

Eritema pigmentado fixo induzido por ácido acetilsalicílico – indução de tolerância com um protocolo otimizado

Fixed drug eruption induced by acetylsalicylic acid – a successful tolerance induction with an optimized protocol

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ABSTRACT

Introduction: Fixed drug eruption (FDE) is a delayed-type hypersensitivity reaction presenting as recurrent, well-demarcated skin lesions at the same site upon re-exposure to a specific drug. While the standard management involves drug withdrawal, tolerance induction protocols (TIP) may provide an alternative for patients requiring continued treatment. **Case description:** A 76-year-old male, with prior FDE to diclofenac and ibuprofen at the left scapular region, developed FDE to acetylsalicylic acid (ASA) at the same site following an acute coronary syndrome. A rapid TIP failed, prompting a modified slow TIP using a manipulated oral ASA formulation. The target dose (100 mg/day) was achieved by day 46, which he maintained over five years of follow-up without FDE recurrence. **Conclusion:** This case emphasizes the role of close monitoring and protocol flexibility in achieving drug tolerance while minimizing adverse effects.

Keywords: Acetylsalicylic acid, acute coronary syndrome, fixed drug eruption, tolerance induction protocol.

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RESUMO

Introdução: O eritema pigmentado fixo (FDE) é uma reação de hipersensibilidade tardia que se manifesta por lesões cutâneas recorrentes, bem delimitadas, no mesmo local após reexposição a um fármaco específico. Embora a abordagem padrão consista na suspensão do fármaco, protocolos de indução de tolerância (TIP) podem ser uma alternativa quando é necessário manter o tratamento. **Descrição do caso:** Um doente do sexo masculino, 76 anos, com FDE prévio ao diclofenac e ibuprofeno na região da escápula esquerda, desenvolveu FDE ao ácido acetilsalicílico (AAS) no mesmo local após uma síndrome coronária aguda. Por falência do protocolo rápido de indução de tolerância, implementou-se um protocolo lento com manipulado oral de AAS. A dose-alvo (100 mg/dia) foi atingida no dia 46, que o doente manteve durante cinco anos de seguimento sem recorrência de FDE. **Conclusão:** Este caso realça o papel da monitorização rigorosa e da adaptação do protocolo na obtenção de tolerância farmacológica, minimizando os efeitos adversos.

Palavras-chave: Ácido acetilsalicílico, eritema pigmentado fixo, protocolo de indução de tolerância, síndrome coronária aguda.

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INTRODUCTION

Fixed drug eruption (FDE) is a type IV hypersensitivity reaction that recurs in the same cutaneous location upon re-exposure to the offending drug. It is characterized by sharply demarcated, violaceous or erythematous plaques that typically resolve with residual hyperpigmentation. Intraepidermal CD8⁺ T cells in the lesional skin are the final effector cells in epidermal injury of FDE (1).

While avoidance of the offending agent is the mainstay of treatment, a tolerance induction protocol (TIP) may be required when the drug is essential, as in cardiovascular disease management (2).

Acetylsalicylic acid (ASA) plays a central and life-saving role in antithrombotic therapy for cardiovascular conditions, including acute and chronic coronary syndromes and prosthetic valve replacements (2).

This case report highlights the complexity of managing FDE in a patient requiring ASA therapy post-acute

coronary syndrome, emphasizing the role of a TIP in achieving drug tolerance and ensuring patient safety.

The terms “desensitization” and “tolerance induction” are often used concomitantly in the literature but refer to conceptually distinct approaches. According to the European Academy of Allergy and Clinical Immunology (EAACI), drug desensitization is defined as the induction of a temporary state of tolerance through the administration of increasing doses over a short period, a concept primarily developed for immediate, IgE-mediated reactions in which the underlying mechanism involves progressive inhibition of mast cell degranulation. In contrast, on delayed drug hypersensitivity, EAACI acknowledges that slower protocols may be more appropriate for T-cell-mediated reactions, as they allow adequate time to monitor for delayed cutaneous reactions before each dose escalation (3). In this case, we use the term “tolerance induction” as it more accurately reflects the slow, stepwise protocol used, with intervals of several days between dose increments.

CASE PRESENTATION

A 76-year-old male with hypertension, dyslipidemia, and benign prostatic hyperplasia was admitted to the emergency department due to an acute coronary syndrome. He had experienced FDE on the left scapula two years before to diclofenac and ibuprofen, confirmed by another Allergy Department. At that time, etoricoxib was identified as a safe alternative anti-inflammatory agent, as the patient had no prior history of coronary events and did not require antiplatelet therapy.

