

Piperacillin-Induced DRESS: Distinguishing Features Observed in a Clinical and Allergy Study of 8 Patients

R Cabañas,^{*1,5} O Calderón,^{*1} E Ramírez,^{2,5} A Fiandor,^{1,5} N Prior,^{1,5} T Caballero,¹ P Herránz,^{3,5} I Bobolea,¹ MC López-Serrano,¹ S Quirce,¹ T Bellón^{4,5}

¹Department of Allergy, Hospital La Paz Health Research Institute (IdiPAZ), Madrid, Spain

²Department of Clinical Pharmacology, Hospital La Paz Health Research Institute (IdiPAZ), School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain

³Department of Dermatology, Hospital La Paz Health Research Institute (IdiPAZ), Madrid, Spain

⁴Research Unit, Hospital La Paz Health Research Institute (IdiPAZ), Madrid, Spain

⁵Consorcio Piel en RED

*These authors contributed equally to this study.

■ Abstract

Background: DRESS (drug reaction with eosinophilia and systemic symptoms) syndrome is characterized by fever, rash, eosinophilia, and multiorgan failure. Previous reports have described differences in clinical and laboratory findings of DRESS syndrome depending on the inducing drug. Piperacillin has been reported as the drug responsible for this syndrome in 3 patients.

Objective: To analyze and describe the clinical, laboratory, and allergy study findings of piperacillin-induced DRESS.

Patients and Methods: Retrospective case series of patients diagnosed with DRESS associated with piperacillin-tazobactam (Pip/Taz) according to the Kardaun diagnostic score criteria. Assessment of causality was established using the Spanish Pharmacovigilance System and the lymphocyte transformation test (LTT). The allergy study included skin and epicutaneous tests.

Results: Eight patients were diagnosed with DRESS due to Pip/Taz (3 probable and 5 definite cases). Skin rash was observed in all cases and facial edema in 50%; the mean latency period was 18 days. Fever was present in 7 patients. Liver and kidney injuries were detected in 6 and 3 patients, respectively. All patients had eosinophilia and a full recovery. The LTT to Pip/Taz was strongly positive in all patients, with a stimulation index of over 6. Three of 3 patients had a positive intradermal test to Pip/Taz, and 1 of 4 had a positive patch test. All patients had a negative LTT to carbapenems.

Conclusions: We have reported on the first case series of piperacillin-induced DRESS. A latency period of 18 days, skin rash, eosinophilia, fever, liver injury, and good prognosis were the most common features. The allergy study, and the LTT in particular, was highly useful for identifying Pip/Taz as the culprit drug and piperacillin as the responsible active ingredient.

Key words: Allergy study. DRESS syndrome. Drug reaction with eosinophilia and systemic symptoms. Lymphocyte transformation test. Piperacillin-tazobactam.

■ Resumen

Antecedentes: El síndrome DRESS se caracteriza por fiebre, erupción cutánea, eosinofilia y afectación multiorgánica. Publicaciones previas han descrito diferencias en la presentación clínica y analítica de este síndrome dependiendo del fármaco inductor. Se han publicado 3 casos de DRESS inducidos por Piperacilina.

Objetivo: Analizar y describir las características clínicas, analíticas y el estudio alergológico del DRESS inducido por Piperacilina.

Pacientes y métodos: Estudio retrospectivo de una serie de pacientes diagnosticados de DRESS (de acuerdo a escala diagnóstica de Kardaun) por Piperacilina-Tazobactam (Pip/Taz). El establecimiento de causalidad se estableció según el algoritmo del Sistema Español de Farmacovigilancia y el Test de Transformación Linfocitaria (TTL). El estudio alergológico incluyó también pruebas cutáneas y epicutáneas.

