HEPATIC AND INTESTINAL CHANGES IN RATS TREATED WITH T-0126, A MICROsomAL TRIGlyceride TRANSFER PROTEIN (MTP) INHIBITOR

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ABSTRACT — In the present study, we investigated the potential toxic effects of 2-week oral treatment with T-0126, a novel microsomal triglyceride transfer protein (MTP) inhibitor, on the liver and intestine in male and female rats. Administration of T-0126 decreased serum lipids and resulted in fat accumulation in the liver and the small intestine. In addition, slight changes in the liver, including an increase in serum aminotransferase (AST and ALT) activity, presence of focal inflammatory lesions, and prolongation of PT and APTT were observed after treatment with T-0126. These changes may be related to a mechanism based on malabsorption of fat, fat-soluble antioxidants, and vitamin K, although we cannot exclude other potential mechanisms such as direct cytotoxicity of T-0126.

KEY WORDS: Microsomal triglyceride transfer protein inhibitor, Liver, Intestine, Fat accumulation, Rat

INTRODUCTION

Microsomal triglyceride transfer protein (MTP) is a heterodimeric lipid transfer protein localized in the endoplasmic reticulum of hepatocytes and enterocytes. As MTP catalyzes the transfer of triglyceride and cholesterol ester to apoB particles (very low density lipoprotein [VLDL] or chylomicrons) (Wetterau et al., 1992; Jamil et al., 1995), MTP inhibitors are expected to be strong antilipemic agents that act by preventing VLDL and chylomicrons secretion from the liver and intestine (Wetterau et al., 1998; Sorbera et al., 2000; Robl et al., 2001; Chang et al., 2002; Kawanishi et al., 2005).

It has been reported that abetalipoproteinemia patients, who have MTP gene defect, show fat accumulation in duodenum, fatty liver, fat malabsorption, ancythocytosis and various neurological problems (Ohashi, 1998). It has also been reported that heterozygous MTP knockout mice show fat accumulation in the liver (Raabe et al., 1998, 1999). Therefore, MTP inhibitor-treated animals may show similar fat accumulation in duodenum, fatty liver, and fat-soluble vitamin malabsorption.

Wetterau et al. (1998) reported that an MTP inhibitor developed by Bristol-Myers Squibb has strong lipid-lowering effects but produces secondary effects, such as fat accumulation in hepatocytes and

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enterocytes. Beside this information, there are only a few reports on the toxicity of MTP inhibitors.

In the present study, we investigated the potential toxic effects of 2-week oral treatment with T-0126, a novel MTP inhibitor (Kawanishi et al., 2005), on the liver and intestine in male and female rats.

MATERIALS AND METHODS

Animals

Forty-two male and 42 female Crj:CD(SD)IGS rats (5 weeks old) were purchased from Charles River Japan (Kanagawa, Japan), and acclimated in our laboratories for about one week. The animals were housed in stainless-steel cages (three or four animals / cage) in a barrier-system animal room under controlled conditions (temperature: 23 ± 2°C, humidity: 55 ± 5%, 12 hr light/dark cycle) and fed CE-2 pellets (CLEA Japan, Kanagawa, Japan) and tap water ad libitum throughout the experimental period.

All experiments in this study were approved by the Ethics Committee of Tanabe Seiyaku Co., Ltd. and all efforts were made to minimize animal suffering.

Treatment

The rats were administered orally with T-0126 (Fig.1) at doses of 1, 3, 10, 30, and 100 mg/kg/day (n=4 for main groups, n=3 for toxicokinetic groups, for each dose and sex) for 14 days. Dosage levels for this study were selected based on the following two reasons: (1) an increase in serum aminotransferase activity was observed in 10 mg/kg or higher group of female rats in a preliminary 2-week oral dose toxicity study, (2) preliminary TK study showed almost the same plasma concentration between 100 and 300 mg/kg treatment groups. The test compound was suspended in 0.5% sodium carboxymethyl cellulose (Kokusan Chemical, Tokyo, Japan) containing 0.1% NIKKOL (HCO-60) (Nikkо Chemicals, Tokyo, Japan) aqueous solution just before use. The dosing volume was set as 10 mL/kg. Control animals were treated in the same way as the animals treated with T-0126 except that T-0126 was substituted by its vehicle. At 24 hr after the 14th administration of T-0126 or vehicle, animals in the main groups were killed by taking out whole blood from the aorta abdominalis under ether anesthesia.

