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Increased P-gp inhibition at the human blood brain barrier can be safely achieved by performing PET during peak plasma concentrations of tariquidar

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ABSTRACT

The permeability-glycoprotein (P-gp) efflux transporter is densely expressed at the blood-brain barrier (BBB) and its resultant 'spare capacity' requires substantial blockade to increase the uptake of avid substrates. This has blunted the ability of investigators to measure clinically meaningful alterations in P-gp function. This study, conducted in humans, examined two P-gp inhibitors (tariquidar, a known inhibitor, and disulfiram, a putative inhibitor) and two routes of administration (intravenous and oral) to maximally increase brain uptake of the avid and selective P-gp substrate ^{11}C-desmethyl-loperamide (dLop), while avoiding side effects associated with high doses of tariquidar.

Methods: Forty-two ^{11}C-dLop positron emission tomography (PET) scans were obtained from 37 healthy volunteers. PET was performed with ^{11}C-dLop under five conditions: 1) injected under baseline conditions without P-gp inhibition; 2) injected one hour after IV tariquidar infusion; 3) injected during IV tariquidar infusion; 4) injected after oral tariquidar; and 5) injected after disulfiram. ^{11}C-dLop uptake was quantified with kinetic modeling using metabolite-corrected arterial input function or by measuring the area under the time-activity curve in brain from 10 to 30 minutes.

Results: Neither oral tariquidar nor oral disulfiram increased brain uptake of ^{11}C-dLop. Injecting ^{11}C-dLop during tariquidar infusion, when plasma tariquidar concentrations reach their peak, resulted in brain uptake of radioligand approximately five-fold greater than baseline. Brain uptake was similar with 2 and 4 mg/kg IV tariquidar; however, the lower dose was better tolerated. Injecting ^{11}C-dLop after tariquidar infusion also increased brain uptake, though higher doses (up to 6 mg/kg) were required. Brain uptake of ^{11}C-dLop increased fairly linearly with

increasing plasma tariquidar concentrations, but we are uncertain whether maximal uptake was achieved.

Conclusion: We sought to increase the dynamic range of P-gp function measured after blockade. Performing ^{11}C-dLop PET during peak plasma concentrations of tariquidar, achieved with concurrent administration of IV tariquidar, resulted in greater P-gp inhibition at the human BBB than delayed administration, and allowed use of a lower, more tolerable dose of tariquidar. Based on prior monkey studies, we suspect that plasma concentrations of tariquidar did not fully block P-gp; however, higher doses of tariquidar would likely be associated with unacceptable side effects.

Keywords: P-glycoprotein (P-gp), positron emission tomography (PET), *N-desmethyl*-loperamide, tariquidar.

INTRODUCTION

The efflux transporter P-glycoprotein (P-gp) is a component of the blood-brain barrier (BBB) and a proposed mechanism of drug resistance (*1*). Under physiological conditions, P-gp acts at high capacity, completely blocking entry into the brain of avid substrates, including radiolabeled substrates. Over 50% of P-gp transporters may need to be inhibited pharmacologically in order to increase uptake of radiolabeled substrates into a range measurable by PET *(2)*. Notably, the P-gp inhibitor tariquidar has been shown to increase brain uptake of the substrate positron emission tomography (PET) radiotracers ^{11}C -*N-desmethyl*-loperamide (^{11}C-dLop) and ^{11}C -*(R)*-verapamil two-to-three fold compared to baseline (*3-6*).

To detect pathological overexpression of P-gp using PET, normal P-gp function (which is already of high capacity) must be distinguished from P-gp overexpression (which has even higher capacity). Treating subjects with a fixed dose of tariquidar prior to PET imaging would hypothetically increase radiotracer uptake into a dynamic range where differential response to inhibition—caused by differential P-gp function—could be measured.

In order to achieve increases in radiotracer brain uptake into this range, however, past studies have required high intravenous (IV) doses (> 2 mg/kg) of tariquidar that were associated with adverse drug reactions *(4, 7, 8)*. In addition, because these studies administered the PET radiotracer after completion of tariquidar infusion, they may have missed the window of peak P-gp inhibition and, thus, the most reliable measurement of increased P-gp inhibition. While tariquidar is the only third generation P-gp inhibitor that has been found to be safe for human administration, other potential methods of pharmacological inhibition of P-gp include oral administration of tariquidar (*9*) or oral administration of disulfiram, a drug whose metabolites have been shown to inhibit P-gp in vitro (*10-12*).

This study sought to determine whether increased inhibition of P-gp at the human BBB could be safely achieved and reliably measured by changing the timing or route of administration of tariquidar, or by using disulfiram. ^{11}C-dLop PET was performed on healthy volunteers under baseline conditions or after P-gp inhibition. For the P-gp blocked condition, ^{11}C-dLop was injected either one hour after IV tariquidar infusion, during IV tariquidar infusion, after oral tariquidar, or after disulfiram.

