Mr. A and Mr. B corresponded to rebound psychosis, and further Mr. B's episode indicates the development of tolerance to neuroleptics.

We consider that oral high dose administration may induce a high elimination dose from the body over a certain period of time, increasing the risk of fluctuation of the psychotic symptoms (Iyo et al., 2012), whereas LAI form may yield a stable plasma level of the drugs and an optimal percentage of D2R occupancy over time of period, which prevent the fluctuation and then improve treatment-resistant DSP (Kane et al., 2003; Eerdenkens et al., 2004). The use of clozapine may improve their symptoms (Kane et al., 1988), but clozapine has risks of profound side effects such as agranulocytosis and cardiomyopathy and needs intensive monitoring of these side effects. Therefore, the present cases suggest alternative approaches for treatment-resistant DSP to clozapine. However, the frequency of DSP was estimated to be approx. 50% among patients with schizophrenia, indicating high heterogeneity (Chouinard and Chouinard, 2008), and patients with typical DSP such as our two cases might be a part of treatment-resistant schizophrenia in actual clinical practice. Therefore, further studies are needed to confirm our strategy for the treatment of DSP.

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Contributors

N. Kanahara was an attending physician and provided guidance about this report. H. Kimura was an attending physician and wrote this report. H. Watanabe and M. Iyo supervised throughout all process from treatment for patients to writing this report. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare no conflict of interest.

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Title: Optimal Extent of Dopamine D2 Receptor Occupancy by Antipsychotics for Treatment of Dopamine Supersensitivity Psychosis and Late-onset Psychosis

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Abstract

Several studies have proposed an optimal dopamine D2 receptor occupancy by antipsychotics (OOC) to establish optimal pharmacological treatment of schizophrenia. However, there are limitations to the use of the OOC, especially in application to patients with treatment-resistant schizophrenia, including dopamine supersensitivity psychosis (DSP) or late-onset psychosis (LOP). It has been suggested that D2 receptor density is up-regulated by chronic treatment of antipsychotics in DSP, whereas it may be low in LOP due to age-related reduction. In estimation of the proposed OOC, these alterations have not been taken into account, which may be one of the factors contributing to the limited application of this index. We here hypothesized that there is an optimal range in the number of D2 receptors available for dopamine binding to elicit adequate neurotransmission in the treatment of patients with schizophrenia. We then estimated the OOC under the assumption that the range is constant while D2 density is variable. The results showed that the OOC and plasma level of antipsychotics increase with an increase in the D2 density, but decrease with a decrease in the D2 density. That is, if the range of OOC is 65-78% in a standard D2 density, it becomes 82-89% under two-fold up-regulated density and 42-63% under a 40% reduced density. The results also indicated that the reduction of the plasma antipsychotic level is greater during a given time period in patients with higher D2 density, since they need a higher antipsychotic dose to achieve the raised OOC, which would account for the clinical features of DSP, e.g., acute exacerbation after a discontinuation of antipsychotics. On the

other hand, in patients with lower D2 density, only a lower antipsychotic dose will achieve the OOC, and a small increase in the dose will result in a greater increase in occupancy and induce extrapyramidal side effects (EPS) more easily. Furthermore, the reduction of the plasma antipsychotic level during the time period is smaller, which prolongs EPS after discontinuation of antipsychotics in LOP. We also attempted to develop a strategy for the prevention and treatment of patients with DSP or LOP by focusing on D2 density.

I. Introduction

Schizophrenia is a disabling mental illness with a lifetime prevalence of 0.4-1.0% worldwide (1), and the course of illness is usually chronic with relapses despite treatment (2). For decades, the standard treatment protocol has included the administration of D2 dopamine receptor blockers as effective antipsychotics, especially for the amelioration of psychotic symptoms (3,4). Evidence-based or expert consensus guidelines for the dosing of various antipsychotics have been published to improve the quality of care of patients with schizophrenia (5). However, it has been reported that a substantial percentage of patients receive daily antipsychotic doses above the recommended range (6), and that such overly high doses of antipsychotics, while not always ideal, are often clinically justifiable (7).