Throughout the study period, all animals in the main groups were observed for clinical signs daily, and their body weight, food consumption and water consumption were recorded once every two or three days. Animals in the main groups were also subjected to hematolοgy and blood chemistry examination, and autopsied after one-night fasting. Liver, kidneys, heart, lungs, spleen, and intestine were weighed and analyzed biochemically. Histopathology and electron microscopy were also performed after one-night fasting.

Hematology

The following parameters; erythrocyte count (RBC), hemoglobin (Hb), hematocrit (Ht), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), reticulocyte ratio (Ret), platelet count (PLT), and leukocyte count (WBC) were measured in blood samples obtained from all animals in the main groups at autopsy using automatic blood cell counters; M-2000 and R-3000 (Sysmex, Hyogo, Japan). Differential leukocyte count was determined from blood smears under a light microscope. Prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen (Fg) were measured using an automated blood coagulation analyzer (Sysmex CA-5000, Hyogo, Japan).

Biochemistry

The following parameters; aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactose dehydrogenase (LDH), alkaline phosphatase (ALP), creatine kinase (CK), glucose (GLU), total cholesterol (TCHO), HDL cholesterol (HCHO), triglyceride (TG), phospholipid (PL), total protein (TP), albumin (ALB), urea nitrogen (UN), creatinine (CRE), Calcium (Ca), inorganic phosphorus (Pi), sodium (Na), potassium (K), and chloride (Cl) were measured using an automatic analyzer (Hitachi 7150, Tokyo, Japan).

Small pieces of the liver and small intestine were

Vol. 32 No. 2
Hepatic and intestinal changes in rats treated with an MTP inhibitor.

**Fig. 2.** Changes in RBC (A, B), reticulocyte (C, D), WBC (E, F), and neutrophil (G, H) in T-0126-treated female (A, C, E, G) and male (B, D, F, H) rats.
Mean ± S.D. *: p<0.05, **: p<0.01: Significantly different from the vehicle group by parametric-Dunnett’s method.
quickly frozen in liquid nitrogen and used for measurement of cholesterol (TCHO) and triglyceride (TG). Lipids were extracted according to Folch's method (Folch et al., 1957), and TCHO and TG were colorimetrically measured using spectrophotometer with commercial assay kits: Corestezyme-V, Triglyzyme-V (Eiken Chemical, Tokyo, Japan), respectively.

**Light microscopy**

Liver, small intestine, and mesenteric lymph nodes were fixed in 10% neutral buffered formalin. Paraffin sections (4 µm) were stained with hematoxylin and eosin (HE) and examined under a light microscope.

**Electron microscopy**

Small pieces of the liver were fixed in 2.5% glutaraldehyde and 2.0% formaldehyde, postfixed in 1% osmium tetroxide, and embedded in epoxy resin. Ultrathin sections were double-stained with uranyl acetate and lead citrate, and observed under a JEOL-1210 electron microscope (JEOL, Tokyo, Japan).

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**Fig. 3.** Changes in prothrombin time (A, B), activated partial thromboplastin time (C, D), and fibrinogen (E, F) in T-0126-treated female (A, C, E) and male (B, D, F) rats. Mean ± S.D. *: p<0.05, **: p<0.01: Significantly different from the vehicle group by parametric-Dunnett's method.
Hepatic and intestinal changes in rats treated with an MTP inhibitor.

Fig. 4. Changes in serum triglycerides (A, B), total cholesterol (C, D), HDL cholesterol (E, F), and phospholipid (G, H) in T-0126-treated female (A, C, E, G) and male (B, D, F, H) rats. Mean ± S.D. *: p<0.05, **: p<0.01: Significantly different from the vehicle group by parametric-Dunnett's method.
Plasma drug concentration

In the toxicokinetic groups, blood samples were collected via the jugular vein with heparinized syringes at 2, 4, 8 and 24 hr after the 1st and 13th administration of test compound. Blood was stored in ice quickly after collection, and plasma was separated after centrifugation and stored at -20°C in a freezer until analysis. Drug concentrations in the plasma were measured using a high-performance liquid chromatography (HPLC) system. The value below quantification limit (10 ng/mL) was considered as zero.

