Drugs 2003; 63 (22): 2435-2436
0012-6667/03/0022-2435/$33.00/0

Miglustat

A Viewpoint by Timothy M. Cox

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Although it is more than 20 years since Norman Radin proposed the use of inhibitors of key steps in the biosynthesis of glycolipids as a means to reduce toxic lysosomal storage in the neuronopathic sphingolipidoses, it is only recently that this strategy has emerged in the clinic. Although enzyme replacement therapy (ERT) has been strikingly successful for the treatment of type 1 Gaucher's disease, it does not offer the prospect of a definitive cure for either neuronopathic Gaucher's disease or those sphingolipid storage diseases in which chronic neurological manifestations are prominent. The recent clinical trials of miglustat provide scientific support for substrate reduction therapy and a boost to further pharmaceutical endeavours in the whole field of the sphingolipid disorders.

The predicted effect of miglustat is a reduction in leukocyte and red blood cell membrane glycolipids, thereby reducing the lysosomal accumulation of glucocerebroside in the macrophages which infiltrate the viscera in type 1 Gaucher's disease. Reduced membrane glycosphingolipids were demonstrated in the clinical trials, as was a clear therapeutic effect on visceral enlargement and blood parameters.

Unfortunately, miglustat has significant adverse effects, including a high frequency of transient diarrhoea, as well as tremor and in several instances, peripheral neuropathy. Rigorous monitoring of cognitive function and for signs of peripheral neuropathy is recommended. The slow onset of effect means that miglustat should not be used in patients with severe disease. With the present state of knowledge, miglustat cannot be used in children.

Very few patients are truly intolerant of ERT infusions, but a minority of type 1 Gaucher's disease patients opt not to receive them, either because of cost or perceived difficulties in administration. In addition, some patients prefer not to be tied to infusions once satisfactory control has been established with ERT. Although not yet tested, there are patients with neuronopathic Gaucher's disease (type 3) who might benefit from a therapy with the potential to penetrate the blood-brain barrier. Miglustat should not be used in preference to ERT as the primary treatment for Gaucher's disease, but its availability should allow further clinical trials in other neuronopathic glycosphingolipidoses (G_{M1} and G_{M2} gangliosidoses; Fabry's disease, Niemann Pick disease type C) and does provide access to a slowly effective therapy for mild Gaucher's disease.

In developed countries, miglustat has a clear position only as a second-line therapy, but its introduction offers the hope of important pharmaceutical experimentation and the application of inhibitors of glycolipid biosynthesis to a whole range of disorders, sufferers of which, at present, have little hope of amelioration. ▲