

# Probenecid hypersensitivity in AIDS: a case report

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**Background:** Cidofovir plus probenecid is a new therapeutic alternative for refractory cytomegalovirus and acyclovir-resistant herpes infections in AIDS patients. Probenecid is used in conjunction with the antiherpetic medication (cidofovir) in order to reduce the incidence of nephrotoxicity by cidofovir.

**Objective:** To present therapeutic alternatives for successful administration of probenecid to AIDS patients who develop a hypersensitivity reaction to the medication.

**Methods and Results:** We describe a patient with AIDS who was being treated with the cidofovir/probenecid combination for a peri-anal acyclovir-resistant herpetic infection. The patient subsequently developed a cutaneous hypersensitivity reaction to probenecid alone. A pretreatment regimen consisting of prednisone, H<sub>1</sub> and H<sub>2</sub> blockers was administered before the dosing of probenecid in order for the patient to continue with the antiviral therapy.

**Conclusion:** Cutaneous hypersensitivity reactions to probenecid may be seen more frequently with the increasing use of cidofovir in AIDS patients. Our pretreatment protocol is one therapeutic alternative to be considered in order to continue with probenecid.

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## INTRODUCTION

Probenecid has been used for many years as a therapeutic agent for chronic gout because it interferes with renal tubular secretion of organic acids (ie, uric acid). In addition, the drug has been utilized in combination with medications such as penicillin and cephalosporins. Probenecid maintains therapeutic blood levels of medications with rapid renal excretion by decreasing drug clearance in the urine.<sup>1</sup> Recently, probenecid has been used in combination with the new antiviral agent cidofovir. Cidofovir has particular efficacy for the treatment of herpes viruses in patients who are infected with the human immunodeficiency virus (HIV).<sup>2,3</sup>

Unfortunately, cidofovir when used alone has been associated with renal toxicity. In order to avoid this side effect, the medication is delivered in combination with probenecid in an effort to decrease the concentration of cidofovir in the urine. A favorable renal protective response has been demonstrated in animal models that compared cidofovir alone versus cidofovir plus probenecid.<sup>4</sup>

The incidence of adverse drug reactions is increased in patients with the acquired immunodeficiency syndrome (AIDS) when compared with the general population. This has been clearly demonstrated with respect to sulfonamides, various other antibiotics, aromatic anticonvulsants, and antituberculosis agents.<sup>5</sup> It appears that probenecid can be added to the growing list of medications associated with an increased incidence of adverse reactions in the AIDS population.

We present a case of a cutaneous hypersensitivity reaction to probenecid in an individual infected with HIV and the successful readministration of the

medication with the use of a pretreatment protocol.

## CASE REPORT

A 48-year-old African-American male was referred for an urticarial eruption associated with the administration of probenecid. The patient's medical history included infection with HIV for at least 10 years with a recent CD4 count of 98 cells/mm<sup>3</sup> and an RNA viral load of 1200 copies/mL. Clinical complications or problems have included an urticarial reaction to sulfamethoxazole/trimethoprim (treated with desensitization) and a 5-year history of peri-anal herpes simplex type 2 (HSV2) infection. The patient had no other prior history of urticaria.

Despite ongoing oral acyclovir therapy, the patient developed recurrence of his ulcerative peri-anal lesions. Cultures of the active lesions confirmed the HSV2 infection. Due to the progression of his lesions, the patient was started on intravenous cidofovir in combination with probenecid. The initial therapy consisted of cidofovir at doses of 5 mg/kg once weekly for 2 weeks and then every 2 weeks. Probenecid was given at a dose of 2 g orally three hours before a cidofovir infusion and 1 g at two and eight hours after the infusion.

The cidofovir/probenecid regimen was tolerated without side effects for five treatments. During this time interval, the patient developed a progressive decline in his renal function that was considered to be drug induced. This prompted discontinuation of all medications; however, the patient thought he was to proceed with the cidofovir/probenecid cycle. While off all other medications for a period of 1 week, the patient took 2 g of probenecid. Upon arrival to the Infectious Disease Clinic, he developed generalized

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urticaria within one hour of the ingestion. He experienced no other symptoms such as angioedema, hypotension, or shortness of breath. The reaction could not be attributed to any other medications, infections, or other common etiologies. He did not receive any cidofovir that day. The rash resolved within one hour after taking 50 mg of diphenhydramine. Two weeks later, he mistakenly took another dose of the probenecid. The patient developed the same reaction within 30 minutes of the ingestion. Again, he responded appropriately to antihistamine therapy. Oral acyclovir therapy was reinitiated as an alternative approach.

The patient's renal function normalized but his herpetic infection reappeared despite the acyclovir. In view of his excellent response to the cidofovir/probenecid regimen, a second trial was initiated. In consultation with the Allergy-Immunology department, the patient was premedicated with the following regimen (Table 1): 40 mg of prednisone 13, 7, and 1 hours prior to the first dose of probenecid; and 300 mg of cimetidine and 50 mg of diphenhydramine one hour prior to all doses of probenecid. Using the outlined protocol, the patient received three treatments of cidofovir/probenecid without complications.

