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Comparative study of the behavior of terbium, samarium, and ytterbium intravenously administered in mice

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Abstract

Objectives: To investigate the difference or similarity in biological behavior of rare earth elements, distribution and excretion of Tb, Sm, and Yb administered in mice were examined.
Materials and methods: Male mice (5 weeks old) were administered intravenously with chlorides of Tb, Sm, or Yb at 1 or 10 mg element/kg body weight. After 20 h and 6 days of administration, five mice of each group were sacrificed and the liver, spleen, lung, and kidney were taken out. The concentrations of administered elements in these organs, urine, and feces were determined by high-frequency plasma-mass spectrometry.
Results: Element-depending differences in the concentrations of administered elements were not so marked in each organ. Organ-dependent differences in the concentrations, however, were marked and the order varied on doses: spleen > liver > lung > kidney in 10 mg/kg group and spleen ≧ liver > lung = kidney in 1 mg/kg group. Excretion ratio to administered dose in urine was 0.1–5.7%. The excretion amounts were the highest at first day, then decreased. Total amounts for 6 days were Yb > Tb ≒ Sm, and excretion ratio was higher at lower dose for each element. Excretion amounts of Tb and Yb in feces were larger than those in urine, increased with dose, and corresponded to 10.3–16.8% of dose.
Conclusion: The distribution and excretion behavior of Tb, Sm, and Yb indicated differences although their physicochemical properties are resemble.

Keywords: Terbium; Samarium; Ytterbium; Mouse; Intravenous administration

1. Introduction

Rare earth elements are widely used in various industries. Many workers engaged in a manufacturing process of raw materials or products are exposed to these elements. The behavior of rare earth elements in biology is of interest in connection with their biological effects, however, the information on their toxicity or pharmacological effects are insufficient. We previously reported that the distribution of Tb administered intravenously and intraperitoneally in mice were much different depending on the administration route but the increase of calcium concentrations in organs in which Tb was incorporated was observed similarly [1,2]. Intravenously injected Tb was distributed mainly in liver, lung, and spleen, but distribution pattern was changed with dosage [2]. We also investigated the distribution of 12 kinds of rare earths elements, such as Y, La, Ce, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, and Yb, at the dose of 25 mg/kg [3]. Main organs of distribution, liver, spleen, and lung, were common for all elements, but their concentration ratio in lung and spleen was different depending on the elements. Twelve elements can be divided in three groups: (1) lung > spleen: Eu, Gd, Tb, Dy, and Y; (2) lung ≒ spleen: Nd, Sm, Ho, and Er; (3) lung < spleen: La, Ce, and Yb. In the present study, distribution and excretion of Tb, Sm, and Yb, one of the elements in each group were investigated at lower doses, and a point in common and that of difference in the behavior of these elements in mice was discussed.

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2. Experiments

Male Crj-ICR mice (Nippon Bio-Supply Center) of 5 weeks old were i.v.-injected from tail vein with Tb, Sm, or Yb at dose of 1 or 10 mg element/kg body weight. The administered solutions were prepared by dissolving chlorides of these elements in 5% glucose solution immediately before injection. Mice of control group were injected with a 5% glucose solution. Each group consisted of 10 mice. After a single injection, urine and feces were separately collected every day from five mice in each group using a metabolic cage made of hard glass. Twenty hours and 6 days after the administration, five mice in each group were anesthetized with ethyl ether and sacrificed by dislocation of the cervical vertebrae. Perfusion with 5% glucose from aorta and portal vein was carried out, then liver, spleen, lung, and kidney were excised. Organ samples and feces of 0.05–0.1 g or urine 0.4 ml were accurately weighed in Teflon bottle and digested with ultrapure nitric acid and hydrogen peroxide in a microwave oven. The concentrations of administered elements were measured by microwave-induced plasma-mass spectrometry (MIP-MS, P-7000, Hitachi) or inductively coupled plasma-mass spectrometry (ICP-MS, Eran6000, Perkin-Elmer).

3. Results and discussion

A significant change in the body weight, organ weights, and hematocrit values was not observed after the administration of Tb, Sm, or Yb.

