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Abstract

The effect of Picibanil, a streptococcal agent, on the development of liver injury after operations for urogenital cancer was studied retrospectively in the light of serum alanine aminotransferase (ALT) activity. The series comprised 32 cases receiving Picibanil and 33 controls with otherwise comparable clinical backgrounds. Picibanil reduced the incidence of postoperative ALT rise over 50 U/l within 6 weeks but increased it thereafter. The increase in ALT activity after 6 weeks was relatively small and was seen more often in patients given blood transfusions. It was interpreted as retardation and suppression of ALT rise and as being related to the induction of interferon or to immunopotentiation. Other antihepatotoxic effects of Picibanil, due to its antioxidant activity, for example, may also account for the prevention of the early postoperative rise in ALT activity.

KEYWORDS: picibanil, immunopotentiator, interferon inducer, serum alanine aminotransferase, postoperative liver injury, urogenital cancers

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—— BRIEF NOTE ——

EFFECT OF STREPTOCOCCAL PREPARATION (PICIBANIL) ON THE POSTOPERATIVE RISE IN SERUM ALANINE AMINOTRANSFERASE ACTIVITY IN PATIENTS WITH UROGENITAL CANCER

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Abstract. The effect of Picibanil, a streptococcal agent, on the development of liver injury after operations for urogenital cancer was studied retrospectively in the light of serum alanine aminotransferase (ALT) activity. The series comprised 32 cases receiving Picibanil and 33 controls with otherwise comparable clinical backgrounds. Picibanil reduced the incidence of postoperative ALT rise over 50 U/l within 6 weeks but increased it thereafter. The increase in ALT activity after 6 weeks was relatively small and was seen more often in patients given blood transfusions. It was interpreted as retardation and suppression of ALT rise and as being related to the induction of interferon or to immunopotentiation. Other antihepatotoxic effects of Picibanil, due to its antioxidant activity, for example, may also account for the prevention of the early postoperative rise in ALT activity.

Key words: Picibanil, immunopotentiator, interferon inducer, serum alanine aminotransferase, postoperative liver injury, urogenital cancers.

Picibanil*[1] is a streptococcal preparation developed initially as an immunopotentiator for cancer immunotherapy (1). It also induces interferon as demonstrated recently by Matsubara *et al.* (2) with a mouse system. A clinical trial of Picibanil as an interferon inducer for treatment of chronic HB_sAg-positive hepatitis has been started, even though the treatment of hepatitis B-virus infection with interferon, which was initiated by Greenberg *et al.* (3), is still controversial (4, 5). In view of the originally described action of interferon in

*[1], OK-432 (Chugai Pharmaceutical Co., Ltd.).

inhibiting the reduplication of virus (6), prevention rather than treatment of virus hepatitis with interferon would be more rational.

In the present study, the preventive effect of Picibanil on postoperative liver injury was investigated retrospectively in urogenital cancer patients who underwent surgery. The urogenital operation was chosen, because it has minimal direct effects on the hepatobiliary system. The alteration of serum alanine aminotransferase (ALT, L-alanine: 2-oxoglutarate aminotransferase EC 2. 6. 1. 2) activity was followed as a sensitive and most frequently positive marker of acute hepatic injury following operation (7–9). Since compounds known as immunopotentiators also inhibit the induction of toxic liver injury caused by non-viral agents (10), patients who had no blood transfusion were also included in this study. Therefore, the effect of Picibanil was evaluated not only as an interferon inducer (or immunopotentiator) but also as a general antihepatotoxic agent. The curative effects of Picibanil on urogenital cancer patients are reported elsewhere (11, 12).

