Theoretical Investigation of Aspirin Dosage Regimen to Exhibit Optimal Antiplatelet Effects and Decrease Risk of Upper Gastrointestinal Lesions

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We investigated dosage regimens for aspirin therapy in regard to antiplatelet effects in patients without gastrointestinal lesions. Findings for inhibition of biosynthesis of thromboxane B₂ (TXB₂) and prostaglandin E₂ (PGE₂) were simulated based on pharmacokinetic and pharmacodynamic models using an irreversible process of inhibition of cyclooxygenase-1 (COX-1) by aspirin. We found that the inhibition of biosynthesis of TXB₂ at a steady state was greater than 90% when the dose of aspirin administered exceeded 81 mg, which was considered to exhibit a sufficient antiplatelet effect. Furthermore, it was confirmed that a dose of 162 mg or more is needed to exert an immediate antiplatelet effect on the initial day of administration. On the other hand, the inhibition of biosynthesis of PGE₂ ranged from 40–90% when aspirin was administered at a dose of 10.125–324 mg. Thus, the risk of gastrointestinal lesions differed in a dosage-dependent manner. The biosynthesis inhibition of PGE₂ was calculated to be 37.9%, with that value set as the target level for prevention of gastrointestinal disorders. We also noted a difference between platelets and gastric mucosa cells in regard to the turnover rate of COX-1, and attempted to simulate the inhibition of biosynthesis of TXB₂ and PGE₂ following administration of aspirin. However, it was not possible, as the inhibition of biosynthesis of TXB₂ was greater than 90% and that of PGE₂ was less than 37.9%, even with various dosage regimens. Our findings suggest that it is difficult to determine a rational dosage regimen of aspirin to exert an antiplatelet effect without inducing gastrointestinal lesions.

Key words aspirin; antiplatelet effect; gastrointestinal lesion; thromboxane B₂; prostaglandin E₂; cyclooxygenase-1

Platelets play an important role in haemostasis and their hyperfunction participates in cardiovascular thrombosis, such as myocardial infarction, angina pectoris, and cerebral infarction.1) Aspirin has antiplatelet effects and is given at low doses for prevention of cardiovascular thrombosis recurrence. However, low-dose aspirin-induced gastrointestinal side-effects are becoming an important problem in clinical practice.2) The gastrointestinal lesions induced by aspirin include ulcers and erosions without subjective symptoms, such as pain, and are generally discovered by the presence of hematemesis or fecal occult blood.3,4) Moreover, aspirin has antiplatelet effects, which can cause more serious gastrointestinal reactions such as bleeding, perforation, and other events, leading to hospitalization or death. In addition, patients with cerebral or myocardial infarction often receive long-term aspirin therapy for secondary prevention. Thus, prevention of gastrointestinal lesions induced by aspirin is an important issue in patients receiving long-term administrations.

Aspirin irreversibly inhibits the enzyme cyclooxygenase-1 (COX-1) and depresses the synthesis of thromboxane A₂ (TXA₂) as parts of its antiplatelet effects that last for the duration of the life of platelets.5) On the other hand, COX-1 is expressed constitutively by normal tissues, including gastrointestinal mucosa, and synthesizes prostaglandin E₂ (PGE₂) from arachidonic acid. PGE₂ plays important roles in protection of gastrointestinal mucosa, such as secretion of gastric mucus and gastric acid, and increasing gastric mucosal blood flow. It has also been proposed that the synthesis of PGE₂ is depressed and gastroduodenal lesions induced in individuals taking aspirin.6)

We have noted a difference between platelets and gastric mucosa cells in regard to the turnover rate of COX-1. In theory, an aspirin dose that inhibits only that platelet enzyme would be the most reasonable to elicit an antithrombotic effect and should be associated with the least amount of side effects. However, there are scarce experimental data available regarding the risk of gastroduodenal mucosal injury as a function of aspirin dose, while the ideal clinical dose of aspirin that has no risk of gastrointestinal mucosal damage is unknown.