Statistical analysis

Statistical significance of the difference between the control and the treatment groups was determined by parametric-Dunnett’s method (Dunnett, 1955). Spearman’s rank correlation coefficient was calculated to determine the correlation between serum aminotransferase activity and hepatic lesions.

Fig. 5. Changes in serum AST (A, B), serum ALT (C, D), and serum ALP (E, F) in the T-0126-treated female (A, C, E) and male (B, D, F) rats. Mean ± S.D. *: p<0.05, **: p<0.01: Significantly different from the vehicle group by parametric-Dunnett’s method.
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RESULTS

Clinical signs and changes in body weight, food consumption, and water consumption

No clinical signs were observed in any animal during the experimental period, except for a slight loss of fur and perioral smudge in some rats. No apparent changes in body weight, food consumption and water consumption were recorded.

Hematological findings

Female: Prolongation of PT and APTT, and an increase in neutrophil count were observed in the 100 mg/kg group. An increase in reticulocyte ratio and a slight decrease in fibrinogen level were also observed in the 100 mg/kg group. No abnormal findings were observed in the other parameters.

Male: Slight prolongation of APTT and a slight increase in neutrophil count were observed in the 100 mg/kg group. No abnormal findings were observed in the other parameters. (Figs. 2 and 3)

Blood chemistry findings

Female: Serum AST and ALT levels in all T-
Fig. 7. Changes in lipid levels in the liver (A to D) and intestine (E to H) in T-0126-treated female (A, C, E, G) and male (B, D, F, H) rats. Mean ± S.D. *: p<0.05, **: p<0.01. Significantly different from the vehicle group by parametric-Dunnett’s method.
0126-treated groups were slightly higher than those in the control group and showed apparent individual variance within each group. There was no dose-dependency observed, and only differences in ALT of the 100 mg/kg group and in AST of the 30 mg/kg group were statistically significant. Serum TG and TCHO levels decreased in 3, 10, 30, and 100 mg/kg groups. Serum HCHO level decreased in 3, 10, and 30 mg/kg groups. Serum PL level decreased in the 100 mg/kg group. Serum ALP level increased in the 100 mg/kg group. An increase in serum LDH and CK levels was observed in two female rats in the 10 mg/kg group.

Male: Serum TG level in the 30 mg/kg group decreased, although it showed apparent individual variance and no statistical significance. Serum glucose level slightly increased in the 1 and the 10 mg/kg groups. No abnormal findings were observed in the other parameters. (Figs. 4, 5, and 6)

**Lipids contents in the liver and intestine**

Female: Liver TG content increased in all T-0126-treated groups. Intestinal TG and TCHO contents increased in the 30 and 100 mg/kg groups.

Male: Liver TG content did not dose-dependently

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**Fig. 8.** Changes in relative liver weight (A, B), relative small intestine weight (C, D), and relative spleen weight (E, F) in T-0126-treated female (A, C, E) and male (B, D, F) rats. Mean ± S.D. *: p<0.05, **: p<0.01: Significantly different from the vehicle group by parametric-Dunnett’s method.
### Table 1-1. Microscopic findings in 2-week oral toxicity study of MTP inhibitors in female rats.

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- : no, + : slight, 2+: moderate, 3+: severe change. Numerals represents the number of animals with corresponding change. Vehicle: 0.5%CMC-0.1%NIKKOL(HCO-60) aqueous solution.

### Table 1-2. Microscopic findings in 2-week oral toxicity study of MTP inhibitors in male rats.

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- : no, + : slight, 2+: moderate, 3+: severe change. Numerals represents the number of animals with corresponding change. Vehicle: 0.5%CMC-0.1%NIKKOL(HCO-60) aqueous solution.
change, while liver TCHO content dose-dependently increased. Intestinal TCHO content increased in the 100 mg/kg group. (Fig. 7)

**Organ weight**

Female: An increase in relative liver weight was observed in all T-0126-treated groups. Increases in relative small intestine and spleen weights were also observed in the 30 and 100 mg/kg groups.

Male: A slight increase in relative liver weight was observed in the 3, 10 and 100 mg/kg groups, and an increase in relative small intestine weight was observed in the 100 mg/kg group. (Fig. 8)

**Macroscopic findings**

Female: Discoloration of the liver was observed in all T-0126 treated groups, and discoloration of the small intestine was observed in the 10, 30 and 100 mg/kg groups. Although a slight hemorrhage in the thymus was observed in the 10, 30 and 100 mg/kg groups, no gross findings were observed in the other organs examined.

