

On the simulation of the time-course of dopamine D2 receptor occupancy from the pharmacokinetics of antipsychotics

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We have read with great interest the elegant paper by Takano et al. (2004) regarding the estimation of the time-course of dopamine D2 receptor (D2R) occupancy from plasma pharmacokinetics of antipsychotics, with special emphasis on risperidone. It is our view that studies aiming to achieve a correct equation that could predict the level of central D2R blockade based on the measurement of antipsychotic blood levels are valuable in helping clinicians to more objectively control the treatment of patients. We have three comments that could be helpful in this research field.

First, the function of time describing the levels of an antipsychotic in the blood that was used to estimate D2R occupancy in the work of Takano et al. (2004) was:

$$C(t) = me^{-bt}, \quad (1)$$

where C is the plasma concentration, m is the estimated plasma maximal concentration at 0 h, b is a constant dependent on the plasma half-life ($t_{1/2}$) of the drug (in fact, $b = \ln 2/t_{1/2}$), and t is the time after the drug administration. As can be seen in Figure 2 of Takano et al., the estimated D2R occupancy was in most points smaller than the data obtained from PET scans. One factor contributing to this underestimation could be that the absorption state and particularly the time necessary to reach the peak concentration of the antipsychotic in blood (t_{peak}) were not taken into account. We propose the following modified function of time to describe the drug levels in blood:

$$C(t) = (m/t_{\text{peak}})tH(t_{\text{peak}} - t) + me^{-b(t - t_{\text{peak}})}H(t - t_{\text{peak}}), \quad (2)$$

where $H(x)$ is the Heaviside function. Note that equation (2) is essentially equation (1) shifted to the right plus a linear factor until the plasma maximal

concentration is reached. Plots of equations (1) and (2) for olanzapine are shown in Figure 1a. Using the same equation for D2R occupancy employed by Takano et al. (2004):

$$D_{2,\text{occ}} = 100 \times C(t)/(ED_{50} + C(t)), \quad (3)$$

where $D_{2,\text{occ}}$ is the percentage level of D2R occupancy and ED_{50} is the apparent in-vivo affinity parameter, we can see in Figure 1b that by using equation (2) instead of equation (1) the levels of D2R blockade become higher after t_{peak} . Although in the work of Takano et al. (2004) this influence was minimal, since risperidone presents a t_{peak} of 2 h, in studies simulating other antipsychotics with higher t_{peak} (such as olanzapine) this factor can have more marked influences on the results.

Secondly, we disagree with the conclusion that the half-life of the D2R occupancy ($T_{1/2}$) becomes longer as ED_{50} becomes smaller and vice versa as suggested by the simulations performed by varying the ED_{50} of the drug (shown in Figure 3 of Takano et al.). ED_{50} (plasma concentration to block 50% of D2R), similarly to K_d , can be regarded as a parameter inverse to the affinity of the antipsychotic to D2R. The maximal plasma concentration (m) of the antipsychotic is also dependent on the affinity to D2R (i.e. the less potent the antipsychotic, the higher its effective dose and plasma concentration) and, therefore, drugs with lower affinity will present greater m and vice versa. Our main point is that the parameter m in the work of Takano et al. (2004) was estimated by the first ED_{50} used (6.4 ng/ml) for risperidone, which can be done using equation (3), but then it was held constant to simulations with others values of ED_{50} . Since m is dependent on ED_{50} , if m is corrected to each new ED_{50} , for example by fixing for each ED_{50} a value of m able to block 87% of the receptors (as in their work for the first ED_{50} given), one can see that the $T_{1/2}$ does not change. In summary, once the same levels of D2R blockade are achieved with distinct antipsychotics, $T_{1/2}$ is not dependent on the affinity of the drug. On the other hand, the second set of simulations in the work by Takano et al. (2004) we consider to be legitimate and very illustrative in showing the dependence of $T_{1/2}$ on the plasma half-life of the drug ($t_{1/2}$). They have shown that varying $t_{1/2}$ of

Address for correspondence: Dr A. B. L. Tort, Departamento de Bioquímica, ICBS, UFRGS, Avenida Ramiro Barcelos, 2600-Anexo, CEP 90035-003, Porto Alegre, RS, Brasil.
Tel.: (55-51) 33165557/33165558 Fax: (55-51) 33165540/33165535
E-mail: adrianotort@hotmail.com