In order to establish an optimal treatment strategy to achieve the highest rate of response with the lowest incidence of side effects of antipsychotics, an optimal plasma level of antipsychotics has been explored (8). At the same time, the D2 receptor occupancy of antipsychotics estimated by using positron emission tomography (PET) and single photon emission tomography (SPECT) has provided more direct information on the relationships between the effects of antipsychotics and their sites of action, i.e., D2 receptors, in the living human brain (9). Such imaging indicates that there is an optimal D2 receptor occupancy of antipsychotics (OOC) (9). However, there are limitations to the use of either the optimal plasma level or OOC (10), especially in application to patients with treatment-resistant

schizophrenia (11,12).

II. D2 receptor density and treatment-resistant schizophrenia

It has been estimated that more than half of treatment-resistant schizophrenia cases may be related to dopamine supersensitivity psychosis (DSP) (13), and the proposed features of DSP are shown in Table 1. DSP, which was initially a problem in the 1970s, has recently been on the rise again, possibly as a result of patients switching their antipsychotic therapy from first-generation antipsychotics (FGA) to second-generation antipsychotics (SGA) (13,14). One of the mechanisms underlying DSP is suggested to be up-regulation of dopamine D2 receptor density, since the density of these receptors has been shown to increase by at least two-fold following chronic treatment with antipsychotics (15), a finding that agrees with postmortem studies (16). In experimental animals as well, chronic or subchronic treatment of D2 receptor antagonists increases D2 receptor density (17,18,19), and induces behavioral supersensitivity (19). Taken together, these results suggest that one of the mechanisms underlying DSP is up-regulation of D2 receptor density following long-term treatment of antipsychotics, although there has also been a study suggesting that no up-regulation occurs (20). The treatment difficulty in patients with DSP may therefore be due to increased density of D2 receptors.

On the other hand, approximately 10% of all cases of first-episode schizophrenia occur in individuals over the age of 45—that is, they are cases of late-onset psychosis (LOP). These elderly patients sometimes show

therapeutic effects at lower doses of antipsychotic medication than younger patients, but there is a general tendency for greater susceptibility to extrapyramidal side effects (EPS) and tardive dyskinesia (TD) in these patients (21). Because the D2 receptor density in the human brain decreases with age (22,23,24) at a rate of about 10% per decade (24), this age-related reduction may be associated with the difficulty in treatment of these individuals, suggesting an etiology opposite that in treatment-resistant DSP.

Taken together, these findings suggest that alteration in D2 density may play important roles in the treatment resistance of patients with DSP or LOP, in the inappropriateness of the reported OOC for these patients, and in the discrepancy in antipsychotic doses between the evidence-based recommendations in guidelines and real clinical settings. Therefore, we here consider the OOC and plasma level of antipsychotics from the viewpoints of ligand-receptor interaction and estimation of the D2 receptor occupancy, although there may be other factors influencing treatment difficulty in these patients, such as differences in the pharmacokinetics of antipsychotics, including gene-based or age-related differences.

III. Optimal D2 receptor occupancy and plasma level of antipsychotics, and D2 receptor density

1. The number of D2 receptor-dopamine complexes and the response to dopamine

It is known that dopamine exhibits its activity by binding to D2 receptors in a dose-dependent manner (25,26). On the other hand, the level

of dopamine may determine the number of D2 receptor-dopamine complexes under a constant level of D2 density, whereas the density of D2 receptors may determine the number of such complexes under a constant level of dopamine (26). When antipsychotics occupy only a percentage of D2 receptors, the remainder of the D2 receptors may be available for dopamine binding and formulation of the D2 receptor-dopamine complexes; we refer to these as available D2 receptors (Fig. 1). PET studies suggest that there is an OOC for the treatment of patients with schizophrenia (9,27), which suggests that there may be an optimal range in the number of available D2 receptors to yield adequate dopamine neurotransmission via D2 receptors in schizophrenia.

