

Hypoglycemia Predicts Higher Mortality in CAP

BY KATE JOHNSON

MONTREAL — Patients with hypoglycemia at the time of hospitalization for community-acquired pneumonia have an increased risk of death, compared with patients with normoglycemia, according to a study reported at the World Diabetes Congress.

“Hypoglycemia is an easy-to-measure variable on admission, and should be a

red flag to alert physicians to possible high-risk pneumonia patients,” said John-Michael Gamble, of the University of Alberta (Edmonton).

Because an influx of community-acquired pneumonia (CAP) cases resulting from pandemic influenza A(H1N1) is expected in hospital intensive care units, quick recognition of high-risk factors is particularly important, Mr. Gamble said in an interview.

His prospective study included 956 CAP patients admitted to six Edmonton hospitals between 2000 and 2002, for whom random venous blood glucose tests measured 6.1 mmol/L or lower.

Hypoglycemia was defined as a measurement less than 4.0 mmol/L, and normoglycemia was defined as a measurement between 4.0 mmol/L and 6.1 mmol/L.

The primary outcome of the study

was in-hospital mortality. Secondary outcomes included 30-day and 1-year mortality. The mean age of the patients was 65 years, and 15% resided in nursing homes.

Hypoglycemia was present at hospital admission in 54 patients (6%); among those patients, fewer than half (46%) were previously diagnosed diabetes patients.

The mortality rate was significantly greater at all time points among patients with hypoglycemia at admission, compared with normoglycemic patients, Mr. Gamble reported.

The in-hospital and 30-day mortality rates were both 20% for patients with hypoglycemia at admission, compared with 9% and 10%, respectively, in those with normoglycemia.

Similarly, at 1 year, patients with hypoglycemia at admission had a 35% mortality rate, compared with 25% in those patients with normoglycemia.

In addition to adjusting for age, sex, comorbidities, medication, and nursing home residence, the study adjusted for pneumonia severity index (PSI), smoking status, presence of advance directives, previous pneumococcal vaccine, and direct admission to the ICU. Several additional sensitivity analyses included clinical markers of physiologic stress, exclusion of patients admitted to the ICU, and exclusion of patients with diabetes.

Whether high or low, blood glucose abnormalities in general “may serve as a marker for sicker patients,” commented Dr. Silvio Inzucchi, professor of medicine and clinical director of the section of endocrinology at Yale University, New Haven, Conn. Among nondiabetic patients, blood glucose abnormalities may be “particularly dangerous,” Dr. Inzucchi explained in a separate presentation at the meeting.

Endocrinologists and intensivists are facing a “pendulum swing” regarding inpatient glucose control, Dr. Inzucchi noted, in light of a recent publication suggesting “very surprisingly” that intensive versus conventional control of hyperglycemia is associated with a 15-fold increase in hypoglycemia and significantly higher mortality (27.5% versus 24.9%) (N. Engl. J. Med. 2009;360:1283-97).

As a result, Dr. Inzucchi helped draft the recent American Association of Clinical Endocrinologists and American Diabetes Association Consensus Statement on Inpatient Glycemic Control, which recognizes the potential hypoglycemic risks of intensive control and recommends relaxing target blood glucose levels (Diabetes Care 2009;32:1344-5; Endocr. Pract. 2009;15:353-69).

“Specifically in the case of CAP, we need to look at the risks and benefits of treating admission hypoglycemia,” Mr. Gamble commented.

Mr. Gamble said he had no conflicts of interest. Dr. Inzucchi declared paid lecturing with Novo Nordisk, an advisory board agreement with Medtronic Inc., research sponsored by Eli Lilly Co., and CME program participation in which Sanofi-Aventis was a funding source. ■

TYGACIL® (tigecycline) Brief Summary

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INDICATIONS AND USAGE

TYGACIL is indicated for the treatment of adults with complicated skin and skin structure infections caused by *Escherichia coli*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus agalactiae*, *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Streptococcus pyogenes*, *Enterobacter cloacae*, *Klebsiella pneumoniae*, and *Bacteroides fragilis*.

TYGACIL is indicated for the treatment of adults with complicated intra-abdominal infections caused by *Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella oxytoca*, *Klebsiella pneumoniae*, *Enterococcus faecalis* (vancomycin-susceptible isolates), *Staphylococcus aureus* (methicillin-susceptible and -resistant isolates), *Streptococcus anginosus* grp. (includes *S. anginosus*, *S. intermedius*, and *S. constellatus*), *Bacteroides fragilis*, *Bacteroides thetaiotaomicron*, *Bacteroides uniformis*, *Bacteroides vulgatus*, *Clostridium perfringens*, and *Peptostreptococcus micros*.

