

Review Article

Terbutaline and Associated Risks for Neurodevelopmental Disorders

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Received 25 May 2014; Accepted 26 June 2014; Published 15 July 2014

Academic Editor: Nobuo Masataka

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Preterm labor often leads to a preterm birth and has been shown to be the most important determinant of risk for perinatal morbidity and mortality. While medication management has been utilized by physicians to delay preterm labor, the results these medications achieve remain inconsistent, in addition to increasing the risk to the developing fetus. Terbutaline has been among the most commonly used β_2 -adrenoreceptor (β_2 AR) agonists in the management of preterm labor. The research suggests that tocolytic terbutaline therapy carries a significant risk for the mother and the child, which can be magnified by extended exposure, sex of the fetus, and administration during critical fetal developmental periods. This paper highlights the research on terbutaline in treatment of preterm labor, along with the possible associated cognitive deficits in adolescents who were treated with terbutaline in utero. Two case summaries are presented to illustrate the potential deficits in clinical presentations of adolescents with history of intrauterine exposure to terbutaline. Publicizing the association between terbutaline and these deficits can not only assist obstetricians and expectant mothers in making a more informed choice in the treatment of preterm labor but also provide neuropsychologists and pediatricians with information helpful in understanding the etiology of these impairments.

1. Introduction

The term preterm labor refers to a labor with a spontaneous onset prior to completing 37th week of gestation [1]. Preterm labor occurs in approximately 20% of all pregnancies and can be associated with extreme risks for the developing fetus [2]. More common in twins and multiple pregnancies, preterm labor is especially dangerous pre- and early postviability (i.e., approximately 25th week of gestation, [3]). Moreover, preterm labor often leads to a preterm birth—the single most important determinant of risk for perinatal morbidity and mortality [4, 5]. Approximately 11% of all birth in the United States are preterm [5]. Data suggest preterm birth survival rates plummet from 90% at 28-29 weeks of gestation to 20–30% at weeks 22-23 [5]. When delivering a child prior to 37 weeks of gestation, the child is at an increased risk for neurobehavioral deficits later in life [6].

Since odds of both mortality and neurocognitive impairments dramatically diminish as gestational age progresses

from 22 to 28 weeks, physicians will frequently opt for tocolysis treatment to reverse preterm labor and allow further development of the fetus [5]. Among the most common tocolytic drugs are adrenoreceptor agonists that stimulate adrenalin β -receptors (β AR), thus relaxing the uterine smooth muscle [5]. While this intervention is intended to be brief, two days or less, physicians do sometime continue the treatment for longer periods of time [5].

Terbutaline has been among the most commonly used β_2 -adrenoreceptor (β_2 AR) agonists in the management of preterm labor [5]. The Food and Drug Administration has approved terbutaline for treating respiratory disorders, such as asthma, due to its bronchial dilation and vascular smooth muscle relaxation effects [1, 7, 8]. But the drug has also been used off label as a tocolytic, administered intravenously for acute intervention and subcutaneously or orally for maintenance treatment [1, 5]. Despite its popularity, terbutaline's efficacy and safety in terms of maternal and neonate outcomes have been questioned for a number of years [1, 5, 9].

Specifically, while terbutaline can be effective in responding to acute episodes of preterm labor, research has shown that maintenance therapy with tocolytics does not decrease the risk for recurring preterm labor or preterm delivery nor does it improve perinatal outcomes [5, 10]. Frequently, an administration of a tocolytic only serves to delay the preterm labor [9]. In 2003, the American College of Obstetrics and Gynecology published a practice bulletin for the management of preterm labor, stating that “neither maintenance treatment with tocolytic drugs nor repeated acute tocolysis improve perinatal outcome; neither should be undertaken as a general practice” [11].

In addition to the questionable effectiveness common to tocolytic therapy in general, terbutaline expressly demonstrates a history of adverse maternal effects. Many researchers have reported potential negative cardiac side effects, such as pulmonary edema, myocardial ischemia, cardiac arrhythmias, and hypotension, in mothers being treated with terbutaline [1, 12, 13]. In 2011, the Food and Drug Administration (FDA) reacted to the mounting evidence of terbutaline’s adverse effects, as well as the 16 maternal deaths associated with terbutaline since its introduction to the market, and required a black box warning restricting the duration of terbutaline preterm labor treatments (i.e., 72 hours), route of administration (i.e., no oral administration), and setting (i.e. only inpatient facilities, [4]).

