Pharmacokinetics of Stable Caesium after Single Administration of Caesium Chloride in Japanese Black Cattle

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Pharmacokinetic (PK) parameters of stable caesium (SCs) were determined in adult Japanese Black Cattle (JBC, n=20). They were divided into two groups, i.e., intravenous (IV) and oral (PO) administration groups, and each of them was administered 133CsCl solution (20 mg/kg b.w.). SCs in biological samples was measured by ICP-MS, and their concentration-time courses were monitored for 182 days. The PK parameters determined in plasma and blood in each group were as follows (mean±SD): area under the concentration-time curve (AUC;µg/L·h): 0.54±0.06 (IVp), 0.42±0.05 (POp), 0.87±0.11 (IVb), and 0.71±0.33 (POb), mean residence time (MRT; day): 20.9±3.2 (IVp), 19.3±2.9 (POp), 24.7±3.6 (IVb), and 23.6±5.2 (POb), bioavailability (F%); 82±29 and 83±38, clearance (CL; mL/min/kg): 0.46±0.05 (IVp), 0.49±0.06 (POp), 0.29±0.04 (IVb), and 0.31±0.08 (POb), and distribution volume (Vd; L/kg) was 3.3 (Vdp) and 4.4 (Vdb). The biological half-life of the terminal elimination phase (T1/2) was estimated to be approximately 30 days. The urine recovery for the dose was 28±6 (IV) and 28±8 (PO), and the fecal recovery was 85±21 (IV) and 122±42% (PO). The time course via both routes of administration showed similar biphasic distribution and elimination profile in any biological samples and elucidated by compartment analysis with consideration of background level. Based on the PK parameters, elimination profile of radioactive caesium (RCs) from the JBC kept long in the RCs contaminated area can be explained.

Key Words: caesium, Japanese Black Cattle, pharmacokinetics, biological half-life, Fukushima Dai-ichi Nuclear Power Plant Accident

1. Introduction

Large amounts of radionuclides such as tellurium-132 (132Te), iodine-131 (131I), caesium-134 (134Cs) and caesium-137 (137Cs) were released into the atmosphere by Fukushima Dai-ichi Nuclear Power Plant Accident (FDNNPPA) occurred in March 2011.1) Of these nuclides, 131I and 132Te have short physical half-lives (T1/2) of 8 days and 78.2h, respectively. Consequently, nine years after FDNPPA, it is no longer necessary to consider the effects of these nuclides. On the other hand, and 137Cs (T1/2; 30.0 years) is still remain in large quantities in the environment,2) and their contribution to human external exposure from soil and air is considered not to be small, but depending on the location. Caesium is known to be easily taken up into the muscles in animals due to its chemical properties like potassium.3, 4) Therefore, human consumption from livestock meat containing radioactive caesium (RCs) is considered to have a
relatively large effect of internal exposure. Since FDNPPA, the Food Sanitation Act manages food marketing in accordance with provisional standards from March 17, 2011 and new standards took over from April 1, 2012. The new standard for caesium radioactivity in foods has been decided to be below 10 Bq/kg for drinking water, 50 Bq/kg for milk and infant food, and 100 Bq/kg for general food.

As for beef, the meat is to be tested for radioactivity at the time of slaughter before shipment to the market, and if the beef exceeds the contamination criterion (100 Bq/kg), they will be discarded. Japanese Ministry of Agriculture, Forestry and Fisheries has described that the biological half-life of RCs is 25–30 days for calves, 30–40 days for steers, and 50–60 days for heifers.\textsuperscript{5) Four reports have estimated radioactive caesium (RCs) concentration in muscle from its blood or urine RCs level in cattle.\textsuperscript{4, 6–8) However, there are no reports on the characteristics of pharmacokinetic (PK) parameters related to absorption, distribution, and elimination of RCs in cattle. If PK parameters of cattle is evaluated, it is possible to explain how to reduce RCs in meat before slaughter. In this study, we examined to clarify the PK parameters of caesium in cattle by using stable caesium (SCs; as caesium chloride). As a reason for the use of SCs, the difference is only a mass number, i.e., SCs is 133 and RCs is 134 or 137, and caesium is an alkali metal and, like potassium and sodium, exists in the body fluid as ions in the body. Consequently, the behavior of RCs and SCs is essentially the same and follow the law of mass action. Therefore, RCs and SCs follow the same PK parameters, and they would be expected to be absorbed, distribute, and eliminate the same manner in cattle.\textsuperscript{9)}

