Original Article

Evaluation of gastrointestinal injury and blood flow of small bowel during low-dose aspirin administration

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Low-dose acetylsalicylic acid has been widely used. We evaluated small bowel and gastric injuries during acetylsalicylic acid administration using video capsule endoscopy and gastroduodenal endoscopy. We also investigated blood flow using contrast-enhanced ultrasonography. Six healthy volunteers were enrolled in this preliminary study. The subjects were administered 100 mg of enteric-coated aspirin daily for 14 days. Video capsule endoscopy and gastroduodenal endoscopy were simultaneously performed before administration and on days 1, 3, 7 and 14. Contrast-enhanced ultrasonography was performed before administration and on day 2, and 8. Video capsule endoscopy after administration of low-dose acetylsalicylic acid revealed small bowel mucosal damages of petechiae and erythema in all cases, and denuded area in one case. The total number of lesions in the small bowel increased according to duration of low-dose acetylsalicylic acid administration. However, the total number of lesions in the stomach peaked on day 3. Contrast-enhanced ultrasonography showed that the time-intensity curve peak value and Areas under the curves after acetylsalicylic acid administration were reduced. We observed not only gastric mucosal injuries but also small intestinal injuries with short-term low-dose acetylsalicylic acid administration. Acetylsalicylic acid administration also caused a decrease in small intestinal blood flow. Contrast-enhanced ultrasonography is useful for evaluation blood flow in the small bowel mucosa.

***Key Words*: small-intestine, capsule endoscopy, low-dose aspirin, contrast-enhanced ultrasonography, healthy subject**

It is well known that nonsteroidal antiinflammatory drug (NSAIDs) induce upper gastrointestinal (GI) complications, such as ulcer, bleeding and perforation. Recently, low-dose acetylsalicyclic acid (ASA) has been used for secondary prevention of cardiovascular events.[1–3] Sakamoto *et al.*[4] reported that conventional use of NSAIDs induced upper-GI complications (odds ratio: 6.1, 95% CI: 2.7–13.4). ASA also induced GI complications 5.5 fold (odds ratio: 5.5, 95% CI: 2.5–11.9) as well conventional use of NSAIDs in the Japanese population. Thus, it is becoming clear that ASA,[5–6] as well as NSAIDs caused upper GI complications. The ACCF/ACG/AHA expert consensus in 2008 reported that the use of low-dose ASA (75 to 325 mg per day) was associated with a 2- to 4- fold increased risk of upper GI complications and that PPIs should be used for gastroprotection strategies in patients at high risk for GI bleeding.[7] However, in some cases, sites of obscure GI bleeding (OGIB) were not detected despite examination by colonoscopy and upper endoscopy examination.[8] Lanas *et al.*[9] carried out a study to determine the time trends of hospitalizations resulting from GI complications originating both from the upper and lower GI tract in the Spanish general population and to determine the risk factors, severity, and clinical impact of these GI events. They showed that the incidence of upper GI complications decreased from 87/100,000 in 1996 to 47/10,000 in 2005, whereas the incidence of lower GI complications increased from 20/100,000 to 33/100,000. In Japan, "The Japanese Study Group for Double-Balloon Endoscopy" (JSG-DBE) established a database in subjects indicated for double-balloon endoscopy. Frequency of GI bleeding in NSAIDs users was significantly higher than that in non-NSAIDs users (79% vs 44%). Mucosal breaks were detected by double-balloon endoscopy in 51% of the NSAIDs users and in 5% of non-NSAID users.[10,11] These results showed that we should observe GI complications for patients with NSAIDs, as well as the relief of pain.

In 2001, the Food and Drug Administration approved a wireless VCE device (Given Diagnostic Imaging System, Given Imaging Ltd, Norcross, GA), which has since altered the management of patients with OGIB through its ability to directly image the small bowel mucosa.[12,13] Since the development of VCE, the clinical significance and frequency of adverse events with non-selective NSAIDs in the lower GI tract have been increasingly reported. Using capsule endoscopy, Graham *et al.* reported that more small-intestinal injuries were observed in 71% of NSAID users than in 10% of non-NSAID users.[14] In the same year, several studies using capsule endoscopy showed that the incidences of NSAID-induced small-intestinal injuries in healthy subjects were 55% to 68%.[15,16] On the other hand, investigation about the small intestinal injury development of symptoms by low-dose ASA is also advanced. Endo *et al.* reported that short-term low-dose ASA administration in healthy volunteers induced mild mucosal damage but not mucosal breaks.[17] Smesuol *et al.*[18] reported that short-term low-dose ASA administration induced small intestinal injuries with more severity. Thus, whether low-dose ASA induces small intestinal injury is still controversial. However, taking of low-dose ASA may be suggested a possibility to have played a certain role for small intestinal injury.

