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Ecological effect of ceftazidime/avibactam on the normal human intestinal microbiota

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ABSTRACT

Ceftazidime/avibactam is a new combination of the antibiotic ceftazidime with the novel, non-β-lactam β-lactamase inhibitor avibactam. The purpose of the present study was to investigate the effect of ceftazidime/avibactam on the human intestinal microbiota following intravenous (i.v.) administration. Twelve healthy volunteers received ceftazidime/avibactam by i.v. infusion (2000 mg ceftazidime and 500 mg avibactam) given over 2 h every 8 h on Days 1–6 (inclusive) and a single dose on Day 7. Faecal samples were collected on Day−1 (pre-dose), during administration on Days 2, 5 and 7 and post-dose on Days 9, 14 and 21. Samples were cultured on non-selective and selective media. The number of *Escherichia coli* and other enterobacteria decreased significantly during administration of ceftazidime/avibactam, whereas the number of enterococci increased. Lactobacilli, bifidobacteria, clostridia and *Bacteroides* decreased significantly during ceftazidime/avibactam administration. The effects on lactobacilli, bifidobacteria and *Bacteroides* were similar in the 12 volunteers, whilst clostridia showed different ecological patterns among the volunteers. Toxigenic *Clostridium difficile* strains were detected in five volunteers during the study. In four of the volunteers, loose stools were reported as adverse events. Plasma samples were collected on Days −1, 2, 5 and 7. Ceftazidime and avibactam concentrations in plasma (ceftazidime 0–224.2 mg/L of plasma and avibactam 0–70.5 mg/L of plasma) and faeces (ceftazidime 0–468.2 mg/kg of faeces and avibactam 0–146.0 mg/kg of faeces) were found by bioassay. New colonising resistant clostridia were found in five volunteers and lactobacilli were found in three volunteers.

1. Introduction

The prevalence of multidrug-resistant strains among Gram-negative bacteria is increasing [1–3]. Compared with infections due to antimicrobial-susceptible Gram-negative bacteria, infections due to multidrug-resistant strains lead to longer hospital stays, increased mortality and greater hospitalisation costs [4]. Bacteria producing extended-spectrum β-lactamases (ESBLs) are considered to be resistant to most cephalosporins, penicillins and monobactams [5,6]. Avibactam is a novel, non-β-lactam β-lactamase inhibitor with a spectrum of activity encompassing class A, class C and some class D β-lactamases. Avibactam, when combined with ceftazidime, has been shown to be active against strains that express a combination of β-lactamase types as well as strains that are concomitantly resistant to other antibacterial agents such as fluoroquinolones [6,7]. Clinical studies have shown that the combination ceftazidime/avibactam for the treatment of intra-abdominal infections and complicated urinary tract infections is favourable, with a low incidence of adverse effects [8,9].

The normal microbiota acts as a barrier against colonisation by potentially pathogenic micro-organisms and against overgrowth of already present opportunistic micro-organisms [10,11]. Administration of antimicrobial agents, therapeutically or as prophylaxis, causes disturbances in the ecological balance between the host and the normal microbiota [10,11]. Knowledge about the interaction between antimicrobial agents and the normal microbiota gives the clinician the possibility to choose agents associated with lesser degrees of ecological disturbance [10,11]. Consequently, the risk of development of resistant strains and transfer of resistance elements between micro-organisms is reduced [10,11].

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Consideration of the ecological consequences is also an important step to prevent the distribution of resistant strains between persons [10,11]. Resistant micro-organisms that are well recognised pathogens isolated from the normal microbiota during antimicrobial administration include ESBL-producing enterobacteria, meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci, quinolone-resistant *Clostridium difficile* and metronidazole-resistant *Bacteroides fragilis* [10–12]. The extent to which disturbances occur depends on the spectrum of the agent, the dose, the route of administration, pharmacokinetic and pharmacodynamic properties, and in vivo inactivation of the agent [13]. Parenterally administered agents that are excreted in the bile or the intestinal mucosa may interfere with the normal intestinal microbiota [11]. As a consequence, antibiotic-resistant micro-organisms may increase in number [10,11].

The primary objective of this study was to investigate the effect of administration of ceftazidime/avibactam on the intestinal microbiota of healthy volunteers. The secondary objectives were: to investigate the safety, tolerability and pharmacokinetics of ceftazidime/avibactam in healthy volunteers; to measure ceftazidime/avibactam plasma and faecal concentrations using bioactivity techniques; and to describe the in vitro susceptibility of new colonising bacteria in the intestinal microbiota to ceftazidime/avibactam during and after ceftazidime/avibactam administration.

2. Materials and methods

2.1. Study design

This was an open-label, multiple-dose study (EudraCT 2012-004921-25) in healthy volunteers designed to investigate the effect on the intestinal microbiota of ceftazidime/avibactam in 13 healthy volunteers (7 females and 6 males) during multiple administration over 7 days. One female volunteer withdrew from the study on Day 2 after six doses owing to personal reasons and was not evaluated. Thus, 12 volunteers completed the study.

