The effect of CYP3A4 inhibitors on dopamine transporter imaging using [^{123}I]I-FP-CIT SPECT

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ABSTRACT

Background: DAT SPECT imaging with [^{123}I]I-FP-CIT can be used as a tool to support the diagnosis of Parkinson's disease and dementia with Lewy bodies. [^{123}I]I-FP-CIT undergoes some metabolic changes in the body. One of the metabolic pathways occurs through the cytochrome P450 3A4, leading to the formation of [^{123}I]I-nor-β-CIT, which crosses the blood-brain barrier. There are medications that inhibit CYP3A4 enzymes, which could potentially affect the metabolism of [^{123}I]I-FP-CIT. Our hypothesis is that the inhibition of CYP3A4 enzyme will lead to a more reliable diagnosis of PD and DLB.

Methods: To study the effect of CYP3A4 inhibitors on the DAT imaging we conducted a case-control study. 8 patients were in the cases group who used CYP3A4 inhibitors (verapamil, amiodarone and diltiazem), and 31 patients were in the control group who don't use CYP3A4 inhibitors. To assess the effect of CYP3A4 inhibitors on the DAT binding of [^{123}I]I-FP-CIT, the striatal binding ratios was analyzed.

Results: In patients with normal DAT imaging, the mean binding ratio of striatal [^{123}I]I-FP-CIT was statistically significantly higher in CYP3A4 inhibitor users than non-CYP3A4 inhibitor users (approximately 19%), while in patients with abnormal DAT imaging, no significant difference was observed.

Conclusion: For quantitative assessment and for scientific research, it appears that CYP3A4 inhibitors may have an effect on the binding of [^{123}I]I-FP-CIT and its metabolite. However, due to our small sample size, we cannot currently make a statement on this. Additional research with strong CYP3A4 inhibitors is therefore desired to determine the effect.

Key words: [^{123}I]I-FP-CIT, DAT imaging, Dopamine transporter, CYP3A4 inhibitors

INTRODUCTION

Idiopathic Parkinson's disease (PD) and other parkinsonian syndromes are neuropathologically characterized by the degeneration of dopaminergic cells, resulting in a loss of dopamine and dopamine transporters at the dopaminergic nerve terminal in the striatum (1). Dopamine transporter (DAT) imaging can be used to distinguish Parkinson's disease from essential tremor, and it can also distinguish dementia with Lewy bodies (DLB) from Alzheimer's disease, as there is also a loss of

DAT in the striatum in DLB, but not essential tremor and Alzheimer's disease (2-4).

In PD, the DAT expression is markedly reduced in the striatum, primarily affecting the posterior putamen in the early stages of the disease. As the disease progresses, it extends to the anterior putamen and the caudate nucleus (5-7). To evaluate the integrity, or the degree of loss of dopaminergic nerve endings, the radiopharmaceutical [^{123}I]I-N-ω-fluoropropyl-2β-carbomethoxy-3β-(4-iodophenyl)tropane ([^{123}I]I-FP-CIT), can be used clinically, among other things, which binds to the DAT and is derived from cocaine. The DAT SPECT technique (licensed as DaTSCAN^{TM}) is utilized for this purpose (8).

After intravenous injection, [^{123}I]I-FP-CIT undergoes some metabolic changes in the body, reminiscent of cocaine metabolism. The main metabolic pathway involves the hydrolysis of the ester group (Figure 1). In this process, the ester bond is cleaved, resulting in the formation of [^{123}I]I-FP-CIT acid (60%). However, this metabolite is likely not lipophilic enough to cross the blood-brain barrier (9). Another metabolic route involves N-demethylation, catalyzed by cytochrome P450 3A4 (CYP3A4), leading to the formation of lipophilic [^{123}I]I-nor-β-CIT (10). This metabolite is also a radioactive tracer which is formed in a small amount (<4%), but may pass the blood-brain barrier.