MATERIALS AND METHODS

Thirty-seven healthy volunteers (age 29.1 ± 6.9 years, 18 female) were included. Volunteers with serious medical or psychiatric illness, those using illicit drugs, and those taking medications other than oral contraceptives were excluded. The study was approved by the NIH Combined Neurosciences Institutional Review Board. All participants gave written informed consent before entering the study. Subjects were monitored for changes in blood pressure, temperature, heart rate, and respiration rate before and after tariquidar infusion. These parameters, as well as electrocardiogram tracing, were similarly monitored after ^{11}C-dLop injection. Blood and urine laboratory tests were repeated within 24 hours of study completion. Plasma was drawn to measure total tariquidar concentration for 16 subjects and free fraction of tariquidar for 5 subjects. Methods for measuring total and free concentration of tariquidar are given in the Supplemental Methods.

^{11}C-dLop Imaging

^{11}C-dLop was prepared by the methylation of its primary amide precursor with ^{11}C-iodomethane, as described previously (*13*). The radiotracer was obtained in high radiochemical purity (100%) and with a specific activity of 101 ± 50 GBq/μmol at the time of injection.

Fourteen ^{11}C-dLop scans were performed without P-gp inhibition (baseline).The remaining 28 scans were performed with P-gp inhibition. Methods for PET imaging and tariquidar preparation are given in Supplemental Methods.

IV tariquidar with delayed radiotracer injection. Scan data from seven subjects who received either 4 mg/kg or 6 mg/kg of IV tariquidar in a previously published study (*4*) were included in this study for comparison. For these subjects, ^{11}C-dLop was injected approximately 60 minutes after completion of the tariquidar infusion.

IV tariquidar with concurrent radiotracer injection. Twelve subjects received IV tariquidar at doses of either 2 mg/kg (n = 10, 4 female, body weight 71.2 ± 18.7 kg) or 4 mg/kg (n = 2, 1 female, body weight 72.8 ± 19.4 kg). Subjects had two IV catheters placed (one in each antecubital vein) prior to imaging. Under both dose conditions, tariquidar was infused at a rate of 4 mg/kg/hr through one catheter. Halfway through the tariquidar infusion (at 30 minutes for the 4 mg/kg group and at 15 minutes for the 2 mg/kg group), ^{11}C-dLop was injected through the other catheter. Arterial sampling was not performed.

Oral tariquidar administration. To determine the dose strategy for oral tariquidar, we performed pharmacokinetic studies in healthy volunteers (see Supplemental Methods). Based on

the results, three additional subjects (all male, body weight 76.1 ± 16.5 kg) received oral tariquidar at a dose of 1500 mg 10 – 12 hours before ^{11}C-dLop injection. Arterial sampling was not performed.

Oral disulfiram administration. Disulfiram was administered at two doses: 500 mg oral disulfiram as a one-time dose 10 hours before ^{11}C-dLop injection (n = 3, all male, body weight 83.37 ± 11.97), or 2.5 g over 4 days before ^{11}C-dLop injection (n = 3, all female, body weight 78.13 ± 24.58). Subjects were given written and oral instructions to abstain from alcohol-containing products for two days prior and two weeks after disulfiram administration. Arterial sampling was performed.

^{11}C-dLop Image Analysis

Reconstructed PET images were realigned and normalized to stereotactic space using pixelwise modeling software (PMOD 3.0). The Montreal Neurologic Institute template was used to define a region of composite neocortex by creating a weighted average of activity from the frontal, parietal, occipital, and temporal cortices. Regions were manually adjusted when necessary to exclude cerebrospinal fluid space and choroid plexus.

The concentration of radioactivity was expressed as standardized uptake value (SUV): SUV = (measured activity per cm^3 brain / injected activity) • (g of body weight). The area under the time-activity curve from 10 to 30 minutes ($AUC_{10\text{-}30}$) for each composite brain region was calculated using the trapezoidal method.

For those subjects with metabolite-corrected plasma data, rate constants (K_1 and k_2) and total distribution volume (V_T) were calculated using a one-tissue compartmental model. The total

concentration of radioactivity in whole blood was used for vascular correction, assuming that blood constitutes 5% brain volume.

Because the posterior pituitary lacks a BBB and prior baseline PET scans have shown high uptake of ^{11}C-dLop in this organ (*6*), we measured activity in the pituitary gland to estimate brain uptake of ^{11}C-dLop in complete absence of P-gp (see Supplemental Methods).

Statistical Analysis

Statistical analysis was performed using SPSS 17.0. Group differences in ^{11}C-dLop uptake were evaluated using the Mann Whitney U test. To determine if the tariquidar-^{11}C-dLop dose-response curve best fit a linear or nonlinear model, we used the Curve Estimation function in SPSS to perform linear and nonlinear (quadratic, cubic, and sigmoidal) regressions. The estimated EC_{50} value and its 95% confidence interval were determined using R software package (www.r-project.org) using a log-normal dose-response model.

RESULTS

Safety Analysis

Tariquidar was generally well-tolerated in subjects who received the lowest doses (2 mg/kg IV and 1500 mg PO). Two subjects who received 2 mg/kg IV reported a mild metallic taste during the tariquidar infusion. Two subjects who received 4 mg/kg IV tariquidar experienced light-headedness and conjunctival injection, and one of these subjects had a brief syncopal episode immediately after the PET scan that resolved without sequelae. One subject who received 6 mg/kg IV tariquidar complained of metallic taste accompanied by nausea that resolved once tariquidar infusion was stopped.

