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Reduction of ^{223}Ra retention in the Large Intestine during Targeted Alpha Therapy with $^{223}RaCl_2$ by Oral $BaSO_4$ Administration in Mice

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Abstract

Targeted alpha therapy with $^{223}RaCl_2$ is used to treat skeletal metastases of hormone-refractory prostate cancer. The intravenous injection of $^{223}RaCl_2$ causes gastrointestinal disorders such as nausea, abdominal discomfort, and diarrhea as frequent clinical adverse events caused by radiation. $BaSO_4$ is known to display Ra^{2+} ion uptake in its structure and is clinically used as a contrast agent for X-ray imaging following oral administration. Here, we investigated the feasibility of a method to reduce ^{223}Ra retention in the large intestine with $BaSO_4$ by biodistribution studies in mice. $^{223}RaCl_2$ biodistribution was examined in ddY mice after intravenous administration (10 kBq/mouse).

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$BaSO_4$ (100 mg/mouse) was orally administered 1 h before $^{223}RaCl_2$ injection. We also investigated the effect of laxative treatment on $BaSO_4$ activity, since laxatives are clinically used with $BaSO_4$ to avoid impaction in the large intestine. The results shows $BaSO_4$ significantly reduced ^{223}Ra retention in the large intestine after $^{223}RaCl_2$ injection in mice when compared with the control without $BaSO_4$ administration ($P < 0.05$). Excretion of ^{223}Ra into the feces was significantly increased by $BaSO_4$ administration ($P < 0.05$). Laxative treatment did not affect $BaSO_4$ activity in reducing ^{223}Ra retention, although no additional effect of laxative treatment to ^{223}Ra excretion was observed in mice. $BaSO_4$ administration was effective in reducing ^{223}Ra retention in the large intestine during $^{223}RaCl_2$ therapy, and laxative treatment did not attenuate $BaSO_4$ activity. This method could be useful in reducing adverse events caused by radiation exposure to the large intestine during $^{223}RaCl_2$ therapy.

Keywords: targeted alpha therapy; ^{223}Ra; $BaSO_4$; large intestine; radiation exposure.

1. Introduction

Prostate cancer is the most common cancer among men worldwide [1]. Androgen deprivation is mainly used in the treatment of prostate cancer [2]. Despite the initial positive effect, this treatment is not curative, and majority of these patients eventually become castration-resistant [3, 4]. Most patients with castration-resistant prostate cancer (CRPC) develop skeletal metastases [5] that are a major cause of disability, reduced quality of life, and eventual death [6-8]. Several bone-targeted therapies using bisphosphonates, denosumab, and β^- emitter $^{89}SrCl_2$ have been used to treat skeletal metastases in patients with CRPC; however, these treatments are palliative and do not improve patient survival [6, 7, 9, 10].

$^{223}RaCl_2$ is an alpha particle-emitting compound and the active pharmaceutical ingredient of the first bone-targeted therapy that is reported to increase overall survival in patients with CRPC who develop skeletal metastases [6, 11]. This drug is approved by the Food and Drug Administration and used for treating patients with advanced CRPC, specifically in men with skeletal metastasis after surgery or symptomatic bone metastases without known visceral metastatic disease, in clinical practice [12]. ^{223}Ra ($T_{1/2}$ = 11.4 days) is the sixth element in group 2 of the periodic table. This group contains calcium and is known as the group of alkaline earth metals [11]. Once intravenously injected into the patients, ^{223}Ra behaves as bone-seeking calcium mimetic, and selectively forms complexes with the bone mineral, hydroxyapatite, in activated osteoblastic regions of the bone with a high turnover near metastatic lesions. ^{223}Ra generates four alpha particles in the decay process, in which approximately 95% of the total radiation energy is released by alpha decay [13]. The alpha particles emitted from ^{223}Ra can damage adjacent cancer cells by causing severe double-strand DNA breaks with a high linear energy transfer [14, 15]. A randomized phase III trial (ALSYMPCA) using $^{223}RaCl_2$ indicated a significant improvement in overall survival in men with bone metastatic CRPC (median overall survival of 14 months vs. 11.2 months in those on placebo) [6]. $^{223}RaCl_2$ is now widely used as the first alpha particle-emitting radiopharmaceutical compound.

