

# [Herpes simplex virus antiviral drug resistance](https://assignbuster.com/herpes-simplex-virus-antiviral-drug-resistance/)

* Omer Baskan

The increasing drug resistance of the herpes simplex virus

Abstract

Herpes simplex infections remain very common worldwide, the development of new treatments is of vital importance, particularly for the severely immunocompromised individuals due to the increasing emergence of HSV resistant strains being reported. The standard treatment for HSV still remains highly effective, however there is an ever increasing risk that drug resistant HSV will become more prevalent due to the reliance on a limited group of drugs: acyclovir, foscarnet and cidofovir. This review aims to address the failure of previous studies conducted, which include the focus on treating acyclovir resistant HSV with foscarnet and cidofovir but not aiming to discover new compounds which might be used to treat HSV instead. A valuable source for new treatments is the abundance of natural compounds which exhibit antiviral properties. Several candidates are addressed and discussed in this review.

Introduction

A large family of DNA viruses commonly known as herpesviridae is largely known for causing diseases in humans as well as animals. The most prevalent forms of the virus family are known as HSV-1, HSV-2, Varicella zoster virus, Epstein-Barr virus and Cytomegalovirus. All five mentioned members of the herpesvirus family (herpesviridae) are known to infect humans (Sandri-Goldin, 2006), in total there 8 herpesviruses which can infect humans, these include human herpesvirus 6 and 7, and finally Kaposi’s sarcoma-associated herpesvirus (Carter & Saunders, 2013). So far there are more than 130 herpesviruses which can affect a range of animals (Brown & Newcomb, 2011). Herpesviruses are latent therefore they can remain in most people undetected, as the virus establishes itself in the ganglia of the peripheral nervous system (Stevens, 1975). It is reported that more than 90% of adults have been infected with the aforementioned species of the virus (Chayavichitsilp et al ., 2009).

Once an HSV infection occurs it will establish latency and can then multiply in large numbers as it has been reactivated, this then allows for the infection of a new host. In people who have a competent immune system the infection can be both painful and distressing but most importantly it is seldom life threatening. As a result the risks associated with herpes simplex are underestimated by people. However individuals with a HSV infection who also happen to have an impaired immune system can have life threatening symptoms which can result in death (Severson & Tyring, 1999). The preferred treatment of choice is the use of acyclovir (Morfin & Thouvenot, 2003) but due to its widespread use it has led to the emanation of HSV strains which are resistant to acyclovir (Morfin & Thouvenot, 2003). Resistant strains were first reported in 1982 (Sibrack et al ., 1982). Therefore, surveys were conducted which showed that there was a recurring low incidence rate of acyclovir resistant strains among immunocompetent patients which was 0. 6% (Englund et al ., 1990). However among patients who have an impaired immune system the acyclovir resistant strains which were recovered showed a frequency ranging from 3 to 6%, this figure then reaches 14% among patients who have received a bone marrow transplant (Englund et al ., 1990).

This review aims to deal with the features attributed with the emanation of acyclovir resistant HSV as well as the epidemiological features. Whilst addressing the severity of the emerging drug resistance strains of HSV and its impact on immunocompromised patients. This review will also aim to highlight potential natural compounds which are new candidates for the development of new antivirals to combat HSV, as well as many compounds which should have further investigation into its antiviral properties.

Epidemiology

It is rare for resistance to ACV to occur in immunocompetent patients but there have been reports that described that there is a below 1% occurrence of ACV resistance in the population (Nugier et al ., 1992). Most acyclovir resistant HSV isolated from patients with competent immune systems have been detected because of repeatedly having genital herpes. The observed occurrence ranged from 3. 5 to 8. 6% (Fife et al. , 1994). In most cases the course of antivirals remained unchanged, there was only three cases of genital herpes were use of acyclovir was unsuccessful due to HSV being resistant to acyclovir (Mouly et al ., 1995).

