

## Methotrexate Therapy in Obstetrical Diseases

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### Abstract

Our study is a review of Methotrexate therapy in obstetrical diseases such as: hydatidiform mole, and medical abortion. In the medical world, methotrexate is a cytostatic drug used in neoplastic diseases. The clinical pharmacology data regarding methotrexate is presented, alongside route of administration and therapeutic effects in malignant disease, hydatiform mole, and medical abortion. The use of methotrexate in medical abortion and ectopic pregnancy is a great accomplishment, as it replaces a surgical intervention marred by characteristic side effects, with similar results.

**Keywords:** Methotrexate, obstetrics, gynecology, tubal pregnancy, HCG human chorionic gonadotrophine hormon.

### 1. Introduction

In the medical world, methotrexate is a cytostatic drug used in neoplastic diseases such as lymphoblastic leukaemia, leukaemic meningitis, Burkitt lymphoma, mycosis fungoides, osteosarcoma, as well as severe forms of psoriasis and rheumatoid arthritis.

Methotrexate was first used in obstetrics and gynaecology in the year 1956 for the treatment of trophoblastic gestational disease [1]. We present general data regarding methotrexate as a drug.

### 2. Methotrexate – General Pharmacology

Methotrexate is part of a cytostatic group of drugs called antimetabolites. In the same group, we have 5-fluorouracil, an antimetabolite of uracil, and capecitabine, a prodrug of 5'-deoxy 5 fluoridine [2]. The chemical formula was first described in 1946. Methotrexate is an 8 amino 10 methyl pteroylglutamic acid (Fig.1).

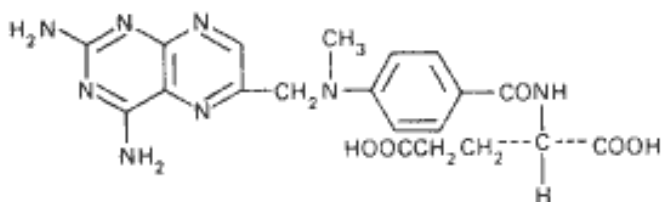


Fig. 1 The chemical formula of methotrexate (2)

The chemical name: (+)-N-[p-[[[2,4-Diamino-6-pteridinyl)methyl] methylamino] benzoyl]-L-glutamic acid; N-[4-[[[2,4-diamino-6 pteridinyl)methyl][methylamino]benzoyl]-L-glutamic acid.

Antimetabolites inhibit the synthesis of purine (guanine, purine) or pyrimidine (uracil) nucleotidic precursors or they compete with these in DNA or RNA synthesis. The maximum cytostatic effect is specific of the S phase of the cellular cycle. Folic acid is a structural metabolite of certain enzymes that take part in the synthesis of nucleic acids, followed by cellular division.

### Pharmacodynamics

Cells with active proliferation (malignant cells of the bone marrow, oral, intestinal and bladder mucosa, and foetal cells) are generally more sensitive to the stopping of cellular division. When cell proliferation in malignant tissues is higher than in the majority of normal tissues, methotrexate can influence malignant growth, without irreversible effects on normal tissues [2].

### Pharmacokinetics

**Absorption.** In adults, absorption following oral administration depends on the dose. The maximum serum concentration is obtained in 1-2 hours. At doses of 30 mg/m<sup>2</sup> or smaller, methotrexate is generally well absorbed, with an average bioavailability of 60%. Absorption of doses higher than 80 mg/m<sup>2</sup> is significantly lower, possibly due to saturation effect [2].

**Halving time.** Halving time for methotrexate is 3-10 hours in patients who are administered less than 30 mg/m<sup>2</sup> or lower doses (in psoriasis or rheumatoid arthritis). In patients who are administered higher doses, halving time is around 8-15 hours.

**Excretion.** Renal excretion is the primary elimination pathway and it depends on dosage and the route of administration. Methotrexate is excreted unmodified in a percentage of 80-90% in the first 24 hours. There also exists a biliary excretion amounting to 10% or less of the administered dose. Renal excretion is accomplished through glomerular filtration and active tubular secretion [2].

