Perspectives on Switching Oral Acyclovir from Prescription to Over-the-Counter Status: Report of a Consensus Panel

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The proposed switching of oral acyclovir from prescription to over-the-counter (OTC) status for the 5-day episodic treatment of genital herpes was considered by a consensus panel. It was concluded that self-diagnosis/misdiagnosis, misuse, and adverse drug effects were potential problems with the OTC use of acyclovir. While acyclovir reduces asymptomatic shedding of herpes simplex virus type 2, the reduction in transmission of virus potentially resulting from increased acyclovir use was felt to be of unknown extent but likely to be of benefit overall. The availability of acyclovir would likely be improved. There were differences in opinion as to whether widespread availability of acyclovir (prescription or OTC) may speed the development of viral resistance. However, all panel members felt that granting OTC status may set an undesirable precedent for the switch from prescription to OTC use of other systemically administered antiviral agents. The effect of this precedent, in terms of accelerating development of multidrug-resistant bacteria, was a major concern of all panel members. The consensus was that the switch of acyclovir to OTC status could not be supported.

In the current era of cost-containment, more and more products are being switched from prescription to over-the-counter (OTC) status in the United States. Such switching may reduce the overall cost of health care and empower consumers [1]. Recent switches in the United States have involved products for the treatment of heartburn/indigestion, asthma/allergies, diabetes, and yeast infections.

However, such switches are not made without serious consideration of the possible consequences. Before prescription-to-OTC switches are approved, the U.S. Food and Drug Administration (FDA) specifically reviews whether consumers can recognize the symptoms of the condition to be treated, the safety of the product, proposed labeling, consumers’ understanding of such labeling, and other issues [1, 2].

On 19 May 1994 an FDA public hearing and Antiviral/Nonprescription Drugs Advisory Committees Joint Meeting were held to consider issues related to the switch from prescription to OTC use of oral acyclovir for the treatment and suppression of genital herpes. A range of issues that needed to be addressed before OTC status could be granted emerged from these meetings. These issues included (1) viral resistance; (2) transmission of herpes simplex virus (HSV) through asymptomatic shedding; (3) education (public health programs) and counseling programs proposed by the manufacturer if acyclovir were made available for OTC use; (4) effect on screening for and reporting of other sexually transmitted diseases (STDs); (5) self-diagnosis and misdiagnosis of disease; (6) misuse, including use in pregnancy and overdose toxicity; (7) safety, adverse-reaction reporting, and postmarketing surveillance; (8) accessibility (drug cost and coverage); (9) labeling; and (10) episodic vs. suppressive treatment.

On 2 February 1996 an independent ad hoc panel, composed of the present authors, met to revisit the FDA findings. The panel heard presentations from persons in the industry and the medical community. This article summarizes the data presented and the findings of this ad hoc panel. Consideration was given to the potential OTC status of oral acyclovir only for the episodic treatment of recurrent genital herpes, not for suppression of the disease.

Epidemiology of Genital Herpes

Most cases of genital herpes are caused by HSV type 2 (HSV-2), with the remainder caused by HSV type 1 [3]. The incidence of genital herpes and seroprevalence of HSV-2 antibody have been increasing rapidly since the 1960s [4]. During the late 1970s, the overall seroprevalence of HSV-2 antibodies in 15–74-year-olds was 16.4% [5]. By 1989–1991, this seroprevalence had increased by almost one-third to 21.7% [6].
The disease is thus considered to be pandemic and a prominent public health problem [7, 8]. It is estimated that 44 million people in the United States are infected with HSV-2, although as many as 70% do not recognize their disease [7, 9]. It is this pool of unaware individuals who probably pose the most risk for disease transmission, as they are neither treated for nor counseled about their infection [7].

**Efficacy of Acyclovir in the Treatment of Genital Herpes**

Genital herpes has been successfully treated with oral acyclovir for many years (11 years in the United States and 13 in the United Kingdom). Acyclovir (200 mg five times daily for 5 days) has been widely used in the episodic treatment of recurrent episodes of genital herpes, where it shortens time to healing as well as duration of viral shedding and decreases new lesion formation [10–12]. It is also effective as suppressive therapy (800 mg/d in two or four doses) [10, 13–15] and has been shown to significantly reduce subclinical viral shedding when used long-term [16].