We evaluated small bowel and gastric injuries during low-dose ASA administration using VCE and gastroduodenal endoscopy. We also investigated blood flow in the small intestine using contrast-enhanced ultrasonography (low mechanical harmonic index imaging).

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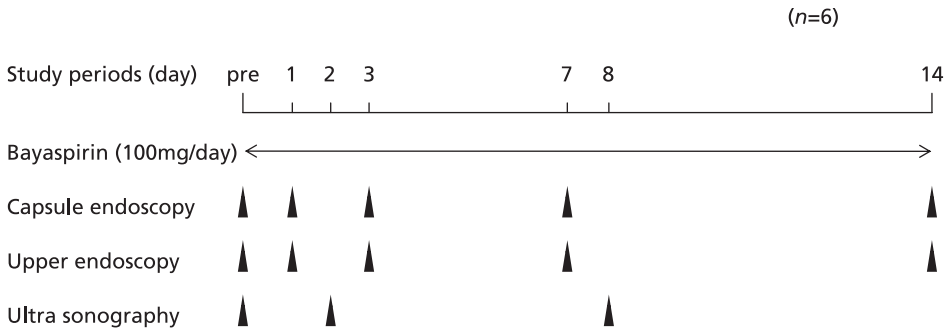

Fig. 1. Study design.

Materials and Methods

A preliminary trial was performed in six healthy volunteers. The study protocol was approved by the Ethics Committees of Hokkaido University Hospital, and written informed consent was obtained from all subjects.

Inclusion and exclusion criteria. Inclusion criteria were healthy subjects without gastric conditions such as erosions, erythema, bleeding, and ulcer on endoscopy. Subjects who habitually smoked or drank alcohol and subjects who took any medicines were excluded.

Study design. This study was an open-label and single-arm trial. VCE and gastroduodenal endoscopy were performed before administration and on days 1, 3, 7 and 14 (five times in total). All eligible subjects were administered aspirin at 100 mg once daily for a period of two weeks (Fig. 1). Subjects that developed any symptoms warranting discontinuation of treatment or with incomplete post-treatment VCEs were excluded from final analysis. A time-intensity curve (TIC) for blood flow in the small intestine was plotted from recorded ultrasonographic images with Image Lab software. Areas under the curves (AUCs) and TIC peak value were calculated from TIC.

Gastroduodenal endoscopy. Gastroduodenal endoscopy was performed using a GIF-XQ240 (Olympus, Tokyo, Japan) after 3 min local anesthesia of the pharynx with lidocaine. Endoscopic findings were assessed by one endoscopist.

Capsule endoscopy. A Given video capsule system (Pillcam™, Given Imaging Ltd., Yoqneam, Israel) was used for this study. Subjects fasted 12 h before swallowing the capsule. A light snack was permitted 4 h after capsule ingestion. Data were collected for up to 8 h after capsule ingestion. Repeat VCE of the small intestine due to system failure (image loss or low signal) was permitted only if capsule excretion was confirmed. All video images were analyzed by two skilled reviewers who were blinded for subjects and timing to be examined VCEs. All images were saved for final comprehensive analysis at the completion of all post-treatment VCEs.