**Toxicity.** The toxicity of the drug towards healthy tissues depends on the length of exposure to methotrexate. When a patient has a slow elimination of the drug due to renal ailments, accumulation in the serous tissues or due to other causes, the serum concentration can remain elevated for a long period of time. Toxicity due to high doses or slow excretion is reduced through the administration of calcium folinate (factor citrovorum) [2].

**Overdose.** To reduce the toxicity and counteract effects due to methotrexate overdose, treatment with calcium folinate is indicated. Administration must begin as early as possible. When the interval between the administration of methotrexate and that of calcium folinate is higher, the efficiency of folinate in alleviating methotrexate toxicity decreases.

### Therapeutic guide regarding methotrexate and calcium folinate treatment

- The administration of methotrexate must be delayed if the leukocyte count is lower than 3000/mm<sup>3</sup>; platelet count lower than 75.000, serum bilirubin higher than 1,2; TGP and TGO twice higher than normal, or if the patient presents with persistent pleurisy.
- Evaluation of renal function: serum creatinine must be normal, clearance higher than 60ml/min; if during treatment, creatinine grows by 50% or more, compared to the initial value, it is necessary to determine the creatinine clearance, which must be higher than 60ml/min.

- c. Patient hydration and urine alkalinization: 1000ml/m<sup>2</sup> of intravenous fluid is administered 6 hours before the methotrexate i.v drip. Hydration with 125 mL/m<sup>2</sup>/hour(3l/m<sup>2</sup>/day) during the i.v. and 2 days after ending it. Urine is alkalinized to obtain a pH higher than 7. Alkalinization can be achieved through the administration of oral or intravenous sodium bicarbonate.

#### **Metotrexat – brand names**

**Abitrexate**, injection 25 mg/mL- 2 mL; sol.inj. 25 mg/mL- 20 ml (Abic, Israel) **Antifolan**, tablets 2,5 mg; injection powder./perf. 50 mg (Sindan, Romania)

**Methotrexat "Lederle"**, tablets 2,5 mg; tablets 10 mg; injection 25 mg/mL- 1 mL; injection. 25 mg/mL- 2 mL; injection. 25 mg/mL- 20 mL; injection 25 mg/mL- 40 ml; injection 25 mg/mL- 200 mL (Wyeth Lederle, Austria)

**Methotrexat Ebewe**, solution for injection and infusion 5 mg/mL- 1 mL; solution for injection and infusion 10 mg/mL-1 mL; solution for injection and infusion 10 mg/mL- 5 mL; solution for injection and infusion 100 mg/mL - 5 mL solution for injection and infusion 100 mg/mL- 10 mL; solution for injection and infusion 100 mg/mL- 50 mL; (Ebewe, Austria).

#### **Trophoblastic gestational disease**

Trophoblastic gestational disease is a complex clinical and anatomic pathology entity which defines a benign and malignant proliferation of the chorionic villi of the trophoblast during pregnancy. In partial mole, the trophoblastic hyperplasia is focal, with stromal inclusions, with a triploid karyotype 69XXX, 69XXY, 69XY. The additional haploid set is usually of paternal origin [3]. If the foetus is present, it shows the signs of the triploidy: multiple foetal malformations, growth retardation, syndactyly, and hydrocephalus [4]. Complete molar pregnancy is characterized through the absence of embryonic or foetal tissue, chorionic villi show a general ballooning, trophoblastic hyperplasia is diffuse, stromal inclusions are absent, and the karyotype is 46XX and 46XY of paternal origin [5].

#### **Results and Discussions**

##### **Treatment of persistent trophoblastic gestational disease**

##### **Mono-chemotherapy**

The use of methotrexate and actinomycin D in the treatment of metastatic and non-metastatic persistent trophoblastic gestational disease with low risk has led to the improvement of disease prognosis and to the obtaining of remission phases [6].

##### *a. The use of methotrexate*

There are several methotrexate administration protocols, with similar results.