The concentrations of administered elements in liver, spleen, lung, and kidney after 6 days were shown in Fig. 1. Element-depending differences in the concentrations of administered elements were not so marked in each organ, however, organ-dependent differences in that were clear. In the 10 mg/kg groups (Fig. 1A), the highest concentrations were observed in spleen (179–310 μg/g), then followed by liver (57–79 μg/g), lung (5.7–8.6 μg/g), and kidney (1.8–3.7 μg/g). In 1 mg/kg group (Fig. 1B), the order of organs was not changed practically but the concentrations in spleen (6.8–8.8 μg/g) and liver (3.6–6.4 μg/g) became similar range, and concentrations in lung (0.25–0.29 μg/g) were almost the same with or a little lower than those in kidney (0.26–0.36 μg/g). At dose of 25 mg/kg [3], the concentrations in lung (300–1022 μg/g) and in spleen (377–1565 μg/g) were higher than that in liver (129–158 μg/g), and were much higher than that in kidney (2–7 μg/g). These results indicated that the distribution pattern of Tb, Sm, or Yb in these organs was different depending on the dose.

The concentrations of Tb, Sm, and Yb in liver of 10 mg/kg group were 11.2, 12.2, and 15.8 times of that of 1 mg/kg group, and those in kidney were 5.1, 12.0, and 11.2 times of 1 mg/kg group, respectively. These ratios were 35.2, 26.1, and 40.7 times in spleen and 29.9, 23.2, and 26.9 times in lung indicating that these elements deposited in spleen and lung more easily at higher dose.

At dose of 25 mg/kg, the concentrations of administered elements in lung were Tb > Sm > Yb, where Tb concentration was about three times of Yb [3]. Such marked differences were not observed in 10 and 1 mg/kg groups (Fig. 1). In spleen of 1 and 10 mg/kg groups, the concentrations of administered elements were Tb > Sm ≧ Yb although the reverse order was observed in 25 mg/kg group. In liver, the concentrations were Sm > Tb ≧ Yb (Fig. 1).

Distribution amounts of administered elements were the largest in liver for all groups then followed by spleen, which showed higher concentration but had much lighter weight than liver. Six days after injection, 25.1–41.7 and 39.8–56.7% of administered elements were deposited in livers of 1 and 10 mg/kg groups, respectively. Amounts in spleen were 1.9–2.5 and 5.7–8.8% of 1 and 10 mg/kg groups.

The concentrations of these elements in liver after 20 h were higher than that after 6 days indicating that a part of elements was excreted from body or transferred to other organs. Decreasing ratio of concentrations was about 40, 28, and 45–50% for Tb, Sm, and Yb, respectively. As shown in Fig. 2 excretion amounts of Yb in urine were larger than those of Tb and Sm. In most cases, the amounts were large on the first day, then decreased. Yb amounts of 10 mg/kg group were 1.3–2.7 times larger than those of 1 mg/kg group except first day

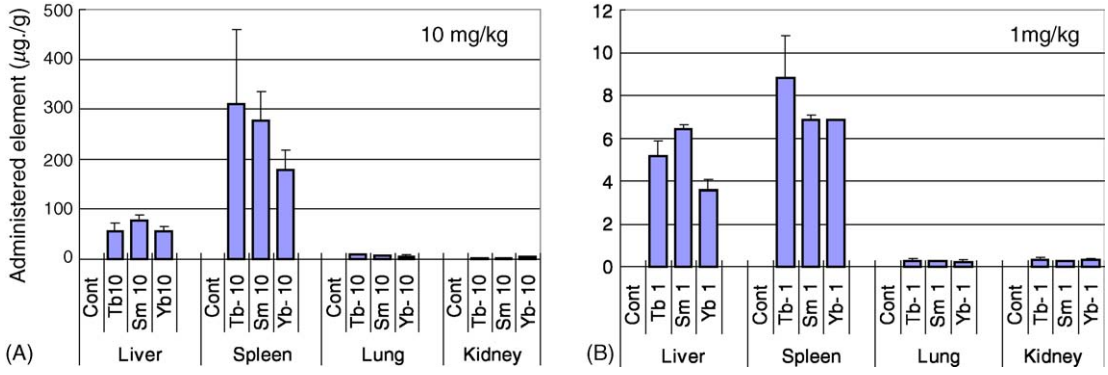

Fig. 1. Concentrations of administered elements in liver, spleen, lung, and kidney of mice at dose of 10 mg/kg (A) and 1 mg/kg (B).