Contrast-enhanced ultrasonography (CE-US). The longitudinal view of the small intestine was imaged in the left upper abdomen. Baseline US and contrast-enhanced US were performed with a 7.5 MHz center frequency linear transducer using an ultrasound unit SSA-790A (AplioXG(TM), Toshiba Medical Systems Corp., Otawara, Japan) The imaging mode was pulse subtraction. Prior to CEUS, 20 mg of scopolaminebutylbromide was injected intravenously to suppress peristalsis. Perflubutane microbubbles (Sonazoid, Daiichi Sankyo, Tokyo, Japan), a lyophilized preparation reconstituted for injection, were injected intravenously at a concentration of 0.05 ml/kg. Ten seconds after contrast medium injection, enhanced signals from blood flow in the small intestinal wall were captured until 45 s on cine clipsequipped with ultrasound unit. Regions of interests of fixed sizes were placed in the mucosal area of the small intestine at three regions. A TIC of blood flow enhancement signal in the small intestine was plotted from recorded ultrasonographic images using ImageLab, which was developed by C++ software dedicated to US images obtained by AplioXG.[19] AUC and TIC peak value (maximum intensity) were calculated from the TIC. These values were used to estimate small intestinal blood flow inside the mucosal layer (Fig. 2).

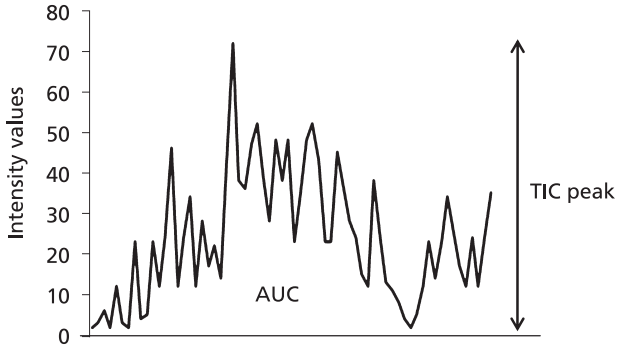

Fig. 2. Time-intensity curve (TIC) for blood flow in the small intestine using contrast-enhanced ultrasonography. Typical image of TIC was shown to upper. These intensity curves by measured ultra sonography indicated for blood flow in the small intestine. The vertical arrow was defined as the TIC peak value and area under curve (AUC) was calculated.

Review of VCE. Investigators who were to evaluate the results of video VCE of the small intestine were required to attend a standardized training session on use of the Given Diagnostic System. These two investigators (U.N. and S.F.) were instructed to mark any significant lesions with a blinded condition and to evaluate lesions according to the criteria for determination of endpoints. It is difficult or impossible to evaluate erosion from an ulcer with capsule endoscopy. If different results between the two investigators existed, the two investigators achieved a consensus.

Evaluation of gastric injury. In this study, mucosal injuries of the upper GI were shown as sum total number of erythema, petechiae, erosion, and ulcer.

Evaluation of small intestinal injury. In this study, mucosal injury of the small intestine was defined as lesions with slough surrounded by erythema. Denuded area was defined as reddened area without villi. Total small intestinal mucosal injury was defined as sum total number of petechiae, erythema, and denuded area (Fig. 3). Small intestinal blood flow was expressed in AUC and maximum intensity.

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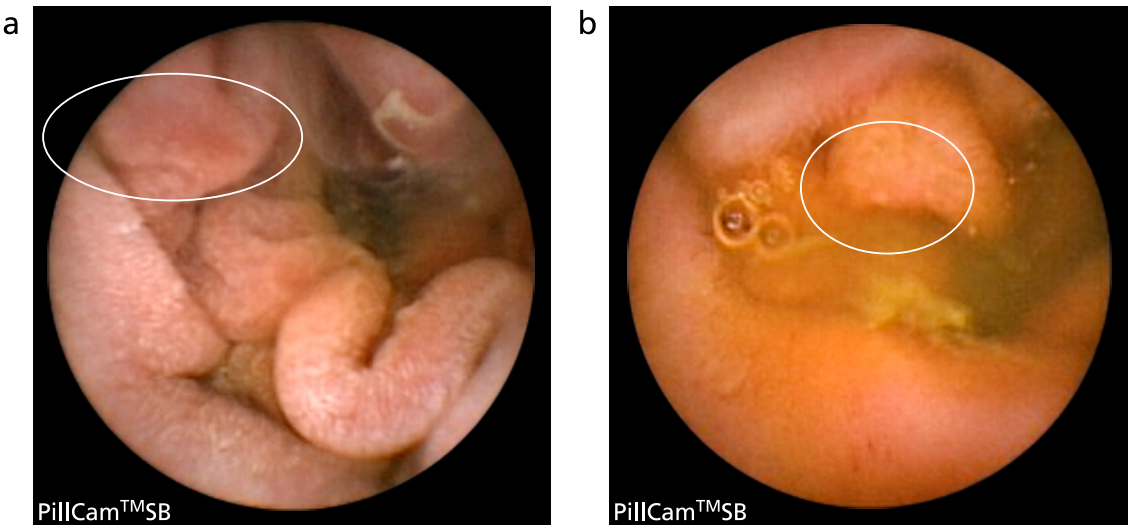

