〔短　　報〕

A Survey on Prescriptions of Gastric Secretion Inhibitors during the Proton Pump Inhibitor Supply Restriction

注射用プロトンポンプ阻害薬供給停止時の胃酸分泌抑制薬処方量の推移

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Summary：Over recent years, achieving a stable supply of medicines has become difficult in Japan for various reasons. In October 2021, the supply of original brand-name injectable omeprazole, an intravenous proton pump inhibitor (PPI), was suspended on the Japanese market. Consequently, even though the brand-name injectable omeprazole was not adopted, the supply of two injectable PPIs used at the University of the Ryukyus Hospital was restricted. Eventually, the supply was discontinued until the end of June 2022. In response, a switch to alternative injectable and oral gastric secretion inhibitors was recommended at the University of the Ryukyus Hospital. In this study, the volume of gastric secretion inhibitors prescriptions was surveyed to determine the status of alternative drug prescriptions when the supply of intravenous PPIs was discontinued. The volume of intravenous and oral gastric secretion inhibitors prescriptions in hospitals was examined before and after the restriction on the supply of intravenous PPIs. Data were extracted from electronic medical records. During the suspension of the PPI injection supply, the number of prescriptions for injectable omeprazole and lansoprazole significantly decreased (*P* value: <0.001 and <0.001), whereas the number of prescriptions for injectable H_2-receptor inhibitors significantly increased (*P* value: <0.001). No significant changes in the number of prescriptions for oral gastric secretion inhibitors were observed. The study results highlight the importance of maintaining a stable supply of drugs administered via the same route, even when the same drugs that can be administered through other routes are available.

Key words：proton pump inhibitor, H_2-receptor inhibitor, stable supply, original brand drugs, generic drugs

要旨：【背景】近年，本邦では様々な理由から医薬品の安定供給困難事例が多発している．2021 年 10 月，プロトンポンプ阻害薬（PPI）の先発品である注射用オメプラゾールの国内供給が停止された．その結果，先発品の注射用オメプラゾールの採用がないにも関わらず，琉球大学病院（当院）で使用されていた 2 種類の注射用 PPI の供給が制限され，2022 年 6 月末に院内供給が停止となり，代替の注射剤および経口胃酸分泌抑制剤への切り替えを推奨した．本研究では，PPI の注射製剤の供給が中止された際の代替薬の処方状況を明らかにするため，胃酸分泌抑制薬の処方量を調査検討した．
【方法】PPI の注射製剤の供給が制限された前後の当院における胃酸分泌抑制薬の注射剤および経口剤の処方量を調査した．データは電子カルテから抽出した．
【結果】PPI 注射剤の供給停止期間後，注射剤であるオメプラゾールおよびランソプラゾールの処方数は供給停止前に比べて有意に減少した（*P* 値：<0.001 および <0.001）が，注射剤である H_2 受容体拮抗剤の処方数は有意に増加した（*P* 値：<0.001）．経口胃酸分泌抑制薬の処方量には有意な変化は認められなかった．
【結論】本研究の結果として，他の経路で投与可能な同じ薬剤が入手可能な場合でも，同じ経路で投与される薬剤の安定供給を維持することの重要性が示唆された．

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Background

In Japan, government-led efforts have been expended to promote the use of generics and biosimilars. In particular, the "Roadmap for Further Use of Generic Drugs" was formulated in April 2013[1], and the volume share of generics reached 79.0% in September 2022[2]. Nonetheless, over recent years, achieving a stable supply of pharmaceuticals has become a problem in Japan, with problems in the procurement of active pharmaceutical ingredients[3] causing difficulties in the supply of cefazolin generic drug (GE) products in 2019[4, 5] and with several GE manufacturers being subjected to administrative punishment from 2021[6] owing to fraudulent manufacturing, resulting in product recalls and suspension of business; consequently, the GE supply has become unstable. Under these circumstances, the supply of brand-name injectable omeprazole, a proton pump inhibitor (PPI), was discontinued in October 2021[7]. The University of the Ryukyus Hospital had adopted omeprazole GE and Takepron®, an original intravenous lansoprazole product, as PPIs for injection, and the brand-name injectable omeprazole was not used. However, the supply of these adopted drugs also became unstable because of the increased domestic demand for injectable PPIs following the suspension of the supply of brand-name omeprazole product for injection, and the University of the Ryukyus Hospital was temporarily unable to meet the in-house demand. In response to this problem, we have announced and promoted changes for alternative drug prescriptions, not only in injectable formulations but also in oral formulations, considering that several gastric secretion inhibitors have been adopted in the hospital.