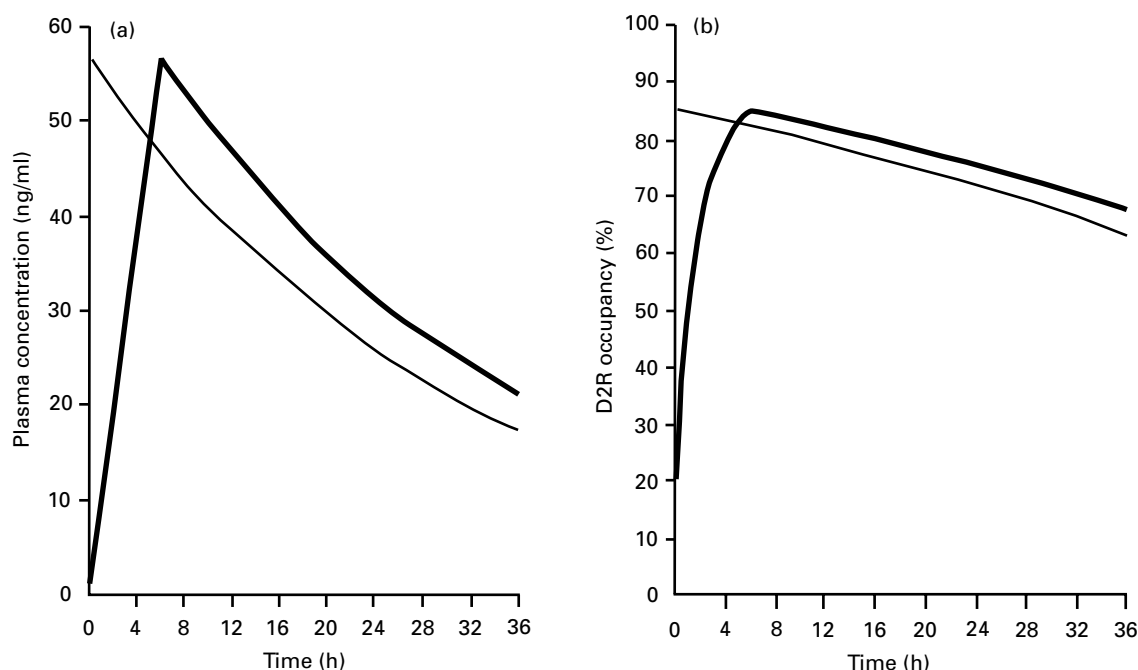


Figure 1. Plasma concentrations of the drug (a) and levels of D2R occupancy (b) as a function of time obtained by two distinct simulations with olanzapine. Simulation B (—) differs from simulation A (—) by considering the time necessary for the plasma concentration of the drug to reach the peak. Note that D2R occupancy levels predicted without taking into account the kinetics of the absorption phase are lower after t_{peak} . For these simulations, olanzapine was considered to have a t_{peak} of 6.1 h (Baldessarini and Tarazi, 2001), an ED_{50} of 10 ng/ml, and a $t_{1/2}$ of 21 h (Takano et al., 2004).

the drug would produce a change in $T_{1/2}$ in the same direction. Of note, Kapur et al. (2000) have recently shown only transiently high D2R occupation by quetiapine, in a work questioning whether there is a need of continuous D2R blockade to achieve control of symptoms in schizophrenia. In the same way, the transient blockade observed by Kapur et al. (2000) was due to the short half-life presented by quetiapine (6 h), and not by its known low affinity to D2R (or large ED_{50}).

Thirdly, we would like to comment on the concept of the half-life of D2R occupancy ($T_{1/2}$). When we are dealing with plasma drug concentrations, an equation like (1) does present a concept of half-life, since the same time necessary to reduce 50% of plasma concentration is independent on the drug level (e.g. since $t_{1/2}$ of risperidone is 19 h, it will take 19 h to the drug drop from 6 ng/ml to 3 ng/ml and a further 19 h to drop from 3 ng/ml to 1.5 ng/ml and so on). However, the equation describing D2R occupation [equation (3)] does not follow this pattern, since the time necessary to reach half of the levels is dependent on the drug level. Therefore, we question this concept, which should be carefully analysed, especially when data from different works are compared. Moreover, given

the dependence on the initial drug level, we propose that $T_{1/2}$ should be defined for a fixed occupancy interval, e.g. we should consider in the literature $T_{1/2}$ for receptor occupancy as the time necessary for a decrease of D2R occupancy from 80% to 40%.

We hope these comments will aid future receptor imaging studies to help provide important results that can improve clinical practice.

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Statement of Interest

None.

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Adriano B. L. Tort¹, Diogo O. Souza¹, Diogo R. Lara²

¹ *Departamento de Bioquímica, ICBS, UFRGS, Porto Alegre, Brasil*

² *Faculdade de Biociências, PUCRS, Porto Alegre, Brasil*