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Original article

Piperacillin-tazobactam-induced fever in chronic respiratory diseases: Safe challenge test under premedication[☆]

Fièvre induite par la piperacilline-tazobactam en contexte de pathologies respiratoires chroniques : réintroduction sous prémédication possible

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ABSTRACT

Background. – Bronchial bacterial colonisation, particularly to *Pseudomonas aeruginosa* (PA), in patients with chronic lung diseases are associated with morbidity and mortality. An increased risk of allergy to beta-lactams has been reported in patients with chronic respiratory diseases. Data on beta-lactams allergy have extensively been published but little is known about antibiotic-induced fever.

Objective. – To describe safe exposure to piperacillin-tazobactam with premedication in patients presenting piperacillin-tazobactam-induced fever.

Methods. – Here we report data from patients who had piperacillin-tazobactam-induced fever with a safe re-exposure to this antibiotic with a premedication. This antibiotic was used to eradicate or to treat infection of PA in chronic respiratory diseases.

Results. – Six patients were enrolled (4 women, 2 men). Two patients had COPD, one had non-CF bronchiectasis and three patients had CF. Liver function test abnormalities have been reported in three patients, and two of them had non-severe bicytopenia. Eosinophil count was lower than 1,5 G/L in all patients. Skin tests to piperacillin-tazobactam remained negative in all patients who have been tested. Four out of six patients had a provocation test. All of them had fever within the 24 hours following the test. Two patients had a safe re-exposure with a premedication of corticosteroids and antihistamines. No fever occurred in the patients receiving the premedication.

Conclusion. – A provocation test with piperacillin-tazobactam with a premedication in patients who had piperacillin-tazobactam-induced fever seems to be safe. Other diagnoses such as DRESS and severe criteria of drug fever must be ruled out before considering a provocation test.

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R É S U M É

Introduction. – Les colonisations bronchiques chroniques, notamment à *Pseudomonas aeruginosa* (PA), sont associées à une surmortalité des patients porteurs de maladie respiratoire chronique. Un surrisque de réactions allergiques a été montré chez ces patients. Des données ont été publiées sur les allergies aux bêta-lactamines mais peu concernent les fièvres médicamenteuses.

Patients et méthodes. – Nous rapportons les données rétrospectives de patients atteints de maladie respiratoire chronique ayant eu une fièvre induite par l'association piperacilline-tazobactam dans le traitement d'éradication ou d'exacerbation respiratoire à PA, et ayant eu une réintroduction sans fièvre à l'aide d'une prémédication, au Centre Hospitalo-Universitaire de Toulouse.

Mots clés :

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Résultats. – Parmi les 6 patients inclus (4 femmes et 2 hommes), deux étaient porteurs d'une BPCO, trois de mucoviscidose et un de dilatation de bronche non-mucoviscidose. Des modifications du bilan hépatique ont été rapportées chez trois patients dont deux associées à des anomalies hématologiques non sévères. L'éosinophilie sanguine était inférieure à 1,5 G/L chez tous les patients. Les tests cutanés étaient négatifs chez tous les patients testés. Quatre patients sur les 6 ont eu un test de provocation à la piperacilline-tazobactam avec reproduction de la fièvre dans les 24 heures. Deux patients ont eu une réintroduction avec prémédication par corticothérapie et par antihistaminique sous surveillance hospitalière, sans réapparition de la fièvre.

Conclusion. – Dans un contexte de fièvre isolée induite par la piperacilline-tazobactam, la réintroduction sous prémédication semble bien tolérée. Cela implique d'avoir écarté au préalable les diagnostics différentiels comme le DRESS et les signes gravité de fièvre médicamenteuse.

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1. Background

Respiratory diseases are highly prevalent across the world. One billion people suffer from acute or chronic respiratory conditions and, globally, 4 million people die prematurely from chronic respiratory diseases [1]. In conditions such as COPD or bronchiectasis, structural changes in the bronchi expose patients to a high risk of bacteria colonisation resulting in high morbidity and mortality. Indeed, it has been shown that 43% of patients diagnosed with COPD and 63% of patients with bronchiectasis are colonised with bacteria [2].

The isolation of *Pseudomonas aeruginosa* from the sputum samples of patients with chronic respiratory diseases such as cystic fibrosis (CF) or COPD, is an important step in the natural course of the diseases [3,4]. Antibiotic regimens for the eradication of *P. aeruginosa* or treatment of *P. aeruginosa* infection are well established. In CF patients, it delays or prevents the onset of chronic *P. Aeruginosa* infection which is associated with negative effects on lung function and survival [5–7].

