Chapter 5

Ertapenem

a | Pharmacokinetics of ertapenem in patients with multidrug-resistant tuberculosis

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Abstract

Treatment of multidrug resistant (MDR) and extensively drug resistant (XDR) tuberculosis (TB) is becoming more challenging because of increased level of drug resistance against second line tuberculosis drugs. One promising group of antimicrobial drugs are carbapenems. Ertapenem is an attractive carbapenem for the treatment of MDR and XDR-TB because its relative long half-life enables once daily dosing.

A retrospective study was performed for all MDR-TB suspected patients at the Tuberculosis Center Beatrixoord of University Medical Center Groningen (Haren, The Netherlands) who received ertapenem as part of their treatment regimen between the first of December 2010 and the first of March 2013. Safety and pharmacokinetics were evaluated.

Eighteen patients were treated with 1000 mg ertapenem for a mean of 77 days (range 5-210). Sputum smear and culture were converted in all patients. Drug exposure was evaluated in 12 patients The mean AUC_{0-24} was 544,9 (range 309 – 1130) mg*h/L. The mean Cmax was 127.5 (73.9 – 277.9) mg/L.

In general ertapenem treatment was well tolerated during MDR-TB treatment and showed a favourable PK/PD profile in MDR-TB patients. We conclude that ertapenem is a highly promising drug for the treatment of MDR-TB that warrants further investigation.

INTRODUCTION

Treatment of multidrug resistant (MDR) and extensively drug resistant (XDR) tuberculosis (TB) is becoming more challenging because of increased level of drug resistance against second line tuberculosis drugs. New drugs are being evaluated in clinical trials, but only bedaquiline and delamanid have entered the market to date. Therefore, antimicrobial drugs, which have been developed and labeled for other bacterial infections may be of potential use in the treatment of MDR-TB.

One promising group of antimicrobial drugs are carbapenems [1, 2]. An early in vitro experiment showed that imipenem and meropenem were active against *J* [3]. Chambers and co-workers showed that imipenem has anti-mycobacterial activity in mice and humans [4]. Imipenem and meropenem are currently listed as group 5 drugs for the treatment of MDR-TB [5]. More recently, clinical experience of carbapenems in MDR-TB patients showed promising results [6, 7].

Carbapenems are poor substrates for beta lactamase C (BLaC) due to rapid acylation and slow deacylation. Therefore, unlike beta-lactams, they are not rapidly hydrolyzed by BLaC and therefore maintain their potential activity against *M. tuberculosis* [8]. The binding of carbapenems to the LD transpeptidases results in inhibition of the peptidoglycan polymerization of the cell wall [9]. Combined with a beta lactamase inhibitor, such as clavulanate, activity against *M. tuberculosis* is higher [10].

Efficacy of carbapenems is correlated with the percentage of time the free plasma drug concentration transcends the MIC (Tfree>MIC). Maximal bactericidal activity is reached if the time above MIC is at least 40% of dosing interval [11, 12]. To reach this target for gram positive, gram negative and anaerobic bacterial infections ertapenem is given intravenously in a dose of 1000 mg once daily [13]. Ertapenem has the advantage over other carbapenems because of a long half-life of 4 h enabling once daily dosing [12], which is attractive for MDR-TB treatment. Another advantage is that ertapenem is not affected by drug-drug interactions as it is neither metabolized by cytochrome P450 nor a substrate for P-glycoprotein [14].

To include ertapenem among the other carbapenems as a group 5 drug for the treatment of MDR-TB additional pharmacokinetic and safety data are urgently needed [15]. Therefore the objective of this study was to evaluate pharmacokinetics and safety in patients that received ertapenem as part of their treatment MDR-TB regimen.

PATIENTS AND METHODS

Patients

All patients suspected to MDR-TB at the Tuberculosis Center Beatrixoord of the University Medical Center Groningen (Haren, The Netherlands) who received ertapenem as part of their treatment regimen between first of December 2010 and the first of March 2013 were included in this retrospective study. The study was evaluated by the Medical Ethical Review Board of the University Medical Center Groningen (metc 2013-492). The need for written informed consent was waived for the retrospective collection and analysis of anonymous data because it was not required under Dutch Law (WMO). For each MDR-TB suspects, age, gender, weight, length, ethnicity, drug susceptibility pattern, localization of tuberculosis, antiretroviral therapy, sputum conversion, adverse effects induced by ertapenem, dose, total exposure to ertapenem, and duration of treatment were collected.

Drug susceptibility to Ertapenem

Drug susceptibility testing (DST) of ertapenem was performed with and without clavulanic acid using the Middlebrook 7H10 agar dilution method at the Dutch National Tuberculosis Reference Laboratory (National Institute for Public Health and the Environment RIVM), Bilthoven, The Netherlands) [16].