Resultados: Ocho pacientes diagnosticados de DRESS por Pip/Taz (3 diagnóstico probable y 5 definitivo). Todos los casos presentaron erupción cutánea y el 50% edema facial, tiempo medio de latencia de 18 días. 7 presentaron fiebre y se detectó afectación hepática y renal en 6 y 3 pacientes, respectivamente. Todos los pacientes presentaron eosinofilia y una recuperación completa. El TTL a Pip/Taz fue

muy positivo en todos los pacientes con un Índice de Estimulación > 6. 3/3 pacientes presentaron prueba intradérmica positiva a Pip/Taz y 1/4 parche positivo. Todos los pacientes tuvieron TTL negativo a carbapenémicos.

Conclusiones: Presentamos la primera serie de casos de DRESS inducido por Piperacilina. Un tiempo de latencia de 18 días, erupción cutánea, eosinofilia, fiebre y afectación hepática junto a un buen pronóstico fueron las características más comunes. El estudio alergológico, principalmente el TTL, fue muy útil para identificar a la Piperacilina/Tazobactam como el fármaco responsable y concretamente a la Piperacilina.

Palabras clave: Estudio Alergológico. Síndrome DRESS. Reacción inducida por fármaco con eosinofilia y síntomas sistémicos. Test de Transformación Linfocitaria. Piperacilina/Tazobactam.

Introduction

Drug reaction with eosinophilia and systemic symptoms (DRESS) [1], also known as drug-induced hypersensitivity syndrome (DIHS) [2], is a life-threatening multiorgan system reaction characterized by skin rash, fever, enlarged lymph nodes, hepatitis, and leukocytosis with eosinophilia [3]. Aromatic anticonvulsant drugs and allopurinol have been reported to be the most frequent eliciting agents. However, in our hospital piperacillin/tazobactam (Pip/Taz) is the leading cause of DRESS, accounting for 26% (6/23) of cases studied at the allergy department from 2006 to 2010 [4]. As far as we know, there are only 3 reported cases of DRESS induced by piperacillin [5-7]. Previous reports have described differences in the clinical and laboratory findings of DRESS depending on the inducing drug [8]. These data prompted us to analyze the features of DRESS due to Pip/Taz in our series.

Patients and Methods

A retrospective analysis was performed of clinical data from 8 patients diagnosed with DRESS syndrome induced by Pip/Taz at our allergy department between 2006 and 2012. The study was conducted in accordance with Spanish laws regarding the protection of personal data [9]. Patients 7 and 8 were included in the multinational RegiSCAR registry with interview numbers 501-0040 and 501-0042. Our patients signed appropriate informed consent forms.

DRESS syndrome was diagnosed when a score of 4 or more (probable or definite diagnosis) was obtained using the scoring system proposed by Kardaun et al [10]. We also applied the Japanese Consensus Group Criteria [11]. All patients were evaluated by a multidisciplinary group composed of a dermatologist, a pharmacologist, and an allergist.

The pattern of liver damage was classified according to the International Consensus Meeting criteria for drug-induced liver disorders [12]. The RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria were used for staging patients with acute kidney injury [13].

Herpes viral antibodies including human herpesvirus 6 were determined by indirect immunofluorescence. Skin biopsies were taken according to the dermatologist's criteria.

The patients were studied at the allergy department after discharge and at least 4 weeks after the acute episode. To identify the eliciting drug, a detailed history was taken

and the following allergy tests performed: the lymphocyte transformation test (LTT) and epicutaneous, prick, and intradermal (ID) tests [14,15].

LTTs were performed with Pip/Taz (added to the medium at concentrations ranging from 0.1 to 250 µg/mL), other β-lactam antibiotics (amoxicillin, penicillin G, ceftriaxone, cefuroxime, imipenem, or meropenem), and any other suspect drugs. The LTT was performed as previously described [7,16]. The drugs used were intravenous pharmaceutical preparations reconstituted with RPMI, except for single preparations of piperacillin and tazobactam, which were purchased from Sigma-Aldrich. A stimulation index (SI) of 3 or more was considered positive for β-lactam antibiotics; a score of 2 or more was considered positive for other drugs. An LTT for a given drug was regarded as positive particularly when the SI was positive at more than 1 concentration. LTTs were performed between 3 and 9 months after the acute episode.

