Significance of Gastric Analysis with Particular Reference to the Diagnosis of Zollinger-Ellison Syndrome

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ISHIMORI, A., MIURA, Y., SAKURADA, H., YAMAGATA, Su., TSUDA, K., KAWAMURA, T., ARAKAWA, H. and YAMAGATA, S. *Significance of Gastric Analysis with Particular Reference to the Diagnosis of Zollinger-Ellison Syndrome.* Tohoku J. exp. Med., 1975, 117 (1), 15-21 — Various criteria in gastric analysis currently used for the diagnosis of the Zollinger-Ellison syndrome were assessed in cases of endoscopically normal gastric mucosa, gastric ulcer and duodenal ulcer. New criteria consisting of $BSV > 350$ ml/hr, $BAO > 25$ mEq/hr, $MAO > 60$ mEq/hr, and $BAO/MAO > 0.7$ were proposed to differentiate the Zollinger-Ellison syndrome and peptic ulcer. ——— gastric analysis; BAO; MAO; peptic ulcer; Zollinger-Ellison syndrome

Although it requires further confirmation by finding a high level of circulating gastrin, the diagnostic value of gastric analysis using certain criteria has been stressed for differentiating the Zollinger-Ellison syndrome from ordinary peptic ulcer (Marks et al. 1961; Segal 1965; Aoyagi and Summerskill 1966; Ruppert et al. 1967; Zollinger and Moore 1968). However, it has been pointed out that some of these criteria sometimes give false positive results in patients with duodenal ulcer (Kaye et al. 1970), as well as false negative results in patients with the Zollinger-Ellison syndrome (Lewin et al. 1973). The present study concerns an examination of these criteria in cases not only of duodenal ulcer, but also of gastric ulcer and endoscopically normal gastric mucosa, with particular reference to the diagnosis of the Zollinger-Ellison syndrome.

METHODS

Subjects. All cases were examined endoscopically as well as radiologically and divided into three distinct groups. They were 235 cases of endoscopically normal gastric mucosa without any upper gastrointestinal abnormalities, 83 cases of active gastric ulcer and 75 cases of active duodenal ulcer. The absence of anemia, electrolyte imbalance and other abnormalities which may influence gastric secretion was confirmed in all these cases.

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Gastric analysis. Following one hour basal secretion, AOC-tetrapeptide, 4 $\mu\text{g}/\text{kg}$ body weight, was injected subcutaneously and the collection of gastric juice was continued for another one hour (Yamagata et al. 1970). Throughout the test, gastric juice was collected by continuous suction with an aspirator (Yayoi Co., Ltd., Tokyo) and was pooled every 10 minutes. Acidity was measured by titration to pH 7.0 using an automatic pH-stat (model HM-5A and HS-2A of TOA Electronics, Ltd., Tokyo).

RESULTS

The present study deals with the following five criteria recommended for the diagnosis of the Zollinger-Ellison syndrome: namely, basal secretion volume (BSV), basal acid output (BAO), maximal acid output (MAO), ratio of basal to maximal acid output (BAO/MAO), and ratio of basal to stimulated acid concentration (BAC/MAC).

Fig. 1 shows percentages of positive cases on different diagnostic criteria of BSV in the three groups. The asterisk represents the percentage on the criterion, $\text{BSV} > 100 \text{ ml/hr}$, which has been proposed by Zollinger and Moore (1968). When this criterion was employed, false positive results were obtained in 31.5% of the cases of endoscopically normal gastric mucosa, in 39.8% of the gastric ulcer patients, and in 66.7% of the duodenal ulcer patients, respectively.

Fig. 2 demonstrates similar results for BAO. The criterion, $\text{BAO} > 15 \text{ mEq/hr}$, recommended by Aoyagi and Summerskill (1966) yielded 1.0% of false positive results in the cases of endoscopically normal mucosa, 1.2% in the gastric ulcer patients, and 8.0% in the duodenal ulcer patients. When another recommended

Fig. 1. Examination of criteria of basal secretion volume (BSV) in gastric analysis for diagnosis of the Zollinger-Ellison syndrome. The asterisk represents the criterion proposed by Zollinger and Moore ($\text{BSV} > 100 \text{ ml/hr}$). Each group was expressed in the following manner in Figs. 1 through 5.

□, cases of endoscopically normal gastric mucosa; ▤, cases of gastric ulcer; ▨, cases of duodenal ulcer.

