Drug interactions between ATOvaquone used in MAlaria prophylaxis and antiretroviral agents in HIV-1 infected patients (ATOMA)

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To determine the effect of antiretroviral agents (low-dose ritonavir + lopinavir, low-dose ritonavir + atazanavir, efavirenz) on the pharmacokinetics of single-dose atovaquone determined by intersubject comparison. Secondary objectives: - to...

Ethical review	Approved WMO
Status	Pending
Health condition type	Protozoal infectious disorders
Study type	Interventional

Summary

ID

NL-OMON29726

Source
ToetsingOnline

Brief title
ATOMA

Condition

- Protozoal infectious disorders

Synonym
malaria, prophylaxis of plasmodium falciparum malaria

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: atovaquone, HIV, interaction, malaria

Outcome measures

Primary outcome

The effect of lopinavir/ritonavir, atazanavir/ritonavir and efavirenz on

atovaquone pharmacokinetics (AUC, Cmax).

Secondary outcome

The effect of lopinavir/ritonavir, atazanavir/ritonavir and efavirenz on

proguanil pharmacokinetics (AUC, Cmax).

Adverse events of a single dose atovaquone/proguanil (250/100 mg), alone, or in

combination with lopinavir/ritonavir, atazanavir/ritonavir or efavirenz.

Study description

Background summary

Atovaquone is marketed in a 250mg QD dose with proguanil for use in the treatment and prophylaxis of malaria (Malarone®). Due to its convenience, this agent is frequently used as a prophylactic measure by HIV-infected patients who travel from western countries to areas endemic with malaria such as Africa, Asia and South America.

Unfortunately, there are indications for drug interactions of atovaquone with some frequently prescribed antiretroviral drugs. Although no data are available, the Summary of Product Characteristics of Kaletra® (lopinavir/ritonavir) and Norvir® (ritonavir) warn for reduced atovaquone plasma levels in combined use.

There is indirect evidence that increased glucuronidation of atovaquone is the most likely mechanism of this potential interaction with antiretroviral agents.

Until recently, only high-dose ritonavir was known to induce glucuronosyl

transferase. Data are accumulating, though, that also low-dose ritonavir is still able to induce glucuronidation enzymes.
The ability of low dose ritonavir to induce glucuronidation, makes that an interaction between atovaquone and all boosted Protease Inhibitor regimes is conceivable.

A similar interaction may occur between atovaquone and the NNRTIs nevirapine and efavirenz. For instance, efavirenz reduces plasma concentrations of another substrate for glucuronyltransferase, pravastatin, by 40%.

Summarizing, a substantial number of HIV patients that travel to areas endemic with malaria use Malarone®. This makes it is very useful to know if any relevant interaction occurs between atovaquone (and proguanil) and antiretroviral agents. Therefore, we propose to do a clinical study on potential interactions between antiretroviral agents and atovaquone/proguanil when used as prophylaxis of malaria. Lopinavir/ritonavir and atazanavir/ritonavir will be used as examples of boosted PIs and efavirenz as an example of an NNRTI.

Study objective

To determine the effect of antiretroviral agents (low-dose ritonavir + lopinavir, low-dose ritonavir + atazanavir, efavirenz) on the pharmacokinetics of single-dose atovaquone determined by intersubject comparison.

Secondary objectives:
- to determine the effect of antiretroviral agents (low-dose ritonavir + lopinavir,
low-dose ritonavir + atazanavir, efavirenz) on the pharmacokinetics of single-
dose proguanil determined by intersubject comparison.
- To evaluate the safety of combined use of single-dose atovaquone/proguanil and lopinavir/ritonavir, atazanavir/ritonavir and efavirenz.

Study design

Open-label, multi-centre, phase-IV, single-dose trial

Intervention

All subjects receive a single dose Malarone® (atovaquone / proguanil 250/100 mg).

