

A CLINICAL PHARMACOLOGICAL APPROACH TO THE RATIONAL USE OF ANTI-INFLAMMATORY DRUGS IN PREGNANT WOMEN

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ABSTRACT

Nonsteroidal anti-inflammatory drugs (NAID) are a group of drugs that are widely used in clinical practice. Pregnant women also use NSIDs quite often - both as prescribed by a doctor and independently. However, information about the safety of their use in this category of patients in Russian-language sources is limited.

Keywords: unwanted adverse reactions, non-steroidal anti-inflammatory drugs, pregnant women, fetus.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NAIDs) are a group of drugs that are widely used in clinical practice, many of which can be purchased without a prescription. The popularity of NAIDs is explained by the fact that they have anti-inflammatory, analgesic and antipyretic effects and bring relief to patients with corresponding symptoms - inflammation, pain, hyperthermia [1].

MATERIALS AND METHODS

We used studies and descriptions of clinical cases from the databases reprotox (by subscription), Medline (as of 2011), as well as the manual of K. Schaefer [4]. Due to the limited scope of the article, studies were selected whose results were not refuted by subsequent, more recent and better-conducted studies. The purpose of the search was to study the frequency of adverse reactions (ADRs) in pregnant women.

Inclusion criteria. The work included studies on humans, pregnant women, and descriptions of clinical cases of using NAID systemically (enterally and parenterally).

Exclusion criteria. The work did not include experiments on animals, as well as studies without describing the results, local use of NAID, and the use of combined drugs.

RESULTS AND DISCUSSION

There is general information about the use of any drugs during pregnancy. Thus, the following rules must be observed [4]:

- prescribe drugs according to strict indications, only if the expected benefit outweighs the possible risk to the fetus;
- a pregnant woman should use only those drugs that have been tested over many years of practice. The prerequisite is data on the absence of embryotoxic properties in these agents. The use of a new drug carries an element of risk. From the NAID group, this applies to a greater extent to selective cyclooxygenase-2 (COX-2) inhibitors, the effect of which on the course of pregnancy has not been sufficiently studied;

- strive for monotherapy and limit the use of combination drugs;
- choose the minimum therapeutic dose of drugs;
- assess the risks: the disease may be a risk factor for the normal development of the fetus;

Severe stressful situations (for example, pain) can also threaten the normal course of pregnancy. Lack of treatment may pose a higher risk to the unborn child than treatment itself. NAID is often used for pain relief and as an antipyretic. In this case, paracetamol (Acetaminophen) is considered the drug of choice. According to most guidelines, drugs can be prescribed at any stage of pregnancy in normal doses. In the first and second trimesters of pregnancy, ibuprofen and diclofenac are used as anti-inflammatory drugs. Starting from the 30th week of gestation, you should refrain from using them due to the risk of premature closure of the ductus arteriosus in the fetus, the occurrence of oligohydramnios and impaired renal function in the newborn. Low-dose therapy with acetylsalicylic acid (80–300 mg/day) can be carried out without restrictions for appropriate indications [4]. Two papers describe an increased risk of spontaneous abortion as a result of NAID use. However, the small number of observations in both studies makes this conclusion questionable [2]. There are no indications of an increased risk of fetal malformations in humans when using drugs in this group. A retrospective analysis of data from the Swedish Birth Registry, covering 2557 newborns whose mothers took NAID in the first trimester, showed that the risk of developmental defects was not generally increased, and the incidence of mild cardiovascular defects (mainly atrial and interventricular defects) was only slightly increased (for septal defects). No connection with any specific drug from the NAID group was observed [3]. NAIDs are known to prolong pregnancy in animals and humans. Prostaglandins of groups E and F regulate uterine contractility, and several hours before birth their synthesis sharply increases, which is associated with the induction of COX-2. It is believed that these substances play a decisive role in the onset and development of labor [5]. These data formed the basis for the use of drugs as tocolytics when there is a threat of premature birth. In the “Formula of Drugs in Obstetrics and Gynecology” edited by V. Radzinsky (2011), indomethacin is presented as a tocolytic from the NAID group, which has been used for this purpose since 1974 [2]. However, when using these drugs in late pregnancy, quite serious adverse reactions can occur. The most common occurrence of NAID use in the third trimester (after 28–30 weeks) is premature closure of the ductus arteriosus in the fetus, which can lead to fetal/newborn pulmonary hypertension and death. This effect has been demonstrated in rats and in some cases in humans [3]. It is known that the occurrence of ADR is associated with suppression of prostaglandin synthesis. In the ductus arteriosus, this effect leads to smooth muscle contraction and cessation of function. Currently, indomethacin is used in neonatology, used to close the functioning ductus arteriosus in premature newborns. The greatest therapeutic effect develops in children between 28 and 34 weeks and decreases with gestational age 34–36 weeks [2]. At the same time, the effect was not noticed when using paracetamol. Apparently, this is due to the fact that paracetamol is a weak COX inhibitor [3].

Paracetamol (Acetaminophen). Paracetamol is not always classified as a NAID, since the drug is almost devoid of anti-inflammatory activity. This is probably due to the suppression of COX only in the brain, but not in the site of inflammation [4]. Due to the fact that paracetamol is the drug of choice as an antipyretic and analgesic during pregnancy, you should focus on it. It

is known that studies have not revealed the teratogenic effect of paracetamol in humans [5]. A population-based case-control study using data from the National Birth Defects Prevention Study not only found no association between paracetamol and any birth defects, but also demonstrated a statistically significant reduction in the risk of neural tube defects and anotia. /microtia (absence or hypoplasia of the auricle), cleft lips and gastroschisis [3]. Recently, there have been reports of a possible connection between taking paracetamol during pregnancy and cryptorchidism in newborn boys. COX inhibitors - paracetamol, ibuprofen and acetylsalicylic acid (Aspirin) have demonstrated the ability to influence the endocrine system in rainbow trout. In humans, Aspirin blocks the androgenic response to human chorionic gonadotropin (hCG), and since hCG-stimulated androgen production plays a key role in normal testicular descent, exposure to COX inhibitors during the vulnerable period of pregnancy may have a negative effect. A study conducted as part of the Danish National Birth Cohort Study described an association between paracetamol use in the first and second trimesters of pregnancy and cryptorchidism in the offspring [4]. At the same time, the results of this study seem debatable by some researchers, since the 95% CI included one (adjusted RR 1.33; 95% CI 1.00–1.77).

CONCLUSION

During pregnancy, the drug of choice as an analgesic and antipyretic is paracetamol, which can be prescribed to women at any stage of pregnancy in normal doses. In the first and second trimesters of pregnancy, well-tested NAIDs such as ibuprofen and diclofenac can be used as anti-inflammatory drugs. Starting from the 30th week, you should refrain from using them due to the risk of premature closure of the ductus arteriosus in the fetus, the occurrence of oligohydramnios and impaired renal function in the newborn; if their use is unavoidable, perform an ultrasound examination once or twice a week to identify possible complications (changes in hemodynamics in the ductus arteriosus, the occurrence of oligohydramnios).

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