Fig. 2. Examination of criteria of basal acid output (BAO) in gastric analysis for diagnosis of the Zollinger-Ellison syndrome. The asterisk and dagger represent the criteria proposed by Aoyagi and Summerskill ($\text{BAO} > 15 \text{ mEq/hr}$), and Segal ($\text{BAO} > 20 \text{ mEq/hr}$), respectively.

Fig. 3. Examination of criteria of maximal acid output (MAO) in gastric analysis for diagnosis of the Zollinger-Ellison syndrome. The asterisk represents the criterion proposed by Segal ($\text{MAO} > 60 \text{ mEq/hr}$).

criterion, $\text{BAO} > 20 \text{ mEq/hr}$ (Segal 1965), was used, the false positive results diminished to 0.4%, 0%, and 2.6%, respectively.

The recommended criterion, $\text{MAO} > 60 \text{ mEq/hr}$ (Segal 1965), was found to be so strict that none of our cases studied exceeded this figure, as shown in Fig. 3.

Fig. 4. Examination of criteria of BAO/MAO in gastric analysis for diagnosis of the Zollinger-Ellison syndrome. The asterisk represents the criterion proposed by Marks et al. (BAO/MAO > 0.6).

Fig. 5. Examination of criteria of BAC/MAC in gastric analysis for diagnosis of the Zollinger-Ellison syndrome. The asterisk represents the criterion proposed by Ruppert et al. (BAC/MAC > 0.6).

Results on BAO/MAO were treated in the same way and illustrated in Fig. 4. False positive cases on the recommended criterion, BAO/MAO > 0.6 (Marks et al. 1961), were seen in 14.1% of the cases of endoscopically normal gastric mucosa, in 4.8% of the gastric ulcer patients, and in 5.3% of the duodenal ulcer patients.

Fig. 5 shows that the highest false positive result of 34.7% was obtained in

Fig. 6. Classification of cases according to the number of fulfilled criteria in gastric analysis. ■, 4 criteria fulfilled; ▨, 3 criteria fulfilled; ▤, 2 criteria fulfilled; ▩, 1 criterion fulfilled; □, none of the criteria fulfilled.

the duodenal ulcer patients on the criterion of $BAC/MAC > 0.6$ recommended by Ruppert et al. (1967).

In Fig. 6, the cases in each group are classified according to the number of criteria fulfilled. Here, $BAO > 20$ mEq/hr was adopted as the recommended criterion instead of $BAO > 15$ mEq/hr. It is shown that none of our cases fulfilled all of the five recommended criteria. One out of 75 duodenal ulcer patients (2%) and 1 out of 235 cases of endoscopically normal gastric mucosa (0.4%) fulfilled 4 recommended criteria but $MAO > 60$ mEq/hr. 3 recommended criteria were fulfilled in 14 cases of endoscopically normal gastric mucosa (6%), in 1 duodenal ulcer patient (1%), and 4 gastric ulcer patients (4%).

DISCUSSION

Kaye et al. (1970) expressed the view concerning the diagnostic value of gastric analysis that none of the criteria currently used for the diagnosis of the Zollinger-Ellison syndrome is entirely reliable in the differentiation of this syndrome from ordinary duodenal ulcer because of the overlap. They examined 3 criteria; namely, basal acid output > 15 mEq/hr (Aoyagi and Summerskill 1966), ratio of basal to stimulated acid output > 0.6 (Marks et al. 1961), and ratio of basal to stimulated acid concentration > 0.6 (Ruppert et al. 1967).

In the present study 2 other criteria, namely basal secretion volume > 100 ml/hr (Zollinger and Moore 1968) and maximal acid output > 60 mEq/hr (Segal 1965) were examined further, and the effect of changing values of these criteria was also studied. It should be also mentioned that cases of endoscopically normal gastric mucosa were tested in this study in addition to patients with gastric ulcer and duodenal ulcer for comparison.

The incidence of false positive results for 3 criteria ($BAO > 15$ mEq/hr, $BAO/MAO > 0.6$, $BAC/MAC > 0.6$) obtained in the present cases of duodenal ulcer seems to be somewhat higher than that reported by Kaye et al. (1970) and Lewin et al. (1973). A high incidence of false positive results was also obtained for the

criterion, $BSV > 100$ ml/hr. Therefore these criteria could not be regarded as strict enough for the differentiation of duodenal ulcer and the Zollinger-Ellison syndrome. Necessary changes for these criteria in order to exclude duodenal ulcer from the Zollinger-Ellison syndrome would be $BAO > 25$ mEq/hr, $BAO/MAO > 0.7$, $BAC/MAC > 1.0$ and $BSV > 350$ ml/hr according to the results obtained in the present study. Although the proposition of $BAC/MAC > 1.0$ seems to be problematic, these figures exclude most cases of duodenal ulcer reported by Kaye et al. (1970).