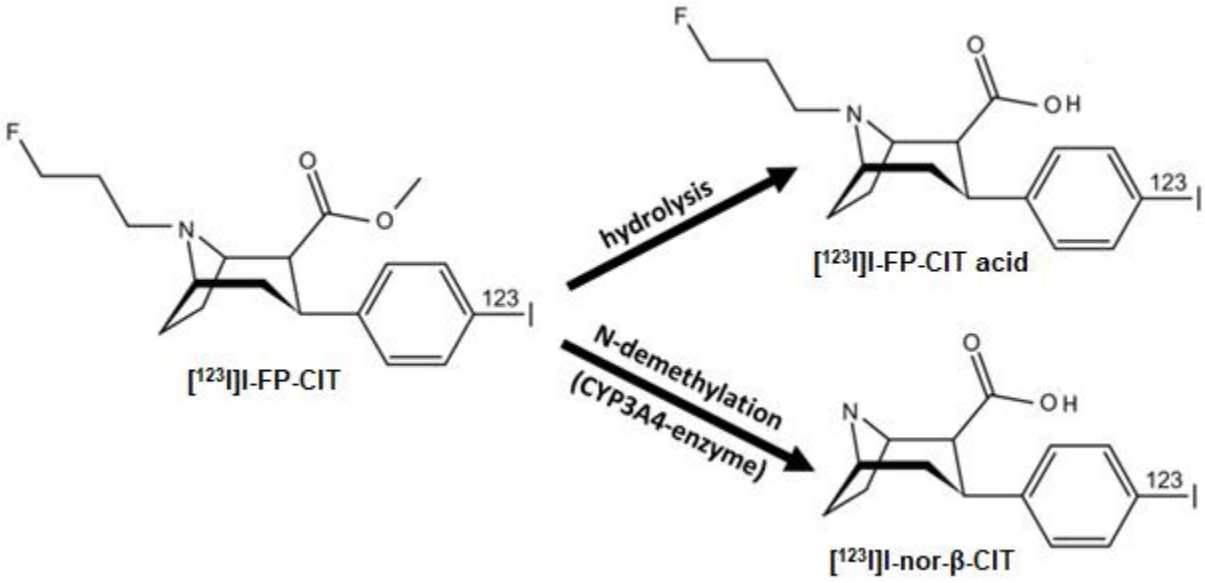

Figure 1 The metabolism of [^{123}I]I-FP-CIT: The main metabolic pathway involves the hydrolysis of the ester group. In this process, the ester bond is cleaved, resulting in the formation of [^{123}I]I-FP-CIT acid (60%). However, this metabolite is likely not lipophilic enough to cross the blood-brain barrier (9). Another metabolic route involves N-demethylation, catalyzed by cytochrome P450 3A4 (CYP3A4), leading to the formation of lipophilic [^{123}I]I-nor-β-CIT (10). This metabolite is a radioactive tracer formed in a small amount (<4%), but may pass the blood-brain barrier.

For a quantitative assessment of the [^{123}I]I-FP-CIT SPECT images, the striatal binding ratio (SBR) is determined (11). This means that the specific binding in the DAT-rich striatum is compared to a brain area almost devoid of DAT (e.g. the occipital cortex). It is known that the radiotracer [^{123}I]I-FP-CIT has a higher affinity for the DAT compared to the serotonin transporter (SERT), respectively 1.67 and 16.3 nM (12, 13). Within the striatum, the concentration of DAT is much higher than for SERT (14). The concentration of SERT is also low in the occipital cortex, and cerebellum, but it is not negligible (15). Previous studies have also demonstrated that the affinity for SERT is higher for [^{123}I]I-nor-β-CIT than for [^{123}I]I-FP-CIT (9, 16). So, since this metabolite may pass the blood-brain barrier, this metabolite may impact the SBR. Theoretically, this may result in increased binding in the reference region and consequently leading to a lower SBR. As a consequence, this discrepancy may potentially lead to an overestimation of striatal DAT binding, which might influence the diagnostic accuracy.

There are medications that can inhibit CYP3A4 enzymes, which could potentially affect the metabolism of [^{123}I]I-FP-CIT. Therefore, we believe that the quantification of striatal [^{123}I]I-FP-CIT binding may be influenced by CYP3A4 inhibitors (17), which could be relevant for diagnostic imaging techniques and research on conditions such as PD.

Our hypothesis is that if the CYP3A4 enzymes are inhibited, there will be less formation of the radioactive [^{123}I]I-nor-β-CIT metabolite. Consequently, there will be less binding in the occipital cortex, where SERT is more prevalent compared to the striatum. Given that the diagnosis of PD and DLB relies on striatal DAT-binding rather than SERT-binding, we expect a decrease in background activity in users of CYP3A4 inhibitors. If this is true, this might lead to a less reliable quantification of striatal DAT binding using [^{123}I]I-FP-CIT SPECT in subjects using these inhibitors.