2. Materials and methods

2.1 Samples

Twenty Japanese Black Cattle (JBC, 16 females and 4 heifers) reared on farms in National Livestock Breeding Center (Nishi-Shirakawa-gun, Fukushima Prefecture) were subjected to this research. Their age ranged from 27 to 127 months old and weighed 382 to 692 kg. The experiment was repeated two times, investigated 10 cattle each. The first experimental period lasted 26 weeks from August 2017 to February 2018, and the second one was from June 2018 to December 2018. During the experimental period, they were raised in cattle shed in National Livestock Breeding Center site and were fed with pasture (roll up silage), and tap water was freely consumed.

Prior to the experiment, 10 cattle were divided into 2 groups: an intravenous administration group (IV, \( n=5 \)) and an oral administration group (PO, \( n=5 \)). On the first day of the experiment, each cattle was administered a single dose of caesium chloride (CsCl: purity 99.9\%, Wako Pure Chemicals, Osaka) solution at a dose of 20 mg/kg body weight into the cervical vein (IV) or the rumen by means of a feeding tube (E-7, Fuji Systems, Tokyo) via nostrils (PO).

Samples taken in this study were blood, plasma, red blood cells (RBC), urine, feces, skeletal muscles, and internal organs (liver and kidneys). They were collected at the fixed time of the experiment. Blood (5 mL) were collected from the cervical vein with syringes which contains heparin sodium solution at 0, 1, 4, 8, 12, 24h, 2, 4, 8 days, and 2 weeks after administration, and every 2 weeks interval until 26 weeks. Immediately after blood collection, the hematocrit (Ht) was directly measured by spinning a blood-filled capillary tube in a centrifuge. Plasma was obtained by centrifuge of blood (1,500 \( \times g \) for 10 min). SCs concentrations in RBC (Crbc) were calculated with Eq. (1) by using those in blood (Cb) and plasma (Cp), and hematocrit (Ht).

\[
Crbc = \frac{100 \times Cb \times (100 - Ht)}{Ht} \quad (1)
\]

Urine was collected by stimulation of the perineal skin and subsequently its specific gravity was measured by using urine specific refractometers.
Fecal sample was taken directly from the rectum of each cattle. The sampling intervals for urine and feces were the same as that for blood samples except for 4 and 12 h. Blood, plasma, and urine samples were frozen, while fecal samples were stored refrigerated until analysis. Skeletal muscles and internal organs samples from each two cattle were taken on weeks 4, 8, 12, 18 and 26 after administration. The cattle were euthanized by exsanguination under anesthesia with xylazine followed by and pentobarbital injection. The euthanasia was carried out by veterinarians in accordance with the regulations for animal experimentation of the Livestock Breeding Center. Immediately after euthanasia, the following samples were collected.

Skeletal muscles: Musculus masseter, Neck (mixture of several muscle pieces), Sirloin (Longissimus lumborum), Fillet (M. psoas major), M. biceps femoris, M. quadriceps femoris

Internal organs: Liver, Heart, Kidney (right and left)

The skeletal muscles and internal organs from JBC (female, 32 months old, B.W. 335 kg) as additional background (BG) samples were also obtained from Kitasato University. All samples of skeletal muscle and internal organs were minced and packed into cryotubes and kept frozen until analysis.

2.2 Measurement of SCs

2.2.1 Pretreatment of samples

As for blood, plasma and urine, each sample was diluted with ultra-pure water in the range of 25 to 5,000 times into microtubes, added 400 μL of 5% nitric acid and 200 μL of 5 ppb indium solution (115In, standard for atomic absorption, Wako Pure Chemicals, Osaka, Japan), and centrifuged at 15,000 x g for 10 min. Thereafter, the supernatant was collected, filtered (0.45 μm, Kurabo, Osaka, Japan), and its filtrate was used as a measurement sample. The pretreatment of the samples from feces, muscles and organs obeyed wet ashing method by using a microwave. Approximately 150 mg from each sample was put into a pressure-proof Teflon vessel with polypropylene jacket (Fuse Manufacturing, Shizu-kuishi, Japan), 750 μL of 60% nitric acid was added. The vessels containing samples were tightly sealed and placed in a microwave oven (keeping at 200 W for 2 min, stop for 1 min, keeping again at 200 W for 2 min). In the case of feces, it was further heated at 200 W for 2 min. and then centrifuged (2,000 x g for 5 min) to remove impurities. Dissolved samples were diluted with ultra-pure water in the range of 25 to 2,000 times, then subsequent steps were the same as above.

