Unexpected outcome (positive or negative) including adverse drug reactions

Aciclovir desensitisation and rechallenge

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Correspondence to Dr Pradhib Venkatesan, pradhib.venkatesan@nuh.nhs.uk**Summary**

A 29-year-old patient with HIV developed a facial angioedema hypersensitivity reaction to aciclovir when treated for acute retinal necrosis secondary to a herpes virus infection. She developed a similar reaction to famciclovir. Successful rapid desensitisation with oral aciclovir was performed and she became tolerant to aciclovir. She successfully completed 28 months of continuous treatment with no further reactions. However, 28 months later she experienced blurred vision and resumed taking oral aciclovir without a preceding desensitisation regimen. No allergic reaction occurred.

BACKGROUND

Only two cases of successful aciclovir desensitisation are described in the literature – one using a rapid desensitisation regimen and one a slow desensitisation programme. Our patient was HIV positive and required aciclovir to treat acute retinal necrosis (ARN). While her CD4 count was low she needed a desensitisation regimen so she could tolerate aciclovir. Interestingly, when her CD4 count improved on antiretroviral medication, she was able to take aciclovir without a preceding desensitisation programme and no allergic reaction occurred. This case report extends experience of drug rechallenge to aciclovir.

CASE PRESENTATION

A 29-year-old Thai woman was diagnosed with HIV. She presented with oral candidiasis but was otherwise well. Her presenting CD4 count was 20 cells/mm³ and she was commenced on highly active anti-retroviral therapy (HAART) – combivir and nevirapine, plus fluconazole and co-trimoxazole. She reacted to both co-trimoxazole and nevirapine with maculopapular rashes and was switched to dapsone and efavirenz without incident. Subsequently, she was treated for a chest infection with amoxicillin and developed a widespread maculopapular rash which ceased on interruption of amoxicillin therapy. Three months later her CD4 count had risen to 60 cells/mm³, but her haemoglobin had fallen to 6.9 g/l. In case this was due to the zidovudine component of combivir, she was switched to lamivudine and tenofovir and her haemoglobin improved. She complained of increasingly blurred vision and was diagnosed clinically as having bilateral ARN.

INVESTIGATIONS

Our patient had serum antibodies to herpes simplex virus (HSV), varicella zoster virus (VZV) and cytomegalovirus (CMV). Peripheral blood CMV PCR was negative. A vitreal biopsy was not performed as the risk of retinal detachment was considered too great.

DIFFERENTIAL DIAGNOSIS

Our patient was diagnosed with ARN by the ophthalmology team, the peripheral nature of which they considered was consistent with HSV or VZV infection rather than CMV infection.

TREATMENT

In view of the clinical picture, the ophthalmologists elected to treat with aciclovir 10 mg/kg three times/day intravenously and dexamethasone 0.1% eye drops topically four times/day. Six days after commencing aciclovir, the patient developed an erythematous macular rash and facial angioedema but no audible wheeze or dyspnoea. Intravenous hydrocortisone 100 mg and intravenous chlorpheniramine 20 mg were administered and the swelling and rash resolved. Subsequent doses of aciclovir were preceded by intravenous hydrocortisone 100 mg for the following 2 days without incident. Hydrocortisone was then reduced to 20 mg, but 3 days later the patient again developed the rash, angioedema and, on this occasion, chest tightness. Hydrocortisone was increased to 50 mg intravenously three times/day prior to aciclovir administration and she was switched to oral cetirizine 40 mg once daily. While on high-dose intravenous hydrocortisone, her CD4 count fell to 2 cells/mm³, which was attributed to steroid usage. Four weeks after the initiation of treatment for ARN, the patient's eyesight improved and she was switched to oral famciclovir, but 2 days later her skin deteriorated and she required extensive emollients. There was no angioedema or chest tightness and further doses were administered with hydrocortisone cover. Five and a half weeks after commencing antiviral treatment, a rapid oral desensitisation programme was commenced for aciclovir which was covered with oral prednisolone 40 mg. The schedule used is shown in table 1.

Temperature, pulse and blood pressure were monitored half hourly during the proceedings and a physician was present throughout. The desensitisation programme was

Table 1 Schedule of aciclovir desensitisation programme

Drug	Dose (mg)	Tablet (T) or liquid (L)	Volume (ml)	Concentration (mg/ml)	Time administered (min)
Prednisolone	40	T	NA	NA	0
Aciclovir	0.04	L	0.1	0.4	60
	0.1	L	0.25	0.4	75
	0.2	L	0.5	0.4	90
	0.4	L	1	0.4	105
	0.8	L	0.2	4	120
	1.6	L	0.4	4	135
	3.2	L	0.8	4	150
	6	L	1.5	4	165
	12	L	0.3	40	180
	24	L	0.6	40	195
	50	L	1.25	40	210
	100	L	2.5	40	225
	200	T	NA	NA	240
	400	T	NA	NA	255
	800	T	NA	NA	270

NA, not applicable.

administered without incident; no angioedema, rash or chest tightness developed and the patient's blood pressure and temperature remained stable throughout. She was discharged home 6 weeks after initial admission on oral aciclovir 800 mg five times/day and gradually reduced her oral steroids over the subsequent 6 weeks. Her progress was closely monitored and after 6 months the sight in her left eye deteriorated. Intravitreal ganciclovir was injected after which the retinitis improved. She developed cataracts in both eyes that were successfully resected. She has had no further flare up of the ARN.