TYGACIL is indicated for the treatment of adults with community-acquired pneumonia infections caused by *Streptococcus pneumoniae* (penicillin-susceptible isolates), including cases with concurrent bacteremia, *Haemophilus influenzae* (beta-lactamase negative isolates), and *Legionella pneumophila*.

CONTRAINDICATIONS

TYGACIL is contraindicated for use in patients who have known hypersensitivity to tigecycline.

WARNINGS AND PRECAUTIONS

Anaphylaxis/Anaphylactoid Reactions

Anaphylaxis/anaphylactoid reactions have been reported with nearly all antibacterial agents, including TYGACIL, and may be life-threatening. TYGACIL is structurally similar to tetracycline-class antibiotics and should be administered with caution in patients with known hypersensitivity to tetracycline-class antibiotics.

Hepatic Effects

Increases in total bilirubin concentration, prothrombin time and transaminases have been seen in patients treated with tigecycline. Isolated cases of significant hepatic dysfunction and hepatic failure have been reported in patients being treated with tigecycline. Some of these patients were receiving multiple concomitant medications. Patients who develop abnormal liver function tests during tigecycline therapy should be monitored for evidence of worsening hepatic function and evaluated for risk/benefit of continuing tigecycline therapy. Adverse events may occur after the drug has been discontinued.

Mortality Imbalance and Lower Cure Rates in Ventilator-Associated Pneumonia

A study of patients with hospital acquired pneumonia failed to demonstrate the efficacy of TYGACIL. In this study, patients were randomized to receive TYGACIL (100 mg initially, then 50 mg every 12 hours) or a comparator. In addition, patients were allowed to receive specified adjunctive therapies. The sub-group of patients with ventilator-associated pneumonia who received TYGACIL had lower cure rates (47.9% versus 70.1% for the clinically evaluable population) and greater mortality (25/131 [19.1%] versus 14/122 [11.5%]) than the comparator.

Use During Pregnancy

TYGACIL may cause fetal harm when administered to a pregnant woman. If the patient becomes pregnant while taking tigecycline, the patient should be apprised of the potential hazard to the fetus. Results of animal studies indicate that tigecycline crosses the placenta and is found in fetal tissues. Decreased fetal weights in rats and rabbits (with associated delays in ossification) and fetal loss in rabbits have been observed with tigecycline [see **USE IN SPECIFIC POPULATIONS**].

Tooth Development

The use of TYGACIL during tooth development (last half of pregnancy, infancy, and childhood to the age of 8 years) may cause permanent discoloration of the teeth (yellow-gray-brown). Results of studies in rats with TYGACIL have shown bone discoloration. TYGACIL should not be used during tooth development unless other drugs are not likely to be effective or are contraindicated.

Clostridium difficile Associated Diarrhea

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including TYGACIL, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B which contribute to the development of CDAD. Hypertoxic producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Patients With Intestinal Perforation

Caution should be exercised when considering TYGACIL monotherapy in patients with complicated intra-abdominal infections (cIAI) secondary to clinically apparent intestinal perforation. In cIAI studies (n=1642), 6 patients treated with TYGACIL and 2 patients treated with imipenem/cilastatin presented with intestinal perforations and developed sepsis/septic shock. The 6 patients treated with TYGACIL had higher APACHE II scores (median = 13) versus the 2 patients treated with imipenem/cilastatin (APACHE II scores = 4 and 6). Due to differences in baseline APACHE II scores between treatment groups and small overall numbers, the relationship of this outcome to treatment cannot be established.

Tetracycline-Class Effects

TYGACIL is structurally similar to tetracycline-class antibiotics and may have similar adverse effects. Such effects may include: photosensitivity, pseudotumor cerebri, and anti-anabolic action (which has led to increased BUN, azotemia, acidosis, and hyperphosphatemia). As with tetracyclines, pancreatitis has been reported with the use of TYGACIL.

Superinfection

As with other antibacterial drugs, use of TYGACIL may result in overgrowth of non-susceptible organisms, including fungi. Patients should be carefully monitored during therapy. If superinfection occurs, appropriate measures should be taken.

Development of Drug-Resistant Bacteria

Prescribing TYGACIL in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, 2514 patients were treated with TYGACIL. TYGACIL was discontinued due to adverse reactions in 7% of patients compared to 6% for all comparators. Table 1 shows the incidence of treatment-emergent adverse reactions through test of cure reported in ≥2% of patients in these trials.