Disulfiram was well-tolerated by all subjects. One subject experienced a mild, transient disulfiram-ethanol reaction three days after the PET scan due to unwittingly consuming food prepared with wine.

Imaging Results

When ^{11}C-dLop was injected in the baseline condition, uptake of activity in brain was negligible, in agreement with previous studies. Brain time-activity curves reached a plateau at < 0.2 SUV (Fig 1). Both K_1 and k_2 values were low, resulting in V_T values of 1.20 ± 0.16. $AUC_{10\text{-}30}$ values for composite neocortex were 2.94 ± 0.66 SUV • min (Table 1). Individual region of interest values are shown in Supplemental Table 1.

When ^{11}C-dLop was injected ~60 minutes after tariquidar infusion, brain uptake of ^{11}C-dLop was approximately two- to four-fold greater than at baseline (Table 1). Brain time-activity curves reached plateaus of ~0.3 and ~0.6 SUV during delayed administration of tariquidar at 4 and 6 mg/kg IV, respectively. The resulting $AUC_{10\text{-}30}$ values for composite neocortex were 1.7 - 3.4 times greater than baseline.

When ^{11}C-dLop was injected during infusion of tariquidar, brain uptake of ^{11}C-dLop was approximately five-fold greater than at baseline (Figs 1 & 2, Table 1). Brain time-activity curves reached plateaus of 0.4 - 1.4 SUV and 0.7 - 1.1 SUV during concurrent administration of tariquidar at 2 and 4 mg/kg IV, respectively. The resulting $AUC_{10\text{-}30}$ values for composite neocortex were ~5 times greater than baseline, ~3 times greater than delayed administration of 4 mg/kg IV tariquidar, and ~1.5 times greater than delayed administration of 6 mg/kg IV tariquidar. At baseline, ^{11}C-dLop uptake in pituitary was 17-times greater than in composite neocortex (Supplemental Fig 1). After P-gp inhibition, uptake in pituitary was 3.5-times greater

than in composite neocortex. ^{11}C-dLop uptake in pituitary was similar at baseline and after P-gp inhibition (~2.7 *vs.* ~2.5 SUV).

Oral tariquidar did not increase brain uptake of ^{11}C-dLop. Measured values for $AUC_{10\text{-}30}$ did not differ from those in baseline scans (Fig 3, Table 1). Results from the pharmacokinetic study for oral tarquidar are given in Supplemental Results.

Neither low- nor high-dose disulfiram administration was associated with ^{11}C-dLop uptake into brain greater than baseline (Fig 4, Table 1). Disulfiram did not result in changes in V_T, K_1, k_2, or $AUC_{10\text{-}30}$. Plasma free fraction of ^{11}C-dLop was slightly lower in disulfiram-treated subjects than in subjects who had ^{11}C-dLop under baseline conditions (12 ± 1% vs. 15 ± 2%; p = 0.0426, Mann Whitney U test). However, V_T / f_p values did not differ between disulfiram-treated and baseline subjects (p = 0.2284).

Dose-Response Of Tariquidar On ^{11}C-dLop Uptake

We measured plasma concentrations of tariquidar for subjects who had concurrent radiotracer injection, oral tariquidar, and one subject who had delayed radiotracer injection. For the concurrent group, plasma concentrations of tariquidar were 1040 ± 360 ng/mL (1609 ± 556 nM) for the 2 mg/kg dose and 1438 ± 528 ng/mL (2224 ± 817 nM) for the 4 mg/kg dose. Plasma concentrations of tariquidar after oral administration were 133 ± 46 ng/mL (205 ± 71 nM), or only 13% of the concentration achieved with concurrent administration of 2 mg/kg IV. The subject who had IV tariquidar (4 mg/kg) with delayed radiotracer injection had plasma concentrations of 232 ng/mL (358 nM), or 22% of the mean value for subjects who had concurrent injection of radiotracer at the same dose of tariquidar. Free fraction of tariquidar was

0.0054 ± 0.0002 for the five subjects who had ^{11}C-dLop imaging and 0.0053 ± 0.0003 for all 21 subjects who had free fraction measured.

^{11}C-dLop uptake into brain increased linearly with total concentration of tariquidar at low and moderate concentrations of the inhibitor; however, at higher concentrations, the PET response appeared to plateau (Fig 5). Goodness of fit was greater for the sigmoidal model (r^2 = 0.81) than linear (r^2 = 0.30), quadratic (r^2 = 0.65), or cubic (r^2 = 0.66) models. The estimated EC_{50} value and the 95% confidence interval were 306 ng/mL (20, 592). Estimated maximum for ^{11}C-dLop uptake and the 95% confidence interval was 15 SUV • min (12, 19). This maximum corresponds to peak uptake of 0.8 SUV in brain. Brain uptake of radiotracer did not correlate with free concentration of tariquidar in plasma (r = - 0.61, p = 0.28); however, free fraction was only measured in five subjects.