**Issues for Consideration**

The FDA public hearing and Antiviral/Nonprescription Drugs Advisory Committees Joint Meeting in May 1994 identified 10 broad issues for consideration with regard to OTC acyclovir. One of these is not relevant to this commentary (episodic vs. suppressive treatment), as the panel considered only the possible OTC availability of oral acyclovir for 5 days' episodic treatment. However, the panel identified another issue for consideration: precedence (which will be discussed later in this article).

**Viral Resistance**

Acyclovir is widely used in the therapy for many infections caused by HSV, including life-threatening diseases (neonatal herpes and herpes encephalitis) treated with the intravenous product. There is real concern that heavy use of acyclovir may enhance the development of resistance. Even though only the 5-day oral formulation for recurrent genital herpes is being considered for OTC status, it is likely that such an application would increase the overall consumption of acyclovir.

Since HSV is an obligatory intracellular parasite, herpes virus resistance is different from bacterial resistance in that the primary concern of viral resistance is its development in the individual patient. Transmission of resistant virus from patient to patient is a theoretical concern. Acyclovir resistance is due to selection of resistant variants under selective pressure. Almost all acyclovir resistance has been seen in immunocompromised individuals. The patients who have had clinically resistant lesions have predominantly been HIV-infected persons with CD4 cell counts of <50/mm³.

Resistance of HSV to acyclovir has been identified and monitored since 1973 (prior to the introduction of the drug). Over 5,000 viral isolates have been evaluated, mainly from immunocompetent patients. In a plaque reduction assay, 0.3% of 1,139 isolates from untreated immunocompetent patients were found to have reduced susceptibility in vitro to acyclovir (MIC, ≥2 μg/mL). This was similar to the prevalence among treated individuals (0.5% of 582 isolates) [17].

The frequency of resistance in immunocompromised patients is higher, averaging 4.9% between 1982 and 1990 [18, 19]. The prevalence of resistant strains of virus in only those immunocompromised patients who shed virus during therapy ranged from 4.1% to 10.9% [18–21]. The majority (92%) of the resistant variants are thymidine kinase–deficient and are somewhat attenuated in virulence in vivo [22].

There are differing opinions among panel members as to whether increased resistance to nucleoside analogs, which now include famciclovir and valacyclovir, would be an inevitable outcome of use over time of this class of drugs. The increased availability of acyclovir may speed the development of resistance by several years; however, it is possible that the nucleoside analogs will be replaced by new drug classes, such as the protease inhibitors, before such resistance is widespread.

**Asymptomatic Shedding and Transmission of HSV**

Unrecognized disease and asymptomatic viral shedding are key factors in the transmission of infection [23, 24]. Suppressive acyclovir therapy has been shown to reduce subclinical viral shedding by 96% in women [16], but it has yet to be confirmed in clinical trials whether reduced viral shedding leads to reduced transmission of infection.

If acyclovir does lead to reduced transmission, its availability OTC and increased usage could lead to decreased transmission by allowing individuals to treat their outbreaks without visiting a physician. Increased use, however, would depend on improved recognition of signs and symptoms. The panel believes that the risks of transmission will not be eliminated without patient education and counseling about barrier forms of contraception. Such an education program is outlined below.

**Education**

The dissemination of information to herpes sufferers or potential herpes sufferers is generally inadequate. Many physicians do not diagnose the infection correctly [9], or they counsel patients inadequately [24–26].

In general, the public are poorly informed about genital herpes and STDs [27]. A survey of American women conducted by the Campaign for Women’s Health and the American Medical Women’s Association indicated that women want information about STDs. Specifically, there is interest in how to recognize signs and symptoms of disease. Unfortunately, many women at risk for STDs do not consider themselves at risk. It has been
shown, however, that those with more knowledge of STDs are more likely to use safer sex practices [28]. Thus, large-scale education programs could likely help to prevent STD transmission.

