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 anti-infective 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 2 February 1996 an independent ad hoc panel, composed of the present authors, met to revisit the FDA findings. The meeting was held on 2 February 1996 and sponsored by Glaxo Wellcome. Reprints or correspondence: Dr. Merle Sande, Department of Internal Medicine, The University of Utah, 4C104 School of Medicine, 50 North Medical Drive, Salt Lake City, Utah 84132.

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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 immuno-competent 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 decreased 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-detection 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 91.9 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 physi-
cians 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 poten-
tial 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 mult dru g-
resistant bacteria [38–40]. Resistance of common or re-
emerging pathogens to standard antibiotic therapies is becom-
ing an increasingly important factor in the management of
community-acquired and nosocomial infections [41]. Over-
use 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 anti-
bacterials to OTC status. While we believe that increased resis-
tance 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 pre-
scription to OTC status should not be supported for the follow-

ing reasons: OTC use would set a precedent for other antini-
fective products, and OTC use could hasten the development of
viral resistance.

Precedence is the major issue. Microbial resistance is inevita-
ble in the long term, and the availability of an OTC antiviral
drug would be expected to speed application for OTC antibiot-
ics and consequent resistance. Self-diagnosis, misdiagnosis,
unuse, 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
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 accessi-
bility. It would seem prudent to support such a consumer educa-
tion 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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