Table 1. Incidence (%) of Adverse Reactions Through Test of Cure Reported in ≥2% of Patients Treated in Clinical Studies

Body System Adverse Reactions	TYGACIL (N=2514)	Comparators* (N=2307)
Body as a Whole		
Abdominal pain	6	4
Abscess	3	3
Asthenia	3	2
Headache	6	7
Infection	8	5
Cardiovascular System		
Phlebitis	3	4
Digestive System		
Diarrhea	12	11
Dyspepsia	2	2
Nausea	26	13
Vomiting	18	9
Hemic and Lymphatic System		
Anemia	4	5
Metabolic and Nutritional		
Alkaline Phosphatase Increased	4	3
Amylase Increased	3	2
Bilirubinemia	2	1
BUN Increased	3	1
Heating Abnormal	4	3
Hypoproteinemia	5	3
SGOT Increased ^b	4	5
SGPT Increased ^b	5	5
Nervous System		
Dizziness	3	3
Skin and Appendages		
Rash	3	4

* Vancomycin/Aztreonam, Imipenem/Cilastatin, Levofloxacin, Linezolid.

^b LFT abnormalities in TYGACIL-treated patients were reported more frequently in the post therapy period than those in comparator-treated patients, which occurred more often on therapy.

In Phase 3 double-blind studies that included a comparator and employed a 1:1 randomization, death occurred in 4.7% (107/2274) of patients receiving TYGACIL and 3.8% (85/2264) of patients receiving comparator drugs. In a pooled analysis of these studies, the risk difference of all-cause mortality was 1.0% (95% CI -0.3, 2.2) between TYGACIL and comparator treated patients. No significant differences were observed between treatments by infection type (see Table 2). Generally, deaths represented complications of the underlying disease or progression of disease. A causal relationship to TYGACIL has not been established.

Table 2. Patients with Adverse Events with Outcome of Death by Infection Type

Infection Type	TYGACIL n/N	%	Comparator n/N	%	Risk Difference* % (95%CI)
cSSSI	6/566	1.1	1/550	0.2	0.9 (-0.3, 2.2)
cIAI	24/817	2.9	17/825	2.1	0.9 (-0.8, 2.6)
CAP	12/424	2.8	11/422	2.6	0.2 (-2.3, 2.7)
HAP	65/467	13.9	56/467	12.0	1.9 (-2.6, 6.4)
Non-VAP ^a	40/336	11.9	42/345	12.2	-0.3 (-5.4, 4.9)
VAP ^a	25/131	19.1	14/122	11.5	7.6 (-2.0, 16.9)

CAP = Community-acquired pneumonia; cIAI = Complicated intra-abdominal infections; cSSSI=Complicated skin and skin structure infections; HAP = Hospital-acquired pneumonia; VAP=Ventilator-associated pneumonia.

* The difference between the percentage of patients who died in TYGACIL and comparator treatment groups.

^a These are subgroups of the HAP population.

Note: The Phase 3 Studies include 300 and 305 (cSSSI), 301 and 306 (cIAI), 308 and 313 (CAP), and 311 (HAP).

In comparative clinical studies, infection-related serious adverse events were more frequently reported for subjects treated with TYGACIL (7%) versus comparators (6%). Serious adverse events of sepsis/septic shock were more frequently reported for subjects treated with TYGACIL (2%) versus comparators (1%). Due to baseline differences between treatment groups in this subset of patients, the relationship of this outcome to treatment cannot be established [see **WARNINGS AND PRECAUTIONS**].

The most common treatment-emergent adverse reactions were nausea and vomiting which generally occurred during the first 1 – 2 days of therapy. The majority of cases of nausea and vomiting associated with TYGACIL and comparators were either mild or moderate in severity. In patients treated with TYGACIL, nausea incidence was 26% (17% mild, 8% moderate, 1% severe) and vomiting incidence was 18% (11% mild, 6% moderate, 1% severe). In patients treated for complicated skin and skin structure infections (cSSSI), nausea incidence was 35% for TYGACIL and 9% for vancomycin/aztreonam; vomiting incidence was 20% for TYGACIL and 4% for vancomycin/aztreonam. In patients treated for complicated intra-abdominal infections (cIAI), nausea incidence was 25% for TYGACIL and 21% for imipenem/cilastatin; vomiting incidence was 20% for TYGACIL and 15% for imipenem/cilastatin. In patients treated for community-acquired bacterial pneumonia (CABP), nausea incidence was 24% for TYGACIL and 8% for levofloxacin; vomiting incidence was 16% for TYGACIL and 6% for levofloxacin.