The switch from prescription to OTC products could provide an opportunity for such large-scale education programs. Pharmaceutical companies often conduct large advertising and educational campaigns for OTC products, reaching consumers via television, magazines, and other popular media. These campaigns can focus on the disease as well as the therapy and educate not only consumers but also health care providers.

The panel was advised by Glaxo Wellcome (Research Triangle Park, NC) that the switch to OTC acyclovir would be accompanied by a major education program on STDs in general and genital herpes in particular. The campaign would highlight the risks of transmission and would promote safe sex practices. The panel agreed that such a campaign could be very useful if carried out in a medically responsible fashion, and it encouraged that such a program be implemented regardless of whether a switch to OTC acyclovir takes place.

**Counseling and STD Screening**

The OTC availability of acyclovir could lead to a decrease in counseling if patients did not consult a doctor for their first genital herpes outbreak. Decreased physician contact could promote disease transmission; on the other hand, most patients with genital herpes feel that their health care providers do not adequately counsel them. It is possible that a switch to OTC use of acyclovir could aid awareness of this and related STDs through accompanying education campaigns [25]. In addition, advertising may stimulate patients with suspicious lesions to seek medical care.

**Self-Diagnosis and Misdiagnosis of Disease**

Patients are usually able to recognize symptoms of recurrent active disease, as shown by clinical studies that ask patients with recurrent genital herpes to self-initiate treatment [11, 15, 29]. Another study showed that patients with unrecognized disease can be taught to recognize symptoms of genital herpes [30]. Thus, the panel felt that self-diagnosis of disease by patients with previously diagnosed genital herpes was not the major issue.

Misdiagnosis of disease is a potential problem, although it was reassuring that the Symptom Recognition and Self-Treatment Study conducted in public health clinics by Glaxo Wellcome showed that there was little confusion between syphilis and genital herpes on the part of the 3,000 patients interviewed [31]. Most important, people with lesions who elected to self-initiate treatment of their lesions did not delay coming into the clinic. There was no difference in the time from onset of symptom or sign to clinic visit between those who self-treated and those who did not. However, the sample in this study was self-selected, in that the patients had already chosen to visit a clinic for the treatment of their disease. Nonetheless, we believe that a consumer education program, if done effectively, could minimize misdiagnosis by highlighting different STD symptoms.

**Misuse, Including Use in Pregnancy, and Overdose Toxicity**

OTC acyclovir could be misused as a suppressive therapy, even though it would be sold and packaged as a 5-day course of treatment. It could also be used inadvertently or deliberately during pregnancy or taken as an overdose.

Opinions vary on the potential misuse of OTC acyclovir for suppression of genital herpes. Suppressive therapy with acyclovir is effective and safe [32] and may also reduce disease transmission. Underdosing could promote the development of resistant virus. Nonetheless, the panel agreed that misuse of OTC acyclovir for suppressive therapy is likely to be minimal because of the packaging and pricing of the OTC product. Nonreimbursement for OTC acyclovir is also likely to encourage patients to obtain a prescribed course of suppressive therapy.

The effect of use of acyclovir during pregnancy has been monitored by a registry. Since December 1994, known outcomes were recorded for 746 exposures to the drug during pregnancy. A total of 515 exposures occurred during the first trimester, with a 3.7% incidence of first-trimester birth defects, an incidence that does not differ from that reported for the general population [33]. Thus, although we would not encourage use of acyclovir during pregnancy, we believe that its inadvertent use would be unlikely to lead to increased birth defects.

The risk of overdose with OTC acyclovir is low. The bioavailability of oral acyclovir is only 15%–21% [34]. Patients with severe herpes infections receiving acyclovir (10 mg/kg iv 3 times daily) have mean plasma peaks of 9.19 μM. An 800-mg dose of oral acyclovir produces plasma peaks of only 6.9 μM [35, 36]. Thus, it would be difficult to overdose on OTC acyclovir. In addition, the overall good safety profile of acyclovir (described below) is reassuring.