In experimental animals, it is known that chronic treatment of dopamine agonists compensatively decreases D2 density (28), whereas chronic treatment of D2 receptor antagonists compensatively increases D2 density (17,18,19). Our recent study indicated that a subchronic treatment with aripiprazole, a partial D2 receptor agonist, did not alter the D2 density in drug naïve rats, possibly because this treatment maintained adequate neurotransmission, but reduced the D2 density that had been increased by a preceding subchronic treatment of haloperidol, a D2 full antagonist. These results suggest that an over-blockade of dopamine transmission via D2 receptors compensatively increases D2 density, whereas an over-stimulation decreases the density. On the other hand, adequate dopamine transmission maintains the density.

Considering these findings together, we hypothesize that

compensatory changes in D2 density may occur to maintain a certain optimal range in the number of available D2 receptors that are necessary for adequate D2 receptor neurotransmission. We also propose that the optimal range of the number of available D2 receptors may be constant in the antipsychotic treatment of patients with schizophrenia, even when the D2 receptor density is varied.

2. Optimal occupancy and plasma level of antipsychotics, and the number of D2 receptors

The ideal D2 receptor occupancy of antipsychotics (OC) estimated by using PET is expressed as follows (27,29,30):

$$OC = [P / (P + ED50)] \quad \text{... Eq.1}$$

where P is the plasma level of the antipsychotic drug and ED50 is the estimated plasma level of the antipsychotic drug associated with 50% receptor occupancy. Then, the OOC is expressed as follows:

$$OOC = [OP/(OP + ED50)], \quad \text{... Eq.2.}$$

where OP is the corresponding optimal plasma level.

Equations 1 and 2 indicate that the occupancy is determined by the plasma level and is independent of D2 receptor density. Therefore, the number of available D2 receptors may differ with the D2 receptor density even under the same occupancy. That is, as shown in Fig.1, even when the number of available D2 receptors is within the optimal range of available D2 receptors under the standard condition of D2 density, it may be lower under the down-regulated condition and higher under the up-regulated condition

even under the same occupancy.

We calculated the OOC under the optimal number of available D2 receptors as a constant and the D2 receptor density as a variable. Here, the relationship between the ratio of the optimal number of available D2 receptors to the standard D2 density (ROA(s)) for an individual patient, and the OOC for standard D2 density (OOC(s)) is expressed as follows:

$$OOC(s) = 1 - ROA(s). \quad \ldots \text{Eq.3}$$

Then, ROA(s) becomes:

$$ROA(s) = 1 - OOC(s). \quad \ldots \text{Eq.4}$$

The ROA(s) may be known if OOC(s) is estimated by using PET or SPECT (9). Next, the optimal number of available D2 receptors, OA, is as follows:

$$OA = ROA(s) \times Rt(s) \quad \ldots \text{Eq.5}$$

where Rt(s) is the standard D2 receptor density. An OOC is then expressed as follows:

$$OOC = 1 - OA/Rt \quad \ldots \text{Eq.6}$$

where Rt is the D2 receptor density. From Eq.5 and Eq.6, OOC becomes:

$$OOC = 1 - ROA(s) \times Rt(s)/Rt \quad \ldots \text{Eq.7}$$

Equation 7 indicates that the OOC is a dependent variable of Rt/Rt(s), where Rt/Rt(s) is the ratio of the D2 receptor density to the standard D2 receptor density. It is indicated that an increase in OOC occurs with an increase in D2 density, i.e., up-regulation, whereas a decrease in OOC occurs with a decrease in the density. For example, if the range of the OOC is 65-78% under standard D2 density (9), it increases to 82-89% under two-fold up-regulated density, whereas it decreases to 42-63% under a 40% reduction

in the D2 density (Fig.2A).