To date, no study has investigated whether the route of administration or same-component medicines are preferred for inducing a change to an allogeneic drug under a drug supply restriction. Therefore, the present study aimed to examine prescription fluctuations under injectable PPI supply instability and to investigate prescription trends for the same drug and similar drugs administered via different routes before and after a period of PPI supply suspension.

Methods

Study design

The surveillance covered the period around June 16, 2022 (from May 17, 2022, to August 9, 2022) when the supply of injectable PPIs was unstable. Data on prescription quantities (vials, ampoules, packets, tablets, and capsules) of injectable gastric secretion inhibitors (omeprazole, lansoprazole, and famotidine) and five of the most frequently prescribed oral gastric secretion inhibitors (esomeprazole, lansoprazole, rabeprazole, vonoprazan, and famotidine) used in our hospital in May 2022 were extracted from electronic medical records (MegaOakDWH, NEC Corp.). Ranitidine for injection, which had been adopted in our hospital, was excluded because it was no longer on the market. Oral raftidine was also excluded because the number of prescriptions was very small.

Statistical analysis

The statistical analysis was performed on two groups, before and after 30 days around June 16, 2022 (from May 17, 2022, to July 15, 2022). Parametric and nonparametric tests were performed for normally distributed and non-normally distributed data, respectively. The before and after groups were compared using Welch's *t*-test for parametric and unequal-variance data and the Mann-Whitney *U* test for nonparametric data. For multi-group analyses, the Kruskal-Wallis test was employed, followed by the Steel-Dwass test. Statistical analysis was performed using EZR version 1.55 (Saitama Medical Center, Jichi Medical University)[8], with statistical significance set at $P<0.05$.

Ethics approval

This study does not involve personal information.

Therefore, it does not constitute Medical or Health Research Involving Human Subjects.

Results

Supply of PPIs for injection and the response of the pharmacy department

Fig. 1 shows the PPI supply during the study period (from May 17 to August 9, 2022), as well as the response and notifications to the hospital from the pharmacy department. On June 3, 2022, the stock of 20 mg omeprazole for injection became unstable in the hospital owing to a supply adjustment. As the supply of the two adopted injectable PPIs was expected to be insufficient to meet the demand in the hospital from around June 16, the pharmacy department requested doctors and pharmacists in the hospital to consider switching to other drugs (e.g., injectable drugs with the same effect or oral drugs with the same component). The pharmacy department's request was not specified as a drug indication, and the drug indication was left to the physician's discretion. On June 27, orders in the electronic medical record system were suspended due to the end of in-hospital stocks of injectable PPIs. On July 1, prescription orders were resumed because of the arrival of injectable PPIs.

Trends in the prescription of injectable gastric secretion inhibitors before and after the PPI supply restriction

Fig. 2 presents the number of daily prescriptions during the study period (from May 17 to August 9, 2022). The number of prescriptions for 20 mg omeprazole for injection and 30 mg Takepron® for injection peaked on June 23 and June 21, respectively, but declined to zero on June 29 and July 7, respectively. As for 20 mg famotidine for injection, an H_2-receptor inhibitor with no supply restriction (an average of approximately 15.5 ampoules in the immediately preceding month; Table 1), the number of prescriptions from June 27 increased to 53, 60, 53, and 59 ampoules on June 28, June 29, June 30, and July 1, respectively.