Epicutaneous tests were performed with Pip/Taz at 30% in petrolatum with readings at 48 and 96 hours. Prick and ID tests were performed with benzylpenicilloyl polylysine (0.04 mg/mL) and sodium benzylpenicilloate (0.5 mg/mL), Pip/Taz (0.2/0.025-2/0.25 mg/mL), penicillin G (10 000 IU/mL), amoxicillin (1-20 mg/mL), and meropenem or imipenem (5-0.05 mg/mL). Skin tests were performed at least 4 weeks after discontinuation of treatment with corticosteroids and resolution of the DRESS syndrome. The readings were taken immediately and at 6 and 24 hours [15].

Pip/Taz was identified as the culprit drug based on a positive LTT result and a review of the patient's medication history and clinical course. Causality was assessed using the methods of the Spanish Pharmacovigilance System [17].

Results

Demographics and Clinical Findings

Eight patients were diagnosed with DRESS syndrome due to Pip/Taz (Table 1). Three cases were considered probable and 5 were considered definite according to the Kardaun scoring system [10]. Based on the Japanese Consensus Group Criteria [11], 5 patients were diagnosed with DRESS (3 atypical, 2 typical). Rash and fever occurring simultaneously were the first manifestations in 4 patients, followed by eosinophilia 4 to 9 days later. In the other 4 patients, eosinophilia or fever were the earliest features. The latency period ranged from 8 to 28 days.

Table 1. Clinical, Laboratory Findings, and DRESS Diagnosis in Our Series of 8 Patients

Clinical Findings	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Results
Sex	F	M	F	M	M	M	M	F	3F/5M
Age, y	43	61	67	83	77	59	60	39	60.5 median
Exanthema latency time, d	21	14	24	28	14	21	20	8	18.75 mean
Skin resolution time, d	16	7	21	35	2	28	18	16	17.8 mean
Facial edema	No	Yes	Yes	No	Yes	No	No	Yes	4/8
Enlarged lymph nodes	Yes	No	Yes	No	No	No	Yes	Yes	4 yes/4 no
Fever (temperature <38.5°C)	38.5	38.8	38.5	37.2	38.5	38.6	38.9	40	7/8
Laboratory Findings									
Leukocytosis (>11x10 ³ /μL)	6.8	23.2	6.9	18.4	6.0	10.0	7.7	23.0	
Eosinophilia, eosinophils/μL	1050	5900	1130	3250	1300	1100	800	2600	
Atypical lymphocytes (>5%)	Yes	No	No	No	No	No	Yes	No	
AST (15-37) IU/L	66	28	69	90	36	59	161	22	
ALT (30-65) IU/L	108	21	102	104	105	117	240	13	
GGT (5-85) IU/L	897	50	74	1458	479	166	361	132	
AP (35-104) IU/L	310	70	75	461	286	59	100	117	
R (Ratio ALT ^a /AP ^a) ^a	0.6	-	2.2	0.4	0.6	3.2	3.8	-	
Cr (0.60-1.20), mg/dL	0.8	0.78	1.6	2.35	1	1.44	0.7	0.6	
Ratio Cr max/baseline Cr ^b	-	-	1.6	2.6	-	1.48	-	-	
Reactivation of HHV-6 ^c	Yes	No	Yes	No	No	ND	No	Yes	
Suggestive histology	ND	ND	ND	Yes	ND	ND	Yes	Yes	
Diagnostic score (Criteria of Kardaun et al.) ^d	7	5	7	6	5	5	7	6	
Diagnostic score (Japanese Consensus Group Score Criteria) ^e	7	3	7	4	4	5	6	5	

Abbreviations: ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; Cr, serum creatinine; Cr max, maximum creatinine value; F, female; GGT, gamma glutamyl transpeptidase; HHV-6, Human herpesvirus 6; M, male, ND, not done.

R = (ALT^a / AP^a), ALT^a (ALT/upper normal value ALT) and AP^a (AP/upper normal value AP).

