

**Egyptian
Pharmaceutical
Vigilance Center
(EPVC)**

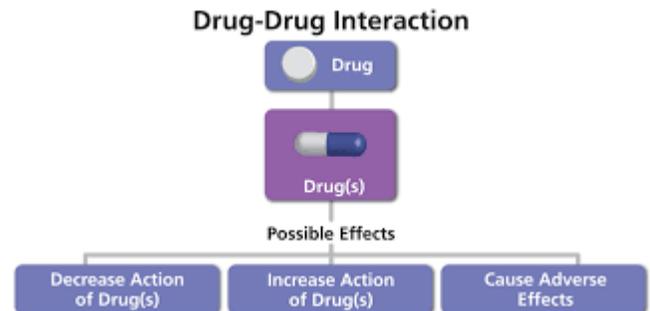
**Pharmacovigilance
Department**

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Case Report from Alexandria -Raised liver enzymes due to Drug-Drug interaction



The regional center in Alexandria has received a yellow card concerning a fifty-six years old female who was receiving Methotrexate-Tizanidine-hydroxychloroquine-Diclofenac (suspected drugs) for treatment of Rheumatoid arthritis, and other concomitant drugs like Insulatard, Actrapid, Concor plus, Eltroxin, Glucophage SR 1000 and Blokaten.

Then she experienced increased liver enzymes, the physician suspect that may be a Drug-Drug interaction between suspected drugs mentioned before that may lead to this reaction.

All suspected drugs used may lead to the reaction (increased liver enzyme) as an ADR, So the physician decided to stop Tizanidine and advised the patient to make liver enzymes analysis on this day as a base line then to repeat it after one month of stopping Tizanidine. The patient stops taking Tizanidine, and did liver enzymes one month later, the liver enzymes decreased.

Suspected Drugs:

Methotrexate (formerly *Amethopterin*) is an antimetabolite used in the treatment of certain neoplastic diseases, severe psoriasis, and adult rheumatoid arthritis.

Tizanidine is a central alpha-2-adrenergic agonist indicated for the management of spasticity.

Hydroxychloroquine Tablets - The drug possesses antimalarial actions and also exerts a beneficial effect in lupus erythematosus (chronic discoid or

systemic) and acute or chronic rheumatoid arthritis. The precise mechanism of action is not known.

Diclofenac sodium is a non-steroidal anti-inflammatory drug (NSAID) recommended for the treatment of: rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and many other diseases

(Elevated liver enzymes) = Increase in ALT & AST

The blood test for **aspartate aminotransferase (AST)** is usually used to detect liver damage. It is often ordered in conjunction with another liver enzyme, **alanine aminotransferase (ALT)**, or as part of a liver panel or comprehensive metabolic panel (CMP) to screen for and/or help diagnose liver disorders.

Sometimes AST may be used to monitor people who are taking medications that are potentially toxic to the liver. If AST levels increase, then the person may be switched to another medication.

(Rheumatoid arthritis) (RA): RA is a systemic inflammatory disease that manifests itself in multiple joints in the body. This inflammation usually affects the lining of the joints (synovial membrane), but can also affect other organs. This inflamed joint lining leads to erosions of the cartilage and bone and sometimes causes joint deformity. Pain, swelling, and redness are common joint symptoms.

RA causes are unknown, but it is believed to result from a faulty immune response.

Labeled information:

Methotrexate 2.5 mg Tablets Summary of product Characteristics (SmPC) stated under section 4.8 **Undesirable effects:** *Hepatic toxicity resulting in significant elevations of liver enzymes, acute liver atrophy, necrosis, fatty metamorphosis, hepatitis, periportal fibrosis or cirrhosis or death may occur, usually following chronic administration.*

Tizanidine 4mg Tablets SmPC stated under section 4.8 **Undesirable effects:**

Slight increases in hepatic serum transaminases were observed in a number of toxicity studies at higher dose levels. They were not consistently associated with histopathological changes in the liver.

Hydroxychloroquine Tablets SmPC stated that: *Isolated cases of abnormal liver function tests have been reported; rare cases of fulminant hepatic failure have also been reported.*

Diclofenac SmPC stated that: *Effects on the liver include occasional reports of elevation of serum aminotransferase enzymes (ALT, ST) and rarely abnormal liver function, hepatitis and jaundice.*

Methotrexate / tizanidine Drug-Drug interaction

Coadministration of methotrexate with other agents known to induce hepatotoxicity may potentiate the risk of liver injury. Methotrexate, especially at higher doses or with prolonged treatment, has been associated with hepatotoxicity including acute hepatitis, chronic fibrosis, necrosis, cirrhosis, and liver enzyme elevations.