DISCUSSION

Performing ^{11}C-dLop PET imaging during peak plasma concentrations of tariquidar resulted in greater P-gp inhibition at the BBB than injecting radiotracer after a delay. This concurrent administration strategy allowed use of a lower dose of tariquidar, expected to result in fewer adverse events. In contrast, neither 1500 mg of oral tariquidar nor oral disulfiram inhibited P-gp. These results suggest that the ability of tariquidar to inhibit P-gp at the BBB depends on the concentration of tariquidar in plasma. These results also suggest that oral tariquidar and disulfiram are not viable alternatives to IV tariquidar for inhibiting P-gp.

In a previous study from our laboratory, we injected ^{11}C-dLop approximately one hour after tariquidar infusion was completed, and other studies using ^{11}C-*(R)*-verapamil injected the radiotracer approximately one to three hours post-tariquidar (*7, 8*). One of the studies using ^{11}C-

(R)-verapamil showed that plasma concentrations of tariquidar declined rapidly after infusion and were followed by a long terminal phase, remaining stable at ~500 ng/mL (773 nM) for several hours (*8*). Therefore, in our prior study using ^{11}C-dLop, we presumed that this terminal phase represented the concentration of tariquidar required to effectively inhibit P-gp at the BBB, given that plasma concentrations between 150 – 200 ng/mL (230 - 310 nM) inhibit P-gp activity on leukocytes (*9*). However, subsequent studies demonstrated that greater concentrations of tariquidar are required to block P-gp activity at the BBB than on leukocytes (*14, 15*). Therefore, by administering ^{11}C-dLop after completion of the tariquidar infusion, we may have missed the time window of maximal P-gp inhibition at the BBB. No previously published report or study has tested the efficacy of injecting substrate radiotracers during the tariquidar infusion, when plasma concentrations of this inhibitor peak (~ 1,000 ng/mL or 1,500 nM during a 2 mg/kg infusion). In this study, ^{11}C-dLop PET imaging was performed during infusion of 2 mg/kg or 4 mg/kg tariquidar. We observed brain uptake comparable to that seen when performing ^{11}C-dLop PET one hour after infusion of 6 mg/kg tariquidar (*4*). These results suggest that concurrent administration of radiotracer allows the use of lower doses of tariquidar while yielding a similar degree of P-gp inhibition. This method also reduces the amount of time required to administer tariquidar and perform the ^{11}C-dLop PET scan.

Studies have been conducted in drug-resistant cancer patients investigating the use of tariquidar to improve the efficacy of chemotherapy (*16, 17*). These studies have failed to increase penetration of chemotherapy drugs, perhaps because tariquidar was given at too low a dose (< 4 mg/kg IV) with too long an interval between administration of tariquidar and chemotherapy. The results from this study suggest that low-dose tariquidar has the potential to effectively inhibit P-gp and increase penetration of substrate medications when both the inhibitor and active drug are

simultaneously administered intravenously. While it would be ideal to infuse tariquidar over the entire time course of the ^{11}C-dLop PET scan, we infused at a fast rate over a short interval to achieve high plasma concentrations while avoiding toxicity. Peak uptake of ^{11}C-dLop occurs within the first few minutes after injection with very little washout thereafter (*6*). Therefore, we don't expect the short tariquidar infusion time to have caused large variance in the $AUC_{10\text{-}30}$ data. Rapid clearance of tariquidar from plasma may alter kinetics of P-gp substrates that reversibly bind in brain, however. Therefore, longer infusion time may be preferred for P-gp radiotracers such as ^{11}C-*(R)*-verapamil.

The adverse events observed using high doses of tariquidar (4 - 6 mg/kg IV) may have been caused by high amounts of the excipient, propylene glycol, delivered alongside tariquidar. In support of this theory, infrequent, mild side effects were observed when lower amounts of propylene glycol were delivered (2 mg/kg IV tariquidar), and no side effects were observed when no propylene glycol was delivered at all (1500 mg oral tariquidar). However, oral tariquidar may be more tolerable simply because of its low bioavailability.

Oral tariquidar did not increase brain uptake of ^{11}C-dLop, most likely because oral administration resulted in very low plasma concentrations. Repeated administration of high oral doses of tariquidar could theoretically result in stable, high plasma concentrations over time. Whether this strategy would effectively inhibit P-gp and improve penetration of substrate medications in a clinical setting remains to be seen.

Similarly, disulfiram did not increase ^{11}C-dLop brain uptake, even at a dose of 2.5 g over four days. Disulfiram metabolites irreversibly inhibit P-gp in vitro (*10*), making this drug, which is inexpensive and commercially available, an attractive alternative to tariquidar for P-gp inhibition in a clinical setting. However, high doses of disulfiram have been associated with

hepatic, neurological, and dermatologic side effects *(18)*. Our results suggest that either disulfiram metabolites do not inhibit P-gp at the BBB in vivo, or that doing so would require doses so large they would likely be toxic.