Drug hypersensitivity reactions are common adverse effects of antibiotics, especially beta-lactams [8]. Due to repeat, multiple exposure, the worldwide prevalence of beta-lactam allergy in CF patients has been reported as high as 36% [9]. Desensitisation protocols have been published in a context of IgE-mediated beta-lactam allergy [10]. Drug-induced fever has also been described with piperacillin-tazobactam in particular, which is one of the antibiotics most widely used in the eradication of *P. aeruginosa* [11]. However, little is known about piperacillin-tazobactam-induced fever and the primary concern is patient's safety following re-exposure. This paper describes safe re-exposure to piperacillin-tazobactam with premedication in patients presenting piperacillin-tazobactam-induced fever.

2. Methods

We retrospectively reviewed data from the medical records of patients who developed fever with piperacillin-tazobactam used to eradicate *P. aeruginosa* or treat *P. aeruginosa* infection in chronic respiratory diseases between October 2016 and January 2019 at Toulouse University Hospital Centre. Piperacillin-tazobactam-induced fever was defined as fever occurring during or shortly after administration of the antibiotic, with no fever being apparent prior to the antibiotic infusion. After a physical examination and appropriate biological, microbiological tests and, if required, medical imaging exams, there were no arguments to suggest another causative factor or other adverse effects associated with the antibiotic, especially severe delayed hypersensitivity such as drug reaction with eosinophilia and systemic symptoms (DRESS) and no arguments linking the drug-induced fever to another medication. Furthermore, the fever disappeared within 72 hours after

the discontinuation of piperacillin-tazobactam. The study has been approved by the *Comité d'évaluation des protocoles de recherche observationnelle* (CEPRO) of the *Société de pneumologie de langue française* (SPLF) and the approval identification number is CEPRO 2020-050.

Demographic data, characteristics of the initial reaction and details of skin allergy and challenge tests were collected. After written consent was obtained, skin tests were performed at the recommended concentration. Briefly, skin prick test and intradermal test until the concentration of 20 mg/ml of piperacillin and 2,5 mg/ml of tazobactam with an immediate reading at 20 minutes were performed. The test was considered positive when the diameter of the wheal was at least 3 mm for skin prick test, and 3 mm greater than that of the wheal measured immediately after injection for the intradermal test, and surrounded by erythema [12]. The challenge test was conducted the same day when the skin tests were considered negative in immediate reading. Patients received 3 intravenous infusions of piperacillin-tazobactam (an initial dose of 400 mg/50 mg, followed by 1000 mg/150 mg after 1 hour, then 2600 mg/300 mg after a further hour) with regular monitoring during the infusion and 2-hour post-infusion monitoring in the hospital setting. Premedication comprised one antihistamine tablet the day before the infusion and on the infusion days, and corticosteroids 1 mg/kg/day 1 h before the infusion.

3. Results

Six patients were enrolled in the study (4 women, 2 men) (Table 1). Two patients had COPD, one had non-CF bronchiectasis and three patients presented CF. Time to reaction (between the first infusion and the reaction) ranged from 1 day to 18 days, with a median time of 3.5 days. The fever reached 39°C in four patients and 38,4°C in one patient. All the patient had antipyretic like paracetamol. No corticosteroid nor antihistamine nor increased usual dose of antihistamine were administered. The duration of fever after piperacillin-tazobactam discontinuation was 24 hours in five patients, and 48 hours in one patient. Four patients had a co-prescription of tobramycin, one patient had a co-prescription of ciprofloxacin and one had no antibiotic co-prescription. A negative challenge test was available for all other antibiotics. Two patients presented erythema with itching during the initial reaction. One patient, who did not take his usual long-term treatment (inhaled tiotropium, fluticasone and vilanterol, and oral montelukast) for one day, also suffered from respiratory symptoms. Two patients had non-severe bicytopenia (lymphopenia up to 0.5 G/L, neutropenia up to 1.2 G/L, thrombopenia up to 70 G/L) associated with liver function test abnormalities. Another patient had liver function test near normal abnormalities with no blood test abnormalities, regarded as a non-allergic adverse effect of the antibiotics. The eosinophil blood

Table 1

Demographic characteristics of patients with piperacillin-tazobactam-induced fever, skin tests and challenge test.

