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Letter to the Editors

Half the dose of antipsychotic in case of extrapyramidal symptoms

Keywords: Schizophrenia; Antipsychotic; Dose; D_2; EPS; Occupancy

Dear Editors,

In the last decade, the use of in vivo radioligand neuroimaging in psychiatry has provided important information for the understanding of therapeutic action and extrapyramidal symptoms during antipsychotic therapy (Farde et al., 1992; Nordstrom et al., 1993). In fact, the existence of a therapeutic window for D2R occupancy is currently accepted, since a level above 65% of blockade is related in most cases to antipsychotic efficacy, while extrapyramidal symptoms (EPS) typically appear when more than 78% of D2R are blocked (Farde et al., 1992; Nordstrom et al., 1993; Kapur et al., 2000, Kapur and Mamo, 2003).

The kinetic of the antipsychotic–D2R interaction obeys the law of mass action, which can be represented as

$$[A] + [D_2] \overset{k_{on}}{\rightarrow} [AD_2] \overset{k_{off}}{\rightarrow} [A] + [D_2]$$

where $[A]$ stands for the concentration of antipsychotics, $[D_2]$ for free D2R, $[AD_2]$ for blocked D2R by antipsychotics, and k_{on} and k_{off} denote the association and dissociation rate constants, respectively. The affinity of the antipsychotic for the D2R is inversely proportional to its equilibrium dissociation constant (K_d), defined by k_{off}/k_{on}. A straightforward derivation from the law of mass action predicts that the fraction of D2R occupancy (D_{2Occup}) is given by $D_{2Occup}=100\times[A]/([A]+K_d)$. Moreover, this last result has a peripheral equivalent, which is given by

$$D_{2Occup} = \frac{100 \times C}{C + ED_{50}} \tag{1}$$

where C is the plasmatic concentration of the drug, whereas ED_{50}, the concentration on plasma able to block 50% of D2R, is equivalent to K_d. If we isolate C in Eq. (1), and using the index D_{2Occup} to denote the dependence on D_{2Occup}, we get

$$C_{D_{2Occup}} = \frac{D_{2Occup}}{100 - D_{2Occup}} ED_{50}. \tag{2}$$

Using Eq. (2), we calculate the "therapeutic" index, which is defined as the fraction between the upper and lower bound of effective dosage without EPS, getting

$$\frac{C_{78}}{C_{65}} = \frac{ED_{50}78}{100-78} \cdot \frac{100-65}{ED_{50}65} = 1,9. \tag{3}$$

This last result has two relevant clinical consequences: i) once 65% of D2R blockade is achieved by an antipsychotic, the dosage cannot be doubled in order to keep the D2R blockade inside the therapeutic window of D2R occupation without EPS. ii) on the other hand, we can also conclude that, once EPS is present (meaning $D_{2Occup}>78\%$), the model predicts that antipsychotic dosage could be halved and the level of D2R blockade should remain above 65%, which is compatible with therapeutic effect in most of patients. Such drastic reduction is intuitively too aggressive, because the hyperbolic relationship between dose and occupancy is not taken into account. In Fig. 1 we have plotted a function as Eq. (1), where we can observe the validity of this claim. Note that in cases of parkinsonism with very

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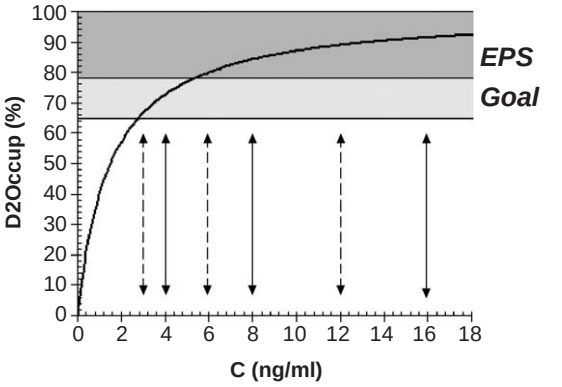

Fig. 1. Plot of the percentage of D2R occupation (D_{2Occup}) obtained using Eq. (1) for different plasmatic concentrations of a fictitious antipsychotic (C). We choose $ED_{50}=1.5$ ng/ml. Note that the plot is qualitatively the same for drugs of any D2R affinity (ED_{50}). D2R occupation above 78% induces EPS and the range of occupation between 65% and 78% is the goal for antipsychotic efficacy without EPS. Any drug concentration responsible for a D2R occupation greater than 78% can be halved and the level of D2R blockade remains above 65%. The arrows illustrate two fictitious examples. The continuous arrows denote a case of a patient which had its drug concentration halved firstly from 16 to 8 ng/ml, which required another halving to 4 ng/ml in order to reach D_{2Occup} value inside the therapeutic window, whereas the dashed arrows represent a similar case for values of 12, 6 and 3 ng/ml.

high D2R occupancy, it is also possible that, even after halving the dosage, the blockade still remains above 78%, which would require further halving of the dosage and so on.

Since in clinical practice a minority of patients should require blockade above 70%, we suggest the following algorithm for changing antipsychotic dosage when EPS appear: halve the dosage and introduce anticholinergic treatment for 3–4 days (the longer the plasmatic half-life, the more days), observing both psychotic and motor symptoms. Then titrate down the anticholinergic treatment and if EPS reappear, halve the antipsychotic dose again, reintroduce anticholinergic treatment, wait a few of days and so on. In case EPS does not recur and clinical effectiveness fails to take place or diminishes, we recommend a slow increase of the medication, since the level of D2R blockade should be inside the putative therapeutic window ($D_{2Occup} \geq 65\%$).

We hope this suggestion can be tested in clinical practice and using in vivo radioligand studies, which can be especially helpful for patients on antipsychotics with high D2R affinity, such as typical antipsychotics and risperidone.

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