OUTCOME AND FOLLOW-UP

After 6 months of oral aciclovir 800 mg five times/day, her dose of aciclovir was gradually reduced over the following 22 months and finally stopped after 28 months of treatment when her CD4 count was 443 cells/mm³ and her HIV viral load undetectable on a HAART regimen of Atripla one tablet daily. While visiting family in Thailand 28 months later, she again experienced blurred vision. She did not access medical care but took empirical aciclovir 400 mg orally four times/day without a preceding desensitisation programme. On this occasion she experienced no allergic reaction and after 14 days she ceased the medication. Her vision cleared within 2 days of starting treatment. At that time her CD4 count was 595 cells/mm³ and her viral load was undetectable.

DISCUSSION

HIV positive patients are 100 times more likely to experience an allergic reaction to medication compared with the non-HIV population.¹ The reasons proposed are multifactorial and include immune hyperactivation, changes in drug metabolism, patient cytokine profiles, increased susceptibility to oxidative stress, concurrent opportunistic infections and genetic predisposition.² When our patient presented with a CD4 count of 20 cells/mm³, she experienced allergic reactions to multiple drugs including cotrimoxazole, nevirapine and amoxicillin. She still mounted an allergic response to aciclovir and famciclovir despite an increase in CD4 count to 60 cells/mm³. In most cases of drug hypersensitivity, the patient will cease taking the

drug and often there are numerous alternative therapies available. However, a patient with ARN must receive anti-viral therapy or lose their sight. Aciclovir is the treatment of choice for HSV or VZV mediated ARN. Famciclovir is a recognised alternative to aciclovir in patients allergic to aciclovir.³ However, in our patient cross-reactivity occurred and she also developed an allergy to the famciclovir. Although intravitreal injection with foscarnet is a recognised treatment for ARN, intravenous therapy is not. This, coupled with the knowledge that our patient had already been anaemic, and 20–50% of AIDS patients develop anaemia with foscarnet therapy, led us to proceed with aciclovir desensitisation.

The tempo of the reaction and the clinical picture were in keeping with an IgE mediated rather than a cell mediated immune reaction. There are no commercially available serological assays for aciclovir specific IgE. Patch testing with solutions of drugs is possible but is often difficult to interpret and in such a heavily immunosuppressed patient obtaining a reliable result would have been questionable. Only two cases of aciclovir desensitisation are described in the literature, one with IgE mediated and the other with cell mediated hypersensitivity.^{4 5} When IgE mediated hypersensitivity is suspected, rapid desensitisation is used, whereas when cell mediated hypersensitivity occurs, a graded desensitisation programme is indicated. Graded desensitisation was used by Kawsar *et al.*⁵ However, our patient was speculated to have an IgE mediated reaction and hence a rapid desensitisation programme was adopted. A rapid desensitisation regimen aims to alter effector cell responses. A course of increasing drug doses from very small quantities, beginning at 10⁻⁶ of therapeutic levels, to therapeutic levels is administered with drug challenge occurring every 15–30 min. Despite rises in total IgE levels in HIV patients, it is likely that most drug-induced reactions in AIDS patients are non-IgE mediated and it is not known why or how the desensitisation or challenge protocols work in these patients. Henry *et al.*⁴ successfully administered a rapid desensitisation programme to an AIDS patient with recurrent genital herpes infections who developed angioedema secondary to aciclovir. We co-administered our desensitisation regimen with steroids as the patient's underlying diagnosis of ARN was felt to be

so serious that ceasing antiviral treatment in response to further allergy was not viable. The regimen we successfully administered was largely based upon the programme used by Henry *et al.*⁴

In HIV negative patients, interruption of therapy is usually associated with a further allergic reaction when rechallenged with the same drug. However, without medical consultation our patient took aciclovir without a preceding desensitisation regimen at a time when her HIV was controlled and her CD4 count recovered to 595 cells/mm³. Remarkably, this did not precipitate an allergic reaction.

Learning points

- ▶ It is possible to desensitise a patient to aciclovir if the clinical indication dictates that the drug cannot be stopped.
- ▶ Patients with HIV are more likely to develop hypersensitivity reactions to drugs than the non-HIV population, especially when their CD4 count is low.
- ▶ In patients with HIV, if good virological control is established and immune reconstitution occurs, they may no longer react to medication with a hypersensitivity reaction when rechallenged.

As much of the drug hypersensitivity experienced by HIV patients is poorly understood and thought to be multifactorial, it is speculated that this may be due to restoration of immune system regulation once a patient is established on HAART with good virological control. However, at lower CD4 counts rechallenge with full doses does not always lead to reactions in HIV patients with allergy to trimethoprim-sulfamethoxazole.⁶ This case report extends experience of drug rechallenge to aciclovir.

Competing interests None.

Patient consent Obtained.

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