ANTIPSYCHOTIC MEDICATION DURING PREGNANCY AND POSSIBLE BIRTH DEFECTS

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INTRODUCTION

Among CNS disorders, psychosis is one of the most common disorder with an annual estimated prevalence of 0.01 to 0.05 % of all the world population (van Os et al, 2009). The lifetime risk of developing psychosis is probably between 0.7 to 0.9 % (Delieu et al, 2009). In European countries prevalence of psychosis is between 2.5 to 5.3 in 1000 person (Naqvi, 2008). Although population based surveys in the developed countries like United States, Netherland and New Zealand, have found somewhat higher prevalence rates for psychotic symptoms, 28%, 17.5% and 20.1% respectively, while in Britain, the prevalence of psychotic symptoms is approximately 5.5% (Jenkins, 2010). The annual psychotic symptom rate is about 3.9% in African countries. The prevalence of psychosis was observed 6.0% in rural Africa, while rates of disorder were unsurprisingly lower 0.7% in a population-based urban sample (Jenkins, 2010). Schizophrenia is estimated to affect more than 33 million people in developing countries (Chisholm et al, 2008). Bipolar disorder accounts for about 11% of the neuropsychiatric disease burden in developing countries (Bale et al, 2001). Between 25 and 50% of patients in developed countries with bipolar disorder attempt suicide and as many as 15% are successful (Bale et al, 2001). In India, about 4.3 to 8.7 million people are suffering with psychotic disorders (Hicks, 2010). The prevalence of psychosis is higher in women than man in the world population including India. The typical age of onset is late adolescence or early adulthood, placing women at risk for episodes throughout their reproductive years (Yonkers et al, 2004). Hormonal fluctuations, emotional stress and other factors such as personal and social changes in the women of childbearing age set them on stage of psychosis. In pregnant women the annual incidence of psychosis has been reported to be 7.1 cases per 100,000 person (Duran et al, 2008). The etiology of psychosis and its manifestation are difficult to interpret in women if they become pregnant or expected to be pregnant during psychosis. Women with a history of psychotic disorder are at a higher risk of psychiatric illness because it has high rates of unplanned pregnancies, particularly two fold risk of post-natal depression (USPSTF, 2009).

TERATOGENICITY OVERVIEW

Birth defects are known to occur in 3-5% of all newborns (Lather et al, 2011). They are the leading cause of infant mortality in the United States, accounting for
A psychotic episode can be significantly affected by mood. While people experiencing a psychotic episode in the context of mania may form grandiose delusions, stress is known to contribute to and trigger psychotic episodes. Short-lived stress, as well as long-lasting stress, can both contribute to the development of psychosis. While people experiencing a psychotic episode may exhibit specific receptor or enzyme-mediated teratogenesis with the narrow window of opportunity to intervene in pregnancy and lactation on fetal/neonatal birth defects, medication use during pregnancy because pregnant women do not present for prenatal care until embryogenesis is complete (i.e., after 58 days postconception). Intervention is further complicated because many women are not aware of the potential adverse effects of drugs and chemicals on pregnancy. A review published in 2010 identified 6 main teratogenic mechanisms associated with medication use: folate antagonism, neural crest cell disruption, endocrine disruption, oxidative stress, vascular disruption and specific receptor or enzyme-mediated teratogenesis (van Gelder et al, 2010).

PSYCHOSIS AND PREGNANCY

A psychotic episode can be significantly affected by mood. While people experiencing a psychotic episode in the context of mania may form grandiose delusions, stress is known to contribute to and trigger psychotic states. A history of psychologically traumatic events, and the recent experience of a stressful event, can both contribute to the development of psychosis. Short-lived psychosis triggered by stress is known as brief reactive psychosis.
psychosis, and patients may spontaneously recover normal functioning within weeks (Jauch et al., 1988). In some rare cases, individuals may remain in a state of full-blown psychosis for many years, or perhaps have attenuated psychotic symptoms (such as low intensity hallucinations) present at most times.

Maternal psychosis is associated with higher rates of prenatal substance abuse, obstetrical complications, and infant death. Women with psychosis have very less ideas about pregnancy that complicate their perinatal course or aberrant parenting styles that may impair child development. It means there is a high risk of obstetric complications, some evidence of stillbirths and neonatal deaths, and some evidence of an association with sudden infant death syndrome also (Howard, 2005). A study investigating the psycho-social outcomes of pregnancies in women with a history of psychotic disorder, 27% of women with psychotic episode and 38% with non-psychotic depression in the first year after birth were reported (Howard et al., 2004).

Another aspect of mental illness during pregnancy is the possible direct effect of maternal illness per se on the fetus. Pregnancy and the post-partum period appear to confer an even greater risk for women with bipolar disorder. Psychotic relapse during pregnancy is rare but women with a history of affective psychosis are at a high risk of post-partum relapse. Several lines of investigation have demonstrated that a history of psychosis increases the risk for post-partum psychosis (PPS). Rates of relapse are estimated at 30-50% during the post-partum period.

