THERAPEUTIC DILEMMA

Unusual Amiodarone Toxicity in a Child

Bahram Kakavand, MD and Thomas G Di Sessa, MD

Department of Pediatrics, College of Medicine, University of Kentucky, Lexington, Kentucky

KEYWORDS adverse drug effect, amiodarone, antiarrhythmic, propafenone, toxicity

J Pediatr Pharmacol Ther 2008;13:93-95

Downloaded from http://meridian.allenpress.com/jppt/article-pdf/13/2/93/1784320/1551-6776-13_2_93.pdf by guest on 27 February 2024

The following is a contrived report that has been created as a teaching case in the area of pediatric pharmacotherapy.

CASE

A 20-month-old, 10 kg male was diagnosed with a narrow QRS tachycardia and a long RP interval shortly after birth. He had been tried on a variety of antiarrhythmic drugs including atenolol, sotalol, sotalol/flecainide combination, amiodarone, amiodarone/flecainide combination and amiodarone/propafenone combination. The tachycardia had been difficult to control; however, the last combination of amiodarone/propafenone seemed to maintain normal sinus rhythm with rare brief breakthroughs that were managed by adjusting the drug dosages to patient's weight and body surface area. The amiodarone dose was 4 mg/kg/day and the propafenone dose was 500 mg/m^2/day divided in 4 doses. Eight months into the therapy the patient developed sleepiness. Further inpatient evaluation revealed other symptoms including somnolence, tremor, ataxia, drooling and poor oral intake. Pediatric neurology was consulted. A magnetic resonance imaging of the brain and electroencephalogram were considered normal, upon which the neurology service signed off. Serum concentrations of amiodarone and its metabolite were 0.3 μg/mL (0.47 μmol/L) and 0.4 ug/mL, respectively. The reference range for amiodarone in the serum is 0.5-2.5 μg/mL (0.8-3.9 0.47 μmol/L). Thyroid function test, ammonia level, plasma amino acids and urine organic acids were all normal or negative. The electrocardiogram showed normal sinus rhythm at 102 beats per minute. QRS was 89 msec, and QTc was 460 msec.

ABBREVIATIONS DEA, N-desethylamiodarone

A review of the literature revealed that central and peripheral neurotoxicity was indeed associated with amiodarone.[1-6] One case of peripheral neuropathy associated with propafenone has also been reported.[7] Amiodarone was discontinued, and the patient received supportive care. Within 1 week the somnolence, ataxia and tremor resolved; however, drooling persisted for 4 weeks. Three weeks after discontinuing amiodarone the patient developed a sustained tachycardia at 200 beats per minute. Sotalol 40 mg/m^2/day and propafenone at previous dose were started. This combination controlled the tachycardia. The sotalol dose was later increased to 60 mg/m^2/day. The patient remained free of arrhythmia (except for short breakthroughs) and other neurological symptoms for more than 2 months. Subsequently it was decided to proceed with an ablation procedure in order to discontinue the very potent antiarrhythmic drugs with potentially serious side effects. The procedure was successful and the medications were stopped. At the end of the ablation an endomyocardial

Address correspondence to: Bahram Kakavand, MD, University of Kentucky, Pediatric Cardiology, 800 Rose St., MN 472, Lexington, KY 40536-0298, email: bkakavand@uky.edu
© 2008 Pediatric Pharmacy Advocacy Group

biopsy was performed because of a history of an unexplained mild left ventricular dilation and hypertrophy. The biopsy was suggestive of a mitochondrial disorder. This was later confirmed by a peripheral muscle biopsy. In the ensuing months the patient began having episodes of staring spells, but the full spectrum of the neurological symptoms that prompted the first admission never recurred. He was started on phenytoin (Dilantin) which controlled the symptoms to a great extent. He has been given a very poor prognosis by several experts.

DISCUSSION

Amiodarone, originally developed as an antianginal agent, is a potent Class III antiarrhythmic medication with indication for treatment of ventricular and supraventricular tachycardia in children and adults.[8,9] Amiodarone effect can be divided into acute and chronic. Acutely it is a potent inhibitor of Na^+ (I_{Na}) and Ca^{++} (I_{Ca}) current. This function is shared with Class I and IV antiarrhythmic drugs.[10] Amiodarone also exerts some inhibitory effect on outward K^+ currents. Amiodarone effect is use dependent, exerting its maximum potency during tachycardia. With chronic use of the drug the outward potassium current inhibition becomes prominent. While the refractory period and the QT interval are not affected significantly in the acute phase, there is a considerable prolongation of these parameters with chronic use. Other electrophysiologic effects of amiodarone include for example sinus bradycardia and slowing of AV node conduction.

Pharmacologically amiodarone is a benzofuran derivative (2-butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone hydrochloride). Following oral administration in adults, amiodarone is slowly and variably absorbed. The bioavailability of amiodarone is approximately 50%, but has varied between 35 and 65%. Amiodarone has a large volume of distribution, averaging about 60 L/kg, because of extensive accumulation in various sites, especially fat tissue and highly perfused organs. It is metabolized to N-desethylamiodarone (DEA) by cytochrome P450 enzyme group. DEA possesses Class III properties and it is believed to have concurrent effects with chronic use of the parent drug. In a recent study by Saul et al. the amiodarone half-life in a very small number of children was determined to be between 6.9 and 11.4 days.[11] This is much shorter than the value reported for adults (approximately 53 days).