Fig. 3. Mucosal injury of the small intestine during capsule endoscopy. a: Petechiae b: Denuded area was defined as reddened area without villi.

Evaluation of adverse events. Clinical laboratory and physical examinations were performed to assess safety before and after study, and for observation of adverse events.

Statistical analysis. Comparisons of temporal injury, AUC, and maximum intensity were carried out by Wilcoxon's test with correspondence. It was analyzed for the correlation coefficient about the relation between AUC and small intestinal injury. AUC and max intensity of 6 subjects were expressed as mean, standard deviation, absolute difference, and 95% confidential interval. All statistical analyses were performed using SAS® version 8.2 (SAS Institute, Cary, NC). Data were expressed as mean values ± SD. p values <0.05 were considered significant.

Results

Mucosal injuries on post 1st, 3rd, 7th and 14th days detected by capsule and gastroduodenal endoscopy. The time-course changes of gastric mucosal injuries are shown in Table 1. The total numbers of gastric mucosal injuries were 0.8 ± 1.6 on the 1st day, 5.5 ± 6.9 on the 3rd day, 1.0 ± 0.9 on the 7th day and 3.3 ± 4.4 on the 14th day. These numbers were not significantly different from the basal numbers of gastric injuries. The total numbers of small intestinal injuries were 13.5 ± 19.7 on the 1st day, 13.5 ± 20.5 on the 3rd day, 13.5 ± 12.0 on the 7th day and 18.0 ± 18.5 on the 14th day. These numbers were also not significantly different from the basal numbers of intestinal injuries.

Time-intensity curve (TIC) for blood flow in the small intestine. AUC of the TIC decreased from 223.6 ± 106.6 (basal level) to 166.6 ± 94.8 on the 2nd day (difference: −56.9, 95% CI: −113.5– −0.5, $p = 0.0484$) and 125.0 ± 85.8 on the 8th day (difference: −98.5, 95% CI: −199.5– −2.4, $p = 0.0539$) (Table 2). Max intensities decreased from 26.3 ± 4.2 (basal level) to 21.9 ± 8.4 on the 2nd day (difference: −4.4, 95% CI: −12.1– −3.3, $p = 0.2044$) and to 18.8 ± 7.3 on the 8th day (difference: −7.5, 95% CI: −16.5– −1.4, $p = 0.0847$) (Table 2).

Relationships among small intestinal injury, gastroduodenal injury, and small intestinal blood flow. A significant correlation between total numbers of gastric and small intestinal injuries was found on the 3rd day ($y = -1.58 + 2.74x$, $p = 0.0325$) (Fig. 4). There were no significant correlations on the other days.

Adverse events. Clinical symptoms were not observed throughout the study.

Discussion

Although small intestinal injury caused by NSAID use is an important clinical research theme,[20] it is a still more important for ASA-use in order to lead to fatal. And it may be slight mucosal injury; it is still unknown whether low-dose ASA-induced slight mucosal injury is correlated with serious clinical symptoms.

In this preliminary study, there were some healthy subjects in whom injuries of both the gastric and small intestinal mucosa were induced in the very early phase (at 1 or 3 days). The degree of injuries was slight, such as petechiae, and no erosion or ulcer was observed. The point which should be mentioned especially was to be stratified in the category between easy and hard to cause injury (Table 1). In addition, each subject was following a different course. In case 1, there were no gastric and small intestinal injuries throughout the study period, whereas in case 2, gastric mucosal injuries were observed strongly on the 3rd day and disappeared after that. Moreover small intestinal injuries were observed strongly on the 1st and 3rd days and disappeared after that in case 2. In case 3, although severe gastric mucosal injuries were observed, there was little small intestinal injury. In case 4, there was no injury to the stomach, but injury to the small intestine was observed. In case 5, there were injuries to the gastric mucosa and small intestine, and small intestinal injury showed periodic recurrence. In case 6, continuous taking low-dose ASA was increasing injury to gastric and small intestine, pile up medication days. In cases 2, 5 and 6, similar changing was observed in both the occurrence of small intestinal injury and decrease in blood flow.

