Fetal Exposure to 3,4-Diaminopyridine in a Pregnant Woman with Congenital Myasthenia Syndrome

Ana Pelufo-Pellicer, Emilio Monte-Boquet, Eva Romá-Sánchez, Carlos Casanova-Sorní, and Jose L Poveda-Andrés

OBJECTIVE: To report a case of fetal exposure to pyridostigmine and 3,4-diaminopyridine (3,4-DAP) in a pregnant woman with congenital myasthenia syndrome (CMS).

CASE SUMMARY: A 31-year-old woman with postsynaptic CMS, not genetically characterized, was being treated with pyridostigmine and 3,4-DAP. She decided to become pregnant, despite having been informed about the paucity of available information on the possible risks of these drugs for the fetus. The dose of pyridostigmine remained stable throughout the pregnancy (60 mg every 8 h), and the 3,4-DAP dose was adjusted according to the patient's level of fatigue (20 mg/day, with occasional additional doses of 5 mg). At 25 weeks' gestation, ultrasonography confirmed the presence of only one umbilical artery. The results of other tests were normal. At 38 weeks' gestation, a healthy male neonate was born. His APGAR scores were 9 and 10 at 1 and 5 minutes, respectively. Five months later, the infant was healthy and his pediatric progress had been uneventful.

DISCUSSION: It was difficult to find information about the possible congenital defects related to the use of 3,4-DAP because it is a rarely used drug. This case attracted our interest because it is an uncommon disease, and we found no reports on the use of 3,4-DAP during pregnancy. To our knowledge, as of this writing, this is the first published report of the use of 3,4-DAP during pregnancy.

CONCLUSIONS: A successful pregnancy with a healthy infant was achieved after fetal exposure to 3,4-DAP and pyridostigmine.

KEY WORDS: congenital myasthenia syndrome, 3,4-diaminopyridine, pyridostigmine, pregnancy.

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Congenital myasthenia syndromes (CMS) are clinically characterized by localized or widespread muscle weakness, which is increased by effort. The symptoms include ptosis, eye muscle paralysis, and deglutition disorders.[1] Some instances of CMS can be treated effectively with drugs such as cholinesterase inhibitors, of which pyridostigmine is the most commonly used. The use of 3,4-diaminopyridine (3,4-DAP) improves neuromuscular transmission and enhances acetylcholine release from nerve terminals. This drug acts by blocking presynaptic potassium channels, thus prolonging the action potential.[2-4]

CMS can worsen in pregnancy, so it is essential to follow a suitable treatment regimen; however, the drugs used can be a risk to the fetus. We describe the case of a pregnant woman with CMS who was treated with pyridostigmine and 3,4-DAP. At 9 weeks' gestation, she was referred to the genetic and prenatal diagnosis unit (GPDU) for an overall evaluation. The drug information center of the pharmacy department was requested to evaluate the congenital malformation risk due to these drugs. This report, together with the necessary tests, was considered necessary before an informed decision could be made about whether to proceed with the pregnancy.

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Case Report

A 31-year-old pregnant woman had suffered from postsynaptic CMS (not genetically characterized) for 8 years. She was severely ill, with significant fatigue, widespread neuromuscular weakness (she was unable to raise her arms and, if she did so, could hold them up for only a few seconds), and blurred vision. It was a great effort for her to stand and walk a short distance (eg, 15 m) without help. Her relapses were so serious that she was admitted to the hospital in a state of almost complete paresis–paralysis with compromised respiratory function. Therefore, she was partially dependent in terms of daily life activities. Treatment was pyridostigmine 60 mg every 8 hours and 3,4-DAP 75 mg/day, which was sometimes increased (once to 105 mg/day) depending on the woman's level of fatigue and widespread neuromuscular weakness. Although her symptoms were moderately relieved by this regimen, no functional improvement was achieved.

The patient had had a previous pregnancy, which was voluntarily terminated because her condition was considered too clinically unstable to support the pregnancy. She was then admitted to the hospital with clinical worsening of neuromuscular weakness after the sudden withdrawal of pyridostigmine and 3,4-DAP when she became pregnant. Some time later, the patient decided to become pregnant again. In agreement with her neurologist and pharmacist, she began a progressive reduction of the 3,4-DAP dose to 25–35 mg/day in the preconception period. At 8 weeks' gestation, she consulted the obstetrics–gynecology department to evaluate the possible effects these drugs could have on the fetus/newborn. Following the standard procedure, the GPDU requested an interdepartmental consultation with the drug information center to formulate a teratogeny report. We performed an exhaustive search of the primary, secondary, and tertiary sources available according to the standardized methodology in the subprocess of drug information.