- the most frequently used protocol is intra-muscular or intravenous 0,4mg/kg body weight for 5 days.
- a second option: 1-1,5 mg/kg body weight in 4 doses in the 1-3-5-7 days, followed by administration of folic acid (citrovorum acid) in doses of 0,1-0,14mg/kg body weight in the 2-4-6-8 days.

Literature first reported the association of methotrexate and folic acid in the treatment of trophoblastic gestational disease was in the years 1964 [7].

Starting with the year 1977, the combination methotrexate-folic acid has represented the first-choice treatment in persistent trophoblastic gestational disease [8].

##### **First line chemotherapy – combined EMA/CO chemotherapy**

Combined EMA/CO chemotherapy is used in patients with metastatic trophoblastic gestational disease and in those with a prognosis score with high risk. In all protocols for combined chemotherapy for trophoblastic gestational disease, etoposide is used alongside methotrexate and actinomycin D.

*EMA/CO regimen, treatment scheme:*

*First session:*

Day 1:

- etoposide 100mg/ m<sup>2</sup>;
- methotrexate 100mg/ m<sup>2</sup> intravenous as loading dose, followed by 200 mg/m<sup>2</sup> intravenously for 12 hours;

Day 2:

- folic acid (citrovorum acid) 15mg intravenous, administered 24 hours after methotrexate and repeated 4 times at a 12 hour interval.
- actinomycin D 0,5 mg intravenous.

6 days break.

*Second session:*

Day 8:

- cyclophosphamide 600 mg/m<sup>2</sup> intravenous;
- vincristine 1 mg/m<sup>2</sup>

The cycle is repeated every 2 weeks until 3 negative values of the human gonadotropin hormone (hCG).

### **Fertility after persistent trophoblastic gestational disease**

In patients with persistent trophoblastic gestational disease successfully treated through chemotherapy, a normal future reproductive function is expected. Future products of concepts have a low risk of foetal abnormalities and malformations [9, 10].

### **Methotrexate in induced medical abortion. Classification**

Medical abortion (induced) can be:

- *legal*, which is performed with the boundaries of the law by qualified medical personnel (specialized physicians);
- *illegal* – which is provoked through various methods. Known in literature as septic or unsafe abortion.

*Legal abortion* can be therapeutic in cases where:

- the foetus endangers the life of the mother;
- the pregnancy is a result of rape or incest (ethical abortion);
- the foetus has severe abnormalities or severe intra-uterine growth retardation (eugenic abortion).

In Romania, therapeutic abortion can be performed up to 24 weeks [11]. By request, abortion can be performed legally up to 14 weeks of gestational age.

In Romania, abortion has become possible as of 26 December 1989, through the abolishment of the communist decree. Between 1990-1992, the rate of requested medical abortion was of 200 abortions per 1000 fertile females with ages between 15 and 44, which corresponds to approximately 3 abortions for one live newborn and a total rate of 3,4 abortions per one fertile female between 15 and 44 years old. This rate was the highest in the world at the time [11, 12].

### **Induced abortion through medical treatment with methotrexate and misoprostol (see Fig 2)**

Medical abortion induction methods as an alternative to surgical procedures first appeared in Europe and China starting with the year 1990 [13].

### **Inclusion criteria:**

- haemodynamic stable patients;
- intra-uterine pregnancy 56-63 days old or less since the date of the last menstrual cycle;
- pregnancy age confirmed through trans-vaginal ultrasound;
- available blood tests;
- Rh factor – administration of antiD immunoglobulin if patients are RH negative and have no previous isoimmunization;
- complete blood count: RBC, WBC, PLT;
- hepatic enzymes: TGO, TGP;

- renal function: creatinine, uric acid, urea;
- signed informed consent regarding the drugs used, potential side effects, success and failure rate of the treatment as well as the potential need for surgical intervention.

**Exclusion criteria:**

- known allergies to the 2 compounds (methotrexate and misoprostol) ;
- haematological ailments: leukopenia ( $<3000/\text{mm}^3$ ) or thrombocytopenia ( $<100000/\text{mm}^3$ )
- hepatic ailments;
- renal ailments;
- asthma or other pulmonary ailments;
- HIV or AIDS infection.

