INTRODUCTION

Postoperative hyperbilirubinemia is sometimes encountered after not only hepatobiliary operations but also after highly invasive abdominal surgery, postoperative intraperitoneal infection, and generalized circulatory impairment (e.g., long-term hypotension). Hyperbilirubinemia after subtotal thoracic esophagectomy, involving thoracotomy and/or laparotomy, is the most well-known type of postoperative hyperbilirubinemia. It is transient, and usually has a benign course, but sometimes persists and leads to a serious outcome. The causes of this postoperative hyperbilirubinemia include: 1) bilirubin overload because of blood transfusion during surgery, etc.; 2) hepatocellular dysfunction; 3), and mechanical stenosis of the extrahepatic bile ducts. Schmid defined hyperbilirubinemia due to hepatocellular dysfunction, in which there is an increase of conjugated bilirubin as well as accumulation of bile in enlarged biliary canaliculi, as “benign postoperative intrahepatic cholestasis,” and suggested that this type of cholestasis is caused by hyposecretion of bile due to transient hepatocellular dysfunction.

Clinical Study

Dipyridamole Prevents Hyperbilirubinemia Caused by Intrahepatic Cholestasis after Resection of Esophageal Cancer

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Abstract: Hyperbilirubinemia after subtotal esophagectomy, involving thoracotomy and/or laparotomy, is the most well-known type of postoperative hyperbilirubinemia. Dipyridamole, a drug used to treat ischemic heart disease, influences the metabolism and transport of adenosine and adenosine nucleotide, and it potentiates the action of adenosine. In this study, we first found that dipyridamole prevented liver dysfunction by an experiment using dogs and then performed a clinical study to evaluate the effect of preoperatively administered dipyridamole on the occurrence of hyperbilirubinemia.

Total bilirubin (T-Bil) exceeded 2.0 mg/dl during the observation period in five patients (45.5%) from the dipyridamole (Persantin, Boehringer)-treated group (P group), but it exceeded 3.0 mg/dl in only two of them (maximum value: 3.46 mg/dl). In the untreated group (NP group), however, T-Bil exceeded 2.0 mg/dl in nine patients (69.2%) and exceeded 3.0 mg/dl in seven of them (maximum value: 6.42 mg/dl). In the P group, direct bilirubin (D-Bil) exceeded 1.0 mg/dl in two patients (maximum value: 1.08 mg/dl). In the NP group, it exceeded 1.0 mg/dl in seven patients (maximum value: 3.66 mg/dl). In a comparison between the P and NP groups, the P group showed significantly lower values of both T-Bil and D-Bil (p < 0.05).

Dipyridamole may prevent liver dysfunction by minimizing intrahepatic cholestasis.

Key words: Dipyridamole, Hyperbilirubinemia, Intrahepatic cholestasis, Esophageal cancer, Portal blood flow

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hypofunction induced by severe surgical invasion\(^2\). However, the pathophysiology of postoperative hyperbilirubinemia is still not sufficiently clear, and no effective treatment has been established. We hypothesized that postoperative hyperbilirubinemia could be caused by interruption in the hepatic blood circulation and conducted the present study to investigate this possibility. It is known that catecholamine receptors and adenosine receptors are involved in the regulation of hepatic hemodynamics\(^3,4\). Dipyridamole, a drug used to treat ischemic heart disease, influences the metabolism and transport of adenosine and adenosine nucleotide, and it potentiates the action of adenosine\(^5\). This adenosine-potentiating action of dipyridamole induces the enlargement of hepatic blood vessels (the portal venous system) and results in an increase of hepatic blood flow. Therefore, we hypothesized that transient hepatic dysfunction caused by persistent hypoxia could be treated with dipyridamole to increase hepatic blood flow and prevent the occurrence of hyperbilirubinemia by increasing the hepatic blood flow during surgery.

In the present study, we first conducted an experiment using dogs to examine the effect of dipyridamole on portal venous flow, and then performed a clinical study to evaluate the effect of preoperatively administered dipyridamole on the occurrence of hyperbilirubinemia.