Weighing the risks and benefits of treating pregnant and breastfeeding women with antipsychotics requires assessment of clinical effectiveness versus the risks of toxicity to mother, fetus, neonate and children in later life. It is thought that one solution may be to cease therapy with these medications when pregnancy is contemplated or confirmed. However, women who stop taking medications during pregnancy experience high relapse rates (Cohen et al., 1998). Suicidal behaviour, poor self-care, inadequate nutrition and poor antenatal clinic attendance, with a consequent lack of fetal monitoring, can all present risk to the fetus.

**ANTIPSYCHOTIC MEDICATIONS**

All major classes of psychotropic medications, including antipsychotics, can be assumed to diffuse readily across the placenta to the fetus or to be excreted into milk. The mechanism of this transfer depends on a number of pharmacokinetic factors, such as (1) the drug’s lipid solubility, (2) its molecular weight, (3) maternal blood levels, (4) plasma protein binding, (5) oral bioavailability in the mother and the infant, (6) the pK (pH at which the drug is 50% ionized) (Pacifici et al., 1995) and (7) the half-life of the drug in maternal and neonatal circulation. Of these many factors, perhaps the two most important and useful are the lipid solubility and the molecular weight of the drug. Compounds with a molecular weight less than 600 are relatively permeable, and those with a molecular weight greater than 1,000 are considered relatively impermeable (MacKay et al., 1976).

Antipsychotic drug development has come a long way, from the serendipitous discoveries of chemicals by trial and error. Chlorpromazine came to the attention of psychiatry through a convoluted history (Lehmann and Ban, 1997). It came in the world market in 1952. It had taken almost 60 years to develop chlorpromazine since Ehrlich’s clinical observation of methylene blue in 1891 from an antimalarial, to an antihistamine, to an anesthetic, and eventually to an antipsychotic medication.

Although chlorpromazine remained the most prescribed antipsychotic agent throughout the world since 1960s and early 1970s, many drugs with similar antipsychotic efficacy but different chemistry, potency, and side-effect profiles were introduced into the market (Shen, 1994). Among the 40 or more antipsychotic drugs were introduced to the world by 1990 (Poldinger and Wider, 1990) viz. trifluoperazine, thioridazine, chlorprothixene, thiothixene, haloperidol, etc. The last of this series approved by the US Food and Drug Administration (FDA) was loxapine, a dibenzodiazepine, in 1975 (Shen, 1994). Despite this proliferation of antipsychotic drugs, only 11 depot preparations of eight different compounds were marketed in the world by 1990 (Poldinger and Wider, 1990; Shen, 1998). Of these, only two (fluphenazine and haloperidol) were available in the US market (Shen, 1994).

In 1954, 2 years after chlorpromazine first came into clinical use, acute extrapyramidal symptoms (EPS) including parkinsonism, dystonias, and akathisia began to be described and recognized as side effects associated with the use of chlorpromazine and reserpine. In a 1961 report (Ayd, 1961), the prevalence of EPS in patients treated with antipsychotic drugs was estimated as 38.9%. The majority of clinicians and pharmacologists became convinced of an absolute connection between EPS and the clinical effectiveness of antipsychotic drugs. This attitude was reinforced with the introduction of haloperidol in 1958 by Haase and Janssen (Hippius, 1996). Tardive dyskinesia induced by chlorpromazine and its related antipsychotic drugs has been recognized as a concern since 1959 after the first report from France (Hippius, 1989). German psychiatrists working with G. Stille at Wander Pharmaceuticals in Bern, Switzerland, in the early 1960s worked to refute the concept that EPS and antipsychotic efficacy were linked (Hippius, 1996). Their work led to the introduction of clozapine, an antipsychotic with no EPS or minimally associated EPS (Shen, 1994). Clinical confirmation of this profile for
clozapine was provided in open studies by Austrian (Gross and Langner, 1966) and German (Bente et al, 1966) investigators in 1966, and later by Swiss researchers (Angst et al, 1971) in a double-blind study in 1971. The Wander Company, the manufacturer of clozapine at that time, found itself in a bizarre situation. Clozapine was briefly marketed and quickly withdrawn (Hippius, 1989). Besides the embarrassment of lacking of EPS, the initial enthusiasm for Clozapine was further dampened by reports from Finland that life-threatening incidents of agranulocytosis were associated with Clozapine treatment (Idanpaan-Heikkila et al, 1997).