Materials and methods. The patients with urogenital cancers, who were admitted to the Okayama University Hospital and underwent surgery, were divided into two groups based on the use of Picibanil. Their clinical backgrounds are listed in Tables 1 and 2. Cases with hepatobiliary involvement at the time of

TABLE 1. CLINICAL BACKGROUND OF PATIENTS IN THE PICIBANIL-TREATED AND CONTROL GROUPS

Clinical background	Number of patients	
	Picibanil	Control
Diagnoses:		
Renal cell carcinoma	7	4
Renal pelvic carcinoma	5	2
Bladder carcinoma	14	18
Ureteral carcinoma	0	1
Ureteral carcinoma + bladder carcinoma	4	2
Testicular carcinoma	1	2
Penile carcinoma	0	4
Prostatic carcinoma	1	0
Blood transfusion:		
On operation[a]	19(2)	18(2)
None throughout hospitalization	13	15
Operation:		
Nephrectomy	7	5
Nephrectomy + partial cystectomy	8	5
Total cystectomy	12	5
Partial cystectomy	1	8

Table 1 Continued

Table 1 Continued

Clinical background	Number of patients	
	Picibanil	Control
Ileal conduit	1	1
Bilateral ureterocutaneostomy	0	2
Transurethral coagulation	1	0
Amputation of the penis	0	4
Castration	1	3
Exploratory laparotomy	1	0
Radiation or chemotherapy after operation:		
Irradiation (^{60}Co or Linac)	2	6
Irradiation (^{60}Co or Linac) + FOBEM[b] ± FT-207	13	3
Irradiation (^{60}Co or Linac) + 5-fluorouracil, mitomycin C, bleomycin or cyclophosphamide (single or in combination)	0	8
FOBEM ± FT-207	12	4
5-fluorouracil, FT-207, mitomycin C, bleomycin, actionomycin D, cyclophosphamide, vincristine, carboquone or thio-TEPA (single or in combination other than FOBEM)	1	8
Medroxyprogesterone acetate and diethylstilbestrol diphosphate and/or (5-fluorouracil or FT-207, ifosfamide, vincristine and adriamycin)	4	1
None	0	3

a, During or with close temporal relation to the operation. The number of patients with initiation of blood transfusion before operation is given in parentheses; and *b*, FT-207 + vincristine + bleomycin + cyclophosphamide + mitomycin C.

TABLE 2. CLINICAL PARAMETERS OF PATIENTS IN PICIBANIL-TREATED AND CONTROL GROUPS

Clinical parameters	Picibanil	Control
Calendar years for period studied	1973-1978	1971-1976
Age	58.5±12.5 (20-74)	60.2±11.5 (30-77)
Preoperative ALT activity (U/l)	17.6±13.3 (3-69)	15.7± 9.8 (4-44)
Maximum postoperative day in ALT follow-up (days)	59.8±35.8 (23-194)	55.2±30.4 (22-148)
Amount of blood transfused (ml)	1116± 707 (200-2800)	1481±1053 (400-4500)
Total dose of Picibanil administered (KE)	18.9±19.5 (1.2-75.6)	0

Values are given as mean±standard deviation and/or range. The numbers of cases studied were 32 (5 female) for Picibanil and 33 (6 female) for the control.

operation, such as hepatitis, other inflammatory diseases, metastasis of malignant tumors or the non-metastatic hepatic dysfunction associated with renal

carcinoma (13), are not included. Picibanil was started preoperatively in 11 cases and postoperatively in 21 cases. The listed doses of Picibanil were injected subcutaneously, usually starting with 0.2 KE and increasing up to 1 or 2 KE and maintaining the maximum doses thereafter. Preoperative doses ranged from 3 to 66 KE with a mean and standard deviation of 17.5 and 18.0 KE, respectively. Serum ALT activity was determined by a UV method with an SMA-12/60 Technicon Auto Analyzer II at 37.5°C at the Central Laboratory, Okayama University Hospital and expressed as U/l. By this method the upper limit of normal values was 37 U/l. Changes in ALT activity were followed every one to two weeks for the period listed in Table 2 with a minimum of three determinations. Incidentally, patients with increased ALT activities had no diagnostic hepatitis or cholestasis of known etiology. The independence in cross classification was analyzed by the χ^2 test and the difference in mean value by Student's *t*-test.

Results. Patients in the Picibanil-treated and control groups were similar in the distribution of diseases and operative procedures, age, number of cases with blood transfusion, amount of blood transfused, preoperative ALT activity and follow-up period, even though the calendar years for the study of these two groups differed slightly (Tables 1 and 2). Postoperative radiation and chemotherapy were somewhat different for the two groups, more of FOBEM combination being found in the Picibanil-treated and other combinations of chemotherapeutics in the control (Table 1). However, no prevalence in ALT elevation was found among patients receiving different postoperative treatments. Thus any differences should not affect comparisons between the two groups.