^aHepatocellular pattern if R > 5, cholestatic if R < 2, mixed if 2 < R < 5 [12]

^bAcute kidney injury: Risk (1.5 x baseline Cr), Injury (2 x baseline Cr), Failure (3 x baseline Cr) [13].

^cAssessed by indirect immunofluorescence 2-3 weeks after onset.

^dDRESS diagnosis according to Diagnostic Score Criteria of Kardaun et al [10] (Total score < 2 excluded, 2-3: possible, 4-5: probable, >5: definite)

^eDRESS diagnosis according to the Japanese Consensus Group Criteria [11] (5 criteria: atypical; 7 criteria: typical).

Laboratory Findings

All the patients had eosinophilia (range, 800-5900 eosinophils/μL), with counts normalizing within 1 to 8 weeks; 2 patients had atypical lymphocytes. Two patients initially developed leukopenia, followed by eosinophilia. Six of the 8 patients had liver abnormalities (cholestatic injury pattern and mixed pattern in 3 cases each) [12]. Patient 8 had elevated gamma-glutamyl transferase at baseline. Three patients had renal impairment, which was staged as “risk” in 2 cases and “injury” in the other [13]

Skin biopsy was performed in 3 of the 8 patients, all of whom had histologic findings suggestive of DRESS, including a dermal lymphocytic infiltrate and occasionally scattered necrotic keratinocytes.

Treatment and Outcome

Pip/Taz was discontinued in all patients, who were treated with H₁ receptor antagonists. One patient also received topical corticosteroids and 6 received systemic corticosteroids (3 for less than 1 week and 3 for more than 2 weeks). The mean time for skin symptom resolution after antibiotic withdrawal was 17.8 days. Liver and renal abnormalities resolved between 1 to over 4 weeks after drug avoidance. All patients recovered without complications.

Allergy Study

All 8 patients had a positive LTT to Pip/Taz (Figure). The SI was over 6 (range, 6.46-57.92) for at least 2 concentrations in the 8 patients. An LTT to piperacillin was later performed

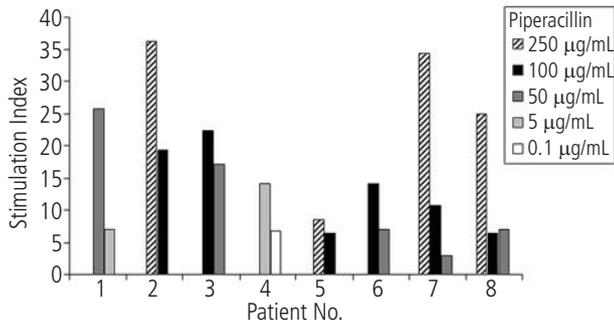


Figure. Proliferation of patients' peripheral blood mononuclear cells (PBMCs) in a lymphocyte transformation test. The PBMCs were incubated for 6 days with increasing concentrations of a pharmaceutical preparation of piperacillin/tazobactam (4/0.5 g). Final concentrations of piperacillin in the cell cultures with a stimulation index > 3 are shown.

Table 2. Results of Lymphocyte Transformation Test (LTT), Intradermal Tests, and Epicutaneous tests with piperacillin/tazobactam in 8 Patients

Patient No.	Patch Test	Intradermal Test	LTT (SI) ^c
1	-	ND	3.3, 7, 14.3, 25.8
2	-	^a (+) (7x9 mm)	19, 36
3	ND	ND	4.06, 17.17, 22.33, 25.25
4	-	^a (+) (10x10 mm)	5.8, 6.3, 7.7
5	ND	^a (+) (8x10 mm)	4.44, 6.46
6	+	^b (-)	3.5, 3.8, 7.03, 13.5
7	ND	ND	10.6, 34.63
8	ND	ND	4.82, 24.9, 46.73, 57.92, 46.89

Abbreviations: ND, not done; -, negative; +, positive, SI, stimulation index.

