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AMBITION-*cm*
AMBIsome Therapy Induction OptimizatioN

Work Practice Document: 6
Contra-indicated drugs

Title of study	High Dose AMBISOME© on a Fluconazole Backbone for Cryptococcal Meningitis Induction Therapy in sub-Saharan Africa: A Phase III Randomized Controlled Non-inferiority Trial		
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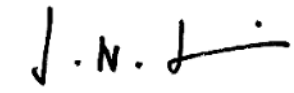
Approved by	Joseph Jarvis CI		14/06/2018

Revision History:		
Version Number	**Effective Date**	**Reason for Change**
1.0		First version
1.1	14/06/2018	Removal of antivirals as contraindicated medication with flucytosine

Working Practice Document 6: Contra-indicated drugs

Purpose

This document lists drugs that are contra-indicated with study medications and those that should be used with caution with study medications

References

1. AMBITION Trial protocol
2. Joint Formulary Committee. *British National Formulary*. 66 ed. London: BMJ Group and Pharmaceutical Press; September 2013

Scope

This WPD applies to drugs which are contra-indicated with fluconazole and flucytosine. Although Fluconazole is Non-CTIMP it will be given along with Ambisome and so is included in this WPD.

No drugs are absolutely contra-indicated with Ambisome and Amphotericin B deoxycholate. Drugs which should be used in caution are outlined here.

Materials

Trial Treatment

British National Formulary

Drug information inserts

1. Fluconazole

Contra-indications

Hypersensitivity to the active substance, to related azole substances, or to any of the excipients.

The following medicinal products known to prolong the QT interval and which are metabolised via the cytochrome P450 (CYP) 3A4 are contraindicated in patients receiving fluconazole:

- Erythromycin
- Cisapride
- Astemizole
- Pimozide
- Quinidine
- Terfenadine

Drugs to avoid/use with caution

Other drugs which can prolong QT interval and should be used with caution with fluconazole

- Antibiotics (quinolones e.g. ciprofloxacin, macrolides e.g. clarithromycin, pentamidine)
- Psychiatric drugs (cisapride, haloperidol, chlorpromazine)
- Antiemetics (domperidone)
- Antiarrhythmics (amiodarone, procainamide)
- Antimalarials (halofantrine)

Drugs which may necessitate monitoring for QT prolongation

- Bedaquiline

See WPD 18: ECG for management of QT prolongation

2. Amphotericin B deoxycholate

Contra-indications

Hypersensitivity to the active substance or to any of the excipients.

Interaction with other medicinal products and other forms of interaction

Concomitant administration of nephrotoxic drugs (NSAIDS such as ibuprofen or diclofenac, aminoglycosides such as gentamicin) or antineoplastics should be avoided if at all possible.

The hypokalaemia following amphotericin B therapy may potentiate the toxicity of digitalis glycosides or enhance the curariform actions of skeletal muscle relaxants.

Corticosteroids and Corticotrophin (ACTH) may increase the potassium loss due to amphotericin B.

Flucytosine toxicity may be enhanced during concomitant administration, possibly due to an increase in its cellular uptake and/or impairment of its renal excretion.

Acute pulmonary reactions have occasionally been observed in patients given amphotericin B during or shortly after leukocyte transfusions. It is advisable to separate these infusions as far as possible and to monitor pulmonary function.

3. Ambisome (liposomal amphotericin B)

Contra-indications

Hypersensitivity to the active substance or to any of the excipients

Interaction with other medicinal products and other forms of interaction

No specific interaction studies have been performed with AmBisome.

However, the following medicinal products are known to interact with amphotericin B and may interact with AmBisome:

Nephrotoxic medications: Concurrent administration of AmBisome with other nephrotoxic agents (for example ciclosporin, aminoglycosides, polymixins, tacrolimus and pentamidine) may enhance the potential for drug-induced renal toxicity in some patients. However, in patients receiving concomitant ciclosporin and/or aminoglycosides, AmBisome was associated with significantly less nephrotoxicity compared to amphotericin B. Regular monitoring of renal function is recommended in patients receiving AmBisome with any nephrotoxic medications.

Corticosteroids, corticotropin (ACTH) and diuretics: Concurrent use of corticosteroids, ACTH and diuretics (loop and thiazide) may potentiate hypokalemia.

Digitalis glycosides: AmBisome-induced hypokalemia may potentiate digitalis toxicity.

Skeletal muscle relaxants: AmBisome-induced hypokalemia may enhance the curariform effect of skeletal muscle relaxants (e.g. tubocurarine).

Antifungals: No evidence of benefit from the use of flucytosine with AmBisome has been observed. Whilst synergy between amphotericin and flucytosine has been reported, concurrent use may increase the toxicity of flucytosine by possibly increasing its cellular uptake and/or impairing its renal excretion.

Antineoplastic agents: Concurrent use of antineoplastic agents may enhance the potential for renal toxicity, bronchospasm and hypotension. Antineoplastic agents should be given concomitantly with caution.

Leukocyte transfusions: Acute pulmonary toxicity has been reported in patients given amphotericin B (as sodium deoxycholate complex) during or shortly after leukocyte transfusions. It is recommended these infusions are separated by as long a period as possible and pulmonary function should be monitored.

4. Flucytosine

Contra-indications

- Hypersensitivity to the active substance or to any of the excipients.
- in breastfeeding women.

Interaction with other medicinal products and other forms of interaction

There is contradictory evidence concerning a drug interaction between flucytosine and cytarabine. Strict monitoring of blood levels is required if the two medicines are given concurrently.

Flucytosine (5FC) must be given with caution to patients with impaired renal function. Renal impairment may lead to accumulation of the drug. Dosage adjustments should be made in patients with renal insufficiency to prevent progressive accumulation of active drug (See WPD 8). Concomitant administration of nephrotoxic drugs (NSAIDS such as ibuprofen or diclofenac, aminoglycosides such as gentamicin) or antineoplastics should be avoided if at all possible.

Flucytosine must be given with extreme caution to patients with bone marrow depression. Frequent monitoring of hepatic function and of the full blood count is indicated during therapy.

See WPD 8 – Toxicity management, for management of neutropenia, anaemia and renal toxicity

See WPD 16 – ART Antifungal interactions for interactions

Training

Each staff member receives or has direct access to applicable Working Practice Documents (WPDs).

Each staff member reviews the applicable WPDs once a year.

All WPD training is documented and tracked in the training log located in the Investigator Site File (ISF)

New staff are trained on applicable WPDs within 30 days of employment and all WPDs within 90 days of employment.

Staff members whose duties fall within this WPD scope are retrained within 14 days of the approval of each WPD revision.

Staff signatures: (signing below indicate that you have read this SOP and understand the material contained in it)

Date	Name (Please print)	Signature