**SUBJECTS AND METHODS**

**(A) Effect of dipyridamole portal venous flow in dogs**

Fifteen adult mongrel dogs (body weight: 8–15 kg) were anesthetized with Nembutal (25 mg/kg, i.v.) and used in this experiment. After intubation, the animals were immobilized with a muscle relaxant (Succin, 2 mg/kg, i.v.), and maintained on a respirator. Measurement of systemic arterial pressure (SAP) and central venous pressure (CVP) as well as blood collection were performed using polyethylene tubes inserted via the femoral artery and vein. Measurement of portal venous pressure (PVP) and intraportal administration of the test drug were done using a polyethylene tube inserted via a branch of the mesenteric vein, the tip of which was placed in the porta hepatis region. Measurement of hepatic arterial blood flow (HAF) and portal venous flow (PVF) was performed with an ultrasonic blood flow meter. All the circulatory parameters were simultaneously recorded on a pen recorder, and data were entered into a microcomputer. Statistical significance of differences was tested by ANOVA and the Student’s t-test.

(This experimental study was conducted under the auspices of the Animal Care and Use Committee of Yamanashi Medical University.)

**Protocol 1.** Effect of intravenous dipyridamole on the hepatic circulation (dose-response study)

Dipyridamole was administered intravenously to 5 out of 15 animals, and the dose was gradually increased from 100 μg/kg to 200 μg/kg, 300 μg/kg, and 400 μg/kg. The heart rate (HR), systemic arterial pressure (SAP), hepatic arterial blood flow (HAF), portal venous pressure (PVP), portal venous flow (PVF), and portal vascular resistance (PVR; PVP/PVF) were measured.

**Protocol 2.** Effect of dipyridamole in an endotoxinshock model

After intraportal administration of 2 mg/kg of lipopolysaccharide (LPS), hepatic hemodynamics (systemic arterial pressure, central venous pressure, hepatic arterial blood flow, portal venous pressure, portal venous flow, and...
portal vascular resistance) and liver function (GOT, GPT, and LDH) were compared between 5 dogs in a dipyridamole-pretreated group and 5 dogs in an untreated group. In the dipyridamole-pretreated group, 1 mg/kg of dipyridamole was given intravenously 20 min before the administration of LPS, while the control group received the same volume of physiological saline. Blood samples were intravenously collected before LPS administration, as well as 30, 60, 120, 180, 240, and 300 min after LPS administration.

(B) Inhibitory effect of dipyridamole on postoperative hyperbilirubinemia

1. Subjects and method of dipyridamole administration

The subjects were patients with thoracic esophageal cancer who underwent subtotal esophagectomy with 2-field dissection and esophageal reconstruction using a gastric tube at Yamanashi Prefectural Central Hospital between August 1991 and December 1994. All operations involved right thoracotomy and laparotomy performed by the same surgeon. All patients were anesthetized with a gaseous anesthetic (GOI or GOE). Patients were returned to the ICU with endotracheal intubation, and were ventilated for 4 to 5 days postoperatively. Postoperative nutrition was started with intravenous hyperalimentation (IVH) from 3 to 4 days after surgery, and tube feeding was not performed. No restrictions were placed on the method or duration of preoperative adjuvant therapy, but patients found to have leukopenia or abnormal liver function preoperatively were excluded from the study.

Patients meeting the above conditions were divided at random into a dipyridamole (Persantin, Boehringer)-treated group (P group) and an untreated group (NP group). The P group was administered 10 mg of dipyridamole diluted with 10 ml of physiological saline twice a day (morning and evening) intravenously from the first to the fifth postoperative day. Consent to participation in the study was obtained from the subjects preoperatively.

2. Evaluation method

The following parameters were compared between the two groups: gender, age, preoperative treatment, type of inhalation anesthetic, operating time, blood loss, volume of blood transfusion, postoperative complications, stage of disease, time of starting IVH (days postoperatively), and time of start of oral feeding (days postoperatively).

To assess the effect of dipyridamole on hyperbilirubinemia in the P and NP groups, the concentration-time profiles and maximum values were compared for total bilirubin (T-Bil) and direct bilirubin (D-Bil) as the primary endpoints. The same comparison was made for ALP, γ-GTP, GOT, GPT, hemoglobin (Hb), white blood cell count (WBC), platelet count (Plt), total protein (TP), CH-E and CRP as secondary endpoints.

3. Statistical methods

The chi-squared test and Student’s t-test were used to assess the statistical significance of differences between the groups. Two-way ANOVA was performed to examine the primary/secondary endpoints, using the GML procedure in SAS software. We first prepared a data set using “subject”, “administration of the test drug” and “time” as the variables for each item assessed so as to effectively utilize data on patients in whom some measurements were missed. Using this SAS data set, we then performed statistical analysis with a model having each parameter investigated as the characteris-
tic value and “drug”, “time,” and the “drug-time interaction” as factors.

