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Pancreatitis in tigecycline Phase 3 and 4 clinical studies

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Objectives: To examine the incidence of pancreatitis among subjects enrolled in the tigecycline clinical trial programme, summarize cases and examine concomitant use of other pancreatitis-causing medications.

Methods: Subject data from Phase 3 and 4 comparative tigecycline studies were included in the analysis; investigator-reported adverse events of 'pancreatitis', 'necrotizing pancreatitis' or 'pancreas disorder' were reviewed. Data were summarized and cases were reported. No statistical comparisons were made. The incidence of overall pancreatitis with 95% CIs was calculated. The Wilson score method was used to calculate CIs.

Results: Nineteen subjects with investigator-determined pancreatitis were identified from the programme database, which included 3788 subjects treated with tigecycline and 3646 subjects treated with a comparator. There were 9 cases identified among the tigecycline-treated subjects [9 of 3788 (0.24%; 95% CI, 0.11–0.45)] and 10 cases among the comparator-treated subjects [10 of 3646 (0.27%; 95% CI, 0.13–0.50)]. The demographic characteristics of the subjects with pancreatitis were similar between treatment groups. The median duration of tigecycline therapy was 8.0 days compared with 11.0 days of comparator treatment. Concomitant or prior exposure to a Badalov class I medication was evident in the majority of subjects who developed pancreatitis. A numerically higher number of tigecycline-treated subjects were exposed to furosemide prior to the onset of pancreatitis than comparator-treated subjects.

Conclusions: Pancreatitis was uncommon in subjects treated with tigecycline, with an occurrence of <1%. Concomitant medications known to cause pancreatitis should be considered when prescribing tigecycline, but may not identify those at risk of developing pancreatitis.

Keywords: adverse events, glycylcycline, furosemide

Introduction

Pancreatitis is a serious and potentially fatal disease with diverse aetiology, including medications. Pancreatitis is a recognized, but uncommon, side effect of orally administered tetracycline.[1] The exact mechanism of tetracycline-induced pancreatitis is not known.

Tigecycline is a glycylcycline antibiotic and an analogue of the semi-synthetic tetracycline, minocycline. Cases of pancreatitis in patients receiving tigecycline have been reported.[2–9] In several of these cases, concomitant or prior exposure to another drug (e.g. acetaminophen,[3,6] omeprazole[8] and propofol[4]) with a known association with drug-induced pancreatitis was evident from the case report descriptions. We conducted this study to examine the incidence of pancreatitis among subjects enrolled in the tigecycline clinical trial programme, in the context of predisposing conditions and use of other medications associated with pancreatitis.

Methods

Subject data from 13 Phase 3 and 4 comparative tigecycline studies were included in the analysis. The tigecycline dose was a 100 mg loading dose followed by 50 mg every 12 h, administered by intravenous infusion over 30–60 min except for the diabetic foot infection trial that tested a dose of 150 mg every 24 h. The population for the analysis included subjects in the modified intent-to-treat population who received at least one dose of tigecycline or comparator (vancomycin, imipenem/cilastatin, ceftriaxone and metronidazole, levofloxacin, ertapenem, linezolid, aztreonam, ampicillin/sulbactam and amoxicillin/clavulanate). Three of the comparator drugs were included in the original Badalov class designation: metronidazole (class Ia), ceftriaxone (class III) and ampicillin (class IV).[10] Investigator-reported adverse events of 'pancreatitis', 'necrotizing pancreatitis' or 'pancreas disorder' were reviewed and subject cases were summarized. Demography was described and risk factors, including medical history, procedures and concomitant medications known to cause pancreatitis using the Badalov classification,[10] were