Postoperatively, serum levels of ALT, in most cases, showed either no apparent peak or only one peak. The mean maximum activity of serum ALT for the Picibanil-treated group was slightly less than that for the control, although the difference was not statistically significant (Table 3). The difference

TABLE 3. POSTOPERATIVE ALTERATIONS IN ALT ACTIVITY IN THE PICIBANIL-TREATED AND CONTROL GROUPS

Clinical parameters	Picibanil	Control
Maximum ALT activity (U/l)	47.4±40.9 (5-191)	61.7±60.5 (9-235)
Postoperative day for maximum ALT activity (days)	28.3±23.5 (1-100)	30.9±25.3 (4-127)

Values are given in mean ± standard deviation and range. For numbers of cases studied, see the legend to Table 2.

in mean postoperative days between the two groups for maximum ALT activity was not significantly different. The numbers of cases with definite increases in

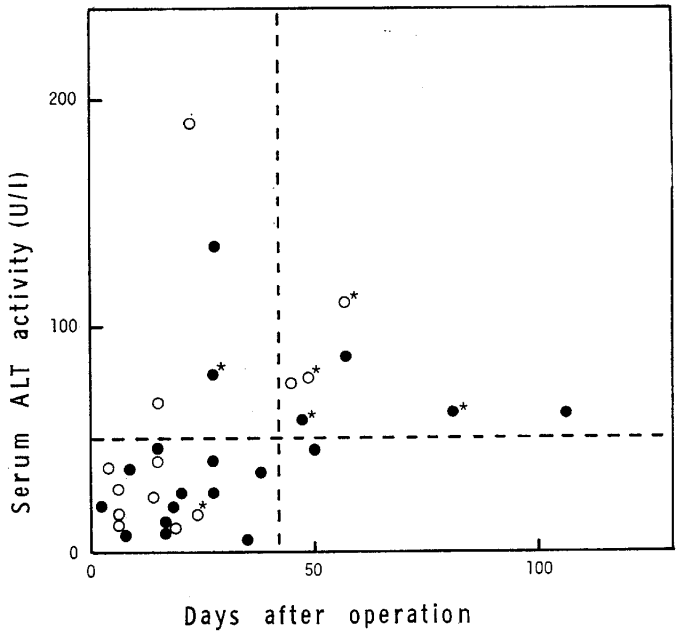

Fig. 1. Maximum rises in serum ALT activity after operation in patients treated with Picibanil. ●, with blood transfusion; ○, without blood transfusion; and *, the maximum value in the last determination of available data. A dotted holizontal line was drawn at a serum ALT activity of 50 U/l and a dotted vertical line at 42nd day (6 weeks after operation).

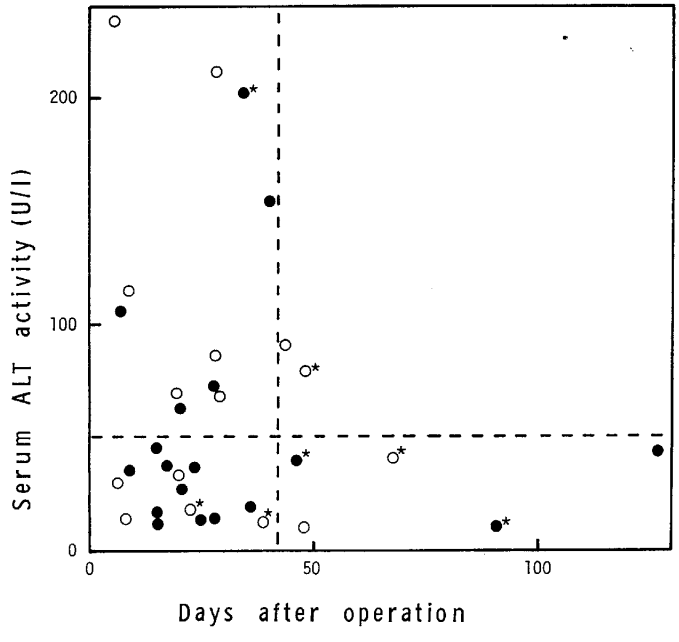

Fig. 2. Maximum rises in serum ALT activity after operation in control patients. Symbols, see the legend to Fig. 1.

maximum ALT activity (>50 U/l) were similar; 11 out of 32 (34.4%) for the Picibanil-treated, and 13 out of 33 (38.4%) for the control (*cf.* Figs. 1 and 2).