A comparison of the change in the average number of prescriptions per day for each drug for 30 days before and after June 16 revealed that the number of prescriptions for 20 mg injectable omeprazole and 30 mg injectable Takepron® significantly decreased (from 31.1 to 19.6 vials, P=0.005, and from 12.1 to 6.4 vials, P=0.007, respectively) after the supply restriction, whereas the number of prescriptions for 20 mg injectable famotidine significantly increased (from 15.5 to 31.7 ampoules, P=0.0002) (Table 1). Prior to the supply restriction, 20 mg omeprazole for injection was the most prescribed injectable gastric secretion inhibitors, with significantly more prescriptions for 20 mg injectable omeprazole than for 30 mg Takepron® and 20 mg famotidine (P value: <0.001 and <0.001). A comparison of daily mean values for 30 days after June 16 indicated that the number of prescriptions for 20 mg injectable famotidine was significantly higher than that for the other two drugs. The total drug costs for omeprazole, lansoprazole and famotidine calculated at 2022 standard drug prices, were JPY 197,760, 141,710 and 47,433 (total 386,903) before supply restrictions, but decreased to JPY 120,922, 73,153 and 90,695 (total 284,770) after supply restrictions.

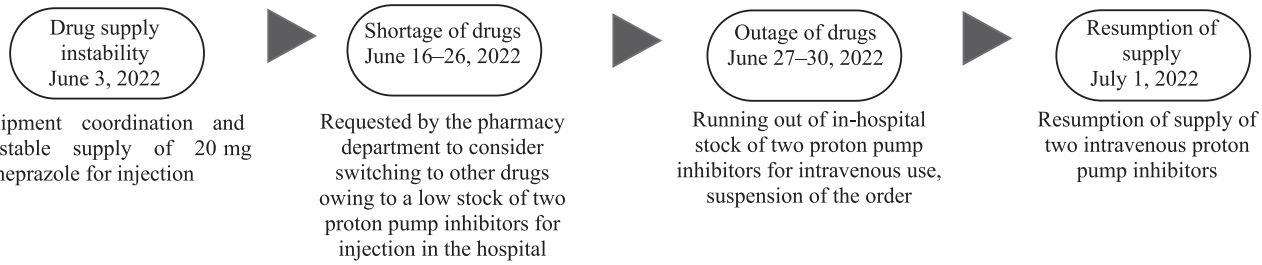

Fig. 1 Supply of injectable proton pump inhibitor preparations during the period covered and the response of the pharmacy department