Table 1. Summary of pancreatitis cases

Test drug	Subject characteristics (clinically relevant history/procedures[a])	Day of onset[b]	Outcome/complications	Severity	Non-study class I–II medications prior to pancreatitis (class)[c]; time period of exposure relative to test drug	Investigator-determined relationship
Tigecycline[d]	76 yo, F: intra-abdominal abscess (ERCP day 1)	7	resolved	severe	oestrogen (Ib); P acetaminophen (II); P, C, A	possibly related
	69 yo, M: complicated cholecystitis	2 (necrotizing pancreatitis)	death day 3 from MODS	life-threatening	furosemide (Ia); C, A	probably not related
	31 yo, M: peritonitis/large bowel perforation	13	resolved	moderate	furosemide (Ia); A acetaminophen (II); C, A	probably not related
	48 yo, F: complicated appendicitis	3	NR	moderate	metronidazole (Ia); P	probably related
	73 yo, M: MRSA primary bacteraemia[e]	13	persisted; candidaemia/sepsis day 30; death day 35	moderate	furosemide (Ia); P, C acetaminophen (II); P, C	probably not related
	69 yo, M: CABP	9	resolved	moderate	furosemide (Ia); P, C, A	probably not related
	50 yo, M: HAP	20	resolved; necrotizing pancreatitis at enrolment; surgical drainage of the post-necrotic cyst on day 26; drainage of abdominal cavity and sequestrectomy on day 47	moderate	metronidazole (Ia); P furosemide (Ia); C	definitely not related
	63 yo, M: HAP	5	resolved	mild	furosemide (Ia); P, C omeprazole (Ib); P	probably related
	70 yo, F: HAP (gastric ventricular resection, Billroth II and splenectomy on day 2)	6	persisted; *Pseudomonas/Serratia* pneumonia with *Pseudomonas* bacteraemia day 8; septic shock/death day 9	life-threatening	enalapril (Ia); P, C furosemide (Ia); P, C amiodarone (Ib); P, C propofol (II); P, C	probably not related
Imipenem	42 yo, M: peritonitis; small bowel perforation (Roux-en-Y anastomosis on day 1)	5	resolved	moderate	omeprazole (Ib); P	probably not related
	35 yo, M: post-traumatic peritonitis	5 (post-traumatic pancreatitis)	resolved	moderate	none	probably not related
	78 yo, M: HAP	8	resolved; necrotic bowel and surgery day 13; pneumonia and bacteraemia day 14; septic shock/death day 15	life-threatening	enalapril (Ia); P, C furosemide (Ia); P, C, A metronidazole (Ia); P propofol (II); P, C	definitely not related
	40 yo, M: HAP	13	persisted	mild	acetaminophen (II); P, C, A propofol (II); P	probably not related
	44 yo, M: HAP (necrotizing pancreatitis at enrolment)	26 (chronic pancreatitis)	persisted	mild	metronidazole (Ia); P furosemide (Ia); P omeprazole (Ib); P	definitely not related
	57 yo, F: HAP	18 (chronic pancreatitis)	persisted	mild	enalapril (Ia); P, C, A furosemide (Ia); C, A metronidazole (Ia); P	probably not related

Ceftriaxone/ metronidazole	91 yo, F: complicated diverticulitis	16	resolved; haematemesis day 15; aspiration pneumonia with respiratory failure day 16; CHF day 17; MI and ARF day 18; died in hospice day 35	mild	furosemide (Ia); P, C, A acetaminophen (II); C	probably not related
	34 yo, M: complicated diverticulitis	3	resolved	mild	metronidazole (Ia); P, C acetaminophen (II); P	probably not related
Vancomycin	44 yo, F: cSSSI (history of chronic pancreatitis)	3 (relapse of chronic pancreatitis)	persisted	mild	none	probably not related
	66 yo, M: MRSA perianal abscess[e]	20	resolved	moderate	none	definitely not related

A, after; ARF, acute renal failure; C, concomitant with; CHF, congestive heart failure; cSSSI, complicated skin and skin structure infection; CABP, community-acquired bacterial pneumonia; ERCP, endoscopic retrograde cholangiopancreatogram; F, female; HAP, hospital-acquired pneumonia; M, male; MI, myocardial infarction; MODS, multiple organ dysfunction syndrome; MRSA, methicillin-resistant *Staphylococcus aureus*; NR, not reported; P, prior to; yo, years old.

