REVIEW ARTICLE

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Systematic Review of Piperacillin-Induced Neutropenia

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Abstract

Because penicillin agents are implicated in granulopoiesis inhibition, healthcare professionals frequently consider discontinuation of such therapy in patients with decreasing white blood cell counts. No systematic review to date has described piperacillin and the patient population at risk for this adverse drug reaction (ADR).

This review sought to assess the occurrence of piperacillin-induced neutropenia, describe characteristics of affected patients and assess the reporting modalities that most accurately classify this ADR. Case reports, cohort studies and clinical trials identified by comprehensive searches of PubMed and the US FDA Adverse Event Reporting System (AERS) database were reviewed for patient demographics, duration and dose of piperacillin or piperacillin-tazobactam treatment and the occurrence of neutropenia. Causality assessments were performed.

Six published case reports, three cohort studies, 178 clinical trials and two compilations of phase I–III trials were reviewed. Review of case reports was notable in that the duration of β-lactam therapy prior to the noting of leukopenia always exceeded 15 days. No deaths were recorded in this group. Among 13 816 patients enrolled in non-neutropenic fever studies, the occurrence of piperacillin-induced neutropenia was rare: five patients (0.04%) developed neutropenia; none died. The demographics for this group were poorly documented. Through the AERS database, we identified 366 unique cases of piperacillin or piperacillin-tazobactam-induced haematological abnormalities, including neutropenia (n = 183, 50.0%), leukopenia, (n = 99, 27%), agranulocytosis (n = 58, 15.8%) and others. In 62 cases, patients received between 1 and 14 days of therapy (mean 7.7 + 4.1 days). Overall, there were 82 (22.4%) deaths.

Reports of haematological ADRs among patients receiving piperacillin or piperacillin-tazobactam are rare. Report of neutropenia associated with piperacillin usage prior to 15 days of therapy is a novel finding that requires further evaluation. Current reporting methods poorly characterise patient groups at risk.

Penicillin agents have long been associated with inhibition of granulopoiesis, with individual cases reported as early as 1946.[1,2] Evidence exists for a dose-dependent relationship between the degree of bone marrow suppression and cumulative penicillin agent dose.[1,3,4] Piperacillin, a parenteral, semi-synthetic, extended-spectrum penicillin, should theoretically induce similar reactions, and several reports and a cohort study support this assumption.[5-13] However, the reporting of such reactions has been

sporadic and existing reports inadequately describe the population at risk. Neutropenia has been noted to occur in <1% of cases,[14] but the true incidence is not yet known. Herein, we report the results of an extensive, systematic review and describe characteristics of affected patients. We also assess the reporting modalities that most accurately classify this adverse drug reaction (ADR).

1. Search Methodology

1.1 Investigators

The Research on Adverse Drug events And Reports (RADAR) project is a National Cancer Institute (NCI)-funded collaboration of oncologists, infectious disease specialists, pharmacists, clinical pharmacologists and statisticians affiliated with the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Northwestern Memorial Hospital, Feinberg School of Medicine (Northwestern University), and the Veterans Affairs (VA) Midwest Center for Health Services and Policy Research. Described elsewhere, this pharmacovigilance project focuses on identification and analysis of potentially fatal ADR information obtained from the US FDA, Centers for Disease Control and Prevention (CDC), RADAR collaborators, previously published manuscripts, attorneys, patients, physicians and published clinical trials.[15]

1.2 Data Sources

Case reports and cohort studies were identified using PubMed medical subject heading (MeSH) search terms for 'piperacillin', 'tazobactam' and 'piperacillin-tazobactam combination product'. Each of these terms was combined with the Boolean combiner 'AND' to match with the following outcomes: 'agranulocytosis', 'pancytopenia' and 'neutropenia'.

The original search generating the list of references was completed on 23 February 2005. References cited in these publications were subsequently reviewed. Clinical trials were identified through a PubMed search with the MeSH term 'piperacillin' and limits of clinical trials only. Hence, reported trials in which piperacillin was administered should have been captured.

Only English language manuscripts were reviewed. Full manuscripts were obtained for all publications meeting the inclusion criteria. All manuscripts available as 'abstract only' through PubMed were obtained through the Galter Library at Northwestern University or through inter-library loan.

