and the group consisted of 19 males and 6 females. The mean age of controls was 28.7 ± 9.4 years with 5 males and 2 females.

For 25 patients, using an Olympus JF 20 or JF 200 side-viewing duodenoscope, we carried out ERP by the standard method. All patients were premedicated with atropine and 60% Urografin was utilized as a contrast medium. The pancreatograms were categorized as mild(normal main pancreatic duct and 3 or more abnormal side branches), moderate(abnormal main pancreatic duct and more than 3 abnormal side branches), or marked(abnormal main pancreatic duct, more than 3 abnormal side branches and one or more of: large cavity, obstruction, filling defects, severe dilatation or irregularity) changes by Cambridge classification(Axon *et al.* 1984).

The bentiromide test was performed in the usual way. All drugs were discontinued at least 48 hours before and during the test. All subjects were made to fast overnight and voided urine prior to the test. Under these conditions, N-benzoyl-L-tyrosyl-para-aminobenzoic acid(NBT-PABA, 15 mg/kg) was administered orally with 200 ml of water. Urine samples were collected for 6 hours after administration

of NBT-PABA. Urinary PABA concentration was determined by spectrometry under the DACA method, in which para-dimethylamino cinnamaldehyde is used as a coloring agent. Then the cumulative 6-hour recovery rate of PABA in the urine was calculated. The results of the bentiromide test were compared with the pancreatic ductal abnormalities in each patient.

Kruskal-Wallis test and Mann-Whitney U test were used to analyze the mean differences. In order to analyze the relationship between pancreatic ductal changes and pancreatic exocrine function, linear regression analysis was carried out.

RESULTS

The cumulative 6-hour recovery rate of PABA in the urine is shown in Table 1 and Fig. 1. The patients with chronic pancreatitis had a rate of $55.8 \pm 24.2\%$, which was significantly lower than that of the control group($82.0 \pm 10.0\%$). Among the 25 patients, however, 7 revealed a normal PABA recovery rate. According to the Cambridge classification, the pancreatograms of the patients were categorized as mild changes in 4 patients, moderate changes in 5 patients, and severe changes in 16 patients. In the mild-changes group, the average 6-hour recovery rate of PABA was $56.9 \pm 21.6\%$ with subnormalities in 3(75%) patients, while in the marked-changes group, the average was $47.2 \pm 23.7\%$ with subnormalities in 14(87.5%) patients. The values of both

Table 1. The average cumulative 6-hour PABA recovery rate in urine according to changes revealed by ERP

	No. of cases	6-hour urine PABA recovery rate(%)
Control	7	82.0 ± 10.0
Chronic pancreatitis	25	
Mild changes	4	$56.9 \pm 21.6^*$
Moderate changes	5	78.4 ± 10.5
Marked changes	16	$47.2 \pm 23.7^*$

*: $P < 0.05$ vs. control

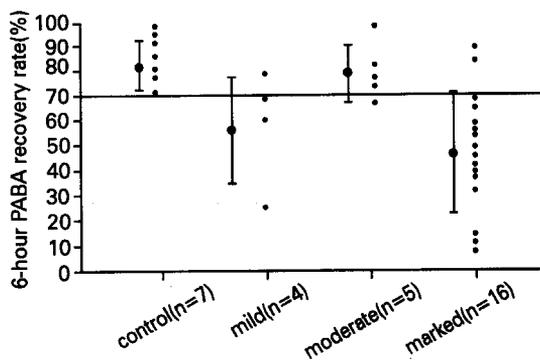


Fig. 1. Distribution of cumulative 6-hour PABA recovery rate in urine of patients with chronic pancreatitis.

mild- and marked-changes groups were significantly lower than those in the control group. In the moderate-changes group, however, the urinary PABA recovery rate of $78.4 \pm 10.5\%$, with a subnormality in only 1(20%) patient, implied a statistically insignificant value compared to the control group. Among the various pancreatogram-based groups, there was no significant difference in the 6-hour recovery rate of PABA in the urine. In addition, the percent recovery rate of PABA in 25 patients with chronic pancreatitis had no correlation with the pancreatic ductal changes obtained by ERP.

DISCUSSION

Among the various pancreatic exocrine function tests, the traditional pancreozymin-secretin test(P-S test) is the best-known for its precision. It has been reported that the P-S test has a sensitivity of 85 to 90%, and a specificity of 80 to 90%(Nakano *et al.* 1974; Braganza *et al.* 1982; Malfertheiner *et al.* 1986). Hayakawa *et al.* concluded that the results of the P-S test had a precise relationship with the pancreatic ductal morphologic changes demonstrated by ERP(Hayakawa *et al.* 1992). The test, however, causes pain to patients because it requires duodenal intubation. The analytic method is also somewhat intricate and it is less readily available in institutions. The bentiromide test used in this study, reported by Kato *et al.* has been known as a non-invasive method for the evaluation of pancreatic exocrine function(Kato *et al.* 1977). After being ingested, NBT-PABA is specifically broken down by pancreatic chymotrypsin with the liberation of PABA. Released PABA is absorbed through the digestive tract and excreted by the kidneys after conjugation in the liver. Therefore, measurement of PABA in the urine after administration of NBT-PABA indirectly reflects exocrine function.

