Use of amiodarone during pregnancy

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Summary: Two cases are reported in which amiodarone was administered during pregnancy for longer periods than has been reported previously. Limited placental transfer of amiodarone and its desethyl metabolite was observed in both cases. A normal child resulted from each pregnancy despite, in one case, amiodarone therapy throughout the entire pregnancy. However, caution is urged in the use of amiodarone during pregnancy in view of the limited data available.

Introduction

Amiodarone is used increasingly for the control of ventricular and supraventricular arrhythmias. The drug contains a high proportion of iodine (75 mg per 200 mg) and uncertainty as to the effect of this iodine load on the fetus has limited the use of amiodarone in pregnancy. Two recent reports (McKenna *et al.*, 1983; Pitcher *et al.*, 1983) have documented the use of amiodarone in the later stages of pregnancy without adverse effects to the fetus. We report two further cases, one involving a patient who conceived whilst receiving amiodarone and continued use of the drug throughout her pregnancy, the other a patient who received amiodarone for the final 17 weeks of her pregnancy.

Case reports

Case 1

A 31 year old woman presented in atrial fibrillation with signs of tight mitral stenosis. She subsequently underwent open mitral valvotomy and annuloplasty, following which she was in sinus rhythm; a month later she reverted into atrial fibrillation. Despite adequate control of heart rate with digoxin she became markedly limited by dyspnoea on exertion. She reverted to sinus rhythm following a D.C. shock. Before this, amiodarone had been started in a dose of 200 mg tds. She continued on amiodarone 200 mg/d, hydrochlorothiazide and amiloride (Moduretic), warfarin and an oral contraceptive. Although the return to

sinus rhythm produced some symptomatic improvement, she was still markedly dyspnoeic on effort. Ultrasound studies suggested there was, again, significant mitral stenosis. The patient then discontinued her oral contraceptive and, despite being warned as to the risks of pregnancy, both with regard to herself and the fetus, she became pregnant. The pregnancy was reported and confirmed at seven weeks and warfarin was discontinued immediately.

It was considered essential to continue amiodarone to maintain sinus rhythm, as it was thought that a relapse into atrial fibrillation would produce marked haemodynamic deterioration. She was, therefore, maintained on amiodarone 200 mg/d for the remainder of her pregnancy. At six months the patient was admitted in acute pulmonary oedema. At this stage the mitral valve area on 2D ultrasound was 1 cm². Despite these problems the pregnancy proceeded uneventfully, albeit using increasingly large doses of diuretics. At 37 weeks a healthy girl was delivered by Caesarian section. Immediately following delivery the mother went into acute pulmonary oedema and required ventilation for 24 h. Subsequently, she made a satisfactory recovery and underwent mitral valve replacement. The child weighed 3.5 kg at birth and routine neonatal examination was normal in all respects; there was no goitre and no corneal changes were visible. Thyroid function tests measured at birth from cord blood were: thyroxine 209 nmol/l, thyroid stimulating hormone (TSH) 3.2 µU/ml; at one week thyroxine remained at 207 nmol/l but TSH was less than 1 µU/ml. Table I shows amiodarone and desethylamiodarone concentrations in maternal plasma at intervals throughout the pregnancy and in maternal plasma, cord plasma, amniotic fluid and placenta at the time of delivery. These compounds were measured using high-performance liquid chromatographic techniques (Storey *et al.*, 1982; Storey *et al.*, 1983). At

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Table 1 Amiodarone and desethylamiodarone concentrations in Case 1.

<i>Time</i>	<i>Sample</i>	<i>Amiodarone (mg/l)</i>	<i>Desethylamiodarone (mg/l)</i>
3 months pre-partum	Maternal plasma	0.7	0.8
2 months pre-partum	Maternal plasma	0.7	0.9
1 month pre-partum	Maternal plasma	0.5	0.7
Birth	Maternal plasma	0.5	0.8
Birth	Cord plasma	0.05	0.15
Birth	Amniotic fluid	0.02	0.11
2 months post-partum	Maternal	0.6	0.6
		<i>mg/kg wet weight</i>	
Birth	Placenta	34	300

mitral valve replacement, two months later, concentrations of both compounds (amiodarone/desethylamiodarone) in myocardium and subcutaneous fat were 9/47 and 197/43 mg/kg wet weight, respectively, whilst the patient was receiving 200 mg amiodarone daily.

Case 2

A 27 year old primigravida was admitted to hospital at 22 weeks gestation with a 24 h history of rapid increase in pulse rate, vomiting and feeling faint. She had a 13 year history of intermittent palpitations, diagnosed one year previously as due to paroxysmal atrial tachycardia, for which she had received, successively, propranolol and metoprolol; on admission she was receiving metoprolol 50 mg three times daily. On examination she had a sinus tachycardia, rate 150 beats/min, which was not controlled by either additional doses of metoprolol or intravenous verapamil. Therapy with oral amiodarone was started, 200 mg four times daily for one week. She was discharged two weeks later with a heart rate of 100 beats/min, receiving amiodarone 200 mg twice daily and metoprolol 25 mg twice daily.

She was re-admitted two months later complaining of palpitations, tiredness and nausea; her heart rate was 130 beats/min. Amiodarone dose was increased to

200 mg three times daily, metoprolol was stopped and frusemide, 40 mg twice daily, was added to her medication for the treatment of pulmonary oedema. During the following three weeks of hospital care her pulmonary oedema resolved but her palpitations persisted. Her heart rate was in the range 100–130 beats/min, whilst measurements of fetal heart rate were in the range 100–120 beats/min.

In the 39th week of pregnancy she went into spontaneous labour followed by elective Anderson forceps delivery of a healthy boy weighing 2.9 kg. Apgar scores were 9 and 10 at 1 and 5 minutes respectively. Neonatal examinations were all normal.

Blood samples were collected from the mother during the pregnancy and at delivery for the measurement of amiodarone and desethylamiodarone, together with a sample of placenta. The results are summarized in Table II.

Discussion

In both cases maternal plasma concentrations of amiodarone and desethylamiodarone were consistent with chronic therapy on the prescribed dose throughout the pregnancy (Holt and Storey, 1983) and cord blood concentrations at delivery show a degree of transplacental passage of the two compounds similar

Table II Amiodarone and desethylamiodarone concentrations in Case 2

<i>Time</i>	<i>Sample</i>	<i>Amiodarone (mg/l)</i>	<i>Desethylamiodarone (mg/l)</i>
1 month pre-partum	Maternal plasma	1.5	1.6
Birth	Maternal plasma	1.1	1.2
Birth	Cord plasma	0.16	0.26
		<i>(mg/kg wet weight)</i>	
Birth	Placenta	72	492

to that previously reported (McKenna *et al.*, 1983; Pitcher *et al.*, 1983). There are no data on placental concentrations of amiodarone and desethylamiodarone for comparison with these cases but both contained comparatively high concentrations of desethylamiodarone (Holt *et al.*, 1984); tissue samples obtained in Case 1 at mitral valve replacement contained concentrations of both compounds of the same order as those previously found (Storey *et al.*, 1983).

Previous reports have documented the use of amiodarone during only the final seven (McKenna *et*

al., 1983) and three (Pitcher *et al.*, 1983) weeks of pregnancy. One of our patients (Case 1) continued amiodarone throughout the pregnancy and, to our knowledge, this is the first documented case in which this has occurred; the other patient was exposed to the drug for the final 17 weeks of her pregnancy. Although the fetus was exposed to the potential teratogenic effects of amiodarone, a normal child resulted in each case. However, despite this successful outcome, there is no reason for other than continued caution in the use of amiodarone during pregnancy.

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