RESULTS

(A) Effect of dipyridamole in dogs

Protocol 1. Effect of intravenous dipyridamole on the hepatic circulation (dose-response study)

As shown in Figs. 1 and 2, intravenously administered dipyridamole reduced the systemic arterial pressure and markedly increased the portal venous flow in a dose-dependent manner. Portal venous pressure tended to increase, while portal vascular resistance was decreased.

Protocol 2. Effect of dipyridamole in an endotoxic-shock model

As shown in Figs. 3 and 4, immediately after intraportal administration of LPS, the systemic arterial pressure, central venous pressure, hepatic arterial blood flow, and portal venous flow all decreased rapidly, while portal venous

Fig. 1. Dose-response curves for intravenous dipyridamole. HR: heart rate, SAP: systemic arterial pressure, HAF: hepatic arterial blood flow. All values are mean ± SE. * Significant difference (P < 0.05).
pressure and portal vascular resistance were markedly increased. Although these values gradually returned toward the pre-administration levels, systemic arterial pressure and portal venous flow remained lower. Hepatic arterial blood flow became higher than before LPS administration after about 30 min. In both the P and NP groups, a marked decrease of systemic arterial pressure was observed immediately after LPS administration, but the return to pre-administration levels was more rapid in the P group than in the NP group and the former group had a higher systemic arterial pressure than the latter. A transient and rapid decrease of portal venous flow was also observed in both groups, but this decrease was smaller in the P group than in the NP group. Examination of the changes in GOT, GPT, and LDL, all of which are indicators of hepatic dysfunction, demonstrated smaller increases in the P group than in the NP group (Fig. 5).
(B) Effect of dipyridamole on postoperative hyperbilirubinemia

(a) There were nine men and one woman in the P group versus 11 men and one woman in the NP group. The median age was 62.0 ± 12.8 years in the P group and 66.9 ± 10.8 years in the NP group, and the average weights were 56.2 ± 7.9 kg and 53.7 ± 2.8 kg, respectively. There were no significant differences (p < 0.05) between the groups in any background factor.

(b) The macroscopic disease stage was as follows: two patients were in stage I, one was in stage II, four were in stage III, and three were in stage IV in the P group, while one patient was in stage I, seven were in stage III, and four were in stage IV in the NP group.

(c) Preoperative treatment was performed in nine out of 22 patients. In the P group, only
chemotherapy was administered in two patients, radiotherapy was given in one patient, and both therapies were given to one patient. In the NP group, only chemotherapy was performed in three patients, radiotherapy was done in one patient, and both therapies were given to one patient.

(d) The inhalation anesthetic varied with the timing of surgery. In the first half of the observation period, isoflurane (GOI) was used more often, while enflurane (GOE) was used more often in the latter half. In the P group, GOI was used in two patients and GOE was given to eight patients. In the NP group, GOI was used in four patients and GOE was given to eight patients. During anesthesia, hemodynamics remained stable in all patients.

(e) The mean operating time, mean blood loss, and mean blood transfusion volume were 304 ± 58.4 min, 661.5 ± 197.3 ml, and 160 ±
370 ml, respectively, in the P group versus 310 ml, 82.8 min, 796.7 ml, and 280 ml in the NP group. There were no significant differences (p > 0.05) between the two groups.

(f) IVH was started 3.8 ± 1.4 days postoperatively in the P group and 3.8 ± 1.3 days postoperatively in the NP group. There was no significant difference between the two groups. Oral intake was started 10.9 ± 2.2 days postoperatively in the P group and 13.8 ± 3.7 days postoperatively in the NP group, with the starting time being significantly earlier in the P group.

< 2 > Parameters assessed

No significant differences were detected between the P and NP groups with respect to preoperative hematological/biochemical data.

(a) Primary endpoints
For T-Bil, in the P group, a single peak was observed at 5 to 6 days after surgery, and the value was within the normal range on the 10th postoperative day. In the NP group, two peaks were seen, one on the 1st day and the second at 6 to 8 days postoperatively, and the T-Bil level had not returned to the normal range on the 14th day postoperatively (Fig. 6). T-Bil exceeded 2.0 mg/dl during the observation period in five patients (45.5 %) from the P group, but it exceeded 3.0 mg/dl in only two of them (maximum value: 3.46 mg/dl). In the NP group, however, T-Bil exceeded 2.0 mg/dl in nine patients (69.2 %) and exceeded 3.0 mg/dl in seven of them (maximum value: 6.42 mg/dl).

