- Amphotericin B is **extensively bound to plasma proteins** and is **distributed throughout the body, becoming highly tissue bound**.
- **Amphotericin B does cross the placenta.**
- **Amphotericin B is Poorly crossing BBB.**
- **Blood-Brain Barrier (BBB).**
- **Metabolized in liver.**
- **Terminal half-life of up to 15 days.**

- **Dosage adjustment is not required in** patients with **compromised hepatic function, *but when renal dysfunction* is due to the use of conventional amphotericin B, the total daily *dose is decreased by 50% .***

- **Adverse effects: Amphotericin B has a low therapeutic index.**
- **A total adult daily dose should not exceed 1.5 mg/kg**. Small test doses are usually administered to assess the degree of a patient's negative responses, **such as anaphylaxis or convulsions. Other toxic manifestations include the following:**

- **Fever and chills: Premedication** with a **corticosteroid or an antipyretic** helps to prevent this problem.
- **Renal impairment:** Despite the low levels of the drug excreted in the urine, patients may exhibit a **decrease in glomerular filtration rate and renal tubular function. Creatinine clearance can drop, and *potassium and magnesium are lost.***
- ***Azotemia*:** (elevated blood urea) is **exacerbated** by other **nephrotoxic drugs, *such as*** *aminoglycosides, cyclosporine, or pentamidine,* **although adequate hydration can decrease its severity.**

- **Hypotension: accompanied by hypokalemia,** *requiring potassium supplementation.* **Care** must be exercised **in patients taking digoxin.**
- **Anemia:** This may be exacerbated in **patients infected with HIV who are taking zidovudine.**
- **Thrombophlebitis (** التهاب الوريد الخثري**):** Adding **heparin** to the infusion can **alleviate** this problem.

- **Interactions**
- **Flucytosine : Toxicity of flucytosine is increased** and allows a lower dose of amphotericin B. **Amphotericin B may also facilitate entry of flucystosine into the fungal cell.**
- **Diuretics or cisplatin: Increased renal toxicity and increased risk of hypokalemia**
- **Corticosteroids: Increased risk of hypokalemia.**

- **Interactions**
- **Aminoglycosides : Increased risk of serious renal damage**, monitor kidney function closely
- **Ganciclovir, Tenofovir, Adefovir: hematological** and **renal** side-effects **of amphotericin B are increased.**
- **Transfusion of leukocytes :** Risk of **pulmonale damage occurs**. Space the intervals between the application of amphotericin B and the transfusion, and monitor pulmonary function.

- **Azole = Imidazole = Ketoconazole**
- ***First orally active azole*** available for the ***treatment of systemic mycosis.***
- **Mechanism of action**: Fungistatic.
- They **inhibit C-14 α-demethylase** , thus **blocking** the **demethylation** of **lanosterol** to **ergosterol** the principal **sterol of fungal membranes.**

- **Antifungal spectrum**: Ketoconazole is active against many fungi, including : **Histoplasma, Blastomyces, Candida, and Coccidioides, *but not aspergillus species.***
- **Resistance**: This **is** becoming a significant **clinical problem**, particularly in the protracted therapy required for those **with** advanced **HIV infection.**

- **Pharmacokinetics:**
- **Only orally.** It requires **gastric acid** for dissolution and is **absorbed through the gastric mucosa.**
- **Administering acidifying agents, such as cola drinks, before taking the drug can improve absorption in patients with achlorhydria.**
- It is **extensively bound to plasma proteins.**
- **Penetration into tissues is limited.**
- **It *does not enter the CSF*.**
- **Extensive metabolism** occurs in the **liver**, and **excretion** is primarily through the **bile.**

- **Adverse effects**:
- In addition to **allergies**, **dose-dependent gastrointestinal disturbances**, including **nausea, anorexia, abdominal pain and vomiting**, are the most common adverse effects of ketoconazole treatment.
- ***Dose reductions*** should be considered in patients ***with severe liver disease.***

- **Drug interactions and contraindications:**
- **By inhibiting CYP3A4, CYP1A2, CYP2C9 ketoconazole** can **potentiate** the **toxicities** of **drugs** such as:
- **cyclosporine, phenytoin, tolbutamide, Buspirone, Calcium channel blockers, glimepiride, glipizide, losartan, montelukast, nateglinide, warfarin, zafirlukast and warfarin, Sildenafil, Tadalafil.**