Acyclovir resistant among certain HSV infections is about 5% (Christophers et al ., 1998), this is only among immunocompromised patients who are most at risk of contracting an acyclovir resistant HSV. Infections caused by HSV among bone marrow transplant patients shows that patients that have received a bone marrow of either autologous or allogeneic origin have the same risk of developing an HSV infection. Resistance to acyclovir was detected only among allogeneic bone marrow transplant patients, this led to the discovery of the prevalence of resistance reaching 30% in patients who have had an allogeneic bone marrow transplant (Morfin et al ., 2004).

HSV strains that have been isolated from 3000 patients have been tested and have shown that half of them were immunocompetent whereas the other half had a immunocompromised system (Morfin & Thouvenot, 2003). The resistance of acyclovir was 0. 3% among immunocompetent and 4% among immunocompromised (Morfin & Thouvenot, 2003). Concerning the certain type of immunosuppression present, the resistance has been detected as 2. 8% among solid organ transplant patients, 3. 5% among HIV infected patients and at 29% for allogeneic transplant patients (Morfin & Thouvenot, 2003). These results show that the prevalence of acyclovir resistant HSV was stable in 2003 compared to previous studies published more than 10 years ago. This level of stability is same for both immunocompetent and immunocompromised patients. As suggested by previous studies, resistance to acyclovir is a major concern for allogeneic bone marrow transplant patients.

Mechanism of resistance

Nucleoside analogues make up the majority of antiherpetic drugs in clinical use (Morfin & Thouvenot, 2003). Acyclovir is a guanosine analogue, as is penciclovir. Cidofovir is a phosphonate molecule which is derived from cytidine and foscarnet has a very different structure, as it is analogous to a pyrophosphate.

The mechanism of action for acyclovir and penciclovir involve two viral enzymes. These are thymidine kinase which is for the first phosphorylation of the activation step and DNA polymerase, which is used as a target for the triphosphate form. Only two phosphorylations are needed for cidofovir for it to obtain the active diphosphate molecule, with both being performed by cellular kinases. Foscarnet only acts directly on the viral DNA polymerase (Figure 1; De Clercq et al ., 2001).

There are three mechanisms which are involved in HSV resistance to acyclovir: an alteration of thymidine kinase substance specificity, an alteration of DNA polymerase activity and a loss of thymidine kinase activity (Larder et al ., 1983). The viral gene encoding for thymidine kinase can have a mutation occur within them resulting in 95% of acyclovir resistance isolates presenting a thymidine kinase deficient phenotype (Hill et al ., 1991). Recovery of thymidine kinase deficient, altered and positive virus in a single isolate can lead to a detection of resistance of susceptible viruses (Nugier et al ., 1992).

These mutations that can cause resistance, occur spontaneously during viral replication therefore viruses which are resistant can then be selected for antiviral treatment. Functional DNA polymerase is required for viral replication but not for thymidine kinase. Therefore, there is a higher probability of a viable acyclovir resistant virus being caused by a mutation in the thymidine kinase gene, than by a mutation which occurs in the DNA polymerase.

Viral pathogenesis of mutant viruses depends on the resistance phenotype. However to DNA polymerase and thymidine kinase altered mutants, thymidine kinase deficient HSV is known to be impaired for pathogenesis in animal models (Morfin & Thouvenot, 2003). Therefore they fail to reactivate from a latent form in explanted tissue ganglia (Kosz-Vnenchak et al. , 1990). Thymidine kinase activity is not involved in the formation of latent infections but it is required for the virus to reactivate from latency (Efstathiou et al. , 1989). After isolation of resistant HSV, the reactivations tend to be associated with the original, thymidine kinase positive and acyclovir sensitive strain (Morfin & Thouvenot, 2003). Although, there are few reports checking reactivations due to the acyclovir resistant virus associated with the thymidine kinase altered virus (Kost et al., 1993) or thymidine kinase deficient virus (Morfin et al ., 2000).