Male: Discoloration of the liver was observed in the 3, 10, 30 and 100 mg/kg groups, and discoloration of the small intestine was observed in the 100 mg/kg group. Although a slight hemorrhage in the thymus was observed in one rat of each 30 and 100 mg/kg groups, no gross findings were observed in the other organs examined.

**Light microscopy findings**

Summarized findings are shown in Table 1.

Apparent vacuolization of hepatocytes was observed in all T-0126-treated groups of female and male rats (Fig. 10C). The vacuoles were confirmed as lipid droplets by Sudan black stain (data not shown).

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**Fig. 9.** Relationship between histopathological findings and serum aminotransferases in T-0126-treated female rats.

\( \rho \): Spearman’s rank correlation coefficient.
Lipid droplets of various sizes were mainly distributed in the midzonal and periportal areas. Spearman's rank correlation coefficient between the severity of the vacuolation and the AST and the ALT levels in female rats were $\rho=0.489$ (p=0.02) and $\rho=0.385$ (p=0.06), respectively (Figs. 9A and 9B). In all treatment groups of female rats, focal inflammation containing mononuclear cells and neutrophils was observed, mainly in the periportal area (Figs. 10B and C). Spearman's rank correlation coefficients between the severity of the inflammation and the AST and the ALT levels in female rats were $\rho=0.682$ (p=0.00) and $\rho=0.726$ (p=0.00), respectively (Figs. 9C and 9D), and that between the severity of the inflammation and the vacuolation was $\rho=0.194$ (p=0.36) (Fig. 9E). Slight inflammation was also observed in many male rats; however, the lesion was slight and cannot be distinguished from so-called microgranuloma, which is sometimes observed in normal control rats. Histopathologically, no apparent changes were observed in the spleen or lymph nodes.

In the intestine, an increase in the length of villi and vacuolization of the epithelium were observed in female rats treated with T-0126 at 30 and 100 mg/kg.

![Fig. 10. Light micrographs of the liver of control (A) and T-0126 (100 mg/kg)-treated (B, C) female rats. Severe changes in the fatty midzonal and periportal areas, focal lesions of mononuclear cells, and neutrophil infiltration are observed (B). HE stain, bar = 200 \mu m (A, B) and 50 \mu m (C).]
Hepatic and intestinal changes in rats treated with an MTP inhibitor.

and in male rats treated with T-0126 at 100 mg/kg (Fig. 11).

Electron microscopy findings
Ultrathin sections from the livers of female rats treated with T-0126 at 100 mg/kg were examined. Electron microscopy revealed hepatocytes with many round-shaped and medium-electron density lipid droplets (Fig. 12A), and very little glycogen granule. Electron microscopy also confirmed that the inflammatory lesions consisted of mainly lymphocytes and macrophages as well as cell debris in some lesions (Fig. 12B).

Plasma drug concentrations
In general, Cmax and AUC0-24hr values increased in a dose-dependent manner in both male and female rats treated with T-0126. In the 100 mg/kg-treated groups, Cmax and AUC0-24hr values in the female rats were 2-4 fold higher than those in the male rats. (Fig. 13, Table 2)

DISCUSSION
In the present study, we investigated the potential toxic effects of 2-week oral treatment with T-0126, a novel microsomal triglyceride transfer protein (MTP) inhibitor, on the liver and intestine in male and female rats. In our experiments, T-0126 decreased serum lipids and resulted in fat accumulation in the liver and the small intestine. In addition, slight changes in the liver, including an increase in serum aminotransferase (AST and ALT) activity and presence of focal inflammatory lesions were observed after treatment with T-0126.

It is known that MTP inhibitors prevent VLDL and chylomicron secretion from the liver and intestine, and produce accumulation of lipids in the liver and small intestine. It has also been reported that an MTP inhibitor developed by Bristol-Myers Squibb induces fat accumulation in hepatocytes and enterocytes (Wetterau et al., 1998). Our results in this study strongly support these findings, which are common to MTP inhibitors.

