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Flu-Like Syndrome, Bronchoconstriction and Fever Caused by 5-Methoxypsoralen: The First Case Report and Literature Review

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Key Words

Phototherapy · Adverse drug reaction · 5-Methoxypsoralen · 8-Methoxypsoralen

Introduction

Photochemotherapy with psoralens and UVA (PUVA) is a very effective therapeutic option based on the interaction of a photoactive drug and light usually employed for the treatment of psoriasis and of other skin disorders, such as atopic dermatitis, vitiligo and cutaneous lymphoma. The psoralens most widely used for oral PUVA are 8-methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP), tricyclic furocoumarins naturally present in a large number of plants [1]. The chemical formula and the molecular composition of 5-MOP and 8-MOP present only slight differences; however, these are sufficient to make them 2 different chemical compounds capable of different reactions and interactions.

PUVA is generally well tolerated, but adverse events may occur. Besides the photosensitizing effect, which represents the therapeutic basis of PUVA, the commonest side effects complained of by the patients after oral intake of psoralens are nausea, vomiting, anorexia (mainly for 8-MOP), insomnia, anxiety and headache [1–3].

Although very rarely or exceptionally, a series of potentially serious side effects has also been found: while anaphylaxis has been reported due to both oral 5-MOP and 8-MOP [2, 3], exanthematous drug reaction [4], urticaria [5], bronchoconstriction [6–8], asthma exacerbation [9], drug fever [10, 11] and flu-like symptoms such as headache, fatigue and muscle aches [12] have been published related to 8-MOP intake only. To our knowledge, in fact, none of the symptoms mentioned above have been associated with oral 5-MOP in the literature.

Our report describes a case of fever, bronchoconstriction and flu-like syndrome in a patient during PUVA therapy with oral 5-MOP.

Case Report

A 53-year-old male anaesthetist with a widespread, histologically proven psoriasis vulgaris was treated with oral photochemotherapy (PUVA) after failure of multiple intensive topical treatments and poor response to UVA-UVB phototherapy. PUVA was begun according to our standard protocol: 2 h after oral administration of 5-MOP 100 mg (Geralen[®], 1.2 mg/kg body weight), the patient was irradiated with an initial UVA dose of 0.5 J/cm². Then, UVA doses were gradually increased (mean of 0.5 J/cm² at each session) up to a maximal dosage of 7.5 J/cm² UVA 3 times a week, with a nearly complete resolution of the skin disease in about 2 months.

The patient did not experience any side effects for the first 24 treatments, while he complained of high fever (39°C), bronchoconstriction (dyspnoea, tachypnoea and dry cough), malaise, headache and asthenia (flu-like symptoms), progressively increasing in severity, after the 25th, 26th and 27th treatments. These symptoms were reported to arise about 10 h after PUVA therapy and to abate spontaneously the day following the therapy. The patient was otherwise healthy and reported that he had felt well before each of the last 3 PUVA treatments. When PUVA was discontinued, no signs or symptoms appeared again. Three years before, the patient had undergone an annual course of UVA-UVB phototherapy without any kind of adverse reactions. There was no history of concomitant drug consumption, inflammatory diseases or infections. Blood analysis did not reveal any laboratory abnormalities neither before PUVA treatment nor after the drug reaction.

Two months later, in order to evaluate if 5-MOP was the cause of the febrile-bronchoconstrictive-flu-like reactions, an oral provocation test was performed with the therapeutic dosage (100 mg) of 5-MOP without further UVA irradiation. Ten hours later, the patient complained of high fever (39°C), bronchoconstriction and flu-like symptoms like those he had experienced 2 months earlier. A phototest with UVA and UVB alone gave no adverse event.