The purpose of the present study was to develop a rational aspirin dosage regimen for optimal antiplatelet effects and prevention of gastrointestinal lesions. We investigated the inhibitory action of COX-1 on both platelets and gastric mucosa with repeated administrations of aspirin, based on pharmacokinetic and pharmacodynamic models of the irreversible inhibition process of COX-1 by aspirin.

MATERIALS AND METHODS

Data Used for Analysis We used previously reported data for time curves of biosynthesis inhibition for both TXB₂ in platelets and PGE₂ in gastric mucosa with doses of 81 mg of aspirin per day and 325 mg of aspirin every third day for 46 d.7) TXA₂ is extremely labile and rapidly converted in a nonenzymatic manner to the relatively stable TXB₂. Thus, the concert ratio of TXB₂ was used for analysis instead of TXA₂.
in plasma. We utilized the nonlinear least squares program MLAB (Civilized Software Inc.) for the analysis.

Pharmacokinetic Model of Aspirin The time course of plasma concentration following oral administration of aspirin was analyzed using the following one-compartment pharmacokinetic model with the absorption process (Eq. 1).

\[
C_p = \frac{k_a \cdot F \cdot D}{V_d (k_a - k_e)} \cdot (e^{-k_e \cdot t} - e^{-k_a \cdot t})
\]  

(1)

Where \(C_p\) (\(\mu g/mL\)), \(k_a\) (h\(^{-1}\)), \(k_e\) (h\(^{-1}\)), \(F\), \(D\) (mg), and \(V_d\) (L) represent the plasma concentration of aspirin, absorption rate constant, elimination rate constant, bioavailability, dose, and distribution volume, respectively. To estimate the pharmacokinetic parameters of \(k_a\), \(k_e\), and \(V_d\), the plasma concentration-time curve of aspirin after oral administration at 80mg\(^3\) was fitted to Eq. 1 using the nonlinear least squares methods. Moreover, the bioavailability value used was 0.8.\(^9\)

Pharmacodynamic Model of TXB\(_2\) and PGE\(_2\) Aspirin irreversibly inhibits the enzyme COX-1 in platelets and gastric mucosa. The effects of inhibition of COX-1 in platelets and gastric mucosa was analyzed using our previously constructed pharmacodynamic model\(^{10}\) (Fig. 1).

We assumed that COX-1 in platelets and gastric mucosa is synthesized by \(k_0\) and \(k_0^{'}\), respectively, at a constant biosynthesis rate in the absence of aspirin. Those were eliminated by \(k_{el}\) and \(k_{el}^{'}\), which represented the apparent turnover rate constants of COX-1. Thus, Eqs. 2 and 3 were formed.

\[
\frac{dE}{dt} = k_0 - k_{el} \cdot E
\]  

(2)

\[
\frac{dE^{'}}{dt} = k_0^{'} - k_{el}^{'} \cdot E^{'}
\]  

(3)

In those, \(E\) and \(E^{'}\) represent the amount of COX-1 in platelets and gastric mucosa, respectively. It was considered that COX-1 levels in platelets and gastric mucosa are maintained at a constant quantity. Thus, Eqs. 3 and 4 were equal to 0, as Eqs. 5 and 6 were formed in the absence of aspirin.

\[
E_0 = \frac{k_0}{k_{el}}
\]  

(4)

\[
E_0^{'} = \frac{k_0^{'}}{k_{el}^{'}}
\]  

(5)

In those, \(E_0\) and \(E_0^{'}\) represent the amount of COX-1 in platelets and gastric mucosa in the absence of aspirin, respectively. COX-1 in platelets and gastric mucosa irreversibly inhibits the second-order rate constants of \(K\) and \(K^{'}\) in the presence of aspirin, and are inactivated. In addition, \(C_p\) was calculated using Eq. 1 of pharmacokinetic model of aspirin shown in ‘Pharmacokinetic Model of Aspirin’ of Materials and Methods.

\[
\frac{dE}{dt} = k_0 - k_{el} \cdot E - K \cdot C_p \cdot E
\]  

(6)

\[
\frac{dE^{'}}{dt} = k_0^{'} - k_{el}^{'} \cdot E^{'} - K^{'} \cdot C_p \cdot E^{'}
\]  

(7)