Study burden and risks

Clinical studies concluded that Malarone® in the dosage used in the

prophylaxis of malaria, had no more side effects than placebo.
Likewise, clinical practice has proven that atovaquone/proguanil for malaria prophylaxis is well tolerated.
The risk to which we expose all participants in this study with a single dose of Ma-larone therefore seems very small.
The needles that are used for blood sampling may cause local irritation and pain.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Healthy volunteers:
1.Subject is at least 18 and not older than 65 years of age on the day of dosing of atovaquone/proguanil.

2.Subject does not smoke more than 10 cigarettes, 2 cigars, or 2 pipes per day for at least 3 months prior to the first dosing.
3.Subject has a Quetelet Index (Body Mass Index) of 18 to 30 kg/m2, extremes included.
4.Subject is in good age-appropriate health condition as established by medical history, physical examination, results of biochemistry, haematology and urinalysis testing within 4 weeks prior to the first dose.Results of biochemistry, haematology and urinalysis testing should be within the laboratory's reference ranges (see Appendix A). If not, the subject is included on condition that the Investigator judges that the deviations are not clinically relevant. This should be clearly recorded.
5.Subject has a normal blood pressure and pulse rate, according to the Investigator's judgement.;HIV patients:
1.HIV-infected as documented by positive HIV antibody test and confirmed by Western Blot.
2.CD4+ > 200 * 106 /L.
3.Subject is at least 18 and not older than 65 years of age at the day of dosing of atovaquone/proguanil.
4.Subject has a Quetelet Index (Body Mass Index) of 18 to 30 kg/m2, extremes included.
5.Use of lopinavir/ritonavir, atazanavir/ritonavir or efavirenz for at least 1 month in a dose of 400/100mg bid, 300/100 mg QD, or 600 mg QD respectively.

Exclusion criteria

Healthy volunteers:
1.History of sensitivity/idiosyncrasy to atovaquone/proguanil or chemically related compounds or excipients.
2.Positive HIV test.
3.Positive HbsAg test (hepatitis B) or positive hepatitis C test.
4.Therapy with any drug (for two weeks preceding dosing), except for paracetamol.
5.Creatinine clearance < 60 mL/min (calculated from serum creatinine).
6.Current diarrhoea.
7.History of or current abuse of drugs, alcohol or solvents.
8.Participation in a drug trial within 60 days prior to the first dose.
9.Donation of blood within 60 days prior to the first dose.
10.Pregnant female (as confirmed by an HCG test performed less than 3 weeks fore the first dose) or breast-feeding female.
11.Abnormal serum transminases, determined as levels being > 3 times up-per limit of normal (see Appendix A for normal ranges of clinical laboratory values).
12.Febrile illness within 3 days before the first dose;HIV patients:
1.History of sensitivity/idiosyncrasy to atovaquone/proguanil or chemically related compounds or excipients.
2.Suspicion of non-adherence to the HIV medication.
3.Current diarrhoea.
4.Pregnant female (as confirmed by an HCG test performed less than 3 weeks before the first dose) or breast-feeding female.
5.Abnormal serum transminases determined as levels being > 3 times upper limit of normal

(see Appendix A for normal ranges of clinical laboratory values).
6.Creatinine clearance < 60 mL/min (calculated from serum creatinine).
7.Any change in antiretroviral medication within 1 month immediately preceding the dose of atovaquone/proguanil.
8.Concomitant use of medications that interfere with atovaquone or proguanil pharmacokinetics: anti-coagulants, aurothioglucose, chloroquine, cimetidine, fluoxetine, fluvoxamine, metoclopramide, omeprazole, magnesiumtrisilicate, rifabutin, rifampin, tetracycline, thyphoid vaccine, topiramate.
9.Use of a HAART regime containing both lopinavir/ritonavir and an other protease inhibitor or an NNRTI.
10.Use of a HAART regime containing both atazanavir/ritonavir and an other protease inhibitor or an NNRTI.
11.Use of a HAART regime containing both efavirenz and one or more protease inhibitors or nevirapine.
12.Active hepatobiliary or hepatic disease
13.Alcohol abuse

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-01-2007
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Malarone
Generic name:	Atovaquone / Proguanil

Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-09-2006
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2006-002864-24-NL
CCMO	NL12993.091.06