別記様式第 6 号（第 16 条第 3 項、第 25 条第 3 項関係）

論 文 審 査 の 結 果 の 要 旨

博士の専攻分野の名称	博士（　医学　）	氏名	MAIDINA ABUDUWAILI
学 位 授 与 の 条 件	学位規則第 4 条第①・2 項該当		

論　文　題　目
Serum Gastrin and Pepsinogen Levels after Administration of Acid Secretion Inhibitors for Ulcers due to Endoscopic Submucosal Dissection in Patients with Early Gastric Cancer
（早期胃癌患者における内視鏡的粘膜下層剥離術による潰瘍に対する酸分泌抑制剤投与後の血清ガストリンおよびペプシノーゲン値について）

論文審査担当者

主　　査　　教授　　大毛　宏喜　　印

審査委員　　教授　　大上　直秀

審査委員　　講師　　仙谷　和弘

〔論文審査の結果の要旨〕

Gastrin is an important gastrointestinal hormone involved in gastric acid secretion. It is synthesized and secreted by G cells in the gastric pylorus and duodenum, and acts on the wall cells of the gastric body to promote gastric acid secretion. Though, gastrin has been well-known to increase in Zollinger-Ellison syndrome and autoimmune gastritis and measured in clinical practice, the measurement assay was different between Japan and western countries. Total gastrin assay and G17 assay have been used in Japan and western countries, respectively. However, the correlation between these two assays have not been clarified yet.

Recently, gastrin levels have been reported to increase after administration of proton pump inhibitors (PPIs) due to a negative feedback function to gastric acid secretion inhibition. When the endoscopic submucosal dissection (ESD) is performed for gastric tumors, acid secretion inhibitors such as PPI are used to treat ulcers after ESD.

In 2014, a new category of acid secretion inhibitors called potassium ion-competitive acid blocker (P-CAB) became available, expanding treatment options. However, the amount of change in serum gastrin levels before and after use has been not clear. On the other hand, both PPI and P-CAB have a strong acid secretion inhibitory effect, and there is a concern that they increase serum gastrin levels, which play an important role in the progression of gastrointestinal cancer.

The purpose of this paper was to investigate the effects of acid secretion inhibitors on serum gastrin, pepsinogens, and G17 levels, further examined the associated factors of these alterations.

Between July 2017 and March 2019, the author enrolled 167 patients at Hiroshima University Hospital who had blood tests before and after ESD for gastric cancer. Patients were excluded for PPI or P-CAB usage before ESD. To

analyze the extent of changes in G17, and pepsinogen produced by acid inhibitors, the levels of these blood markers were compared before and after administration. The median amount of change in gastrin and PG levels were used to classify the group as large if it was higher than the median value (Large group) and small if it was lower (Small group). Associated factors with the elevation of serum markers were compared between the two groups.

Additionally, to examine the changes in G17 levels before and after administration, 10 cases from PPI group and 10 cases from P-CAB group were randomly selected for analysis. Fasting serum were collected on the day of the ESD and 4 weeks later and stored at -20 °C until analysis. The levels of serum gastrin (using Gastrin RIA Kit II; Dainabot, Tokyo, Japan), G17 (using Gastrin-17 Advanced ELISA, Biohit, Finland), and PG (using LZ test; Eiken, Tokyo, Japan) and the anti-*H. pylori* antibody titers (using E-plate; Eiken, Tokyo, Japan) were evaluated

After treatment with the PPI and P-CAB, the gastrin, PGI, and PGII levels increased. Before the administration of acid-secretion inhibitors, the median levels of serum gastrin, PGI, and PGII were 110.5 pg/mL , 36.4 ng/mL, and 8.9 ng/mL, respectively. After administration, the levels significantly increased to 300 (a 167.5-pg/mL increase) pg/mL, 64.7 (a 24.5-ng/mL increase) ng/mL, and 15.8 (a 5.05-ng/mL increase) ng/mL, respectively. The serum G17 level significantly increased (Wilcoxon's signed-rank test $P<0.001$) after administration of the PPI and P-CAB. An examination between the total gastrin and serum G17 levels revealed a correlation ($r=0.85$, $P<0.001$), and the G17 level was approximately 20% of the total gastrin fraction.

The "Large group" and "Small group" classified according to fluctuation of gastrin value and pepsinogen value were then compared to examine the host factors that contributed to the differences in the extent of changes in the gastrin and PG levels. In the case of gastrin, 89% of the patients in the Large group used PCAB; the PCAB usage was significantly higher in the Large group than in the Small group ($P=0.001$). Univariate analysis revealed that the drug type was the only host factor that contributed to an increased level of gastrin.

This paper revealed the correlation between gastrin and G17, which demonstrated the validity of gastrin assay which has been used in Japan. Furthermore, in population having high potential of carcinogenesis who had developed gastric cancer and undergone gastric ESD, P-CAB resulted in a rapid increase of gastrin compared to PPI. This point should be considered when selecting acid secretion inhibiters like PPI and P-CAB. As for carcinogenesis risk by long term administration of P-CAB, further study is needed.

This paper greatly contributed for the understanding the influence of acid secretion inhibitor to gastrin expression in patients' serum and provided the important data for future research and clinical practice by showing the correlation of two gastrin measurement assays which differ between in Japan and in western countries. Therefore, all the committee members admitted that this paper is of sufficient value to confer the author in Medical Science.