We assumed that the proportion to the ratios of \(E\) to \(E_0\) and \(E^{'}\) to \(E_0^{'}\) were \(\epsilon\) and \(\epsilon^{'}\), respectively. Therefore, Eqs. 6 and 7 were changed to Eqs. 8 and 9.

\[
\frac{dE}{dt} = k_0 - k_{el} \cdot E - K \cdot C_p \cdot \epsilon \cdot E
\]  

(8)

\[
\frac{dE^{'}}{dt} = k_0^{'} - k_{el}^{'} \cdot E^{'} - K^{'} \cdot C_p \cdot \epsilon^{'} \cdot E^{'}
\]  

(9)

To estimate the values for \(k_{el}\), \(k_{el}^{'}\), \(K\), and \(K^{'}\), we simultaneously fitted the biosynthesis inhibition of TXB\(_2\) and PGE\(_2\) time curves using data for the plasma concentration time courses after administration of aspirin at doses of 81 and 325mg in Eqs. 8 and 9, respectively. In addition, we confirmed that the concentration of aspirin in plasma increases in a dose-dependent manner.

Optimal Inhibition Rates of Biosynthesis of TXB\(_2\) and PGE\(_2\) The rate of effective inhibition of TXB\(_2\) biosynthesis was set at greater than 90\%, based on a clinical report.\(^5,^{11}\) On the other hand, there is no report regarding the relationship between gastrointestinal disorders and inhibition of PGE\(_2\) biosynthesis. However, it was shown that significant biosynthesis inhibition of PGE\(_2\) did not occur with an aspirin dose of 10mg/d as compared with a placebo.\(^{12}\) Therefore, the parameters estimated using the above pharmacokinetic model were used and an inhibition of biosynthesis of PGE\(_2\) time curve was simulated by using the plasma concentration after administration of aspirin at dose of 10mg each day. We used the pharmacodynamic parameters \(k_{el}\) and \(K^{'}\), which were estimated using method 3, while the pharmacokinetic parameters used were \(k_a\), \(k_e\), and \(V_d\), which were estimated using method 2. Thus, the rate of preventive inhibition of biosynthesis of PGE\(_2\) was set lower than the mean value for inhibition of biosynthesis of PGE\(_2\) obtained using the above pharmacodynamic model.

Simulation of Inhibition of Biosynthesis of TXB\(_2\) and PGE\(_2\) after Administration of Aspirin at Various Dosage Regimens The inhibition of biosynthesis of TXB\(_2\) and PGE\(_2\) following aspirin administration at various dosages was...
simulated using Eqs. 8 and 9. We investigated a rational dosage regimen of aspirin for antiplatelet effects without inducing gastrointestinal disorders.

**RESULTS**

**Analysis of Time Course of Plasma Concentration of Aspirin** The time course of plasma concentration of aspirin following a single administration at 80 mg along with fitted curve based on the nonlinear least square method are shown in Fig. 2. The estimated pharmacokinetic parameters of aspirin are presented in Table 1. The values for $k_a$, $k_e$, and $V_d$ were $2.128566 \pm 0.039939$ h$^{-1}$, $2.128561 \pm 0.041472$ h$^{-1}$, and $29.9 \pm 0.3$ L, respectively. The fitted curve was well matched to the time course of plasma concentration of aspirin.

**Analysis of Time Courses of TXB$_2$ and PGE$_2$ Biosynthesis** The time courses of TXB$_2$ and PGE$_2$ biosynthesis after repeated administrations of aspirin based on the nonlinear least squares method with fitted curves are shown in Fig. 3. The estimated pharmacodynamic parameters for aspirin are presented in Table 2. The values for $k_{el}$, $k_{el}/uni$, $K$, and $K/uni$ were $0.00505 \pm 0.00065$ h$^{-1}$, $0.0101 \pm 0.0015$ h$^{-1}$, $3.31 \pm 7.88$ mL·µg$^{-1}$·h$^{-1}$, and $1.22 \pm 0.02$ mL·µg$^{-1}$·h$^{-1}$, respectively. The fitted curves were matched to the observed data. The mean residence time periods ($1/k_{el}$ and $1/k_{el}/uni$) of COX-1 in platelets and gastric mucosa as estimated by the values for $k_{el}$ and $k_{el}/uni$ were approximately 8 and 4 d, respectively.