MATERIALS AND METHODS

Subjects

A total of 39 patients were selected for this case-control study. These patients underwent DAT imaging at the Amsterdam University Medical Centers (Amsterdam UMC, Amsterdam, the Netherlands) between January 2016 to August 2023 in routine practice to support or exclude dopaminergic degeneration. We first selected patients who were using a CYP3A4 inhibitor. Subsequently, we proceeded to choose patients for the “control group” who had approximately similar characteristics to the case group. This resulted in eight cases and 31 controls. We chose approximately

four times more controls because this condition (cases) occurs less frequently than the absence of that condition (controls). This way, a more reliable conclusion is drawn. We excluded patients with unknown medication information. Patients taking the following medications were also excluded: dexamphetamine, methamphetamine, phentermine, ephedrine, methylphenidate, dexmethylphenidate, modafinil, armodafinil, fentanyl, codeine, haloperidol, bupropion. These are medications that significantly decrease the striatal binding of [^{123}I]I-FP-CIT (18).

We carefully matched cases from the database for age, gender, smoking, alcohol use, drugs use, diagnosis of PD or DLB, amount of radioactivity administered, and the result of the DAT imaging to the control group.

Data acquisition and processing

To examine the impact of the CYP3A4 inhibitor on the DAT binding of [^{123}I]I-FP-CIT, we collected patient data from Electronic patient dossier (Epic). For the assessment of striatal DAT availability, it was automatically quantified using the Brain Registration and Analysis Software Suite (BRASS; HERMES Medical, Sweden). Hereby, we used the following parameters: background, left and right striatum ratio, left and right putamen ratio, and left and right caudate nucleus ratio.

Before the patients underwent DAT imaging, they get a potassium iodide orally to block thyroid uptake of free radioactive iodide. Imaging was performed three hours after intravenous bolus injection of [^{123}I]I-FP-CIT (approximately 110 MBq) (11). Imaging was performed on the brain-dedicated SPECT scanner, InSPira HD system (Neurologica, Boston, MA, USA). Striatal DAT availability was automatically quantified using the Brain Registration and Analysis Software Suite (BRASS; HERMES Medical, Sweden).

Region-of-Interest Analysis

BRASS aligns the SPECT data with a template containing predefined regions-of-interest (ROI) for the whole striatum and its subdivisions (i.e. caudate nucleus and putamen) and the occipital cortex. The occipital cortex served to measure nonspecific activity/reference area (19). To calculate the specific-to-nonspecific binding potential (non-displaceable binding potential; BPND, i.e., DAT availability) the following formula was used: BP_{ND} = (mean striatal binding − mean occipital cortex binding)/mean occipital cortex binding.

Data analysis

The background activity was corrected for weight and administered activity (background/(activity/kg body weight)).

To analyze the SBR in patients with a normal DAT image, the average ratio was calculated from the left and right side of the caudate nucleus, putamen, and striatum, because in healthy people its equal on both sides. For the analysis of the binding ratios in patients with an abnormal DAT image, the value of the hemisphere that is the lowest is used to ensure consistency.

Statistical analysis

To compare groups as appropriate, we used two different tests. The unpaired T-test was used for continuous variables, which were presented as mean ± standard deviation (SD) for parametric and nonparametric data, respectively. Additionally, Fisher's exact test was performed for categorical variables, which were presented as count and percentage (%).

The unpaired T-test was used to assess the research question, in which a distinction was made between a normal and abnormal DAT binding ratios of [^{123}I]I-FP-CIT. Statistical significance was defined as $P<0.05$. IBM SPSS statistics version 28 (SPSS, Inc., Chicago, IL, USA) was employed to conduct the statistical analysis.

RESULTS

Characteristics

For our study, we included 39 patients, of which eight belonged to the cases group. The patient characteristics are shown in table 1. The CYP3A4 inhibiting drugs in this population are: verapamil, amiodarone, and diltiazem. The group of CYP3A4 inhibitor users didn't differ significantly in terms of sex, age, BMI, diagnosis of PD, diagnosis of DLB, smoking, alcohol use, medication use, result of the DAT imaging and amount of administered activity from the control groups.

