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Case Report

Successful cholecalciferol desensitisation in a case of delayed hypersensitivity

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Conflict of Interest
The authors have no financial conflicts of interest.

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ABSTRACT

Hypersensitivity to cholecalciferol (vitamin D_3) or its active metabolite, calcitriol, is an exceedingly rare clinical phenomenon, with only 2 previously reported cases of suspected immediate hypersensitivity. Diagnosis of delayed drug hypersensitivity reactions is inherently difficult due to the lack of any robust *in vitro* diagnostic assay, particularly in those patients for whom provocation testing confers an unacceptable risk. In these situations, diagnosis relies on reproducible clinical manifestations following administration of the culprit agent, resolution upon its withdrawal and exclusion of other potential differential diagnoses. Based on these criteria, we propose the first reported case of delayed hypersensitivity to cholecalciferol successfully managed with a desensitisation protocol to pure cholecalciferol.

Keywords: Drug hypersensitivity; Cholecalciferol; Calcitriol; Immunologic desensitisation

INTRODUCTION

Hypersensitivity to cholecalciferol (vitamin D_3) or its active metabolite, calcitriol, is an exceedingly rare clinical phenomenon. In the 2 previously reported cases, the clinical manifestations were suggestive of IgE-mediated hypersensitivity, although this could not be confirmed by *in vivo* or *in vitro* testing in either report [1, 2]. Here, we describe the first reported case of successful desensitisation for delayed hypersensitivity to cholecalciferol. Informed consent was obtained from the patient.

CASE REPORT

In March 2016, a 76-year-old Caucasian woman was referred to our allergy service with a provisional diagnosis of cholecalciferol hypersensitivity. She had a significant history of vitamin D deficiency (21 nmol/L; reference range, 50–150 nmol/L) and severe osteoporosis with T-scores of −4.7 and −4.0 at her lumbar spine and femoral neck, respectively. She had radiological evidence of vertebral crush fractures and had previously suffered a minimal

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trauma fracture of her humerus. Her serum calcium levels were replete, maintained on calcium carbonate 1,500 mg daily. Her other medical history included mechanical aortic and mitral valve replacements and atrial flutter for which she was anticoagulated with warfarin. She had a previous diagnosis of nodal osteoarthritis but had experienced no disease flares in the preceding 5 years.

The patient's first reaction to cholecalciferol occurred 2 years prior when she was prescribed a commercial cholecalciferol tablet, (OsteVit-D, Key Pharmaceuticals, Sydney, Australia; cholecalciferol 25 micrograms). After 3 weeks of therapy she developed a nonpruritic truncal morbilliform eruption as well as synovitis of her metacarpophalangeal and interphalangeal joints of bilateral hands. These manifestations were attributed to the cholecalciferol preparation by her general practitioner. Upon cessation of cholecalciferol, her rash and synovitis resolved. She was referred to an endocrinologist for management of vitamin D deficiency and osteoporosis, who suspected that the reaction was due to an excipient in the original preparation (excipients: croscarmellose sodium, maize starch, magnesium stearate, glycerol, titanium dioxide, hydroxypropylmellose, talc, lactose, sucrose, gelatin) and therefore rechallenged the patient to a liquid cholecalciferol preparation with different excipients (Ostelin Vitamin D Liquid, Sanofi, Brisbane, Australia; excipients: natural orange oil sweet, medium chain triglycerides). On this occasion, after 2 weeks of treatment, the patient developed synovitis of both hands, now associated with a more extensive morbilliform eruption, sparing her face. She was postulated to have a true cholecalciferol allergy and replacement therapy was abandoned.

Her reactions appeared stereotypic and suggestive of a delayed drug hypersensitivity reaction (DHR), which resolved on both occasions upon cessation of cholecalciferol. There had been no other changes to her medications, detergents or cosmetics. Alternative explanations such as intercurrent viral infection, contact allergy or inflammatory arthritis were deemed unlikely from the clinical assessment.

There were no features of severe cutaneous adverse reaction with no evidence of mucosal ulceration or desquamation, nor was there evidence of organ dysfunction with unchanged full blood count, liver and renal function tests. Inflammatory markers were not assessed at either time point. There was some concern at the possibility of an immune-complex mediated process on account of her prominent arthralgias and synovitis; cutaneous vasculitis could not be excluded as her lesions had resolved by the time she presented for skin biopsy. Such a reaction would normally pose a contraindication to desensitisation [3]. However, as her fracture risk was significant and antiresorptive therapy was precluded by vitamin D deficiency, a desensitisation protocol was devised and administered over 8 days (**Table 1**). The preparation utilised in this protocol was a compounded pure cholecalciferol syrup. The decision was made to desensitise to pure cholecalciferol rather than a commercial preparation to ensure that the desensitisation was specific for cholecalciferol rather than an excipient. Although it was possible that she was not cross-sensitised to ergocalciferol (vitamin D_2), this analogue was not available in Australia and thus, not a feasible alternative.