In this study, we administered the bentiromide test to 25 patients who had shown definite ductal changes due to chronic pancreatitis on ERP. The urinary PABA recovery rate was significantly lower in the patient group than in the control group. However, 7 patients had a recovery rate of more than 70% of PABA. Compared to the P-S test or

Lundh's test, whose sensitivities are both over 85%, the bentiromide test seems to be less sensitive (Delchier and Soule, 1983; Tanner *et al.* 1984), which may result from the nature of the test, measuring only the activity of chymotrypsin. Though not as sensitive or specific as the P-S test, but considering the fact that the bentiromide test is less annoying and that it is relatively simple to analyze the specimen, the test can be useful for those who are unsuitable for an invasive diagnostic test. In addition, the sensitivity and specificity of the bentiromide test can be improved by combined measurement of serum PABA concentration(Weizman *et al.* 1985; Tanner *et al.* 1988). In a comparative study, the results of the bentiromide test were well correlated with that of the P-S or Lundh's test; Imamura *et al.*(1978) reported that bicarbonate concentration and amylase output measured by the P-S test were correlated with the 8-hour urinary recovery rate of PABA, and Hoek *et al.*(1981) concluded that trypsin activity measured by Lundh's test was correlated with the result of the bentiromide test.

Though not yet established, pancreatic bicarbonate secretion and digestive enzyme activity appear to decrease in proportion to the degree of destructive changes of pancreatic parenchymal tissue observed in histologic study(Hayakawa *et al.* 1992). Thus, some researchers have investigated the possible relationship between pancreatic ductal changes, which are expected to reflect parenchymal damage, and pancreatic exocrine function. Oguri concluded that a linear relationship could be found between the degree of abnormalities in the pancreatograms obtained by ERP and the following: the degree of reduction of volume output, maximal bicarbonate concentration, and amylase output measured during the P-S test(Oguri, 1979). Especially, bicarbonate excretion was found to have a precise correlation with ductal changes by Malfertheiner *et al.*(1986). Braganza *et al.* also supported the findings of Oguri(Oguri, 1979; Braganza *et al.* 1982). Contrary to their suggestions, however, Nakano *et al.*(1974) reported that a considerable discrepancy existed between morphological and functional tests and that the pancreatic function test had no value. Similarly, Elsberg *et al.* could not find any relationship between ERP and the P-S test(Elsberg *et al.* 1981). In our study, the degree of ductal morphological

changes had no correlation with the amount of decrease in urinary PABA recovery. There was also a wide overlap in the urinary PABA recovery rate between the various groups categorized by the ERP findings. For example, only 1 of 5 patients with moderate ductal changes revealed the decreased urinary PABA recovery rate, and 2 of 16 patients with marked changes even revealed a normal recovery rate. If the relationship between ductal changes and exocrine function impairment is to be established, it is inferred from our results that a comparison of exocrine function with pancreatic histology, as well as with ductal morphologic changes, should be performed simultaneously. According to Braganza *et al.* pancreatic ductal changes were closely associated with the amount of bicarbonate output (Braganza *et al.* 1982). In addition, Ronly *et al.* stated that the output of pancreatic enzyme did not precisely reflect the exocrine functional impairment (Ronly *et al.* 1978). In our study the bentiromide test, which entirely depends on the pancreatic enzyme chymotrypsin, may not have accurately detected mild functional impairment. As mentioned previously, some of the patients with relatively preserved ductal morphology revealed severely impaired exocrine function, while some with far-advanced ductal abnormalities revealed the normal exocrine function. These findings are thought to result from several factors: first, the disease process of chronic pancreatitis is inherently uneven (Sarles, 1986); second, both acinar and ductal structures are not uniformly affected (Braganza *et al.* 1975; Sarles, 1986); third, primarily the small duct can be destroyed while the main pancreatic duct is relatively spared (Braganza *et al.* 1975); fourth, the adaptive parenchymal hypertrophy of relatively uninvolved tissue may compensate the impairment of exocrine function (DiMagno *et al.* 1979; Braganza *et al.* 1982). Thus, it can be inferred from this discussion that both morphologic study of the pancreatic duct and an exocrine function test are required to evaluate the degree of progress in chronic pancreatitis.

