



Hôpitaux de Lyon

DI-050: Drug-induced fever caused by

Piperacillin-tazobactam in adults with cystic fibrosis

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Background

Piperacillin/Tazobactam (PT) (Tazocilline®, Pfizer, France) is a combination of a broad-spectrum semisynthetic penicillin and a beta-lactam inhibitor generally used as an antipseudomonal antibiotic to treat infected adults with Cystic Fibrosis (CF) developing pulmonary exacerbation. Fever is one of the uncommon adverse effects of PT and is the focus of this paper. Because fever is usually associated with infectious disorders, it is frequently misdiagnosed.

Purpose

Report all cases of drug induced fever related to an intravenous course of PT from our Cystic Fibrosis Center.

Material and methods

Retrospective review of the medical history of every patient, of the 250 adult patients followed-up in our CF Center in Centre Hospitalier Lyon Sud, who was exposed to intravenous courses of PT between January 2004 and August 2013.

Results

116 adult patients were treated with 385 courses of intravenous PT during this period. We recorded 9 patients (7.8% of patients, 2.6% of courses) who developed a fever greater than 38.5°C during treatment. Pyrexia occurred after a mean of 6.8 days (range 1-19) and subsided through discontinuation of the course within a mean time of 1.6 days (range 1-3).

patients	Genotype	FEV1 (forced expiratory volume in 1 second)	identified bacteria	antibiotic courses	lag-time after initiation (days)	lag-time after discontinuation (days)	rechallenge	total number of PT courses
1	DF508, DF508	20%	Pseudomonas aeruginosa (P.a.) Stenotrophomonas maltophilia Staphylococcus aureus (S.a.)	PT 4g 3/day Clindamycin 600mg 3/day	1	1	no	2
2	DF508, E60X	79%	P.a. S.a.	PT 4g 2/day Tobramycin 400mg 1/day	10	3	no	3
3	DF508, DF508	37%	P.a.	PT 6g 3/day Tobramycin 400mg 1/day	15	1	no	3
4	DF508, DF508	23%	P.a. S.a.	PT 16g continuous-infusion/day Tobramycin 300mg 1/day	1	3	no	6
5	DF508, DF508	26%	P. a.	PT 6g 2/day Tobramycin 350mg 1/day	19	2	no	3
6	DF508, N1303K	28%	P.a. S.a.	PT 18g continuous-infusion/day Tobramycin 400mg 1/day	1	1	no	2
7	DF508, CFTR dele2	44%	P.a. Streptococcus agalactiae Escherichia coli	PT +Tobramycin (unknown doses)	1	1	no	2
8	DF508, 3659 delC	82% ; 75%	P.a. MRSA	PT 8g 2/day ; 18g continuous-infusion/day Tobramycin 450mg 1/day	13 ; 1	2 ; 1	yes	4
9	DF508, 1717- 1G- >A	27%	Proteus mirabilis	PT 18g continuous-infusion/day Tobramycin 1000mg 1/day	6	1	no	2

Discussion:

Biases which explain a higher percentage in our CF population than in general population:

1. CF patients → hyperimmune state + frequent antibiotic exposure → more likely to develop allergic reactions
2. CF adults → more exposed to antibiotic courses than children → more episodes of drug-induced fever (DIF)
3. PT : one the three most used antipseudomonal antibiotics by physicians in our Cystic Fibrosis Center in CHLS

This side effect corresponds to an allergic reaction to PT on which several studies already report high incidence (24% to 72%). Some patients develop fever only one day after their first administration, while a delay of about 10 days is generally expected. Our results based on a larger sample than previous studies suggest that an earlier reaction to PT may remain unnoticed until a subsequent dose is administered.

Conclusion

Drug-induced fever caused by PT might be under-estimated, especially in the adult CF population. Because the symptoms may be undiagnosed, being aware of this not so uncommon phenomenon is important in order to provide the best cares.