Title of Project: Species Difference in Pharmacokinetics of Widely Used Drugs: a PET Microdosing Study

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Research Area: Nuclear Medicine, Radiological Science
Keyword: Positron Emission Tomography, Pharmacokinetics, Species Difference

[Purpose and Background of the Research]
Drugs are essential for treatment of diseases. Drug has been developed based on the absorption, distribution, metabolism, and excretion in animals. Some compounds were not effective in men, or other compounds induced unexpected side effects. These discrepancies can be reduced if we know human pharmacokinetics during very early stage of drug development. The PET microdosing study has been designed to estimate tracer-dose pharmacokinetics in humans for candidate compounds of drugs.

In the present study, we study species similarity or difference in pharmacokinetics of drugs now used in the clinical setting.

[Research Methods]
By means of Positron Emission Tomography (PET), we preliminarily investigated pharmacokinetics of acetylcholine esterase inhibitor Donepezil chloride, which is used in patients with Alzheimer's disease, in rats and humans. In rats, high accumulation of C-11 Donepezil was found in liver immediately after venous administration. The target organ brain showed only 2% uptake of total administered dose. Radioactivity of metabolized drug was found in the intestine and urinary tract 30 min after injection (Figure 1).

In humans, high accumulation was found not only in liver but pancreas and myocardium. The target organ brain showed similar uptake (2%) (Fig. 2).

Based on this preliminary study, we revealed that 1) Only small amount of Donepezil was uptaken by the target organ although the drug is already proved to be effective to slow down the progression of symptoms, 2) Donepezil administered was immediately excreted through hepato-biliary and urinary tracts after administration, and 3) there was a species difference in non-target-organ accumulation.

[Expected Research Achievements and Scientific Significance]
We extend our preliminary analysis on the species difference in pharmacokinetics of drugs commonly used in the clinical setting. We reveal the pharmacokinetic requirement of candidate compounds in the early stage of new drug development and when it is used in the clinical setting.

[Publications Relevant to the Project]
Hasegawa Y, Kanai Y, Hasegawa S, Okamoto T, Matsui T, Shimosegawa E, Kurachi Y, Hatazawa J.

[Term of Project] FY2012-2016

[Budget Allocation] 121,200 Thousand Yen

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