^aIntradermal tests performed at 2-0.25 mg/m piperacillin-tazobactam concentration. Intradermal test result is expressed as wheal diameters in mm.

^bIntradermal tests performed at 0.2-0.025 mg/m piperacillin-tazobactam concentration.

^cSI >3 are shown.

Table 3. Lymphocyte Transformation Test With α -Lactams Performed in our Series of Patients

Patient	Pip-Taz	Pip	Taz	Amoxicillin	Cloxacillin	Penicillin G	Ceftriaxone	Cefuroxime	Imipenem/Meropenem
1	P	P	N	N	ND	ND	ND	N	N/ND
2	P	P	N	SP	ND	N	N	N	N/ND
3	P	P	N	ND	ND	P	ND	N	ND/N
4	P	P	SP	N	ND	P	P	P	ND/N
5	P	SP	N	N	ND	SP	ND	N	ND/N
6	P	ND	ND	N	ND	ND	SP	SP	N/ND
7	P	P	N	ND	P	SP	N	ND	ND/N
8	P	ND	ND	SP	ND	P	N	ND	ND/N

Abbreviations: N, Negative if SI <3; ND, not done; Pip, piperacillin; P, positive if SI >3 at more than 2 concentrations; SP, slightly positive if SI >3 at 1 concentration; Taz, tazobactam.

in 6 patients, with positive results (range, 4.8-9.8). Patient 4 also had a positive LTT for tazobactam.

Three out of 3 patients had a positive ID reaction to Pip/Taz at a concentration of 2/0.25 mg/mL; the test was negative at lower concentrations (Table 2). One of these patients also had a positive delayed ID reaction. The ID tests were negative in the control individuals. One patient out of 4 had a positive patch test to Pip/Taz; this patient experienced accidental re-exposure to this drug some months later and developed a maculopapular rash and an increase in liver enzymes 5 hours after a single dose.

The results of LTTs performed with other β -lactams are shown in Table 3. ID with benzylpenicilloyl polylysine, minor determinant mixture, penicillin G, and amoxicillin and patch tests performed with penicillin and amoxicillin were negative in the 3 patients tested. The LTT was negative to meropenem (n=5) or imipenem (n=3) in the 8 patients. Patch and ID tests with meropenem or imipenem performed in 4 patients were negative. One of these patients tolerated meropenem some months later.

We did not observe any recurrence of DRESS in our patients with either the ID or epicutaneous tests.

Causality Assessment

Pip/Taz was considered to be "probably" related to DRESS in all cases.

Discussion

The frequency of DRESS induced by β -lactam antibiotics is highly variable in the literature [18,19]. As far as we know, only 3 cases of piperacillin-induced DRESS have been reported [5-7]. Circulating antigens derived from piperacillin and the drug derived-epitopes on proteins have been detected and fully characterized in an interesting paper by Whitaker et al [20], whose findings confirm our hypothesis that long-term treatment with very high doses of this reactive drug could be a risk factor for developing a T cell-mediated drug reaction. This would also explain why Pip/Taz is the leading cause of DRESS syndrome in our hospital [4], where this drug is frequently used at high doses, as in the article above, and for

long periods of time. It would also explain why the mean time of cutaneous symptom resolution is 18 days (the half-life of modified human serum albumin is 19 days).

Various authors have described differences in clinical and laboratory findings of DRESS syndrome depending on the inducing drug [8]. The mean latency period of 18 days in our series was slightly shorter than that usually reported for DRESS syndrome (3-6 weeks) [3]. Um et al [18] found that the latency period in antibiotic-induced DRESS was significantly shorter than in anticonvulsant-induced DRESS [18].

All our patients presented skin rash, and they had a higher frequency of facial edema (50%) and fever (87.5%) than reported by Cacoub et al (33% and >50% respectively) [21]. Enlarged lymph nodes were observed in 50% of patients; this frequency is similar to that reported for most drugs [18,21], but lower than the rate of 83% described for minocycline [22]. The liver was the most commonly involved internal organ in our series. Renal involvement has been reported more frequently in allopurinol-induced DRESS, while lung involvement appears to be more common in minocycline-induced DRESS [8].

