Flecainide in the treatment of fetal tachycardias

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Abstract

Fourteen mothers were treated with flecainide for fetal atrial tachycardias associated with intrauterine 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 intrauterine 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

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

<table>
<thead>
<tr>
<th>Case No</th>
<th>Gestation at presentation</th>
<th>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>31</td>
<td>23</td>
<td>SVT</td>
<td>&lt;5 days</td>
<td>3 weeks</td>
<td>+</td>
<td>Mild</td>
<td>A and W</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mild</td>
<td>A and W</td>
</tr>
<tr>
<td>3</td>
<td>33</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>4</td>
<td>34</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>7</td>
<td>37</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>8</td>
<td>38</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>9</td>
<td>39</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>10</td>
<td>40</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>11</td>
<td>41</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>12</td>
<td>42</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>13</td>
<td>43</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
<tr>
<td>14</td>
<td>44</td>
<td>23</td>
<td>SVT</td>
<td>&lt;24 h</td>
<td>2 weeks</td>
<td>+</td>
<td>Mod</td>
<td>A and W</td>
</tr>
</tbody>
</table>

SVT, supraventricular tachycardia; AF, atrial flutter; A and W, alive and well; IU, intrauterine; 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.

Results
The table shows the clinical details and results of treatment in 14 patients. In one patient (case 14) treatment with flecainide was stopped after 2 days because the fetus was found to be in atrial flutter and there was only mild fetal heart failure. In another patient (case 13) treatment was changed to digoxin after 2 weeks because only intermittent rate control had been achieved with flecainide. The remaining 12 fetuses converted to sinus rhythm in less than 5 days, most within 48 hours. In four of the 12 flecainide was stopped after conversion. In patient 7 flecainide was stopped at 33 weeks' gestation, 5 weeks after the start of treatment, and the arrhythmia did not recur. In patient 9 flecainide was stopped 2 days after conversion. Sinus rhythm was maintained for 3 days before the supraventricular tachycardia recurred. A second course of flecainide restored sinus rhythm. Patient 10 required two courses of flecainide but the drug was stopped at 34 weeks' gestation and the rhythm disturbance did not recur. In patient 12, an initial short course of flecainide controlled the tachycardia but the arrhythmia recurred. This mother was then maintained on flecainide treatment until delivery close to term.

Of the 12 patients who were successfully converted, there was one spontaneous intrauterine death. This occurred 3 days after treatment with flecainide was started. The fetus had converted to sinus rhythm and died within 24 hours of cordocentesis. All the remaining patients showed some resolution of hydrops at delivery; the most complete was in those fetuses remaining longer in utero after conversion of cardiac rhythm. Two patients had peritoneal drainage 2 weeks after conversion; one had a peritoneal shunt positioned before conversion; in neither did fluid reaccumulate. In two patients, drainage was performed less than a week after conversion but the ascites reaccumulated though it did improve or resolve with time. In one fetus the abdomen was drained just before delivery. All the patients (nine of the surviving 11) who delivered at less than 38 weeks' gestation were spontaneous deliveries except for patient 4 who required elective delivery at 32+ weeks because of severe pre-eclampsia.

Comparison of cord and maternal serum concentrations of flecainide indicated placental transfer of approximately 80% of the drug and showed that all fetuses had concentrations within the therapeutic range (400–800 μg/l).

Six of the 11 infants who were successfully treated with flecainide before birth and were born alive had recurrence of tachycardia postnatally. Five were treated with digoxin alone during the first year of life. One neonate required propranolol in addition to digoxin. In this last patient compromised left ventricular function recovered over the first 4 months of life. Five neonates required no treatment. The infant who suffered a cot death at four months old was not taking any treatment.

Discussion
Outcome in this group of patients compares favourably with our earlier results in a study of fetal atrial tachycardias. 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 diagnosed before birth and if ventricular flutter is present the drug should be changed to digoxin. A further attraction of flecainide is that it can be used for ventricular tachycardias. These are much less common prenatally but do occur.
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 con-
duction of every beat would be impossible to
distinguish. 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 infar-
tion 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 fleca-
lide.\textsuperscript{14} One our 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 fleca-
lide\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 infor-
mation 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
arrhythmias 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 obstet-
rician practised in management procedures 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.

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*Br Heart J* 1991 65: 46-48
doi: 10.1136/hrt.65.1.46

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