Management of HSV infections with acyclovir resistance

In order to manage an HSV infection which is resistant to acyclovir we currently have to use several antiviral drugs. Many of the acyclovir resistant HSV isolates tend to be resistant to penciclovir but this occurs rarely. Some isolates can be resistant to acyclovir but still be susceptible to penciclovir as there have been reported cases; mechanisms of resistance to acyclovir of these particular strains was most likely an altered thymidine kinase protein (Sutton & Boyd, 1993) or it could have been that a mutation occurred in the viral DNA polymerase (Suzutani et al ., 2003). The thymidine kinase protein allows for acyclovir to become active but only in cells which are infected with HSV (Morfin & Thouvenot, 2003). Cidofovir and foscanet act directly on the viral DNA polymerase without the need of activation by viral thymidine kinase. The molecules cidofovir and foscarnet are both active on the HSV which is resistant to acyclovir, this is due to a mutation in the thymidine kinase gene (Blot et al ., 2000), however in clinical practice the molecules cidofovir and foscarnet are associated with high levels of toxicity. Managing a acyclovir resistant HSV infection can be further improved by decreasing immunosuppressive treatments for the patient (Collins & Oliver, 1986).

In vitro detection of resistance

In vitro evaluation of HSV susceptibility to antiviral drugs is based on the determination of viral replication inhibition in the presence of increasing concentrations of antiviral drugs. There are three techniques which are available to reveal viral replication: plaque reduction assay which is the reference technique, dye uptake method (Langlois et al ., 1986) and DNA hybridisation test (Swierkosz et al., 1987). The dye uptake method and DNA hybridisation test are known to be less time consuming as the reading cytopathic effect is automatable (Morfin & Thouvenot, 2003). The concentration of antiviral drugs can be determined by the three techniques mentioned which can lead to viral replication inhibition by 50% (inhibitory concentration 50%, IC50). To discriminate between the resistant strains, IC50 thresholds must be defined for every single virus and antiviral drug set. The values are determined using the mean value obtained for susceptible viruses. These thresholds are arbitrary and the detection of resistance is coming from the evolution of IC50 values of sequential isolates from a patient. There has been a development of several screening techniques using a limited number of viral dilutions and antiviral drug concentrations (Danve et al ., 2002).

The phenotypic methods all require isolation of viral strains on the cell cultures. This is time consuming and can delay the adaptation of antiviral treatment according to in vitro susceptibility (Danve et al ., 2002). Therefore genotypic tests are being developed in order to detect the resistant virus strains at a much shorter time delay (Morfin & Thouvenot, 2003). The viral genes which are used to encode thymidine kinase and DNA polymerase are amplified by PCR and the products then produced by PCR can be then sequenced. The main area of concern lies in the fact that many nucleotide substitutions can be found and they must then be identified as the mutations which are responsible for resistance. This interpretation will made easier as more results on mutations detected in the resistant isolates are then collected for future comparison and analysis.

Natural products with anti-herpes simplex virus activity

A phenolic compound known as Caffeic acid which is shown below, is an effective substance in Plantago major (Figure 2; Bourne et al ., 1999). It has been shown to exhibit strong activity against HSV-1 but decreased activity against HSV-2 (Mundinger & Efferth, 2008). Reducing the number of hydroxyl groups from the phenolic compound has also shown to reduce activity against HSV-1 (Chiang et al ., 2002).

Curcumin (Figure 3A) which is shown below is another phenolic compound and is mainly present in the spice turmeric and was found to inhibit genes of HSV-1 by an unknown mechanism (Mundinger & Efferth, 2008). It has also been previously shown that curcumin is slightly active against HSV-2 in vitro. An in vivo assay with the use of a mouse model of intravaginal HSV-2 infections showed that curcumin can provide significant protection (Mundinger & Efferth, 2008). In a further experiment cineole (Figure 3B), exhibited very similar results to curcumin, whilst eugenol (Figure 3C) provided results in the mouse model which showed the most promise (Mundinger & Efferth, 2008).