However, enthusiasm for the drug was maintained by a small cadre of clinical investigators and G. Honigfeld at Sandoz, who observed that Clozapine was remarkably effective in treatment-resistant patients. This led to a landmark double-blind study of clozapine in a well-defined group of treatment-resistant patients whose blood cell counts were closely monitored during treatment (Idanpaan-Heikkila et al, 1997), and ultimately to its introduction to the US market in 1990. Clozapine was first marketed in association with an intimately linked system of blood monitoring and drug availability in patients previously demonstrated to be treatment-resistant. Its initial use in studies and clinics established that it was useful not only for treating positive symptoms (such as hallucinations, delusions, disorganized behavior, and disorganized speech) associated with schizophrenia but also for treating negative symptoms (such as severe social withdrawal, inactivity, apathy, affective flattening, and poverty of thought) (APADSMMD, 1994). This activity rapidly destroyed the general conviction that the efficacy and EPS profile were linked, and led to an emerging concept of “atypical” antipsychotic drugs. Although no precise definition of this concept has ever been established, a drug with the property of “atypicality” shows a clinical profile with a low propensity to induce EPS (or EPS-sparing) (Copoloy, 1997) and with efficacy for the negative symptoms of schizophrenia. Other characteristics commonly identified as atypicality are an efficacy in treatment-refractory patients and, sometimes, a failure to induce a serum prolactin elevation.

Clozapine’s success quickly led to the development of other atypical antipsychotic drugs. The first of these, risperidone, was approved in 1994 (Marder and Meibach, 1994), olanzapine in 1996 (Beasley et al, 1996), sertindole in 1997 (in some countries outside of the United States) (VanKammen et al, 1996), and Quetiapine in 1997 (Arvantis and Miller, 1997). Due to cardiac safety concerns raised by the FDA (Drici et al, 1998), the manufacturer of Sertindole has abandoned an effort to seek a US marketing license. Ziprasidone (Prakash et al, 1997) was still under regulatory review as of February 1999. All atypical antipsychotic drugs currently marketed in the United States belong to the group of mixed receptor antagonists (Fleischbacker, 1995). Risperidone is an improvement from the chemical structure of haloperidol; olanzapine and quetiapine are derived from that of clozapine. Among the mixed receptor antagonists, clozapine, olanzapine, and Quetiapine can be logically categorized as multireceptor. Clozapine analog antagonists, and risperidone, sertindole, and ziprasidone can be grouped together as serotonin/dopamine antagonists (Shen, 2004). The chemical structures of typical antipsychotic drugs in the former class have a three-ring nucleus, but those in the latter class do not. As a group, all of these marketed atypical antipsychotic drugs have been demonstrated in double-blind clinical trials to have reduced or minimal EPS at clinically effective doses and some efficacy in treating the negative symptoms of schizophrenia (Beasley et al, 1996; Marder and Meibach, 1994; VanKammen et al, 1996; Arvantis and Miller, 1997).

However, only clozapine has been demonstrated to provide efficacy in treatment refractory schizophrenic patients. In addition, none of these drugs except risperidone (Shiwach and Carmody, 1998) show elevated serum prolactin levels after chronic administration.

The attempt to explain how atypical antipsychotic drugs work and how they differ among themselves has caught the imagination of many basic scientists and clinicians. The comparison of the ratio of plasma $K_i$ (pKi) values for serotonin 2A (5-HT2A) and dopamine 2 (D2) binding activity has been most strongly proposed as providing the potential pharmacological basis of the unique clinical effects of atypical antipsychotic drugs (Meltzer et al, 1989), but relationships between D2 and D3, D4, and $\alpha_2$ have also been proposed (Pickar, 1995). Researchers are still trying to interpret the information for the receptor profiles of atypical antipsychotic drugs. (Arnt and Skarsfeldt, 1998). However, pKi values involving variable neurotransmission of the drugs are still useful to predict side effects, as shown elsewhere (Richelson, 1990).

**CLASSICAL APDS DURING PREGNANCY AND BIRTH DEFECTS**

For several decades, carbamazepine was assumed to be safer for the treatment of epilepsy during pregnancy than phenytoin or the other hydantoins. In 1993, a case report was published that reported a suicide attempt by a nonepileptic gravida during the period of spinal closure. The result was a fetus with a very large meningomyelocele (Little, 2007). In 1989, Jones et al. published a case-control study of carbamazepine and concluded that the study drug was the cause of an increased frequency of birth defects (Little, 2007). Other epidemiologic studies throughout the 1990s were conducted, and in 2006 the association of neural tubes defects with carbamazepine exposure during early pregnancy is generally accepted as causal, and the risk is quantified at about 1 percent, compared to about 0.1
percent in the general population. Quantitative estimates of risks for birth defects (strength and statistical significance of associations between agent exposures in pregnant women and abnormalities in their offspring) are obtained only through epidemiological studies.

Chlorpromazine is a derivative of aliphatic phenothiazines, and it readily crosses the placenta (Singh and Padmanabhan, 1978). Studies on phenothiazines in general and chlorpromazine in particular have concluded that there is no increase in morphological or developmental abnormalities associated with that treatment (Wisner and Perel, 1996). Animal reproductive studies in rodents and monkeys have shown that doses higher than maximum human therapeutic doses can cause teratogenic effects such as cleft palate and anomalies of the central nervous system, eye, and skeletal system (Hannah et al, 1982).