However, a clinical imaging study revealed that high radioactivity of ^{223}Ra is found in the large intestine after intravenous injection of $^{223}RaCl_2$, and dosimetry analysis demonstrated that the large intestine receives high radiation exposure [16]. As a consequence, the high retention of ^{223}Ra in the large intestine causes

gastrointestinal disorders, such as nausea, abdominal discomfort, and diarrhea, as the most frequent clinical adverse events [11]. Therefore, methods to reduce ^{223}Ra retention in the large intestine in $^{223}RaCl_2$ therapy are needed. Here, we focused on the administration of $BaSO_4$, which has been reported to have the property of taking up Ra^{2+} ion in its structure [17, 18]. It has been demonstrated that the Ra^{2+} ion is decreased in $BaSO_4$ powder suspensions because of the absorption of Ra^{2+} ion into the open micropores of $BaSO_4$ [17, 18]. Since $BaSO_4$ with oral administration is already used as a contrast agent for X-ray imaging in clinical settings [19], we hypothesized that it can be useful to reduce the ^{223}Ra retention in the large intestine. Therefore, we examined the effects of $BaSO_4$ on the biodistribution of ^{223}Ra in mice. In clinical practice, $BaSO_4$ is usually used with laxatives to avoid $BaSO_4$ impaction in the colon [19]. Thus, we also examined the effect of laxative use on $BaSO_4$'s activity in reducing the retention of ^{223}Ra in the large intestine.

2. Materials and methods

2.1. Radionuclides

^{223}Ra ($T_{1/2}$ = 11.4 days) was produced using a ^{227}Ac/^{227}Th/^{223}Ra generator system. ^{227}Ac ($T_{1/2}$ = 21.8 years) was obtained from the Institute for Materials Research, Tohoku University, using a method previously reported [20]. Briefly, ^{223}Ra produced from the disintegration of ^{227}Ac was purified by separation of ^{227}Ac and ^{227}Th ($T_{1/2}$ = 18.7 days) as a contaminant using a tandem combination of UTEVA Resin, DGA Resin, and Prefilter Resin. These resins were obtained from Eichrom Technologies, LLC (Lisle, IL). In this system, 4 M HNO_3 was used as an eluate; ^{223}Ra was passed through three cartridge system, while ^{227}Th and ^{227}Ac were retained by UTEVA Resin and DGA Resin, respectively. The eluate containing ^{223}Ra was evaporated by heating (90℃) to dryness, resuspended in H_2O, and evaporated again to eliminate HNO_3. The resultant ^{223}Ra was resuspended in saline and the solution was filtered through a sterile filter (0.2 µm, Whatman); the pH was confirmed to be neutral before injection. The radioactivity of ^{223}Ra was quantified using a germanium semiconductor detector (ORTEC, SEIKO EG&G, Tokyo, Japan). After ^{223}Ra separation, ^{227}Ac was recovered from DGA Resin with 0.1 M HCl for ^{223}Ra ingrowth.

2.2. In vivo biodistribution

ddY male mice (six-weeks old) were obtained from Japan SLC (Hamamatsu, Japan). Mice were allowed to acclimatize for one week before initiating the experiments. All animal experimental procedures were approved by the Animal Ethics Committee of the National Institutes for Quantum and Radiological Science and Technology (QST, Chiba, Japan) and conducted in accordance with the institutional guidelines.

Experiment 1: The effect of oral $BaSO_4$ administration on the biodistribution of $^{223}RaCl_2$ was examined in mice (Figure 1A). $^{223}RaCl_2$ (10 kBq/mouse in 100 µL saline) was intravenously injected into mice. $BaSO_4$ (100 mg/mouse dissolved in 200 µL saline; $BaSO_4$ group) or saline (200 µL; control group) was orally administered 1 h before $^{223}RaCl_2$ injection. The timing of administration of $BaSO_4$ was decided based on the observation of excretion of $BaSO_4$ in mouse feces at different times following its oral administration without $^{223}RaCl_2$ injection; described in Supplemental Data (Supplementary figure S1). $BaSO_4$ dose was decided based on its