Given the urgency and the need to prevent further myocardial damage, ASA monotherapy was administered despite his history of drug hypersensitivity reaction. Two days post-initiation, he developed a well-demarcated, erythematous, pruritic macular lesion on the left scapu-



Figure 1. Left scapular lesion two days after starting acetylsalicylic acid therapy

lar region (same anatomical site of previous FDE reactions), accompanied by two cervical blisters (Figure 1).

The lesions caused significant discomfort to the patient and raised concerns regarding ASA continuation. Following prompt referral to our Allergy Department, ASA was discontinued, and he was prescribed prednisolone (PD) 40 mg daily (tapering over 10 days) and bilastine (BL) 20 mg twice daily, resulting in lesions resolution with residual hyperpigmentation.

Baseline laboratory work-up, including complete blood count and liver function tests, was normal.

The decision to pursue ASA tolerance induction rather than switching to an alternative antiplatelet agent was made in collaboration with the Cardiology Department, considering the patient's clinical context, anticipated cardiovascular benefit, and the urgency of the consultation. A comprehensive pre-procedural evaluation was undertaken to assess indications and contraindications, ensuring the expected cardiovascular benefit outweighed potential risks and no equally safe and effective therapeutic alternative was available at that time. Absolute contraindications, including drug-induced autoimmune disorders or severe organ dysfunction, were excluded.

The TIP was fully explained to the patient, and written informed consent was obtained prior to protocol initiation. It was implemented in accordance with the European EAACI Drug Allergy Interest Group guidelines (3).

A one-day rapid TIP (Protocol 1 – Table 1) was initiated at our Day Hospital, based on protocols used for immediate hypersensitivity reactions (3-5). It consisted of increasing oral doses every 15 minutes, starting at 0.01 mg and targeting 138.88 mg. Intravenous access, emergency medications, and resuscitation equipment were available throughout.

The procedure went without incident. However, lesion recurrence occurred at the same site the following day, requiring reintroduction of PD, topical methylprednisolone (TMPD), and BL.

A modified TIP was therefore implemented (Protocol 2 – Table 2) using a manipulated oral ASA for-

Table 1. Acetylsalicylic acid tolerance induction protocol

Day	Step	Interval between doses	Formulation	ASA dose (mg)	Cumulative dose/day (mg)	Clinical response/treatment
Rapid ASA TIP (Protocol 1)						
1	1	15 min	Solution A	0.01	0.01	No reaction
	2	15 min		0.02	0.03	
	3	15 min		0.05	0.08	
	4	15 min	Solution B	0.1	0.18	
	5	15 min		0.2	0.38	
	6	15 min		0.5	0.88	
	7	15 min	Solution C	1	1.88	
	8	15 min		2	3.88	
	9	15 min		5	8.88	
	10	15 min		10	18.88	
	11	15 min		20	38.88	
	12	15 min		40	78.88	
	13	15 min		60	138.88	
2	15	24 h	Tablet	100	100	Mild recurrence of lesions. Re-initiation of PD 40mg daily, TMPD, and BL 20mg twice daily. Protocol 1 interrupted
Slow modified ASA TIP (Protocol 2)						
3-26	1	24 h	Solution D	50	50	No reaction/ PD was suspended on day 17
27-34	2	24 h		60	60	No reaction/ TMPD and BL were suspended on day 31
35-39	3	24 h		70	70	No reaction
40-42	4	24 h		80	80	
43-45	5	24 h		90	90	
46	6	–	Tablet	100	100	Tolerated

Solution A: 0.05 mg/mL; Solution B: 0.5 mg/mL; Solution C: 5 mg/mL (water as diluent); Solution D: 10 mg/mL (distilled water as diluent).
Abbreviations: ASA – Acetylsalicylic acid; BL – Bilastine; PD – Prednisolone; TIP – Tolerance induction protocol; TMPD – Topical methylprednisolone.

mulation with progressively increasing doses. Given the ambulatory nature of this protocol, the patient received structured education on early warning signs

(fever, new skin lesions, mucosal involvement, arthralgia) and maintained direct contact with our team, with regular reassessments.

By day 46, the patient tolerated a daily ASA dose of 100 mg, which he maintained as lifelong therapy. PD was discontinued on day 17, TMPD and BL on day 31. Over five years of follow-up, the patient remained asymptomatic and fully adherent to daily ASA therapy.