In light of terbutaline’s ability to cross the placenta, research studies have also investigated the long-term implications for children born to mothers treated with terbutaline. For example, Hadders-Algra et al. [14] found that some children exposed to tocolytics in utero later evidenced impaired school performance. Other investigations discovered higher prevalence of motor developmental delays, cognitive dysfunction, and psychiatric diagnoses in children with a history of intrauterine terbutaline exposure [9]. In their study, Pitzer et al. [9] ascertained that more severe impairments were seen in children who were born full term, whose mothers were given terbutaline in their third trimester, as supposed to those children who were exposed to terbutaline in utero during the second trimester. Similarly, Rhodes and colleagues [2] suggested that terbutaline administered to mothers during critical periods acts as a neurotoxicant that elicits biochemical alterations and structural damage in the immature brain.

Establishing a causal link between fetal terbutaline and later neurobehavioral impairments is problematic. There are many different factors that can contribute to the early onset of labor (e.g., maternal stress, infections, smoking, and many other psychosocial and environmental variables, [9]) which are also associated with later cognitive and behavioral difficulties. Thus, it is difficult to delineate between the detrimental effects of terbutaline from the potential effects of these additional variables [9]. Terbutaline affects beta noradrenergic receptors and while beta 2 noradrenergic receptors are most known for cardiovascular and pulmonary physiology, these receptors are also involved in sympathetic nervous system responses like the fight or flight responses and also may be related to psychiatric symptoms and fetal growth including axonal growth [15, 16]. Nonetheless, research using animal models seems to provide further support for a direct

relationship between the drug and the impairments mentioned above. For example, Garofolo and colleagues [17] found indication of adverse effects on cell development in fetal tissues. Specifically, researchers observed changes in the DNA synthesis and content in the cerebellum, as well as evidence of cell death in the neonatal cardiac tissue [17]. Moreover, the investigation discovered that the changes were dependent on the particular phase in the fetal development during which the drug was administered and whether the fetus was male or female [17]. Both of those factors determine patterns of cell replication and differentiation, thus rendering different cell population vulnerable to terbutaline’s β AR stimulation [17].

Other studies have also noted terbutaline-induced alterations in neurotransmitter pathways. For example, an administration of terbutaline during critical developmental periods led to upregulation of α_2 ARs in the heart and liver, as well as the central nervous system (CNS), an irregularity connected to heightened reactivity to stressors [15, 18]. Additionally, an upregulation of serotonin (5HT) receptors and corresponding 5HT synaptic hyperactivity was evident consequent to terbutaline administration during prenatal and early neonatal stages [19]. All of these changes in the brain biochemistry are commonly associated with neurobehavioral difficulties and multiple psychiatric conditions [18, 19].

Animal research has suggested that fetal terbutaline exposure can cause cerebellar abnormalities similar to those found in some imaging studies involving autistic spectrum disorders (ASD) brain abnormalities [17]. Furthermore, recent studies have established an association between prenatal terbutaline exposure and autism spectrum disorders. Croen et al. [20] found that while brief exposure to terbutaline did not clearly present a significant risk for ASD, exposure greater than two days during the 3rd trimester was associated with more than a fourfold increased risk independent of indication. Connors and colleagues [21] discovered a greater risk for ASD diagnoses postterbutaline exposure. Their findings indicated that both overstimulations of β_2 ARs caused by the drug action of terbutaline and a genetic polymorphism of the β_2 ARs resulting in a desensitization of those receptors elicited similar cellular responses and ASD-associated anomalies in the developing fetal brain [21].