Fetotoxic effects such as fetal death, decreased fertility and viability, and decreased fetal weight gain (Hannah et al, 1982) visual disturbances (Lancet 1971) and behavioral abnormalities (Umemura et al, 1983), are also reported, but embryotoxic effects are not reported. Adequate and well-controlled epidemiologic studies to determine the teratogenic potential of chlorpromazine have not been done in pregnant women.

Many clinical studies have shown the safety and efficacy of low-dose chlorpromazine during all stages of gestation (Harer, 1956) or to promote analgesia, amnesia, and sedation during labor. However, there are some instances of marked idiosyncratic falls in blood pressure, which could be dangerous to the mother and the fetus (Harer, 1956; Potts et al, 1961).

In a case report 52 women who were given chlorpromazine during late pregnancy, 3 women receiving high doses (500 to 600 mg daily) gave birth to neonates with respiratory distress and cyanosis (Sobel, 1960). Extrapyramidal signs have been also reported in several infants born to women who were treated with chlorpromazine during late pregnancy, suggesting a withdrawal syndrome (Levy et al, 1974). The frequency of these complications appears to be low, and they are usually transient, though some may last for several months. In one study involving 142 neonates, in utero exposure to chlorpromazine during the first 4 months of pregnancy did not result in a significantly higher risk of congenital anomalies (Slone et al, 1977). Similar results were found in other studies also (Heinonen et al, 1977). In a prospective study of 12,764 women contrasting results were observed; a higher number of birth defects occurred in neonates of 189 women receiving chlorpromazine, during the last trimester (Rumeau-Rouquette et al, 1976). In a metaanalysis of data (74,337 live births) on outcome following first trimester phenothiazines exposure in an effort to assess evidence of overall increased risk, conferring an additional risk of 4 in 1,000 (Altshuler et al, 1996).

Chlorpromazine is excreted in the breast milk of nursing mothers in low concentrations up to 3% of maternal daily dosage per kilogram of body weight (Yoshida et al, 1998). An another study found no adverse effects in 6 neonates nursed by mothers taking chlorpromazine, of whom four were nursed for 3 months, one for 7 weeks, and one for 1 month (Ayd, 1964). Estimations based on data collected from five lactating women taking the drug showed that the nursing infant would be expected to ingest between 0.03% and 1.3% of the lowest pediatric dose (Wiles et al, 1978).

Studies indicate that Haloperidol (HAL) readily crosses the placenta in both animals and humans. The potential reproductive toxicity of haloperidol has not been adequately evaluated in animals. However, reproductive studies at doses equivalent or higher than the recommended human dose have revealed teratogenic effects such as cleft palate, micromelia, and central nervous system and skull malformations (Singh and Singh, 2004; Singh and Singh, 2001). Fetotoxic effects such as fetal death and decreased fetal and postnatal growth have been reported in rats, mice, and hamsters. Long-lasting alteration of behavior in rats and mice (Singh and Singh, 2002; Williams et al, 1992) and embryotoxic effects such as embryonic death in hamsters (Gill et al, 1982) have also been reported.

No adequate and well-controlled studies to determine fetal risk associated with haloperidol have been done in humans. The pregnancy outcomes for 98 women receiving small doses of haloperidol (0.6 mg) twice daily, 92 received haloperidol during the first trimester, and 6 received haloperidol during the second trimester showed no effect on intrauterine survival, neonatal survival, birth weight, or sex ratio, no malformations were observed in the offspring. Low-dose haloperidol in the first trimester of pregnancy has no detrimental effect on the weight of the fetus, the length of pregnancy, fetal or neonatal mortality or incidence of malformations (Van Waes and Van de Velde, 1969). However, a separate report describes two cases of severe limb malformation in infants of mothers treated with haloperidol during the first trimester. Haloperidol causes increased incidence of fetal resorption, delayed delivery, and neonatal death at doses 2- to 10-fold higher than the maximum doses used in humans (Dollery, 1999). Although haloperidol is significantly excreted in breast milk, no adverse effects in nursing infants have been reported (Stewart et al, 1980; Whalley et al, 1981). Animal studies have shown that haloperidol excreted in milk causes drowsiness and impairment of motor activity in the breast-fed offspring. Studies in animals indicate that Fluphenazine which belongs to the piperazine phenothiazine group, readily
crosses the placenta and accumulates in fetal tissue (Nath et al, 1996). Two studies in which rats were treated with doses up to 100 mg/kg orally throughout pregnancy found no adverse effects in the offspring (Shepard, 1992). Contradictory results were reported in pregnant mice given this drug, with a significantly higher incidence of skeletal defects, dilated ventricles, and reduction in fetal weight and length (Abdel-Hamid et al, 1996). Multiple malformations in chick embryos and cleft palate in fetal mice have been reported (Szabo et al, 1974).