The volunteers received ceftazidime/avibactam (2000 mg ceftazidime and 500 mg avibactam) by intravenous infusion given over 2 h every 8 h on Days 1–6 (inclusive) and as a single dose on Day 7.

The duration of the study for each healthy volunteer was 6 weeks. The study comprised five visits: Visit 1 (screening), screening evaluations occurred within 21 days prior to Visit 2; Visit 2 (treatment period), eligible healthy volunteers were admitted to the study centre on Day−1 (within 24 h prior to the first infusion on Day 1) for baseline assessments to be performed. The healthy volunteers remained resident at the study centre until the completion of assessments on Day 8. Intravenous infusion of ceftazidime/avibactam every 8 h on Days 1–6 and as a single dose on Day 7 were administered to the healthy volunteers; Visit 3 (Day 10), an outpatient visit; Visit 4 (follow-up), a post-study follow-up took place on Day 14; and Visit 5 (end-of-study assessment), the end-of-study assessment took place on Day 21.

2.2. Volunteers

In total, 13 healthy volunteers were included and 12 completed the study. Volunteers were recruited through the Clinical Pharmacology Trial Unit website of the Karolinska University Hospital (Stockholm, Sweden). Volunteers were given written and oral information about the study and signed an informed consent form at the screening visit prior to any investigational procedure. Physical examination was carried out on each volunteer at the screening visit, including measurement of blood pressure, heart rate and clinical laboratory tests as well as an interview on medical and surgical history. Inclusion criteria were men and women aged 18–45 years and normal findings in the medical history and physical examination. The acceptable range of body mass index (BMI) for the volunteers was between 19 kg/m^2 and 30 kg/m^2. Female volunteers were of non-childbearing potential or were willing to take adequate contraceptive measures during the entire study period and for 3 months after completion of the study. Volunteers had to adhere to the visit schedule and concomitant therapy prohibitions and must be compliant with the treatment (screening visit).

Exclusion criteria were as follows: volunteers with an underlying known disease, a surgical or medical condition such as history of predisposition to candidiasis overgrowth, known or suspected achlorhydria or surgery that bypasses or excludes the duodenum, myasthenia gravis and hepatic impairment; volunteers with known allergy or sensitivity to the active substance or to any of the excipients or components of the formulation being tested; volunteer was currently enrolled in another investigational drug or device study or participated in such a study in the past 3 months prior to the screening visit; volunteer had not undergone at least a 4-month washout period following treatment with any systemic or topical antibiotics; volunteer had used prohibited medications prior to the study and an unwillingness to refrain from use during the study, such as antibiotics, barbiturates, carbamazepine, primidone, phenytoin, bivalent or trivalent ions, i.e. aluminium, zinc, calcium, magnesium or iron preparations, quinapril, activated charcoal, cholestyramine, bismuth chelates and sucralfate, isotretinoin, methoxyflurane, sulphonylurea, oral antidiabetic agents, and anticoagulants of the dicoumarol type; volunteer had a clinically significant laboratory abnormality at the screening laboratory evaluation; volunteer presented seropositivity for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody and/or human immunodeficiency virus (HIV); volunteer had a history of chronic alcoholism (>7 unit of alcohol per week, 1 unit corresponding to 360 mL of beer or 150 mL of wine or 45 mL of spirits); volunteer had a history of drug abuse or had positive test results for any drug abuse; volunteer drank excessive quantities of tea, coffee and/or beverages containing caffeine (>5 cups/day or ca. 500 mg of caffeine per day) or ate excessive quantities of chocolate; and volunteer was vulnerable as defined in the ICH Guideline for Good Clinical Practice.

2.3. Approvals

The study protocol submitted to the Regional Ethics Committee in Stockholm (Stockholm, Sweden) and to the Medical Products Agency (Uppsala, Sweden) was approved before starting the trial.

2.4. Collection of plasma samples

Plasma samples for determination of ceftazidime and avibactam concentrations by bioactivity assay were collected in the opposite to in which the ceftazidime/avibactam was being infused. Plasma samples were collected on Day −1, Day 2 at 2 h after the start of administration, Day 5 at 2 h after the start of administration, and Day 7 at 2, 4 and 12 h after the start of administration.

2.5. Collection of faecal samples

Faecal samples were collected on Day −1 (pre-dose), during administration on Days 2, 5 and 7 and post-dose on Days 9, 14 and 21 according to the study design. In case no specimen was obtained from faeces passed on a specified collection day or no specimen was passed on that day, the first subsequent faecal specimen passed after that day was collected. If more than one specimen was passed on a specified collection day, only the first specimen of that day was collected. Faecal samples (10 g) were collected in sterile plastic containers and were kept at 4 °C until transportation to