[a]Relevant clinical information at the time of enrolment, including medical conditions (e.g. cholithiasis) or procedures (e.g. endoscopic retrograde cholangiopancreatography) known to cause or elevate the risk of pancreatitis.

[b]Study day relative to start of therapy.

[c]Excludes medications given after test drug that were started after pancreatitis diagnosis.

[d]All tigecycline subjects who developed pancreatitis received a 100 mg loading dose then 50 mg every 12 h.

[e]Resistant pathogen study.

identified. No statistical comparisons were made. The incidence of overall pancreatitis with 95% CIs, using the Wilson score method, was calculated.

The protocol for each study included in the Phase 3 and 4 study programme was reviewed and approved by an Independent Ethics Committee or Institutional Review Board in accordance with local regulations and good clinical practice. All patients signed an Institutional Review Board- or Independent Ethics Committee-approved informed consent form prior to study participation.

Results

Nineteen subjects with investigator-determined pancreatitis were identified from the programme database of comparative studies, which included 3788 subjects treated with tigecycline and 3646 subjects treated with a comparator. Nine cases of pancreatitis were identified among the tigecycline-treated subjects [9 of 3788 (0.24%; 95% CI, 0.11–0.45)] and 10 cases were identified among the comparator-treated subjects [10 of 3646 (0.27%; 95% CI, 0.13–0.50)]. The demographic characteristics (age, sex, race, weight and height) of the subjects with pancreatitis were similar between treatment groups. Most subjects were white (66.7% tigecycline, 80.0% comparator) and male (66.7% tigecycline, 70.0% comparator), with a mean age (standard deviation) over age 50 years [61.0 (14.9) tigecycline, 53.1 (19.4) comparator]. The median duration of tigecycline therapy was 8.0 days compared with 11.0 days of comparator treatment.

A summary of the subject data for each of the cases of pancreatitis is provided in Table 1. Two cases of necrotizing pancreatitis in tigecycline-treated subjects were considered related to a pre-existing episode of necrotizing pancreatitis at the time of enrolment or to an endoscopic retrograde cholangiopancreatogram. Two of nine tigecycline cases of pancreatitis were considered 'probably related' and one was considered 'possibly related' to tigecycline treatment by the investigator; none of the comparator cases was considered 'probably related' or 'possibly related'. No time pattern for onset of pancreatitis could be determined for the tigecycline- or comparator-treated patients, regardless of relationship to treatment, severity or outcome; however, all cases were of intermediate latency (within 1–30 days) as described by Badalov.[10] The three deaths that occurred in the tigecycline treatment group occurred in patients where the pancreatitis was considered 'probably not related' to tigecycline and the deaths were attributed to causes other than the pancreatitis event (sepsis and/or organ failure.) Two deaths were reported in the comparator-treated pancreatitis patients; neither death was considered related to treatment.

Exposure to a Badalov class I–II medication at any time in relation to the test drug (but prior to the pancreatitis) occurred in all 9 (100%) tigecycline-treated subjects with pancreatitis and 7 of 10 (70.0%) comparator-treated subjects with pancreatitis. The time period breakdown of the exposure ('prior to', 'concomitant with' or 'concomitant with, but not prior to' tigecycline or comparator) and the specific class I–II medication exposures are provided in Table 2. More tigecycline-treated subjects (77.8%) were exposed to furosemide at any time prior to the development of pancreatitis than subjects treated with comparator (40.0%).

Exposure to specific medications known to cause pancreatitis and exposure by Badalov class were similar between tigecycline- and comparator-treated subjects. Among subjects exposed to class I–II medications, 9 of 2682 (0.34%) tigecycline and 7 of