clinical dose [21]. Mice were sacrificed 1, 2, 4, 6, and 24 h after $^{223}RaCl_2$ injection. In this experiment, four mice were prepared for each time point in both groups. Blood, liver, kidney, small intestine, large intestine, spleen, and femur were harvested and weighed; small and large intestines were isolated with the contents. Feces and urine that were excreted from mice were accumulated for 1, 2, 4, 6, and 24 h after $^{223}RaCl_2$ injection, respectively, and collected for measurement of radioactivity. ^{223}Ra radioactivity of organs, feces, and urine was quantified with a γ-counter (Auto-well gamma counter ARC-370M, Aloka, Tokyo, Japan) according to a previously reported method [22-24]. Percentage of injected dose per gram (%ID/g) was calculated for blood and organs. For feces and urine, percentage of injected dose (%ID) was calculated.Experiment 2: The effect of laxative treatment on $BaSO_4$ activity after $^{223}RaCl_2$ injection was also examined in ddY male mice (Figure 1B). In this experiment, mice were administered $BaSO_4$, 1 h before the intravenous injection of $^{223}RaCl_2$ in a similar manner as described in experiment 1, with ($BaSO_4$ + laxative group) or without ($BaSO_4$ group) laxative treatment (n = 4/group). For the laxative treatment, 50% glycerin enema solution (0.3 mL) (Yoshida Pharmaceutical, Tokyo, Japan) was administered rectally 3 h after the intravenous injection of $^{223}RaCl_2$. The timing of laxative treatment was decided based on the observation of experiment 1. For comparison purposes, mice administered with saline instead of $BaSO_4$ without laxative treatment were also examined (control group) (n = 4/group). The biodistribution study was conducted 1 h after glycerin enema (4 h after $^{223}RaCl_2$ injection) because the laxative treatment caused the excretion of feces within 1 h after glycerin administration in mice as described in Supplemental Data (Supplementary figure S2). Biodistribution measurement was performed in a similar manner as described in experiment 1.

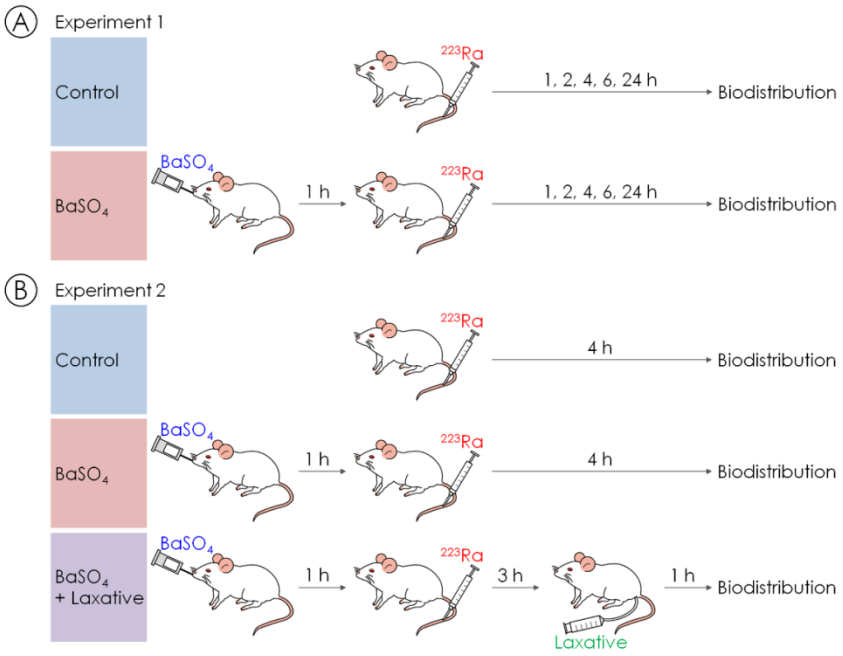

Figure 1: Summary of the ^{223}Ra biodistribution study. (A) Experiment 1. Biodistribution study of ^{223}Ra with or without $BaSO_4$ to examine the effect of $BaSO_4$ administration after $^{223}RaCl_2$ injection. (B) Experiment 2. Biodistribution study of ^{223}Ra with laxative treatment after $BaSO_4$ administration to examine the effect of laxative treatment on the effect of $BaSO_4$ administration after $^{223}RaCl_2$ injection.