We found that the tariquidar-^{11}C-dLop dose-response curve best fit a sigmoidal curve, suggesting that the PET response plateaued at high concentrations of tariquidar. Bauer and colleagues similarly showed that brain uptake of ^{11}C-*(R)*-verapamil did not increase with doses of tariquidar greater than 6 mg/kg IV (*7*). While these results suggest that plasma concentrations of tariquidar > 1,000 ng/mL completely inhibit P-gp at the BBB, we do not know whether P-gp was maximally blocked in these experiments. We suspect that that the apparent plateau in ^{11}C-dLop uptake was caused by noise and variability of the biological response. In our earlier study, we estimated the first-pass extraction of ^{11}C-dLop to be ~40% in monkey brain when the PET scan was performed after P-gp inhibition with (2R)-anti-5-{3-[4-(10,11-dichloromethanodibenzo-suber-5-yl)piperazin-1-yl]-2-hydroxypropoxy}quinoline trihydrochloride (DCPQ) (*5*). Therefore, we would expect complete blockade of P-gp to result in high ^{11}C-dLop uptake in brain. Instead, the mean uptake was < 1 SUV in the concurrent tariquidar group (Fig 1), suggesting that P-gp was still preventing ^{11}C-dLop from entering the brain to some extent at the highest concentrations of tariquidar achieved in this study.

Because both ^{11}C-dLop and tariquidar are lysosomotropic (*19*), the apparent plateau in ^{11}C-dLop uptake could have been due to tariquidar outcompeting ^{11}C-dLop in lysosomes at higher concentrations of tariquidar. This possibility is speculative as we have no evidence that tariquidar enters brain. Tariquidar is not only an inhibitor of ABCB1 but also a substrate for ABCG2 (*20*), which thereby blocks its entry into brain. Further studies are required to determine if tariquidar enters brain at high plasma concentrations.

^{11}C-dLop uptake in the pituitary did not increase after P-gp inhibition, suggesting that its lack of BBB allows entry of ^{11}C-dLop independent of P-gp. That pituitary uptake was several-fold greater than brain uptake after tariquidar supports our conclusion that P-gp was not completely blocked in this study.

Although we didn't measure plasma radioactivity in most subjects in this study, we believe that increased brain radioactivity was due to P-gp inhibition, not increased ^{11}C-dLop in plasma. We previously showed IV tariquidar with delayed injection of radioligand increased brain radioactivity without increasing ^{11}C-dLop in plasma (*4*). Also, we recently performed concurrent tariquidar-^{11}C-dLop PET in a separate study and peak plasma concentration of ^{11}C-dLop was similar (7.6 SUV) to reported values for subjects at baseline (*4*).

One limitation of this study is that we did not perform genetic testing to correct for the presence of known polymorphisms on the *ABCB1* gene. Some of these polymorphisms decrease P-gp expression or function *(21)* and may contribute to inter-individual differences in PET response to tariquidar. Another limitation is that most PET scans were analyzed by calculating the area under the time-activity curve from 10 – 30 minutes (AUC_{10-30}) to avoid the need for arterial sampling. Full quantification of the PET data may have resulted in less variance in ^{11}C-dLop uptake values. However, we do not think the simplified AUC_{10-30} measure introduces a large amount of error because our previous report showed a strong correlation between AUC_{10-30} and K_1 values for ^{11}C-dLop (*4*). Moreover, because ^{11}C-dLop rapidly clears from plasma (*6*), avoiding use of the arterial input function may actually reduce error in quantifying uptake of ^{11}C-dLop in brain. Another limitation is that free fraction of tariquidar was measured in only a subset of subjects. Because only tariquidar that is not bound to proteins in plasma is available to bind to and inhibit P-gp, only the free concentration of tariquidar would be expected to correlate with

^{11}C-dLop uptake into brain. However, we found very small variance in the free fraction of tariquidar (coefficient of variation = 6%), suggesting we would have seen a similar dose-response relationship using the free concentration of tariquidar.

CONCLUSION

Performing ^{11}C-dLop PET imaging during peak plasma concentrations of tariquidar resulted in increased P-gp inhibition at the human BBB and allowed use of lower doses of the inhibitor. Based on prior studies in monkeys, we suspect that plasma concentrations of tariquidar did not fully block P-gp; however, higher doses of tariquidar would likely be associated with unacceptable side effects. This paradigm of concurrent administration of tariquidar and P-gp substrate drug may have potential for treating diseases associated with P-gp overexpression (e.g., multi-drug resistant cancer).

