Flecainide in the treatment of fetal tachycardias

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Abstract

Fourteen mothers were treated with flecainide for fetal atrial tachycardias associated with intraterine cardiac failure. Twelve of the 14 fetuses responded by conversion to sinus rhythm. One of the 12 fetuses subsequently died in utero. The remaining fetuses suffered no morbidity and were alive and well 3 months to 2 years after delivery. The two fetuses in whom atrial tachycardia did not convert with flecainide were successfully treated with digoxin. These results compare favourably with previous forms of antiarrhythmic treatment. After recent reports of the side effects of flecainide treatment, however, it has been advised that this drug should be confined to high risk patients and those with life threatening arrhythmias. The use of flecainide for fetal arrhythmias should be limited to patients with severe fetal hydrops and supraventricular tachycardias. It should not be the first drug of choice in atrial flutter.

Flecainide is a potent class 1c antiarrhythmic drug that is available in the treatment of atrial, junctional, and ventricular arrhythmias. It acts on the fast sodium channel and slows conduction throughout the conduction system; its greatest effect is on the His bundle. It was effective and apparently safe in babies and children. It was also successful for tachycardia in a fetus. However, recent reports of an increase in the incidence of sudden death in adults with ventricular extrasystoles on maintenance flecainide treatment after myocardial infarction have led to recommendations that its use is restricted to patients with life threatening arrhythmias. The intraterine development of a fetal tachycardia and heart failure is certainly a life threatening condition; fetal mortality is reported to be 20-50%. The variety of drugs reported to be useful in the treatment of fetal tachycardias—for example, digoxin, verapamil, quinidine, procainamide, amiodarone, and propranolol—gives some indication of the difficulty of managing these cases successfully. We used flecainide in a group of 14 patients with fetal tachycardia. We present our results and recommendations for the use of this drug in this condition in the light of increasing concern about its safety.

Patients and methods

Fourteen patients presenting consecutively over a two year period with a fetal tachycardia and cardiac failure were treated with flecainide (an oral dose of 300 mg per day given to the mother). The table summarises the data on these patients. In all except patient 14, gross fetal hydrops was evident at presentation. The gestational age ranged from 23 to 36 weeks (mean 31). The rhythm disturbance was atrial flutter in two and supraventricular tachycardia in 12. One fetus had evidence of reduced left ventricular function on cross sectional, M mode, and Doppler evaluation. Congenital heart disease did not underlie the arrhythmia in any patient.

All patients were treated in hospital. Maternal serum concentrations of flecainide were monitored regularly and maternal electrocardiograms recorded weekly. Maternal serum concentrations of 400-800 μg/l of flecainide were associated with live births. Flecainide was not used in a group of 14 patients with fetal tachycardia. We present our results and recommendations for the use of this drug in this condition in the light of increasing concern about its safety.

Summary of the clinical details and outcome in 14 fetuses treated with flecainide

<table>
<thead>
<tr>
<th>Case No</th>
<th>Gestation at Delivery</th>
<th>Rhythm</th>
<th>Time to conversion</th>
<th>Duration of treatment</th>
<th>Drainage procedure</th>
<th>Hydrops at delivery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30</td>
<td>37+</td>
<td>AF &lt;4h</td>
<td>1 week</td>
<td>+</td>
<td>Mild</td>
<td>A and W</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>36</td>
<td>SVT &lt;5 days</td>
<td>3 weeks</td>
<td>+</td>
<td>Mild</td>
<td>A and W</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>51+</td>
<td>SVT &lt;5 days</td>
<td>3 days</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>52</td>
<td>SVT &lt;5 days</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>5</td>
<td>23</td>
<td>23</td>
<td>SVT &lt;24h</td>
<td>3 days</td>
<td>-</td>
<td>Mod</td>
<td>IU death</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>37</td>
<td>SVT &lt;24h</td>
<td>1 week</td>
<td>-</td>
<td>Mild</td>
<td>A and W</td>
</tr>
<tr>
<td>7</td>
<td>38</td>
<td>39</td>
<td>SVT &lt;48h</td>
<td>5 weeks, F stopped, no recurrence</td>
<td>+</td>
<td>None</td>
<td>A and W</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>35+</td>
<td>SVT &lt;24h</td>
<td>5 days</td>
<td>-</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>9</td>
<td>32</td>
<td>33</td>
<td>SVT &lt;24h</td>
<td>3 days, F stopped, reverted, F converted again</td>
<td>Mod</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>10</td>
<td>32</td>
<td>38</td>
<td>SVT &lt;24h</td>
<td>1 days, F stopped, reverted, F 1 week, stopped</td>
<td>Mod</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>11</td>
<td>32</td>
<td>38</td>
<td>SVT &lt;24h</td>
<td>3 days</td>
<td>-</td>
<td>None</td>
<td>A and W</td>
</tr>
<tr>
<td>12</td>
<td>33</td>
<td>38</td>
<td>SVT &lt;48h</td>
<td>4 days, F stopped, reverted, F till delivery</td>
<td>+</td>
<td>Mild</td>
<td>A and W</td>
</tr>
<tr>
<td>13</td>
<td>33</td>
<td>39</td>
<td>SVT &lt;48h</td>
<td>4 days, F stopped, reverted, F till delivery</td>
<td>+</td>
<td>None</td>
<td>A and W</td>
</tr>
<tr>
<td>14</td>
<td>34</td>
<td>38</td>
<td>AF</td>
<td>2 days, changed to D, converted</td>
<td>-</td>
<td>None</td>
<td>A and W</td>
</tr>
</tbody>
</table>

SVT, supraventricular tachycardia; AF, atrial flutter; A and W, alive and well; IU, intraterine; D, digoxin; F, flecainide.
were maintained; two patients required 400 mg a day to achieve this. Maternal serum and cord concentrations of flecainide were measured at cordocentesis and delivery.