**Optimal Rates for Inhibition of Biosynthesis of TXB$_2$ and PGE$_2$** The time course of inhibition of biosynthesis of PGE$_2$ following repeated administrations of aspirin at a dose of 10 mg was simulated by substituting $k_{el}$ and $K'$ in Eq. 9. The mean ratio of inhibition of biosynthesis of PGE$_2$ was 37.9% and that value was used as the target level of inhibition of biosynthesis of PGE$_2$ for prevention of gastrointestinal disorders. Thus, we concluded that the ratio for inhibition of biosynthesis of PGE$_2$ to prevent gastrointestinal disorders was lower than 37.9%.

**Simulation of Inhibition of Biosynthesis of TXB$_2$ and PGE$_2$ after Administration of Aspirin at Usual Dosage Regimens** Results of simulations of inhibition biosynthesis of PGE$_2$ and TXB$_2$ following repeated administrations of aspirin at a dose of 81 mg daily are shown in Fig. 4. The ratio of inhibition of TXB$_2$ biosynthesis at a steady state was greater than 90%, which was expected to exert adequate antiplatelet effects at a dose of 81 mg per day of aspirin. However, the ratio of inhibition of PGE$_2$ biosynthesis at a steady state was 81.6%, which was suggested to induce gastrointestinal disorders.

**Simulation of Inhibition of Biosynthesis of TXB$_2$ and**
PGE₂ Following Repeated Administrations of Aspirin at Various Doses

Results of simulations of inhibition of biosynthesis of TXB₂ and PGE₂ following repeated administrations of aspirin at doses of 10.125, 20.25, 40.5, 81, 162, and 324 mg are shown in Fig. 5. Biosynthesis inhibition of TXB₂ at a steady state after administration of aspirin at doses of more than 81 mg was sufficient for exerting an antiplatelet effect, though the times to reaching a steady state varied. Moreover, the initial dose required was greater than 162 mg for biosynthesis inhibition of TXB₂ at more than 90%, which was expected to be sufficient for antiplatelet effects from the first day of administration. On the other hand, the risk of gastrointestinal disorder differed by dosage. Thus, the ratio of inhibition of PGE₂ biosynthesis associated with an increased dose ranged from 37.9 to 89.5%.

The relationships between daily dose of repeated administrations of aspirin for 14 d and inhibition of TXB₂ and PGE₂ biosynthesis at a steady state are shown in Fig. 6. When aspirin was given daily at a dose of 81 mg for 14 d, the mean ratio for inhibition of biosynthesis of TXB₂ and PGE₂ was 94.0% and 81.6%, respectively. On the other hand, at a dose of 10 mg, those were 76.9% and 37.9%, respectively. Therefore, the optimal biosynthesis inhibition of TXB₂ and PGE₂ was...
not established at those 2 doses. Consequently, it is considered that the antiplatelet effects of aspirin therapy for preventing gastrointestinal lesions is difficult to determine, even with changes in daily dose.

**Optimal Dosages of Aspirin** Prevention of gastrointestinal lesions was difficult to obtain when aspirin was given once a day. Thus, there was a difference in the turnover rate of COX-1 between platelets and gastric mucosa. Inhibition of biosynthesis of TXB$_2$ and PGE$_2$ was simulated by repeated aspirin administration regimen 1 (81 mg on day 1, 5 mg on day 2) or regimen 2 (162 mg on day 1, 5 mg on day 2), with the results shown in Fig. 7. We considered that the dose of aspirin should be set at greater than 81 mg for an antiplatelet effect and lower than 10 mg for prevention of gastrointestinal lesions, based on data shown in Figs. 5–7. Moreover, aspirin irreversibly inhibits COX-1 and its effects last for the duration of the life of platelets. Therefore, different doses based on the desired effect, 81 mg or more for an antiplatelet effect and less than 10 mg for prevention of gastrointestinal lesions, are useful. Inhibition of the biosynthesis of PGE$_2$ was always greater

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**Fig. 6.** Dose–Response Curves of Inhibition of Biosynthesis of TXB$_2$ and PGE$_2$ at Steady State after Oral Administration of Aspirin

- TXB$_2$, - - - PGE$_2$.