2.3. Statistical analysis

Data are expressed as means with corresponding standard deviations. *P* values were calculated using a 2-tailed *t*-test for comparisons between 2 groups or 1-way analysis of variance (ANOVA) for comparisons among multiple groups. Time-activity curves were analyzed using two-way ANOVA. *P* values less than 0.05 were considered statistically significant.

3. Results and discussion

3.1. Experiment 1: Effect of $BaSO_4$ on the biodistribution of $^{223}RaCl_2$

The effect of oral $BaSO_4$ administration on the biodistribution of $^{223}RaCl_2$ was observed in this study. Prior to the experiment, to determine the timing of $BaSO_4$ administration, we examined the excretion of $BaSO_4$ into the feces after oral administration (Supplementary figure S1). White-colored feces containing $BaSO_4$ were observed after 1 h of its oral administration (Supplementary figure S1). Therefore, the timing of $BaSO_4$ administration was decided as 1 h before $^{223}RaCl_2$ injection in this study.

We examined the biodistribution of $^{223}RaCl_2$ with ($BaSO_4$ group) or without (control group) oral $BaSO_4$ administration 1, 2, 4, 6, and 24 h after $^{223}RaCl_2$ injection. Figure 2 shows differences in the biodistribution of $^{223}RaCl_2$ in the blood, liver, kidney, small intestine, large intestine, spleen, and femur between control and $BaSO_4$ groups. ^{223}Ra radioactivity in the large intestine peaked between 2 and 4 h after $^{223}RaCl_2$ injection, and oral $BaSO_4$ administration significantly reduced ^{223}Ra radioactivity in the large intestine at 1, 2, and 4 h after $^{223}RaCl_2$ injection compared with that in the control group ($P < 0.05$) (3.02 ± 1.19 %ID/g and 5.64 ± 0.91 %ID/g at 1 h, 4.89 ± 0.60 %ID/g and 8.92 ± 0.44 %ID/g at 2 h, and 4.44 ± 1.82 %ID/g and 7.77 ± 2.46 %ID/g at 4 h, for $BaSO_4$ and control groups, respectively). For further analysis, a time-activity curve of ^{223}Ra in the large intestine was also prepared (Supplementary figure S3) based on $^{223}RaCl_2$ biodistribution data (Figure 2) for $BaSO_4$ and control groups. Based on analysis of the time-activity curve, ^{223}Ra radioactivity in the large intestine was significantly lower in the $BaSO_4$ group than in the control group ($P < 0.05$); the area under the curve of ^{223}Ra radioactivity in the large intestine decreased by 27% in the $BaSO_4$ group compared with that in the control group (Supplementary figure S3). We also confirmed that ^{223}Ra was accumulated in the femur in both control and $BaSO_4$ groups with no significant differences between the two groups in terms of biodistribution (Figure 2). There was no significant difference in ^{223}Ra radioactivity in the blood, liver, kidney, small intestine, and spleen between the two groups in terms of biodistribution (Figure 2).

^{223}Ra radioactivity in the feces and urine with time were measured for $BaSO_4$ and control groups (Figure 3). The time-activity curves showed increase of ^{223}Ra excretion in the feces in the $BaSO_4$ group compared with the control group with a significant difference ($P < 0.05$) (Figure 3A); the increase of ^{223}Ra in the feces was observed with slight delay from decrease of ^{223}Ra in the large intestine in the $BaSO_4$ group (Figure 3A, Supplementary figure S3). There was no significant difference in time-activity curves of ^{223}Ra in the urine between control and $BaSO_4$ groups (Figure 3B).

