

Drug-Eluting Coronary Stents: Hypersensitivity Reactions to Paclitaxel

A Case Report

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Key Words

Drug-eluting stents • Taxus™ • Paclitaxel • Hypersensitivity reactions

Abstract

Background: Drug-eluting stents become increasingly popular for the treatment of coronary artery disease. Consequently, side effects including hypersensitivity reactions have to be anticipated. **Case Report:** Here we report on a patient with an anaphylactic reaction 2 weeks after implantation of a polymer-based paclitaxel-eluting stent (Taxus™, Boston Scientific). The patient presented with disseminated wheals, pruritus, bronchial asthma and acute synovitis. The reaction was successfully treated with initial intravenous injection followed by oral antihistamine treatment for 1 month until all stent-bound paclitaxel was assumed to be eluted. Thereafter no further anaphylactic reaction occurred. **Conclusion:** This sequence of events points towards a causal relation of the stent implantation and hypersensitivity reaction with a central role of paclitaxel. The increasing use of this type of stent should therefore be carefully monitored for such adverse reactions.

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Introduction

Restenosis due to intimal hyperplasia within the stented segment is a major lim-

itation of conventional coronary artery stent implantations. Drug-eluting stents (DES) like paclitaxel-eluting stents have been demonstrated to decrease clinical and angiographic restenosis rates compared to conventional uncoated stents [1–3].

In the context of polymer-based paclitaxel-eluting stents, only little is known about the hypersensitivity potential of paclitaxel [4]. Turkoglu et al. [5] report about a patient who developed anaphylactoid reactions with erythematous rash, tingling sensations all over the body and a drop of systolic blood pressure. Paclitaxel, a well-known chemotherapeutic agent for several malignant diseases, is known to cause hypersensitivity reactions (HSRs) under on-cological conditions. A premedication containing histamine H₁ and H₂ receptor antagonists in combination with glucocorticoids is therefore recommended before application [6, 7].

We here report on a patient with severe HSRs which subsided after paclitaxel had entirely eluted from his stent within 4–6 weeks (product information Taxus® Liberté™, Boston Scientific Corp., Natick, Mass., USA).

Case Report

Case History

The 68-year-old male was admitted to our hospital because of night sweats, dis-

seminated wheals, pruritus, asthma-like breathing discomfort and acute synovitis. Two weeks prior to the onset of symptoms a polymer-based paclitaxel-eluting stent had been implanted because of critical coronary artery disease in the distal part of his right coronary artery with a good clinical outcome (Taxus Stent®, Boston Scientific Corp.; 20/3.0 mm). The patient's current and long-standing medication was clopidogrel, metoprolol, low-dose acetylsalicylic acid and simvastatin which were stopped except for acetylsalicylic acid and clopidogrel. The allergological and atopic past medical history was unremarkable.

His dermatological symptoms were characterized by urticaria covering large areas of his skin with a predominance on the extensor surface of the arms, the neck and back of his feet. Swelling was mainly found on the palms and soles. These symptoms had already persisted for 2 days and had been refractory to oral antihistamine treatment.

Clinical and Laboratory Examinations

Physical examination was normal. By further clinical and laboratory examinations, physical causes, chemicals and chronic inflammatory as well as infectious diseases could be excluded. Leukocytes were slightly increased to 10,000/μl as were C-reactive protein at 44 mg/ml (normal <5 mg/ml) and lactate dehydrogenase at 324 U/l (normal <247 U/l).

Table 1. Skin prick test

Substance	Conc., %	Vehicle	20/40 min	24 h	48 h
Histamine	0.0001	aqua	++++	neg.	neg.
NaCl	0.9	–	neg.	neg.	neg.
Plavix® 75 mg (clopidogrel)	native ¹	saline	neg.	neg.	neg.
Beloc Zok® (metoprolol)	native ¹	saline	neg.	neg.	neg.
ASS® 100 mg (acetylsalicylic acid)	native ¹	saline	neg.	neg.	neg.
Zocor® 10 mg (simvastatin)	native ¹	saline	neg.	neg.	neg.
Pantozol® (omeprazole)	native ¹	saline	neg.	neg.	neg.
Paclitaxel (3.0 mg/10 ml)	0.10	aqua	neg.	neg.	neg.
Paclitaxel (3.0 mg/10 ml)	1.00	aqua	neg.	pos.	neg.
Paclitaxel (3.0 mg/10 ml)	10.0	aqua	neg.	pos.	neg.