The FDA Adverse Event Reporting System (AERS) database was searched, targeting the time period of 1998 through the second quarter of 2005 using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms. We concurrently searched the AERS database for adverse events (neutropenia, granulopenia, granulocytopenia, agranulocytosis, leukopenia, lymphocytopenia, lymphopenia, monocytopenia, myelosuppression, leucopenia) plus drug names (Zosyn, piperacillin, tazobactam, Pipracil, Tazosin). We used age, sex and event date to identify and remove possible duplicate reports.

1.3 Event Definition

The following definition was used for neutropenia in case reports and cohort studies: neutropenia, reported event and absolute neutrophil count of ≤500 cells/mm^3. Both criteria were required for inclusion of the event. The report of an ADR during a clinical trial was considered true presence of that event.

1.4 Data Extraction

1.4.1 Case Reports

Case reports were evaluated using a standardised data-extraction instrument. Assessed items included the drug used (piperacillin or piperacillin-tazobactam), the indication for antibacterial treatment, numbers of patients reported, age, sex, race, other concurrent medications, alternate explanations for the reported ADR (e.g. malignancy, chemotherapy administration or previous utilisation of colony stimulating factors indicating a predisposition for neutropenia), duration of treatment with piperacillin (preceding event), history of penicillin allergy, the status of drug rechallenge, serology supporting drug cause of the ADR, management of the ADR and mortality.

1.4.2 Retrospective Cohort Studies

Cohort studies were assessed for all of the aforementioned variables evaluated in the case reports as well as mean cumulative piperacillin dose received prior to ADR diagnosis; funding source of study; status of reviewer blinding; and assessments of whether cases and controls were observed using identical methodology.

1.4.3 Clinical Trials

The clinical trials were evaluated for the type of trial (phase I, phase II, phase III, pharmacokinetic, observational or non-specified clinical), study funding source (industry, government or non-profit), indication for drug, drug used (piperacillin or piperacillin-tazobactam), number of patients, patient demographics, daily dose of piperacillin or piperacillin-tazobactam (g/day) received, days of therapy administered, number of neutropenic events occurring within non-neutropenic fever trials, number of deaths associated with ADRs, whether piperacillin exposure preceded the ADR, serological confirmation of the ADR and alternate explanations for the ADR (presence of malignancy, history of recent chemotherapy receipt or recent colony-stimulating factors use for reasons other than drug-induced neutropenia).

1.4.4 Adverse Event Reporting System Database

The following variables were summarised from cases identified in the AERS database: MedDRA preferred term, patient age and sex, year of report, reporter's occupation, reporter's designation of the role of piperacillin or piperacillin-tazobactam in the ADR (primary suspect, secondary suspect, concomitant medication), indication for antibacterial treatment, patient outcome (hospitalisation, death, other, life threatening, required intervention and long-term disability), source (company representative, health professional, literature, foreign language, study and other), dosage and duration of treatment. Outcomes were not mutually exclusive and multiple outcomes could exist for any patient primarily due to updates to cases received by the FDA. Thus, new outcomes could be added to a case. Complete data were not available for all cases. To examine the overall clinical course of each case, we linked follow-up reports back to the original reports.

1.5 Report Completeness

Reporting methodologies were assessed for ADR case completeness. The existence of data at the patient-level was required for each patient experiencing neutropenia associated with piperacillin. Documentation of baseline patient variables typically obtained during a history and physical (drug, dose, duration, age and sex), report of appropriate laboratory findings (e.g. absolute neutrophil count) and presence of serologically confirmed diagnoses were assessed. All data were evaluated as dichotomous variables.

1.6 Data Analysis and Statistical Evaluation

Descriptive statistics reported include number, mean, standard deviation and the domain for ordinal

Table I. Case reports of piperacillin-induced neutropenia[a]