In conclusion, the bentiromide test is considered to be useful in evaluating pancreatic exocrine function in patients with chronic pancreatitis, especially those who cannot tolerate an invasive test. However, because there is a large discrepancy between ductal morphologic changes and exocrine functional im-

pairment, it is recommended to conduct both tests in order to accurately assess the degree of progression in patients with chronic pancreatitis.

REFERENCES

- Axon ATR, Classen M, Cotton PB, Cremer M, Freeny PC, Lees WR: Pancreatography in chronic pancreatitis: international definitions. *Gut* 25: 1107-1112, 1984
- Berg JD, Chesner IM, Allen-Narker RAC, Buckley BM, Lawson N: Exocrine pancreatic function as determined in a same-day test with use of bentiromide and p-aminosalicylic acid. *Clin Chem* 32: 1010-1012, 1986
- Braganza JM, Howat HT, Kay G: The relative potency of the Crick-Harper-Raper unit and the GIH clinical units of secretin. *Gut* 16: 549-552, 1975
- Braganza JM, Hunt LP, Warwick F: Relationship between pancreatic exocrine function and ductal morphology in chronic pancreatitis. *Gastroenterology* 82: 1341-1347, 1982
- Delchier JC, Soule JC: BT-PABA test with plasma PABA measurements: evaluation of sensitivity and specificity. *Gut* 24: 318-325, 1983
- DiMagno EP, Malagelada JR, Go VLW: The relationship between pancreatic ductal obstruction and pancreatic secretion in man. *Mayo Clin Proc* 54: 157-175, 1979
- Elsborg L, Bruusgaard A, Strandgaard L, Reiniche V: Endoscopic retrograde pancreatography and the exocrine pancreatic function in chronic alcoholism. *Scand J Gastroenterol* 16: 941-944, 1981
- Hayakawa T, Kondo T, Shibata T, Noda A, Suzuki T, Nakano S: Relationship between pancreatic exocrine function and histological changes in chronic pancreatitis. *Am J Gastroenterol* 87: 1170-1174, 1992
- Hoek F, Sanders GTB, Teunen A, Tytgat GNJ: In vitro and in vivo analysis of the PABA test compared with the Lundh test-influence of intraluminal pH. *Gut* 22: 8-14, 1981
- Imamura K, Nakamura T, Miyazawa T, Abe Y, Kobayashi M, Takebe K, Toyota T: Oral administration of chymotrypsin labile peptide for a new test of exocrine pancreatic function (PFT) in comparison with pancreozymin-secretin test. *Am J Gastroenterol* 69: 572-578, 1978
- Kato K, Izumiya S, Sakakura M, Hirayama A, Ishii K: Study on the exocrine pancreatic function by the oral administration of N-benzoyl-L-tyrosyl-para-aminobenzoic acid. *Gastroenterol Jpn* 12: 289-292, 1977
- Malfertheiner P, Buchler M, Stanescu A, Ditschuneit H: Exocrine pancreatic function in correlation to ductal and parenchymal morphology in chronic pancrea-

- titis. *Hepato-gastroenterol* 33: 110-114, 1986
- Nakano S, Horiguchi Y, Takeda T, Suzuki T, Nakajima S: Comparative diagnostic value of endoscopic pancreatography and pancreatic function test. *Scand J Gastroenterol* 9: 383-389, 1974
- Oguri T: *Statistical evaluation on the correlation between endoscopic retrograde cholangiopancreatography and pancreozymin secretin test-structure and function in chronic pancreatitis*. In Takemoto T, Kasugai T, eds. *Endoscopic retrograde cholangiopancreatography*. Tokyo, Igaku-Shoin, 1979, 48-57
- Ronly P, Lukes PJ, Gamklou R, Jagenburg R, Nilson A: A comparative evaluation of endoscopic retrograde pancreatography and secretin-CCK test in the diagnosis of pancreatic disease. *Scand J Gastroenterol* 13: 777-781, 1978
- Sarles H: Etiopathogenesis and definition of chronic pancreatitis. *Dig Dis Sci* 31: 91S-107S, 1986
- Tanner AR, Fisher D, Ward C, Smith CL: An evaluation of the one-day NBT-PABA/¹⁴C-PABA in the assessment of pancreatic exocrine insufficiency. *Digestion* 29: 42-46, 1984
- Tanner AR, Robinson DP: Pancreatic function testing: serum PABA measurement is a reliable and accurate measurement of exocrine function. *Gut* 29: 1736-1740, 1988
- Weizman Z, Forstner GG, Gaskin KJ, Kopelman H, Wong S, Durie PR: Bentiromide test for assessing pancreatic dysfunction using analysis of para-aminobenzoic acid in plasma and urine. *Gastroenterology* 89: 596-604, 1985