Table 2. Subjects receiving pancreatitis-causing non-study medications

	Tigecycline		Comparator	
	pancreatitis ($n=9$), *n* (%)	no pancreatitis ($n=3779$), *n* (%)	pancreatitis ($n=10$), *n* (%)	no pancreatitis ($n=3636$), *n* (%)
Exposure to pancreatitis-causing non-study drugs				
Exposure *prior to* test drug[a]	7 (77.8)	2694 (71.3)	7 (70.0)	2547 (70.0)
class I	7 (77.8)	1453 (38.4)	6 (60.0)	1414 (38.9)
class I–II	7 (77.8)	2002 (53.0)	7 (70.0)	1920 (52.8)
Exposure *concomitant with* test drug[a]	9 (100.0)	2910 (77.0)	7 (70.0)	2823 (77.6)
class I	6 (66.7)	1463 (38.7)	4 (40.0)	1431 (39.4)
class I–II	8 (88.9)	2187 (57.9)	5 (50.0)	2132 (58.6)
Exposure *concomitant with, but not prior to,* test drug[a]	5 (55.6)	1759 (46.5)	5 (50.0)	1686 (46.4)
class I	2 (22.2)	728 (19.3)	1 (10.0)	690 (19.0)
class I–II	3 (33.3)	1188 (31.4)	2 (20.0)	1166 (32.1)
Exposure at *any time* in relation to test drug[a]	9 (100.0)	3290 (87.1)	7 (70.0)	3173 (87.3)
class I	9 (100.0)	1979 (52.4)	6 (60.0)	1890 (52.0)
class I–II	9 (100.0)	2673 (70.7)	7 (70.0)	2586 (71.1)
Specific class I–II medications to which subjects were exposed at any time in relation to test drug[b]				
Class Ia	8 (88.9)	1692 (44.8)	5 (50.0)	1660 (45.7)
enalapril	1 (11.1)	298 (7.9)	2 (20.0)	323 (8.9)
furosemide	7 (77.8)	670 (17.7)	4 (40.0)	680 (18.7)
metronidazole	2 (22.2)	716 (18.9)	4 (40.0)	649 (17.8)
Class Ib	3 (33.3)	678 (17.9)	2 (20.0)	623 (17.1)
amiodarone	1 (11.1)	105 (2.8)	0	108 (3.0)
conjugated oestrogens	1 (11.1)	14 (0.4)	0	12 (0.3)
omeprazole	1 (11.1)	513 (13.6)	2 (20.0)	461 (12.7)
Class II	4 (44.4)	1578 (41.8)	4 (40.0)	1582 (43.5)
acetaminophen	3 (33.3)	1491 (39.5)	3 (30.0)	1495 (41.1)
propofol	1 (11.1)	205 (5.4)	2 (20.0)	198 (5.4)

[a]Includes all classes (I–IV) in the Badalov system.[10] A positive case report with positive rechallenge corresponds to a class I drug (strongest correlation). A class II designation indicates at least four cases with consistent latency reported in the literature. Classes III and IV include medications with fewer case reports and no consistent latency (weaker correlation).
[b]List includes only those class I–II medications present in pancreatitis cases in this analysis.

2593 (0.27%) comparator subjects developed pancreatitis. For those with furosemide exposure, 1.03% of tigecycline and 0.58% of comparator subjects developed pancreatitis. Propofol-exposed subjects developed pancreatitis in 0.49% and 1.00% of tigecycline- and comparator-treated subjects, respectively.

Discussion

Based on clinical trial data, the incidence of pancreatitis associated with tigecycline exposure is uncommon at an incidence rate of 0.24%. Of the nine cases of pancreatitis in subjects treated with tigecycline, however, only one-third were probably or possibly related based on investigator-determined relationship to tigecycline use. Pancreatitis has been identified in pharmacovigilance databases during post-approval use of tigecycline.[9,11,12] Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish causal relationship to drug exposure.

Pancreatic drug injury is often idiosyncratic and mechanistically may represent hypersensitivity or toxic metabolite formation rather than direct toxicity.[10] The mechanism of tigecycline-induced pancreatitis is unknown, but is likely to be similar to that of other tetracyclines. Hypertriglyceridaemia[13] and toxic metabolite formation[14] have been proposed as possible mechanisms that contribute to tetracycline-induced pancreatitis; however, lipid levels were not captured in our subjects and, therefore, correlations with the onset of pancreatitis cannot be made. Alternatively, Gilson *et al*.[2] have hypothesized that high biliary concentrations of tigecycline might play a role in the development of pancreatitis.

