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Tolevamer Potassium Sodium

Toxin-Binding Polymer
Treatment of C. difficile-Associated Diarrhea

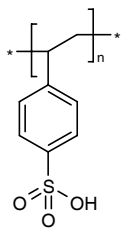
Rec INNM; USAN

GT267-004
GT160-246 (sodium salt)
Exodif™

Poly[1-(4-sulfophenyl)ethylene] potassium sodium salt

4-Ethenylbenzenesulfonic acid potassium salt polymer with 4-ethenylbenzenesulfonic acid sodium salt

Potassium sodium poly(styrene-4-sulfonate)



Tolevamer

CAS: 081998-90-5

CAS: 028038-50-8 (sodium salt)

CAS: 028210-41-5 (free acid)

EN: 289294

Abstract

Tolevamer is a nonantibiotic polymer therapy designed to treat *Clostridium difficile*-associated diarrhea (CDAD). Preclinical pharmacology studies suggested that tolevamer inhibits toxin-mediated intestinal damage by binding and subsequently neutralizing *C. difficile* toxins A and B. Tolevamer did not demonstrate antimicrobial activity *in vitro* or *in vivo*. In preclinical animal studies, tolevamer was excreted primarily in the feces, with more than 90% being excreted in the first 24 h after dosing. At doses up to 15 g/day, tolevamer proved safe and well tolerated in clinical trials. In terms of resolution of diarrhea, tolevamer administered at a dose of 6 g/day was noninferior to vancomycin administered at a dose of 500 mg/day. Patients treated with tolevamer at a dose of 6 g/day had a lower recurrence rate (7%) than those treated with vancomycin (19%).

Synthesis

Tolevamer can be synthesized as follows. Polymerization of *p*-bromostyrene (I) in refluxing benzene in the presence of benzoyl peroxide affords poly(*p*-bromostyrene) (II) (1), which undergoes metalation to the polystyryl lithium (III) by treatment with butyl lithium in THF or benzene (1, 2). Exposure of (III) to sulfur dioxide atmosphere generates an intermediate polysulfinic acid (IV), which spontaneously oxidizes to the sulfonic acid tolevamer (3). Tolevamer is reported to dissolve in basic solutions to form the corresponding salts (3). Scheme 1.

In a different procedure, the potassium salt of tolevamer can be synthesized as follows. Chlorosulfonation of phenethyl bromide (V) with $ClSO_3H$ gives 4-(2-bromoethyl)benzenesulfonyl chloride (VI), which undergoes simultaneous elimination of HBr and sulfonyl chloride hydrolysis in boiling ethanolic KOH to furnish potassium 4-vinylbenzenesulfonate (VII). Subsequent polymerization of (VII) in DMF solution in the presence of *tert*-butyl peracetate as initiator gives rise to tolevamer potassium (4). Scheme 2.

Background

Clostridium difficile-associated disease (CDAD) is one of the most common causes of antibiotic-associated diarrhea in hospitalized adults in North America. With an incidence of more than 300,000 cases/year in the U.S., and rising, the cost of the treatment and hospitalization asso-

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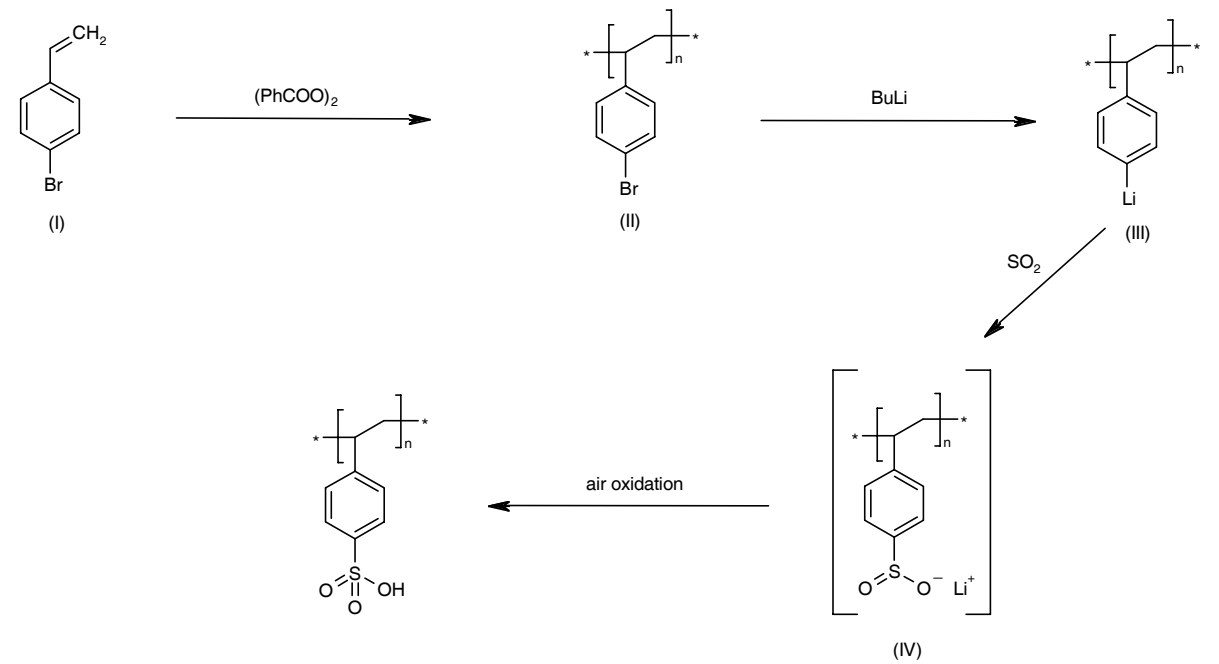
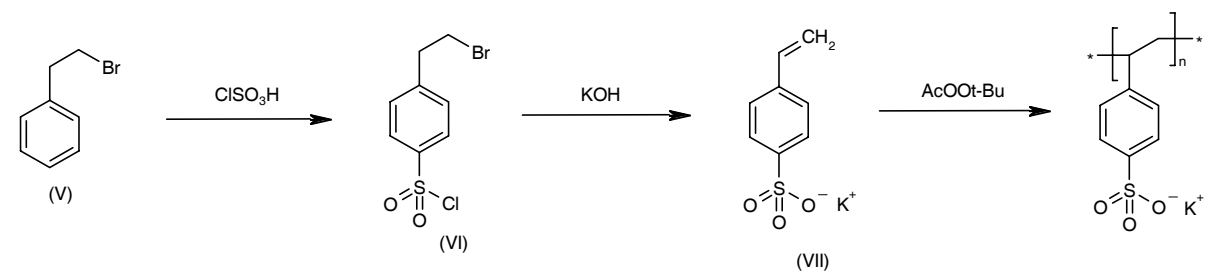
Scheme 1: Synthesis of Tolevamer