Preparation of the patient's current medication (clopidogrel, metoprolol, acetylsalicylic acid, simvastatin, omeprazole).

¹Suspended in 0.9% saline, and paclitaxel was applied in skin prick testing. The skin reaction was read after 20 min, 40 min, 24 h and 48 h.

Table 2. Epicutaneous test

Substance	Conc., %	Vehicle	48 h	72 h	168 h	10 days
Plavix® 75 mg (clopidogrel)	native ¹	vas.	neg.	neg.	neg.	neg.
Beloc Zok® (metoprolol)	native ¹	vas.	neg.	neg.	neg.	neg.
ASS® 100 mg (acetylsalicylic acid)	native ¹	vas.	neg.	neg.	neg.	neg.
Zocor® 10 mg (simvastatin)	native ¹	vas.	neg.	neg.	neg.	neg.
Pantozol® (omeprazole)	native ¹	vas.	neg.	neg.	neg.	neg.
Paclitaxel (3 mg/10 ml)	0.10	saline	neg.	neg.	neg.	neg.
Paclitaxel (3 mg/10 ml)	1.00	saline	neg.	neg.	neg.	neg.
Paclitaxel (3 mg/10 ml)	10.0	saline	neg.	neg.	neg.	neg.

Preparation of the patient's current medication (clopidogrel, metoprolol, acetylsalicylic acid, simvastatin, omeprazole).

¹Suspended in vaseline (vas.), and paclitaxel diluted in 0.9% saline was applied epicutaneously. The skin reaction was read after 48 h, 72 h, 168 h and 10 days.

Treatment and Course of Disease

After intravenous administration of clemastine at a dose of 0.2 mg/h and ranitidine at a dose of 4.2 mg/h for 6 days, urticaria completely disappeared. However, 24 h after treatment had been started, the patient complained of widespread arthralgia in nearly all joints of his lower and upper extremities. Sonographic examination revealed inflammatory articular effusions and tenosynovitis. Because of the unclear trigger, no anti-inflammatory or antibiotic therapy was started. Within the 10 days of hospital treatment all symptoms subsided. The oral antihistamine treatment with levocetirizine 5 mg/day was continued for 1 month until all stent-

bound paclitaxel was assumed to be eluted. After having stopped this antihistaminic protection, no further anaphylactoid reaction developed. During the 19 months of follow-up until now, no restenosis of the stent has occurred.

Allergological in vivo and in vitro Examinations

The allergological testing included skin prick and epicutaneous testing with non-toxic paclitaxel dilutions and the patient's further medication. All results were negative (tables 1, 2) except for a late reaction after 24 h in the skin prick test with two paclitaxel dilutions (1.00 and 10.0%; table 1) which had completely disappeared at 48 h.

No commercial in vitro test system is available for the investigation of paclitaxel-specific IgE. Paclitaxel is a 0.85-kDa molecule with a protein binding affinity of 89–98%. Specific IgE-binding to paclitaxel bound to 67-kDa human serum albumin is expected at approximately 68 kDa. To elucidate the role of specific IgE in paclitaxel-induced HSRs, an IgE immunoblot has been performed as previously described [8]. In brief, 1.5 ml of paclitaxel Mayne solution (3.5 mg/10 ml and 7 mg/10 ml, respectively) diluted 3:1 with 20% human serum albumin was substituted with sample buffer (Roti-Load 1, 4 × conc., Carl Roth GmbH, Karlsruhe, Germany), boiled at 95°C and separated

in a 12.5% sodium dodecyl sulfate-polyacrylamide gel, thereafter transferred onto nitrocellulose membranes (Schleicher & Schuell, Dassel, Germany) by wet gel blotting. Washing and incubation steps were performed as described [8]. For detection by autoradiography, iodine-125-labeled anti-IgE goat antibodies (IgE Tracer, IBL-Hamburg, Germany) diluted 1:20 in buffer were used. Sera from a healthy volunteer and a birch-pollen-allergic patient served as controls. No paclitaxel-specific IgE binding was detected in the index patient.

