Dopamine transporter imaging pet tracer [^{18}F] FE-PE2I: From lab to clinic

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ABSTRACT

Introduction: As one of the new dopamine transporters (DAT) positron emission tomography (PET) tracers, [^{18}F] FE-PE2I is an option to be used for dopaminergic imaging in Parkinsonian syndromes (PS). This review focused on [^{18}F] FE-PE2I within the PS scope, from the development of the tracer and its radiolabelling chemistry, to preclinical as well as clinical evaluation. **Materials and Methods:** [^{18}F] FE-PE2I was developed as an improvement to the established PET DAT imaging agent [^{11}C]PE2I as the latter has several drawbacks: slow kinetics and late peak equilibrium, which restrict the imaging duration to up to 40 minutes; and the presence of blood-brain barrier permeable radiometabolites, which potentially interferes with the quantification of the brain imaging. From a radioisotope standpoint, PET imaging in DAT using ^{18}F offers many benefits over ^{11}C: the longer half-life of ^{18}F enables for imaging at later time points and a longer imaging period for improved quantification; the lower energy and shorter positron range of ^{18}F provide better spatial resolution; and labelling with ^{18}F would also make it easier to produce and deliver the tracer to centres without a cyclotron, thereby enabling for a wider usage of the tracer, from research to clinical applications. The radiolabelling chemistry was established and optimised, from a two-step aliphatic nucleophilic radiofluorination method, to a simplified and more convenient one-step method. This method was subsequently adopted and further optimised, utilising automated Good Manufacturing Practice (GMP)-compliant radiosynthesis modules, resulting in higher radiochemical yield and molar activity, necessary for the increasing demand in clinical application. Results: The preclinical evaluation has demonstrated that FE-PE2I ligand is potent and selective for DAT. It has a better in vitro binding affinity than PE2I to DAT. The in vivo binding competition and displacement studies showed that [^{18}F] FE-PE2I was reversible, highly selective and specific for DAT, and has high BPND values in caudate and putamen in vivo, which consistent with the established information on DAT-distribution pattern in the brain. With faster kinetics and relatively fast metabolism and elimination, it has more favourable pharmacokinetics and PET imaging advantages over [^{11}C]PE2I. It also produced less abundant of more lipophilic radiometabolite, which helps in better DAT quantification in the brain, and showed quicker imaging time. Clinical evaluations in human subjects have shown that this radiotracer is safe, with effective dose in the range among doses for other DAT imaging tracers and for 18F-labelled tracer ([^{18}F] FDG). [^{18}F] FE-PE2I was also comparable to the established DAT imaging agent like [^{123}I] FP-CIT in quantifying DAT availability, and cerebral perfusion standard imaging agent such as [^{15}O] H2O in estimating relative cerebral blood flow (rCBF) for diagnosing PS and its differential diagnoses. Imaging DAT with [^{18}F] FE-PE2I permits faster patient throughput due to its faster kinetics, therefore, allowing for a reduced time between injection and imaging, and a shorter imaging protocol. Conclusion: [^{18}F] FE-PE2I has been validated to be a better option for DAT imaging and can be clinically used in diagnosing PS and its differential diagnoses. Recently, this tracer has been listed in the EANM practice guideline/SNMMI procedure standard for dopaminergic imaging in PS to be used in clinical settings.