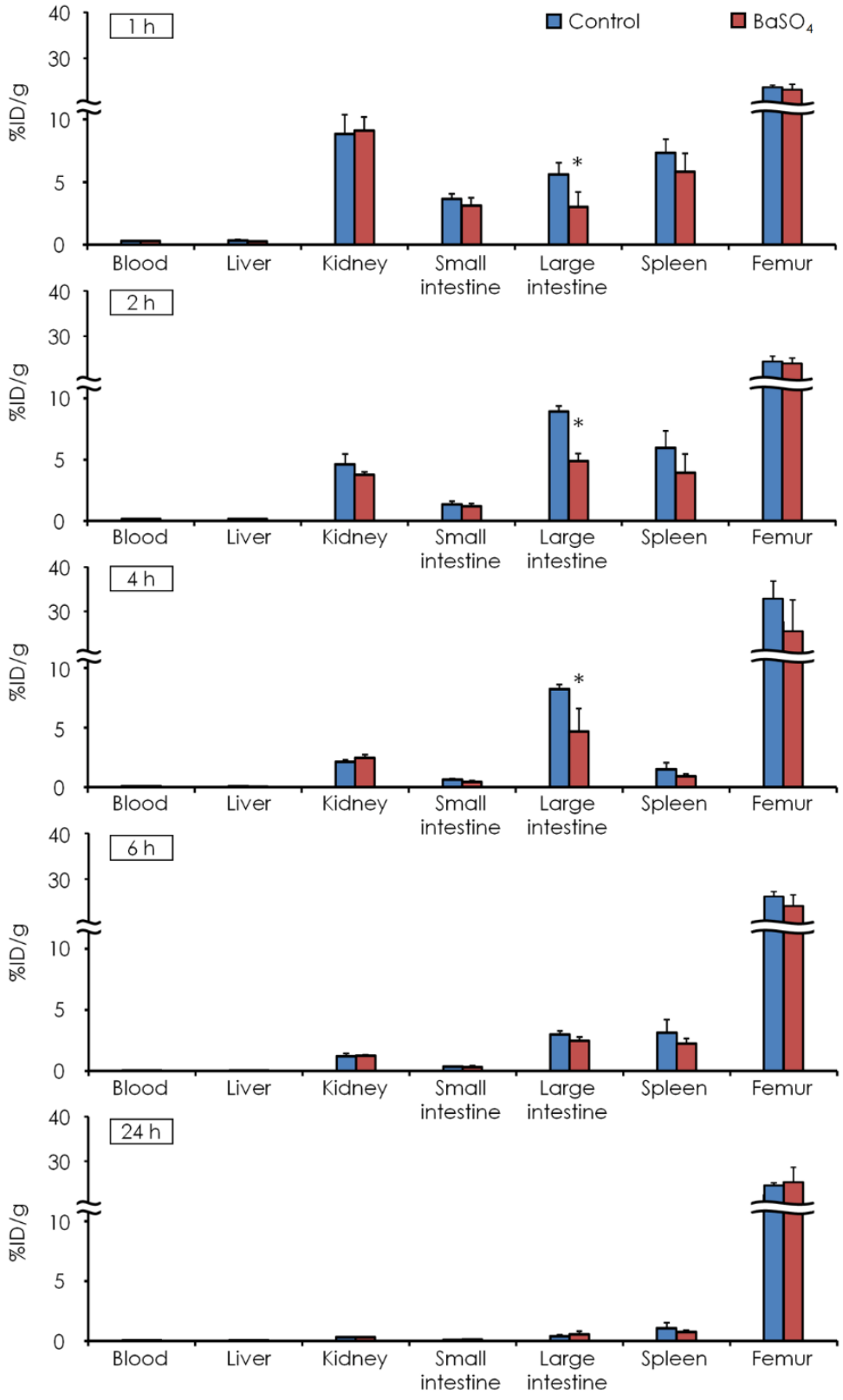

Figure 2: The effect of $BaSO_4$ administration on the biodistribution of ^{223}Ra. Data were obtained 1, 2, 4, 6, and 24 h after $^{223}RaCl_2$ injection. Values are expressed as %ID/g for organs (liver, kidney, small intestine, large intestine, spleen, and femur) and blood. Values are shown as mean ± SD; n = 4. Asterisks indicate statistical significance (*$P < 0.05$) in comparison to the control at each time point.