Smecuol *et al.*[18] reported serious small intestinal injuries, including erosion, ulcer, and bleeding taking low-dose ASA in 10 healthy subjects. However, no serious small intestinal injury was detected in the 6 healthy subjects in the present study. In other studies we examined the number of the redness lesions by dividing it into a group having mucosal break and the group who do not have. It was significantly different. Therefore, it is thought that the number of the redness lesions suggests the degree of the injury. And we should know that not all individuals equally responded to low-dose ASA. This has been called "ASA resistance". Hovens *et al.*[21] found great differences in the prevalence of ASA resistance in a meta-analysis of patients taking ASA for secondary prevention and calculated mean prevalence of 22.4%, 26.0% and 27.3% in patients with CAD, stroke and miscellaneous diseases.

Table 1. The effect of low-dose aspirin-induced upper and lower injuries

	Subject number	pre	1	3	7	14 (days)
Upper GI injuries	1	1	1	1	1	1
	2	0	0	18	1	0
	3	0	4	7	2	12
	4	0	0	0	0	2
	5	4	0	7	2	2
	6	0	0	0	0	3
mean ± SD		0.8 ± 1.6	0.8 ± 1.6	5.5 ± 6.9	1.0 ± 0.9	3.3 ± 4.4
Lower GI injuries						
petechiae	1	0	3	1	2	0
	2	0	56	58	14	21
	3	0	2	0	2	6
	4	1	12	0	5	9
	5	14	4	9	24	6
	6	0	3	13	34	49
erythema	1	0	0	0	0	0
	2	0	1	0	0	3
	3	0	0	0	0	1
	4	0	0	0	0	3
	5	1	0	0	0	1
	6	0	0	0	0	6
denuded	1	0	0	0	0	0
	2	0	0	0	0	3
	3	0	0	0	0	0
	4	0	0	0	0	0
	5	0	0	0	0	0
	6	0	0	0	0	0
Total number of injuries (mean ± SD)		2.7 ± 5.5	13.5 ± 19.7	13.5 ± 20.5	13.5 ± 12.0	18.0 ± 18.5

Number of injuries were calculated as total number of small intestinal and gastric petechiae, erythema, and denuded.

Table 2. Time-intensity curve (TIC) for blood flow in the small intestine

	Subject number	pre	2	8 (days)
AUC	1	139.4	37.4	24.3
	2	286.7	222	201.2
	3	94	86.4	79.8
	4	295.4	286	254.4
	5	160	139.7	107
	6	364.9	228	83.3
mean ± SD		223.6 ± 106.6	166.6 ± 94.8	125.0 ± 85.8
Differences			–56.9	–98.5
95% CI			–113.5– –0.5	–199.5–2.4
p = value			0.0484	0.0539
Max intensity	1	21.6	6.5	10.4
	2	24.5	31.4	31.3
	3	22	20.6	19.4
	4	30.2	26.2	20.8
	5	31.4	22.4	13.2
	6	28.3	24.5	17.7
mean ± SD		26.3 ± 4.2	21.9 ± 8.4	18.8 ± 7.3
Differences			–4.4	–7.5
95% CI			–12.1–3.3	–16.5–1.4
p = value			0.2044	0.0847

However, the mechanisms of ASA resistance are still not clear.

Moreover, in case 2, mucosal injuries were restored in both upper and lower. Kawai *et al.*[22] reported that low-dose ASA-induced GI complications were occurred at 3 days and were reduced at 7 days after the start of ASA administration. This phenomenon was concluded as adaptation. Adaptation may be also observed in our study. Increasing permeation of the small intestine is known to be one of mechanisms causing injury. AUC of the TIC and maximum intensity in the small intestine were significantly decreased on day 2 (from 223.6 ± 106.6 to 166.6 ± 94.8, difference; –56.9, 95% CI; –113.5– –0.5, $p = 0.0484$) (Table 2).

