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Featured Article

Biomathematical screening of amyloid radiotracers with clinical usefulness index

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Abstract

Introduction: To facilitate radiotracers' development, a screening methodology using a biomathematical model and clinical usefulness index (CUI) was proposed to evaluate radiotracers' diagnostic capabilities.

Methods: A total of 31 amyloid positron emission tomography radiotracers were evaluated. A previously developed biomathematical model was used to simulate 1000 standardized uptake value ratios with population and noise simulations, which were used to determine the integrated receiver operating characteristics curve (Az), effect size (Es), and standardized uptake value ratio (Sr) of conditions-pairs of healthy control–mild cognitive impaired and mild cognitive impaired–Alzheimer's disease. CUI was obtained from the product of averaged Az($\overline{\text{Az}}$), Es($\overline{\text{Es}}$), and Sr($\overline{\text{Sr}}$).

Results: The relationships of $\overline{\text{Az}}$, $\overline{\text{Es}}$, and $\overline{\text{Sr}}$ with CUI were different, suggesting that they assessed different radiotracer properties. The combination of Az, Es, and Sr complemented each other and resulted in CUI of 0.10 to 5.72, with clinically applied amyloid positron emission tomography radiotracers having CUI greater than 3.0.

Discussion: The CUI rankings of clinically applied radiotracers were close to their reported clinical results, attesting to the applicability of the screening methodology.

Keywords: Alzheimer's disease; Amyloid; Biomathematical model; Clinical usefulness; Positron emission tomography (PET)

1. Introduction

Amyloid imaging, using positron emission tomography (PET), provides in vivo imaging of the cerebral amyloid load in an individual. As amyloid load shows greater changes in the early stages of Alzheimer's disease (AD) [1], amyloid imaging allows for early diagnosis of possible AD conversion and differential diagnosis of various neurodegenerative diseases. To quantify the amyloid load, standardized uptake value ratio (SUVR) is commonly used with thresholds established to classify the subjects into amyloid β (Aβ) positive or negative [2–5]. An individual classified as Aβ-positive has high SUVR in cortical areas. This indicates a high amount of amyloid fibrils, and hence a high probability of cognitive

Software: A software written in Matlab for screening radiotracers using the proposed screening methodology and clinical usefulness index is available: http://www.rim.cyric.tohoku.ac.jp/software/CUI-Software.

Ethical approval: This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest: The authors declare that they have no conflicts of interest.

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impairment. In contrast, an individual classified as Aβ-negative has sparse to nondetectable amount of amyloid fibrils and a low possibility of cognitive impairment [2]. The greater the SUVR differences between two conditions, the easier it is to set thresholds for diagnosing the subjects with higher accuracy. However, this is dependent on the radiotracers whereby good radiotracers show clear differences between the subject conditions and vice versa for poorer tracers.

The development of a successful diagnostic radiotracer is hampered by the limitations of conventional radiotracers' development process [6]. It is a long, tedious, and iterative process of identifying the right chemical compounds, followed by lead optimization via iterative processes of conducting multiple in vitro experiments and preclinical testing before clinical testing [6]. Moreover, it focuses on a few physicochemical or pharmacologic properties (e.g., lipophilicity, selectivity to target sites) to evaluate radiotracers [6,7]. In vitro and preclinical results may not translate well to clinical performance because of the lack of consideration to the possible in vivo kinetics of the radiotracers during development [6,7].

Previously, we had developed a biomathematical model to predict the in vivo binding capability of amyloid PET radiotracers in terms of cortical SUVR, under healthy control (HC) and AD conditions, representing Aβ-negative and Aβ-positive diagnosis [8]. In this study, we proposed a screening methodology using amyloid PET radiotracers by extending the previous model to include the noise level of the imaging modality, population variation, and clinical usefulness evaluation [8]. As SUVR was used to measure amyloid load in clinical studies, it was chosen as the outcome parameter of interest [8].

Clinical usefulness reflects the diagnostic capability of a radiotracer to differentiate the subject conditions. Conventionally, it is evaluated using methods such as receiver operating characteristics (ROCs) and effect size. ROC evaluates the sensitivity and specificity of a radiotracer in diagnosing the subjects' conditions correctly [9]. Effect size is used to determine the strength of the differences in measured values between two subject groups [10]. In amyloid imaging, differences in SUVRs between HC and AD are often used [2,4].

To support decision-making in moving candidate radiotracers for clinical evaluation, the use of a common index can help in comparing candidate radiotracers from within and across institutions, and with clinically applied radiotracers. In this study, a clinical usefulness index (CUI) was proposed for objective evaluation of the diagnostic power of the radiotracer in differentiating subjects, based on its cortical binding capability, in terms of SUVR. The range of amyloid loads between representative subject conditions of HC and mild cognitive impaired (MCI) and between MCI and AD was used to represent the conditions of low and high amyloid loads, respectively. CUI was defined as the product of the averaged of the area under the ROC curve (Az), effect size (Es), and SUVR ratios (Sr) of conditions-pairs of HC-MCI and MCI-AD. The relationships among Az, Es, Sr, and CUI were investigated. The feasibility of the screening methodology with CUI was investigated by comparing the ranking of CUI values with clinical results of clinically applied amyloid PET radiotracers.

2. Materials and methods

The proposed screening methodology (Fig. 1) consisted of the previously developed amyloid biomathematical model [8] (Fig. 1A), with population and noise simulations, and tracer evaluation based on CUI (Fig. 1B). A total of 31 (12 clinically applied and 19 candidates) amyloid PET radiotracers were evaluated (Table 1).

2.1. Amyloid biomathematical model

Details of the biomathematical model used in this study are found elsewhere [8]. We briefly summarize the model in predicting SUVR in the following sections.

2.1.1. Generation of physicochemical and pharmacologic parameters

Molecular volume and lipophilicity of each radiotracer were represented by McGowan volume (V_x, cm^3/mol/100) and Moriguchi log P (M log P, unitless), which were generated based on the chemical structure of the radiotracer using commercial software, dproperties (Talete, Italy). In silico free fractions of the radiotracer in tissues (f_{ND}, unitless) and in plasma (f_p, unitless) were calculated using M log P, from the following relationships [8]:

$$f_{ND} = 7.717e^{-1.634 \cdot \mathrm{MlogP}} \quad (1)$$

$$f_p = 0.936 \cdot {f_{ND}}^{0.600} \quad (2)$$

Dissociation constant, K_D, the only in vitro parameter, was extracted from the literature (Table 1). Fixed available target binding sites (B_{avail}) of 4, 20, and 50 nM were used to represent the amyloid loads under HC, MCI, and AD conditions, respectively [40].

2.1.2. Derivation of 1-tissue-compartment model kinetic parameters

The biomathematical model (Fig. 1A) was based on a simplified 1-tissue-compartment model, assuming that the radiotracers cross the blood-brain barrier by passive diffusion [7,8]. The influx rate constant (K_1, mL/cm^3/minutes) was derived using the modified Renkin and Crone equation, with compound-specific permeability (P, cm/minutes) and fixed values of capillary surface area (S = 150 cm^2/cm^3 of brain) and perfusion (f = 0.6 mL/cm^3/minutes) as follows [7]:

$$K_1 = f\left(1 - e^{\frac{-PS}{f}}\right) \quad (3)$$