Discussion
Outcome in this group of patients compares favourably with our earlier results in a study of fetal atrial tachycardias.11 In our previous series of 12 hydropic fetuses treated with digoxin and verapamil there were two deaths and a high rate of postnatal complications in the remaining 10. Control of the arrhythmia was achieved in seven of 12 compared with 12 of 14 in the present study but the main difference was in the speed of conversion—the mean time to conversion in the former group being 2–3 weeks compared with 48 hours in the flecainide group. Though the mean age at delivery was similar (35 weeks) in the digoxin and verapamil series and in the flecainide series, the main causes of morbidity in our earlier series were related to the complications of prematurity, especially ischaemic bowel disease. Quick control of the rhythm and time for some resolution of the hydrops will result in an infant in better condition at delivery and may even delay the onset of premature labour. It is possible that our current management procedures, such as peritoneal drainage, also contributed to the improved morbidity. Immediate resuscitation of the newborn is easier if tense ascites has been drained—even if just before delivery. Resolution of hydrops prenatally takes 1–2 weeks after rhythm control even with drainage procedures but the more complete it is before birth the less hazardous will be the postnatal course.

The ability to achieve therapeutic drug concentrations in the fetus quickly and the high rate of responsiveness make flecainide an attractive alternative to other drugs that are less well transferred by the placenta. The speed of achieving conversion allows the drug to be stopped after rhythm control as it was in four cases. In one, the hydrops had completely resolved and the arrhythmia did not recur; in the others there was a recurrence of tachycardia but this was quickly brought under control a second time. Flecainide probably should not be used for atrial flutter because it can increase the ventricular response and therefore increase the heart rate. In the two patients with atrial flutter treated with flecainide, treatment was changed to digoxin after only 2 days in the first patient and in the other patient digoxin had failed to convert or slow the rhythm after 3 weeks with maternal serum concentrations of digoxin at 2 µg/l (patient 1). Some digoxin still present in the fetus may have protected it from adverse effects and potentiated the conversion with flecainide, which occurred within 48 hours.

Thus it is imperative that the type of rhythm disturbance be established before birth and very likely not be confused with supraventricular or multifocal tachycardia. The neonate with supraventricular tachycardia may be symptomatic after birth and may have been treated with digoxin blindly but is assessed and correctly identified by M-mode echocardiography before treatment is started.12 A further attraction of flecainide is that it can be used for ventricular tachycardias. These are much less common prenatally but do occur.13
Though in most cases it should be possible to distinguish between atrial and ventricular tachycardias on the M mode echocardiogram, a ventricular tachycardia with retrograde conduction of every beat would be impossible to identify. Other drugs used to treat atrial tachycardias such as digoxin or verapamil are contraindicated for a ventricular tachycardia. Recent reports of sudden deaths in adults treated with flecainide after myocardial infarction are of great concern. We were treating young healthy women but any risk to maternal health must be avoided. The fetus with a tachycardia and severe hydrops is at high risk and therefore potentially dangerous treatment can be considered on its merits but the results of this treatment, which remains experimental at this stage, must be closely evaluated. The evidence from adult studies suggests that poor ventricular function, high drug concentrations, and the presence of cardiac failure are risk factors for the arrhythmogenic effect of flecainide.\textsuperscript{14} Our one patient with poor left ventricular function did well and we maintained careful control of drug concentrations. All our fetuses had severe cardiac failure and it is only because they were so compromised that treatment with a high risk drug was considered. Digoxin is the only antiarrhythmic drug with a positive inotropic effect that is safe in the presence of heart failure and this is not adequately or sufficiently quickly transferred by the placenta in most patients. Amiodarone has no negative inotropic effect but it is known to depress thyroid function; this could affect normal development if it occurred prenatally. Studies of an animal model suggested that immature cardiac tissues may be less sensitive to flecainide\textsuperscript{15} but this needs to be substantiated in clinical practice.

Initially we attributed the unexplained death in our series to the cordocentesis procedure, but this patient may have died of an arrhythmia induced by flecainide. We performed fetal blood sampling in the past as part of our protocol for the management of hydropic tachycardic fetuses in order to estimate the blood gases, karyotype the fetus, and monitor drug concentrations. We judged that the information gained from this procedure justified the risk (1–2%).\textsuperscript{16} The death of patient 5 led us to question this policy and also to re-examine the criteria for the use of flecainide. Our current policy does not include routine fetal blood sampling.

Flecainide proved to be a useful drug in the management of fetal tachycardias. However, its use should be limited to patients with supraventricular tachycardia and those with at least moderate or severe hydrops. Patients must be carefully selected and monitored. In addition, mothers must be fully informed of the risks of treatment. Accurate diagnosis and optimum management depend on treatment by a paediatric cardiologist experienced in the management of arrhythmias and an obstetrician or paediatrician skilled in management procedures and in obtaining fetal blood samples for blood gas monitoring—for example, where fetal hypoxia is suspected. Use of flecainide is specifically restricted and its role needs to be further assessed in centres where a large database of results can be collected for analysis.

We thank Dr N Rutter for allowing us to include the data from one of his patients in this report.

14 Morganroth J. Risk factors for the development of proarrhythmic events. \textit{Am J Cardiol} 1987;59:32E–7E.
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