The mean (SD) time reported for DRESS recovery is 6.4 (9.4) weeks [21]. In our series, this time was shorter and all patients had a complete recovery. DRESS induced by piperacillin appears to be a milder form of the disease, with a benign course and favorable prognosis. These observations are consistent with previous reports suggesting that antibiotic-induced DRESS is less severe than anticonvulsant- or allopurinol-induced DRESS [18,23,22].

There is no consensus on the diagnostic criteria for DRESS. We diagnosed our patients according to the scoring system described by Kardaun et al [10], which is used by the RegiSCAR study group, and compared our results with those obtained using the Japanese Consensus group criteria [11]. We agree with other authors that the Japanese criteria are more suited to diagnosing the severest cases of DRESS [19].

Solely on clinical grounds, it is not always possible to identify drugs responsible for severe drug reactions. As drug-specific T cells play a central role in mediating these reactions [3], patch tests, ID tests [14,15], and LTTs are frequently used for diagnosis [16]. The LTT offers numerous advantages over patch and ID tests, including absolute safety and simultaneous assessment of T-cell responses to multiple drugs. In our series, LTTs to Pip/Taz were performed 3 to 9 months after the onset of the reaction and were strongly positive in all patients. Our results are in agreement with previous reports that showed positive LTT results 5 to 7 weeks after the onset of DRESS and even at 1 year [3,24].

Even though ID tests to Pip/Taz at 2/0.25mg/mL were only performed in 3 patients, they were positive in all cases, suggesting an apparently good correlation between the ID test at this concentration and the LTT.

Negative LTT, ID, and patch test results to carbapenem in our patients, together with good tolerance to meropenem in 1 patient, suggest that carbapenems could be well tolerated by patients with DRESS due to Pip/Taz.

Based on our experience, the LTT is a useful technique for diagnosing Pip/Taz-induced DRESS syndrome, but the other methods used, in particular ID testing, can also be helpful for reaching a diagnosis.

Limitations

This was a retrospective study with a small number of patients. Skin biopsy was not routinely performed, and patch and ID tests were not performed in all patients.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

The results of this study have been previously presented in part as a poster or oral presentation:

1. Oral presentation at the 30th Congress of the European Academy of Allergy and Clinical Immunology. June 11-15, 2011. Istanbul, Turkey. Calderón O, Cabañas R, Prior N, Fiandor A, Caballero MT, Quirce S, López-Serrano MC, Bellón T. DRESS Syndrome Induced by Piperacillin-Tazobactam in six patients.
2. Poster presentation at the 5th Drug Hypersensitivity Meeting (DHM5) of the European Academy of Allergy and Clinical Immunology. April 11-14, 2012. Munich, Germany. Calderón O, Fiandor A, Bobolea I, López-Serrano MC, Quirce S, Bellón T, Caballero MT, Prior N, Cabañas R. DRESS Syndrome Induced by Piperacillin-Tazobactam in six patients.
3. Oral communication at the XXVIII National Meeting of SEAIC. October 17-21, 2012. Pamplona, Spain. Calderón O, Fiandor A, López-Serrano MC, Quirce S, Bellón T, Caballero MT, Prior N, Cabañas R. DRESS Syndrome Induced by Piperacillin-Tazobactam in Eight Patients.
4. Poster presentation at the 69th Annual Meeting of the American Academy of Allergy, Asthma and Immunology. February 2013. San Antonio, Texas, USA. Calderón O, Fiandor A, Caballero T, Bellón T, Prior N, López-Serrano MC, Quirce S, Cabañas R. DRESS Syndrome Induced by Piperacillin-Tazobactam in eight patients.

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■ **Rosario Cabañas**

Departamento de Alergia
Hospital Universitario La Paz
Paseo de la Castellana, N° 261
28046 Madrid, Spain
E-mail: charo.cabanias@gmail.com