Drug	Primary indication	No. of patients	Age	Sex	Race	Other medications	Duration of treatment (days)	Neutropenia (n)	Rechallenged Y/N (if Y was rechallenge definitive Y/N)	Time to return of labs to normal (days)	Serology (n)	Management	Died (n)	Reference
Pip-tazo	Osteomyelitis	1	54	F	NR	Ceftazidime, amikacin	28 + 12 on ceftazidime	1[b]	N	NR	0	d/c agent	0	5
Pip-tazo	Osteomyelitis	1	29	M	NR	Cefazolin, ciprofloxacin, gentamicin	18 + 7 on nafcillin + 10 on cefazolin. Total of 28 on β-lactam	1	N	5	0	d/c agent	0	6
Pip	Pneumonia	1	39	M	White	Cefazolin, mezlocillin, tobramycin	7 + 22 on mezlocillin + 10 on cefazolin	1	N[c]	5	0	d/c agent	0	7
Pip-tazo	Abscess	1	19	M	NR	Amikacin	21	1[b]	N	6	0	d/c agent	0	8
Pip	Cystic fibrosis	1	3	F	NR	Tobramycin	15	1	N	5	0	d/c agent	0	9
Pip-tazo	Abscess	1	18	F	NR	0	17	1	N	2	1, IgG to pip	d/c agent	0	10
Pip	Osteomyelitis	1	46	M	NR	Nafcillin, tobramycin	24 + 28 on nafcillin	1	N[c]	4, 2	0	d/c agent	0	11
Pip-tazo	Pneumonia	1	50	M	NR	Azithromycin, streptokinase	20	1	N	4	0	d/c agent	0	13

a None of the cases stated another explanation for the event, such as cancer, chemotherapy or growth factor administration within 6 months of the event. In addition, none of the patients reported a history of pip allergy.

b ANC did not meet our definition of ≤500 cells/mm^3.

c Rechallenge occurred with piperacillin after mezlocillin[7] and naficillin[11]

ANC = absolute neutrophil count; **d/c** = discontinued; **IgG** = immunoglobin G; **n** = number; **N** = no; **NR** = not recorded; **pip** = piperacillin; **tazo** = tazobactam; **Y** = yes.

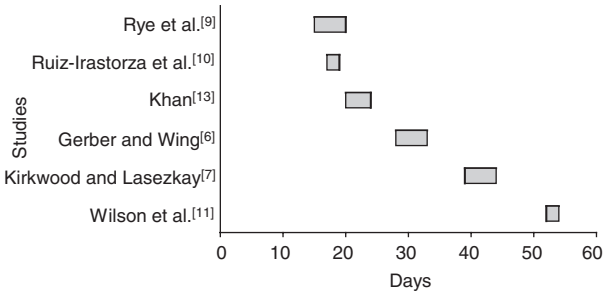

Fig. 1. Time to the development and resolution of neutropenia (shading represents time with abnormal laboratory values). Lag time (from therapy to neutropenia) is days on β-lactam until shaded period begins.

measures and number and percent for categorical measures.

2. Results

Our search identified ten case report publications, four cohort studies, 373 clinical trials, two reviews of phase I–III trials and 468 safety reports in AERS. Following exclusion of cases that did not meet the necessary criteria, this paper will review data from six case reports, three cohort studies, 178 clinical trials, two trial reviews and 366 cases from AERS.

2.1 Case Reports

Among ten identified case reports, six (60%) met the inclusion criteria (two were not available in English[16,17] and two did not meet our definition of neutropenia).[5,8] The remaining cases described three patients with piperacillin-induced neutropenia, and three with piperacillin-tazobactam-induced neutropenia (table I). Of the six cases eligible for inclusion, the mean patient age was 30.8 ± 17.9 years (range 3–50 years). Four cases were male, and race was only reported for one case. Underlying diagnoses included osteomyelitis, pneumonia, cystic fibrosis infection and abscess. Mean length of piperacillin therapy was 16.8 ± 5.7 days (7–24 days) and mean length of combination therapy with β-lactams was 28.5 ± 14.5 days (15–52 days). Neutropenia always occurred after at least 15 days of β-lactam therapy. Normalisation of laboratory parameters was documented for all cases and averaged 3.8 ± 1.5 days (2–5 days) [figure 1]. Two patients diagnosed with neutropenia subsequently received antibacterial re-challenge with recurrence of neutropenia. No patient with drug-induced neutropenia had a cancer diagnosis, had previously received chemotherapy or had received growth hormone. Serological confirmation (immunoglobulin G [IgG] antibody to piperacillin) was available for one patient and no patient died. Each case report included information in each of the assessed categories (history/physical, laboratory and serology).

2.2 Retrospective Cohort Studies

Three cohort studies met the inclusion criteria (table II). Reports were 47%, 100% and 0% complete for history and physical, laboratory documentation, and pathology, respectively.

