

Increasing dose regimen in children with reactions to ceftazidime

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Summary

Background Of 87 consecutive patients with cystic fibrosis treated with 859 courses of intravenous ceftazidime, 15 patients experienced reactions to drugs.

Objective To see if by varying the means of administration further courses of treatment with ceftazidime could be tolerated in subjects who had experienced drug reactions.

Methods Starting with a dose of 1 mg per hour, and doubling the dose every hour, ceftazidime was administered at increasing dosage by continuous infusion, reaching a rate of 150–300 mg/kg/day. Thereafter the full daily dose was given in three divided bolus doses. For patients who tolerated the maximum infusion rate but reacted adversely to bolus doses, the procedure was restarted, and once the normal daily dose rate had been achieved, treatment was completed by continuous intravenous infusion rather than bolus doses.

Results Of the 15 patients, three patients with urticaria and four patients with non-urticarial itchy rash tolerated further courses of ceftazidime without adverse reactions, and two patients have not had further treatment with intravenous antibiotics. The increasing dose regimen was tolerated in five of the remaining six patients, and further courses of treatment were tolerated in the four patients in whom this was required. One patient had recurrent urticaria despite three attempts at using the regimen, and treatment was given with alternative antibiotics.

Conclusion A continuous drug infusion regimen of starting at a very low dosage and then increasing the dosage offers the potential for further treatment in some children with cystic fibrosis with adverse reactions to ceftazidime.

Keywords: ceftazidime, drug reaction, urticaria, desensitization, cystic fibrosis

Clinical and Experimental Allergy, Vol. 25, pp. 1211–1217. Submitted 25 October 1994; revised 10 February 1995; accepted 28 April 1995.

Introduction

Ceftazidime has good activity against *Pseudomonas aeruginosa* and a low incidence of adverse reactions [1–4], and is commonly used in the management of *Pseudomonas aeruginosa* respiratory tract infections in cystic fibrosis. Alternative antibiotics are available but are not without drawbacks. Aminoglycosides carry the potential for ototoxicity and nephrotoxicity and consequently there is a need to measure serum concentrations

and make dosage adjustments during treatment. There is a high reported incidence of hypersensitivity type reactions to piperacillin [5,6]. Imipenem is associated with the development of resistance, the risk of central nervous system toxicity and nephrotoxicity with the imipenem and cilastatin combination [7]. Ticarcillin in combination with clavulanic acid (to protect against betalactam ring destruction) requires the latter to penetrate tissues effectively in order to confer antibiotic protection. Ciprofloxacin is not recommended in children and adolescents due to concerns with arthropathy in weight bearing joints, and the rapid development of resistance is a further drawback.

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Hypersensitivity type reactions have been reported in 0.5–2.7% of patients in clinical trials assessing the safety profile of ceftazidime [8–11] and in 3.5–13% of patients with cystic fibrosis treated with ceftazidime [5,12–14]. The purpose of this report is to document reactions to ceftazidime in cystic fibrosis and to report our experience of an increasing dose regimen by which subsequent treatment can be tolerated.

Subjects and methods

Of 149 patients with cystic fibrosis attending the cystic fibrosis clinic at Booth Hall Children's Hospital in 1993, 87 had received one or more courses of intravenous antibiotics between 1981 and 1993 at this hospital, and we studied these 87 patients. Patients who received intravenous antibiotic therapy at other hospitals (e.g. their local district general hospital) were not studied. Children colonized with *Pseudomonas aeruginosa* were routinely treated with 14 day courses of anti-pseudomonas antibiotics every 3 months. The antibiotic chosen was ceftazidime (150 mg or 300 mg/kg body weight/24 h in three divided doses given intravenously over 10–20 min, unless antimicrobial sensitivity indicated the organism was resistant to ceftazidime. We used the higher dose when the organism was intermediate in sensitivity or the lung disease was unusually severe. (It should be noted that the manufacturers recommended maximum daily dose is 150 mg/kg/day in three divided doses). All patients received long-term oral flucloxacillin as prophylaxis against *Staphylococcus aureus* infections, and no patient reported reactions to flucloxacillin.