Scheme 2: Synthesis of Tolevamer Potassium



ciated with CDAD is substantial. CDAD presentation may vary from mild watery stools to life-threatening colitis and toxic megacolon (5-9).

Traditionally, CDAD is managed by antimicrobial therapy with vancomycin or metronidazole. However, the recurrence rates and resistance associated with these antibiotic therapies are increasing. With the rising incidence and increasing morbidity and mortality rates associated with CDAD, alternative treatment options are actively being sought (5, 6, 10). Several other strategies have been used in refractory CDAD, including multiple treatment modalities, ion-exchange resins, fecal enemas and bowel irrigation, and intravenous immunoglobulin, and a number of treatments are under investigation, including the antiparasitic agent nitazoxanide, the rifampin analogues rifaximin and rifalazil, the metronidazole analogue tinidazole and the glycodepsipeptide antimicrobial ramoplanin (5, 6).

Tolevamer is a nonantibiotic, high-molecular-weight (> 400 kDa) toxin-binding polymer designed for the oral treatment of CDAD. By noncovalently binding and subsequently neutralizing *C. difficile* toxins A and B, tolevamer protects the gastrointestinal tract from damage caused by the toxins, while allowing the restoration of normal bacterial growth, in contrast to antibiotic therapies. Treatment with the nonantibiotic tolevamer is also expected to be associated with less development of bacterial resistance (5, 6, 10). Originally formulated as the sodium salt, tole-

vamer is currently being developed as the potassium sodium salt to prevent exacerbation of hypokalemia due to binding of intestinal potassium. No differences have been observed between the two formulations in terms of preclinical profile (10).

Preclinical Pharmacology

The dissociation constants on a per polymer basis for tolevamer binding to *C. difficile* toxins A and B were 125-133 nM and 5.3-8.7 μM, respectively, at physiological salt levels in pulsed ultrafiltration experiments. Under low-salt conditions (0.05 M), the binding of tolevamer to toxin A was essentially irreversible, whereas the dissociation constant for the binding of tolevamer to toxin B was 120.9 nM. It was calculated that about 800 monomer units of tolevamer would bind 1 molecule of toxin A (10-12).

The ability of tolevamer to inhibit the effects of *C. difficile* toxins A and B on Vero cell protein synthesis was also studied. Tolevamer (5 mg/ml) completely blocked the activity of toxin A (5 ng/ml) and almost completely blocked (90% inhibition) the activity of toxin B (1.25 ng/ml); it also completely inhibited toxin-induced cell rounding. In ligated rat ileal loops, 1 mg tolevamer significantly inhibited fluid accumulation caused by 5 μg toxin A, and doses of 2.5-5 mg also significantly inhibited toxin A-induced increases in intestinal permeability; it was more active than cholestyramine in these experiments. In antimicrobial activity assays, tolevamer showed little activity at concentrations up to 5000 μg/ml against a panel of aerobic and anaerobic bacteria and yeasts. Tolevamer did not interfere with the *in vitro* activity of most antibiotics tested, indicating that its activity is nonantimicrobial (10, 13, 14).