The most pertinent study reviewed patients treated with piperacillin-tazobactam for bone-related infections.[12] Patients with neutropenia (n = 14) received more piperacillin or piperacillin-tazobactam (330 ± 114.7g vs 237.3 ± 92.9g) for a longer duration (26.8 ± 9.3 days vs 21.2 ± 8.7 days) than those who did not develop neutropenia (n = 27). Among patients who received >10 days of piperacillin or piperacillin-tazobactam, 14 of 41 (34%) developed neutropenia.

Table II. Cohort studies reporting piperacillin-induced neutropenia[a]

Drug	Primary indication	Sex (n, male)	Assessment blinded to reviewer (Y/N) [if N, was it objective (Y/N)]	Outcome	No. of patients	Mean age (y)	Other medications	Mean duration of treatment (days)	Mean cumulative dose (g)	Patients rechallenged	No. with an endpoint who died	Reference
Pip-tazo	Bone infections	19	N, Y	Neutropenic	14	55.2 ± 14.9	Aztreonam (2), cipro (2), aminoglycoside (3), teicoplanin (1)	26.8 ± 9.3	330 ± 114.7	NR	NR	12
				Non-neutropenic	27	66.7 ± 15.8	Aztreonam (1), cipro (1), cotrimox (1)	21.2 ± 8.7	237.3 ± 92.9			12
Pip	Pseudomonas osteomyelitis	NR	N, Y	Neutropenic	0[b]							18
				Non-neutropenic	6	76	Aminoglycosides	NR	259	N	NR	18
Pip-tazo	Cystic fibrosis	NR	N, Y	Neutropenic	0[c]							19
				Non-neutropenic	38	14	Not differentiated between groups	NR	Not differentiated between groups	N	NR	19

a None of the cases stated another explanation for the event, such as cancer, chemotherapy or growth factor administration within 6 months of the event. In addition, no serological tests were performed for these patients and no odds ratio, relative risk estimate or confidence intervals were provided for the reported events. The funding source was not reported for any of these studies and data regarding race were not available. In all studies, cases and controls were measured in the same way and exposure proceeded the adverse event.

b Two patients did not meet the event definition for neutropenia.

c One patient did not meet the event definition for neutropenia.

Cipro = ciprofloxacin; **cotrimox** = cotrimoxazole (trimethoprim-sulfamethoxazole); **n** = number; **N** = no; **NR** = not recorded; **pip** = piperacillin; **smx** = sulfamethoxazole; **tazo** = tazobactam; **tmp** = trimethoprim; **Y** = yes.

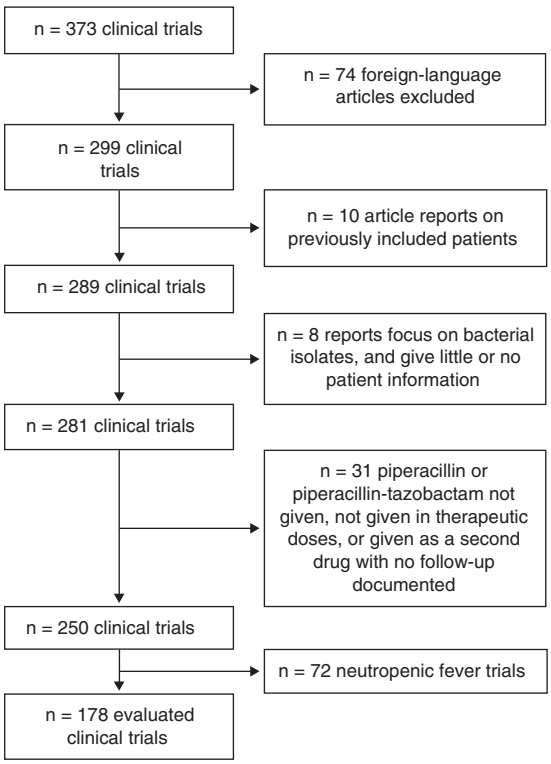

Fig. 2. Clinical trial studies – identification, exclusion and inclusion.

Another cohort study reviewed patients with *Pseudomonas* osteomyelitis who were treated with piperacillin.[18] Six patients received 12–16g of piperacillin daily (mean 15 g/day), and two experienced decreases in white blood cell counts (2300 and 2900 cells/mL, respectively) without becoming overtly neutropenic.