Ultrasonography is less-invasive, reputably performed and increase economic efficiency no incidence of adverse events was

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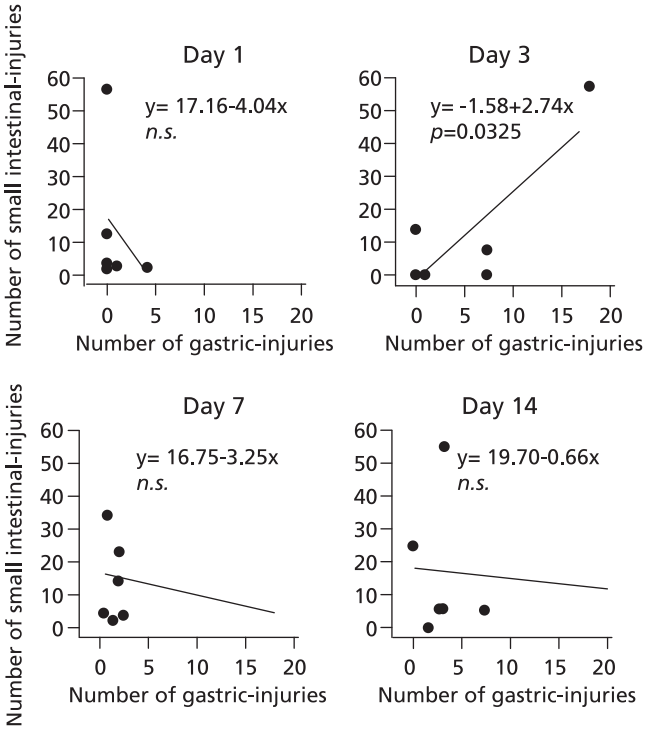

Fig. 4. Relationship between low-dose aspirin-induced small intestinal injuries and gastric injuries. A significant correlation between total numbers of gastric and small intestinal injuries was found on the 3rd day.

self limited. Laser Doppler flowmetry is considered to be the gold standard, but it requires insertion of an endoscope and is difficult to use routinely. We therefore used contrast-enhanced ultrasonography. This method is useful for evaluating blood flow in the mucosal layer of the small intestine. We started this study after having proved reproducibility of the CE-US evaluation.

However, there are limitations to our study; for example, the position of ultrasound probe placement could not be made exactly the same throughout the entire study in one subject. The problem with this method is that correction for ultrasound beam attenuation is needed. However, we tried as much as possible to have the same ultrasound plane according to surroundings structures such as vessels and the layer and thickness of the abdominal wall, so that effects of differences could be kept to a minimum. Also, only one skilled sonographer (M. N) performed ultrasound throughout the study.

There are also problems with penetration in obesity and with intestinal air impairing image quality.[23] The period of each study was two weeks, so that body weight of a subject was not significantly different. We performed ultrasound study in the early morning to avoid peristalsis, and subjects in a fasted state. So there would be almost no influence of a meal and physics.

Another limitation was the inaccuracy of placing the regions of interest (ROI) in the analysis of TIC. The ROIs were placed in a plane of the small intestine to avoid perforator and we tried to put them in the same positions as those in the previous study as much as possible. Therefore, we believe that little mismatching actually occurred.

In conclusion, we observed not only gastric mucosal injuries but also small intestinal injuries in subjects receiving low-dose ASA. Small intestinal blood flow was also decreased ASA administration. It was shown the possibility as diagnostic modality for ultrasonography. It should be needed to research for the preventive effect of tentative drug.

Disclosure

Dr. Kato also received research grants from Eisai Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd. within the last three years.

Abbreviation

ACCF/ACG/AHA	American College of Cardiology Foundation/ American College of Gastroenterology/ American Heart Association
ASA	acetylsalicyclic acid
AUCs	Areas under the curves
CE-US	Contrast-enhanced ultrasonography
GI	gastrointestinal
JSG-DBE	Japanese Study Group for Double-Balloon Endoscopy
NSAIDs	nonsteroidal antiinflammatory drug
OGIB	obscure GI bleeding
PPIs	proton pump inhibitors
ROI	regions of interest
TIC	time-intensity curve
VCE	video capsule endoscopy

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