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Rationale for the Evaluation of Fluoxetine in the Treatment of Enterovirus D68-Associated Acute Flaccid Myelitis

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Enterovirus D68 (EV-D68) has emerged worldwide as an important cause of respiratory disease. Between mid-August 2014 and January 15, 2015, the Centers for Disease Control and Prevention confirmed 1153 cases of EV-D68–associated respiratory illness originating from 49 states. With this outbreak, there have been at least 107 cases of children presenting with acute flaccid myelitis associated with lesions identified on magnetic resonance imaging that were largely restricted to the spinal gray matter.^{1–4} Children with this syndrome typically present with an acute febrile respiratory syndrome followed within 2 weeks by the development of acute flaccid myelitis, characterized by motor weakness, decreased tone and reflexes, and relatively preserved sensation. Weakness is of acute onset, preferentially affects upper limbs, and is often asymmetric. Cranial nerve involvement, including facial weakness, dysarthria, or dysphagia, may occur. Findings from the electrodiagnostic and magnetic resonance imaging studies are consistent with involvement of spinal cord motor neurons. Most patients have an associated cerebrospinal fluid pleocytosis. Paralysis has typically been prolonged and recovery incomplete. The exact role of EV-D68 in this syndrome has not been conclusively established, but approximately 50% of affected children have polymerase chain reaction–amplifiable EV-D68 RNA in nasopharyngeal or other upper respiratory tract secretions but not, to date, in cerebrospinal fluid.^{1,2,4}

The occurrence of EV-D68–associated cases of poliomyelitis-like illness and the prior emergence of enterovirus 71 as the cause of severe and sometimes fatal central nervous system infection have refocused attention on the urgent need to develop effective anti-enteroviral drugs. Three antiviral drugs that are in clinical trials for enteroviral infections—pleconaril, pocapavir, and vapedavir—do not show activity against EV-D68 in vitro,² increasing the urgency to identify novel drugs that could treat EV-D68. If a current Food and Drug Administration–approved drug were found to have antiviral efficacy against EV-D68, this discovery would have several advantages, including the availability of known adverse event and pharmacokinetic profiles.

Zuo and colleagues⁵ screened more than 1100 compounds in the Prestwick Chemical Library to identify potentially novel compounds with antiviral efficacy against enteroviruses. They found that fluoxetine hydrochloride and its metabolite norfluoxetine inhibited the

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replication of coxsackievirus B3 in HeLa cells with a 50% effective concentration of 2.3 μ M, a concentration more than 10-fold less than its cytotoxic concentration. Ulferts and colleagues⁶ subsequently screened the National Institutes of Health Clinical Collections 2 library of 281 compounds for their antiviral efficacy against enteroviruses. They again found that fluoxetine inhibited replication of a variety of enteroviruses, and more specifically, that it inhibited replication of EV-D68 in HeLa cells with a 50% effective concentration of 1.35 μ M, a concentration more than 20-fold lower than its cytotoxic concentration.

The antiviral mechanism of fluoxetine and norfluoxetine remains uncertain. The antiviral activity of fluoxetine has nothing to do with its action as a selective serotonin reuptake inhibitor, as other selective serotonin reuptake inhibitors do not have antiviral effects.⁶ Fluoxetine's antiviral effects appear to be caused by a direct interaction with the highly conserved enteroviral 2C protein. Fluoxetine has structural similarity to a thiazolobenzimidazole compound with anti-enteroviral activity, TBZE-029, that is known to target this protein.⁷ The antiviral effects of both fluoxetine and TBZE-029 are abrogated in enteroviruses containing mutations within amino acid region 224–229 of the 329–amino acid long 2C protein. The mechanism by which an interaction with 2C interferes with viral replication remains unknown; although this protein is essential for viral replication, its essential function is unclear. Protein 2C may play a role in the assembly of viral proteins and RNA into virion particles (encapsidation) and interact with the enteroviral 3C protease that cleaves the translated enteroviral polyprotein into smaller structural and nonstructural proteins. Neither fluoxetine nor TBZE-029 interfere with enteroviral binding, entry into target cells, or viral polyprotein processing.^{6,7} However, treatment of infected cells with these drugs reduces both the amount of viral RNA and protein accumulating. It is therefore likely that the mechanism of action of fluoxetine involves a direct interaction with the viral 2C protein that results in an inhibition of viral RNA synthesis.