Accordingly, Eq.1 becomes:

$$OP = ED50 / (1/ OOC - 1). \quad \ldots \text{Eq.8.}$$

Thereby, Eq.6 and Eq.8 yield:

$$OP = ED50 \times (Rt/OA - 1). \quad \ldots \text{Eq.9}$$

Therefore, higher doses of antipsychotic drug could be used for patients with higher D2 density. A dose increase in these patients would result in a higher plasma level (31), and thereby achieve the raised OOC. Here, when the plasma elimination half-life of the drug is the same, the plasma drug level decreases to a greater degree in cases of higher plasma level than in cases of lower plasma level during the same time period, e.g., one plasma elimination half-life period (Fig.2B). Therefore, the drug level dissociated from the receptors would be higher and the increase in the number of available D2 receptors would be greater in cases of higher plasma level during the same time period.

Equations 8 and 9 also indicate that the administration of lower doses of antipsychotic drug may achieve the OOC and that the corresponding optimal plasma level is lower in cases of lower D2 density (Fig.2A). These potential associations in turn suggest that the level of drug elimination from the plasma would be smaller in cases of lower density than in cases of higher density during the same time period, when the elimination half-life is the same (Fig.2C). Therefore, it would take a longer period of time to increase the number of available D2 receptors in cases of lower D2 density than in cases of higher D2 density.

When the width of OP and the width of the optimal range in number of available D2 receptors are OPw and OAw, respectively, OPw can be defined by the following equation with reference to Eq.9:

$$OPw = ED50 \times (Rt/OAw). \quad \ldots\ldots \text{Eq.10}$$

Equation 10 indicates that the width of the optimal plasma level is proportional to the D2 density, since OAw is constant. Therefore, the dose range is smaller in cases of lower density; that is, the width becomes half when the density becomes half.

In this simulation, we did not take account of such factors as the dissociation rate constant of the drugs from D2 receptors, the blood-brain permeability of the drugs, or the regional cerebral blood flow. Furthermore, the OOC may be associated with the D2 densities of the nucleus accumbens and striatum. If the regional ratio of the D2 density in the striatum to that in the nucleus accumbens is very low compared with that in normal individuals, no dose of antipsychotics will be able to control psychotic symptoms without induction of EPS.

IV. Application of the present findings to clinical settings

1. Late-onset psychosis (LOP)

One of the reported clinical features of antipsychotic treatment of LOP is that even a very low dose of antipsychotics easily induces EPS, which disappears for a prolonged time period after discontinuation of antipsychotics (21,32,33). Here, LOP is considered to be associated with low D2 density. The present study suggests that an increase of antipsychotic dose

readily increases the occupancy and decreases the number of available D2 receptors, thereby increasing the risk of EPS in patients with low D2 density. Furthermore, the reduction of the plasma level is slight during a given time period and the number of available D2 receptors increases slowly in these patients, leading to the prolongation of disappearance of EPS. These features of low D2 density are consistent with those of LOP. Therefore, antipsychotics which can be carefully used in very low doses should be chosen in patients with LOP. Furthermore, antipsychotics with a short plasma elimination half-life and high dissociation constants may be selected to avoid prolongation of EPS after discontinuation. Antipsychotics whose actions correspond to the "fast-off-D2" theory—i.e., antipsychotics that occupy D2 receptors transiently and dissociate rapidly (34)—may also be recommended.

2. Dopamine Supersensitivity Psychosis (DSP)

2-1. Proposed clinical features and the present findings

The present findings well account for the proposed features of DSP (Table 1) (35,36). If patients with DSP have up-regulated D2 density due to over-blockade of dopamine transmission, they may have a history of EPS and/or presence of TD, suggesting that TD can be used as a predictive factor. They generally receive high doses of antipsychotics to achieve a raised OOC and control their psychotic symptoms, and thus are at risk for development of tolerance to antipsychotics. Furthermore, as they receive higher doses of antipsychotics, a reduction or discontinuation of antipsychotics may induce a larger increase in the number of available D2 receptors for dopamine binding

during the same time period in patients with DSP than in those with standard or low D2 density, when the elimination half-life of the drug is the same, i.e., acute relapse or exacerbation of psychosis occurs after dose reduction or discontinuation of antipsychotics. On the other hand, stress increases dopamine levels in the brain (37) and the same level of dopamine may bind to more D2 receptors in competition with preexisting antipsychotics in cases in which D2 density is up-regulated (Fig.1), leading to vulnerability to minor stress. These facts may increase the risk of appearance of relapse or exacerbation of psychosis (38, 39).