Pharmacokinetics and pharmacodynamics

All patients received ertapenem in a dosage of 1000 mg once daily, given as intravenous infusion in 30 min. In all MDR-TB patients routine plasma concentrations were collected at steady state to assess drug exposure to enable individualized dosing. For plasma sampling a peripheral intravenous catheter was inserted. Patency of the peripheral catheter was maintained by a saline drip. Before a blood sample was taken, the drip was stopped and the first 4 mls of blood were discarded. The samples were collected before administration and at t = 1, 2, 3, 4, 5, 6, 8, 12, hrs post-dosage and stored at –80 °C until analysis. Plasma concentrations were assessed and validated using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) in the laboratory of Clinical toxicology and Drugs Analysis of the department of Clinical Pharmacy and Pharmacology at the University Medical Center Groningen [17]. Population pharmacokinetic parameters were calculated using the KinPOP module. Both KinFIT and KinPOP were part of the software package MWPharm 3.82 (Mediware, The Netherlands). The Tfree>MIC was calculated as this has been proposed as the best pharmacokinetic/pharmacodynamic parameter to predict in vivo efficacy of carbapenems [10]. Free drug concentration was assumed to be 5% [12, 18]. Eucast minimal inhibitory concentrations for ertapenem (non-species related) of 0.5 and 1.0 mg/L were used to calculate Tfree>MIC.

Safety and tolerability

Reported adverse effects (AE) in medical charts were used to evaluate the safety of ertapenem. Specific attention was paid to AE's mentioned in earlier studies: i.e. diarrhea and vomiting. The Naranjo algorithm was used to evaluate for causality between adverse effects that occurred and ertapenem [19].

Statistics and pharmacokinetic evaluation

SPSS 20 was used as statistical software (SPSS, Virgina, IL). Correlation between pharmacokinetic parameters and patient characteristics were analyzed using the Spearman correlation coefficient. MIC data were statistical analyzed using a methodology for censored MIC data [20].

RESULTS

Patients

Eighteen patients treated with ertapenem, mean age 29 (range 13 - 66 years), were retrieved. Ertapenem was part of the treatment regimen because of suspected extensive drug resistance, intolerance to second line drugs or combination of both. Based on the results of the drug susceptibility test ertapenem was discontinued in three patients who appeared to have drug susceptible TB. Gender was unequally distributed between patients as 8 were male (44.4%) and 10 patients were female (55.5%). The mean body mass index was 21.3 (range 13.7-32.6) kg/m2. Patients originated predominantly from Africa (11/18) and Europe (5/18). Patients were primarily diagnosed with pulmonary TB (13/18), extra pulmonary sites were involved in 7 patients.

Prescribed dosage of ertapenem was 1000 mg once daily in all patients. Mean total treatment duration of ertapenem was 77 days (range 5-210 days). Drug resistance pattern of the patients to anti-tuberculosis agents are shown in table 1. Most prescribed anti-TB drugs were: moxifloxacin (17/18), injectable (16/18), linezolid (15/18), clofazimine (8/18), clarithromycin (6/18) and pyrazinamide (5/18).

In total 15 patients completed treatment and were cured. Three patients were to lost to follow up. All patients with positive sputum-smear converted within a mean period of 17 days (range 0-97 days). Cultures remained negative after culture conversion and no relapse of MDR-TB was observed.

TABLE 1 Drug resistance patterns of the 18 study patients

Drugs by group #	Resistant	Sensitive
Group 1: first-line oral drugs	17 (94.4)	1 (5.55)
Isoniazid	15 (83.3)	3 (16.6)
Rifampicin	8 (44.4)	8 (44.4)
Pyrazinamide	11 (61.1)	6 (33.3)
Ethambutol	13 (72.2)	4 (22.2)
Rifabutin		
Group 2: injectable agents		
Streptomycin	14 (77.7)	4 (22.2)
Amikacin	3 (16.6)	14 (77.7)
Kanamycin	3 (16.6)	14 (77.7)
Capreomycin	5 (27.7)	12 (66.6)
Group 3: fluoroquinolones		
Moxifloxacin	2 (11.1)	15 (83.3)
Group 4: oral bacteriostatic second-line agents		
Protionamide	7 (38.8)	10 (55.5)
Group 5: agents with unclear role in treatment of drug-resistant TB		
Linezolid		17 (94.4)
Clarithromycin	3 (16.6)	7 (38.8)
Clofamizine		8 (44.4)
Other		
Ertapenem		18 (100)

Data are presented as n (%). TB: tuberculosis. #: groups defined by the World Health Organization.

