genic chemical groups free to mediate various allergic responses.

An alternative explanation may be that the inheritance of an atopic predisposition is genetically linked to the inheritance of poor metaboliser genes. Further studies on atopic patients who have no symptoms of food intolerance are in progress. It is also conceivable that sulphoxidation ability, though largely determined genetically, may be altered by certain environmental influences such as viral infections. Further studies to investigate this are being undertaken.

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(Accepted 2 March 1988)

Obstetric importance, diagnosis, and management of fetal tachycardias

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Abstract

During 1980-7, 23 pregnancies of 22-38 weeks' duration were investigated for fetal tachycardia. Twelve were cases of supraventricular tachycardia, eight of atrial flutter, and three cases in which the rhythm varied between supraventricular tachycardia and atrial flutter. In 11 cases the fetus had developed non-immune fetal hydrops before referral; 12 cases were non-hydrotic at referral but one of this group of fetuses became hydrotic during treatment. No relation was found between the rate or type of arrhythmia and the presence or absence of intrauterine heart failure.

One non-hydrotic infant was delivered electively prematurely. Maternal antiarrhythmic treatment was instituted in the remaining 22 cases. Conversion of the arrhythmia was achieved with digoxin alone in five cases and with a combination of digoxin and verapamil in nine. Control of the arrhythmia was achieved in seven of the 10 non-hydrotic fetuses, and all were delivered at term with no deaths. Of the 12 hydrotic fetuses, control was achieved in seven. Only three of the hydrotic fetuses were delivered close to term. There were two deaths, both in the hydrotic group. Of the whole group, five neonates suffered severe complications of prematurity.

In this series the main benefit of treatment appeared to be in prolonging gestation of those hydrotic fetuses in which conversion was achieved.

Introduction

Fetal tachycardia of over 200 beats a minute requires further investigation. Uncontrolled atrial tachycardias are thought to lead to cardiac failure in utero. These tachycardias occurring in association with non-immune fetal hydrops have been well described.¹⁻³ Hydramnios and premature labour are frequent accompanying features.

Echocardiography successfully distinguishes atrial tachycardias from physiological sinus tachycardias in prenatal life.^{3,5} The best form of antenatal management and most practicable drug or drugs for the treatment of atrial tachycardia, however, are still a matter of

controversy.^{6,8} Because this condition is uncommon most centres have only a limited number of cases on which to base conclusions on management. We present our accumulated experience with this difficult problem.

Patients and methods

Over seven years in a specialised centre for fetal echocardiography 23 fetuses were found to have atrial tachycardias. The fetal heart was examined for structural anomaly.⁹ The arrhythmia was identified by M mode echocardiographic analysis of the relation between atrial and ventricular contraction.^{3,4} The presence and extent of pleural, pericardial, and peritoneal effusions were noted as evidence of cardiac failure. Because the evaluation of skin oedema was considered to be subjective the diagnosis of hydrops was not made on that basis. The presence of associated hydramnios was recorded. Seven fetuses were examined with an Advanced Technology Laboratories mark 3 sector scanner. In the remaining 16 cases, which presented after early 1985, the fetuses were examined with a Hewlett-Packard 77020A phased array scanner.

Antiarrhythmic treatment was given to the mother in 22 cases. Treatment was aimed at restoring sinus rhythm, preventing or reversing cardiac failure, and averting preterm delivery. Digoxin alone or a combination of digoxin and verapamil was used in each case. Mothers were treated with 0.75 mg digoxin daily and the dose adjusted to maintain the maternal serum concentration at 2.6 nmol/l. Verapamil was added in increasing doses to a maximum of 480 mg daily until control was achieved or delivery supervened. Maternal serum concentrations of digoxin and verapamil were measured at regular intervals. Standard and 24 hour electrocardiograms were recorded in mothers taking verapamil. When possible cord blood was sampled at delivery in order to assess the transplacental passage of these drugs.