Reactions were defined as an urticarial rash, a non-urticarial but itchy skin rash, stridor, wheeze, angioedema, vomiting and anaphylaxis. These signs and symptoms were accepted as drug reactions if they occurred within 60 min administration of the antibiotic. Skin-prick testing, intradermal testing or radioallergosorbent assay (RAST) testing were not performed.

The increasing dosage regimen was attempted in patients who had reactions to ceftazidime but who required further courses of treatment with intravenous antibiotics. Premedication or concomitant treatment with antihistamines, bronchodilators or corticosteroids was avoided for fear of masking early warning of an anaphylactic reaction. The procedure was as follows. Ceftazidime was started as an intravenous infusion at 1 mg/h. The dose was doubled every hour until an infusion rate of 6 mg/kg/h (equivalent to 150 mg/kg/24 h 'low dose') or 12.5 mg/kg/h (equivalent to 300 mg/kg/24 h 'high dose') was tolerated. Thereafter, the full daily dose (150 mg/kg body weight) was given in three divided doses. The increasing dose procedure was

continued if cutaneous reactions occurred which were not distressing for the child (e.g. rash with mild itching). Ceftazidime infusion was stopped if cutaneous reactions were distressing or if non-cutaneous reactions (e.g. wheezing) occurred. The increasing dose infusion was recommenced at 1 mg/h as soon as these reactions subsided. Patients who tolerated the maximum infusion rate but who then reacted to subsequent bolus doses received the increasing dose regimen again and were then treated with a continuous infusion of ceftazidime to complete the 14 day course.

Results

Between 1981 to 1993, 87 patients with cystic fibrosis were treated with 1092 courses of 10 intravenous antibiotics (Table 1). Fifty-four patients were treated with ceftazidime alone. The remaining 33 patients were treated with other antibiotics in addition to ceftazidime. Ceftazidime was administered alone in 763 of the 859 courses but in combination with tobramycin in 94 courses, meropenem in one course and timentin (combination of ticarcillin and clavulanic acid) in one course.

Reactions to intravenous antibiotics were observed in 16 of the 87 patients (18%). One patient had a red itchy rash on the 10th day of her first course of imipenem. The rash resolved spontaneously within 24 hours. The patient tolerated another course of imipenem without any adverse effects. She had previously received 21 courses of ceftazidime (combined with tobramycin in five courses). The remaining 15 patients had reactions to ceftazidime during 19 of the 859 courses. Only one patient had a reaction (itchy rash, cough, vomiting) after the first dose of his first course of ceftazidime.

Table 1. Intravenous antibiotics used to treat 87 patients with cystic fibrosis

Antibiotic	Number of patients treated	Number of courses
Ceftazidime	87	859
Tobramycin	27	138
Meropenem	17	59
Timentin	6	17
Aztreonam	5	11
Imipenem	3	4
Carbenicillin	1	1
Lincomycin	1	1
Augmentin	1	1
Chloramphenicol	1	1

Table 2. Details of drug reactions in seven patients who tolerated further courses of ceftazidime and two patients who have not had further treatment

Patient	Course (dose)	Drug reaction	Further courses
G.F.	6th (27th)	Itchy rash	2
S.O.	4th (27th)	Itchy rash	10
S.S.	16th (10th)	Itchy rash	4
V.N.	18th (each dose)	Itchy rash	12
D.R.	2nd (28th)	Urticaria	3
P.K.	1st (25th), 2nd (24th)	Urticaria	1
C.S.	5th (20th), 20th (38th)	Urticaria, angioedema	6
N.L.	1st (1st)	Itchy rash, cough, vomiting	0
S.F.	24th (3rd)	Itchy rash	0

The remaining patients had between two and 28 doses (median 17) of ceftazidime before developing drug reactions during 1–24 courses (median 8). Seven patients (three patients with urticaria and four patients with non-urticarial itchy rash) tolerated further courses of ceftazidime without adverse reactions (Table 2). One patient with an itchy rash and another patient with an itchy rash, cough and vomiting, did not have further treatment. We attempted the increasing dose regimen in the remaining six patients (Table 3).

