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Short Communication

Minimal systemic and high faecal exposure to cadazolid in patients with severe *Clostridium difficile* infection☆

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ABSTRACT

Cadazolid is under development as an oral treatment for *Clostridium difficile* infection (CDI), which is the most common infectious cause of antibiotic-associated diarrhoea. Low systemic cadazolid exposures were previously reported in healthy subjects following both single and multiple oral dosing. The main objective of this study was to investigate systemic cadazolid exposure in patients with severe CDI with potential disrupted lining of the gastrointestinal tract. A single 3000 mg oral dose of cadazolid was administered to six patients with microbiologically-confirmed severe CDI. Plasma and faeces were collected up to 144 h post-dose for determination of cadazolid concentrations. Safety assessments were conducted over the 144-h investigational period. Cadazolid was well tolerated in patients with severe CDI, with no reported drug-related adverse events. Cadazolid systemic exposure following a single 3000 mg oral dose was very low, with a peak plasma concentration (C_{max}) of 2.64 ng/mL and an area under the concentration–time curve (AUC_{0-144}) of 125 ng × h/mL. The median peak daily faecal cadazolid concentration was 5675 times the *C. difficile* MIC_{90} of 0.25 mg/L. In subjects with severe CDI, cadazolid systemic exposure was very low following a single high oral dose. Cadazolid plasma concentrations were similar in magnitude to those previously reported for healthy subjects, whereas total systemic exposure was ca. 5–6 times higher, but was still low. Peak daily faecal cadazolid concentrations were 5675 times the 0.25 mg/L *C. difficile* MIC_{90}, and on Day 4 five of the six patients presented a daily faecal cadazolid concentration ≥1651 times the MIC_{90} [ClinicalTrial.gov ID: NCT02053181].

1. Introduction

Clostridium difficile, a Gram-positive, spore-forming bacterium, is the most common cause of hospital-acquired antibiotic-associated infectious diarrhoea. *C. difficile* infection (CDI) is an increasingly frequent cause of morbidity and mortality among elderly hospitalised patients and exerts a significant burden on healthcare systems [1,2]. *C. difficile* often colonises the human intestinal tract after the normal gut flora has been altered by antibiotic therapy and is the causative organism of antibiotic-associated pseudomembranous colitis. CDI results from the overgrowth of toxigenic strains of *C. difficile* in the colon. Toxins A and B, as well as the binary toxin (e.g. in hypervirulent NAP1/027/BI strains), are considered the main virulence factors for establishment of infection [3,4]. These toxins have been shown to be cytotoxic, causing disruption of the actin cytoskeleton and tight junctions, resulting in decreased transepithelial resistance, fluid accumulation, and destruction of the intestinal epithelium [5,6].

Cadazolid (ACT-179811) is a novel oxazolidinone-type antibiotic with potent activity against *C. difficile* (MIC_{90} = 0.25 mg/L) [7,8]. It acts primarily by inhibiting bacterial protein synthesis [9]. Cadazolid showed potent activity in mouse and hamster models of CDI as well as in an in vitro human gut model with very limited negative effects on bacterial counts of the indigenous gut microflora [7,10].

Cadazolid has previously been shown to be well tolerated in healthy subjects and subjects with CDI [11,12]. In both populations, very low cadazolid systemic exposures were observed following both single and multiple oral doses [11]. In healthy subjects following a single 3000 mg oral cadazolid dose, the majority of the oral dose (94%) was recovered as unchanged drug in the faeces [11]. Cadazolid doses of 250, 500 and 1000 mg twice daily for 10 days were effective in the treatment of patients with CDI [12]. Clinical cure rates were similar to vancomycin while having lower recurrence rates, resulting in higher sustained cure rates [12]. Cadazolid

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is now in phase 3 clinical development. The present study investigated the safety and pharmacokinetics of cadazolid following a single high oral dose in subjects with severe CDI in whom the gastrointestinal tract lining has been reported as possibly being disrupted [5,6].

2. Materials and methods

2.1. Study drug

Cadazolid (Actelion Pharmaceuticals Ltd, Allschwil, Switzerland) was provided in amber bottles (1000 mg/bottle) as a dry powder for oral suspension. A single 3000 mg oral dose (three bottles) was obtained by suspending the contents in each bottle with 25 mL of sterile/mineral water, thoroughly mixing the suspension, and then the total contents of the three bottles were swallowed. Each bottle was then washed twice, with all rinse water swallowed. The whole process had to be completed within 5 min.

