Phase II clinical trial to evaluate an antibiotic regimen pharmacokinetic applicable to outpatient parenteral antimicrobial therapy in *Enterococcus faecalis* infective endocarditis

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Protocol ID: ENDOKINETIC-CEF

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Sponsor: Fundación Pública Andaluza para la Gestión de la Investigación en Salud de Sevilla. (FISEVI)

University Hospital Virgen del Rocío.

1. Abstract

Infective endocarditis (IE) is an uncommon but virulent infection disease. One of the most frequent etiology for this infection is Enterococcus faecalis. IE treatment is difficult due to the characteristics of the infection itself, the bacterial species and the frequent comorbidities of the patients. A bactericidal antimicrobial treatment is mandatory for the resolution of this disease, but most antibiotics do not exhibit this effect against E. faecalis and have prompted the combination of an aminoglycoside and a cell-wall active agent (generally a β-lactam) as the standard treatment. This is a lengthy treatment (4-6 weeks) and its primary side effect is nephrotoxicity. Furthermore, aminoglycoside resistant strain's rates are increasing in USA and Europe, getting more complicated to establish an effective antibiotic regimen. Nowadays, patients with E. faecalis IE are old and often have significant underlying comorbidities with an increased risk of developing nephrotoxicity with aminoglycoside treatment. For this reason, and for the relevance of high-level aminoglycoside-resistant strains, some alternatives have been explored.

A double β-lactam regimen is an option, despite the intrinsically resistance of E. faecalis to cephalosporins. The most studied combination is a regimen based on ampicillin plus ceftriaxone, which has shown a synergistic effect in vitro. This combination is as effective as ampicillin plus gentamycin, but with lower nephrotoxicity. Those patients need at least 4-6 weeks of treatment with a prolonged hospitalization. However, after 2 week of treatment some patients are clinically stabilized and could be benefit of an outpatient parenteral antibiotic therapy (OPAT) program. For that purpose, it is essential to design a treatment regimen, which ensures the effectiveness and safety of the treatment, based on stability and pharmacokinetic and pharmacodynamics (PK/PD) studies of the administered drugs. Furthermore, the logistic and schedule should be simple enough to enable the inclusion in an OPAT program. In order to design an antibiotic regimen suitable for OPAT programs and as effective as the standard therapies for E. faecalis IE, we decided to start a project consisting of a phase II clinical trial and a stability study.

The clinical trial is designed as a phase II, crossover clinical trial. It will be carried out in healthy volunteers, who will receive two different antibiotic regimen based on ceftriaxone. One of the regimens had shown clinical effectiveness in this scenario, but it is not suitable for OPAT programs. In the other hand, a new treatment schema useful in OPAT programs is proposed, but there is still a lack of pharmacokinetic data to support it. The plasma drug concentrations will be measured in both cases, comparing the minimal drug concentration observed and the pharmacokinetic profiles of the two regimens. Likewise, the stability study pursuits to establish the useful life at room temperature of this antibiotic regimen for an OPAT program.

2. Trial identification

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3. Investigador principal del ensayo

Dra. María Victoria Gil Navarro.
Hospital Pharmacy Service
University Hospital Virgen del Rocío.
Manuel Siurot Avenue, s/n. 41013. Sevilla.
Phone.: 955012300. Fax: 955012088. e-mail: mariav.gil.sspa_juntadeandalucia.es

4. Sponsor identification

Fundación pública andaluza para la gestión de la investigación en salud de Sevilla (FISEVI).
University Hospital Virgen del Rocío. Edificio de laboratorios, 6ª floor.
Manuel Siurot Avenue, s/n. 41013. Sevilla Teléfono: 955013295

5. Clinical trial site

University Hospital Virgen del Rocío. Manuel Siurot Avenue, s/n. 41013. Sevilla, Spain.

6. Ethics committee infotmation

Comité de Ética de la Investigación provincial. Doctor Fedriani Avenue 3 41009. Sevilla, Spain,

7. Clinical trial monitor

University Hospital Virgen del Rocío. Manuel Siurot Avenue, s/n. 41013. Sevilla, Spain.

8. IMP identification

a) 4 grams of ceftriaxone in a single short infusion each 24 hours
b) 2 grams of ceftriaxone in a single short infusion each 12 hours

9. Trial type and phase

A phase II, single-centre, open, non-randomized, cross-over, clinical trial.