Table 1 Patient characteristics of the study population

Characteristics	**No CYP3A4 inhibitor users (%)**	**CYP3A4 inhibitor users (%)**	**P-value**
Sex			1.000 *
Male	12 (38.7)	3 (37.5)	
Female	19 (61.3)	5 (62.5)	
Age (years) †	70.2 ± 9.4	71.3 ± 12	0.834 #
BMI (kg/m^2) †	25.2 ± 3.9	25.6 ± 5.7	0.868 #
Parkinson disease			0.508 *
Yes	2 (6.5)	1 (12.5)	
No	29 (93.5)	7 (87.5)	
Dementia with Lewy bodies			1.000 *

Yes	0 (0)	0 (0)	
No	31 (100)	8 (100)	
Smoking			1.000 *
Yes	3 (9.7)	0 (0)	
No	27 (87.1)	8 (100)	
Unknown	1 (3.2)	0 (0)	
Alcohol use			1.000 *
Yes	14 (45.2)	4 (50)	
No	15 (48.4)	4 (50)	
Unknown	2 (6.5)	0 (0)	
Drugs use			1.000 *
Yes	2 (6.5)	0 (0)	
No	23 (74.2)	7 (87.5)	
Unknown	6 (19.4)	1 (12.5)	
Result DAT imaging			0.450 *
Normal [^{123}I]I-FP-CIT binding	18 (58.1)	6 (75)	
Decreased [^{123}I]I-FP-CIT binding	13 (41.9)	2 (25)	
Activity (MBq/kg) †	1.65 ± 0.33	1.59 ± 0.43	0.709 #
CYP3A4 inhibitors			NA
Verapamil	NA	2	
Amiodarone	NA	5	
Diltiazem	NA	1	

† Mean ± standard deviation
# Unpaired t-test
* Fisher's exact test
NA = Not applicable

Analyses of uptake ratios of [^{123}I]I-FP-CIT

We made a distinction between normal and abnormal rated DAT image, where the striatal [^{123}I]I-FP-CIT binding is notably reduced. A total of 13 patients from the control group and two patients from the case group showed abnormal striatal DAT binding ratios of [^{123}I]I-FP-CIT. These patients are the ones who receive a diagnosis of PD, depending on additional criteria such as symptoms. The rest of the patients had normal results in their DAT imaging, excluding dopaminergic degeneration.

The means and standard deviations (SD) for specific-to-nonspecific striatal [^{123}I]I-FP-CIT binding ratios with a normal DAT imaging are described in table 2. The background uptake of [^{123}I]I-FP-CIT was 80.51 ± 15.06 for non-CYP3A4 inhibitor

users and 87.04 ± 33.28 for CYP3A4 inhibitor users. No significant difference was found (p = 0.659). The mean binding ratio of striatal [^{123}I]I-FP-CIT was 2.91 ± 0.78 for non-CYP3A4 inhibitor users and 3.52 ± 0.32 for CYP3A4 inhibitor users. It is statistically significantly higher (approximately 19%) in CYP3A4 inhibitor users than non-CYP3A4 inhibitor users (p = 0.012).

Table 2 Uptake ratios of DAT imaging with normal [^{123}I]I-FP-CIT binding

Characteristics	No CYP3A4 inhibitor users (n=18)	CYP3A4 inhibitor users (n=6)	P-value #
Background	80.51 ± 15.06	87.04 ± 33.28	0.659
Mean caudate nucleus ratio	3.05 ± 0.81	3.68 ± 0.30	0.011
Mean putamen ratio	2.75 ± 0.77	3.35 ± 0.39	0.023
Mean striatum ratio	2.91 ± 0.78	3.52 ± 0.32	0.012

Unpaired t-test

The means and standard deviations (SD) for specific-to-nonspecific striatal [^{123}I]I-FP-CIT binding ratios with an abnormal rated DAT imaging are described in table 3. The background uptake of [^{123}I]I-FP-CIT was 70.92 ± 14.49 for non-CYP3A4 inhibitor users and 88.27 ± 8.32 for CYP3A4 inhibitor users. The side with the lowest binding ratio of striatal [^{123}I]I-FP-CIT was 2.91 ± 0.78 for non-CYP3A4 inhibitor users and 3.52 ± 0.32 for CYP3A4 inhibitor users. No significant difference can be seen, neither in the background (p = 0.124) nor in the striatum (p = 0.987).

