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BRIEF REPORT

Angiotensin II receptor antagonists against migraine in pregnancy: fatal outcome

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Abstract A pregnant young woman with a severe migraine is prescribed candesartan, an angiotensin II type 1 receptor antagonist (AT II antagonists). This has a positive effect—except for severe maldevelopment of her fetus. There is an increase in the use of the fetotoxic drugs, AT II antagonists and angiotensin-converting enzyme inhibitors, as prophylactic treatment of migraines, in addition to their use as hypertensives.

Keywords Migraine · Pregnancy · Fetotoxic medication · Angiotensin II receptor antagonist · Angiotensin-converting enzyme inhibitor · Hypertension

Abbreviations

AT II antagonist	Angiotensin II receptor antagonists
ACE-inhibitors	Angiotensin-converting enzyme inhibitors

Introduction

There is an increase in the use of angiotensin II type 1 receptor antagonists (AT II antagonists) and angiotensin-converting enzyme inhibitors (ACE-inhibitors) as prophylactic treatment of migraines, in addition to their use as antihypertensives. These drugs pass the placenta and have highly adverse effects on the renal organogenesis, leading to maldevelopment firstly of the renal system and secondarily of the lungs [1, 2].

Case story

A 35-year-old woman has a missed abortion. She is given hospital treatment. The fetus is autopsied without conclusive diagnosis. In the woman's next pregnancy, only 6 weeks later, an ultrasound examination is conducted in week 12 and again in week 30. One week later, the midwife finds a declining symphysis to fundus increment, and the woman is therefore immediately referred to the hospital. Anhydramnion is diagnosed. There is severe pathology of the kidneys and bladder. The development of the skull, thorax and possibly the intestines are also pathological. The reasons for the maldevelopment are unclear.

The woman is healthy, apart from suffering a severe common migraine. Before pregnancy, she had three to four attacks every week of unilateral, throbbing pain associated with nausea, vomiting and photophobia, lasting 6–48 h, preceded by transient scintillating scotomas. During pregnancy, the attacks are milder, shorter and less frequent. Throughout both pregnancies, she has been taking candesartan (16 mg/day), pramipexole (0.18 mg 3×) and amitriptyline (25 mg/day) as prophylaxis against migraines, in addition to zolmitriptan and metoclopramide during attacks. Candesartan treatment was initiated more than a year before her first pregnancy by an experienced neurologist who was also consulted during pregnancy. The medication was known to her general practitioner and the doctors who conducted the ultrasound examinations. The hospital obstetricians documented the medication in the admission notes in both pregnancies.

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Nonetheless, the fetus is 33 weeks before doctors become aware that the medication is fetotoxic. Candesartan, an AT II antagonist, is seponated. When the baby is born, he has renal tubular dysgenesis, hypoplasia of the skull and the lungs, and hyaline membranes of the lungs. This is not compatible with life.

Materials and methods

MEDLINE and the Norwegian Database of Adverse Effects [3] were searched for descriptions of fetal injuries related to AT II antagonists ACE-inhibitors. Information about the extent of use of these drugs in Norway was obtained from the National Prescription Database.

Results

Angiotensin II receptor antagonists and ACE-inhibitors reduce blood pressure by blocking the renin-angiotensin system. They also have a positive, prophylactic effect against migraines, although the mechanisms are poorly understood. The colocalization of AT1, glutamate and GABA receptors on medullary rostral ventromedial neurons suggests a nociceptive modulatory [4]. Unfortunately, these drugs cross the placenta and affect the circulation of the fetal kidneys, and, more importantly, reduce stimulation of AT II receptors. This has a highly adverse effect on the renal organogenesis in the second and third trimesters [5]. The kidneys develop abnormally and are unable to produce urine; there is oligohydramnion and thereby, inter alia, maldevelopment of the lungs [1, 2].

The summary of product characteristics in the technical brochures clearly states that these drugs are fetotoxic and should not be used during pregnancy [6]. More than 20 cases of fetal injury/maldevelopment after exposure to AT II antagonists and ACE-inhibitors have been reported in the literature [1, 2]. Two cases have been reported to the Norwegian Database of Adverse Effects. Norway has 4.7 million inhabitants.

In Norway, 1.2% of women aged 30–39 years were dispensed drugs in 2007 that affect the renin-angiotensin system, an increase compared to 2004. More than 50% of childbearing women in Norway are more than 30 years old. The mean age at delivery is increasing and will thus cause the number of pregnant women with hypertension requiring medical treatment to increase. In addition, there is reason to believe that there is an increase in the use of these drugs against migraines. They are well tolerated, and several studies have demonstrated their positive prophylactic effects [7–11]. In American and European guidelines, candesartan is listed among second- and third-line agents, respectively, for migraine prophylaxis [12–14]. In Australia it is not yet listed as an appropriate agent, but is widely used by the neurologists [15]. This also appears to be the case in Norway, although it is difficult to document, as these are not approved drugs against migraines in this country.

Discussion

Migraine is a most disabling disorder, which can be extremely difficult to treat. A variety of drugs from diverse pharmacological classes are in use for migraine prevention. AT II antagonists and ACE-inhibitors are traditional antihypertensives that have proved to be effective also in migraine prophylaxis. Their fetotoxic effects have been demonstrated in humans [1, 2] and well documented in animal research. When administered to rats, mice or piglets during renal development these drugs induce severe renal histological abnormalities, including papillary atrophy, tubulointerstitial fibrosis and tubular atrophy and dilatation [16, 17]. Nonetheless, there is reason to believe that an increasing number of women of reproductive age will use these drugs. They should be advised of the possible hazards, and treatment should be stopped as soon as pregnancy is planned or detected.

Conflict of interest None.

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