D-Bil showed a single broad peak around 4 to 7 days postoperatively in the P group. In the NP group, two peaks were seen, one on the 6th to 7th day and the second one from the 14th day postoperative day onward (Fig. 7). In the P group, D-Bil exceeded 1.0 mg/dl in two patients (maximum value: 1.08 mg/dl). In the NP group, it exceeded 1.0 mg/dl in seven patients (maximum value: 3.66 mg/dl).

In a comparison between the P and NP groups, the P group showed significantly lower values of both T-Bil and D-Bil (p<0.05).

(b) Secondary endpoints
ALP and g-GTP declined to the minimum values at 2 to 3 days postoperatively, and then increased gradually to reach a peak on the 7th to 8th day in both groups. In the P group, there was subsequently a gradual decrease, but the values tended to plateau in the NP group. GOT increased sharply from the day after surgery in both groups. In the P group, GOT decreased again by the 4th postoperative day, but showed a second peak on the 6th postoperative day and gradually declined thereafter. In the NP group, there was a gradual decrease from the day after surgery, and normalization tended to be faster in the P group. GPT increased from the day

![Graph](image-url)

Fig. 6. Change of total bilirubin (T-Bil) on postoperative hyperbilirubinemia. All values are mean ± SE.* Significant difference (P < 0.05) between each value in dipyridamole-pretreated group (open circles) and that in an untreated group (closed circles).
after surgery in both groups, and then returned to the preoperative level by 3 to 4 days postoperatively. Thereafter, there was a gradual increase to around 50 (U/l) in both groups on the 15th postoperative day. No statistically significant difference was seen between the groups with respect to the secondary endpoints.

DISCUSSION

After resection of esophageal cancer, hyperbilirubinemia (T.Bil ≥ 2.0 mg/dl) has been reported to occur at a relatively high incidence of 46.9 to 60.8 % [7,8]. The hyperbilirubinemia is characterized by two peaks, one immediately after surgery and one about a week later [7]. Hyperbilirubinemia occurring immediately after operation shows a predominance of indirect (free) bilirubin, and appears to be caused by bilirubin overload due to blood transfusions and absorption of hematoma [7]. In contrast, delayed hyperbilirubinemia shows a predominance of direct (conjugated) bilirubin; its mechanism of onset is still unclear, although hepatocellular dysfunction and associated cholestasis might be implicated.

In the present study, no early postoperative increase of bilirubin was observed, and delayed-onset, direct bilirubin-predominant hyperbilirubinemia was predominant. The incidence of this type of hyperbilirubinemia was the same as in previous reports. The reason for the lack of early-onset postoperative hyperbilirubinemia was thought perhaps to be because our patients required blood transfusion compared with those reported previously. Hyperbilirubinemia occurring after esophageal cancer surgery, especially that seen after about 1 week, appears to be caused by a mechanism other than intraoperative bleeding and blood transfusion. This elevation of bilirubin appears to be caused by cholestasis, since it is not correlated with the
elevation of GOT and GPT, but there is a correlation with elevation of biliary enzymes such as ALP and γ-GTP.

Bile excretion is largely dependent on the movement of the villi in the biliary canaliculi\(^{11}\). The skeletons of these villi consist of actin filaments and polymerization of these filaments depends on the cellular ATP content, so that a sufficient ATP level in hepatocytes is necessary for the villi to function\(^{10}\). Constriction of the biliary canaliculi is mediated by microfilaments and is considered to occur in canaliculi that have been dilated by ATP and bile transport\(^{12}\).

Irwin reported that the hepatic microcirculation is impaired by highly invasive operations, such as those for esophageal cancer, and the membrane permeability of hepatocytes is increased. Accordingly, ATP is released from hepatocytes into the extracellular biliary canaliculi. As a result, the hepatocyte ATP level is reduced and it may be assumed that various cellular functions are impaired\(^{10}\). Since hepatocytes have a poor nucleic acid storage capacity, the pool of nucleotides such as ATP is rapidly reduced when the hepatic circulation is impaired. Thus, it is assumed that postoperative hyperbilirubinemia is related to a decrease of the ATP level in the hepatocytes.

