

Terbutaline and Autistic Spectrum Disorders

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Terbutaline Generic Names: Brethaire, Brethine, Brican, Bricanyl, Bricar, Bricaril, Bricyn, Terbutalin, Terbutalina [Dcit], Terbutaline Sulfate, Terbutalino [Inn-Spanish], Terbutalinum [Inn-Latin]

Autism has increased from an incident children from <3 per 10,000 (1970s) to > 30 per 10,000 (1990s). In the United Kingdom the illness has increased from <10 per 10,000 to approximately 30 per 10,000 from the 1980's to the 1990's. Autistic Spectrum Disorders (ASD) have increased during the same time frame from 5-10 to 50 to 80 range in the two countries (1). The cause(s) of ASD are not known. However, it appears that genetics as well as toxic exposure play a role in the neurological disease process (2-6).

Premature labor occurs in nearly 20 per cent of all pregnancies in the United States. It is estimated that approximately 1 million women are treated annually with Terbutaline or similar drugs to halt early contractions. Both Terbutaline and the pump for percutaneous perfusion of the drug are not approved by the U.S.F.D.A for this purpose. The FDA issued its first warning in 1997 concerning the potential danger associated with the use of Terbutaline for the prevention of preterm labor (7). Furthermore, the package insert for the drug states "Terbutaline sulfate has not been approved and should not be used for tocolysis (suppression of premature labor). Serious adverse reactions may occur after administration of Terbutaline sulfate to women in labor. In the mother, these include increases heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. Increased fetal heart rate and neonatal hypoglycemia may occur as a result of maternal administration." Also, according to the FDA notice, the infusion pump used for percutaneous administration of Terbutaline has not been approved for this application. Following a single injection Terbutaline crosses the placental barrier and concentrations of the drug in umbilical cord blood levels are 55 % maternal blood levels (8, 9). More information is needed regarding fetal blood levels associated with continuous percutaneous administration of the drug.

Terbutaline is a beta-2 adrenergic receptor (B2AR) agonist, binding to these receptors, causing relaxation of smooth muscle. It is approved by the FDA for as a bronchodilator and is very effective in controlling asthma smooth muscle constriction. However, B2AR are found in the smooth muscle of several organs, including the heart and uterus. Thus, it has been used in an off-label application to control premature uterine contractions. Published studies on women following this type of treatment have revealed adverse effects that include pulmonary edema, maternal, fetal and neonatal death, nausea, vomiting, chest tightness and shortness of breath. Thus, the use of tocolytic agonist is not totally devoid of

risks (10-12). None of these early studies involving the side effects of tocolytic effects of Terbutaline examined the long term effects that may occur in the first 6 years of postnatal life.

Terbutaline (Brethine) is routinely prescribed for severe asthmatics. It is used via two different routes of administration. Intramuscular injection into the lateral deltoid area at a initial dose of 0.25 mg is the initial dose. If no relief from the asthma is observed in 15-30 minutes, then a second injection of 0.25 mg should be considered. The total dose within four hours should not exceed 0.5 mg. Oral dosage is by 2.5 mg tablets up to 3 times daily.

The labeling for Terbutaline carries insufficient warnings regarding pregnancy and effects on the fetus. It states: "Brethine is a considered a pregnancy category B medication. This means that it is probably safe for use during pregnancy...though the full risks are not known. Talk with your healthcare provider about the risks and benefits of using Brethine during pregnancy (see **Terbutaline and Pregnancy** and **Terbutaline and Preterm Labor** for more information)."

Recent published information indicates that Terbutaline treatment is causally linked with autistic disorders. The administration of Terbutaline has been associated with autistic spectrum disorder (ASD) in dizygotic twins (13) Continuous administration of the drug for 2 weeks or more was associated with increased concordance for ASD in twins (relative risk = 2.0), with an increased risk for males (RR = 4.4). Further, a significant association was found between the presence of 16G and 27E polymorphism in the Beta-2-adrenergic receptors in the autistic patients ($p < 0.006$).

The pathological and pharmacological affects caused by Terbutaline administration have been investigated in detail in the neonatal rat brain at stages equivalent to specific times of human brain differentiation. Rodent studies have shown that administration of Terbutaline at critical stages of neurodevelopment causes: 1) Neuronal injury and reactive gliosis affecting the cerebellum, hippocampus and somatosensory cortex; (14) 2) Robust activation of microglia resulting in abnormal behavior; (14) 3) Sensitization of Beta-2-adrenoreceptors to beta-agonists; (14-17) 4) Oxidative stress; (18) 5) Alterations in signaling cascades affecting cell differentiation; (16-18) 6) Possible sensitization to the adverse effects of organophosphate insecticides; (19) 7) Probably other organ effects (heart, lens accommodation, liver lungs, etc.); (20, 25, 26) and 8) Serotonin receptors (5HTA, 5HT2, and 5HT presynaptic transporter) were shown to have a global increase in expression in the midbrain, brainstem and hippocampus following Terbutaline or Chlorpyrifos administration. Males were more affected than females with some regional disparities in the sex selectivity between the two agents. Both chemicals altered 5HT receptor-mediated cell signaling, suppressing stimulatory effects on adenyl cyclase and enhancing inhibitory effects. When both chemicals were administered sequentially the

outcomes were additive (22). Finally, neuroglia activation and neural inflammation have been demonstrated in the brain of patients with autism (21) In summation, during key stages of neurodevelopment, the beta-2-adrenoreceptors are sensitized rather than desensitized. Serotonin receptors are also enhanced in numbers. These affects disrupt down stream adenylyl cyclase signaling, adversely affecting neuronal cell division and differentiation. In addition, Terbutaline activates microglia leading to proinflammatory conditions and gliosis in the developing brain (15-17, 19). Such effects also appear to occur in humans along with neonatal toxicity (13, 22, 26)

We have conducted a preliminary neurological study on 8 ASD boys and have demonstrated neurological impairment (23) Five boys were from one mother with four deliveries who had been treated for preterm labor with each pregnancy. The five boys were diagnosed as follows: age 7 (severe ADHD, hyperopia); age 12 (severe ADHD, Tourette's Syndrome); Age 15 (dizygotic twins, ADHD); age 16 (ADHD, cardiac arrhythmia). The mother of the other three boys used Terbutaline (Breathine) for asthma throughout her pregnancies. These boys ages 8 to 19 were diagnosed with ASD. The fifteen year old also had Tourette's Syndrome and hyperopia). Tourette's Syndrome is a fairly common finding in ASD (24). Family and occupational histories revealed no other causes for the ASD. This included familial presence of ASD, toxic exposures, pesticide use and previous known infections.

The measurements done on the initial eight boys showed an average of 6.8 abnormal functions compared to 1.0 in community dwelling unexposed boys. The 8 boys in this study had the following neurological abnormalities: a) impaired balance; b) visual field quadrant defects; c) excessive errors in finger-tip number writing; and, perceptual-motor slowing with impaired multi-tasking and recognition of missing items in picture completion. All of the boys had intrauterine exposure to Terbutaline. The mother of 5 boys received terbutaline during the third trimester of each pregnancy via a percutaneous thigh pump. The mother of the other 3 boys used Terbutaline (Breathine) throughout each pregnancy. With the third pregnancy she used Breathine less frequently because of a decrease in the severity of her asthma. This child had fewer neurological impairments than were observed in his 2 brothers and higher functioning while interacting with the investigators.

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