## DISCUSSION

Cidofovir is a potent new antiviral agent, a nucleotide analogue, shown to have in vitro and in vivo activity against a broad spectrum of herpes viruses, including cytomegalovirus (CMV), herpes simplex virus types 1 and 2, varicella-zoster virus, and Epstein-Barr virus.<sup>6</sup> Nephrotoxicity is a major side effect associated with the use of cidofovir which includes cases

of irreversible renal damage and appears to be dose dependent. A study by Lalezari et al<sup>4</sup> demonstrated that up to 33% of the patients who did not receive concomitant administration of probenecid developed significant proteinuria.

Probenecid is a drug that inhibits the transport of organic acids across the epithelial barriers, especially in the renal tubules. This effect has a therapeutic advantage by prolonging the duration of serum levels of certain drugs (eg, penicillin) that otherwise would rapidly be cleared by the kidneys.<sup>1</sup> In addition, by decreasing the renal tubular concentration of medications such as cidofovir, probenecid reduces the risk of drug induced nephrotoxicity.<sup>4</sup>

The incidence of hypersensitivity reactions to probenecid are between 2% and 4% in the general population. Usually, these consist of mild skin rashes<sup>1</sup>; however, the incidence of hypersensitivity reactions to probenecid in the HIV population is increased to 11% to 25%.<sup>4,7,8</sup> A study done by Petty et al<sup>7</sup> utilized the combination of probenecid with zidovudine in eight HIV-positive patients. Six of these eight patients developed a rash that was associated with the probenecid. The phase I/II studies from Mount Zion and the National Institutes of Health (NIH), which evaluated the therapeutic potential of the cidofovir/probenecid regimen, reported reactions to probenecid in 3 of 19 (16%) and 2 of 21 (10%) patients respectively.<sup>4,8</sup> All patients in the Mount Zion study with a probenecid reaction were also sulfa allergic. Similarly, the patient described in this report also had a prior history of sulfa hypersensitivity.

The pathogenesis of many of the adverse drug reactions in patients with

HIV has been obscure. It has been suggested, however, that changes in drug metabolism as well as responsiveness to reactive drug metabolites could explain, at least in part, the high rate of adverse drug effects among patients with HIV.<sup>5</sup> The mechanism for reactions to probenecid is unclear, however, there is some structural similarity between probenecid and trimethoprim/sulfamethoxazole in that both drugs have a sulfa moiety.<sup>3</sup>

The use of cidofovir/probenecid regimen in the immunocompromised population is anticipated to increase due to the growing prevalence of CMV and acyclovir-resistant HSV infections in the AIDS population. As a result, the clinician will be faced with frequent hypersensitivity reactions and few alternative medications available. In our case report, two therapeutic options for the management of probenecid hypersensitivity were carefully considered. As outlined in the case report by Lalezari et al,<sup>3</sup> the first approach consists of a desensitization procedure: an oral dose of 10 mg of probenecid that is increased by 10 mg/day on days 1 to 5, 20 mg/day on days 6 to 10, and 250 mg/day on days 11 to 22. This strategy requires daily dosing of probenecid as oppose to the actual therapeutic need of bimonthly dosing. As a result, desensitization was not considered to be an optimal alternative due to the current use of other prescription medications and concerns about chronic probenecid therapy. The second option consisted of a pretreatment protocol as outlined in Table 1. At our institution, an H<sub>2</sub> antagonist is incorporated into the pretreatment protocol with prednisone and an H<sub>1</sub> antagonist. This rationale is based upon data that demonstrated that blockade of both H<sub>1</sub> and H<sub>2</sub> receptors was more effective than H<sub>1</sub> antagonist alone in the prevention of histamine-mediated responses in humans.<sup>9</sup>

The optimum strategy for managing an individual HIV-positive patient with probenecid hypersensitivity remains to be defined. At present, a careful consideration of the patient history, any newer alternative therapies (as

Table 1. Pretreatment Protocol for Prevention of Hypersensitivity Reactions to Probenecid

| Premedications             | Probenecid*     |                 |                 |
|----------------------------|-----------------|-----------------|-----------------|
|                            | Before 1st Dose | Before 2nd Dose | Before 3rd Dose |
| Prednisone, 40 mg, PO      | 13, 7, & 1 h    | None            | None            |
| Cimetidine, 300 mg, PO     | 1 h             | 1 h             | 1 h             |
| Diphenhydramine, 50 mg, PO | 1 h             | 1 h             | 1 h             |

\* Probenecid is administered three/day per dosing of cidofovir.

they become available) and the risk/benefit ratio (particularly as related to corticosteroid use and/or poor medication compliance in the face of dementia) must guide individual management decisions. Further reports of larger population experiences with this problem will be needed to elucidate the long term success rate of one management strategy over another (desensitization versus cyclic pretreatment).

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