Although no adequate, well-controlled studies have determined the teratogenicity of fluphenazine in humans, however, a retrospective study (Brougher, 1960) involving 244 patients taking fluphenazine and 150 controls, detected congenital anomalies in 2.7% of the 226 live and stillborn infants in the exposed group compared with 3.5% among 143 live and stillborn deliveries in the control group. Also, the incidences of spontaneous abortion, perinatal mortality, premature birth, and twinning in the two groups were similar. Currently available clinical data have not shown any teratogenic effects, except for occasional case reports of congenital anomalies (Donaldson et al, 1982; Cleary, 1977). The bulk of the worldwide clinical experience with this drug indicates that pregnant women can be treated with fluphenazine without any ill effects on them or their infants (King et al, 1963). Even though fluphenazine, like other phenothiazines, may be excreted into breast milk, neither the drug nor its metabolites have been quantified in human milk, and its effect on nursing infants is unknown.

The potential reproductive toxicity of thiothixene has not been adequately evaluated in animals. One reproductive study in mice and rabbits given 90 mg/kg/day showed a decrease in conception rate and litter size and an increase in resorption rate, but revealed no teratogenicity (Owaki et al, 1992). To date, no adequate and well-controlled studies on thiothixene therapy during pregnancy have been done in humans. However, this drug should be used during pregnancy only when the physician believes the expected benefits exceed the possible risks to the fetus. There are neither reports on the pharmacokinetics of thiothixene in relation to breast milk nor reports on the effects of this drug on nursing infants. Hence, caution is advised, since chemically related phenothiazines are excreted in breast milk and are reported to cause tardive dyskinesia and possible drowsiness in the breast-fed infant.

ATYPICAL APDS DURING PREGNANCY AND BIRTH DEFECTS

Clozapine, a dibenzodiazepine derivative, readily crosses the placenta. Animal reproductive studies in rats and rabbits have shown no teratogenic, fetotoxic, or embryotoxic affect at doses approximately 2 to 4 times the human dose (Physician’s Desk Reference, 1999). Presently, no epidemiologic studies show an association between congenital anomalies and gestational clozapine therapy in humans. There are many clinical case reports of no apparent fetal adverse effects associated with the use of clozapine before and during gestation (Barnas et al, 1994; Dickson et al, 1998). One of these reports described 14 women who were known to have been exposed to clozapine during gestation with no known adverse sequelae in their newborns (Lieberman et al, 1992). In a case report a woman receiving 200 to 250 mg daily during second trimester and 150 mg during third trimester of pregnancy did not show any teratogenicity and abnormality. On the other hand 5 congenital malformations and 5 perinatal syndromes in 61 children exposed to clozapine were reported (Dev and Krupp, 1995). Clozapine is concentrated into breast milk (Physician’s Desk Reference, 1999; Barnas et al, 1994) and has been known to cause sedation, decreased suckling, restlessness or irritability, seizures, and cardiovascular instability in the nursing infant.

Risperidone is a benzisoxazole derivative and an atypical antipsychotic agent that is chemically unrelated to other antipsychotic agents. Evidence indicates that risperidone easily crosses the placenta. Animal reproductive studies in rats and rabbits have shown no evidence of teratogenic potential at doses higher than the maximum human therapeutic dose but fetotoxic effects such as increase in pup deaths and a significant increase in the number of stillborn pups are reported (Grover et al, 2006; Levinson et al, 2003). Although no adequate, well-controlled studies to determine teratogenicity of risperidone in gestational women have been done, even though reports of animal fetotoxicity exist. In a recent report describing two cases of risperidone treatment before and throughout pregnancy, no complications were observed (Ratmayake and Libretto, 2002). In another case report treatment throughout the pregnancy no teratogenicity is reported (Rodriguez-Salgado, 2008). In a case report agenesis of corpus callosum is reported (Grover and Avasthi, 2004). Risperidone and its metabolite 9-hydroxy-risperidone are excreted into animal milk in concentrations greater than or equal to plasma concentrations. At present, it is not known whether the drug is excreted in human breast milk, though it is suggested that it may cause adverse effects, such as behavior changes, in breast-fed babies.

Olanzapine is an atypical antipsychotic agent belonging to the thienobenzodiazepine group. It is known to cross the placenta (Physician’s Desk Reference, 1999). Animal reproductive studies in rats and rabbits have revealed no evidence of teratogenic effects at doses equivalent to 9 and 30 times higher than the human recommended doses respectively, but have shown increased resorption, increased number of nonviable fetuses, and decreased fetal weight. In a study it was observed that 5% to 14% of olanzapine crosses human
placenta unchanged during a period of 4 hours (Schenker et al, 1999). A study in which 23 pregnancies were followed suggested a favorable risk-to-benefit ratio for the fetus and infant following olanzapine exposure, since spontaneous abortion, prematurity, or major malformation in offspring did not occur (Goldstein et al, 2000). Perinatal complications were observed in some cases with no major malformations (Ernst et al, 2002; Levinson et al, 2003). Evidence suggests that olanzapine is excreted in rat milk, but its excretion in human breast milk has not been studied (Goldstein et al, 2000). In a case report of lactation exposure, no adverse effects were noticed in breast-fed infant.

