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Letter to the Editor

Gadolinium-based contrast agents toxicity in animal studies

The use of gadolinium-based contrast agents (GBCAs) during pregnancy remains controversial, especially talking about the dose that clinically used in patients. The recent article by Dr Kanda [1] in the January 2019 editorial of *Magnetic Resonance Medical Science* presents the new restrictions on the use of linear GBCAs in Japan. Previous study showed that human fetal exposure to GBCAs was not associated with a higher risk of inflammatory/rheumatic skin diseases, as well as of stillbirths and neonatal deaths [2]. But, Dr. Kanda stated that "Although there is a report that fetal mice exposed to 100 doses of linear GBCAs showed behavioral abnormalities, this is an unrealistic exposure in daily clinical practice [3]". However, we want to clarify Dr. Kanda's misunderstanding about the dose that we used in our report.

In our study, we did single injection per day from embryonic day (E) 15 to E19 at a dose of 2 mmol/kg body weight (bw). Previous studies have shown that injections of 5 mmol/kg body weight GBCAs in adult mice have no adverse effects [4,5]. However, we were concerned that the dose might be toxic to the fetus. Therefore, we used two fifths of the dose (2 mmol/kg body weight per day) used in the previous study [5]. Animal dose should be normalized by body-surface area based on the guidelines from Food and Drug Administration (FDA) in 2005 [6]. In case of mice, experimental animal dose should be multiplied by 12.3 [7] to convert to human equivalent dose (HED) (Table 1). Thus, 2 mmol/kg bw in our study is equivalent to human dose of 0.163 mmol/kg (2/12.3). Because the dose used for human is usually 0.1 mmol/kg bw, it is only 1.6 times higher than human dose. The dose that we used is possible to be used in daily clinical practice. Previous studies showed that Boyd et al. [8] did scanning electron microscopy with energy-dispersive x-ray spectroscopy from patients undergone GBCAs approximately 1 to 2 doses of contrast agent depending on the patient's weight. Moreover, Khurana et al. [9] did a study of gadolinium deposition in Nephrogenic Systemic Fibrosis (NSF) patients who had been exposed to 3 to 5 doses of Omniscan over a period of 1.5 to 2.5 years.

Although the clinical implication of gadolinium deposition has not been fully understood, but the potential toxicity of GBCAs becomes a clinical concern. Studies in humans have shown that magnetic resonance imaging with GBCAs at any time during pregnancy was associated with an increased risk of a broad set of rheumatological, inflammatory, and infiltrative skin conditions and with a risk of stillbirth or neonatal death [2]. As the accumulation of GBCAs in the brain, both in human [10] and animals [4,11], the long-term of GBCAs in the brain might cause aberrant development. In animal study, the intrathecal administration of GBCAs in the rat brain caused severe changes, such as

Table 1
Dose conversion of animal dose to human equivalent dose, published by Food and Drug Administration [6].

Conversion of animal doses to human equivalent doses based on body surface area			
Species	To convert animal dose in mg/kg to dose in mg/m^2, multiply by k_m	To convert animal dose in mg/kg to HED[a] in mg/kg, either:	
		Divide animal dose by	Multiply animal dose by
Human	37	–	–
Child (20 kg)[b]	25	–	–
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primates			
Monkeys[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

[a] Assumes 60 kg human. For species not listed or for weights outside the standards ranges, HED can be calculated from the following formula: HED = animal dose in mg/kg × (animal weight in kg/human weight in kg)$^{0.33}$.
[b] This km value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.
[c] For example, cynomolgus, rhesus, and stumptail.

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neurological alterations and seizures [12]. As fetus have longer life expectancies and developing nervous systems, toxic GBCAs deposit in the brain might be more critical for children than adults. Although a simple extrapolation of our research into humans may not be appropriate, it is important to raise the awareness of potential risks of the use of GBCAs on brain development during pregnancy.

In conclusion, the fetal mice that we used in our experiment were not exposed to 100 times dose, but only 1.6 times the normal human dose. Although the results obtained in animal studies cannot be directly applied to patients, thus, we cannot conclude that the GBCA should not be used. However, even though further studies are absolutely necessary, care must be taken to avoid the use of a large number of GBCA in pregnant women.

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