The recurrence of the same type and severity of clinical reactions after 5-MOP intake, as well as the absence of any signs and symptoms after the phototest, strongly suggested that only 5-MOP could be considered the cause of the side effects. The patient refused to undergo any further provocation test with 'placebo tablets' (containing all constituents of the Geralen[®] capsule except 5-MOP) to verify a possible causal role of the excipients contained

Table 1. Summary of the reports of fever, bronchoconstriction or flu-like syndrome caused by PUVA reported in the literature

References	Cases n	Sex	Age years	PUVA treatments before side effects	Latency after PUVA therapy	Duration of clinical manifestations	Type of clinical manifestations	Drug
Anderson et al. [6], 1984	2	F	34	6th and 7th treatments of a 2nd cycle of PUVA	4 h	not reported	bronchial reaction	8-MOP
		F	53	first 2 treatments of a 2nd cycle of PUVA	3–7 h	2–12 h	bronchial reaction	8-MOP
Tóth Kása and Dobozy [11], 1985	1	F	61	first 2 treatments of a 2nd cycle of PUVA	3 h	8–10 h	drug fever, dyspnoea	8-MOP + UVA
Wennersten [9], 1987	3	F	48	18th, 19th, 20th	5 h	not reported	exacerbation of pre-existing asthma	8-MOP
		F	59	15th	24 h	several days	exacerbation of pre-existing asthma	8-MOP
		F	50	17th treatment of a 2nd cycle of Re PUVA	not reported	not reported	exacerbation of pre-existing asthma	8-MOP
Berg [10], 1989	1	M	62	5th, 6th, 7th	2 h	24 h	drug fever	8-MOP
Ramsay and Marks [8], 1988	1	M	57	7th	5 h	2–3 h	bronchoconstriction	8-MOP
Van Coevorden and Coenraads [12], 2002	1	M	54	5th	few minutes	40–48 h	flu-like symptoms (fever, headache, fatigue, muscle aches, vomiting, nausea, dyspepsia)	8-MOP
Total cases	9							

in the formulation. PUVA therapy with 8-MOP has not been considered either.

Discussion

Fever, bronchoconstriction and flu-like syndrome associated with oral psoralen used in photochemotherapy have been rarely reported in the literature (table 1), and to date, only 9 cases have been described. In the previous reports only 1 or 2 of these 3 main clinical manifestations have been complained of by each patient. Generally, these symptoms appeared in adults (54–62 years old) and disappeared again once PUVA was stopped.

Fever, bronchoconstriction and flu-like syndrome have been caused directly by psoralens without irradiation with only 1 exception; in fact, 1 case has been ascribed to an 8-MOP product induced by UVA treatment [11]. The actual underlying pathogenetic mechanisms have not yet been completely defined: some authors suspect an immunologic genesis and hypothesize that these adverse effects may be attributable to an allergic hypersensitivity to psoralen [12], while a toxic reaction seems to be unlikely [13].

No case of fever, bronchoconstriction and flu-like syndrome associated with oral psoralen used in photochemotherapy described up to now has been caused by oral 5-MOP.

Examination of the reported cases regarding fever, bronchoconstriction and flu-like syndrome (table 1) due to 8-MOP shows

that: (1) in healthy patients the signs and symptoms usually begin between the 2nd and 7th PUVA treatments, while in asthmatic patients their onset is later, between the 15th and the 18th PUVA treatments; (2) when reported, the latency time from oral administration of psoralen to clinical manifestations is short and ranges from a few minutes to 24 h; (3) the prognosis, when specified, was good with a self-limited course and complete and spontaneous resolution within 2–48 h.

As in the literature (table 1), our patient was an adult. Like in the cases reported of patients with pre-existing asthma, our patient unexpectedly complained of symptoms after a greater number of PUVA treatments than those observed in healthy patients. In fact, he reported physical problems 10 h after the 25th treatment of PUVA. The kind of symptoms complained of is a further characteristic that distinguishes our case from the others reported in the literature. Our patient simultaneously developed fever, bronchoconstriction and flu-like symptoms while no more than 2 of the 3 main alterations had previously been reported in each patient (table 1). In particular, 8-MOP had induced flu-like syndrome in 1 case [12], drug fever in 2 cases [10, 11] and bronchoconstriction, bronchial reaction or exacerbation of pre-existing asthma in 6 cases [6–9].

Despite the worldwide and extensive use of oral psoralen, the case we describe may be of interest because, to our knowledge,

5-MOP has never been associated with the occurrence of flu-like syndrome, bronchoconstriction and fever. The case reported is also the first in which 3 important side effects caused by oral psoralen (fever, bronchoconstriction and flu-like syndrome) have been observed all together in the same patient. Although these events appear to be rare, dermatologists performing photochemotherapy should recognize the possibility of these complications when using PUVA.

Disclosure Statement

The authors declare that they have no conflict of interest.

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