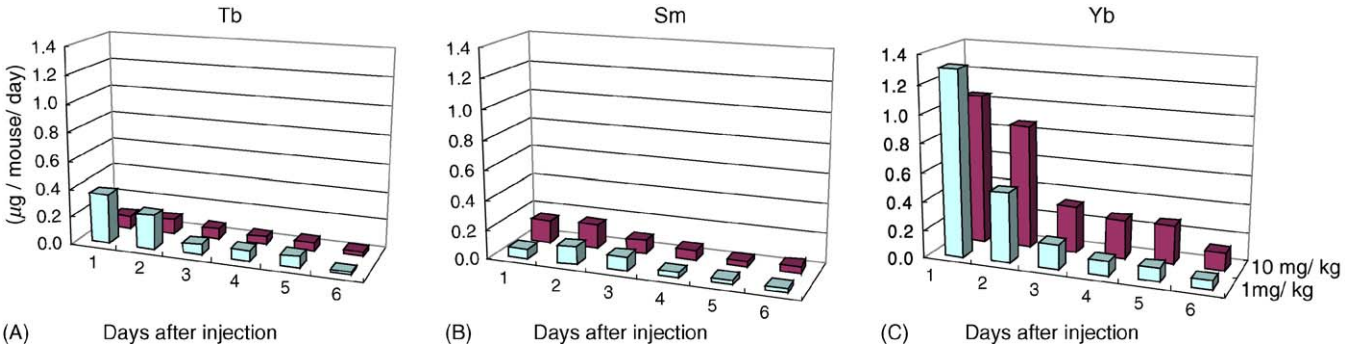

Fig. 2. Amounts of Tb (A), Sm (B), and Yb (C) excreted in urine of mice.

(Fig. 2C). Sm amounts of 1 and 10 mg/kg groups were about the same except first day (Fig. 2B). Tb amounts of 10 mg/kg group, however, were smaller than those of 1 mg/kg group except sixth day (Fig. 2A). Total amounts of Yb for 6 days excreted in urine corresponded to 5.7 and 0.8% of administered Yb of 1 and 10 mg/kg groups, respectively. Those of Tb were 2.1 and 0.1%, and those of Sm were 1.0 and 0.2% of 1 and 10 mg/kg groups, respectively. These results indicated that the excretion amounts in urine for 6 days after injection was very small, ratio of excretion to administered amounts was lower in higher dose, and was different depending on elements administered.

Excretion of Tb and Yb in feces was also measured. Variation of daily excretion amounts was not so large as that in urine. Excretion amounts of 10 mg/kg group were larger than those of 1 mg/kg group for both Tb and Yb. Total amounts of Yb excreted in feces for 6 days corresponded to 10.5 and 16.8% of dose in 1 and 10 mg/kg groups, and those of Tb corresponded to 14.3 and 10.3%, respectively. These results indicated that administered Yb and Tb were excreted in feces dose-dependently and excretion amounts were larger than those in urine. Measurements of Sm contents in feces are in progress.

We reported the faster rate of Tb disappearance from blood plasma in higher dosage groups of intravenous injection, and suggested that the formation of different chemical species of Tb in blood plasma [2]. Formation of colloidal materials of rare earth elements in blood is thought to occur easily at neutral pH. Such materials of yttrium in rat blood were reported [4]. Colloidal materials can be easily taken into lung and spleen by phagocytosis. Tb, Sm, or Yb injected in tail vein were thought to exist in plural chemical forms, such as ion, binding forms with proteins or other components, and/or colloidal materials, and deposited in liver, spleen, and other organs.

In liver, these elements were deposited in various fractions, such as cell membrane, mitochondria, microsome, and cytosol fractions [3], and the presence of plural chemical species in cytosol was suggested [5]. The administered elements bound loosely to components in liver are thought to be excreted in bile and then feces, or be transported to kidney through bloodstream and excreted in urine. The present data of liver and urine suggested that the affinity with liver components was Sm > Tb > Yb, and easiness of excretion through the kidneys was Yb > Tb, Sm. Rare earth elements ions have radii similar to Ca ion and have been used as Ca ion probes in biochemical studies in vitro [6]. Ionic size is Sm > Tb > Yb, where Sm ion is a little smaller than Ca ion. Rare earth ions interact with nucleic acids, amino acids, and proteins [7]. Stability constants of rare earths-complex with hydroxycarbonic acids, polyaminopolycarbonic acid, and some amino acids is Yb > Tb > Sm. These differences in properties of Tb, Sm, and Yb may contribute the difference in the behavior of these elements in mice.

Many experimental studies have been carried out on biological behaviors of various metals [8]. In general, liver, kidney, and bone are accumulating organs of most metals administered orally or intravenously although there are characteristic organs of particular metals, such as pancreas for Co, central nervous system (CNS) for Mn, and lung for Cr. Main organs of rare earth deposition are consistent with most metals, and further studies on bone are required. Among main excretive routes of absorbed metals, urine was predominant with V, Cr, Mo, Pb, and Cd, bile and feces with copper. Sm, Tb, and Yb are latter type if anything, and have characteristics of considerably low rates of excretion.

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