Finally, a cohort study of 38 paediatric patients with cystic fibrosis utilised piperacillin-induced fever to dichotomize cases into children with febrile and afebrile reactions.[19] The authors noted decreases in plasma leucocytes and thrombocytes in three patients but did not characterise differences between the groups because of limited enrolment.

2.3 Clinical Trials

The initial literature search identified 373 clinical trials. Seventy-four non-English language articles were excluded and 49 additional articles were excluded because either piperacillin or piperacillin-tazobactam was not the principal study antibacterial, the focus was not on human subjects, or required information was missing (figure 2). An additional 72 studies evaluated neutropenic fever and hence were excluded. Evaluated studies (n = 178) were funded by government (n = 5), industry (n = 72) or non-profit organisations (n = 19). The funding source was not apparent for 85 studies. Overlap existed for three of these studies funded by both the government and industry.

The most common indications for piperacillin or piperacillin-tazobactam treatment in these clinical trials were for antimicrobial prophylaxis (n = 43, 24%), intra-abdominal infections (n = 29, 16%) and pharmacokinetic/pharmacodynamic analyses (n = 23, 13%), which together accounted for over half of all piperacillin or piperacillin-tazobactam use.

The evaluated trials included data from 13 816 patients who received piperacillin as a study agent. Among patients enrolled in non-neutropenic fever trials, five patients developed neutropenia (0.04%). For cases of piperacillin-induced neutropenia, completeness was 0% for all categories (history and physical, laboratory and serology). Death was not noted to occur among patients with neutropenia who had received a dose of piperacillin or piperacillin-tazobactam.

2.4 Review Articles

Early compilations of phase I and phase III clinical studies evaluating therapy with piperacillin failed to document significant associated rates of granulopoiesis inhibition or reductions in erythrocytes and megakaryocytes.[20] A total of 474 patients in phase I trials received piperacillin, tazobactam or a combination of both drugs, and only one patient was found to have neutropenia.[20] Furthermore, it is unclear if this was a drug-related event. Phase III studies included 1111 patients who received piper-

Table III. Drug characteristics of the MedWatch cases from the US FDA Adverse Event Reporting System database[a]

Drug [n (%)]	
Piperacillin-tazobactam	255 (69.7)
Piperacillin	111 (30.3)
Primary suspect	169 (46.2)
Concomitant	147 (40.2)
Secondary suspect	50 (13.7)
Most common dosages in g/day [n (%)][b]	
>16	10 (6.5)
12–16	99 (64.3)
8–12	18 (11.7)
<8	27 (17.5)
Treatment duration (days)[c]	
Minimum	1
Maximum	50
Median	19
Mean	17.7
Standard deviation	9.6

a The search identified a total of 366 cases for 468 individual safety reports.

b Data from 154 cases.

c Data from 165 cases.

acillin or piperacillin-tazobactam in combination with an aminoglycoside. No cases of neutropenia were documented. A review of phase II and phase III studies evaluating the efficacy and safety of piperacillin or piperacillin-tazobactam in 142 bacteremic patients also failed to document adverse hematological events.[21]

2.5 Adverse Event Reporting System Database

We evaluated 468 individual safety reports, including the occurrence of leukopenias NEC (not elsewhere classified) among 366 persons who received piperacillin or piperacillin-tazobactam (details of the characteristics of these reports are summarised in table III, table IV, table V and table VI). Piperacillin-tazobactam was listed as having been received in the majority of cases (69.7%). The drug, alone or in combination with tazobactam, was the primary suspect or secondary suspect in 46.2% and 13.7% of the cases, respectively, for a total of 219 cases (59.8%). The MedDRA preferred terms were neutropenia (50%), leucopoenia (27%), agranulocytosis (15.8%) and febrile neutropenia (7.4%). Patients ranged in age from 1 month to 87 years. Mean duration of therapy, reported in 165 of the cases was 17.7 ± 9.6 days (median 19 days). Dechallenge, reported in 107 cases, was positive among 94 (87.9%) and negative in 13 (12.1%) cases. Rechallenge, reported in eight cases, was positive in six (75%) of the cases.