![Fig. 11. Light micrographs of the jejunum of control (A) and T-0126 (100 mg/kg)-treated (B) female rats. Increases in the length of villus and vacuolization of the epithelium are observed in T-0126 (100 mg/kg)-treated rat (B). HE stain, bar = 100 μm (A, B).](image-url)
T-0126 decreases plasma lipid level in male rats at 1 through 7 hr after the treatment (Kawanishi et al., 2005). However, in this study, serum lipids levels decreased in T-0126-treated female rats, not in male rats. It must be because the serum sample was taken at 24 hr after the treatment, although the reason for the difference between two sexes is unknown. Plasma drug concentrations in female rats were higher than those in male rats, but this alone may not explain the difference in serum lipid levels between male and female rats.

Previous studies have shown that lipid accumulation was more easily induced in female animals than in male animals, due to the female hormone estrogen (Negishi and Aizawa, 1975; Katoh et al., 1993; Yin et al., 2000). This phenomenon was also reported in some animal models, such as orotic acid- or ethanol-treated fatty liver models. Since the lipid-lowering effect of MTP inhibitors is accompanied by lipid accumulation in hepatocytes, it is suggested that the effect of MTP inhibitors might be stronger in females than in males.

![Electron micrographs of a hepatocyte (A) and a focal inflammatory lesion (B) in one of the female rats treated with T-0126 at 100 mg/kg. The hepatocyte shows many lipid droplets (A). The lesion consists of lymphocytes, macrophages and some cell debris (arrow head). Bar = 5 μm (A, B).]
Hepatic and intestinal changes in rats treated with an MTP inhibitor.

Serum glucose level slightly increased in the 1 and the 10 mg/kg groups of male rats, although the mechanisms and the relationship between the glucose and the lipid levels were obscure.

The increase in serum AST and ALT was observed only in female rats, not in males. As these changes did not correlate with the dose of T-0126, individual differences were remarkable. It is difficult to explain the reason for the sex difference. The change observed in female rats was very severe, and may therefore be related with liver injury.

Liver inflammation as well as AST and ALT elevation would not be due to lipid accumulation, because the correlation coefficients between lipid accumulation and those inflammation parameters were low, and AST and ALT elevation and the inflammatory lesions correlated well with each other. Moreover, we have found that some MTP inhibitors, which induce similar inflammatory lesions, do not produce lipid accumulation, or they induce similar lipid accumulation but no inflammatory lesions (in-house data).

Increases in serum LDH and CK levels were observed in two female rats in the 10 mg/kg group, although there was no dose-dependency.

The increase in spleen weight observed in female rats may be related to inflammation, although apparent histopathological changes were not observed in the spleen. According to a mechanism based on fat malabsorption, one possibility for inflammation is decrease in fat-soluble antioxidants level, such as vitamins E, CoQ10 and lycopene. On the other hand, such liver inflammation has not been reported in MTP knockout mice (Raabe et al., 1999). Therefore, there could be other reasons for the changes; for example, these compounds might have a direct cytotoxic effect.

ALP is widely distributed in the small intestine,

Fig. 13. Plasma drug concentrations after the 1st administration (A, B) and the 13th administration (C, D) in the T-0126-treated female (A, C) and male (B, D) rats.
Mean ± S.D. The value below quantification limit (10 ng/mL) was considered as zero. All of the values in groups below were below quantification limit: 24 hr after the first administration in male 3, 10 mg/kg groups, and 24 hr after the 13th administration in male 1, 3, 10, 30 mg/kg groups.
Table 2-1. Toxicokinetic parameters in 2-week oral toxicity study of MTP inhibitors in female rats.

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<td>Dose</td>
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<td>3 mg/kg</td>
<td>10 mg/kg</td>
<td>30 mg/kg</td>
<td>100 mg/kg</td>
</tr>
<tr>
<td>No.of animals</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1st administration</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.319 ± 0.060</td>
<td>0.731 ± 0.142</td>
<td>1.65 ± 0.21</td>
<td>4.20 ± 0.31</td>
<td>31.3 ± 1.9</td>
</tr>
<tr>
<td>AUC 0-24 hr (µg-hr/mL)</td>
<td>4.30 ± 0.70</td>
<td>9.48 ± 2.73</td>
<td>23.7 ± 5.4</td>
<td>45.2 ± 5.1</td>
<td>430 ± 13</td>
</tr>
<tr>
<td>13th administration</td>
<td>Cmax (µg/mL)</td>
<td>0.380 ± 0.053</td>
<td>0.579 ± 0.118</td>
<td>1.39 ± 0.03</td>
<td>11.9 ± 1.3</td>
</tr>
<tr>
<td>AUC 0-24 hr (µg-hr/mL)</td>
<td>4.64 ± 0.76</td>
<td>6.78 ± 1.82</td>
<td>16.1 ± 0.9</td>
<td>110 ± 14</td>
<td>319 ± 18</td>
</tr>
</tbody>
</table>