Embryo/fetal toxicity in the form of skeletal ossification delays reduced fetal body weight and increased incidence of carpal/tarsal flexure in rat fetuses and in rabbits at 1.2 and 2.4 times the maximum human dose of Quetiapine, a dibenzothiazepine derivative was observed (Montvale, 2001). An increase in fetal and pup death, and decrease in mean litter weight at three times the maximum human dose were also found. In case of human being there are very few reports of quetiapine use during pregnancy. In one case, the 24-year old woman was treated with lithium (1500mg/day) for bipolar disorder, (which was discontinued on her getting pregnant) and with quetiapine, which was maintained at 25mg/day throughout pregnancy. She delivered a healthy infant with no malformations. In the other case, woman who received unknown dose of quetiapine delivered a healthy infant at 38 weeks with Apgar scores of 9 and 10 at 1 minute and 5 minutes, respectively. In another case reported no abnormality during the pregnancy, delivery and in the postnatal period after using quetiapine throughout the pregnancy (Tenyi et al, 2002). Levinson et al found three live births with no malformations and one stillbirth. Quetiapine has been found to be excreted in milk of lactating animals. However excretion in human milk may be possible. Therefore, caution should be exercised in prescribing quetiapine during lactation.

Studies in animals suggest that ziprasidone is associated with anomalies such as ventricular septal defects, other cardiovascular malformations, and kidney alterations. In some studies evidence of developmental delays, possible teratogenic effects and increased still births, at doses similar to human therapeutic doses are reported (Montvale, 2001). However, there is no evidence that these resulted from maternal toxicities. There are no adequate and well-controlled studies in pregnant women. Ziprasidone excretion and that of its metabolites in human milk is not known at present.

Aripiprazole showed developmental toxicity including teratogenic effects in rats and rabbits. When pregnant rats were treated with 10 times the MRHD, slightly prolonged gestation, stillbirths, decreased fetal weight, undescended testes, delayed skeletal ossification and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia along with postnatal effects of delayed vaginal opening and impaired reproductive performance have been observed. Similarly, pregnant rabbits treated with 11 times the maximum human therapeutic doses of aripiprazole during period of organogenesis were found to have increased fetal mortality, skeletal abnormality and decreased fetal weight. There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal malformations when administered to pregnant women or can affect their reproductive capacity. Aripiprazole is excreted in milk of lactating rats, but its excretion in human milk is not known.

MACHENISM OF ACTION ANTIPSYCHOTIC DRUGS

Immediately after the clinical introduction of drugs for psychosis, clinicians observed that patients taking these medications exhibited a Parkinson-like syndrome of tremor, akinesia, and rigidity (Haase and Janssen, 1965). This drug-induced parkinsonism strongly suggested that antipsychotic drugs were interfering with dopamine pathways in the human brain, because Parkinson’s disease was known to be a disease of insufficient dopamine neurotransmission. This clinical observation gave birth to the dopamine hypothesis of psychosis and antipsychotic drug action (Van Rossum, 1967). Although it was suggested that chlorpromazine and haloperidol blocked “5-hydroxytryptamine (serotonin) and monoaminergic (noradrenaline and dopamine) receptors” (Carlsson and Lindqvist, 1963), it was not possible at that time to conclude which of the 3 pathways was selectively affected by antipsychotics. This is because the turnover of noradrenaline, serotonin (5-HT), and dopamine were all simultaneously affected by the antipsychotics (Carlsson and Lindqvist, 1963; Anden et al, 1964). Anden and others speculated that chlorpromazine and haloperidol “reduce the elimination rates of these” metabolites of noradrenaline, 5-HT, and dopamine (Anden et al, 1964). Although Anden and others (Anden et al, 1970) subsequently found that antipsychotic drugs in vivo had a greater effect on dopamine turnover than on noradrenaline turnover, direct in vitro evidence for the selective blockade of dopamine receptors was found only later (Seeman et al, 1976). The multiple clinical and adverse effects of various antipsychotic drugs depend on the combination of receptors occupied, but the dopamine pathway is the primary common target for all antipsychotic drugs. More specifically, “no drug has yet been identified with antipsychotic action without a significant affinity for the D2 receptor” (Su, 1997). There are 5 types of dopamine receptors in human beings (Seeman et al, 1996). Types 1 and 5 are similar in structure and drug sensitivity (Sunahara et al, 1991),
and these 2 receptors are referred to as the “D1-like” group or class of receptors. Dopamine receptor types 2, 3, and 4 are also similar in structure and are, therefore, grouped together as the “D2-like” group. Dopamine receptors 2, 3 and 4, however, have significantly different sensitivities to antipsychotic drugs. Although the D1-like receptors are often mentioned as a primary target for antipsychotic drugs (Lidow et al., 1998).