Formation of a toxic metabolite seems unlikely in the case of tigecycline. First-pass metabolism does not occur, because tigecycline is administered only intravenously. After administration, it distributes widely in the body, but undergoes limited metabolism. Unchanged drug was the predominant drug-related compound in serum, urine and faeces in a metabolic study of [^{14}C]tigecycline administration to healthy volunteers.[15] The major metabolic pathways identified

were glucuronidation of tigecycline and amide hydrolysis followed by N-acetylation to form *N*-acetyl-9-aminominocycline. The glucuronide metabolites were 5%–20% of serum radioactivity and ~9% of the dose was excreted as glucuronide conjugates within 48 h. Unchanged drug is eliminated in the urine as well as by biliary excretion.

Subjects treated with tigecycline or a comparator had a relatively high rate of exposure to Badalov class I–II medications. Despite extensive exposure to these medications, relatively few individuals developed pancreatitis. Our data identified a possible relationship between pancreatitis and furosemide. Pancreatitis due to furosemide is rarely reported in the literature, but has a strong class Ia designation by Badalov.[10] However, the difference in the development of pancreatitis between tigecycline- and comparator-treated subjects exposed to furosemide is small (Table 2), the mechanism of such a relationship is unclear and the limited number of subjects precludes further analysis.

As it has been previously hypothesized[4] in the case of propofol and tigecycline, either agent could sensitize the pancreas to a possible adverse reaction upon subsequent exposure to the other. In this analysis, exposure to propofol resulted in a small difference in pancreatitis incidence between tigecycline- and comparator-treated subjects (Table 2). Drug interactions that resulted in increased exposure or formation of toxic metabolites of either compound do not appear to be likely in the case of either concomitant tigecycline and furosemide administration or concomitant tigecycline and propofol administration. Neither tigecycline nor furosemide are substrates of cytochrome P450 (CYP450) drug-metabolizing enzymes and neither is shown to alter the activity of CYP450 enzymes.[16] Propofol undergoes metabolism, but, because it is not administered chronically, is unlikely to alter the exposure to tigecycline.[17]

Tigecycline had just become commercially available at the time the Badalov classification was published.[10] Tetracycline is considered class Ia and minocycline is considered class III. Based on the available published reports of pancreatitis associated with tigecycline,[2–8] we suggest that tigecycline would have a class Ib designation as the one paediatric patient with a positive rechallenge had sickle cell anaemia, which can be associated with the development of pancreatitis.[5] In addition, pancreatitis has been described in patients with sickle cell anaemia and should be considered as a differential diagnosis of abdominal pain cause in such patients.[18]

From a clinical perspective, one must also consider whether a past history or baseline pancreatitis (unrelated to tigecycline) should preclude future tigecycline exposure. We suggest that caution should be exercised with close monitoring of the patient when tigecycline is the most appropriate therapy. There are documented instances of the safe use of tigecycline in patients with a history of chronic pancreatitis or an episode of acute pancreatitis,[19,20] including one subject reported here who was enrolled for the treatment of hospital-acquired pneumonia with necrotizing pancreatitis at baseline.

There are limitations that should be acknowledged. Pancreatitis was identified by the investigators as an adverse event among patients included in individual clinical studies and therefore diagnosis criteria were not standardized *a priori*. The data do not permit a determination of cause and effect, and rechallenge was not possible in a clinical trial setting. Finally, the results may not be broadly generalizable to clinical practice, where patients may differ from populations and infections studied in the clinical studies.

In our review of clinical trial data, pancreatitis was uncommon in subjects treated with tigecycline, with an occurrence of <1%. Clinician awareness of this potential adverse effect is necessary. Prior or concurrent history of pancreatitis as well as the use of concomitant medications known to cause pancreatitis should be taken into consideration when prescribing tigecycline, but may not identify those at risk of developing pancreatitis.