Table 2-2. Toxicokinetic parameters in 2-week oral toxicity study of MTP inhibitors in male rats.

<table>
<thead>
<tr>
<th>Compound</th>
<th>T-0126</th>
<th>T-0126</th>
<th>T-0126</th>
<th>T-0126</th>
<th>T-0126</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
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<td>3 mg/kg</td>
<td>10 mg/kg</td>
<td>30 mg/kg</td>
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</tr>
<tr>
<td>No.of animals</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>1st administration</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
<td>Mean ± S.D.</td>
</tr>
<tr>
<td>Cmax (µg/mL)</td>
<td>0.125 ± 0.017</td>
<td>0.557 ± 0.043</td>
<td>2.19 ± 0.54</td>
<td>9.55 ± 3.60</td>
<td>14.4 ± 3.5</td>
</tr>
<tr>
<td>AUC 0-24 hr (µg-hr/mL)</td>
<td>1.48 ± 0.15</td>
<td>6.04 ± 2.14</td>
<td>15.6 ± 6.0</td>
<td>53.3 ± 26.0</td>
<td>148 ± 48</td>
</tr>
<tr>
<td>13th administration</td>
<td>Cmax (µg/mL)</td>
<td>0.186 ± 0.013</td>
<td>0.784 ± 0.142</td>
<td>3.19 ± 0.73</td>
<td>9.06 ± 1.98</td>
</tr>
<tr>
<td>AUC 0-24 hr (µg-hr/mL)</td>
<td>1.77 ± 0.20</td>
<td>7.22 ± 2.14</td>
<td>19.8 ± 8.5</td>
<td>58.6 ± 13.7</td>
<td>73.1 ± 30.5</td>
</tr>
</tbody>
</table>

Bile duct, kidney and bone, and isozyme analysis is needed to determine the origin of ALP (Righetti and Kaplan, 1971). In the serum, there are several types of ALP isozymes that originate from different tissues. It is reported that serum ALP of rats is mainly from the small intestine, liver and bones. Inhibition of MTP in the small intestine might change the integrity of ALP transfer from mucosal epithelial cells to serum. Alternatively, the compound might affect the hepatobiliary system directly or indirectly. However, we have not analyzed the isozyme, so the detailed mechanisms of this change are not clear.

In the present study, PT and APTT of rats treated with T-0126 were prolonged. We recently found that some blood coagulation factors and vitamin K levels decrease in MTP inhibitor-treated rats, and that these changes are suppressed by vitamin K (pre-submission data). MTP inhibitors may inhibit absorption of fat and simultaneously fat-soluble vitamins including vitamin K. As a result, production of vitamin K-dependent coagulation factors should be prevented. Therefore, prolongation of blood coagulation time (PT and APTT) should be a common effect of MTP inhibitors.

In this study, slight hemorrhage was observed in the thymus and lymph nodes in some animals, although the lesions were not apparently correlated with the blood coagulation time, so we cannot consider that the hemorrhagic lesion depended on the blood coagulation time in this study. However, it is important to pay attention to such lesions in further toxicological study of MTP inhibitors.

In conclusion, our aim in this study was to examine the potential toxic effects of 2-week oral treatment with T-0126, a novel MTP inhibitor, on the liver and intestine in male and female rats. We found that T-0126 decreases serum lipids and results in fat accumulation in the liver and the small intestine. In addition, slight changes in the liver, including an increase in serum aminotransferase activity, presence of focal inflammatory lesions, and prolongation of PT and APTT were observed after treatment with T-0126. These changes may be related to a mechanism based on malabsorption of fat, fat-soluble antioxidants, and vitamin K, although we cannot exclude other potential mechanisms such as direct cytotoxicity of T-0126.
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REFERENCES