The patient was informed of the paucity of information regarding the use of these drugs during pregnancy and that their use could cause some synergic effects that could modify embryonic or fetal development. Although the fetus was exposed at a time when it was vulnerable to congenital defects, the patient decided to continue her pregnancy. The gynecologist undertook complete monitoring, which included high-resolution ultrasonography for the early detection of congenital defects. The outpatient pharmacist, together with the neurologist, monitored the patient and the progressive dosage reduction of 3,4-DAP. The pharmacist advised the woman to take the lowest dose possible based on the level of fatigue she could withstand.

At 12 weeks' gestation, ultrasonography revealed no marked morphologic fetal abnormalities. After an ultrasonographic anatomical study at 20 weeks' gestation, the possibility that the fetus had only one umbilical artery was raised. An evaluation of the central nervous system (CNS), face, heart, lungs, diaphragm, abdomen, extremities, and spinal column produced normal results. At 25 weeks' gestation, sonography confirmed the presence of only one umbilical artery. The results of all other tests were normal. Further ultrasonography at 34 weeks confirmed the previous results and verified that the amniotic fluid was normal and the estimated fetal weight was 2270 g.

In treating the patient's CMS, drug doses were adjusted according to the level of fatigue she experienced. Thus, the pyridostigmine dose was maintained at 60 mg every 8 hours throughout the pregnancy. The dose of 3,4-DAP was reduced between 15 weeks' gestation and labor to 20 mg/day (divided into 3 or 4 doses). The patient reported that she sometimes required additional doses of 5 mg to control her fatigue. She occasionally required additional bed rest because of the symptoms. The weekly doses of 3,4-DAP before and during the pregnancy and after labor are shown in Figure 1.

Although a cesarean section was planned because of her clinical state, the patient was admitted to the hospital at 38 weeks' gestation when labor began spontaneously with cephalic presentation and ended with an elective cesarean section. A male infant weighing 3025 g, 47 cm long, and with a head circumference of 36 cm was born at term and was considered healthy. The baby had APGAR scores of 9 and 10 at 1 and 5 minutes, respectively. Hematocrit and leukocyte values were normal. He was admitted to the neonatal department for monitoring because he had been born to a mother with CMS.

The baby had a healthy complexion and no respiratory distress; he began enteral nutrition with artificial milk on his first day of life, with good ingestion and tolerance. He had good tone, was active, and his reflexes were good, including vigorous sucking and crying. Renal and cerebral ultrasonography showed no pathology. The neurologist evaluated the infant's neurologic state with an electroencephalogram, which was completely normal. The newborn was discharged and followed up at an outpatient consultation.

After the labor and for the following 5 months (when the mother visited the outpatient pharmacy department), the 3,4-DAP dose was maintained at 45 mg/day. At that time, the mother reported that her infant was in perfect condition. His pediatric progress had been uneventful, and his weight (7 kg at 4.5 mo of age) and height were within normal limits.

Table 1. Classification of Congenital Myasthenia Syndromes

Syndrome	Inheritance	Symptoms	Electromyography	Treatment
Presynaptic				
synthesis and/or storage ACh alterations	autosomal recessive	neonatal onset sudden apnea episodes	decrease after sustained stimulation	cholinesterase inhibitors and 3,4-DAP
synaptic vesicles scarcity	autosomal recessive	bulbar muscles involved	decrease after repeated stimulation	cholinesterase inhibitors
Eaton–Lambert	autosomal recessive	delayed motor development with hypotonicity; mental retardation	post-tetanic facilitation similar to Eaton–Lambert	3,4-DAP
Synaptic				
acetylcholinesterase deficit	autosomal recessive	neonatal onset ptosis; diffuse weakness	repeated response to a unique stimulus	none
Postsynaptic				
slow-channel syndrome	autosomal dominant	onset in infancy or adult age; slow progression with serious involvement of the finger extensors	repeated response to a unique stimulus; decreased response to low frequencies	cholinesterase inhibitors and 3,4-DAP cause worsening; quinidine and fluoxetine are effective
fast-channel syndrome	autosomal recessive	no clinical differences from others	repeated response to a unique stimulus	cholinesterase inhibitors and 3,4-DAP
primary ACh receptor deficiency	autosomal recessive	neonatal or infancy onset the most frequent	decreased response to low frequencies	cholinesterase inhibitors and 3,4-DAP
Unidentified site				
waist	autosomal recessive	infancy or adolescent onset; weakness in pelvic waist	decreased and positive response to ACh esterase inhibitors	cholinesterase inhibitors
associated with facial malformations	autosomal recessive	in Iranian Jews, facial weakness, dysarthria	decreased and positive response to ACh esterase inhibitors	cholinesterase inhibitors