The list of amiodarone's potential side effects is extensive and includes central and peripheral nervous system involvement. Previous reports on adult patients suggest that amiodarone neurotoxicity is possibly unrelated to the drug dose or duration of therapy.[1] Palakurthy et al. published a study of a population of 45 patients who developed some form of neurotoxicity during amiodarone treatment. These authors suggested that decreasing the drug dose lead to improvement of the symptoms in some patients; however, age of the patient and total cumulative dose did not seem to be risk factors for development of neurotoxicity.[3] Besser et al. showed slowing of sensory and motor nerve conduction velocities with dissociation of the action potentials in patients with amiodarone neurotoxicity.[12] The underlying pathological changes have been described by Jacobs et al. Examination of sural nerves showed demyelination with only mild axonal loss. Cytoplasmic changes developed in Schwann cells of myelinated and unmyelinated axons, and involved loss of most recognizable organelles.[13]

In the case presented in this article the patient demonstrated a wide spectrum of neurological symptoms while being on amiodarone and propafenone. While the spectrum of propafenone side effects does not include symptoms experienced by this patient, amiodarone is well known to cause similar symptoms. On the other hand, cenrtral nervous symptoms are inherent to mitochondrial diseases as found later in this patient. The question, however, as to whether the patient's symptoms were caused by amiodarone or the mitochondrial disease will probably remain unanswered. Nonetheless, several points can be made. This patient presented with a wide spectrum of symptoms that resolved upon discontinuing amiodarone (and propafenone). Most symptoms except drooling resolved within one week, which is consistent with the half-life of amiodarone in children. As patient's disease progressed, the only neurological symptom presented by the patient was staring spells. It is quite possible but not conclusive that the initial symptomatol-

Downloaded from http://meridian.allenpress.com/jppt/article-pdf/13/2/93/1784320/1551-6776-13_2_93.pdf by guest on 27 February 2024

ogy was related to amiodarone; or at least amiodarone played a role as a co-factor in conjunction with the underlying disease. Discontinuing the drugs, once a neurologic disorder was ruled out initially (albeit erroneously), was indicated and probably mandatory. As a final point, this case reminds us not to rule out a drug reaction based on the correct prescribed dose or normal drug serum concentrations.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

REFERENCES

1. Arnaud A, Neau JP, Rivasseau-Jonveau T,et al. Neurological toxicity of amiodarone. 5 case reports. Rev Med Interne 1992;13:419-522.
2. Maciel Junior JA. Amiodarone neurotoxicity. Report of 3 cases. Arq Bras Cardiol 1989;53:125-127.
3. Palakurthy PR, Iyer V, Meckler RJ. Unusual neurotoxicity associated with amiodarone therapy. Arch Internal Med 1987;147:881-884.
4. Fraser AG, McQueen IN, Watt AH, Stephens MR. Peripheral neuropathy during long-term high-dose amiodarone therapy. J Neurol Neurosurg Psychiatry 1985;48:576-578.
5. Johnson LN, Krohel GB, Thomas ER. The clinical spectrum of amiodarone-associated optic neuropathy. J Natl Med Assoc 2004;96:1477-1791.
6. Pellissier JF, Pouget J, Cros D, et al. Peripheral neuropathy induced by amiodarone chlorhydrate. A clinicopathological study. J Neurol Sci 1984;63:251-266.
7. Vignati G, Mauri L, Figini A. The use of propafenone in the treatment of tachyarrhythmias in children. Eur Heart J 1993;14:546-550.
8. Etheridge SP, Craig JE, Compton SJ. Amiodarone is safe and highly effective therapy for supraventricular tachycardia in infants. Am Heart J 2001;141:105-110.
9. Laird WP, Snyder CS, Kertesz NJ, et al. Use of intravenous amiodarone for postoperative junctional ectopic tachycardia in children. Pediatr Cardiol 2003;24:133-137.
10. Podrid PJ. Amiodarone. Reevaluation of an old drug. Ann Intern Med 1995;122:689-700.
11. Saul JP, Scott WA, Brown S, Marantz P, Acevedo V, Etheridge SP, Perry JC, Triedman JK, Burriss SW, Cargo P, Graepel J, PhD; Koskelo EK, Wang R, for the Intravenous Amiodarone Pediatric Investigators: Intravenous Amiodarone for Incessant Tachyarrhythmias in Children. A randomized, double-blind, antiarrhythmic drug trial. Circulation 2005;112:3470-3477.
12. Besser R, Treese N, Bohl J, Goebel HH. Clinical, neurophysiologic and biopsy findings in neurotoxic amiodarone syndrome. Med Klin (Munich) 1994;89:367-372.
13. Jacobs JM, Costa-Jussa FR. The pathology of amiodarone neurotoxicity. II. Peripheral neuropathy in man. Brain 1985;108 (Pt 3):753-769.

Downloaded from http://meridian.allenpress.com/jppt/article-pdf/13/2/93/1784320/1551-6776-13_2_93.pdf by guest on 27 February 2024