Protocol administration [13]

If the inclusion criteria are met, the drugs are administered as follows:

Day 1

Methotrexate administered systemically

- a. single dose of 50 or 60 mg/m<sup>2</sup> body surface, intra-muscular. Raising the methotrexate dose does not increase success rate [14].
- b. single oral dose, 25-50 mg with the same efficiency as intramuscular doses [15].

The patient is discharged from hospital. The patient returns for the remainder of the treatment in the 5-7 days.

Day 5 and 7:

Intravaginal misoprostol 800 µg, one of the two options:

1. 4 tablets of 200 µg inserted vaginally with a tampon that will be kept in for 12 hours;
2. 4 ovules of 200 µg inserted in the Douglas cul-de-sac.

Day 12 – Day 14 – according to the results of clinical and ultrasound investigations, the treatment will continue as follows:

- a. If the ultrasound shows an incomplete abortions (ovular remnants in the uterine cavity), treatment consists of a surgical aspiration abortion.
- b. If the ultrasound shows the existence of an intra-uterine sac with or without cardiac activity, an additional dose of 800 µg intravaginal misoprostol or a surgical aspiration, as the patient wishes.
- c. If the ultrasound shows a complete evacuation of the product of conception, the treatment is considered successful.

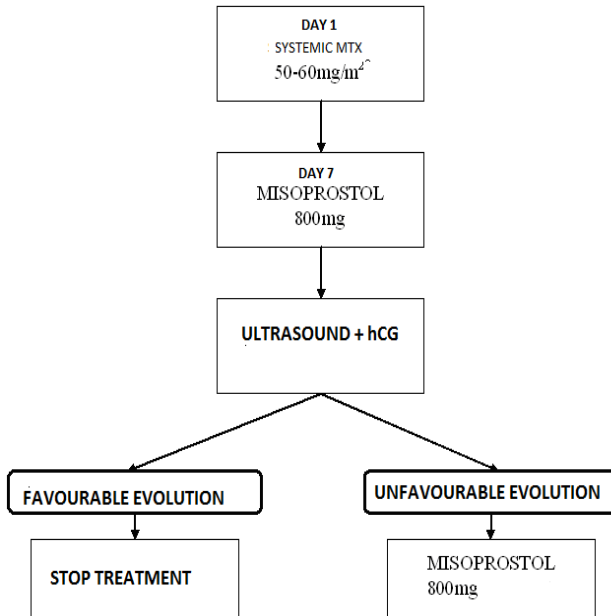


Fig.2 Treatment scheme for medical abortion with methotrexate-misoprostol

## CONCLUSIONS

### Treatment failure and success

**Success** is defined as the complete elimination of the product of conception within the first 7 days since the administration of the first misoprostol dose (days 7-14) or after the administration of the additional dose of misoprostol in days 12-14 (the interval 14-21).

Immediate success – complete abortion is obtained before the administration of misoprostol or during the first 24 hours since administration.

Late or delayed success – complete abortion is obtained after more than 24 hours since the administration of misoprostol.

**Failure** is defined as the incomplete elimination of the product of conception, even after the administration of the additional misoprostol dose, which leads to surgical resolution of the case. Literature studies show a success rate of 90% for pregnancies of 56 days or less [16].

In 12 to 35% of women, abortion is produced in the 20-30 days following administration of misoprostol.

Methotrexate was also used alone for abortion induction, but the success rate is smaller than in the case of combined therapy; abortion is produced 3 weeks following drug administration [17] Methotrexate, a drug used solely in neoplastic disease was also included in obstetrical therapy so as to prevent the transformation of hydatidiform mole in chorionic carcinoma with improvement in the vital prognosis of the patients. Its use in medical abortion and ectopic pregnancy is a great accomplishment, as it replaces a surgical intervention with all of its complications – including those related to anaesthesia – with similar results.

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