Thus, the research suggests that tocolytic terbutaline therapy carries a significant risk for both the mother and the child, which can be magnified by extended exposure, male sex of the fetus, and an administration during critical fetal developmental periods. The use of tocolytics as treatment for preterm labor has been discouraged by the American College of Obstetrics and Gynecology [11] and by the FDA [22], yet such efforts have been met with mixed results. Terbutaline is no longer used to treat preterm labor at some facilities; however, surveys of obstetric providers indicate that terbutaline is still being used as a maintenance tocolytic in other medical communities [23, 24]. Moreover, research investigating the effectiveness of terbutaline tocolytic effects continues to be funded [25]. Thus, even today children who are likely to experience a range of terbutaline-related neurobehavioral and psychiatric difficulties later in their childhood continue to be born. Publicizing the connection between terbutaline

and these deficits can not only assist obstetricians and expectant mothers in making a more informed choice in the treatment employed to arrest preterm labor, but also provide neuropsychologists and pediatricians with information helpful in understanding the etiology of these impairments. The following two case summaries suggest the potential deficits in clinical presentations of adolescents with history of significant intrauterine exposure to terbutaline.

2. Case Studies

2.1. Patient A. Patient A was a 15-year-old African American boy who underwent a neuropsychological evaluation with emphasis on identifying attention deficits. His mother endorsed a number of inattentiveness symptoms, including difficulty sustaining attention, making careless errors, distractibility, daily forgetfulness, and avoidance of difficult tasks. In addition, she reported that patient A was often verbally impulsive and had difficulty with organization.

In terms of patient A's development, his mother reported that, during her pregnancy, she went into preterm labor at 29 weeks of gestation, subsequent to an automobile accident. She was treated with terbutaline and magnesium sulfate and remained on the medication until her 37th week of gestation. Patient A's mother denied any other complications during her pregnancy as well as any tobacco, alcohol, or drug use. While patient A's birth was without any complications, he did appear lethargic after delivery and required oxygen. This neonatal hypoxia clearly placed patient A at risk, but his early development was unremarkable except for slight delay in language development. Although he experienced some ear infections, he did not receive tympanostomy. Patient A also suffered a concussion at the age of seven, yet confusion or a loss of consciousness following the injury was denied. At the time of the evaluation, patient A was in 9th grade and receiving As, Bs, and Cs in his classes. He had been evaluated for inattention in 3rd or 4th grade but had no accommodations or individualized educational plan in place. Family history included no cognitive and developmental disorders or psychiatric difficulties.

Patient A was administered a comprehensive battery of tests assessing a wide range of his cognitive and psychological functioning. The assessments included Behavior Assessment System for Children-2 (BASC-2; [26]), the Developmental and Behavioral History Questionnaire. Additionally, Patient A was evaluated with the Wechsler Intelligence Scale for Children-Fourth Edition (WISC-IV; [27]); California Verbal Learning Test, Children's Version (CVLT-C; [28]); Children's Memory Scale (CMS; [29]); Delis-Kaplan Executive Function System (D-KEFS; [30]); the Wechsler Individual Achievement Test-III (WIAT-III; [31]); Rey Complex Figure Test (RCF; [32]); Nelson-Denny Wisconsin Card Sorting Test (WCST; [33]); Conner's Continuous Performance Test-II (CPT-II; [34]); and the Test of Memory Malingering (TOMM; [35]).

Upon review of patient A's results, a distinct profile of cognitive strengths and weakness emerged. Patient A's overall intellectual functioning was average (FSIQ = 97). While

the majority of assessed domains were in the average range, he evidenced a significant disparity between his verbal comprehension and perceptual reasoning (WISC-IV VCI = 91; 27th percentile and PRI = 110; 75th percentile, resp.). Unsurprisingly, his normative strength could be found within the visual-spatial perceptual domain (WISC-IV, matrix reasoning, 95th percentile). Patient A also excelled at encoding and recalling meaningfully organized material (CMS stories, 84th percentile for initial and 75th percentile for delayed recall).

Conversely, a number of domains represented relative weaknesses for patient A, with his scores falling within the low average range: working memory (WISC-IV WMI = 88; 21st percentile), auditory attention (WIAT-III, sentence repetition; 9th percentile); expressive vocabulary (WIAT-III, expressive vocabulary; 14th percentile), verbal comprehension (WISC-IV, comprehension; 9th percentile), and list learning (CVLT-C; 16th percentile). On all measures of academic achievement, patient A's performance, although within average range, fell below his grade level, with a more significant struggle evident in his phonetic abilities (WIAT-III, pseudoword decoding 18th percentile; 4th grade level), reading (27th percentile; 6th grade level), and reading comprehension when provided standard amount of time (Nelson-Denny 19th percentile).