Death occurred in 82 (22.4%) cases. Piperacillin (n = 11) and piperacillin-tazobactam (n = 12) were

Table IV. Patient characteristics of the MedWatch cases from the US FDA Adverse Event Reporting System database[a]

Adverse event preferred terms [n (%)][b]	
Neutropenia	183 (50.0)
Leukopenia, includes NOS	99 (27)
Agranulocytosis	58 (15.8)
Febrile neutropenia	27 (7.4)
Lymphopenia	8 (2.2)
Myelosuppression	4 (1.1)
Granulocytopenia	2 (0.5)
Age (y)[c]	
Minimum	0.08
Maximum	87.0
Median	53.0
Mean	51.0
Standard deviation	20.8
Sex [n (%)][d]	
Male	204 (55.7)
Female	143 (39.1)
Unknown	19 (5.2)
Outcomes from event [n (%)][e]	
Hospitalisation	157 (43.4)
Death	82 (22.6)
Other	56 (15.4)
Life-threatening	48 (13.3)
Required intervention	17 (4.8)
Long-term disability	1 (0.3)

a The search identified a total of 366 cases for 468 individual safety reports.

b >1 preferred term in eight cases.

c Data from 313 cases.

d Data from 366 cases.

e Data from 362 cases.

NOS = not otherwise specified.

Table V. Characteristics of concomitant medication use and indication for treatment of the MedWatch cases from the US FDA Adverse Event Reporting System database[a]

Concomitant medications reported in >13 cases [n (%)][b]	
Vancomycin	60 (20.0)
Fluconazole	55 (18.3)
Ciprofloxacin	44 (14.7)
Furosemide	39 (13.0)
Omeprazole	29 (9.7)
Metronidazole	27 (9.0)
Morphine	19 (6.3)
Paracetamol (acetaminophen)	18 (6.0)
Prednisone	17 (5.7)
Filgrastim	16 (5.3)
Gentamicin	15 (5.0)
Ranitidine	14 (4.7)
Amikacin	14 (4.7)
Famotidine	15 (5.0)
Indications [n (%)][c,d]	
Osteomyelitis	12 (18.8)
Infection NOS	7 (10.9)
Sepsis	6 (9.3)
Pneumonia	7 (10.9)
Febrile neutropenia	3 (4.7)
Pseudomonas aspiration, urinary tract infection	2 (3.1)

a The search identified a total of 366 cases for 468 individual safety reports.

b Data from 300 cases.

c An additional 34 indications were noted, each in a single report (1.6%). These were: α-haemolytic streptococcal infection; abdominal infection; bacterial infection; cellulitis; colitis ulcerative; C-reactive protein increased; decubitus ulcer; diabetic gangrene; drug use for unknown indication; empyema; endocarditis bacterial; *Escherichia* infection; Gram-negative bacterial infection NOS; injury; lung infection pseudomonal; oral infection; osteomyelitis acute; pancreas infection; periostitis; pneumonia bacterial; pneumonia *Escherichia*; postoperative care; *Pseudomonas* infection; pyrexia; respiratory tract infection; skin ulcer; soft-tissue inflammation; spondylitis; subdiaphragmatic abscess; thrombophlebitis septic; tubo-ovarian abscess; wound infection; and wound infection *Pseudomonas*.

d Data from 64 cases.

NOS = not otherwise specified.

primary or secondary suspects for neutropenia induction in 23 (28%) cases resulting in death. We reviewed concomitant medications for these 23 patients to identify other causes of neutropenia. We found listings for preceding usage of filgrastim for three patients and cancer chemotherapies for three patients, necessitating the exclusion of a total of six patients. Characteristics of the remaining 17 patients where available were age (n = 16, 58.7 ± 19.8 years), sex (n = 16, male = 9), duration of therapy (n = 13, 12.1 ± 9.7 days, range 1–31 days) and dosage (n = 7, 8.9 ± 4.6 g/day, range 2–13.5 g/day).

In 62 patient cases, <15 days of piperacillin-tazobactam had been given. Piperacillin-tazobactam was noted as the primary suspect for induction neutropenia, leucopoenia or agranulocytosis for 32 (51.6%) cases. This subgroup comprised patients who ranged in age from 12 to 87 years (mean 51.6 ± 20.8 years) and had received between 1 and 14 days of therapy (mean 7.7 ± 4.1 days). Concomitant antibacterials, listed for 22 cases, were cephalosporins (n = 16), pencillins (n = 6) and carbapenems (n = 7). Unfortunately, data on treatment durations of these antibacterials were not available. Serious adverse outcomes occurred in 84% of these patients (death n = 18, hospitalisation n = 24, life-threatening reaction n = 10).