These findings indicate that the D1-like receptors are not clinically relevant in the therapeutic action of these drugs. First, D1 antagonists do not clinically improve psychotic signs and symptoms (Karlson et al., 1995). Second, therapeutic maintenance dosages of various antipsychotic drugs occupy low or negligible levels of D1 receptors in the brains of patients with psychosis (Farde and Nordstrom, 1992). For example, therapeutic dosages of haloperidol occupy less than 5% of the dopamine receptors in the brain putamen of schizophrenia patients (Farde and Nordstrom, 1992). Although therapeutic dosages of some antipsychotic drugs, such as clozapine, occupy approximately 36% to 59% of brain dopamine D1 receptors (Nordstrom et al., 1995), there is no currently known reason to believe that these occupied D1 receptors contribute to the unique properties of clozapine. Third, for the D1 dopamine receptor, the binding constants (that is, the dissociation constants, also referred to as the inhibition constants, or Ki values) of various antipsychotic drugs (Seeman and Niznik, 1988) are very much higher than the concentrations of antipsychotic drugs found in the cerebrospinal fluid or in the plasma water of patients (Seeman and Tallerico, 1998). In other words, if the free concentrations of antipsychotic drugs were as high as the values for the binding constants at D1, the drugs would be toxic or lethal to patients. Of the 3 D2-like receptors, only the D2 receptor itself is blocked by antipsychotic drugs in direct relation to their clinical antipsychotic potencies (Seeman et al., 1976; Creese et al., 1976). Although this long-known relation is sometimes criticized as simply a relation between the D2-blocking concentrations and the clinical dosages at which EPS first appear, it is important to note that the concentrations of antipsychotics which block D2 receptors in the brain are precisely identical to the concentrations found in the spinal fluid or plasma water (that is, corrected for drug binding to the plasma proteins) of patients whose psychotic symptoms are successfully controlled by antipsychotics. It is known that the clinical efficacy of antipsychotics is associated with a blockade of 60% to 80% of D2 receptors in the brain (Seeman and Tallerico, 1999; Kapur et al., 1999).

Clozapine and quetiapine, however, have consistently been apparent exceptions. For example, in patients taking therapeutically effective antipsychotic dosages of clozapine, this drug only occupies between 0% and approximately 50% of brain dopamine D2 receptors, as measured by various radioligands using either PET (Kapur et al., 1999) or SPET (Su et al., 1996; Pickar et al., 1996). The atypical antipsychotics occupy many different types of receptors under therapeutic conditions, the apparently low occupancy of D2 by clozapine suggest that D2 is not the major antipsychotic target for clozapine (Brunello et al., 1995). D2 is not the common target for all atypical antipsychotic drugs, but it is 5-HT system or in the balance between 5-HT and dopamine. However, the apparently low occupancy of D2 by clozapine and quetiapine is readily explained by the fact that these 2 antipsychotics rapidly dissociate from the dopamine D2 receptor (Seeman and Tallerico, 1999). This also holds for remoxipride and amisulpride. In vitro test suggest that D2 receptors release clozapine, quetiapine, remoxipride, and amisulpride at least 100 times faster than they release haloperidol or chlorpromazine (Kapur and Seeman, 2001). These in vitro data match those found clinically for clozapine, quetiapine, and haloperidol in schizophrenia patients and healthy volunteers. It has been found by PET (using [11C]raclopride) that the human brain (striatum) occupancy of D2 by quetiapine and clozapine rapidly falls off within 24 hours, in contrast to that for haloperidol, which maintains its D2 occupancy constant over 24 hours (Gefvert et al., 1997; Kapur et al., 2000). Thus, the rapid release of clozapine and quetiapine from dopamine D2 receptors and their replacement by endogenous dopamine would readily account for the low D2 receptor occupancy shown by these atypical antipsychotics. It is important to emphasize that the rapid release of clozapine and quetiapine is a molecular event which occurs quickly, regardless of the clinical dosage used. In other words, even though high dosages of clozapine and quetiapine may be used, these drugs continue to go on and off the D2 receptor rapidly, allowing extensive and frequent access of endogenous dopamine to the receptor. Hence, it appears that some antipsychotics, such as clozapine and quetiapine, occupy D2 receptors only transiently throughout the day. As just mentioned, PET imaging of patients with schizophrenia reveals that the D2 receptor occupancies by clozapine and quetiapine wear off quickly after an oral dosage, and patients may show no occupancy what so ever within 48 hours of the last dose, in contrast to typical antipsychotics, which may continue to occupy D2 receptors for days. This may explain why psychotic relapses of patients on clozapine and quetiapine occur soon after withdrawal of the antipsychotic (Seeman and Tallerico, 1999), much earlier than after withdrawal of conventional antipsychotic drugs such as haloperidol or chlorpromazine.