10. Objectives of the trial

Main objective

To determinate whether 24 hours after the administration of 4 grams of ceftriaxone in a single short infusion, serums levels would be higher than 5 micrograms per mililitre

Secondary objectives

1. To compare the 24 hours area under the curve (AUC) after the administration of 4 grams of ceftriaxone in a single short infusion and the administration of 2 grams of ceftriaxone in a two short infusions separated for 12 hours.
2. To determinate all dose-dependants pharmacokinetics parameters after the administration of 4 grams of ceftriaxone in a single short infusion.
3. To determinate the safety of the administration of 4 grams of ceftriaxone in a single short infusion

11. Design of the trial

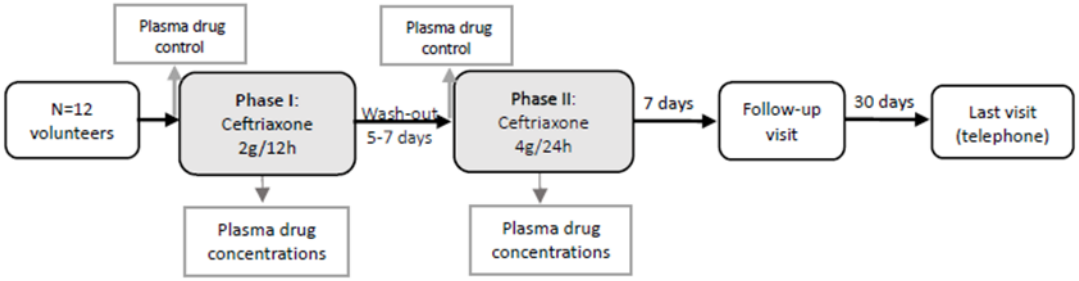
A phase II, single-centre, open, non-randomized, cross-over, clinical trial. It is defined as a non-commercial study with low level of intervention. The study will recruited 12 healthy volunteers. The subjects will be identify by an alphanumeric sequential code order by inclusion. Every individual will received two cycles of treatment. First, each individual will be administrated 2 doses of 2 g of ceftriaxone separated for 12 hours. After a wash-out period (5-7 days) the same individuals will receive a single dose 4 g of ceftriaxone. In both cycles, plasma drug concentrations will be measure during 24 hours. The study will be structured in an initial interview, two phases of treatment and two follow-up visits:

1. First visit: It will involve all the procedures before the sign of the informed consent and the initial clinical and analytical check.

2. Phase I: 2 doses of 2 g of ceftriaxone will be administrated separated for 12 hours. Plasma drug concentration will be measure after 0.5, 1, 2, 3, 6, 8. 10, and 12 hours of each dose.

3. Phase II: A single dose of 4 g of ceftriaxone will be administrated. Plasma drug concentration will be measure after 0.5, 1, 2, 3, 6, 8. 10, 12, 16, 20 and 24 hours after the administration.

4. Follow-up visit: Clinical and analytical check one week after the last dose of ceftriaxone. The last follow-up visit will take place by phone, one month after phase II.



Phases I and II will be separated for a wash-out period of 5-7 days. In order to ensure the absence of ceftriaxone and analytical variations, one additional blood sample will be extract before the beginning phase I and II. Patient follow-up: 1 month.

12. Disease under investigation

Healthy volunteers (Enterococcus faecalis infective endocarditis)

13. End points

Primary end point

Serums levels of ceftriaxone 24 hours after the administration of 4 grams of ceftriaxone in a single short infusion.

Secondary end points

1. Serums levels of ceftriaxone 0.5, 1, 2, 3, 6, 8, 10, 12, 16 y 20 and 24 hours after the administration of 4 grams of ceftriaxone in a single short infusion.
2. Dose-dependants pharmacokinetics parameters after the administration of 4 grams of ceftriaxone in a single short infusion: plasma clearance and volume of distribution.
3. Significant differences between serums levels of ceftriaxone 24 hours after the administration of 4 grams of ceftriaxone in a single short infusion and serums levels of ceftriaxone 24 hours after the administration of 2 grams of ceftriaxone in two short infusion separated for 12 hours.
4. Number of adverse reactions after the administration of 4 grams of ceftriaxone in a single short infusion.
5. Frequency and importance of adverse reactions.

14. Inclusion and exclusión criteria

Inclusion criteria

1. Male and female adult subjects.
2. Weight between 40 and 18 kilograms, both included, and body mass index lower than 34 kilograms per square meter.
3. The subject (or his/her "trusted representative") must have given his/her informed and signed consent approved by an Ethical Committee.
4. The subject must have normal analytical values or abnormal without clinical significance of biochemical parameters, liver and kidney function panel test, hemogram and album level. A medical check will be carry out by workers of Infectious Diseases Department.
5. The subject must have a normal physical examination or abnormal without clinical significance. A medical check will be carry out by workers of Infectious Diseases Department.
6. The medication taken usually by the subjects will be check by the Pharmacy Department in order to find possible interactions with ceftriaxone.

Exclusion criteria

1. Subjects with clinically significant abnormalities in laboratory test or physical exploration. A medical check will be carry out by workers of Infectious Diseases Department.
2. Subjects undergoing an active infection find at the screening.
3. Subjects with any clinical or surgery condition which contraindicate his/her inclusion, check by workers of Infectious Diseases Department.
4. Subjects who has received treatment with cephalosporins 21 days before the trial starts or during the trial (apart from the protocol treatment).
5. Subjects hypersensitive or allergic to cephalosporins or penicillin.
6. Subjects undergoing chronic or acute cutaneous diseases which prevent the treatment administration.
7. Subjects not giving his/her informed and signed consent approved by an Ethical Committee.

15. Clinical trial duration

Estimated of the duration of the trial: 1 year
Estimated dates: 26/04/18-26/04/19