Is the fluoxetine concentration achievable using standard dosing regimens likely to be in the antiviral range? One study of fluoxetine pharmacokinetics in 10 children aged 6 to 12 years and 11 adolescents aged 13 to 18 years found fluoxetine plasma concentrations of 127 ng/mL (to convert to micromoles per liter, multiply by 0.00323),⁸ which is likely below the desired target of a 50% effective concentration. However, fluoxetine and norfluoxetine concentrations in the central nervous system are up to 20-fold higher than those in serum.⁹ A study using fluorine-19 magnetic resonance spectroscopy in 22 adult psychiatric patients receiving fluoxetine, 20 to 40 mg/d, found mean (SD) brain concentrations of fluoxetine and norfluoxetine of 4.24 (2.83) μ g/mL (approximately 14 μ M), although the exact concentration was dependent on both the dose and duration of therapy.⁹ Actual brain concentrations may really be higher than those estimated by fluorine-19 magnetic resonance spectroscopy. These measurements represented steady-state concentrations in patients who had typically been receiving the drug for at least a month. Neither of 2 adult patients who had been taking fluoxetine, 20 mg/d, for 7 to 8 days had brain concentrations of the drug detectable by fluorine-19 magnetic resonance spectroscopy. A third patient who had received fluoxetine, 40 mg/d, for 14 days (the shortest duration of therapy at this dosage studied) had a brain concentration of 0.9 μ g/mL (approximately 3 μ M). In another study using fluorine-19 magnetic resonance spectroscopy in 8 children aged 6 to 15 years who had received a mean fluoxetine dose of 0.36 mg/kg, mean (SD) estimated brain concentrations were 4.54 (3.33)

μM, which were comparable with those seen in adults at the same dose range (5.04 [2.54] μM).¹⁰ These studies suggest that fluoxetine brain concentrations likely exceed the 50% effective concentration for EV-D68 even when the concentrations in plasma may not.

Currently, only oral rather than parenteral formulations of fluoxetine are available. An animal model of EV-D68 myelitis does not currently exist for preclinical testing. Understanding the potential efficacy of fluoxetine in EV-D68–associated myelitis would therefore best be ascertained in a prospective, multicenter, randomized, double-blind clinical trial of the type supported by the Collaborative Antiviral Study Group or the National Institute of Neurological Disorders and Stroke Network for Excellence in Neuroscience Clinical Trials. The adverse effect profile of fluoxetine and its pharmacokinetics are well understood in both adult and pediatric populations; studies of this drug in the treatment of depression in the setting of other viral infections, such as human immunodeficiency virus and hepatitis C, suggest that it is unlikely to adversely affect the development of immunity or other aspects of viral pathogenesis. In conclusion, fluoxetine may represent a currently available candidate antiviral drug that could be quickly tested for efficacy in human clinical trials in patients with EV-D68–associated acute flaccid myelitis.

References

1. Ayscue P, Van Heren K, Sheriff H, et al. Centers for Disease Control and Prevention (CDC). Acute flaccid paralysis with anterior myelitis—California, June 2012–June 2014. *MMWR Morb Mortal Wkly Rep*. 2014; 63(40):903–906. [PubMed: 25299608]
2. Centers for Disease Control and Prevention. Enterovirus D68 for health care professionals. 2014. <http://www.cdc.gov/non-polio-enterovirus/hcp/EV-D68-hcp.html>. Accessed December 15, 2014
3. Maloney JA, Mirsky DM, Messacar K, Dominguez SR, Schreiner T, Stence NV. MRI findings in children with acute flaccid paralysis and cranial nerve dysfunction occurring during the 2014 enterovirus D68 outbreak [published online November 20, 2014]. *AJNR Am J Neuroradiol*.
4. Pastula DM, Aliabadi N, Haynes AK, et al. Centers for Disease Control and Prevention (CDC). Acute neurologic illness of unknown etiology in children—Colorado, August–September 2014. *MMWR Morb Mortal Wkly Rep*. 2014; 63(40):901–902. [PubMed: 25299607]
5. Zuo J, Quinn KK, Kye S, Cooper P, Damoiseaux R, Krogstad P. Fluoxetine is a potent inhibitor of coxsackievirus replication. *Antimicrob Agents Chemother*. 2012; 56(9):4838–4844. [PubMed: 22751539]
6. Ulferts R, van der Linden L, Thibaut HJ, et al. Selective serotonin reuptake inhibitor fluoxetine inhibits replication of human enteroviruses B and D by targeting viral protein 2C. *Antimicrob Agents Chemother*. 2013; 57(4):1952–1956. [PubMed: 23335743]
7. De Palma AM, Heggermont W, Lanke K, et al. The thiazolobenzimidazole TBZE-029 inhibits enterovirus replication by targeting a short region immediately downstream from motif C in the nonstructural protein 2C. *J Virol*. 2008; 82(10):4720–4730. [PubMed: 18337578]
8. Wilens TE, Cohen L, Biederman J, et al. Fluoxetine pharmacokinetics in pediatric patients. *J Clin Psychopharmacol*. 2002; 22(6):568–575. [PubMed: 12454556]
9. Karson CN, Newton JE, Livingston R, et al. Human brain fluoxetine concentrations. *J Neuropsychiatry Clin Neurosci*. 1993; 5(3):322–329. [PubMed: 8369643]
10. Strauss WL, Unis AS, Cowan C, Dawson G, Dager SR. Fluorine magnetic resonance spectroscopy measurement of brain fluvoxamine and fluoxetine in pediatric patients treated for pervasive developmental disorders. *Am J Psychiatry*. 2002; 159(5):755–760. [PubMed: 11986128]