Discontinuation of TYGACIL was most frequently associated with nausea (1%) and vomiting (1%).

For comparators, discontinuation was most frequently associated with nausea (<1%).

The following adverse reactions were reported infrequently (<2%) in patients receiving TYGACIL in clinical studies:

Body as a Whole: injection site inflammation, injection site pain, injection site reaction, septic shock, allergic reaction, chills, injection site edema, injection site phlebitis

Cardiovascular System: thrombophlebitis

Digestive System: anorexia, jaundice, abnormal stools

Metabolic/Nutritional System: increased creatinine, hypocalcemia, hypoglycemia, hyponatremia

Special Senses: taste perversion

Hemic and Lymphatic System: partial thromboplastin time (aPTT), prolonged prothrombin time (PT), eosinophilia, increased international normalized ratio (INR), thrombocytopenia

Skin and Appendages: pruritus

Urogenital System: vaginal moniliasis, vaginitis, leukorrhea

Post-Marketing Experience

The following adverse reactions have been identified during postapproval use of TYGACIL. 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. Anaphylaxis/anaphylactoid reactions, acute pancreatitis, hepatic cholestasis, and jaundice.

DRUG INTERACTIONS

Warfarin

Prothrombin time or other suitable anticoagulation test should be monitored if tigecycline is administered with warfarin [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].

Oral Contraceptives

Concurrent use of antibacterial drugs with oral contraceptives may render oral contraceptives less effective.

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects—Pregnancy Category D [see **WARNINGS AND PRECAUTIONS**].

Tigecycline was not teratogenic in the rat or rabbit. In preclinical safety studies, ¹⁴C-labeled tigecycline crossed the placenta and was found in fetal tissues, including fetal bone structures. The administration of tigecycline was associated with slight reductions in fetal weights and an increased incidence of minor skeletal anomalies (delays in bone ossification) at exposures of 5 times and 1 times the human daily dose based on AUC in rats and rabbits, respectively (28 mcg-hr/mL and 6 mcg-hr/mL at 12 and 4 mg/kg/day). An increased incidence of fetal loss was observed at maternotoxic doses in the rabbits with exposure equivalent to human dose.

There are no adequate and well-controlled studies of tigecycline in pregnant women. TYGACIL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

Results from animal studies using ¹⁴C-labeled tigecycline indicate that tigecycline is excreted readily via the milk of lactating rats. Consistent with the limited oral bioavailability of tigecycline, there is little or no systemic exposure to tigecycline in nursing pups as a result of exposure via maternal milk.

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when TYGACIL is administered to a nursing woman [see **WARNINGS AND PRECAUTIONS**].

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been established. Because of effects on tooth development, use in patients under 8 years of age is not recommended [see **WARNINGS AND PRECAUTIONS**].

Geriatric Use

Of the total number of subjects who received TYGACIL in Phase 3 clinical studies (n=2514), 664 were 65 and over, while 288 were 75 and over. No unexpected overall differences in safety or effectiveness were observed between these subjects and younger subjects, but greater sensitivity to adverse events of some older individuals cannot be ruled out.

No significant difference in tigecycline exposure was observed between healthy elderly subjects and younger subjects following a single 100 mg dose of tigecycline [see **CLINICAL PHARMACOLOGY (12.3)** in full Prescribing Information].

Hepatic Impairment

No dosage adjustment is warranted in patients with mild to moderate hepatic impairment (Child Pugh A and Child Pugh B). In patients with severe hepatic impairment (Child Pugh C), the initial dose of tigecycline should be 100 mg followed by a reduced maintenance dose of 25 mg every 12 hours. Patients with severe hepatic impairment (Child Pugh C) should be treated with caution and monitored for treatment response [see **CLINICAL PHARMACOLOGY (12.3)** and **DOSAGE AND ADMINISTRATION (2.2)** in full Prescribing Information].

OVERDOSAGE

No specific information is available on the treatment of overdose with tigecycline. Intravenous administration of TYGACIL at a single dose of 300 mg over 60 minutes in healthy volunteers resulted in an increased incidence of nausea and vomiting. In single-dose intravenous toxicity studies conducted with tigecycline in mice, the estimated median lethal dose (LD₅₀) was 124 mg/kg in males and 98 mg/kg in females. In rats, the estimated LD₅₀ was 106 mg/kg for both sexes. Tigecycline is not removed in significant quantities by hemodialysis.

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