A Study on Nortriptyline Effects on Fetal

Mehrnoosh Hashemi, and Mehrdad Shariati

Abstract—Antidepressant drugs are those given for minor or major depression. Psychiatric Disorders and Pregnancy Mental illnesses are common in women during their childbearing years. Despite the high prevalence and negative consequences associated with depression and anxiety disorders during pregnancy, information to guide women and their physicians about treatment options is limited. Of all the medications used in pregnancy, antidepressants have the largest body of research, the results of which are now being integrated into clinical practice. Nortriptyline is a tricyclic antidepressant. It affects chemicals in the brain that may become unbalanced and used to treat symptoms of depression. Nortriptyline may also be used for other purposes. Some common side effects associated with Nortriptyline may include fast heart rate, blurred vision, urinary retention, dry mouth, constipation, weight gain or loss, and orthostatic hypotension but adverse effects of prenatal antidepressant exposure on the fetus may be secondary to effects of drugs. Deciding about the use of antidepressants in pregnancy and breastfeeding needs to be made with care. It is strictly recommended a detailed discussion with doctor when making this decision.

Keywords—Tricyclic antidepressants, Nortriptyline, anxiety disorders. Fetus

I. INTRODUCTION

NORTRIPTYLINE is a tricyclic antidepressant. It affects chemicals in the brain that may become unbalanced and used to treat symptoms of depression. Nortriptyline may also be used for other purposes. It could be oral capsule, oral solution, and oral tablet. As well as its needed effects; nortriptyline may cause unwanted side effects that require medical attention. It is also used in smoking cessation. The mechanism by which nortriptyline causes serum aminotransferase elevations and acute liver injury is not known. It undergoes extensive hepatic metabolism and a possible cause of liver injury is production of a toxic intermediate of metabolism [1]. Nortriptyline hydrochloride is administered orally in the form of tablets. Commence dosing prior to quit date at 25 mg/day and then increase to 75 –100mg when feasible over 10 days –5 weeks. The recommended starting time is 10 –28 days prior to the quit date and gradually increase to achieve a maintenance dose of 75–100 mg/day when possible for a total of up to 12 weeks. The physician should maintain therapeutic monitoring for vulnerable subjects, inadequate response and compliance concerns. If discontinuation is required nortriptyline should be tapered as withdrawal symptoms can occur with abrupt cessation. Although 12 weeks is the usual treatment duration, the physician should have the discretion to use the medication for up to 6 months as a recent study shows some decrease in relapse to smoking with extended medication treatment.

Clinical experience with nortriptyline has not identified any differences in tolerability between the elderly and other adult patients. However, greater sensitivity of some elderly individuals cannot be ruled out. Elderly Patients are more likely to have decreased renal function hence a reduced frequency of dosing maybe required. Nortriptyline has not been tested in adolescents and since many adolescent smokers are not yet dependent on nicotine e, nortriptyline for smokers under 18 years is not recommended. [3]

Nortriptyline hydrochloride is 1-Propanamine, 3-(10, 11-dihydro-5H-dibenzocyclohepten-5-ylidene)-N-methyl-hydrochloride. Its molecular weight is 299.8, and its empirical formula is shown in fig.1

II. USE IN PREGNANCY

Despite the high prevalence and negative consequences associated with depression and anxiety disorders during pregnancy, information to guide women and their physicians about treatment options is limited. Of all of the medications used in pregnancy, antidepressants have the largest body of research, the results of which are now being integrated into clinical practice. Nortriptyline is a tricyclic antidepressant. It affects chemicals in the brain that may become unbalanced and used to treat symptoms of depression. Nortriptyline may also be used for other purposes. Treating pregnant and breastfeeding women for depression and anxiety can be a challenge [14] many women who take these drugs may become pregnant and not be aware of their possible adverse effects. Since thalidomide, a drug used to treat morning sickness in pregnancy, was found to be teratogenic, many
Although newer drugs do not appear to cause congenital malformations, some still pose a threat. Nortriptyline should be observed if maternal use of tricyclic antidepressants, late in the third trimester have shown developmental and behavioral abnormalities associated with use of tricyclic antidepressants in pregnancy. There is evidence of interference with central monoamine neurotransmission in rats. Neonates should be observed if maternal use of nortriptyline has continued into the later stages of pregnancy, particularly into the third trimester. Neonates exposed to tricyclic antidepressants, late in the third trimester have shown drug withdrawal symptoms such as dyspnea, lethargy, colic irritability, hypotension or hypertension and tremor or spasms. Epidemiological data suggests that the use of tricyclic antidepressants in pregnancy may be associated with an increase in premature birth. Animal reproduction studies have yielded inconclusive results. Daily feeding of nortriptyline at a diet level of 0.05 percent from Day 5 to Day 20 of the gestation period had no deleterious effects on fetal development of rabbits. Rats fed diets containing the equivalent of 30 mg per kg daily from the time of weaning until maturity and during breeding studies showed no indications of teratogenesis in the fetuses of two litters [2]. During pregnancy, the presence of gastrointestinal disease (that might be pre-existent to pregnancy or develop de novo) presents special challenges to the clinician. Drug therapy requires careful assessment and consideration before conception (for those with pre-existent disease), during pregnancy and in the postpartum period. The focus of therapy must be guided by the dictum “first, do no harm”, but this must sometimes be achieved by overcoming the instinct to delay or withhold treatment that could potentially produce an adverse outcome for the mother or the fetus.