Day 1 of protocol was performed in hospital and vital signs and spirometry were performed every 15 minutes. Doses on days 2–8 were self-administered by the patient at home, using labelled predispensed doses. The patient achieved the target dose of 1,000 units of cholecalciferol without any adverse reaction. This was continued for a period of 2 months with no recurrence of delayed DHR. She underwent a zoledronic acid infusion after this period, with serum 25-hydroxyvitamin D levels now replete at 70 nmol/L.

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Table 1. Cholecalciferol desensitisation protocol*

	Step	Oral dose (unit)	Dilution (units/mL)	Volume (mL)
Administered in hospital	Day 1			
	0 Hour	1	10	0.1
	1 Hour	2	10	0.2
	2 Hours	4	10	0.4
	3 Hours	10	10	1.0
	4 Hours	20	10	2.0
	5 Hours	40	10	4.0
Self-administered at home	Day 2	40	10	4.0
	Day 3	80	10	8.0
	Day 4	160	10	16.0
	Day 5	300	1,000	0.3
	Day 6	600	1,000	0.6
	Day 7	800	1,000	0.8
	Day 8	1,000	1,000	1.0

*This protocol utilises cholecalciferol 1,000,000 units/mL (Professional Compounding Chemist Australia) and medium chain triglyceride oil (Nutricia, Macquarie Park, Australia) as the diluent.

In order to demonstrate that the patient had been successfully desensitised to cholecalciferol and to provide a more feasible ongoing cholecalciferol preparation that did not require specialised compounding, she was rechallenged to the commercial preparation that was implicated in her second reaction (Ostelin Vitamin D Liquid). This was administered in hospital as a single dose challenge of 1,000 units. There was no immediate reaction. Both the commercial and desensitisation preparation were continued for a period of 4 weeks, as the initial reaction to the commercial preparation occurred at 3 weeks. As no further reaction occurred, desensitisation to cholecalciferol was deemed successful and the compounded desensitisation preparation was ceased. The patient remained on the commercial preparation administered daily to maintain tolerance, and at 12-month follow-up, no further reaction had occurred.

DISCUSSION

There is a paucity of literature to guide decisions regarding desensitisation for delayed DHR. Except in clearly defined circumstances such as trimethoprim-sulfamethoxazole for treatment or prophylaxis of immunocompromised patients, desensitisation is rarely attempted (or at least reported) for other situations of delayed DHR. There are many reasons for this reluctance, including difficulties in predicting the trajectory and severity of delayed reactions during desensitisation, as well as inherent difficulties in understanding the immunopathogenic mechanisms underlying individual hypersensitivity reactions [4]. In this case, our patient's stereotypic synovitis and morbilliform rash suggested a type III or IV hypersensitivity reaction, however, there were no associated fevers, haematuria or evidence of cutaneous vasculitis to provide an absolute contraindication to desensitisation. The suspicion of a type III reaction rendered rechallenge with pure cholecalciferol high risk in this patient and similarly, the option of 'treating through' was deemed unfavourable given the likely requirement for high dose corticosteroids to manage recurrent synovitis in a patient who was already severely osteoporotic.

It was felt that the patient-related morbidity from further osteoporotic fractures outweighed the potential risks of desensitisation. Our protocol utilised cautious dosing intervals and increments based on our patient's risk assessment; a more rapid protocol may be acceptable for low risk patients.

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A significant challenge in interpreting published reports of successful desensitisations for delayed DHR is that objective evidence of hypersensitivity is rarely documented. It is possible that a proportion of reports of successful "desensitisations" occurred in nonsensitised patients. Unlike immediate hypersensitivity reactions, there is limited role for skin testing, even with delayed reading, as very few patients demonstrated positive skin tests [3]. For this reason, we elected not to proceed with skin testing; nor did we subject the patient to a provocation test due to the high pretest probability based on 2 recent stereotypic reactions. The lack of any robust *in vitro* assay to diagnose delayed DHR is a major limitation in the assessment of such patients, particularly for those in whom provocation testing would confer unacceptable risk [4]. In the absence of such assays, clinical decision tools can be helpful in determining the likelihood of delayed DHR. Utilising the Naranjo scoring system for the estimation of the probability of drug reaction, our patient's probability of cholecalciferol allergy was classified as "probable" (score of 8); a score of 9 is required to classify the likelihood as "definite" [5]. Hence, we are reasonably confident that our case represented true delayed DHR.

Although specific for cholecalciferol desensitisation, the principles of risk analysis and protocol design illustrated in this case can be applied to other situations of delayed drug hypersensitivity, including high risk scenarios, where desensitisation may not routinely be entertained as a therapeutic option. A greater understanding of the immunopathogenic mechanisms underlying these reactions and development of appropriate diagnostic assays will undoubtedly advance this relatively uncharted area of allergy practice.

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