Five of the six patients were successfully treated with the increasing dose regimen and four were subsequently treated with 14 day courses of ceftazidime. Two patients (cases 1 and 2) tolerated bolus doses following the increasing dose regimen, but case 2 had mild transient urticaria during the fourth post-increasing dose regimen course, when the dose of ceftazidime was increased from 150 mg/kg/day to 300 mg/kg/day). However, he tolerated another four further courses of ceftazidime at the lower dose (150 mg/kg/day). Two patients (cases 4 and 5) required treatment with continuous infusion of ceftazidime as they tolerated the increasing dose regimen but reacted adversely to subsequent bolus doses. Continuous infusion is not within the data sheet recommendations but has been shown to achieve high serum concentrations of ceftazidime [15]. Patient 5 developed an itchy rash and itchy red eyes in the fourth hour of the first desensitization attempt and the procedure was discontinued. He tolerated bolus doses after the second increasing dosage procedure but reacted to the full infusion rate during the third attempt to administer the increasing dose regimen. After the fourth increasing dose procedure, he tolerated ceftazidime infusion but reacted to bolus doses and was therefore treated with continuous infusion for 14 days. Patient 6 had recurrent urticaria despite three attempts with the increasing dose regimen.

The urticaria did not improve with chlorpheniramine, terfenadine or prednisolone and treatment with ceftazidime was abandoned. However, no serious reactions occurred during the increasing dose regimen in any of our patients.

Discussion

The retrospective nature of the study and the lack of data on the possible immunological mechanisms are drawbacks to this retrospective clinical study. Accordingly the terms hypersensitivity and desensitization have been avoided when referring to the drug reactions we observed and the procedure we employed.

In this study, some adverse events may not have been reported or documented. However, it is unlikely that drug reactions to subsequent exposure would be missed. Conversely, signs and symptoms may have been incorrectly believed to be drug reactions. This probably explains why seven of the 15 patients with reactions to ceftazidime tolerated further courses of ceftazidime without adverse reactions. When these patients are excluded, the incidence of reactions to ceftazidime in our patients (9%) is comparable to that found in previous studies (range 3.5–13%) [5,12–14].

The only patient who had a drug reaction to imipenem did so with the first dose. This was possibly due to cross-reacting antibodies to previously administered courses of ceftazidime. However, no patient reacted to more than one antibiotic. Koch *et al.* [5] also found that cross-reactivity was not a common problem in 121 patients with cystic fibrosis despite repeated courses with various antibiotics. They observed that the risk of hypersensitivity type reactions to a given β -lactam agent increased with the number of courses given. In addition, Moss *et al.* [16] found that antibiotic sensitisation in patients with cystic

Table 3. Clinical details of the six patients in whom increasing dose regimen was attempted