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M. W., J. M. K.-B. and A. Q. are employees of Pfizer Inc. P. C. M. is a former employee of Pfizer Inc. All authors own stock in Pfizer Inc.

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References

1 Balani AR, Grendell JH. Drug-induced pancreatitis: incidence, management and prevention. *Drug Saf* 2008; **31**: 823–37.

2 Gilson M, Moachon L, Jeanne L *et al*. Acute pancreatitis related to tigecycline: case report and review of the literature. *Scand J Infect Dis* 2008; **40**: 681–3.

3 Hung WY, Kogelman L, Volpe G *et al*. Tigecycline-induced acute pancreatitis: case report and literature review. *Int J Antimicrob Agents* 2009; **34**: 486–9.

4 Mascarello M, Papa G, Arnez ZM *et al*. Acute necrotizing pancreatitis related to tigecycline. *J Antimicrob Chemother* 2012; **67**: 1296–7.

5 Prot-Labarthe S, Youdaren R, Benkerrou M *et al*. Pediatric acute pancreatitis related to tigecycline. *Pediatr Infect Dis J* 2010; **29**: 890–1.

6 Marshall SR. Tigecycline-induced pancreatitis. *Hosp Pharm* 2009; **44**: 239–41.

7 Lipshitz J, Kruh J, Cheung P *et al*. Tigecycline-induced pancreatitis. *J Clin Gastroenterol* 2009; **43**: 93.

8 Marot JC, Jonckheere S, Munyentwali H *et al*. Tigecycline-induced acute pancreatitis: about two cases and review of the literature. *Acta Clin Belg* 2012; **67**: 229–32.

9 *Tygacil® (Tigecycline) for Injection for Intravenous Use (Prescribing Information)*. Philadelphia, PA: Wyeth Pharmaceuticals Inc., 2013.

10 Badalov N, Baradarian R, Iswara K *et al*. Drug-induced acute pancreatitis: an evidence-based review. *Clin Gastroenterol Hepatol* 2007; **5**: 648–61.

11 Kadoyama K, Sakaeda T, Tamon A *et al*. Adverse event profile of tigecycline: data mining of the public version of the US Food and Drug Administration adverse event reporting system. *Biol Pharm Bull* 2012; **35**: 967–70.

12 Okon E, Engell C, van Manen R *et al*. Tigecycline-related pancreatitis: a review of spontaneous adverse event reports. *Pharmacotherapy* 2013; **33**: 63–8.

13 Elmore MF, Rogge JD. Tetracycline-induced pancreatitis. *Gastroenterology* 1981; **81**: 1134–6.

14 Steinberg WM. Acute drug and toxin induced pancreatitis. *Hosp Pract (Off Ed)* 1985; **20**: 95–102.

15 Hoffmann M, DeMaio W, Jordan RA *et al*. Metabolism, excretion, and pharmacokinetics of [^{14}C]tigecycline, a first-in-class glycylcycline antibiotic, after intravenous infusion to healthy male subjects. *Drug Metab Dispos* 2007; **35**: 1543–53.

16 Hammarlund-Udenaes M, Benet LZ. Furosemide pharmacokinetics and pharmacodynamics in health and disease—an update. *J Pharmacokinet Biopharm* 1989; **17**: 1–46.

17 Horn E, Nesbit SA. Pharmacology and pharmacokinetics of sedatives and analgesics. *Gastrointest Endosc Clin N Am* 2004; **14**: 247–68.

18 Ahmed S, Siddiqui AK, Siddiqui RK *et al*. Acute pancreatitis during sickle cell vaso-occlusive painful crisis. *Am J Hematol* 2003; **73**: 190–3.

19 Di Carlo P, Pantuso G, Cusimano A *et al*. Two cases of monomicrobial intraabdominal abscesses due to KPC-3 *Klebsiella pneumoniae* ST258 clone. *BMC Gastroenterol* 2011; **11**: 103.

20 Shahani L, Khardori N. *Fusobacterium necrophorum* beyond–Lemierres syndrome. *BMJ Case Rep* 2011; doi:10.1136/bcr.07.2011.4527.