When the maximum ALT activities during the course of hospitalization were plotted against the number of postoperative days (Figs. 1 and 2), the maximum increase in ALT activity above 50 U/l within 6 weeks after operation was found in 84.6% of the control patients, as is usually reported (9), whereas it was found in only 36.4% of Picibanil-treated patients. The difference was statistically significant ($P<0.05$)*[2]. When the cases with or without blood transfusion were analyzed separately, a statistically significant level was not reached for either. Conversely, the number of cases with maximum increases in ALT activity over 50 U/l was significantly larger in the treated group than in the control ($P<0.05$) 6 weeks after operation, although the extent of the maximum inerease in ALT activity was much less and the activities were mostly below 100 U/l. Analysis of the data for the cases with blood transfusion and with elevated maximum ALT activities above 50 U/l only gave similar results; the number of cases with increased ALT activities was greater in the control than in the treated before 6 weeks and *vice versa* after 6 weeks. The results could be interpreted as indicating that Picibanil treatment not only prevented the postoperative ALT rise unrelated to blood transfusion but also suppressed and retarded ALT rise related to blood transfusion.

Discussion. The validity of comparing the data between the Picibanil-treated and the control groups is apparent from the statements given under Results. Although the total number of cases studied was limited, the incidence of definite increases in ALT activity (>50 U/l) after operation was relatively large, 34.4% for the Picibanil-treated and 38.4% for the control. This satisfies the minimum statistical requirement for comparing the data, although the difference in the incidence of ALT rise between the two groups was not significant.

Factors involved in the development of postoperative liver injury are numerous: drug allergy with anesthetics, chemotherapeutics, antibiotics, analgesics and other drugs, hypoxia due to hypoperfusion of the liver as a result of direct operative invasion or blood loss, infection by viral agents transmitted through the transfusion of blood and other biological materials, direct invasion of the hepatobiliary system and its postoperative complications. The same applies to the postoperative increase in serum ALT activity. Since patients with hepatobiliary involvement were not included in the present study, the postoperative rise in ALT activity was due to the other factors. Incidentally, hepatitis or

*[2], The dose response in this effect was not apparent, because the doses of Picibanil given were close together except the extreme values given in Table 2. Beneficial effect of preoperative administration of Picibanil was not analyzed due to limitation in the number of cases to be compared.

drug-induced liver injury was not diagnosed in the patients studied. Thus, the postoperative rise in ALT activity is still heterogenous in its etiology and poorly defined. Nevertheless, two signifiicant results emerged from the present study. 1) Picibanil treatment lowered the incidence of early ALT rise (within 6 weeks) after operation whether or not blood had been transfused. 2) It retarded and suppressed the rise in ALT activity over 6 weeks when blood had been transfused.

The early rise in ALT activity after operation is considered as resulting from the direct effect of operation, such as hypoxia due to hypoperfusion of the liver by bleeding and other causes (1 to 2 days after operation) or from drug allergy (after 2 weeks) (9, 14). Picibanil reduced the incidence of the early rise in ALT activity probably by inhibiting the development of liver injury as a general antihepatotoxic agent* as was demonstrated by Yoshikawa *et al.* (10) in the prevention of free radical-induced hepatic injury. Liver injury due to drug allergy may not be blocked by Picibanil as an immunopotentiator, because the lymphocyte stimulation test was more frequently positive for the postoperative cases with ALT elevation (15). The preferential suppression and retardation of the ALT rise after blood transfusion (more or less due to viral agents and the host immune mechanism) may be related to interferon induction or immunopotentiation by Picibanil.

It is beyond the scope of this study to discuss the mechanism of prevention of postoperative liver injury by Picibanil treatment without further information on virus and host immune status. The importance of the present study lies in the fact that it shows the necessity for future studies with a larger number of cases to explore the preventive and curative effects of Picibanil and its related compounds on viral hepatitis and other hepatic injuries.

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