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**Fig. 7.** Inhibition of Biosynthesis of TXB$_2$ and PGE$_2$ during Oral Administration of Aspirin Using Regimen 1 (A) and Regimen 2 (B)

- Simulation curve for TXB$_2$, - - - - - - simulation curve for PGE$_2$, - - - simulation curve for PGE$_2$ that did not induce gastroduodenal disorders.
than 37.9% and no period of recovery of PGE₂ was seen, regardless of the regimen used. In addition, inhibition of TXB₂ biosynthesis was under 90% during that period. Therefore, it is suggested that development of a dosage for an optimal antiplatelet effect without inducing gastrointestinal lesions is difficult, even if the method of aspirin administration is decided.

DISCUSSION

In the present study, we investigated the ideal aspirin therapy for antiplatelet effects without inducing gastrointestinal lesions, based on pharmacokinetic and pharmacodynamic models using the process of irreversible inhibition of COX-1 by aspirin. The half-life of aspirin is reported to be quite short at 0.40±0.13 h, while the maximum drug concentration time is reported to be 0.39±0.14 h. Therefore, we considered that the estimated values for \( k_c \) and \( k_e \) were near to actual values. Moreover, the value of \( T_{1/2} \) based on \( k_c \) was calculated to be 0.33 h, which was in agreement with the above reported value. The estimated \( K \) value for platelets was 3.31±7.88 mL·\( \mu \)g⁻¹·h⁻¹, which was 2.7 times greater than the estimated \( K' \) value for gastric mucosa (1.22±0.02 mL·\( \mu \)g⁻¹·h⁻¹). The estimated \( k_e \) and \( k_d \) values for platelets and gastric mucosa were 0.00505±0.00065 h⁻¹ and 0.0101±0.0015 h⁻¹, respectively. The mean residence time of COX-1 in platelets estimated by using the value of \( k_d \) was approximately 8 d, which matched the life of platelets (8–10 d). On the other hand, the mean residence time of COX-1 in gastric mucosa, estimated by using the value for \( k_d \), was approximately 4 d, which was half that of platelets. Since platelets do not have a nucleus, the apparent turnover rate constant of COX-1 is dependent on platelet lifespan. However, gastrointestinal mucosal cells have a nucleus, thus turnover of COX-1 occurs in the cells. We concluded that turnover of COX-1 in gastric mucosa occurs faster than that in platelets.

There are no known reports regarding the amount of PGE₂ in gastric mucosa without the presence of gastrointestinal lesions. A previous study found that 10 mg/d of aspirin did not significantly suppress gastric PGE₂ nor induce gastric mucosal injury. Based on that finding, we analyzed the biosynthesis inhibition time curve of PGE₂ after administration of aspirin at a daily dose of 10 mg. The mean ratio of inhibition of PGE₂ biosynthesis was calculated to be 37.9%, which was set as the target level of inhibition of biosynthesis of PGE₂ for prevention of gastrointestinal disorders. Another report noted that major and minor gastrointestinal bleeding complications were the same in patients receiving 30 mg and as those receiving 283 mg of aspirin daily. Hence, it was thought that the value for inhibition of PGE₂ biosynthesis used in our study was reasonable.

We simultaneously analyzed the biosynthesis of TXB₂ and PGE₂ using pharmacokinetic and pharmacodynamic models with data obtained with a dose of 81 mg of aspirin per day and 325 mg of aspirin every third day for 46 d. The fitted curves were matched to the observed data, though poorly, because the production of TXB₂ was inhibited until 48 h after the last dose of aspirin. Thus, the error for the estimated \( K \) value (reaction rate constant of aspirin and COX-1 in platelets) was large. It has been reported that no new platelet enzyme appears in circulation for approximately 2 d, because aspirin inhibits COX in megakaryocytes. If this lag time was added to our model, it might be more appropriate. However, the mechanism is not clear. Moreover, the model might become overly complex for the present study. Therefore, this factor was not added to the model and we consider that our method is capable of simulating various dosages using the estimated parameters.