3. Discussion

Piperacillin-induced neutropenia is thought to be caused by proliferation arrest of myeloid cells and is usually reversible; however, IgG antibodies directed against penicillins have been found.[10] Cases of β-lactam induced neutropenia have been suggested to most commonly develop after ≥10 days of therapy.[1,18,22] In our review of case reports, all cases of neutropenia associated with piperacillin occurred after ≥15 days of β-lactam treatment.[6,7,9-11,13] However, we identified a significant number of cases (n = 62) from the AERS database where piperacillin had been administered for <15 days. The data from the AERS database do not allow us to definitively conclude that piperacillin can induce neutropenia prior to 15 days of therapy; however, the number of cases that developed despite brief exposure to piper-

Table VI. Report characteristics of the MedWatch cases from US FDA Adverse Event Reporting System database[a]

Occupation of reporter [n (%)][b]	
Pharmacist	44 (41.9)
Physician	37 (35.2)
Other health professional	21 (19.0)
Consumer	3 (2.9)
Source of report [n (%)][c]	
Health professional	249 (89.9)
Foreign	147 (48.7)
Other	90 (32.5)
Study	54 (19.4)
Company representative	25 (9.0)
Literature	17 (6.1)
Consumer	1 (0.4)

a The search identified a total of 366 cases for 468 individual safety reports.

b Data from 105 cases.

c Data from 277 cases, plus >1 source in 189 cases.

acillin suggests that practitioners should consider its role in neutropenia during this time period.

This review highlights difficulties inherent in identifying cases of piperacillin-induced neutropenia in clinical trial settings, where typically shorter courses of therapy are utilised. These scenarios rarely reflect real-world clinical setting treatment practices. Only phase IV clinical studies, ADR-focused research groups such as RADAR, and improved pharmacovigilance (on the part of the FDA) can successfully capture sufficient numbers of ADRs to assist in adequately characterising populations at greatest risk for rare drug-related adverse events, particularly those that typically involve events that are temporally delayed. The AERS data provide additional information regarding the event and deaths associated with the events; however, a notable limitation is the lack of ability to calculate incidence rates due to the nature of passive, voluntary reporting to MedWatch.

This review did not assess the possibility of double reporting (i.e. events were reported both in clinical trials as well as in the AERS data). We do not believe that this would change the conclusion of this review as neutropenia associated with piperacillin was rare, and double reporting would artificially inflate its occurrence. Finally, the lack of a denominator precludes us from calculating incidence rates or directly comparing results to the other sources. A single search engine was used for the review. It is possible that some cases were missed, but reports of piperacillin-induced neutropenia from clinical trials would likely remain rare, regardless of database used.

It has been proposed that piperacillin is more likely than piperacillin-tazobactam to cause bone marrow toxicity due to a larger typical daily dose (16 vs 12g, respectively).[10] Our review did not confirm this although we recognise our findings are limited by the rarity of the event and its underreporting. The AERS data indicated more events associated with piperacillin-tazobactam, but this may reflect greater recent utilisation of the tazobactam-containing product, which improves the overall effectiveness of the drug. Indeed, the retrospective nature of the study constitutes an intrinsic limitation and potential reporting bias. It is possible that clinicians might have recognised piperacillin-induced neutropenia but were unwilling to report it secondary to eventual favourable clinical outcomes consequent to the use of the drug, the supposition that this is a well known adverse effect, time constraints or temperamental disinclination.

We found that deaths were reported in 22.4% of MedWatch cases, much higher than in case reports or clinical trials. This may reflect the serious nature of the adverse outcomes, prompting reports to the FDA. After eliminating those reports listed as piperacillin or piperacillin-tazobactam as concomitant medication, 23 deaths remained (6.3% of cases). This finding may be reflective of the seriousness of the conditions in which the drug is prescribed. It has been estimated that, due to the voluntary, passive surveillance design of the MedWatch system, <10% of adverse events are reported to the FDA. The

inability to distinguish rare from under-reported events underscores the need for mandatory postmarketing surveillance.

4. Conclusion

Piperacillin-induced neutropenia is a rare event that is generally reversible when occurring in the setting of a clinical trial. MedWatch reports suggest that more serious adverse outcomes occur in other non-clinical trial settings. Therefore, it is important that prospective long-term studies with active surveillance are undertaken to better delineate these relationships.

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