2.2.2 Calibration and measurement of SCs

Standard caesium-133 solution (133Cs, standard for atomic absorption, Wako Pure Chemicals, Osaka, Japan) was diluted in steps with ultra-pure water to make 0 to 20 ppb SCs standard solutions and each has set to contain 115In at 5 ppb. These samples were measured by inductively coupled plasma-mass spectrometer (ICP-MS) (NexION300, PerkinElmer, Massachusetts, USA) for creating a SCs standard calibration curve of linear function. The vertical axis and the horizontal axis of the calibration curve graph were the SCs concentration and the ratio of 133Cs/115In, respectively. Then SCs solutions was diluted in steps with ultra-pure water mixed BG samples (blood, plasma, urine, feces, muscles, and internal organs) for creating calibration curves containing each sample. Based on the SCs standard calibration curve created earlier, calibration curves of linear function were created for each sample with BG corrected. Finally, SCs concentration in each sample was determined by measuring the count of SCs and 115In using ICP-MS, substituting the ratio into each sample calibration curve with BG correction.

2.2.3 PK analysis

Based on the measured SCs concentration-time profiles in each sample, nonparametric and para-
metric procedure were applied. In nonparametric approach, area under the concentration-time curves (AUC), area under the moment curves (AUMC), bioavailability (F), mean residence time (MRT), clearance (CL) and urinary or fecal recovery of the dose were calculated as follows (Eq. (2)–(7)).

\[
AUC = \frac{1}{2} \sum_{i=0}^{n-1} (C_{i+1} + C_i)(t_{i+1} - t_i) + C_0/k
\]

\[
(AUC_{last} = C_0/k)
\]

\[
AUMC = \frac{1}{2} \sum_{i=0}^{n-1} \left( t_{i+1}C_{i+1} + t_iC_i \right) (t_{i+1} - t_i) + \frac{t_0C_0}{k} + \frac{C_n}{kk}
\]

\[
(AUMC_{last} = \frac{t_0C_0}{k} + \frac{C_n}{kk})
\]

Where \( C_n, t_n \) is observed concentration and time from the last concentration data and \( k \) is the first-order rate constant of the terminal elimination phase. Each concentration was corrected with background data prior to calculation.

bioavailability (F\%) = \frac{AUC_{po}}{AUC_{iv}} \times 100

MRT = \frac{AUMC}{AUC}

CL = \frac{F \cdot Dose}{AUC}

Recovery (%) = \frac{Excreted amount}{Dose amount} \times 100

In parametric procedure, compartment models with background level (Fig. 1) were applied to determine PK parameters based on the nonlinear least square method by using a computer software MULTI. Two different equations were applied in the parametric procedure as follows;

i) Three-compartment open model with BG (Eq. (8)) for blood, plasma, and urine in IV, ii) two-compartment open model with first order absorption and bioavailability (F) with BG for RBC and tissues in IV, and PO (Eq. (9)).

i) IV (blood, plasma, and urine)

\[
\begin{align*}
C_t &= P \cdot e^{-\alpha t} + A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} + BG
\end{align*}
\]

\[
\begin{align*}
&\alpha \text{ faster distribution rate constant (day}^{-1}) \\
&\beta \text{ slower distribution rate constant (day}^{-1}) \\
&\pi \text{ elimination rate constant (day}^{-1}) \\
&\text{F: Bioavailability} \\
&\text{BG: Average or median SCs concentration in the sample before CsCl administration} \\
&(\text{If the variation is large, the median value is used.})
\end{align*}
\]

The measured value was expressed in \( \mu g/L \) for liquid samples (blood, plasma, RBC, and urine) and \( \mu g/kg \) for solid samples (feces, muscles, and internal organs).