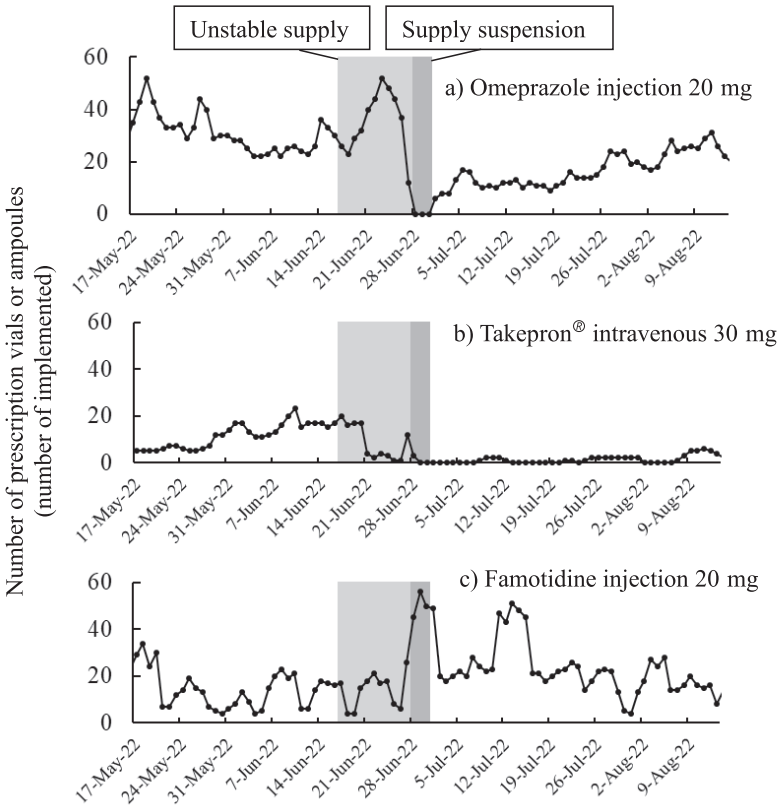

Fig. 2 Trends in the number of daily prescriptions before and after supply restriction on injectable gastric secretion inhibitors. The number of prescriptions per day for injectable gastric secretion inhibitors during the study period was plotted: (a) 20 mg injectable omeprazole, (b) 30 mg intravenous Takepron®, and (c) 20 mg injectable famotidine.

Table 1 Comparison of the daily amount of prescription per drug for injectable gastric secretion inhibitor for 30 days before and after supply restriction

	Before (V or A)	After (V or A)	*P* value
20 mg of omeprazole injection	31.1 ± 7.63	19.6 ± 15.0	< 0.001
30 mg of intravenous Takepron®	12.1 ± 5.44	6.37 ± 7.94	< 0.001
20 mg of famotidine injection	15.5 ± 8.75	31.7 ± 17.4	< 0.001

Data are expressed as mean ± standard deviation.
Statistical analysis was performed using Welch's *t*-test and the Mann-Whitney *U* test.
V: vials, A: ampoules.

Trends in the prescription of oral gastric secretion inhibitors before and after the supply restriction

Table 2 shows a comparison of the average number of prescriptions per day for each drug over 30 days before and after June 16, when the switch to another drug was requested because of supply instability. The number of prescriptions for oral gastric secretion inhibitors remained almost constant (Table 2), with no drugs exhibiting significant changes before and after June 16, when the switch to injectable PPIs and other administration routes was requested. Similarly, no significant changes were observed in the total number of OD preparations available by the simplified suspension method.

Discussion

This study evaluated the trends in in-hospital prescriptions of gastric secretion inhibitors during the period of in-hospital injectable PPI supply instability induced by injectable omeprazole supply constraints and revealed that the injectable H_2-receptor inhibitor was used as an alternative. During the period

Table 2 Comparison of the daily amount of prescription per drug for oral gastric antisecretory drugs for 30 days before and after supply restriction

	Before	After	*P* value
Nexium® granules for suspension 10 mg	11.3 ± 17.3	11.1 ± 9.13	0.305
Nexium® capsules 20 mg	39.6 ± 40.4	37.2 ± 30.3	0.862
Lansoprazole OD tablets 15 mg	71.8 ± 68.1	82.5 ± 68.8	0.688
Sodium rabeprazole tablets 10 mg	14.7 ± 13.8	15.4 ± 14.8	0.939
Takecab® tablets 10 mg	35.2 ± 40.4	34.1 ± 33.5	0.744
Takecab® tablets 20 mg	21.4 ± 20.5	22.5 ± 18.5	0.958
Famotidine OD tablets 10 mg	13.2 ± 14.8	19.9 ± 22.4	0.280
Famotidine OD tablets 20 mg	8.13 ± 8.89	10.9 ± 13.2	0.619
OD formulation	2757.9 ± 50.2	3263.0 ± 53.2	0.395

Data are expressed as mean ± standard deviation for tablets, capsules, and packets.
As all data were nonparametric, the Mann-Whitney *U* test was performed.
OD: orally disintegrating.