Table 3 Uptake ratios of DAT imaging with decreased [^{12I}]I-FP-CIT binding

Characteristics	No CYP3A4 inhibitor users (n=13)	CYP3A4 inhibitor users (n=2)	P-value #
Background	70.92 ± 14.49	88.27 ± 8.32	0.124
Side with lowest caudate nucleus ratio	1.86 ± 0.58	1.80 ± 0.71	0.923
Side with lowest putamen ratio	1.09 ± 0.30	1.17 ± 0.29	0.773
Side with lowest striatum ratio	1.51 ± 0.42	1.50 ± 0.51	0.987

Unpaired t-test

DISCUSSION

This is the first study in which the effect of CYP3A4 inhibitors on [^{123}I]I-FP-CIT is being investigated. In this present study, the background uptake of [^{123}I]I-FP-CIT showed no significant difference, regardless of the DAT imaging result. From this, we can conclude that the use of CYP3A4 inhibitors has no influence on the uptake of [^{123}I]I-FP-CIT and [^{123}I]I-nor-β-CIT in the background regions. Initially, we hypothesized that the uptake of [^{123}I]I-FP-CIT in the background would be lower in users of CYP3A4 inhibitors, resulting in a higher striatal binding ratio. However, we did not observe such an association.

In a normal DAT image, users of CYP3A4 inhibitors showed a significant increase in the striatal binding ratio, as well as in both caudate nucleus and putamen binding ratios, of approximately 19% compared to non-users of CYP3A4 inhibitors. This increased uptake can have two explanations. The first explanation is that CYP3A4 inhibitors bind to peripherally DAT. This means that these drugs bind to peripheral DAT (occurs in much smaller amounts in spleen (20)), resulting in less peripheral binding of [^{123}I]I-FP-CIT and thus in a higher SBR. CYP3A4 inhibitors (verapamil, amiodarone, and diltiazem) to not bind to SERT and DAT, so this can be ruled out (21-23). The second explanation is when CYP3A is inhibited, there is reduced or minimal conversion to [^{123}I]I-nor-β-CIT, so more [^{123}I]I-FP-CIT goes to the brain, specifically to the striatum because the affinity of [^{123}I]I-FP-CIT is higher in that region.

In the abnormal DAT image, the striatal binding was not significantly different (Table 3). We cannot confidently apply the explanations we made for a normal DAT scan to the abnormal DAT image because the population size is very small, with only two patients in the abnormal group, to make a definitive statement.

For clinical practice, Table 3 is important because you assess [^{123}I]I-FP-CIT uptake visually. Therefore, the use of weak and moderate CYP3A4 inhibitors is not relevant for the daily practice of visually assessing the DAT imaging. For quantitative assessment and for scientific research, it appears that CYP3A4 inhibitors may have an effect on the binding of [^{123}I]I-FP-CIT and its metabolite. However, due to our small sample size, we cannot currently make a statement on this. Additional research with strong CYP3A4 inhibitors is therefore desired to determine the effect.

The ratio of specific-to-nonspecific striatal [^{123}I]I-FP-CIT binding at abnormal DAT imaging is lower than at normal DAT imaging. This finding is explained in the study of Booij et al. (1999) (11) and the more recent study Lanfranchi et al. (2022) (4).

There are several limitations in this study. The first limitation is that the population size was too small. Another limitation is that we could not verify whether the patients actually used the CYP3A4 inhibitor or not. We relied on the data documented in the patient records. A final limitation concerns the exclusion criteria, namely that all drug users had to be excluded. So, it would have been good to conduct the study in a larger population and to carry out a prospective study. In this way, explicit inquiries could be made about CYP3A4 inhibitors and drug use, such as whether they are used, how often, etc.

CONCLUSION

In conclusion, based on this data, CYP3A4 inhibitors may have an effect on the striatal [123I]I-FP-CIT binding to DAT. However, due to our small population size, we cannot currently make a statement on this. In the future, a study can be done of strong CYP3A4 inhibitory drugs.

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