This study has been approved by committee on experimental animal ethics in Kitasato University, School of Veterinary Medicine and in National Livestock Breeding Center.
3. Results

3.1 Blood, plasma, RBC, urine, and feces

In IV group, SCs concentrations in blood and plasma reached maximum immediately after administration, followed by SCs in RBC which reached maximum 2–4 days after administration. On the other hand, in PO group SCs plasma concentration reached maximum in 12–24 hours, followed by blood in 1–2 days and RBC for 2–4 days. Immediately after CsCl administration, the SCs in plasma was highest in both groups, but SCs in RBC exceeded over SCs in plasma in 1–2 days after CsCl administration. After that, SCs concentration showed an exponential biphasic degradation curve while maintaining the relationship of plasma < blood < RBC and approached BG at approximately in 180 days after administration (Fig. 2A, 2B).

The SCs concentration ratio (RBC/plasma)-time curve showed similar regardless of the route of administration, although there was variation among individuals for 8–30 days and the average reached around 2–4 (Fig. 3). Table 1 shows PK parameters determined by nonparametric procedure. The bioavailability was approximately 80% for both blood and plasma, mean residence time (MRT) was about 20 days in plasma and 24 days in blood. Plasma clearance was approximately 1.6 times higher than blood clearance.

In urine and feces, SCs concentrations reached highest within 8 h in IV, and within 24 h in PO. Then
the profile showed exponentially biphasic elimination as to the blood sample (Fig. 4A, 4B).

Based on the measured values of urine and feces, the recovery rate up to 26 weeks after CsCl administration was estimated with reference to the daily excretion of beef cattle 2 years of age or older reported by Ministry of the Environment (Ministry of the Environment, 2019). Presuming the excretion of urine was 6.6 kg/day, it was 27.5 ± 5.6% in IV and 27.5 ± 7.8% in PO. On the other hand, feces were 85.0 ± 21.0% in IV and 122.2 ± 42.3% in PO when the average excretion was 20 kg/day. At first glance, the recovery rate of PO in feces was about 1.5 times that of IV, but there was no statistical significance ($P > 0.05$). Comparing total excretion of SCs in urine and feces for 26 weeks, it was higher in fecal excretion than in urine and it was about 3.1 times in IV and 4.4 times in PO (Table 2).

The PK parameters used to create simulation curves of blood, plasma, RBC, urine, and feces were recorded (Table 3). The biological half-lives in elimination phase were approximately 30 days in all samples.
3.2 Skeletal muscles and internal organs

The SCs concentration-time profiles in skeletal muscle, heart, liver, and kidney are shown in Fig. 5. As a result of simultaneous curve fitting with other samples including blood, plasma, and urine, these also appeared to have biexponential elimination profile in both IV and PO. SCs concentration was little bits higher in IV than in PO. The highest SCs concentration was observed in skeletal muscles followed by those in kidney, heart, and liver.

The time dependent changes in SCs ratio of muscle to plasma or RBC is shown in Fig. 6. The SCs ratio of muscle to plasma continued to increase up to 100–120 until approximately 90 days after CsCl administration. After that, it remained higher but did not exceed the maximum. The SCs ratio of muscle to RBC increased up to around 30 until 60–90 days after CsCl administration and remained constant higher level. The SCs ratio of RBC to plasma showed similar increase as shown in Fig. 3, but the ratio decreased in 30–60 days, and remained constant (Fig. 6).

4. Discussion

In pharmacokinetics, the body is conceptually divided into several drug distribution parts as compartment in compartment models based on the behavior of a drug in plasma or in blood. In this study, three-compartment model was observed in IV and two-compartment model with first order absorption in PO.
What is important in the analysis by the three-compartment model is that there are two types of distribution compartment that reaches earlier or later in the dynamic equilibrium with the central compartment, and finally reaches elimination phase in the last as shown in Fig. 1. However, the first compartment only observed in IV and finished in a day and this appeared be masked by the process of absorption in PO. Then major distribution phase continued about 1–2 months till the terminal elimination phase started and it tend to reach BG (Fig. 2). The simulation curves based on the PK parameters in Table 3 well fit to the observed data. The overall behavior in the elimination phase was almost comparable for both routes of administration, suggesting that there is no difference in the elimination process after the dynamic distribution equilibrium is completed. It is independent by the route of administration.