However, the situation is quite different as to MAO. The criterion, $MAO > 60$ mEq/hr, was not fulfilled by all of our cases. Only 1 case out of the 235 cases of endoscopically normal gastric mucosa and 1 case out of 75 duodenal ulcer patients exceeded 40 mEq/hr of MAO, but none of the gastric ulcer patients did in this study. However, the change of this criterion is not practical, since several duodenal ulcer patients reported by Kaye et al. (1970) secreted more than 60 mEq/hr of acid after the maximal stimulation. It should be mentioned in this regard that there would be some variation in MAO depending on race, sex, age, etc.

It is interesting to see how patients with the Zollinger-Ellison syndrome fulfill these newly proposed criteria, but it is clear that the application of our new criteria would increase the incidence of false negative results. Nevertheless, the new criteria will provide a strong support to establish the diagnosis of the Zollinger-Ellison syndrome, especially when radioimmunoassay of gastrin is not available. Furthermore, as shown in Fig. 6, the diagnostic value of gastric analysis will obviously be increased when several criteria are combined together for the judgement, as already pointed out (Lewin et al. 1973).

It has been reported that basal acid secretion can vary widely in some patients with the Zollinger-Ellison syndrome (Winship and Ellison 1967). This corresponds to the variability of blood gastrin level in some of patients with this syndrome (Thompson et al. 1972). Therefore, repeated gastric analysis will be required sometimes to confirm the diagnosis. In other words, even a positive result for any one of the five criteria proposed here should indicate the necessity for further examination. However, because of the false positive results observed in the cases of endoscopically normal gastric mucosa and in the gastric ulcer patients, it should be mentioned that the diagnostic value of the proposed criterion, $BAO/MAO > 0.7$, is to be limited to hypersecretors.

References

- 1) Aoyagi, T. & Summerskill, W.H.J. (1966) Gastric secretion with ulcerogenic islet cell tumor. *Arch. intern. Med.*, **117**, 667-672.
- 2) Kaye, M.D., Rhodes, J. & Beck, P. (1970) Gastric secretion in duodenal ulcer with particular reference to the diagnosis of Zollinger-Ellison syndrome. *Gastroenterology*, **58**, 476-481.
- 3) Lewin, M.R., Stagg, B.H. & Clark, C.G. (1973) Gastric acid secretion and diagnosis of Zollinger-Ellison syndrome. *Brit. med. J.*, **2**, 139-141.
- 4) Marks, I.N., Selzer, G., Louw, J.H. & Bank, S. (1961) Zollinger-Ellison syndrome in a Bantu woman, with isolation of a gastrin-like substance from the primary and

- secondary tumors. *Gastroenterology*, **41**, 77-86.
- 5) Ruppert, R.D., Greenberger, N.J., Beman, F.M. & McCullough, F.M. (1967) Gastric secretion in ulcerogenic tumors of the pancreas. *Ann. intern. Med.*, **67**, 808-815.
 - 6) Segal, H.L. (1965) Physiology of gastric secretion. *Amer. J. Gastroent.*, **44**, 423-430.
 - 7) Thompson, J.C., Reeder, D.D. & Bunchman, H.H. (1972) Clinical role of serum gastrin measurements in the Zollinger-Ellison syndrome. *Amer. J. Surg.*, **124**, 250-261.
 - 8) Winship, D.H. & Ellison, E.H. (1967) Variability of gastric secretion in patients with and without the Zollinger-Ellison syndrome. *Lancet*, **1** 1128-1130.
 - 9) Yamagata, S., Masuda, H., Ishimori, A., Inoue, S., Wada, T., Sato, K., Kinoshita, H., Nose, T., Masuda, M., Kawai, K., Uematus, T., Sato, H., Yunoki, K. & Sasahira, S. (1970) Gastric secretion stimulated by gastrin-like AOC-tetrapeptide. *Tohoku J. exp. Med.*, **101**, 103-117.
 - 10) Zollinger, R.M. & Moore, F.T. (1968) Zollinger-Ellison syndrome comes of age. — Recognition of the complete clinical spectrum and its management. *J. Amer. med. Ass.*, **204**, 361-365.
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