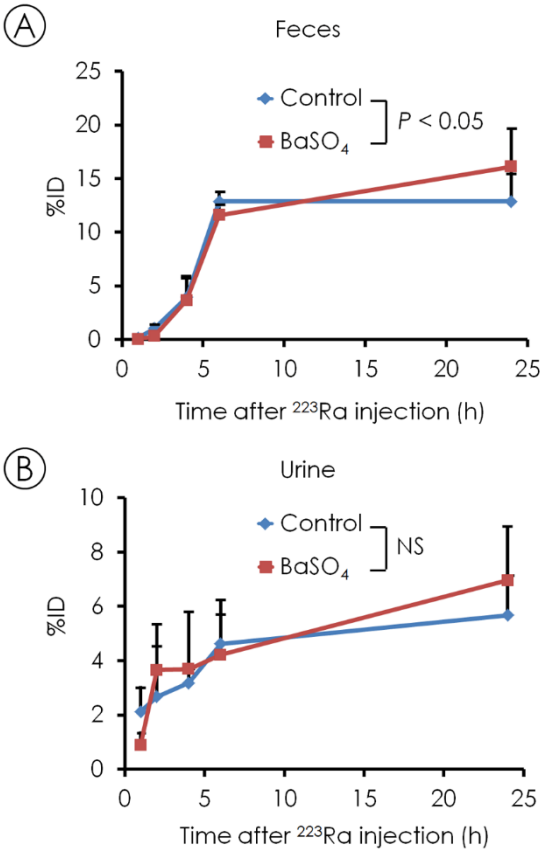

Figure 3: Time-activity curves of ^{223}Ra in the feces and urine for control and $BaSO_4$ groups. The time-activity curves of the feces (A) and urine (B) are shown. Values are expressed as %ID. Values are shown as mean ± SD n = 4. NS = not significant

In experiment 1, we observed that oral $BaSO_4$ administration reduced ^{223}Ra retention in the large intestines of mice and the excretion of ^{223}Ra in the feces was increased by $BaSO_4$ administration. The effect of $BaSO_4$ was evident until 4 h after the administration of ^{223}Ra in mice, when its retention in the large intestine was higher than at later time points.

Previous studies have reported that $BaSO_4$ powder in suspension displays the uptake of Ra^{2+} ion [17, 18]; however, it was unknown whether this phenomenon would take place *in vivo*. Our data showed that via oral administration, $BaSO_4$ was able to reduce ^{223}Ra retention in the large intestine and accelerate the excretion of ^{223}Ra from the large intestine into the feces in mice, suggesting that it would be effective in taking up the Ra^{2+} ion *in vivo* in $^{223}RaCl_2$ therapy.

The reduction of ^{223}Ra retention in the large intestines could be explained by diffusion and incorporation of Ra^{2+} ion into the open micropores of $BaSO_4$ structure [17, 18] after oral BaSO4 administration in mice. In addition, our data showed that the biodistribution of ^{223}Ra in the femur, blood, liver, kidney, small intestine, and spleen, but not in the large intestine, was unchanged by $BaSO_4$ administration, suggesting that $BaSO_4$ does not alter the behavior of ^{223}Ra as a bone-seeking agent in the body, while reducing its retention in the large intestine.

3.2. Experiment 2: Effect of laxative treatment along with oral $BaSO_4$ administration after $^{223}RaCl_2$ injection

Next, we examined the effect of laxative treatment on $BaSO_4$ activity in reducing ^{223}Ra radioactivity in the large intestines in mice, since laxative treatment is clinically used with oral administration of $BaSO_4$ to avoid the impaction of $BaSO_4$ in the large intestine. In this experiment, laxative treatment was provided 3 h after the intravenous injection of $^{223}RaCl_2$ in mice orally administered $BaSO_4$. The timing of laxative treatment was decided based on the observation of experiment 1 that ^{223}Ra radioactivity in the large intestine peaked between 2 and 4 h after $^{223}RaCl_2$ injection. Figure 4 shows the effect of laxative treatment along with $BaSO_4$ administration during $^{223}RaCl_2$ treatment on $^{223}RaCl_2$ biodistribution in the blood, liver, kidney, small intestine, large intestine, spleen, and femur 4 h after $^{223}RaCl_2$ injection in $BaSO_4$ + laxative, $BaSO_4$, and control groups. In the large intestine, $BaSO_4$ + laxative and $BaSO_4$ treatments significantly decreased ^{223}Ra radioactivity compared with that in the control (4.05 ± 1.05 %ID/g and 4.70 ± 1.92 %ID/g for $BaSO_4$ + laxative and $BaSO_4$ alone groups, respectively, vs 8.22 ± 0.41 %ID/g for the control group). $BaSO_4$ + laxative treatment decreased ^{223}Ra radioactivity to a level similar to that with $BaSO_4$ treatment, and laxative treatment did not enhance the effect of $BaSO_4$.