Although inattention was the intent for the referral, patient A's cognitive profile was not suggestive of an ADHD diagnosis. Yet inattention and reduced motivation seemed to play a role in his academic difficulties. Indeed, patient A's academic achievement test scores were below his grade level as well as below his level of intellectual functioning. Thus, considering this discrepancy, as well as his variable cognitive profile, it is thought by the authors that patient A suffered a pre- or postnatal brain insult. Possible etiologies include his prolonged intrauterine exposure to terbutaline and also brief need for oxygen after birth. Though there is no way to determine which variable was causally related to the brain dysfunction, the extreme terbutaline exposure is a strong risk factor. Patient A received a dual diagnoses of learning disability, not otherwise specified, and cognitive disorder, not otherwise specified.

2.2. Patient B. Patient B was an 18-year-old European American female who was referred for a neuropsychological evaluation because of problems with attention. She reported difficulty focusing in her classes, being easily distracted, avoiding tasks that required sustained mental effort, and fidgeting or moving around excessively. Patient B expressed feeling that her attentional problems have become worse in the past few years. She reported no other cognitive issues. In terms of emotional difficulties, at the time of the evaluation, patient B only related that she "[lets] things get to [her]" too easily and is very emotionally sensitive.

With regard to patient B's early development, her mother was treated with terbutaline for 6 weeks to stop and prevent another occurrence of preterm labor. Any other complications during the pregnancy as well as any tobacco, alcohol, or drug use were denied. Patient B was born full-term at

a normal birth weight. The only postdelivery complication was a mild case of jaundice. Patient B achieved her developmental milestones appropriately with the exception of some motoric delays: she began crawling at the age of 12 months and walking when she was 18 months old. Around one year of age, patient B suffered a head injury when she fell out of her mother's arms but was given a clean bill of health at a subsequent emergency room visit. Additionally, at the age of four, she suffered a febrile seizure. At the time of the evaluation, patient B was a recent high school graduate preparing for her first semester in college. She described herself as a "B student" and reported achieving SAT scores of 1710.

Patient B was administered a comprehensive battery of tests assessing a wide range of her cognitive and psychological functioning. The test battery included the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV; [31]), CPT-II [34], the Wechsler Memory Scale-IV (WMS-IV; [36]), D-KEFS [30], the Wide Range Achievement Test-IV (WRAT-IV; [37]), Beck Depression Inventory (BDI-II; [38]), Beck Anxiety Inventory (BAI; [39]), and the Test of Memory Malingering (TOMM; [35]).

A review of patient B's performance revealed the following pattern of strengths and weaknesses. Patient B's overall IQ was average (FSIQ = 100). On measures of intellectual functioning patient B overall performed on par with her peers with a marked normative strength in her verbal abilities (WAIS-IV VCI = 122). A significant discrepancy between her verbal and perceptual reasoning was also noted (WAIS-IV VCI = 122 and PRI = 90). Similarly, patient B's academic achievement reflected this wide incongruity in scores; however all achievement scores were on grade level or higher (WRAT-IV word reading = 120 and numerical operations = 100).

Patient B's performance on test assessing attention was more variable. She evidenced slight weaknesses (i.e., scores in the low average range) on measures of letter sequencing and alternating attention (D-KEFS letter sequencing = 85 and number-letter switching = 85) with a normative strength in word fluency (D-KEFS letter fluency = 120). Patient B's CPT-II profile aligned more closely with a clinical profile than nonclinical one, showing that the patient accrued more omission and commission errors than the average normative scores. Moreover, patient B evidenced significant variability in her reaction times, indicating potential variability in her attention skills as well as slight impulsivity. She also made many perseverative responses and exhibited a declining efficiency in her attention skills as the test progressed. Finally, patient B's scores on measures of working memory fell in the low average range as well (WAIS-IV working memory = 89).