3,4-DAP = 3,4-diaminopyridine; ACh = acetylcholine.

Discussion

The etiology of CMS involves genetic defects at different sites of neuromuscular transmission, some of which have not yet been identified. CMS differs from myasthenia gravis (MG) in its lack of immunological characteristics, and it therefore does not respond to immunosuppressant drugs. All CMS cases described as of this writing, except slow-channel syndromes, are autosomal recessive.[1,5,6] They are classified as rare diseases that affect fewer than 1 person in 500 000. The following criteria must be considered in a diagnosis of CMS[7]:

1. clinical history, which can be a guide in cases of early onset,
2. family background,
3. determination of muscle electrical activity (electromyography),
4. negative response to acetylcholinesterase inhibitors,
5. lack of antibodies against acetylcholine receptors.

Points 4 and 5 are considered essential for a differential diagnosis that distinguishes CMS from MG. Advances in molecular genetics and the correlation of molecular biology with morphologic, microphysiologic, clinical, and electrophysiologic criteria have improved the characterization of the different types of CMS (Table 1).[1,5,7]

Pyridostigmine is a parasympathomimetic drug with anticholinesterase activity used in the treatment of myasthenia syndromes. Although it is a synthetic quaternary ammonium compound that is ionized at physiological pH, the low molecular weight of pyridostigmine allows the nonionized fraction to cross the placenta.[2,8]

In a study performed in rats, the congenital malformation frequency did not increase in descendants of rats treated throughout gestation with pyridostigmine at doses similar to those used for humans.[9] No congenital malformations have been observed after using pyridostigmine in humans, although our review of the literature found no controlled studies of congenital malformations in infants born to mothers treated with pyridostigmine throughout pregnancy.[4,8] Transient muscular weakness has been observed in 10–20% of neonates whose mothers had received high-dose anticholinesterase drugs for treatment of MG in the perinatal period.[2,4,8] Some cases of neonatal myasthenia related to distal multiple arthrogryposis, severe hypotonicity, and respiratory distress have been reported, although most patients presented with mild, transient symptoms.[10] A case report described microcephaly and CNS injury in a newborn whose mother had ingested 8 times the recommended daily dose of pyridostigmine for humans (>40 mg/kg/day) during her pregnancy.[11] The infant's mother had a 10 year history of MG, treated only with pyridostigmine during the gestation period. Despite a normal karyotype, other dysmorphic features were noted in the neonate including a short neck, broad chest, and bilateral campylodactylia and cryptorchidism.

A retrospective cohort study was undertaken between 1967 and 2000 that investigated the consequences of MG in pregnancy, labor, and newborns.[12] The 127 labors among 79 women with MG were compared with 1 988 865 labors among women without MG (reference group). Five (4%) of the 127 infants whose mothers had MG developed malformations classified as severe defects compared with 1.9% in the reference group. The 4 mothers who gave birth to the 5 infants with severe malformations had taken pyridostigmine during their pregnancies.

Information about pyridostigmine and its fetal risk in humans is limited, probably because pregnant patients with myasthenia syndromes are rare. Pyridostigmine is classified by the Food and Drug Administration (FDA) as Fetal Risk C, yet some researchers consider pyridostigmine to be the treatment of choice during pregnancy.[4,13]

Aminopyridines act by blocking potassium channels, and they have been used in the management of a number

