CNPT The Japanese Society of Clinical Neuropsychopharmacology
Clinical Neuropsychopharmacology and Therapeutics
scnp

Are combination therapies with aripiprazole and other antipsychotics pharmacologically rational?

Takahiko Nagamine, M.D., Ph.D.

Division of Psychiatric Internal Medicine, Seiwakai-Kitsunan Hospital, Yamaguchi, Japan

Received July 7, 2011 / Accepted July 19, 2011 / Published August 12, 2011

Aripiprazole is a partial agonist that exerts intrinsic activity on dopamine D2 receptors [1]. In the mesolimbic system, where the density of dopamine D2 receptors is low, aripiprazole acts like an antagonist, and exerts antipsychotic effects [1]. In this system, therefore, it acts as a "net antagonist" [2]. In the tuberoinfundibular system, where dopamine D2 receptor density is high, aripiprazole acts as an agonist, suppressing the secretion of prolactin [3], and therefore acts as a "net agonist" [2]. Aripiprazole is often used in the clinical setting in combination with other antipsychotics [4]; is this use pharmacologically rational?

If an agonist acts on the receptor, it demonstrates physiological activity. If an inverse agonist acts on the receptor, it exhibits activity inverse to the agonistic activity. Antagonists do not have their own physiological activities, but if agonists or inverse agonists are present, antagonists competitively inhibit their actions. Antagonists exert no physiological activities and do not affect constitutive activities even when they act on receptors. Antagonists are "silent" or "neutral" to the receptor activities.

There is an "agonist spectrum" ranging from inverse agonist to full agonist in the magnitude of physiological activity [2]. Within this spectrum, the physiological activity of agonists and inverse agonists gradually decreases as one approaches the middle of the spectrum, which corresponds to antagonists exerting no physiological activity. Generally, in the clinical setting, agonists and antagonists are considered antipodes on the agonist spectrum. However, what is antipodal to an agonist on the agonist spectrum is really an inverse agonist, not an antagonist. There is a common misunderstanding that the action of antagonists is equal to that of inverse agonists; this is because inverse agonists has not been identified accurately.

If aripiprazole is used in combination with other antipsychotics, dopamine receptors are exposed to competition among three substances, i.e., an intrinsic dopamine, a partial agonist (aripiprazole) and an antagonist (ordinary antipsychotic). Although antagonists do not exert their own physiological activity, they can competitively inhibit the action of all substances within the agonist spectrum. Theoretically, an antagonist (ordinary antipsychotic) competitively inhibits not only an intrinsic dopamine but also the action of aripiprazole, resulting in attenuation of the pharmacological action of aripiprazole. In the clinical setting, if aripiprazole is present, other antipsychotic drugs have difficulty binding to the dopamine receptor, and do not work as antagonists, because aripiprazole has high affinity for dopamine receptors [5] and dissociates from them slowly [6]. The use of aripiprazole in combination with other antipsychotics is therefore pharmacologically irrational as far as mesolimbic dopamine receptors are concerned.

However, aripiprazole as an add-on therapy may be beneficial for some patients with antipsychotic-induced hyperprolactinemia to attenuate this adverse event without interfering with the antipsychotic efficacy of the pre-existing medication [7]. The skillful combination of aripiprazole with other antipsychotics may provide a broader therapeutic spectrum and better tolerance because aripiprazole

Corresponding Author: Takahiko Nagamine, M.D., Ph.D., Division of Psychiatric Internal Medicine, Seiwakai-Kitsunan Hospital, 3381 Suzenji, Yamaguchi-shi, Yamaguchi-ken, 747-1221, Japan
e-mail: anagamine@ybb.ne.jp

has serotonin 1A agonistic properties as well as partial dopamine D2 agonistic effects [8]. Such strategic combinations of aripiprazole and other antipsychotics may still prove to be beneficial in certain situations. However, these benefits are not associated with aripiprazole's dopamine system stabilizing effect.

Following the recent introduction of aripiprazole, a partial dopamine D2 agonist, as a new dopamine blocker in the clinical setting, the number of prescriptions written for combinations of antagonists and partial agonists has been increasing. Aripiprazole should be used as monotherapy to obtain its unique pharmacological characteristics. We have to reconsider the meaning of the use of aripiprazole in combination with other antipsychotics from the viewpoint of dopamine receptor activities.

DISCLOSURE

The author declares no conflicts of interest.

REFERENCES

[1] Gründer G, Carlsson A, Wong DF.: Mechanism of new antipsychotic medications: occupancy is not just antagonism. Arch Gen Psychiatry. 2003;60:974-977.

[2] Stahl SM: Stahl's Essential Psychopharmacology. Neuroscientific Basis and Practical Applications. Third Edition. Cambridge University Press 2008

[3] Shim JC, Shin JG, Kelly DL, Jung DU, Seo YS, Liu KH, Shon JH, Conley RR.: Adjunctive treatment with a dopamine partial agonist, aripiprazole, for antipsychotic-induced hyperprolactinemia: a placebo-controlled trial. Am J Psychiatry. 2007;164:1404-1410.

[4] Cobo Gómez JV, Fuste G, Coronas R, Benito N, Barbero JD, Domenech C, García-Parés G.: Combination of aripiprazole and other psychopharmacological treatments in resistant and multi-resistant patients. Curr Drug Saf. 2008;3:210-215.

[5] DeLeon A, Patel NC, Crismon ML.: Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. Clin Ther. 2004;26:649-666.

[6] Carboni L, Negri M, Michielin F, Bertani S, Fratte SD, Oliosi B, Cavanni P.: Slow dissociation of partial agonists from the D2 receptor is linked to reduced prolactin release. Int J Neuropsychopharmacol. 2011; Jun 9:1-12. [Epub ahead of print]

[7] Mihara K, Nagai G, Nakamura A, Fukuji Y, Suzuki T and Kondo T: Improvement in antipsychotic-induced hyperprolactinemia with the addition of aripiprazole in schizophrenic patients. Clinical Neuropsychopharmacology and Therapeutics. 2010;1:1-5.

[8] Newman-Tancredi A, Kleven MS.: Comparative pharmacology of antipsychotics possessing combined dopamine D(2) and serotonin 5-HT (1A) receptor properties. Psychopharmacology (Berl). 2011 Mar 11. [Epub ahead of print]