2.2. Study population

Six Caucasian patients with severe CDI participated in the study after giving written informed consent. Patients had to be aged between 18 and 80 years (inclusive). The severity of CDI was assessed according to the current European guidelines [13] and severe CDI was defined as an episode with at least one sign of severe colitis. The latter included fever (core body temperature >38.5 °C), rigours, haemodynamic instability (including decreased bowel sounds, abdominal tenderness, rebound tenderness and guarding), signs of ileus, rise in serum creatinine, elevated serum lactate, pseudomembranous colitis, distension of the large intestine, colonic wall thickening including low-attenuation mural thickening, pericolonic fat stranding, and ascites not explained by other causes. To be eligible, subjects had to have microbiologically-proven CDI using a validated enzyme-linked immunosorbent assay (ELISA) for the detection of *C. difficile* toxin A (TcdA) and/or toxin B (TcdB), and were receiving metronidazole or vancomycin for the treatment of CDI. The patients could not participate if they were vomiting, had ileus, were not passing stool or were likely to die within 72 h from any cause. Life-threatening or fulminant CDI (white blood cell count $>30 \times 10^9$/L; temperature >40 °C; or septic shock, peritoneal signs or significant dehydration), history of ulcerative colitis or Crohn's disease were also reasons for exclusion. Women of childbearing potential had to have a negative serum pregnancy test at screening and had to use a reliable method of contraception [barrier type devices (e.g. female condom, diaphragm and contraceptive sponge) used only in combination with a spermicide, intrauterine devices, oral contraceptive agent, injectable progesterone depot formulation or levonorgestrel implants].

2.3. Study design

The study was a single-centre, open-label, single oral dose phase 1 study in patients with severe CDI. Each patient resided in the Clinical Research Unit of the University Hospital for Infectious Diseases (Zagreb, Croatia) from the evening prior to dosing until the end of study on Day 7 (144 h), during which time safety and pharmacokinetic assessments were performed. A single oral 3000 mg dose was given following an overnight fast.

The study, which was conducted in full compliance with the principles of the Declaration of Helsinki and with regulations of Croatia, was also approved by the independent Ethics Committee of the Agency for Medicinal Products and Medical Devices of Croatia [Agencija za lijekove i medicinske proizvode (HALMED), Zagreb, Croatia].

2.4. Safety and tolerability assessments

Electrocardiogram (ECG) parameters, vital signs and laboratory parameters (haematology and blood chemistry) as well as treatment-emergent adverse events (AEs) were collected up to the end of study. Treatment-emergent serious AEs (SAEs) were recorded up to the safety follow-up call on Days 10–14.

2.5. Cadazolid pharmacokinetic assessments

Blood samples of 2.7 mL for plasma cadazolid determination were taken pre-dose and at 0.5, 1, 2, 4, 6, 8, 12, 24, 36, 48, 72, 96, 120 and 144 h post-dose. Within 30 min of blood collection, plasma was collected, transferred into polypropylene tubes and then frozen at −20 °C. Cadazolid pharmacokinetic parameters were calculated using non-compartmental analysis (WinNonlin® 5.2; Pharsight Corp., Mountain View, CA).

The intent was to collect all faecal samples over the 144-h investigational period; however, this proved difficult in practice owing to the severity of diarrhoea.

2.6. Bioanalytical analysis

A validated high-performance liquid chromatography coupled to tandem mass spectrometry (HPLC–MS/MS) assay, specific for measurement of unchanged cadazolid in human plasma and faeces, was used [11].

3. Results

3.1. Subject characteristics

Four male and two female Caucasian subjects (aged 24, 69, 73, 75, 80 and 81 years) completed the study as per-protocol. However, the age of the 81-year-old patient was reported as a minor protocol deviation. All patients had started vancomycin or metronidazole treatment between 1 day and 5 days prior to cadazolid administration.

3.2. Safety and tolerability

No clinically relevant effects on mean clinical laboratory parameters, ECG recordings, physical examination or vital signs were observed. No SAEs or deaths occurred during the study. A total of three AEs occurred during the course of the study (candiduria, constipation and hypoproteinaemia), which were of mild or moderate intensity and were judged by the investigator as not related to the intake of cadazolid. Two subjects were treated with concomitant medication, comprising fluconazole for candiduria and mannitol/lactulose for constipation. Cadazolid was generally well tolerated in patients with severe CDI.

3.3. Pharmacokinetics in plasma

Plasma cadazolid concentrations measured over the 144-h investigational period were extremely low (Fig. 1 and Table 1). During the first 8 h following administration, the first cadazolid peak concentration was generally achieved 1–4 h post-dose (median 3 h), with a peak plasma concentration (C_{max}) of 2.2 ng/mL (geometric mean). In four of the six subjects, a second peak occurred between 48 and 144 h (median 120 h), with a C_{max} of 2.1 ng/mL (geometric mean) (Table 1). The maximum observed C_{max} over 144 h was 7.3 ng/mL, which was observed at 144 h post-dose. Total cadazolid systemic exposure measured over the 144-h