when the number of injectable PPI prescriptions was "zero", the number of injectable H_2-receptor inhibitor prescriptions increased, completely replacing the PPI prescriptions in the average number of prescriptions per day over 30 days after the onset of supply instability, as compared to that before 30 days (Fig. 2 and Table 1). The total price of the three drugs decreased by JPY 102,133 due to increased prescribing of cheaper famotidine. In contrast, there was no change in the number of prescriptions for oral gastric secretion inhibitors (Table 2), suggesting that drugs with the same effects and route of administration (instead of drugs with the same ingredients) were selected as alternatives. Injectable PPIs and H_2-receptor inhibitors were used in the intensive care setting to prevent stress gastric ulcers[9, 10] and in the surgical setting as part of the clinical pathway for perioperative management[11-13]. In this study, oral lansoprazole was available with the same ingredients as injectable lansoprazole, and esomeprazole (Nexium®) was available as an equivalent oral substitute for injectable omeprazole and injectable lansoprazole in the hospital. However, the number of prescriptions did not increase to compensate for the decrease in injectable PPI prescriptions. This was considered because injectable drugs were selected for intensive care or surgery and oral medications were difficult to use, particularly under sedation or anesthesia. These results emphasize the need to consider not only the efficacy of drugs but also their route of administration according to the intended use of these drugs when selecting alternative drugs in the event of drug supply instability or interruption.

One of the measures to be taken in case of a drug shortage is to switch to alternative products with the same composition (products from other companies). In the present case, we did not switch to an alternative PPI product with the same composition as a response to the restriction in the supply. In Japan, the handling of drugs used in medical institutions or hospitals is generally determined by the pharmaceutical committee of each institution for so-called "in-hospital" or "out-of-hospital" adopted drugs[14, 15], which are subsequently registered in the in-hospital logistics and ordering system for purchase and prescription. In such an operation, drugs from a particular manufacturer, including their dosages, are specified for use in hospitals, and selection and switching to alternatives are necessary for each case of detailed conditions whenever the drug supply is restricted. This makes it difficult to flexibly respond during a period of supply instability. The drug supply situation in Japan has seen a number of cases of shortages in the supply of ethical drugs[16] since the difficulty in cefazolin GE product supply in 2019[3]. In December 2021, the Ministry of Health, Labour and Welfare issued the "Response to shortages in the supply of ethical drugs"[17], which requires relevant organizations to take action in reallocating resources and quickly restoring a stable drug supply

system. The pharmaceutical supply survey from May 2023 [18] described that "restricted" and "suspended" items accounted for 14.5% and 8.1% of the total pharmaceutical supply in Japan, respectively. However, those in GE were higher, at 33.0% and 11.4%, respectively. The survey also showed the percentage of each reason for "limited shipments" and revealed the large gap in the percentage of "influence of other companies" as a reason for limited shipments in GE (14.6%), compared to 1.5% in brand-name drugs [18]. Against this background, it can be inferred that the impact of supply restriction on certain pharmaceutical companies or drugs is greater in GE than in originator pharmaceutical companies. In the present study, because of the short duration of injectable PPI shortage, a request was made to consider changing the prescription to an injectable equivalent or an oral equivalent with no restriction on supply, rather than purchasing a temporary alternative same-ingredient drug; however, it would have been difficult to change the adopted drug to another GE drug. This study showed that injectable H_2-receptor inhibitors, drugs with the same indications as PPI, were prescribed as alternatives. Based on these results, proposing drugs with the same route of administration and abundant supply as alternatives would be an effective way to address drug supply insecurity in the event of drug-limited shipments or disruptions.

This study has a few limitations. First, it only examined the number of prescriptions for drugs and did not evaluate the actual drug use in each patient. Ethical issues prevented the evaluation of operating conditions, such as the number of ICU and HCU admissions, where gastric secretion inhibitors are commonly used. Second, the actual impact of pharmacy announcements (e.g., requests to stop orders or to consider switching to another drug) on changes in physician prescription trends was not evaluated. It is possible that when a physician attempted to prescribe an injectable PPI, the PPI order was stopped in the system and the H_2-receptor inhibitor, which could have been entered directly on the injectable order screen, was selected. Further investigation of the patient's background and the actual route of administration were required. Thirdly, this study has been conducted in a single centre study, multi-site study may be more valid.

Conclusions

The present study examined the trends in drug prescriptions during drug supply disruptions at our hospital. Our results indicate the importance of maintaining a stable supply of drugs administered via the same route, even when drugs with other routes of administration are available. As the situation of unstable drug supply in Japan continues, it is hoped that the results of this study will aid in counteracting the drug supply instability during supply disruptions.

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Competing interests

The authors declare that they have no competing interests.

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