As reported by Kapur and others (Kapur et al., 2001), the single most powerful predictor of atypicality is the low affinity to, and fast dissociation from, the D2 receptor-not high affinity to any other receptor. This hypothesis is supported by their findings that clozapine and iso clozapine have identical potencies on many
cloned receptors (including muscarinic M1, dopamine D1, dopamine D4, 5-HT1A, and 5-HT2A receptors) but differ five fold in their potency only on D2 receptors. Thus, in several tests of atypicality (for example, early activation of certain genes, catalepsy in animals, and prolactin elevation), clozapine behaves like an atypical antipsychotic. Isoclozapine, however, behaves like a conventional antipsychotic. In addition to blocking dopamine receptors, the new atypical antipsychotic drugs also block 5-HT receptors. Although it has been suggested that the blockade of 5-HT2A receptors may alleviate the parkinsonism caused by D2 blockade (Meltzer et al, 1991), most data do not support this principle. Although it has long been known that the stimulation of 5-HT1A receptors in animals can alleviate catalepsy caused by D2 blockade (Wadenberg, 1992), there do not appear to be any antipsychotics that have this 5-HT1A-stimulating action combined with D2-blocking action. It has recently been proposed that the stimulation of 5-HT2A receptors by an inverse action is an important contribution to atypical antipsychotic action (Weiner et al, 2001). However, because a few important atypical antipsychotics (including remoxipride and sulpiride) have no such stimulating action, it is unlikely that this feature contributes to atypical antipsychotic action. Finally, although the authors (Weiner et al, 2001) propose that M100,907 has the desired stimulating action, this compound has shown no antipsychotic activity in humans.

So, it can be said that atypicals clinically help patients by transiently occupying D2 receptors and then rapidly dissociating to allow normal dopamine neurotransmission. This keeps prolactin levels normal, spares cognition, and obviates EPS. One theory of atypicality is that the newer drugs block 5-HT2A receptors at the same time as they block dopamine receptors and that; somehow, this serotonin-dopamine balance confers atypicality. This, however, is not borne out by the results. While 5-HT2A receptors are readily blocked at low dosages of most atypical antipsychotic drugs (with the important exceptions of remoxipride and amisulpride, neither of which is available for use in Canada) the dosages at which this happens are below those needed to alleviate psychosis. In fact, the antipsychotic threshold occupancy of D2 for antipsychotic action remains at about 65% for both typical and atypical antipsychotic drugs, regardless of whether 5-HT2A receptors are blocked or not. At the same time, the antipsychotic threshold occupancy of D2 for eliciting EPS remains at about 80% for both typical and atypical antipsychotics, regardless of the occupancy of 5-HT2A receptors.

CONCLUSION

Currently available data indicates that there are no antipsychotic preparations on the market that can be considered entirely appropriate or completely safe for expectant and nursing mothers. On the other hand, there have been some studies and case reports of fetal malformations, such as congenital heart disease, perinatal deaths, neurological dysfunction with extrapyramidal manifestations, respiratory distress, rhinorrhea, jaundice, hypotension, and neonatal withdrawal associated with the use of antipsychotics. However, the extensive review of congenital malformations in the infants of women who received antipsychotics during pregnancy reveal the occurrence of only very few cases of congenital defects, the incidence of which are neither higher nor lower than the control groups. Furthermore, some of these antipsychotic drugs (e.g., olanzapine, ziprasidone, aripiprazole) are newer agents and there may not be much experience with them during pregnancy and breastfeeding, unlike that with older agents such as haloperidol or chlorpromazine, where there appears to be an increased risk of congenital malformations on exposure to phenothiazines between weeks 4 to 10 of gestation (Patton et al, 2002). In general, many antipsychotics have been reported to have no apparent adverse consequences during pregnancy. However more research is needed to expand our knowledge about the effects of both psychiatric treatment and available treatments on maternal and fetal health.

In summary, the perinatal risks of psychosis mandate that treatment should not be discontinued routinely without full consideration of the risk of relapse to the mother, which itself may have adverse effects upon carrying the fetus to term as well as neurodevelopment. The clinician must make a risk-benefit assessment that weighs the risks of untreated mental illness against the potential harm of using psychotropic medications to manage this condition in both fetus and mother. For these reasons, clinicians need to help mothers weigh both fetal and neonatal risks of exposure to the drugs against the potential risk they and their infant may incur if the psychiatric illness is not treated. Weighing the risks and benefits of treating pregnant and breastfeeding women with antipsychotics requires assessment of clinical effectiveness versus the risks of toxicity to mother, fetus, neonate and children in later life.

REFERENCES