Discussion

DES have been demonstrated to decrease clinical and angiographic restenosis rates compared to conventional uncoated stents [1, 2]. DES have reduced the occurrence of major cardiac events from 16.4% observed with bare-metal stents down to 7.8% [3]. The stainless-steel struts of the stent are coated with polymers impregnated with drugs that inhibit local intimal hyperplasia. Commercially available stents are impregnated with sirolimus (Sirolimus®; sirolimus-eluting stent, Cypher®, Cordis Corp., Miami Lakes, Fla., USA) or paclitaxel (Taxol®; polymer-based paclitaxel-eluting stent, Taxus Liberté, Boston Scientific) [4, 9]. In the USA, more than two million DES have been implanted, accounting for 75% of all coronary artery stents utilized since 2003 [9].

In patients with documented HSRs after DES implantation, the reaction could be due either to medical procedures associated with stent implantation or to the DES itself [5, 9, 10]. Several components of the DES could be responsible. These include the stent itself, the polymer coating or the drug.

The stent material seems an unlikely culprit because so far no HSRs have

been described for conventional uncoated stents [4].

Patients with known coronary artery disease who have undergone implantation of DES typically require multiple medications [11]. Determining the cause of HSRs in such cases is confounded by the potential for hypersensitivity to concomitant medications. However, in our case, the comedication seems unlikely as these drugs had been taken for a long time before, the allergological testing was negative and no clinical allergic symptoms were found after stopping antihistamines despite continuous intake of this medication. Similarly, the polymer coating is an unlikely cause as it remains in the stent segment whereas paclitaxel is eluted completely within 4–6 weeks after stent implantation (product information of Taxus Liberté, Boston Scientific). Altogether, paclitaxel seems to play the central role for the HSRs in our patient.

Paclitaxel is a 0.85-kDa molecule isolated from the bark of the pacific yew tree (*Taxus brevifolia*) and established as a chemotherapeutic agent for several malignant tumors. It is known to cause HSRs like flushing, chest discomfort, respiratory distress and pulmonary edema [6]. However, so far castor oil derivatives (e.g. Cremophor®) contained in the paclitaxel chemotherapeutic agent for intravenous use have been assumed to be the culprit component [12], and a premedication with histamine H₁ and H₂ receptor antagonists in combination with glucocorticoids is recommended [7].

The paclitaxel concentration of a polymer-based paclitaxel-eluting stent ranges between 1 µg/mm², which is well below any chemotherapeutic application. Furthermore no solubilizers such as Cremophor are contained. Nonetheless, Research on Adverse Drug/Device Events and Reports identified several probable or certain cases of DES-induced hypersensitivity

syndromes with the onset of allergic symptoms and arthralgias 10–100 days after implantation of polymer-based paclitaxel-eluting stents [4, 9, 10].

Based on the allergological evaluation in our case an IgE-dependent specific sensitization to paclitaxel seems unlikely (tables 1, 2). Alternatively, urticaria, asthma-like disease and arthralgia in our patient may indicate a type III serum sickness disease. This may further be supported by the late reaction in the skin prick test to paclitaxel. The time lag between stent implantation and first appearance of clinical symptoms may indicate immunological sensitization. However, no formal proof by serological tests or histological examinations was obtained.

The clinical symptoms may be related to toxic or pseudoallergic effects as indicated by Itoh et al. [13]. They demonstrated that neurokinin NK1 and NK2 receptor antagonists were able to attenuate clinical symptoms of paclitaxel in rat lungs as did chemical sensory denervation with repeated capsaicin treatment. Elevated concentrations of sensory nerve peptides in bronchoalveolar lavage fluids of rats after paclitaxel injection suggest that paclitaxel-mediated HSRs are induced by e.g. substance P and neurokinin A but not by IgE-mediated histamine release [13].

In summary, hypersensitivity to DES is an entity of increasing importance and can result in serious clinical sequelae [14]. Clinicians should be familiar with the symptoms of these HSRs, and any suspected patient with a potential HSR after DES implantation should be evaluated thoroughly and monitored closely. Further clinical trials and continued surveillance of HSRs after DES implantation are important and will help to advance our current understanding of this entity.

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