It is also known that the hepatic ATP pool is increased by the administration of adenosine. Research on liver transplantation conducted by Palombo has demonstrated that the administration of ATP precursors (adenine and adenosine) is effective for increasing the ATP content of hepatocytes\(^{13}\). Dipyridamole potentiates the action of adenosine and thus dilates the hepatic blood vessels. Its pharmacological actions are considered to include both coronary vasodilatation and protection of the myocardium by preventing a decrease of the myocardial ATP concentration and mitochondrial changes in a hypoxemic environment\(^{18}\).

In our animal study, dipyridamole markedly increased the portal venous flow and lowered the portal vascular resistance in a dose-dependent manner. These results are consistent with previous reports suggesting that dipyridamole stimulates adenosine and thus inhibits neurogenic constriction of the portal vein via the A2 receptors\(^{14,15}\). Furthermore, our study of an endotoxic-shock model induced by intraportal administration of LPS showed that dipyridamole increased the portal venous flow and prevented liver dysfunction. Therefore, we confirmed that dipyridamole could potentiate the actions of adenosine on the hepatic circulation, thus increasing hepatic blood flow and maintaining the hepatocellular ATP content.

The suppressive effect of dipyridamole on hyperbilirubinemia in our clinical study was considered to be related to its vasodilatory action in maintaining the portal venous flow. Intraoperative hepatic blood flow is generally reduced by surgical procedures or by positive pressure ventilation during anesthesia. This can result in impairment of the hepatic microcirculation and may cause delayed bile excretion due to impaired activity of the villi in the biliary canaliculi and cholestasis in the hepatocytes. It has been reported that portal venous flow is increased in patients under hypotensive anesthesia when adenosine is administered\(^{16}\) and also that oral administration of dipyridamole elevates portal venous flow\(^{17}\). These reports support the results of the present study. In addition to its vasodilatory action, dipyridamole has also been reported to inhibit cellular uptake of adenosine and to potentiate the action of adenosine by inhibition of adenosine deaminase\(^{4}\). It is assumed that this action would lead to an increase of hepatocellular ATP and thus inhibit hyperbilirubinemia by maintaining the
liver function during severe surgical invasion. As a result, it is considered that this insufficiency of liver microperfusion is improved by the administration of dipyridamole.

The only clinical studies that have assessed the effects of treating postoperative hyperbilirubinemia have employed corticosteroids\(^1\) or prostaglandin E\(I\)\(^2\). In this acute experiment using dogs, LPS, which is a toxic agent, caused liver cell injury, and values of GOT and GPT were increased consequently. On the other hand, in the clinical study, the longer esophageal operative time than other procedures caused liver congestion as seen from the changes of \(\gamma\)GTP, ALP, T-Bil and D-Bil values. In the future, it is hoped that administration of dipyridamole may be effective for preventing the progression from postoperative hyperbilirubinemia to hepatic failure after highly invasive operations such as those on esophageal cancer.

**CONCLUSIONS**

1. The effect of dipyridamole on hepatic blood flow and hepatic function was evaluated using anesthetized dogs with endotoxic-shock created by intraportal administration of LPS.

2. Hepatic circulatory insufficiency and hepatic dysfunction induced by administration of LPS were ameliorated by pre-administration of dipyridamole. These results suggested that an adenosine-mediated system plays an important role in maintaining hepatic blood flow and that dipyridamole could be used to improve the hepatic arterial circulation and liver function after major surgery.

3. The suppressive effect of dipyridamole on hyperbilirubinemia was examined in patients with esophageal cancer, who often develop hyperbilirubinemia that is considered to be caused by cholestasis.

4. The incidence of hyperbilirubinemia (T-Bil \(\geq\) 2.0 mg/dl) was 84.6% in the untreated group, but was only 45.5% in the dipyridamole-treated group.

5. Early postoperative hyperbilirubinemia is caused by intraoperative bleeding and blood transfusion, while the hyperbilirubinemia which appears about one week postoperatively shows a predominance of direct bilirubin and appears to be caused by intrahepatic cholestasis.

6. Dipyridamole, in addition to its vasodilatory action, maintains the portal venous flow and hepatocyte ATP content via its influence on adenosine, and may prevent liver dysfunction by minimizing intrahepatic cholestasis.

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Diprydanole Prevents Hyperbilirubinemia Caused by Intrahepatic Cholestasis after Resection of Esophageal Cancer


