EPVC Newsletter

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Egyptian Pharmaceutical Vigilance Center (EPVC)

Pharmacovigilance Department

Inside this issue:

Case Report from Cairo- Miscarriage Due to Exposure to Ciprofloxacin/Nitrofurantoin During Pregnancy

The regional center in Cairo has received an ICSR concerning a 24-years old pregnant female, who received Ciprofloxacin 1 gm once daily oral for 7 days and Nitrofurantoin for treatment of UTI during the first trimester of pregnancy as per her physician's prescription, this led to Abortion.

The patient was not aware of being pregnant. After 2 weeks of drug administration, she missed her period and realized that she is pregnant. Abortion occurred after 3 weeks of drug administration.

UTI: Urinary tract infections are among the most common bacterial infections during pregnancy due to hormonal and mechanical changes.

Ciprofloxacin: is a fluoroquinolone antibiotic used to treat different types of bacterial infections.

Fluoroquinolone antibiotics can cause serious or disabling side effect so, should be used only for infections that cannot be treated with a safer antibiotic.

Nitrofurantoin is used for treatment and prophylaxis against acute of recurrent uncomplicated lower urinary tract infections or pyelitis either spontaneous or following surgical procedures.

Labeled information:

According to Ciprofloxacin Summary of product Characteristics (SmPC) it was stated under section (Pregnancy Warnings) that:

Animal studies have failed to reveal evidence of embryotoxicity or teratogenicity.

In rabbits, gastrointestinal toxicity was observed with oral doses and resulted in maternal weight loss and increased incidence of abortion, intrauterine deaths, and fetal retardation (but no teratogenicity)

This drug distributes into amniotic fluid. Levels reported were 57% (at 2 to 4 hours) to 1000% (at 10 to 12 hours)

There are no controlled data in human pregnancy.

According to Nitrofurantoin Summary of product Characteristics (SmPC) it was stated under section (Pregnancy Warnings) that:

This drug should be used during pregnancy up to 38 weeks' gestation only if the benefit outweighs the risk.

This drug is contraindicated in pregnant patients at term (38 to 42 weeks' gestation), during labor and delivery, or when the onset of labor is imminent because of the possibility of hemolytic anemia due to immature erythrocyte enzyme systems (glutathione instability).

Recommendations for Healthcare Professionals:

A. **Ciprofloxacin:** US FDA pregnancy **category C** / AU TGA pregnancy **category B3**

Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

This drug should not be used during pregnancy unless the benefit **outweighs** the risk to both fetus and mother.

As a precautionary measure, it is preferable to avoid the use of ciprofloxacin during pregnancy.

B. Nitrofurantoin: *US FDA pregnancy category B / AU TGA pregnancy category A*

Animal studies have failed to reveal evidence of fetotoxicity or teratogenicity. There are no controlled data in human pregnancy.

Nitrofurantoin should be used at the lowest dose as appropriate only after careful assessment, due to the following:

* The risk of "Spontaneous Abortion" if the pregnant woman had a medical history of threatened abortion.
* The possibility of hemolytic anemia in neonates and children under 3 months due to immature erythrocyte enzyme systems (glutathione instability).

References:

1.Emc- Ciprofloxacin SmPC (Click Here)

2. MHRA- Nitrofurantoin SmPC (Click Here)

3. Medscape.com.UTI in Pregnancy (Click Here)

4. Drugs.com- Ciprofloxacin Pregnancy and Breastfeeding Warnings (Click Here)

A case report from Alexandria- Risk of photosensitivity and hearing impairment associated with Acetazolamide

The regional center in Alexandria has received an ICSR concerning an adolescent of 14 years old who was hospitalized suffering from encephalitis. He was administered Penicillin, Aciclovir, Ceftriaxone and Potassium syrup as a treatment. Later, the patient developed brain edema. Then Acetazolamide tablets were given to the patient; as 1 tablet three times daily. Two days later, the patient developed photosensitivity and photophobia; he was unable to open his eyes in light with a desire to stay in the darkness. Also, he developed severe tinnitus in the ear with decreased hearing. The neurosurgeon decreased the dose *of Acetazolamide* to be twice daily. The reactions decreased after decreasing the dose. Then, the dose returned to be three times daily due to the case condition, so the reactions' severity increased again.