Drug susceptibility of M. tuberculosis to ertapenem

All the *M. tuberculosis* strains appeared susceptible to ertapenem. However, actual determination of the MIC was complicated by the fact that ertapenem itself appeared an instable compound at 37°C [17]. This was confirmed by the fact that after 7 days MIC values were lower than after 14 days. In addition, freshly prepared plates showed lower MIC's compared to plates stored at 4°C. The refrigerator-stored plates showed lower MIC's than plates stored at room temperature. If ertapenem was combined with clavulanic acid all MIC's were even lower.

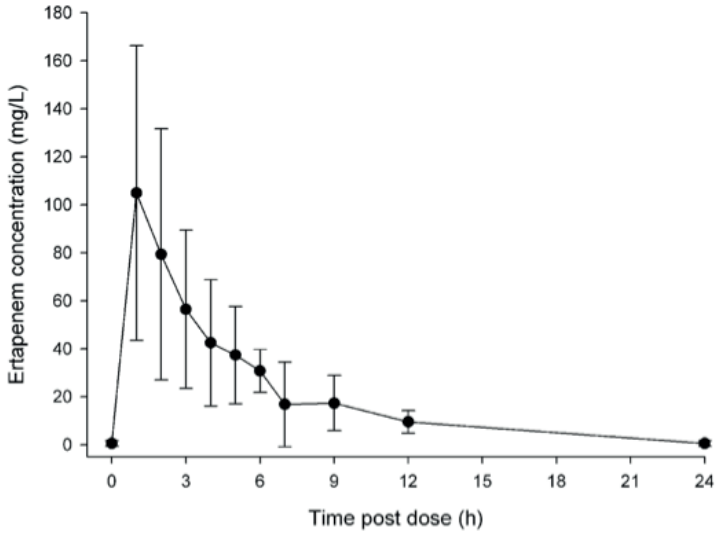

FIGURE 1: Ertapenem plasma concentration–time curves in 12 patients.

Pharmacokinetics and pharmacodynamics

The plasma concentration time curves were obtained in 12 patients with MDR-TB. In the remaining 6 patients routine plasma concentrations were collected at a time point at which they did not yet receive ertapenem or this drug was no longer administered. Three patients had multiple plasma concentration time curves and these were consistent. The mean curve is shown in figure 1. The mean $AUC_{0\text{-}24}$ was 544,9 (range 309 – 1130) mg*h/L. The steady state pharmacokinetic parameters are shown in table 2. Based on a MIC of 0.25 mg/L, 11 out of 12 patients exceeded a minimum of 40% time above MIC. In 9 patients the MDR-TB remained susceptible with a MIC of 0.5 mg/L. Except for 2 patients, none exceeded a minimum of 40% time interval with a MIC of 1 mg/L. The pharmacokinetic population model (KinPOP) of ertapenem showed a clearance of 2.26 (range 0.86-3,19) L/h/1.73m^2 and a volume of distribution of 8.79 (range 4.76-13,57) L.

Safety and tolerability

In general ertapenem was tolerated very well. In three patients treatment with ertapenem was stopped. One of these patients suffered from Crohn's disease and developed MDR-TB after multiple dosages of infliximab, a TNF alpha-blocker [21-22]. This patient experienced allergic fever, shortly after administration of ertapenem and ethambutol. After reintroduction this happened again (Naranjo score= 4). Both adverse events subsided after withdrawal of the offending drug. In the second patient ertapenem was stopped

after an increase in liver enzymes (ASAT: 109 / ALAT: 255) after 13 days of treatment with ertapenem. However, after two months, while this patient was still on treatment without ertapenem, liver enzymes remained elevated (Naranjo score = 1). In one patient kanamycin, linezolid and ertapenem were stopped due to line sepsis. This was considered not-to-be related to ertapenem. After removal of the venous access port, the patient recovered. Ertapenem and a new venous access port were not reintroduced, since it was not indicated anymore, due to low bacillary load at that time and these IV drugs could be substituted with oral antimycobacterial drugs. None of the patients experienced diarrhea, vomiting or dizziness.

TABLE 2 Pharmacokinetic parameters of ertapenem

Study	AUC_{0-24} h·mg·L^{-1}	Cmax mg·L^{-1}	Half-life h	Volume of distribution L	Clearance L·h^{-1}
1 g i.v. in MDR-TB	544.9	127.5	2.4	7.3	2.1
patients	(309–1130)	(73.9–277.9)	(2.047–3.528)	(2.612–11.1)	(0.0884–3.231)
1 g i.v. in healthy	572.1	154.9	4	8.2	1.8
volunteers [18]	(572–672)	(145–175)	(3.8–4.4)		

Data are presented as mean (range) and were calculated using KinFIT. AUC_{0-24}: area under the concentration–time curve up to 24 h; Cmax: maximum observed plasma concentration; MDR-TB: multidrug-resistant tuberculosis.