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FIGURE LEGENDS

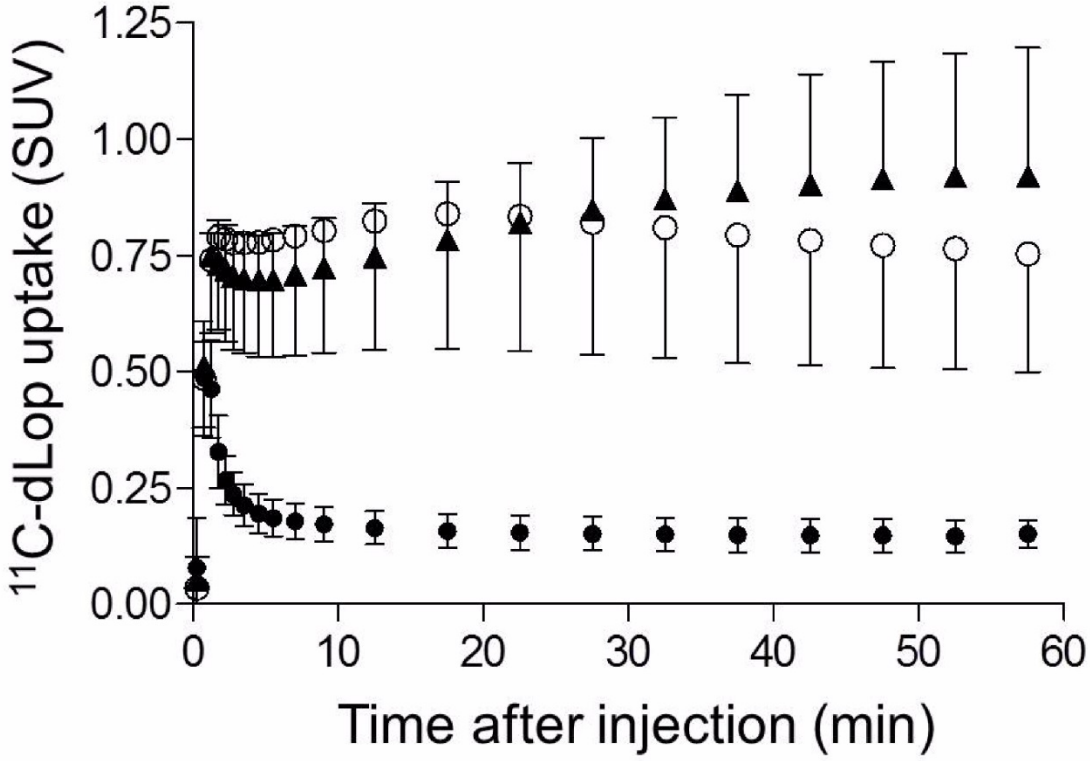

FIGURE 1. Composite neocortex time-activity curves showing brain uptake of radioactivity after ^{11}C-dLop injection. ^{11}C-dLop was injected at baseline (●), and during intravenous infusion of tariquidar at 2 (○) and 4 mg/kg (▲). Error bars denote SD.

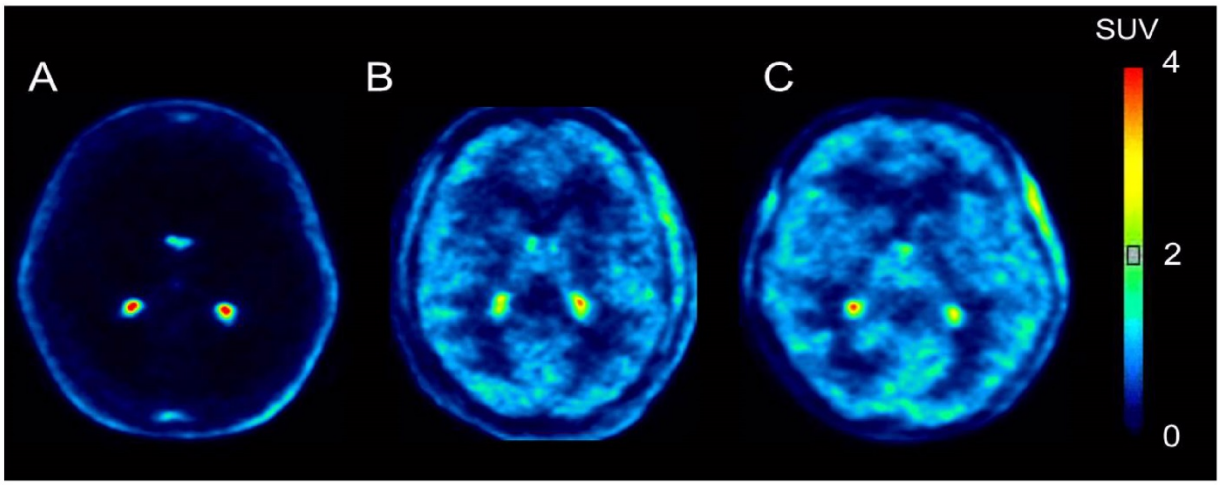

FIGURE 2. Representative images from ^{11}C-dLop PET scans. Images are summed from 10 – 30 minutes post-injection. Radioligand was injected either at baseline (A) or during intravenous infusion of tariquidar at doses of 2 mg/kg (B) and 4 mg/kg (C).