Patients	1	2	3	4	5	6
Gender	F	M	F	M	F	F
Age (years)	58	50	70	31	32	29
Respiratory diseases	COPD	COPD	Non-CF bronchiectasis	CF	CF	CF
Atopy	No	Yes	No	Yes	No	Yes
Long-term antihistamines	No	No	Yes	Yes	No	Yes
Time to reaction (days)	5	1	9	2	2	18
Highest temperature (°C)	39	38,4	39	39	39	NA
Duration of fever after treatment discontinuation (days)	1	1	2	1	1	1
Erythema	Yes	No	No	Yes	No	No
Wheezing	No	Yes	No	No	No	No
Bicytopenia	No	No	No	No	Yes ^a	Yes ^b
CRP (mg/l)	46	38	17,8	NA	60	52
Eosinophil count (G/l)	0.6	0.7	0.3	NA	0.1	0.3
Liver function test increase	Yes ^c	No	No	No	Yes ^d	Yes ^e
Serum tryptase	NA	6,39	NA	NA	NA	NA
Skin tests						
	Negative	Negative	Negative	Negative	Negative	NA
Challenge test						
With no premedication	Fever and feet erythema	Fever	Fever	Fever	NA	NA
With premedication	No reaction ^f	No reaction ^g	NA	NA	NA	NA

NA: not available; M: male; F: female.

^a Lymphopenia up to 0.5 G/L, neutropenia up to 1.3 G/L, thrombopenia up to 135 G/L.^b Neutropenia up to 1.4 G/L, thrombopenia up to 93 G/L.^c ALT 60 IU/l.^d ALT 120 IU/l, GGT 82 IU/l, normal bilirubin rate.^e ALT 1215 IU/l, prothrombin time and clotting factor V 40%.^f Premedication with antihistamine the day before and during the test, and corticosteroids 1 mg/kg/day during the test.^g Same premedication with corticosteroids 1 mg/kg/day for the first 48 hours and discontinuation with no new febrile episode at the end of the 2-week antibiotic treatment phase in hospital setting.

count was below 1.5 G/L in all patients. The median CRP rate was 46 mg/l.

One patient did not have skin tests while another patient had skin tests but no challenge test. Negative piperacillin-tazobactam skin tests were recorded in all of the patients tested. No immediate reaction occurred following the challenge test. The four patients developed fever within 24 hours of the challenge test and one of them presented a feet erythema which disappeared within a day with no medication. Two patients were safely re-exposed with premedication under hospital supervision and one of them had a complete course of antibiotics only on antihistamine after day 1. This patient had an increase of CRP rate at day 3, getting back to normal at the end of the antibiotics course. No other biologic abnormality has been detected. No fever occurred in the patients receiving the premedication.

4. Discussion

The thermoregulatory centre in the pre-optic area of the anterior hypothalamus is responsible for maintaining temperature set point control in humans. During fever, there is an upward shift in the thermoregulatory set point. Elevation of the thermoregulatory set point can be caused by endogenous pyrogens such as prostaglandins, cyclic adenosine monophosphate and nervous system monoamines. Various exogenous pyrogens activate phagocytic leukocytes to produce endogenous pyrogens. The body compensates by increasing heat loss [13–15]. The mechanism of drug-induced fever is not fully understood and different pathophysiological mechanisms might explain this phenomenon, namely the effect of the drug on thermoregulation, the pharmacological action of the drug, exogenous pyrogenicity, idiosyncratic response and hypersensitivity reactions [16]. It has been suggested that drug-induced fever is a non-IgE-mediated delayed hypersensitivity corresponding type III or IV on the International Consensus on drug allergy which could be mediated by immune complex, cytokines or, less likely, T-cells [8,17]. Therefore, these data are old

and only based on animal model, new basic studies are required to better understand drug-induced fever.

The main limitation of the study is the small patient cohort. In fact, only two patients suffering from COPD had a safe challenge test with premedication (oral steroids and antihistamines). Some authors suggest that only corticosteroids are able to suppress fever in drug-induced fever [14]. However, the protocol used in our study combines both oral steroids and antihistamines. Another limitation is the difficulty in confirming the diagnosis of drug-induced fever and eliminating the differential diagnoses. A challenge test was used in 4 patients to confirm that fever relapses following further exposure to piperacillin-tazobactam. Due to the severity of the drug-induced fever (hepatitis, bicytopenia), the two others patients didn't have a challenge test. Other diagnoses such as DRESS, severe cytopenia and hepatitis must be ruled out before arranging a challenge test.

5. Conclusion

Our study is the first to report on a safe challenge test with premedication (oral steroids and antihistamines) in patients presenting piperacillin-tazobactam-induced fever. A larger prospective cohort is required to confirm the safety of such premedication.

Disclosure of interest

The authors declare that they have no competing interest.

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Authors' contribution

All authors have been involved in the study design, data collection and in drafting the article. All of them have given their final approval of the version to be published.

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