Results

Table I summarises the clinical details and outcome of treatment of the fetuses that were not in heart failure

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TABLE I—Clinical details of non-hydropic cases

Case No*	Reason for referral	Gestation at referral (weeks)†	Rhythm	Treatment	Days to control‡	Gestation at delivery (weeks)	Outcome
3	Tachycardia	32	Atrial flutter	<i>Control achieved</i> Digoxin	10	38	Induced onset of labour; alive and well
9	Tachycardia	33	Supraventricular tachycardia/ atrial flutter	Digoxin + verapamil	11	40	Induced onset of labour; alive and well
10	Intermittent tachycardia	34	Supraventricular tachycardia/ atrial flutter	Digoxin + verapamil	28	38	Induced onset of labour; alive and well
13	Tachycardia	36	Atrial flutter	Digoxin	8	38	Induced onset of labour; alive and well
14	Tachycardia	35	Supraventricular tachycardia	Digoxin	10	39	Spontaneous onset of labour; alive and well
17	Tachycardia	32	Supraventricular tachycardia	Digoxin	16	40	Spontaneous onset of labour; alive and well
20	Tachycardia	37	Supraventricular tachycardia	Digoxin	7	40	Spontaneous onset of labour; alive and well
4	Intermittent tachycardia	30	Supraventricular tachycardia	<i>Partial control</i> Digoxin + verapamil	—	38	Spontaneous onset of labour; difficult to control postnatally
2	Tachycardia	38	Supraventricular tachycardia	<i>No control achieved</i> Digoxin	—	38	Spontaneous onset of labour; prolonged antiarrhythmic treatment
8	Tachycardia	35	Supraventricular tachycardia	Digoxin	—	38	Defaulted antenatal care; required direct current conversion and antiarrhythmics
1	Tachycardia	32	Atrial flutter	<i>Control not attempted</i> —	—	32	Induced onset of labour; respiratory distress syndrome; necrotising enterocolitis, left hemicolectomy

*Cases numbered in chronological order in which they presented.

†Overall mean 34.0 weeks.

‡Overall mean ("control achieved" only) 12.9 days.

TABLE II—Clinical details of hydropic cases

Case No*	Reason for referral	Gestation at referral (weeks)†	Rhythm	Treatment	Days to control‡	Gestation at delivery (weeks)	Outcome
5	Hydrops	34	Atrial flutter	<i>Control achieved</i> Digoxin + verapamil	7	37	Elective caesarean section; alive and well
7	Tachycardia	33	Supraventricular tachycardia	Digoxin + verapamil	6	35	Elective caesarean section; alive and well
15	Tachycardia	22	Supraventricular tachycardia	Digoxin + verapamil	42	32	Elective caesarean section; necrotising enterocolitis
16	Hydrops	30	Atrial flutter	Digoxin + verapamil	31	34	Pre-eclamptic toxæmia, spontaneous onset of labour, fetal distress, emergency caesarean section; alive and well
18	Tachycardia	31	Atrial flutter	Digoxin + verapamil	7	33	Cardiotocographic and Doppler findings abnormal; emergency caesarean section; neonatal death 26 days
19	Hydrops	27	Supraventricular tachycardia	Digoxin + verapamil	21	33	Pre-eclamptic toxæmia, cardiotocographic and Doppler findings abnormal; emergency caesarean section; alive and well
22	Hydrops	32	Supraventricular tachycardia	Digoxin + verapamil	18	37	Elective caesarean section; alive and well
6	Hydrops	33	Atrial flutter	<i>Partial control</i> Digoxin + verapamil	—	34	Spontaneous onset of labour; alive and well
12	Hydrops	28	Atrial flutter/supraventricular tachycardia	Digoxin + verapamil	—	31	Spontaneous onset of labour; necrotising enterocolitis, renal failure
11	Hydrops	28	Atrial flutter	<i>No control achieved</i> Digoxin + verapamil	—	31	Intravenous verapamil; intrauterine death
21	Hydrops	28	Supraventricular tachycardia	Digoxin + verapamil	—	33	Spontaneous onset of labour; respiratory distress syndrome, renal failure
23	Hydrops	37	Supraventricular tachycardia	Digoxin + verapamil	—	38	Spontaneous onset of labour; direct current conversion and antiarrhythmics postnatally

*Cases numbered in chronological order in which they presented.

†Overall mean 30.3 weeks.