As shown in Fig. 3 and 6, the time course of the SCs ratio of RBC to plasma was gradually increased after CsCl administration in 14 days, and it followed steadily unchanged. The SCs in RBC also reached maximum in 14 days and decreased almost parallel to SCs in plasma (Fig. 2B). These results indicate a process in which SCs is taken up into RBC from plasma, and thereafter, the ratio reaches to the maximum. Therefore, it is considered that the distribution equilibrium between plasma and RBC has been reached. The time to reach the distribution equilibrium was in 14 days. Then the ratio decreases to converge into approximately 2–4. Since caesium behaves similarly to potassium in the body because they have a similar chemical property and are transported into and out of the cell by active transporters like Na\(^+\), K\(^+\)-ATPases and passive diffusion. Since the ionic radius and the atomic mass number of caesium are much larger than those of potassium, these differences may alter the affinity or rate constant for these intra/extracellular transports.

Regarding excretion of RCs from the body, Leggett et al.\(^{15}\) reported that in humans, 85%, 13%, and 2% are excreted from urine, feces, and sweat, respectively. In contrast, there were reports that cattle excrete RCs more in feces than in urine.\(^{8, 16}\) In this study, the recovery of SCs in feces was comparable to these observations in cattle.

Saito et al.\(^{17}\) reported that high uptake of \(^{137}\)Cs was observed in intestinal bacteria such as the \(Bacteroides\) species and \(Clostridium ramosum\). Rose et al.\(^{18}\) also reported that in humans, bacterial biomass was the major component of the organic fraction of the feces (25–54% of dry solids). Therefore, intestinal bacteria may play some role in fecal excretion of RCs. Concerning RCs behavior in muscles and internal organs, Sato et al. reported that RCs more likely to accumulate in skeletal muscle than in internal organs,\(^{9}\) but RCs was highly accumulated in kidney.\(^{19}\) Similar results in SCs accumulations in organs were also obtained in this study.

Fig. 6 shows SCs concentration ratio-time course in muscle (sirloin, fillet) to that in plasma or in RBC in PO. By considering plasma as extracellular fluid and muscle as intracellular fluid, the increase in the ratio of SCs in muscle to that in plasma reached maximum or distribution equilibrium in around 90 days after administration. However, as shown in Fig. 3, the ratio of SCs in RBC to that in plasma reached earlier (approximately within 30 days) after administration. Therefore, there was delayed distribution equilibrium in muscle than in RBC. This may imply that the muscle is the rate-determining organ of caesium out of the body.

5. Conclusions

In this study, we illustrated the time course of SCs concentration in blood, plasma, RBC, urine, feces, muscles, liver, and kidney based on the measured values with simulation curves. The PK parameters of SCs were clarified, and the biological half-life of the terminal elimination phase was estimated to
be approximately 30 days. Since PK parameters from single administration to JBC are applicable to multiple or continuous dosing of RCs, elimination profile of RCs from the JBC kept long in the RCs contaminated area can be explained.

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要 旨

黒毛和種における安定セシウム単回投与後の体内動態

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黒毛和種（n=20）に塩化セシウム（133CsCl: 20 mg/kg）水溶液を静脈内投与群および経口投与群にそれぞれ投与し安定セシウム（SCs）の薬物動態学的（PK）パラメータを明らかにした。投与前から投与後最長182日までの生体試料中SCsはICP-MSで測定した。各群より得られたPKパラメータ（mean±sd）は以下の通り。濃度-時間曲線下面積（AUC; μg/L·h）: 0.54±0.06 (IVp), 0.42±0.05 (POp), 0.87±0.11 (IVb), および0.71±0.33 (POb), 平均滞留時間（MRT; h）: 20.9±3.2 (IVp), 19.3 (POp) ±2.9, 24.7±3.6 (IVb), および23.6±5.2 (POb), 生体内利用率（F%）: 82±29 および83±38, クリアランス（CL; mL/min/kg）: 0.46±0.05 (IVp), 0.49±0.06 (POp), 0.29±0.04 (IVb), およ
び0.31±0.08 (POb), 分布容積（Vd; L/kg）: 3.3 (Vdp) および4.4 (Vdb)。終末相の生物学的半減期（T1/2）約30日と推定された。投与量に対する回収率（%）は尿で28±6 (IV) および28±8 (PO)、糞便で85±21 (IV) および122±42% (PO) であった。いずれの投与経路でも生体試料中SCs濃度は同様な二相性の分布および消失プロファイルを示し、これらはバックグラウンドレベルを考慮したコンパートメントモデルにより説明された。今回求められた動態パラメータより、長期間放射性セシウムに暴露された環境からの黒毛和種の体内動態を推定することが可能となる。