This study was then repeated but this time with the use of guinea pigs to represent the course of HSV-2 infection. The use of guinea pigs allowed for a more accurate representation of the infection that could occur in humans. The results showed that eugenol was again highly effective (Mundinger & Efferth, 2008). The use of eugenol resulted in fewer animals developing primary infections. Benencia and Courreges have confirmed the effectiveness of eugenol at preventing virus replication (Benencia & Courrèges, 2000). Therefore, it was suggested that eugenol may damage the envelope proteins of the newly-synthesised virus particles (Serkedjieva & Manolova, 1992).

In the animal models, it was shown that capsaicin was effective against HSV. Although, it was noxious when it was applied to the mucous membranes and also caused an unpleasant burning sensation. Consequently, civamide (Figure 4) was tested in animal models as it is less noxious. When civamide was administered prior to the virus challenge it was shown to reduce primary infections, it was also to shown to reduce the effect of the infection after the virus challenge (Mundinger & Efferth, 2008). Civamide was also shown to reduce the latent infection recurrence but only when it was used as a weekly treatment for suppressive maintenance therapy (Bourne et al ., 1999).

Propolis has long been seen as a natural product for antiviral treatments. Nine flavonoids were identified from propolis which were tested for their level of effectiveness against HSV (Amoros et al ., 1992). From the group of substances which were tested, galangin and kaempferol (Figure 5) were shown to have the highest anti-HSV in vitro activity (Lyu et al ., 2005).

A monoterpene which is found in several essential oils named isoborneol (Figure 5), was found to exhibit interesting anti-HSV activity which warranted further investigation. The tests showed that isoborneol was quickly able to inactivate HSV with a 30 minute period of exposure, and it was also completely able to inhibit viral replication at very low concentrations. The presence of isoborneol allowed for the glycosylation of certain viral polypeptides to be inhibited, whilst the glycosylation of cellular proteins remained unchanged. Glycosylation was normal in the presence of isoborneol when copies of the viral proteins were introduced into the cellular genome (Armaka et al ., 1999). These results seemingly indicate that isoborneol may be a promising new candidate for HSV treatment.

Several sulphated polysaccharides have shown to possess anti-HSV activity, and many carrageenans which are mainly found in red seaweed have been shown to be active against HSV infections. In models of intravaginal HSV-2 infection, mice were shown to exhibit significant signs of protection against HSV infections (Bourne et al ., 1999; Talarico et al ., 2004), and they were also protected from infection in the abdominal cavity when carrageenan was administered after infection (Pujol et al ., 2006).

Conclusion

Infections of HSV have a high occurrence globally therefore the number of infections is not expected to decrease significantly over the next couple of years. Due to the increasing number of immunocompromised patients and prolonged period of standardised treatment this can only exacerbate the problems caused by drug resistant HSV.

The increasing use of acyclovir as the immediate antiviral drug of use to treat an HSV infection has increased the fear of the increasing numbers of acyclovir resistant infections, notably in prophylaxis treatments among transplant patients. However, studies that have been conducted have shown that acyclovir resistant HSV is largely a concern for severely immunocompromised patients, such as those patients who have received a bone marrow from an allogeneic origin. When an acyclovir resistant strain of HSV arises it is best to manage the infection with other antiviral drugs which have different mechanisms of action, the most useful two to use would be foscarnet or cidofovir.

There is an urgent need for new treatment options to be developed as current treatment options do remain limited. There is the main use of acyclovir and then the subsequent use of foscarnet or cidofovir which is only used if acyclovir resistance is present. This shows that there is a limited amount of effective treatments available. Therefore, new treatments must be made available in order to avoid any future HSV epidemics.

The antiviral potential of the natural products indicates that there is still a wide range of compounds which could be useful in the battle against drug resistant HSV, mainly HSV which is resistant to acyclovir; as it is the main major concern moving forward. Therefore, it is highly advised that research in this area continues so that an even larger amount of compounds can be identified in order to combat drug resistant HSV.