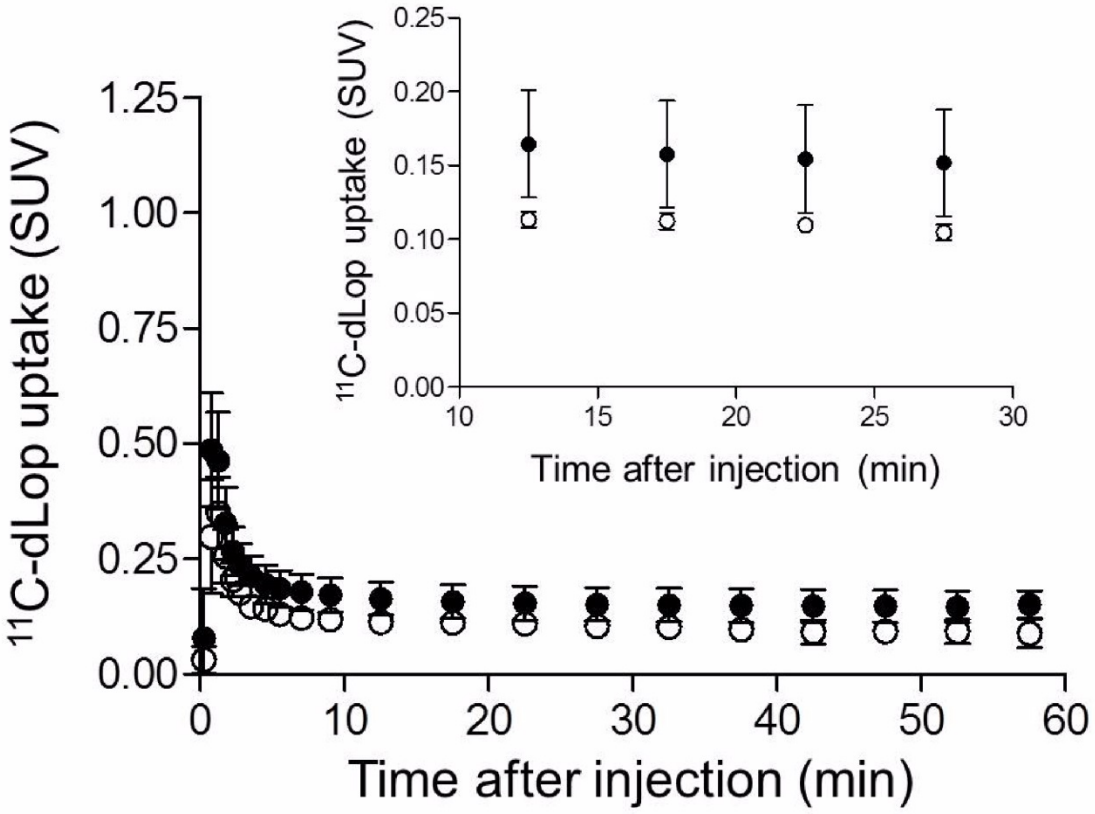

FIGURE 3. Composite neocortex time-activity curves showing brain uptake of radioactivity after ^{11}C-dLop injection at baseline (●) and after 1500 mg oral tariquidar (○). Error bars denote SD.

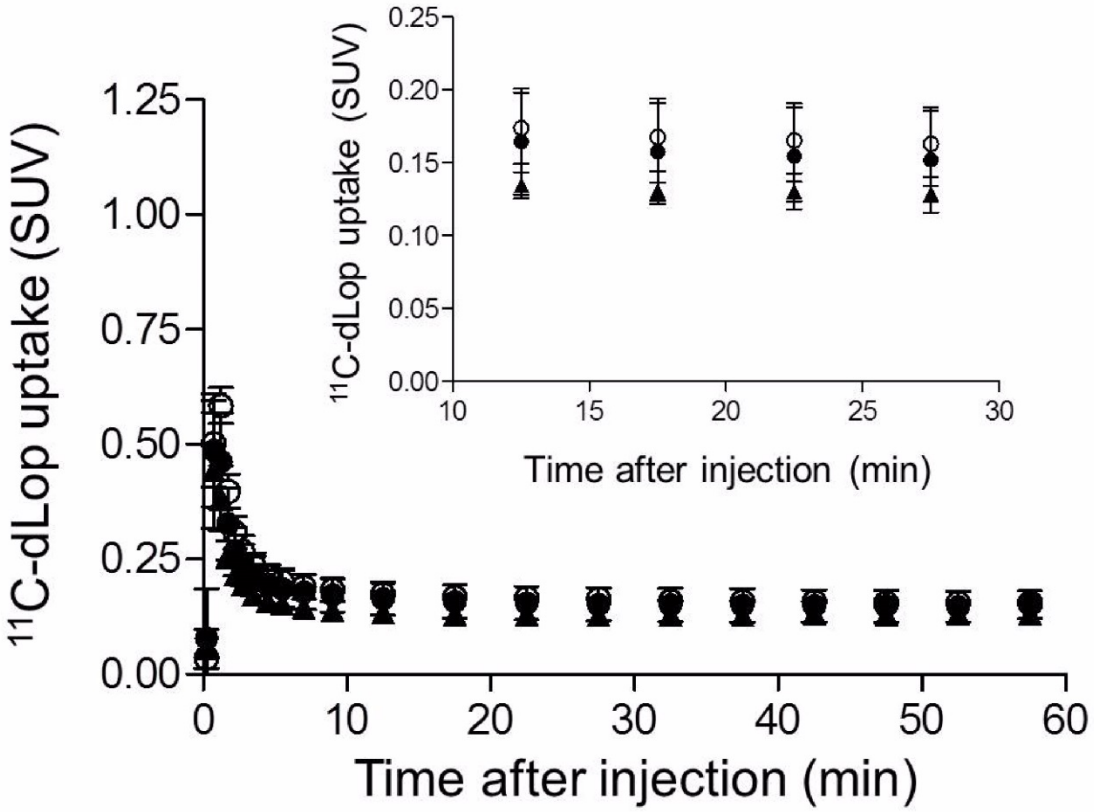

FIGURE 4. Composite neocortex time-activity curves showing brain uptake of radioactivity after injection of ^{11}C-dLop at baseline (●) and after either a one-time dose of 500 mg of disulfiram (○) or 2.5 g of disulfiram over 4 days (▲). Error bars denote SD.