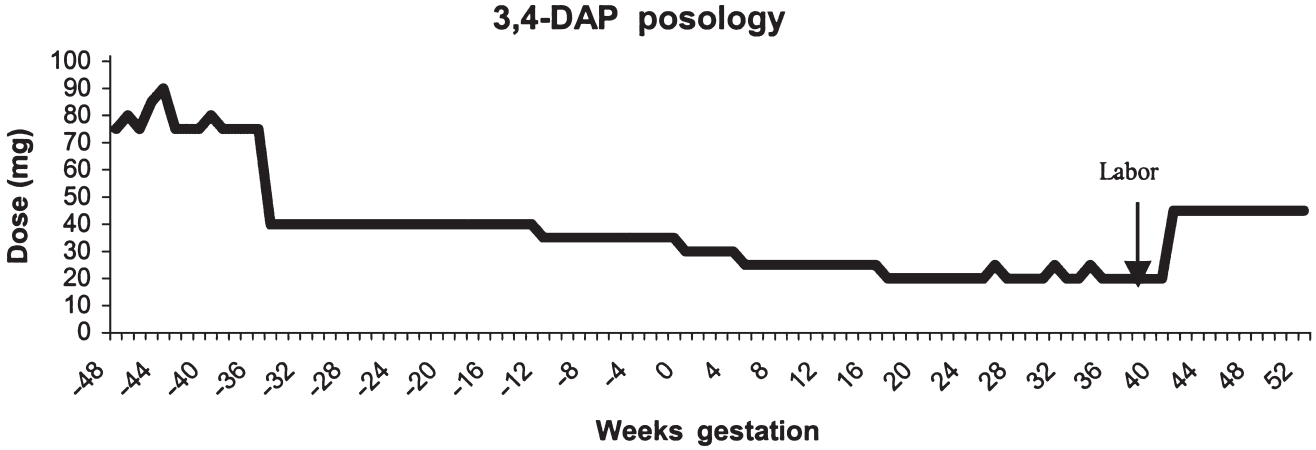

Figure 1. 3,4-Diaminopyridine (3,4-DAP) dose before and during the gestation and after labor.

of neurologic disorders, including myasthenia syndromes and multiple sclerosis, to improve conduction in demyelinated fibers.[2,3] Because no experience with 4-aminopyridine during human pregnancy has been published, the risk of congenital malformations cannot be estimated. The drug's main adverse effects are hepatitis and seizures, which could affect the fetus.[14] On the other hand, people with multiple sclerosis are advised to withdraw from all treatment 2–3 months before conception.[15] 4-Aminopyridine and 3,4-DAP are not classified in any FDA risk factor category.

It was difficult to find information on the possible congenital defects related to the use of 3,4-DAP because it is rarely used.[2,8] Nevertheless, the neurology department of our hospital has considerable experience with its use in patients with different neurologic pathologies (multiple sclerosis, Eaton–Lambert myasthenia syndrome [ELMS], congenital myasthenia).[16-20] 3,4-DAP acts by blocking presynaptic potassium channels, resulting in the prolongation of the action potential. Its effect starts within about 20 minutes after administration of an oral dose. As noted with pyridostigmine, 3,4-DAP has peculiar pharmacokinetic activity, with an elimination half-life of 2 hours, with great interindividual variability. However, it has been empirically verified that the clinical effect does not disappear for 4–6 hours. Therefore, the drug is administered in at least 3–4 daily doses, starting with 5–10 mg per dose and increasing gradually to the point of optimum effect with minimal adverse effects.

Most adverse effects are moderate. The most common are perioral and digital paresthesias or sympathetic and parasympathetic hyperactivity. The most important adverse effects involving the CNS are seizures and mental disorders.[14] In many patients, the combination of 3,4-DAP and pyridostigmine enhances their action on nicotinic receptors so that the dose of 3,4-DAP required is reduced and the potential effects on the CNS decrease, although muscarinic complications remain unaffected.[2,21] Because there is no brand name product that contains 3,4-DAP, our pharmacy department compounds and dispenses capsules of different doses. 3,4-DAP is considered an orphan drug for treatment of ELMS,[22,23] and our pharmacy department manages it through compassionate use for all its indications.[21]

The umbilical cord is normally composed of 3 vessels: 2 arteries and 1 vein. The absence of one of the umbilical arteries is the most common umbilical cord malformation, with an incidence of 0.8% in all single pregnancies and 5% in multiple pregnancies (the incidence average may differ depending on the consulted source).[24-27] In 30% of cases, the absence of an umbilical artery is associated with aberrations in the baby's growth, premature labor, and renal or cardiac malformations.[24-26] There were no such abnormalities in our patient's infant. Renal and cerebral ultrasonography showed no pathology. We have found no references relating the use of drugs by a pregnant woman associated with development of a single umbilical artery. In any case, the prenatal detection of a single umbilical artery demands an extensive evaluation for associated anomalies and close surveillance of the fetus.