Case	Age (years)	Course (dose) when drug reaction observed	Type of drug reaction observed	Increasing dose regimen		
				No. of attempt	Outcome	Further courses
1. L.M.	13.5	11th (2nd)	Itchy rash, red itchy eyes	1	Tolerated bolus doses and completed 14 days treatment	Three courses as bolus doses
2. D.C.	8.0	2nd (26th) 3rd (21st)	Urticaria Urticaria, wheeze, tachycardia vomiting	1	Tolerated bolus doses and completed 14 days treatment	Eight courses; three as bolus doses without problem. One episode of transient (lasting 12 h) urticaria during 4th course, when dose increased from 150 to 300 mg/kg day. Further four courses given as bolus doses at 150 mg/kg day. No further courses of treatment required
3. T.H.	3.3	4th (4th)	Urticaria	1	Tolerated increasing dose by continuous infusion procedure but cutaneous reaction to bolus doses on third day. Procedure re-started, and continued for rest of 14 day course as continuous infusion	Three courses, given as continuous infusion
4. T.B.	8.0	18th (17th)	Urticaria	1	Cutaneous reaction to bolus doses on seventh day. Course not completed.	Three courses, given as continuous infusion
				2	Tolerated increasing dose by continuous infusion procedure but cutaneous reaction to bolus doses. Course completed as continuous infusion.	
5. S.A.	5.5	15th (6th) 16th (6th)	Itchy rash Itchy rash, angioedema	1	Cutaneous reaction in 4th h of infusion. Infusion stopped.	Three courses, given as continuous infusion
				2	Cutaneous reaction in 2nd h of infusion but resolved spontaneously. Tolerated bolus doses and completed 14 day course.	
				3	Cutaneous reaction to full infusion rate. Infusion stopped.	
				4	Tolerated desensitisation procedure but cutaneous reaction to bolus doses. Course completed as continuous infusion.	
6. M.K.	11.5	15th (7th)	Urticaria	1	Cutaneous reaction to bolus doses. Course not completed.	No further courses of cefazidime, because of failure of increasing dose regimen
				2	Cutaneous reaction to bolus doses. Course not completed.	
				3	Cutaneous reaction to bolus doses. Course not completed.	