In a hamster model of CDAD, tolevamer treatment (500, 1000 or 1500 mg/kg/day) reduced the incidence of diarrhea and markedly increased survival rates (90%, 70% and 70%, respectively, *vs.* 10% in controls) among *C. difficile*-infected animals. Tolevamer (1000 mg/kg/day) also protected 80% of the hamsters from death when given starting before infection, whereas cholestyramine (1000 mg/kg/day) protected only 10% of the animals. Although metronidazole initially protected 100% of the hamsters from mortality, 80% relapsed upon removal of the drug, whereas removal of tolevamer did not lead to relapse in the hamsters. Moreover, combination of metronidazole (21 mg/day) and tolevamer (50 or 100 mg/day) followed by tolevamer alone protected 70-90% of hamsters from relapse (10, 13-15).

Pharmacokinetics and Metabolism

The pharmacokinetics of tolevamer were evaluated in rats and dogs. In one study, a single oral dose (602 mg/kg) of [^{14}C]-tolevamer was administered to rats and was found to be excreted in the feces, approximately 90% being excreted within 8-24 h after dosing. No radioactivity was detected in blood or tissues and the small amount detected in the urine was attributed to fecal contamination. Similar results were reported in rats with chemically induced inflammatory bowel disease (10).

In male and female dogs treated with a single oral dose (500 mg/kg) of [^{14}C]-tolevamer, the drug was again excreted primarily in the feces, with very low levels of tolevamer detected in the plasma. The drug was rapidly absorbed and eliminated, with mean peak plasma concentrations (C_{max} = 5683-6175 ng eq/g) and half-life ($t_{1/2}$ = 4.12-5.14 h) being similar in males and females. Over 90% of the radioactivity was eliminated within 24 h (10).

Both studies indicated that tolevamer was essentially not absorbed in the gastrointestinal tract (10).

Safety

The safety and tolerability of tolevamer were evaluated in a double-blind, randomized, placebo-controlled dose-optimization study (6-15 g t.i.d. on days 2-8 before or after a loading dose) carried out in 40 healthy male volunteers. The agent proved to be well tolerated at all doses, with flatulence being the most common adverse event. All adverse events were mild and not related to dose. Potassium balance was seen at all but the highest dose, which was associated with a small decrease in potassium excretion (16).

Clinical Studies

A multicenter, double-blind, active-controlled, parallel phase II study evaluated the safety and efficacy of a tolevamer capsule formulation in patients with mild to moderately severe CDAD. A total of 289 patients were randomized to three groups to receive either 3 g/day tolevamer (n=97), 6 g/day tolevamer (n=95) or 500 mg/day vancomycin (n=97) for 14 days. In the per-protocol analysis, resolution of diarrhea was achieved in 48 of 72 (67%) patients receiving 3 g/day tolevamer, 58 of 70 (83%) patients receiving 6 g/day tolevamer and 73 of 80 (91%) patients receiving vancomycin. Median time to resolution of diarrhea, the primary efficacy endpoint, was 4.0, 2.5 and 2.0 days, respectively, in patients treated with 3 g/day tolevamer, 6 g/day tolevamer and vancomycin. Tolevamer administered at a dose of 6 g/day proved to be noninferior to vancomycin in terms of resolution of diarrhea. In the intent-to-treat population, the median time to resolution of diarrhea was 3.0 days for both high-dose tolevamer and vancomycin and 4.0 days for the lower dose of tolevamer. Patients treated with tolevamer at a dose of 6 g/day showed a lower recurrence rate (7%) *versus* those who received vancomycin (19%). The most common adverse events were similar among the different treatment groups and consisted of minor gastrointestinal complaints. Eight patients discontinued treatment because of adverse events in the low-dose tolevamer group, 11 patients in the high-dose tolevamer group and 7 patients in the vancomycin group. Hypokalemia occurred slightly more often in tolevamer-treated groups (23% at 6 g/day and 17% at 3 g/day) than in the vancomycin-treated group (7%) (17-19). Further studies on

fecal samples from 33 of the 289 patients indicated that the binding of tolevamer to toxins A and B is associated with restoration of components of the anaerobic intestinal microflora during the treatment of CDAD (20).

A palatable oral solution formulation of tolevamer was developed for late-stage clinical studies (21). A phase II clinical trial is under way to investigate the absorption of tolevamer potassium sodium in patients with CDAD (22), a phase III trial is in progress comparing tolevamer potassium sodium to metronidazole and vancomycin in patients with CDAD (23) and a similar trial was recently completed (24), and a third phase III trial was recently commenced to evaluate the safety, tolerability, efficacy and absorption of the drug administered as tablets to CDAD patients (25).

Drug Interactions

The effect of tolevamer on the oral bioavailability of commonly used drugs was evaluated in a 5-week crossover study. In the study, glyburide (0.31 mg/kg), ciprofloxacin (25 mg/kg), warfarin (0.53-0.55 mg/kg) and digoxin (0.26 mg) were administered together with 100 mg/kg tolevamer to 16 beagle dogs (4 dogs per group). The results indicated a possible effect for tolevamer co-administration on ciprofloxacin absorption, an inconclusive effect on glyburide absorption and no effect on warfarin or digoxin absorption (10).

Source

Genzyme Corp. (US).

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