

Interview with Drs. Erik De Clercq and Lieve Naesens, June 2007
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What is the most effective prescription drug to combat HHV-6 infection?

The answer is not straightforward since clinical studies on the effect of antiviral drugs in HHV-6-infected patients have not been performed on a large scale. We can only draw tentative conclusions from small-scale studies in which the drugs were administered for shorter periods. The antiviral drugs foscarnet (or Foscavir®) and cidofovir (or Vistide®) have shown good activity in laboratory tests and single patients. Both compounds can cause kidney toxicity and, hence, long-term use of foscarnet or cidofovir is problematic. Ganciclovir (or Cymevene®) has also been reported to be effective in case studies. Since ganciclovir needs to be administered by intravenous infusion, its oral form (valganciclovir or Valcyte®) would be preferred in long-term studies. But chronic use of ganciclovir or valganciclovir can cause white blood cell depletion due to bone marrow toxicity. So at this moment, we do not have a prescription drug that is ideally suited for long-term use in HHV-6-infected persons.

What are the most promising drugs in the pipeline?

Current research mainly focuses on new antiherpetic drugs with a mode of action that differs from that of foscarnet, cidofovir or ganciclovir. However, these new products are mainly developed for herpesviruses other than HHV-6. The most advanced in clinical development is maribavir, a compound that is developed for cytomegalovirus, which, unfortunately, is not active against HHV-6. Another compound, cyclopropavir, has good activity against HHV-6, but is still in the preclinical stage. Besides, a few experimental compounds have been reported to have anti-HHV-6 activity in cell culture, but these have not yet advanced to preclinical development.

Are there any natural products or herbs that have in vitro efficacy against HHV-6?

Natural products containing seaweeds (such as red marine algae) inhibit HHV-6 replication in cell culture. These products contain negatively charged sugar molecules (also called 'polyanionic polysaccharides') which block the first step in the viral replication cycle, namely absorption of the virus to the cells. In cell culture, these polyanionic compounds are very efficient against HHV-6 as well as other herpesviruses. However, their clinical benefit when given as an oral tablet or capsule is questionable since their absorption from the gut into the blood stream is very limited.

Do the antiviral drugs vary significantly in their effectiveness between HHV-6A and HHV-6B?

Classical antiviral compounds targeted against the viral DNA polymerase, such as foscarnet, ganciclovir and cidofovir, are equally active against HHV-6A and HHV-6B. From the experience in our laboratory, we know that new compounds with a mode of action unrelated to the viral DNA polymerase, may have a different effect on HHV-6A and HHV-6B. Since their mode of action is not completely understood, we have no obvious explanation for this variant-dependency. Note that the cell culture tests with HHV-6A and HHV-6B are performed in different cell lines, so this is a complicating factor.

We know that ganciclovir and foscarnet pass the blood brain barrier reasonably well. What about cidofovir?

In normal individuals, the penetration of cidofovir into the central nervous system is low. However, cidofovir has proven to be effective against severe viral infections of the brain such as 'progressive multifocal leukoencephalopathy' (PML). In these pathologic circumstances, the virus-induced brain inflammation results in a malfunction of the blood brain barrier, allowing cidofovir to enter into the central nervous system.

Will there be an oral form of cidofovir available on the market soon?

A phase I clinical study on an oral form of cidofovir (known as CMX001 or HDP-cidofovir) is ongoing. If this study is successful, this compound will still need to proceed through phase II and III trials before reaching the market. So even if everything proceeds as planned, the development will still take several years.

Do Valtrex or Famvir have any activity against HHV-6?

Valtrex® (Zelitrex®) and Famvir® are the oral forms of acyclovir and penciclovir, respectively. In cell culture, acyclovir has only weak activity against HHV-6. For penciclovir, the activity is even less pronounced.

A new paper out of the NINDS has linked HHV-6B to mesial temporal lobe epilepsy. You recently tested a number of epilepsy drugs for antiviral efficacy against HHV-6B. Do you suspect that the mechanism of action with some of these epilepsy drugs is antiviral?

Antiepileptic drugs are thought to act by direct or indirect inhibition of receptor-mediated neurotransmission. We consider it unlikely that this mode of action could explain a potential antiviral effect on HHV-6, since our HHV-6 tests are done in lymphocyte cells which are very different from neurons.

You and Henry Agut have found that lamotrigine and valproate are both weakly effective against HHV-6B. Are these results clinically relevant?

For valproate, the anti-HHV-6 activity was not very convincing. The activity of lamotrigine is clearly better. Although its anti-HHV-6 concentrations in cell culture were quite high, they appear to be in the same range as the maximum drug concentrations obtained in blood or brain during use of lamotrigine in patients.

Given that valproate doubles the serum level of lamotrigine, would it make sense to use a combination of the two drugs?

Yes. There are a number of clinical reports on the usefulness of this two-drug combination for some psychiatric or epileptic disorders ([Pisani 1999](#), [Morris 2000](#), [Aldenkamp 2002](#), [Cuadrado 2002](#), [Thome - Souza 2003](#)) However, please be aware that higher lamotrigine levels could be associated with increased toxicity.

What do we know about Lamotrigine's mechanism of action?

Lamotrigine blocks neuronal voltage-activated sodium channels, and hence inhibits the release of excitatory amino acids such as glutamate.

You published a paper on arylsulfone derivatives. Do these compounds have the potential to be as effective as foscarnet or ganciclovir?

Yes. In our cell culture studies, these arylsulfone derivatives produce a consistent and complete inhibition of both HHV-6A and HHV-6B. Their therapeutic index (the margin between their antiviral and cytotoxic concentration) is comparable to that of foscarnet and superior to that of ganciclovir.

You have found that amantadine exhibits weak anti-HHV-6 activity. This drug is used by MS patients to relieve fatigue. HHV-6A has been associated with MS. Do you expect that the amantadine doses prescribed for MS might have antiviral effects?

According to a recent literature survey, there is insufficient evidence to conclude that amantadine is effective in reducing fatigue in MS patients. The maximum drug plasma levels obtained with current amantadine doses (100 or 200 mg) are 25- to 150-fold below the concentrations required to inhibit HHV-6 in cell culture. Administration of amantadine at higher doses is unrealistic since this would result in unwanted side effects. Thus, although the moderate antiviral activity of amantadine is an intriguing experimental observation, we believe that this has little clinical relevance.

Has there been any progress on animal models to test HHV-6 antivirals?

The development of animal models for HHV-6 is hindered by the fact that this virus only replicates in human cells. There is one report (by Dr. C. Genain) on an MS-like disease that was induced in marmoset monkeys by injection of HHV-6-infected cells. This intriguing observation still needs to be confirmed by other groups. Also, antiviral drug evaluation in this animal model is highly warranted.

Now that there seems to be a strong interest in HHV-6, will you be stepping up research efforts at Rega Institute to look for improved compounds?

Our Laboratory has a long expertise in antiviral drug development, including antivirals for herpesviruses. We have an ongoing antiviral program for HHV-6, but our funding resources are quite limited, making further expansion difficult.

Is there anything you can tell us about your research objectives?

In the past, we have identified a number of promising lead compounds, such as the arylsulfone derivatives mentioned above, new compounds related to cidofovir, and protein kinase inhibitors such as CMV423. Further optimization of these lead compounds in collaboration with medicinal chemists is ongoing. Besides, we have identified a few novel compounds with modest activity against HHV-6 in cell culture. An intensified input from medicinal chemists, who would have to synthesize new analogues, and a basic understanding of the mode of action of these compounds would be needed to correctly estimate their potential as anti-HHV-6 agents. More funding would be required to achieve these goals.