The safety of drugs used in pregnancy has been assessed in animal studies, trials in pregnant women, and post marketing studies. Unfortunately, because of the absence of prospective, controlled trials in pregnant women, there are limited data on the safety of many medications used to treat gastrointestinal disease during pregnancy. In addition, the safety of drugs in animal studies does not necessarily correlate with their safety in pregnant women, but often is the best information available. The current FDA categories for drug use during pregnancy are defined in Table 1. [4]

III. NORTRIPTYLINE AND SIDE EFFECTS

Antidepressant drugs are those given for minor or major depression, obsessive-compulsive disorder, bipolar disorder and various other related mental illnesses. Their mechanism of action usually involves increasing brain concentration of the biogenic amine/catecholamine neurotransmitters. For example first generation antidepressants called monoamine oxidase inhibitors (MAOI), inhibit the breakdown of serotonin, norepinephrin and dopamine. However, their side effects were much too strong and the effects non-specific. The second generation drugs called tricyclic antidepressants (TCA) blocked reuptake channels for serotonin and norepinephrin. Blocking the neuronal reuptake channel prevented degradation of the neurotransmitters thereby increasing their synaptic concentrations. In recent years, drugs have become more specific in blocking the serotonin reuptake and not norepinephrin. These third generation antidepressants are also selective serotonin reuptake inhibitors (SSRI). SSRI antidepressants tend to have even fewer side effects than TCA and fewer than MAOI Monoamine oxidase inhibitors (MAOI) are usually not indicated for use during pregnancy because of their adverse side effects.[11]

Nortriptyline is an antidepressant that is used to treat mental/mood problems such as depression. Some common side effects associated with Nortriptyline may include fast heart rate, blurred vision, urinary retention, dry mouth, constipation, weight gain or loss, and orthostatic hypotension. It is strictly recommended that if you notice any of these side effects especially worsening of depression or other psychiatric conditions. This is not a complete list of side effects, and

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Nursing mothers the potential benefits must be weighed against the possible hazards [5]. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and paediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients for whom such symptoms are severe, abrupt in onset, or were not part of the patient’s presenting symptoms. It has been reported that the use of nortriptyline in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms. If administered to overactive or agitated patients, increased anxiety and agitation may occur. In manic-depressive patients, nortriptyline may cause symptoms of the manic phase to emerge [6]. Nortriptyline is excreted in limited amounts. The relative infant dose is low and serum levels have been reported as low or undetectable. Safe use of nortriptyline during lactation has not been established; therefore, when the medicine is administered to nursing mothers the potential benefits must be weighed against the possible hazards. The most common side effects include dry mouth, sedation, constipation, and increased appetite, mild blurred vision, tinnitus, often euphoria and mania. An occasional side effect is a rapid or irregular heartbeat. Alcohol may exacerbate some of its side effects and should be avoided. However, the incidence of side effects with nortriptyline is lower than with the first-generation tricyclics. For this reason it is often used in elderly patients instead of other TCAs to reduce side effects and improving patient's compliance. A study with men has found that treatment with nortriptyline is associated with higher risk of suicidal ideation compared to escitalopram [8].

IV. NORTRIPTYLINE EFFECTS ON FETUS

Psychiatric Disorders and Pregnancy Mental illnesses are common in women during their childbearing years. Mood disorders such as anxiety and depression may be exacerbated by the onset of pregnancy and may ensue after delivery. The prevalence of depression can be as high as 10 - 16% during pregnancy [9]. The risk of relapsing into a post-partum depression can be very high depending on the level of depression and treatment course. For example, women who become depressed during pregnancy are at the highest risk of relapse into post-partum depression [10]. Similarly, women who have bipolar or anxiety disorders are also at high risk for developing postpartum relapse. Thus, pharmacological treatment may be necessary in mental illness as an adjunct to other forms of therapy or mandatory and essential. Drugs currently prescribed for mental illnesses have a variety of effects on the fetus during pregnancy and delivery. It should be stressed that untreated psychiatric illnesses pose a tremendous threat to the fetus due to maternal behavior and that discontinuing psychotropic drugs may also exacerbate maternal mental illnesses and cause secondary effects to the fetus.

Adverse effects of prenatal antidepressant exposure on the fetus may be secondary to effects of drugs. Both TCA (Tricyclic antidepressants) and SSRIs (Selective serotonin reuptake inhibitors) are known to cause neonatal withdrawal symptoms when these drugs are used during the third trimester of pregnancy and especially nearing delivery. Symptoms associated with antidepressant withdrawal are collectively called neonatal withdrawal syndrome or neonatal continuation [12]. Deciding about the use of antidepressants in pregnancy and breastfeeding needs to be made with care. It is strictly recommend a detailed discussion with doctor when making this decision. Ideally, you would speak with your doctor about this issue before planning a pregnancy and if possible, with your partner present. The risks and benefits need to be weighed up before decisions can be made about stopping or (re)starting an antidepressant in pregnancy and while breastfeeding. There are now a number of studies examining several thousand infants, suggesting that there is no increased risk of overall birth defects or malformations above the general population risk of 2-3%, with exposure during pregnancy to the SSRI antidepressants (fluoxetine or Prozac, sertraline or Zoloft, citalopram or Cipramil, escitalopram or Lexapro, and fluvoxamine or Luvox), as well as the older tricyclic antidepressants (such as amitriptyline and dothiepin). There have been some studies suggesting a possible increase in cardiac defects with the use of paroxetine (Aropax) in Pregnancy but this has not been substantiated in further studies. The risk of birth defects with the SNRI venlafaxine (Effexor) is far less studied, but the small amount of data available would suggest it is not increased above the norm. Initial studies on the use of mirtazapine (Avanza) during pregnancy have been reassuring with no increase in birth defects or other adverse outcomes [13].

REFERENCES

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