Domperidone as an unintended antipsychotic

DOMPERIDONE, A POTENT BLOCKER OF THE DOPAMINE D2 receptor, used at 30 to 80 mg/d to increase gastric motility and decrease nausea, is also prescribed to promote lactation at up to 160 mg/d, as pointed out in a recent case report of withdrawal symptoms.¹ That these withdrawal symptoms could have a central nervous system etiology was not considered because it has been widely held that domperidone does not cross the blood-brain barrier.^{2,3}

However, the blood-brain barrier has limits. Rejection of domperidone at the blood-brain barrier is a function of the endothelial P-glycoprotein system^{4,5} and perhaps other parts of the ATP-binding cassette (ABC) efflux system.⁶⁻¹⁰ Domperidone at the blood-brain barrier has been investigated to some extent,^{2,4,5} and other studies have reported the ratio of the free concentration of various molecules in the blood plasma water to that in the brain tissue fluid.¹⁰ The maximum ratio for the P-glycoprotein system by itself is about 30^{4,8-10} and for the entire ABC system about 100.^{6,9,10} For domperidone, this is likely to be between 30 and 100.

Steady-state free concentration of domperidone in the plasma water of an average adult taking 160 mg/d would be 20 to 25 nM, with the lower value being a linear extrapolation from the total concentration of 21 ng/mL at 30 mg/d,^{3,11} which is 1.7 ng/mL of free concentration.³ The upper estimate takes into account nonlinearity at this dose.^{3,12} Free concentration in the brain tissue fluid is then 0.2 to 0.8 nM. At 80 mg/d, the free plasma estimate would be 10 nM, with the brain having 0.1 to 0.3 nM; at 30 mg/d, it would be about 3.9 nM of free plasma concentration, with 0.04 to 0.13 nM of free concentration in the brain.

Most measurements of the dissociation constant for domperidone at the D2 receptor are from 0.1 to 0.4 nM.¹³⁻¹⁸ Thus, there could be D2 blockage in the brain of 33% to 89% for 160 mg/d, 20% to 77% for 80 mg/d and 9% to 57% for 30 mg/d. A higher estimate for the minimum blood-brain ratio of 70 lowers the upper estimates of blocking to 78%, 59% and 36%, respectively. The therapeutic range of D2 blocking by the antipsychotic drugs is 50% to 75%.^{19,20} Domperidone has a relatively lower effect on D3 receptors than intended antipsychotics,²¹ but the importance of this is unknown.²² The prevailing theory is that antipsychotics work by blocking

D2 receptors.^{20,23} We see that domperidone between 30 and 160 mg/d could function as an antipsychotic.

It seems plausible that domperidone could produce the same adverse effects as intended antipsychotics, which have many side effects²⁴ and poorly understood withdrawal effects.^{25,26}

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References

1. Papastergiou J, Abdallah M, Tran A, Folkins C. Domperidone withdrawal in a breastfeeding woman. *Can Pharm J (Ott)* 2013;146:210-2.
2. Laduron PM, Leysen JE. Domperidone, a specific *in vitro* dopamine antagonist, devoid of *in vivo* central dopaminergic activity. *Biochem Pharmacol* 1979;28:2161-5.
3. Barone JA. Domperidone: a peripherally acting dopamine₂-receptor antagonist. *Ann Pharmacother* 1999;33:429-40.
4. Schinkel AH, Wagenaar E, Mol CAAM, van Deemter L. P-glycoprotein in the blood-brain barrier of mice influences the brain penetration and pharmacological activity of many drugs. *J Clin Invest* 1996;97:2517-24.
5. Tsujikawa K, Dan Y, Nagawa K, et al. Potentiation of domperidone-induced catalepsy by a P-glycoprotein inhibitor, cyclosporin A. *Biopharm Drug Dispos* 2003;24:105-14.
6. Ek CJ, Dziegielewska KM, Habgood MD, Saunders NR. Barriers in the developing brain and neurotoxicology. *Neurotoxicology* 2012;33:586-604.
7. Warren MS, Zerangue H, Woodford K, et al. Comparative gene expression profiles of ABC transporters in brain microvessel endothelial cells in five species including human. *Pharmacol Res* 2009;59:404-13.
8. Tamai I, Tsuji A. Transporter-mediated permeation of drugs across the blood-brain barrier. *J Pharm Sci* 2000;89:1371-88.
9. Seelig A. The role of size and charge for blood-brain barrier permeation of drugs and fatty acids. *J Mol Neurosci* 2007;33:32-41.
10. Eyal S, Hsiao P, Unadkat D. Drug interactions at the blood-brain barrier: fact or fantasy? *Pharmacol Ther* 2009;123:80-104.
11. Knoppert DC, Page A, Warren J, et al. The effect of two different domperidone doses on maternal milk production. *J Hum Lact* 2013;29:38-44.
12. Raia JJ, Barone JA, Byerly WG, et al. Determination of steady-state dose proportionality of domperidone in healthy volunteers. *Pharmacotherapy* 1990;10:252.
13. Huff RM, Molinoff PB. Quantitative determination of dopamine receptor subtypes not linked to activation of adenylate cyclase in rat striatum. *Proc Natl Acad Sci U S A* 1982;79:7561-5.

14. Lazareno S, Nahorski SR. Selective labelling of dopamine (D₂) receptors in rat striatum by [³H]domperidone but not by [³H]spiperone. *Eur J Pharmacol* 1982;81:273-85.
15. Rosenfeld MR, Dvorkin B, Klein PN, Makman MH. Differential affinities of molindone, metoclopramide and domperidone for classes of [³H]spiroperidol binding sites in rat striatum: evidence for pharmacologically distinct classes of receptors. *Brain Res* 1982;235:205-11.
16. Rzezniczak HW, Gundlach AL, Beart PM. Labelling of high (D-2 receptor) and low affinity sites by [³H]domperidone in homogenates of the corpus striatum of the rat. *Neurosci Lett* 1982;30:63-8.
17. Seeman P, Tallerico T, Ko F. Dopamine displaces [³H]domperidone from high-affinity sites of the dopamine D₂ receptor, but not [³H]raclopride or [³H]spiperone in isotonic medium: implications for human positron emission tomography. *Synapse* 2003;49:209-15.
18. Seeman P. Dopamine D₂ high receptors on intact cells. *Synapse* 2008;62:314-8.
19. Seeman P, Van Tol HM. Dopamine receptor pharmacology. *Trends Pharmacol Sci* 1994;15:264-70.
20. Madras BK. History of the discovery of the antipsychotic dopamine D₂ receptor: a basis for the dopamine hypothesis of schizophrenia. *J Hist Neurosci* 2013;22:62-78.
21. Levant B, Grigoriadis DE, De Souza EB. Relative affinities of dopaminergic drugs at dopamine D₂ and D₃ receptors. *Eur J Pharmacol* 1995;278:243-7.
22. Nakajima S, Gerretsen P, Takeuchi H, et al. The potential role of dopamine D₃ receptor neurotransmission in cognition. *Eur Neuropsychopharmacol* 2013;23:799-813.
23. Seeman P. Schizophrenia and dopamine receptors. *Eur Neuropsychopharmacol* 2013;23:999-1009.
24. Gardner D, Baldessarini RJ, Waraich P. Modern antipsychotic drugs: a critical overview. *CMAJ* 2005;172:1703-11.
25. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatr Scand* 2006;114:3-13.
26. Goudie AJ, Cole JC. Switching antipsychotics. Antipsychotic tolerance, withdrawal and relapse: unresolved issues and research implications. *J Psychopharmacol* 2008;22:815-7.