Conclusions

This case attracted our interest not only because this disease is uncommon, but also for the universal lack of experience in the use of 3,4-DAP during pregnancy. Even though the circumstances were potentially dangerous, the patient decided to continue her pregnancy, with successful results. From our experience, we think it is important to consider 4 requirements: (1) the mother must be advised of the paucity of experience in this field, (2) if she makes the decision to continue her pregnancy, a pharmacist and neurologist must advise her to take the lowest dose of 3,4-DAP possible to control her symptoms, (3) her gynecologist must closely monitor the fetus, and (4) a neurologic examination must be conducted to evaluate the neonate's health. Finally, it is important to emphasize the excellent coordination of the different hospital departments achieved in this case; this allowed close and consistent management of the woman and her infant.

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EXTRACTO

OBJETIVO: Describir un caso de exposición fetal a 3,4-diaminopiridina (3,4-DAP) y piridostigmina en una paciente gestante afectada de un síndrome miasténico congénito (SMC).

RESUMEN DEL CASO: Mujer de 31 años afectada de un SMC postsináptico, no caracterizado genéticamente, en tratamiento con piridostigmina y 3,4-DAP. La paciente decide quedarse embarazada, a pesar de ser informada de la escasez de datos disponibles acerca del riesgo que podía suponer la exposición fetal a estos fármacos. Las dosis de piridostigmina y 3,4-DAP fueron ajustadas según el grado de fatiga de la paciente. En la ecografía de la semana 25, se confirmó la existencia de una arteria umbilical única. El resto de pruebas fueron normales. En la semana 38 de gestación, tiene lugar el parto, naciendo un varón sano, con un APGAR de 9 y 10 en el minuto 1 y 5, respectivamente. A los 5 meses de vida, el bebé se encuentra en perfecto estado, habiendo superado las revisiones de su pediatra con absoluta normalidad.

DISCUSIÓN: Resultó difícil localizar información acerca de posibles anomalías congénitas asociadas al uso de 3,4-DAP, puesto que se trata de un fármaco poco conocido. Este caso despertó nuestro interés, tanto por la infrecuencia de la enfermedad, como por la falta de experiencia de utilización de 3,4-DAP durante la gestación. De hecho, pensamos que se trata del primer caso publicado sobre utilización de 3,4-DAP durante el embarazo.

CONCLUSIONES: Consideramos de gran interés dar a conocer el caso de un embarazo exitoso con un bebé sano tras exposición fetal a 3,4-DAP y piridostigmina.

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RÉSUMÉ

OBJECTIF: Décrire l'évolution de la grossesse d'une femme ayant pris de la pyridostigmine et du 3,4-diaminopyridine (DAP) pour un syndrome myasthénique congénital.

RÉSUMÉ DU CAS: Une femme âgée de 31 ans souffrant d'un syndrome myasthénique congénital, non caractérisé au niveau génétique, a décidé de poursuivre sa grossesse malgré le manque d'informations sur les risques possibles de la pyridostigmine et du DAP sur le fœtus. Les posologies de ces 2 médicaments ont été ajustées selon le niveau de fatigue de la patiente tout au long de la grossesse. A la vingt-cinquième semaine de gestation, un ultrason a révélé la présence d'une seule artère ombilicale. Toutefois, tous les autres tests étaient cependant normaux. Un petit garçon pesant 3025 g, mesurant 47 cm, et ayant une circonférence de la tête de 36 cm est né à terme en santé après 38 semaines de gestation. Ses indices d'apgar étaient, respectivement, de 9 et 10 après 1 et 5 minutes. La croissance de l'enfant semble toujours normale 5 mois après sa naissance.

DISCUSSION: Très peu d'informations sont disponibles sur l'utilisation de la pyridostigmine et du DAP durant la grossesse. Selon une revue de littérature effectuée par les auteurs, il semble d'ailleurs que ce soit le premier cas publié décrivant l'utilisation de DAP durant une grossesse.

CONCLUSIONS: Ce rapport de cas décrit la naissance d'un enfant en bonne santé après une utilisation continue de pyridostigmine et de DAP par la mère durant la grossesse.

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