In terms of her memory, patient B's delayed recall was above average and superior to her immediate recall suggesting above average retention and a slightly weaker initial encoding (WMS-IV logical memory I = 105 and logical memory II = 115). No significant emotional difficulties were revealed in patient B's responses to the administered self-report measures with the exception of a slight elevation in her sense of inadequacy (BASC-S sense of inadequacy scale), which was related to her attention difficulties.

While showing some high average to superior intellectual functioning, patient B exhibited relative weaknesses on measures involving sustained attention, alternating attention, and working memory. Nonetheless, these areas of cognitive functioning were not sufficiently impaired to significantly affect her academic potential. In terms of case conceptualization it is felt that patient B has some likely long-term abnormal cognitive patterns that have not been obvious due to her high level of intelligence. More recently, it is believed that her issues are more noticeable because school becomes more complicated and less structured as one prepares for and enters college. Mild attention and executive issues can become more apparent. However, patient B's attention issues and her pattern of scores across domains of functioning appeared to suggest mild cerebral dysfunction. Thus, she received a diagnosis of cognitive disorder, not otherwise specified. Although the etiology could not be precisely determined, her extended prenatal terbutaline exposure was a significant risk factor in her developmental history.

3. Discussion

Since odds of both mortality and neurocognitive impairments dramatically diminish as gestational age progresses from 22 to 28 weeks, physicians will frequently opt for tocolysis treatment to reverse preterm labor and allow further development of the fetus [5]. Among the most common tocolytic drugs is terbutaline. It may slow or delay preterm labor and have great potential benefits but may be prescribed in ways that carry increased developmental risks.

The cases presented involve two adolescents who experienced an excessive prenatal terbutaline exposure, and who subsequently developed cognitive weaknesses to impairments during their childhood. In both cases there is no significant neurological history, but both have developmental histories involving weaknesses in attention skills. However, aside from the attention issues, these individuals have very different cognitive profiles. Both cases have neuropsychological profiles which are highly unusual and possibly suggestive of early life brain injuries; however, it is conceivable that these individuals could have received some other diagnosis or none at all. Based on prenatal and neonatal history it is possible that patient A may have had two potential brain insults, the terbutaline exposure and the possible effects, from a brief episode of neonatal cyanosis or hypoxia. However, it may just be that time, intensity, and duration of exposure may all be relevant factors in a person's neurocognitive development. Much more research will be needed to understand the effects of these variables. Neither case has a cognitive profile or reported symptoms definitive for either ADHD or a learning disorder. Each case has a very different profile, as one case has a significant relative strength in verbal skills/ability and the other has just the opposite profile. Both report attention problems and there is some evidence that the attention issues occur across settings. Attention skills are highly susceptible to many factors and are thought to be possibly negatively affected by dysfunction in several different brain areas. Neither of these individuals has any

significant psychiatric or other issues which could obviously affect attention skills. Understanding the exact etiology of the attention and other cognitive issues may help in choice of treatment options. Moreover, it may be beneficial for children with significant terbutaline exposure to be closely followed or screened in early childhood, to help determine the need for early intervention. In cases such as these where there is no neurological history, birth trauma history, or family history of ADHD or learning disorders, it may be valuable for clinicians to ask about terbutaline or other prenatal exposures. It may be helpful for clinicians using terbutaline to be aware of the potential long-term developmental issues that may be associated with its use. To help direct relevant clinical decisions, there is a great need for more empirical, controlled, and long-term follow-up studies on the long-term effects of terbutaline.

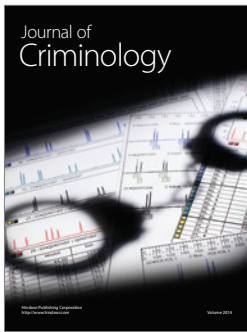
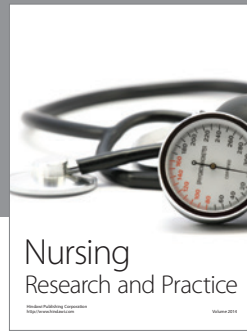
Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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