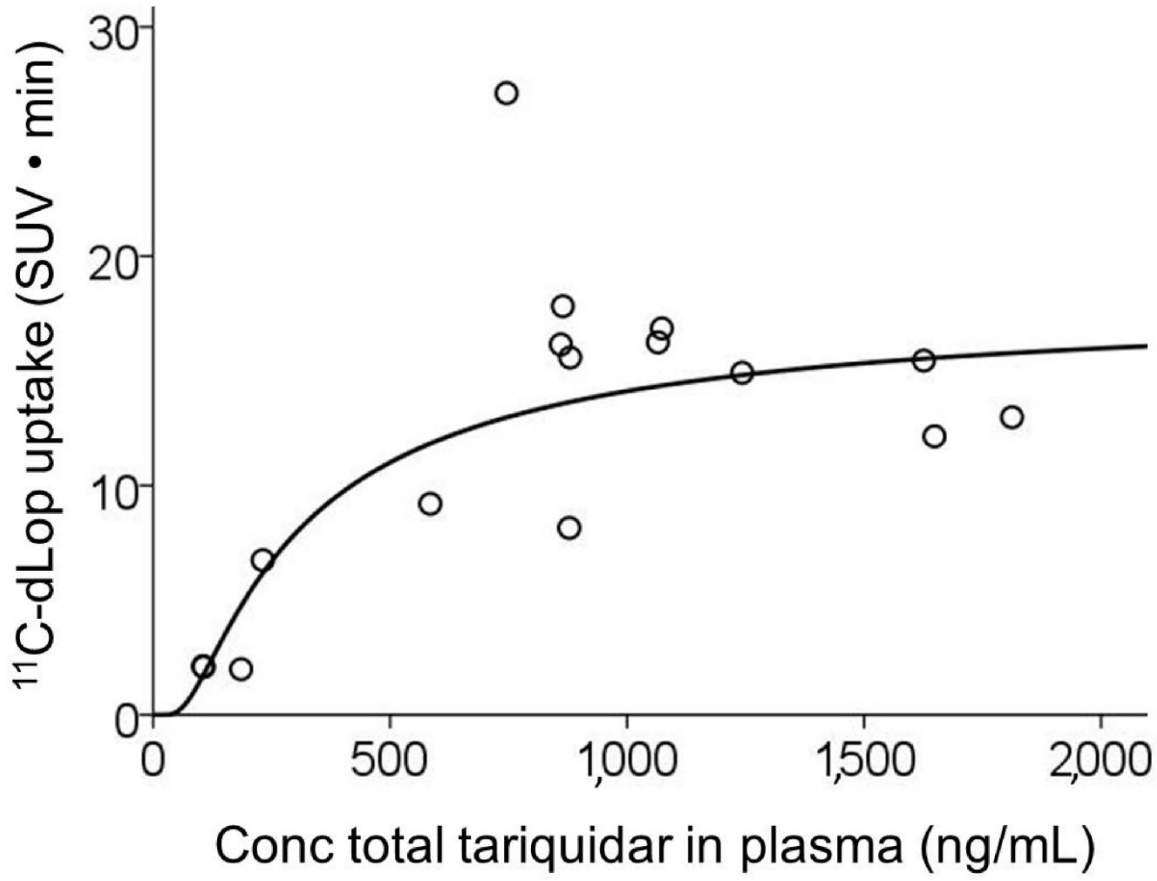

FIGURE 5. Dose-response curve for tarquidar and uptake of ^{11}C-dLop in composite neocortex.

Table 1. Uptake of ^{11}C-dLop in composite neocortex at baseline and after pharmacological inhibition of P-glycoprotein.

	$AUC_{10\text{-}30}$ (SUV · min)	K_1 (mL · cm^{-3} · min^{-1})	k_2 (min^{-1})	V_T (mL · cm^{-3})
Baseline (n=14)	2.94 ± 0.66	0.014 ± 0.002	0.012 ± 0.002	1.20 ± 0.16
Tariquidar				
4 mg/kg concurrent (n=2)	14.61 ± 2.31			
2 mg/kg concurrent (n=10)	15.34 ± 5.25*			
1500 mg oral (n=3)	2.06 ± 0.07			
4 mg/kg delayed (n=4)	5.26 ± 2.26**	0.026 ± 0.009	0.010 ± 0.001	2.56 ± 0.64
6 mg/kg delayed (n=3)	10.05 ± 3.25†	0.049 ± 0.011	0.013 ± 0.001	3.88 ± 0.71
Disulfiram				
500 mg (n=3)	3.13 ± 0.43	0.012 ± 0.001	0.011 ± 0.001	1.14 ± 0.03
2500 mg (n=3)	2.44 ± 0.12	0.012 ± 0.007	0.008 ± 0.003	1.53 ± 0.66

*$p < 0.0001$ *vs.* baseline; **$p = 0.06$ vs. baseline, †$p = 0.003$ vs. baseline
$AUC_{10\text{-}30}$ = area under brain time-activity curve from 10 to 30 minutes; K_1 = rate constant for brain entry; k_2 = rate constant for brain efflux; V_T = total distribution volume. Data are given as mean ± SD.