DISCUSSION

This is the first study, following a clinical report of ertapenem [6], presenting pharmacokinetic and safety data in patients with MDR-TB. In comparison with healthy volunteers, MDR-TB patients showed lower AUC_{0-24} values. Mean values of volume of distribution and clearance of MDR-TB patients were higher compared to healthy volunteers. Our observation is consistent with other studies that showed a lower drug exposure of ertapenem in patients with infectious diseases [23, 25]. More surprising was the inter-variability in AUC between patients with MDR-TB. Other antimycobacterial drugs also show highly variability and lower drug exposure in TB patients as well [2, 26, 27]. It is not yet completely clear why drug exposure is lower in TB patients. Apparently, stage of disease and altered body composition may potentially help to explain this observation.

Since ertapenem belongs to the class of beta-lactams, ertapenem has a time-dependant bactericidal activity. The Tfree>MIC is therefore important to evaluate the efficacy of ertapenem against *M. tuberculosis*. Nicolau and colleagues indicated that in case meropenem showed 40 %T>MIC bactericidal activity is observed whereas 20 %T>MIC appeared to have bacteriostatic activity. Other studies have mentioned this T>MIC as well

[11, 12, 14]. Protein binding of ertapenem was assumed to be 5%, since ertapenem shows concentration-dependent plasma protein binding. Healthy volunteers, whom average a peak plasma concentration of 150 mg/L after the end of infusion of 1 g of ertapenem, have a percentage of 8 % unbound protein. When total drug plasma concentration declines below 50 mg/L peak plasma concentration, the percentage of unbound ertapenem is circa 5% [18]. It is very promising to notice that the non-species related breakpoint of ertapenem of 0.5 mg/L was exceeded for more than 40% of the day in the majority of patients assuming that patients have a protein binding of 5%. At a higher MIC value of 1 mg/L bacteriostatic activity could be expected. Therefore ertapenem seems a very attractive drug for MDR-TB treatment. It seems warranted that doses of ertapenem higher than 1g/day should be used in the treatment of MDR-TB. However, in vitro experiments evaluating PK/PD targets for ertapenem against *M. tuberculosis* have yet to be performed. The hollow fiber infection model is suitable for PK/PD experiments and has already been used successfully before [28].

Besides pharmacokinetics of ertapenem in patients with MDR-TB, additional safety data are described for the first time as well. Only one patient, with Crohn's disease, experienced AE, which might be potentially related to ertapenem. One can speculate this may be related to an infusion related AE, due to a developed immune disorder and eventually a consequence of an infliximab treatment. Drug induced fever is a common AE of infliximab in the treatment of Crohn's Disease [29]. AE's of other carbapenems, such as diarrhoea, nausea, vomiting, headache and rash are well documented and found to be mild [1, 30]. According to the product leaflet, ertapenem is given for a maximum of two consecutive weeks. Previous studies explored the safety and tolerability of ertapenem for this period of time and concluded that adverse side effects were mild to moderate [13]. In our study we showed that AE did not increase during prolonged treatment.

The measurement of actual MIC values was complicated by the fact that ertapenem is an instable compound at 37°C. As drug susceptibility testing for *M. tuberculosis* takes at least two weeks at 37°C, it is highly likely that the initial drug concentration decreases rapidly in time. Unfortunately, with the current drug susceptibility systems, e.g. MGIT or plate, this problem cannot be overcome, as the drug concentration in the medium cannot be corrected for a decrease in concentration due to degradation of the drug. Recently the hollow fiber infection model solved this problem as drug concentrations can be increased to correct for degradation [31]. As systems are expensive and difficult to manage its not likely that routine DST will be performed using hollow fiber systems. Another alternative may be the use of E-tests [32]. This is much cheaper and easier to employ but it is unclear if it can help to overcome the instability of ertapenem.

The most important limitation of our study is the retrospective character and its limited sample size, and absence of control group, thereby preventing a meaningful conclusion on efficacy of ertapenem. Secondly the inability to define MIC for ertapenem in clinical isolates is another limitation. Nevertheless all patients were cured and no relapse was noticed after being treated with combination regimen including ertapenem. Likely the combination of drugs contributed to sputum culture conversion and favorable treatment outcome. This is in line with recently published data on tolerability and outcomes in 5 patients receiving ertapenem [6].

A recent editorial proposed a new classification of antituberculosis drugs. It marked the potential of carbapenems as group 5 drugs, however carbapenems are still in need of proper evaluation and clinical evidence [33]. Before ertapenem can be labeled as a group 5 drug and used as part of MDR-TB treatment, a valid procedure to test drug susceptibility has to be made available. Ideally, the use of ertapenem would be supported by the results of a clinical trial.

In conclusion this study provides new knowledge on the use of ertapenem in patients with MDR-TB, presenting pharmacokinetic and additional safety data.

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