DISCUSSION

FDE presents a therapeutic challenge when the causative drug is indispensable. In the initial rapid TIP, the 15-minute dosing intervals were based on the pharmacokinetics of ASA, which has a plasma half-life of approximately 15-20 minutes, aiming to maintain continuous drug exposure. This protocol was based on published protocols designed for immediate drug hypersensitivity reactions. In the slow modified protocol, multi-day intervals were guided by the kinetics of the delayed immune response, as clinical manifestations in fixed drug eruption typically occur hours to days after drug exposure. Longer intervals were therefore necessary to assess tolerance to each dose before escalation, with the goal of progressively inducing immunological tolerance (3).

TIP for delayed-type hypersensitivity reactions (DTHSR) lack standardization, with reported protocols ranging from rapid desensitization within hours to extended regimens spanning weeks (3-5). Rapid protocols, while time-efficient, carry a higher risk of reaction recurrence and failure (3). Patients who fail rapid protocols may be successfully desensitized with modified slow regimens (3), underscoring the value of protocol flexibility and individualization. Published ASA TIPs have been used mainly in cardiovascular settings, where mostly rapid protocols have been implemented. A notable limitation in some reports is reliance on self-reported hypersensitivity without confirmatory oral provocation (4).

The immunological basis for TIP in FDE remains poorly understood. In a case of allopurinol-induced FDE, Teraki *et al.* demonstrated a significant increase in lesional CD25⁺CD4⁺ T cells during tolerance induction, accom-

panied by a reduction in CD8⁺ T cells (6). The authors proposed that regulatory CD25⁺CD4⁺ T cells suppress CD8⁺ effector T cell activity within FDE lesions, thereby attenuating the local inflammatory response.

In this case, systemic and topical corticosteroids and antihistamines were introduced following lesion recurrence after Protocol I, rather than as formal premedication. Evidence regarding immunomodulatory therapy during DTHSR tolerance induction is limited (3). Corticosteroids may reduce T-cell activation and facilitate tolerance induction, but may also mask early clinical manifestations, complicating safety and efficacy assessment. Importantly, the patient maintained long-term tolerance to daily ASA after complete withdrawal of supportive therapies, supporting true immune tolerance induction rather than a temporary “treating through” strategy dependent on immunosuppression (3).

A notable feature of this case is the occurrence of FDE following exposure to multiple structurally unrelated nonsteroidal anti-inflammatory drugs (NSAIDs), namely ibuprofen, diclofenac and ASA. FDE is classically considered a drug-specific, T-cell-mediated reaction. Cyclooxygenase-1 (COX-1) mediated cross-reactivity, which underlies most immediate NSAID hypersensitivity, is unlikely given the delayed mechanism. The involvement of chemically distinct NSAIDs suggests either broader T-cell reactivity patterns or multiple drug hypersensitivity syndrome, in which sensitization occurs through independent immune mechanisms (7,8). Recurrence at the same anatomical site supports a shared immunopathogenic pathway.

At the time, available guidelines regarding alternative antiplatelet agents were less explicit than current recommendations (9,10). More recent guidelines increasingly advocate an individualized approach. Newer P2Y₁₂ inhibitors, such as ticagrelor and prasugrel, have gained prominence in selected acute coronary syndrome scenarios (9,10).

This case demonstrates that successful TIP requires adapting the protocol to the patient's clinical response.

The failure of the initial rapid TIP motivated a modified slow approach using a manipulated oral formulation, ultimately achieving sustained ASA tolerance. These findings emphasize that protocol flexibility is essential to ensure patient safety and to reach the therapeutic goal.

CONCLUSION

This report demonstrates that successful long-term ASA tolerance may be achieved in selected patients with NSAID-induced FDE through individualized tolerance induction strategies. The absence of lesion recurrence despite continuous daily ASA over five years supports the durability of the induced tolerance.

The case also illustrates the limitations of current NSAID hypersensitivity classifications when confronted with delayed reactions involving multiple chemically unrelated NSAIDs and highlights the importance of multidisciplinary decision-making, balancing guideline-based recommendations with patient-specific factors.

Nonetheless, these findings should be interpreted with caution. As a single case report, the successful outcome cannot be generalized to routine clinical practice.

Tolerance induction in DTHSR should be considered on a case-by-case basis, performed in specialized settings under close supervision, with careful risk-benefit assessment (3).

Conflicts of interest

The authors disclose they have no conflicts of interest.

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