Acetazolamide is an enzyme inhibitor which acts specifically on carbonic anhydrase. It reduces fluid pressure in the eyeball by decreasing fluid formation in the eyeball. It increases the removal of water from the body by the kidney. Also it may block certain nerve discharges that may contribute to seizures

It is indicated in the treatment of:

* *Certain types of glaucoma as:*
  - *chronic simple open angle glaucoma*
  - *secondary glaucoma*
  - *perioperatively in acute angle closure glaucoma where delay of surgery is desired in order to lower intraocular pressure.*
* *Abnormal retention of fluids (edema): Acetazolamide is a diuretic whose effect is due to the effect on the reversible hydration of carbon dioxide and dehydration of carbonic acid reaction in the kidney.*
* *Epilepsy (in conjunction with other anticonvulsants)*

Labeled information:

According to Acetazolamide Summary of product Characteristics (SmPC), it was stated under section (4.8 Undesirable effects) that:

"Adverse reactions during short-term therapy include: paraesthesia, particularly a "tingling" feeling in the extremities; some loss of appetite; taste disturbance, polyuria, flushing, thirst, headache, dizziness, fatigue, irritability, depression, reduced libido and occasional instances of drowsiness and confusion. Rarely, ***photosensitivity*** *has been reported.*

Other occasional adverse reactions include: urticaria, melaena, haematuria, glycosuria, ***impaired hearing and tinnitus****, abnormal liver function, renal failure and rarely, hepatitis or cholestatic jaundice, flaccid paralysis and convulsions."*

Also, it is labeled for Aciclovir that it may cause photosensitivity. According to Aciclovir Summary of product Characteristics (SmPC), it was stated under section (4.8 Undesirable effects) that:

Adverse reactions concerning "Skin and subcutaneous tissue disorders" are pruritus, urticaria, and rashes (including ***photosensitivity****)*

Recommendations:

1. During the administration of Acetazlamide, avoid sun, sunlamps, or tanning booths and use a sunscreen or wear protective clothing, because Acetazolamide may lead to become sunburned more easily
2. Caution should be taken when Acetazolamide is used concomitantly with other drugs that

may cause photosensitivity and/ or hearing impairment.

3. It is recommended to take the dose of Acetazolamide before 6 pm to avoid disturbing sleep as it may increase the amount of urine or cause to urinate more often when you first start taking it.
4. Acetazolamide is contraindicated in case of:
   - Adrenal gland problems, low blood levels of potassium or sodium, kidney problems, liver problems (eg, cirrhosis), high blood levels of chloride, or other electrolyte problems.
   - Kidney stones, a lung disease, certain types of glaucoma (eg, chronic non-congestive angle-closure glaucoma), diabetes, or difficulty breathing
   - Acetazolamide is a sulphonamide derivative. So caution should be taken if you have had a severe allergic reaction (e.g. a severe rash, hives, breathing difficulties, or dizziness) to any other sulfonamide medicine.
   - (Example of sulphonamide medicines: celecoxib, certain diuretics as hydrochlorothiazide, glyburide, sulfamethoxazole …etc.)
   - In patients with hepatic cirrhosis, as this may increase the risk of hepatic encephalopathy.
   - Because of possible additive effects, concomitant use with other carbonic anhydrase inhibitors is not advisable.
5. Some medicines may interact with Acetazolamide:
   - Salicylates (eg, aspirin) because they may increase the risk of acetazolamide's side effects.
   - Other carbonic anhydrase inhibitors (eg, methazolamide), cyclosporine, quinidine, phenytoin, amphetamine, or sodium bicarbonate because the risk of their side effects may be increased by acetazolamide.
   - Primidone, salicylates, lithium, or methenamine because their effectiveness may be decreased by acetazolamide.
   - Acetazolamide should be used with extreme caution in CHILDREN; because safety and effectiveness in children have not been confirmed.