General Precautions of using Methotrexate:

- Co-administration of **methotrexate** with other agents known to induce hepatotoxicity may potentiate the risk of liver injury, so:

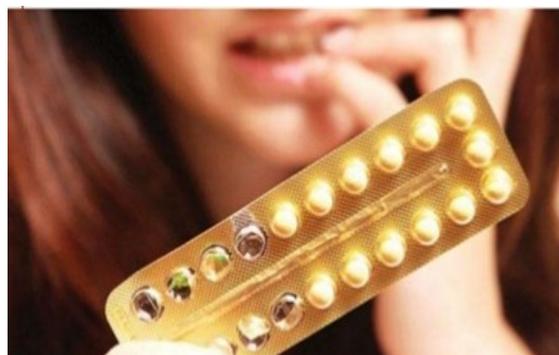
- * Drug-Drug interaction should be checked regularly when using Methotrexate with other drugs that may affect liver.
- * AST/ALT should be monitored regularly during administration of Methotrexate.
- Before beginning methotrexate therapy or reinstating methotrexate after a rest period, assessment of:
 - * renal function,
 - * liver function
 - * blood elements should be made by history,
 - * Physical examination and laboratory tests.
- Methotrexate has some immunosuppressive activity and immunological responses to concurrent vaccination may be decreased. Immunization with live virus vaccines is generally not recommended.
- Pleural effusions and ascites should be drained prior to initiation of methotrexate therapy.
- Serious adverse reactions including deaths have been reported with concomitant administration of methotrexate (usually in high doses) along with some non-steroidal anti-inflammatory drugs (NSAIDs).
- antagonists such as trimethoprim/ sulphamethoxazole has been reported to cause an acute megaloblastic pancytopenia in rare instances.
- Severe, occasionally fatal, cutaneous or sensitivity reactions may occur after the administration of methotrexate and recovery ensured Concomitant administration of folate mostly after discontinuation of the therapy.

References:

1. *Drugs.com - Methotexate* ([Click Here](#))
2. *Drugs.com - Tizanidine* ([Click Here](#))
3. *Drugs.com - Hydroxychloroquin* ([Click Here](#))
4. *Drugs.com - Diclofenac sodium* ([Click Here](#))
5. *Labtestsonline AST test* ([Click Here](#))
6. *Centers for disease control and prevention- Rheumatoid arthritis* ([Click Here](#))
7. *Drug Interaction Report* ([Click Here](#))

A case report from Sohag- Endometrial disorders & Uterine bleeding induced by microcept COCs pills

Sohag Egyptian pharmaceutical Vigilance regional center has received an ICSR about endometrial disorders with Uterine bleeding induced by microcept COCs pills, this case was for female patient 32 years old, who was taking microcept pills once daily since long time as oral contraceptive, Then she complained of Unscheduled or breakthrough vaginal bleeding or spotting *and Endometrial disorders* (Weakness of Uterine lining) , then her Gynecologist advised that Microcet pills should be stopped and prescribed her Kapron ampoules as a treatment . Then the patient recovered.



Microcept:

Combined oral contraceptive tablets, MONOPHASIC, estrogen(ethinylestradiol) 30 microgram, progestogen (levonorgestrel)150 microgram.

The contraceptive effect of Microcept is based on the interaction between various factors, the most important of which are the inhibition of ovulation and changes in the cervical mucus.

The tablets must be taken in the order given on the blister pack, every day at approximately the same time point. One tablet is taken daily for 21 consecutive days. Every subsequent blister pack is started after a 7 day tablet-free interval during which time a withdrawal bleed usually occurs. This bleeding will usually start on the 2nd or 3rd day after the last tablet has been taken and it may not have stopped, before the next blister pack is started.

Endometrial disorders with Uterine bleeding:

Abnormal uterine bleeding (formerly, dysfunctional uterine bleeding [DUB] is irregular uterine bleeding that occurs in the absence of recognizable pelvic pathology, general medical disease, or pregnancy. It reflects a disruption in the normal cyclic pattern of ovulatory hormonal stimulation to the endometrial lining. The bleeding is unpredictable in many ways. It may be excessively heavy or light and may be prolonged, frequent, or random.

About 1-2% of women with improperly managed an ovulatory bleeding eventually may develop endometrial cancer.

Upon search it was found that:

- Inadequate exposure to the active components of a combined oral contraceptive (COC) may lead to therapeutic failure, i.e. pregnancy, which has a large impact on people's life. Inadequate exposure

could also lead to disruption of cycle control and increase the occurrence of breakthrough bleeding, which may affect compliance and cause discontinuation of COC use.

- With all combined oral contraceptives, irregular bleeding (spotting or break through bleeding) may occur, especially during the first months. Hence, the evaluation of any irregular bleeding should be considered after a period of adaptation of approximately 3 cycles.
- If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered, and adequate diagnostic measures are indicated to exclude malignancy or pregnancy.
- If non- hormonal causes are excluded, oral contraceptives with a higher hormonal content may need to be considered. Occasionally withdrawal bleeding during the tablet-free interval may not occur at all. If the tablets have been taken according to the instructions described, it is unlikely that the woman is pregnant. However, if the oral contraceptive has not been taken according to the instructions, before the first absent withdrawal bleed, or if two withdrawal bleeds are overdue, pregnancy should be excluded before the oral contraceptive is continued

References:

1. FDA label-levonorgestrel and ethinyl estradiol tablets ([Click Here](#))
2. Scientific Conclusions Presented By The EMEA ([Click Here](#))
3. MHRA Public assessment report-levonorgestrel and ethinyl estradiol tablets ([Click Here](#))
4. Medscape-Abnormal (Dysfunctional) Uterine Bleeding ([Click Here](#))
5. Webmd-Abnormal Vaginal Bleeding ([Click Here](#))