

Surgery May Improve Intractable Constipation

BY BRUCE JANCIN

FAJARDO, P.R. — Either transabdominal antegrade continence enema or intestinal diversion is an appropriate first-line surgical procedure in children with intractable constipation, according to results of a Massachusetts General Hospital study.

In contrast, primary colonic resection is not a good initial operation for med-

ically refractory constipation. Its failure rate was nearly 80% in this study, Dr. Emily R. Christison-Lagay reported at the annual meeting of the American Pediatric Surgical Association.

“Our current practice is to perform an ACE [antegrade continence enema] procedure in any patient with some evidence of colonic motility and to recommend diversion for those with colonic anergia by early manometry. While the

success rate of ACE is less than that of diversion, it is also associated with fewer complications,” explained Dr. Christison-Lagay of the Boston hospital.

Constipation accounts for up to one-quarter of all pediatric gastroenterology evaluations. Its myriad possible causes include colonic dysmotility, pelvic floor defects, functional disorders of the anorectum, and behavioral disorders.

Most affected patients respond to di-

etary modification and/or medications, but surgery is considered for the small percentage of patients with debilitating constipation who fail medical management.

Because the best surgical strategy for pediatric intractable constipation is not well defined, Dr. Christison-Lagay and her coinvestigators conducted a retrospective study of 45 consecutive patients who underwent one of the three leading procedures: ACE, enteral diversion, or colonic resection.

The patients were a mean of 9 years old, ranging in age from 4 months to 26 years. A total of 16 underwent ACE, 9 had a primary colonic resection, and 20 had primary intestinal diversion.

A satisfactory outcome was defined as passage of stool at least every other day with minimal fecal soiling or—in the case of diversion—a functional enterostomy with regular stool output and no abdominal distention.

Satisfactory results were achieved in 10 of 16 patients in the ACE group. Responders showed improved colonic motility on manometry 1 year post ACE. The responders began daily colonic enemas 1 week post ACE. At 24-month follow-up, all were still using colonic enemas, albeit at a lesser frequency in some cases.

Patients under age 12 had significantly greater success with ACE. A lack of cooperation in administering enemas on the part of teenage patients was cited as a significant contributor to treatment failure.

Of the six nonresponders with persistent constipation, four had a subsequent surgical procedure and two used medical management.

“Unlike some other groups, we haven’t found ACE success is predicted by preoperative colonic motility studies. Some patients with total colonic anergia actually do well with ACE, and some with apparently normal motility do poorly with ACE,” Dr. Christison-Lagay said.

Satisfactory outcome was achieved in 18 of 19 patients who underwent primary enteral diversion with either colostomy or ileostomy. Fourteen eventually had reestablishment of intestinal continuity at a mean of 27 months post diversion, in five cases by simple colostomy or ileostomy reversal and in nine by left colectomy. The decision in favor of left colectomy at the time of reversal was based on motility studies showing dysmotile colon.

Intestinal diversion was associated with numerous complications, notably stomal prolapse, which occurred in 40% of patients.

Only two of nine patients who underwent primary resection had satisfactory outcomes. Four nonresponders remained severely constipated, and three had fecal incontinence. Four of the nine patients underwent further surgery.

Pathologic reports categorized 30% of all study participants as having neurointestinal dysplasia and 20% as having hypovitaminosis. The rates were similar across the three surgical treatment groups.

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. Hypertoxin 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 ^a (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	3
Healing Abnormal	4	1
Hypoproteinemia	5	3
SGOT Increased ^b	4	5
SGPT Increased ^b	5	5
Nervous System		
Dizziness	3	3
Skin and Appendages		
Rash	3	4

^a 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 (CAP), nausea incidence was 24% for TYGACIL and 8% for levofloxacin; vomiting incidence was 16% for TYGACIL and 6% for levofloxacin.

Discontinuation from tigecycline 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 bony 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 overdosage 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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