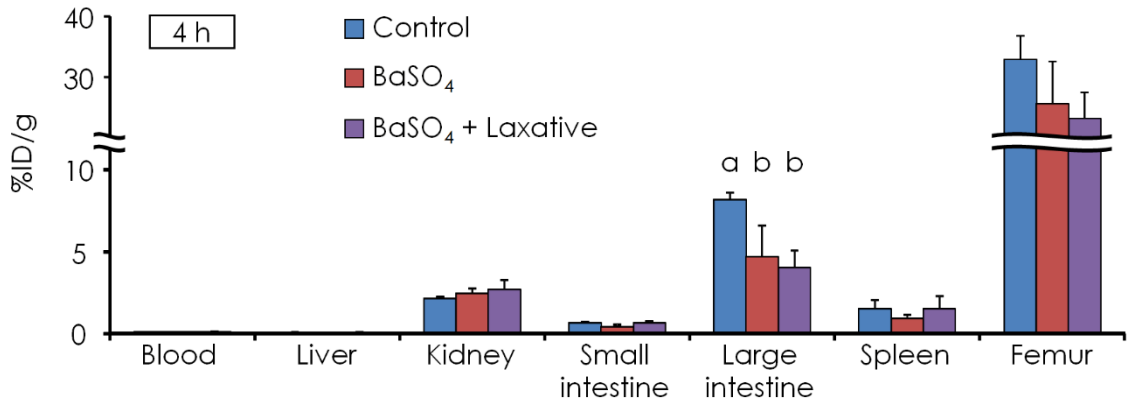

Figure 4: The effect of laxative treatment along with $BaSO_4$ administration after ^{223}Ra injection. Values are expressed as %ID/g 4 h after $^{223}RaCl_2$ injection for organs (liver, kidney, small intestine, large intestine, spleen, and femur) and blood. Values are shown as mean ± SD; n = 4. a, b; Different letters indicate significant differences ($P < 0.05$).

In experiment 2, we demonstrated that the combined $BaSO_4$ and laxative treatment decreased ^{223}Ra retention in the large intestine to a level similar to that after $BaSO_4$ treatment. This indicates that laxative treatment did not attenuate the ability of $BaSO_4$ to reduce ^{223}Ra retention in the large intestine, although it does not enhance the effect of $BaSO_4$. In clinical settings, $BaSO_4$ is already used as a contrast agent for X-ray imaging via oral administration [19]. $BaSO_4$ is not water soluble and may be impacted and retained in the colon; therefore, laxatives are usually used to prevent the impaction of $BaSO_4$ in clinical practice [19]. Our data indicated that $BaSO_4$ effectively reduces ^{223}Ra retention in the large intestine during $^{223}RaCl_2$ therapy and laxative treatment would facilitate the removal of $BaSO_4$ from the large intestine, while maintaining the activity of $BaSO_4$ to reduce ^{223}Ra retention in the large intestine. Therefore, the use of $BaSO_4$ along with laxative treatment could be

useful to reduce adverse effects caused by radiation exposure to the large intestine during $^{223}RaCl_2$ therapy. Our data showed that there is no significant difference in the decrease of ^{223}Ra radioactivity in the large intestine between two treatments, viz., $BaSO_4$ treatment and the combined $BaSO_4$ and laxative treatment in mice. This might indicate that the duration of $BaSO_4$ persistence in the large intestine of mice is not as long as that in humans, and laxative treatment after $BaSO_4$ administration is unnecessary for mice. In fact, it has been reported that gastrointestinal transit in mice is faster than that in humans [25, 26]. In addition, there might be differences in timing of $BaSO_4$ administration and laxative treatment between mice and humans. Therefore, further preclinical and clinical studies on the efficacy and safety of the use of $BaSO_4$, along with laxative treatment, in $^{223}RaCl_2$ therapy are needed.

4. Conclusion

In conclusion, this study demonstrated that oral $BaSO_4$ administration reduces ^{223}Ra retention in the large intestine, and laxative treatment does not attenuate the effect of $BaSO_4$ to reduce ^{223}Ra retention in the large intestine in mice. This method could be useful to reduce adverse effects caused by radiation exposure to the large intestine during $^{223}RaCl_2$ therapy.

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