Next, we simulated the inhibition of TXB₂ and PGE₂ biosynthesis after administration of aspirin at various doses. Those results showed an antiplatelet effect, while the inhibition of biosynthesis of TXB₂ was greater than 90% when the dose of aspirin was greater than 81 mg. On the other hand, the inhibition of biosynthesis of PGE₂ was in a range of 37.9 to 89.5%, thus we concluded that the risk of gastrointestinal disorders differs by dosage. Aspirin irreversibly inhibits COX-1, while platelets cannot synthesize new COX-1, thus low-dose aspirin was adequate to inhibit the biosynthesis of TXB₂. However, it was considered that the inhibition of biosynthesis of PGE₂ occurred in a dose-dependent manner, as the turnover of COX-1 in gastric mucosa is approximately twice as fast as that in platelets. We concluded that the results of our analysis are reasonable, because the approved dosage of aspirin for use as an antiplatelet agent is 81 mg.

On the other hand, aspirin at 81 mg does not exert an antiplatelet effect on the initial day of administration. Thus, it was confirmed that a dose of 162 mg or more is needed to exert an immediate antiplatelet effect in patients with acute cardiovascular thrombosis. This result also agrees with the recommendation of the Japan Stroke Society that patients with acute ischemic stroke at risk for thrombolysis receive aspirin at 160 to 300 mg/d within the first 48 h of symptom onset. Additionally, the American College of Chest Physicians recommends a dose of 160 to 325 mg/d.

We investigated the relationships between different doses repeated for 14 d, and inhibition of biosynthesis of TXB₂ and PGE₂. A dose of aspirin greater than 81 mg was found to be necessary for exerting an adequate antiplatelet effect, while less than 10 mg was shown to be needed for prevention of gastrointestinal lesions. Therefore, it is difficult to gain an antiplatelet effect without inducing gastrointestinal lesions when aspirin is administered to patients at the same dose once daily. However, as noted above, the turnover rate of COX-1 in gastric mucosa is faster than that in platelets. Therefore, we considered that the antiplatelet effect exerted by aspirin and inhibition of biosynthesis of PGE₂ would be recovered to less than 37.9% by dividing the dosage. We simulated administrations of aspirin using regimen 1 (81 mg on day 1, 5 mg on day 2) and regimen 2 (162 mg on day 1, and 5 mg on day 2). However, the inhibition of biosynthesis of TXB₂ was under 90% during the period of administration, while that of PGE₂ was over 37.9%. Since, PGE₂ biosynthesis inhibition was not recovered, it was not possible for inhibition of biosynthesis of TXB₂ to be greater than 90% and that of PGE₂ to be less than 37.9%, even with other dosage regimens (data not shown). No relationship between inhibition of TXB₂ and bleeding tendency has been reported. A previous study found no significant difference for major bleeding complications between patients receiving aspirin at 30 and 283 mg, though episodes of minor bleeding occurred significantly more often in the patients receiving the 283 mg dose. Also in that study, no relationship between inhibition of TXB₂ and bleeding tendency was clearly shown, because TXB₂ was not measured. Therefore, we used only inhibition of TXB₂ (TXA₂) as an indication of the antiplatelet...
effect. All of the pharmacokinetic and pharmacodynamic parameters utilized were mean values, thus individual differences were not analyzed in our study. However, we performed theoretical analysis of the efficacy of aspirin using our pharmacokinetic-pharmacodynamic model. Furthermore, it is thought that a rational dosage of aspirin for individual patients can be determined according to this analytical model. For example, if the personal pharmacokinetic parameters of aspirin are obtained, it would be possible to estimate the inhibition of TXB₂ in individual patients by applying those values to the model. Thus, we considered that the present analytical model was useful to establish rational dosage regimens of aspirin for individual patients.

Our results suggest that it is difficult to determine a rational dosage regimen of aspirin to exert an antiplatelet effect without inducing gastrointestinal lesions. Therefore, it is recommended that along with aspirin, a proton pump inhibitor or H₂ receptor antagonist also be used for prevention of gastrointestinal lesions.

REFERENCES

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