References:

1. Drugs.com Acetazolamide, (Click Here)

2. Emc-Acetazolamide 250mg Tablets(Click Here)

3. emc- Aciclovir 25 mg/ml Concentrate for Solution for Infusion (Click Here)

A case report from Sohag- Severe Thrombophlebitis at the injection site induced by Utoral

The regional center in Sohag had received five ICSRs about Severe Thrombophlebitis at the injection site induced by Utoral IV

4 ICSRs were for adult female patients suffering from colon cancer, and 1 ICSR was for elderly male patient suffering from larynx cancer, the patients started their chemotherapy treatment by administration of Utoral 250 mg ampoule with chemotherapies such as (oxaliplatin, leucovorin, Docetaxel, platinol).

but when the physician shifted Utoral 250 mg ampoule to Utoral 500 vial severe thrombophlebitis appeared , then Utoral 500 vial had been withdrawn and thrombox cream was used for treatment but the reaction was taking long time to be managed when the physician had shifted to Utoral 250 ampoule, the reaction didn't appear again.

Utoral:

Fluorouracil(5-FU), active ingredient of utoral is in the antimetabolite and pyrimidine analog families of medications.

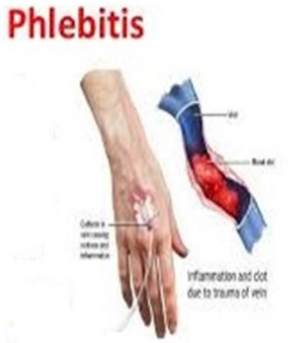
How it works is not entirely clear but believed to involve blocking the action of thymidylate synthase and thus stopping the production of DNA

Fluorouracil has been given systemically for anal, breast, colorectal, esophageal, stomach, pancreatic and skin cancers (especially head and neck cancers).

It has also been given topically (on the skin) for actinic keratosis, skin cancers and Bowen's disease and as eye drops for treatment of ocular surface squamous neoplasia.

Thrombophlebitis:

Superficial thrombophlebitis is a common inflammatory-thrombotic disorder in which a thrombus develops in a vein located near the surface of the skin.



Most superficial veins that develop thrombosis also have phlebitis

The condition presents as redness and tenderness along the course of the vein, usually accompanied by swelling. Bleeding also can occur at the site of a varicose vein.

Upon search it was found that:

- Fluorouracil Injection is recommended for administration either as an intravenous bolus or as an intravenous infusion.
- Do not inject the entire contents of the vial directly into patients. Individualize the dose and dosing schedule of Fluorouracil Injection based on tumor type, the specific regimen administered, disease state, response to treatment, and patient risk factors
- Recommended Dosage for Adenocarcinoma of the Colon and Rectum administered in an infusional regimen in combination with leucovorin alone, or in combination with leucovorin and oxaliplatin or irinotecan, is 400 mg/m2 by intravenous bolus on Day 1, followed by 2,400 mg/m2 to 3,000 mg/m2 intravenously as a continuous infusion over 46 hours every two weeks.
- **IV Administration**
  - IV push injection (50 mg/mL solution needs no further dilution) or by IV infusion

- Toxicity may be reduced by giving the drug as a constant infusion
- Bolus doses may be administered by slow IVP or IVPB
- Warm to body temperature before using
- Solution should be protected from direct sunlight
- 5-FU may also be administered intra-arterially or intra-hepatically
- Use plastic IV containers for continuous infusions (stable in plastic IV bags than in glass bottles)

- Because of angioalgia and phlebitis is occurred administration rate is slow possibly In case of cutting ampoule, fluorouracil ampoule is cut after protecting cloth containing ethanol, because glass fraction is mixed.
- Superficial vein thrombophlebitis of the upper limb is a common and painful complication in patients undergoing intravenous treatments with antineoplastic agents
- Ketoprofen lysine salt is a nonsteroidal anti-inflammatory drug with marked antiphlogistic and analgesic activity, in the 5% gel formulation, it has been used direct successfully in the topical treatment of thrombophlebitis.

References:

1. *FDA-Flourouracil label (Click Here)*
2. *Medscape-fluorouracil (Click Here)*