2-2. Prevention and treatment of DSP

One of the predictors for development of TD is the appearance of EPS in the early phase of antipsychotic treatment (39,40). It has been reported that the incidence of EPS and TD is lower by administration of SGAs than FGAs (41), although the incidence rate of new-onset TD varies among patients with SGAs (42). One of the common features of SGAs is high affinity for serotonin 2A (5-HT2A) receptors as antagonists in the brain, which may reduce inducibility of EPS (43). Therefore, antipsychotics with high affinity for 5-HT2A may have low inducibility of EPS compared with D2 antagonists without high affinity for 5-HT2A. On the other hand, OOC is generally determined by appearance of the EPS for the upper limit and treatment response to psychotic symptoms for the lower limit (9,27). Ideally, one of the characteristic side effects of an excessive blockade of D2 receptors in the nucleus accumbens is reported to be dysphoria (44,45).

Antipsychotics-induced dysphoria may be one of clinical indicators of the upper limit of the OOC for prevention of developing DSP. Furthermore, SGAs are reported to be less likely to elicit dysphoric responses (46). Taken together, these facts indicate that SGAs may be better for prevention of development of DSP than FGAs.

The present study indicates that the length of the plasma elimination half-life of an antipsychotic drug affects the risks of appearance and exacerbation of psychotic symptoms in DSP. Antipsychotics with a long plasma elimination half-lives, or dosage forms with extended-release, i.e., those using osmotic drug release technology (OROS) (47), and long-acting injectable antipsychotics (48) may be recommended to treat patients with DSP, if used at the appropriate dosage. Furthermore, in order to prevent stress-induced dopamine from replacing antipsychotics for binding to D2 receptors, antipsychotics with relatively high affinity for D2 receptors may be useful to prevent the exacerbation of psychosis in patients with DSP. In fact, we found that long-acting injection of risperidone and/or extended-release paliperidone showed dramatic efficacy in patients with treatment-resistant DSP (in preparation).

Our previous preclinical study (19) suggested that chronic treatment with dopamine partial agonists might reverse dopamine supersensitivity and then ameliorate the conditions that readily induce DSP. However, under a dopamine supersensitive state, dopamine agonistic effects may easily induce DSP during the treatment, since aripiprazole may bind more D2 receptors and elicit larger agonistic effects. In fact, it has been reported that

aripiprazole carries risks for the induction of transient DSP (49). From this point of view, aripiprazole may be added to the existing antipsychotics and titrated gradually from a very small dose to avoid exacerbation of psychosis in patients with DSP.

Conclusion

We estimated an OOC under the assumption that the optimal range of the number of D2 receptors available for dopamine binding is constant while D2 density changes. We found that either the optimal plasma level or the OOC changed in correspondence with changes in the D2 density. These results suggest that a higher antipsychotic dose is needed in cases of higher D2 density and that the reduction of the plasma level will be larger within the same time period, which may have greater effects on the exacerbation of psychosis, in cases of higher D2 density. On the other hand, a lower dose of an antipsychotic drug could be used for optimal treatment in cases of lower D2 density, and a reduction of the plasma level of antipsychotics is smaller during a certain time period, which may prolong disappearance of EPS after discontinuation of the drug, in cases of lower D2 density. The results well account for the proposed clinical features of DSP or LOP. It is suggested that SGAs with a long plasma elimination half-life, or in a long-acting injectable form may be recommended if used within the proper dosage in treatment of DSP. On the other hand, low doses of antipsychotics with low affinity for D2 receptors and a short plasma elimination half-life are recommended for the treatment of LOP. Preclinical studies suggest that dopamine partial agonists

may decrease up-regulated D2 density and thereby ameliorate dopamine supersensitivity.

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