In addition, an OTC antiviral agent has the potential for misuse for other viral conditions such as varicella zoster or even the common cold. The potential for the general population to confuse one viral infection with another is certainly a concern.

**Safety, Adverse-Reaction Reporting, and Postmarketing Surveillance**

A wealth of data confirm the safety and efficacy of acyclovir [10–16, 29, 32]. The drug has been used for over 15 years in >30 million people, has been the subject of various postmarketing surveillance studies, and has demonstrated a consis-
tent absence of major adverse effects [37]. Acyclovir continues to be monitored on a worldwide basis and is the focus of the Resistance Monitoring Task Force, consisting of nine clinical virologists, including two from Glaxo Wellcome. This task force, in collaboration with the Centers for Disease Control and Prevention, is sponsoring surveillance and special interest studies in the United States and Canada on acyclovir resistance (E. Kern, personal communication).

Thus, the panel felt that the availability of OTC acyclovir would probably not be associated with significant safety problems, except those related to potential viral resistance, as discussed.

**Accessibility: Drug Cost and Coverage**

The availability of OTC acyclovir will increase accessibility to the product for those patients who do not receive renewable prescriptions from their physicians. It would also increase availability for those patients who are reluctant to visit physicians for STDs, although such patients should be encouraged to consult with physicians for diagnosis and counseling.

Patients who currently pay for their own prescriptions would potentially benefit from a cheaper OTC product. Concern was expressed that health maintenance organizations might not cover the costs of prescription acyclovir if the product achieved OTC status, leading to problems for poorer patients. This potential lack of reimbursement is disturbing, particularly as generic acyclovir will become available in the United States in 1998.

**Labeling**

The panel did not consider labeling to be a major problem because labeling can address all key issues associated with OTC drugs. Patient-package inserts can be worded to minimize misuse of OTC acyclovir, to reinforce the message that the product should be used only when genital herpes has been previously diagnosed, and to encourage use of condoms to prevent viral transmission. However, the fact that few patients pay attention to package inserts could be a problem.

**Precedence**

The increasing resistance of bacteria to antibiotics is a major concern. Hardly a month goes by without an article in the popular press about the critical problem of multidrug-resistant bacteria [38–40]. Resistance of common or re-emerging pathogens to standard antibiotic therapies is becoming an increasingly important factor in the management of community-acquired and nosocomial infections [41]. Overuse or misuse of antibiotics worldwide has been a key factor in facilitating emergence of resistance. Self-prescribing is a key factor in the widespread development of drug resistance in the developing world [42].

The panel believes that switching acyclovir to OTC status would encourage other applications for switching many antibacterials to OTC status. While we believe that increased resistance to acyclovir will eventually occur and that OTC acyclovir might enhance that development, we are more concerned about the precedent it would set. At this time, the panel felt the establishment of a precedent for all antimicrobials is the most compelling reason for not supporting the acyclovir switch.

**Discussion**

Although many of the issues raised about OTC acyclovir at the FDA public hearing and Antiviral/Nonprescription Drugs Advisory Committees Joint Meeting in May 1994 are no longer of major concern, the panel believes that the switch from prescription to OTC status should not be supported for the following reasons: OTC use would set a precedent for other antiviral products, and OTC use could hasten the development of viral resistance.

Precedence is the major issue. Microbial resistance is inevitable in the long term, and the availability of an OTC antiviral drug would be expected to speed application for OTC antibiotics and consequent resistance. Self-diagnosis, misdiagnosis, misuse, and safety are legitimate concerns but do not seem to be major issues at this time.

The effect of OTC acyclovir on asymptomatic shedding and viral transmission is likely to be positive; effects on screening for and the reporting of other STDs and on counseling are less clear. However, they could be influenced positively because OTC use could improve consumer education and drug accessibility. It would seem prudent to support such a consumer education campaign prior to approval of an OTC status for acyclovir, in order to determine its impact on the target population’s understanding of herpes and other STDs.

At this time, the potential benefits do not outweigh the risk that the setting of a precedent and the subsequent availability of OTC antimicrobials would lead to accelerated microbial resistance.

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