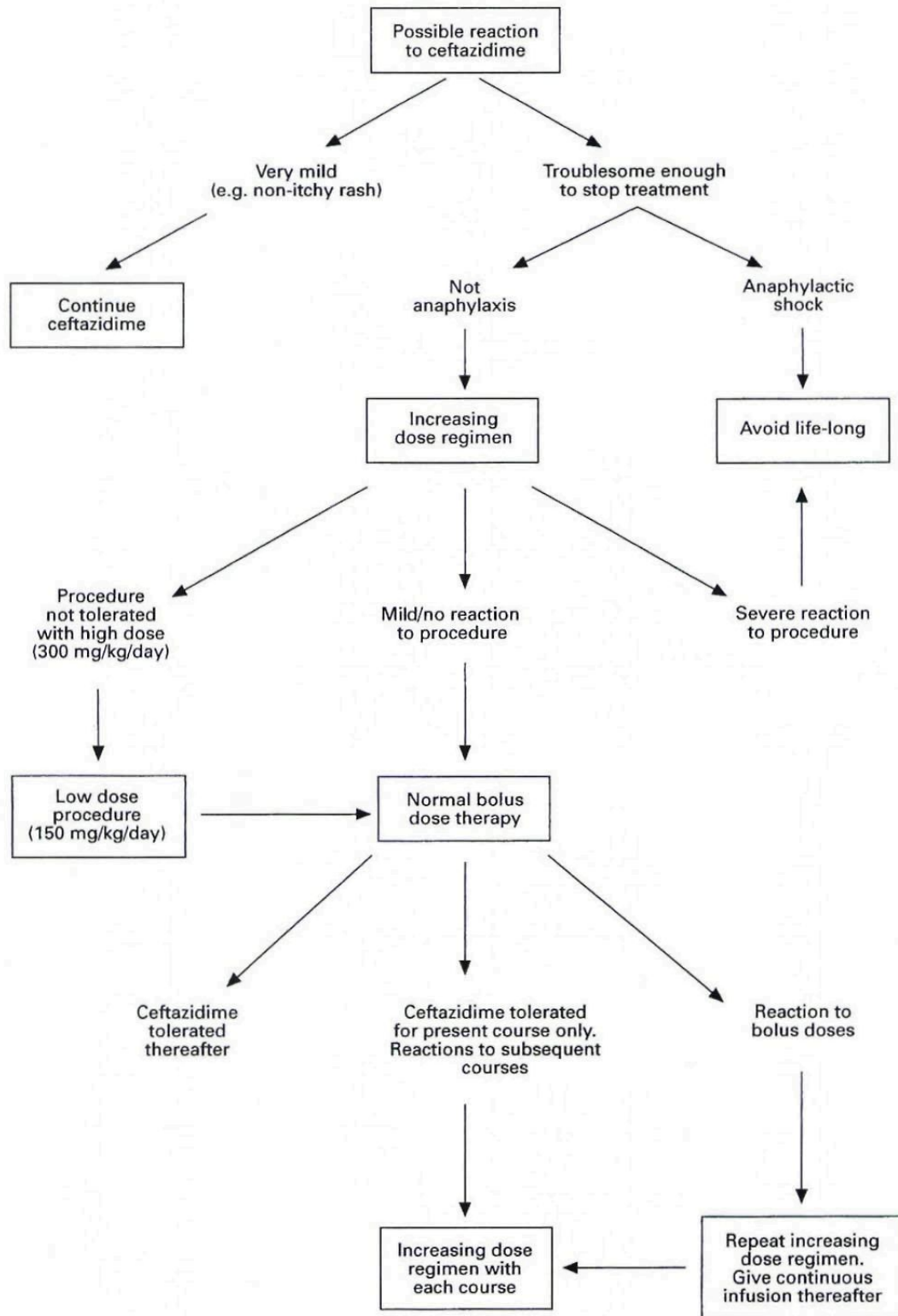


Fig. 1. Flow chart to show the management and increasing dosage procedure in children with drug reactions to ceftazidime.

fibrosis resulted from IgE antibodies directed to drug-specific determinants (perhaps side-chain derived) on β -lactam antibiotic molecules. None of our patients were allergic to flucloxacillin, another β -lactam antibiotic.

Drug reactions to ceftazidime were not life-threatening and the increasing dose regimen allowed further treatment in five of our patients. However, patient 6 did not tolerate ceftazidime despite repeated attempts at the increasing dosage regimen. The only previous report of this approach to ceftazidime drug reaction was in a patient with cystic fibrosis [17]. However, a similar regimen has been attempted in patients with cystic fibrosis with hypersensitivity type reactions to piperacillin [18,19], carbenicillin [20], ticarcillin [18–20] and tobramycin [21]. All used different increasing dosage procedures with oral, intramuscular or intravenous antibiotics. The oral procedure is safe but is not applicable to ceftazidime as it is only available as a parenteral preparation. However, the intravenous procedure has the advantages that the antibiotic can be diluted to allow accurate administration of small quantities, the infusion can be stopped at the first sign of a reaction, and the dose at which the reaction occurs is known.

Figure 1 shows our proposed plan of management in patients with drug reactions to ceftazidime. Clearly the increasing dose regimen must carry a risk of a serious hypersensitivity type reaction [18,21], and the procedure would only be undertaken in hospital with facilities for resuscitation. We avoided antihistamines, glucocorticosteroids and bronchodilators for fear of masking early signs of hypersensitivity type reactions [21–23]. We would not attempt the increasing dosage procedure in a patient with a history of a life-threatening or anaphylactic reaction to ceftazidime. Selective loss of skin-test responsiveness during increasing dosage regimens but rapid return to positive after antibiotic treatment is discontinued suggests that the effect of such regimens is temporary [22,24] and this is consistent with the need for the regimen to be repeated with each course of ceftazidime in two of our patients.

Tolerance can be maintained with an oral agent containing the specific antigen to which the increasing dose procedure was performed [19,20,24]. More investigations are required to determine the specific antigen involved in reactions to ceftazidime and to understand the immunological mechanisms involved in the increasing dosage regimen before a suitable oral agent can be tested. However, despite the lack of an oral agent to maintain tolerance, two of our patients, who had been treated with the increasing dosage regimen, have been treated subsequently with regular courses of ceftazidime without the need for repeat increasing dose procedures.

Acknowledgement

We wish to thank Dr B. M. Phillips for allowing us to study her patients.

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