

Double-blind trial of flupirtine in Creutzfeldt-Jakob disease

Otto et al. report a placebo-controlled double-blind study of flupirtine in patients with CJD. Cognitive decline as assessed by ADAS-cog was less marked under drug treatment.

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Commentary by Patrick Bosque, MD

The rapid progression of dementia in Creutzfeldt-Jakob disease (CJD) corresponds to an exponential proliferation of a pathogenically misfolded prion protein (PrP) in the brain. This exponential increase is presumably brought about by the self-propagating nature of the misfolded form of PrP. Purely symptomatic therapies, currently the mainstay of treatment for more slowly progressive neurodegenerative diseases, are unlikely to provide much benefit to patients with CJD. Useful therapies must impede the accumulation of misfolded PrP, or block the neural dysfunction and degeneration triggered by the misfolded protein.¹

How misfolded PrP causes neurodegeneration is not known. One popular experimental model uses aggregates of a synthetic polypeptide consisting of aminoacids 106–126 of human PrP (PrP106-126).² These aggregates will induce apoptotic death of neurons in tissue culture or retinal cells *in vivo*, but whether this relatively simple experimental

approach faithfully replicates the mechanism of CNS damage in prion disease is an open question.

Inspired by experiments that show reduced apoptosis in cultured neurons exposed to PrP106-126 in the presence of flupirtine, Otto et al. performed a placebo-controlled, double-blinded clinical trial of the drug in patients with CJD. Flupirtine appeared to modestly slow the precipitous cognitive decline in treated patients but did not prolong the duration of survival. Whether this small benefit reflects an alteration in fundamental pathogenic processes or a purely symptomatic effect is not clear.

CJD is such a devastating disease with such a uniformly grim outlook that it is hard to argue against any well-executed treatment trial. However, excellent rodent models of CJD exist. In fact, CJD can be reliably transmitted to certain transgenic mice. It is unlikely that a treatment with an important effect on the fundamental pathobiology of CJD would fail to

show benefit in these animal models. The superiority of rodent experiments over human trials in terms of speed, cost, human safety, and the quality of biological data obtained is so great that one could argue that controlled clinical trials should be confined to compounds that have demonstrated promise in prion-infected rodents. Compassionate use, even without placebo control, of possibly beneficial drugs might still be considered for a patient with established CJD, pending such rodent studies. The recovery of even one such patient would be a dramatic event.

References

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