‡Overall mean ("control achieved" only) 18.8 days.

and table II the clinical details and outcome of treatment of those that were in heart failure. In all cases the fetal heart rate was 240 beats/min or over. No fetus was found to have structural heart disease. Convex hydramnios was a feature occurring in one of the 11 non-hydropic pregnancies and 10 of the 12 with fetal hydrops. There was no difference between the groups in the fetal heart rate or types of disturbed rhythm present.

In the non-hydropic group case 1 (the first in the series) was delivered electively without treatment. This neonate suffered severe complications of prematurity, and all subsequent cases were therefore treated prenatally. All treated patients in this group were delivered after 37 weeks of gestation. None of those in whom rhythm control was achieved required neonatal treatment other than a maintenance dose of digoxin in the first year of life. In the two cases in which successful conversion was not obtained one mother went into labour spontaneously within 24 hours of beginning treatment and the other defaulted from further antenatal care shortly after treatment was

begun. Postnatal control of the tachyarrhythmias was more difficult when control had not been achieved in utero.

One of the hydropic fetuses (case 7) was in sinus rhythm when first seen by us but a reliable history of tachycardia had been obtained at the referring hospital. After admission the tachycardia was recorded echocardiographically. This fetus continued to have intermittent fetal tachycardia. Hydrops developed in one fetus, and in two others progression of hydrops from mild to moderate occurred in the time it took to gain control of the arrhythmia. In two cases a decrease in the severity of hydrops was seen after successful treatment.

Of the seven hydropic fetuses in which rhythm control was obtained, five had uncomplicated neonatal courses. Of the others, one (case 15) was delivered electively at 32 weeks in another centre against our advice. In case 18, an emergency caesarean section was performed five days after cardiotocography and blood flow studies had shown reduced fetal movements and evidence of fetal compromise. In three of the five cases

in which complete rhythm control was not obtained the mother went into spontaneous labour within the first week of treatment. In case 11 maternal treatment had not been successful by 12 days and a 20 gauge needle was therefore inserted into the umbilical vein at its placental insertion under ultrasound guidance and verapamil given directly to the fetus. This resulted in fetal asystole which could not be reversed.

Neither conversion to sinus rhythm nor eventual outcome appeared to be influenced by the initial rhythm disturbance. Table III summarises the relation between rhythm control and the types of arrhythmia in the two groups.

Maternal symptoms of digoxin toxicity necessitating adjustment of the dose were common when serum concentrations rose above 3.3 nmol/l. There were no other maternal complications of antiarrhythmic treatment.

TABLE III—Results of treatment compared with types of rhythm in presence or absence of cardiac failure

Results of treatment	Type of rhythm disturbance		
	Atrial flutter	Atrial flutter/ supraventricular tachycardia	Supraventricular tachycardia
<i>Non-hydrops cases</i>			
Control achieved	2	2	3
Partial control	—	—	1
No control	—	—	2
No treatment	1	—	—
Total	3	2	6
<i>Hydrops cases</i>			
Control achieved	3	—	4
Partial control	1	1	—
No control	1	—	2
Total	5	1	6

Discussion

In over half of our patients the fetal tachycardia had been diagnosed before referral. Nine cases, however, were referred for investigation of non-immune fetal hydrops, and in these the causative tachycardia had not been noted by the referring hospital. In addition, hydrops had been known to be present in some of these cases for up to four weeks before referral. We emphasise the need to consider fetal tachycardia as a cause of non-immune hydrops and to refer these cases promptly. The slightly earlier gestation at presentation of the hydropsic fetuses was thought to be due to the commonly associated hydramnios having aroused clinical suspicion, leading to ultrasound evaluation and the detection of fetal hydrops.

Before maternal treatment is started the type of arrhythmia must be identified. In particular, ventricular tachycardia must be excluded, as this has been recorded prenatally¹⁰ and contraindicates treatment with digoxin and verapamil. The nature of the tachycardia is elucidated by timing of mechanical atrial and ventricular systole on the M mode echocardiogram. In this way atrial flutter and most ventricular tachycardias can be differentiated from other supraventricular tachycardias.³

Our series shows some of the difficulties in assessing attempts at prenatal treatment. The absence of a control group in which tachycardias were not treated hinders analysis and the conclusions drawn. Accurate information on the natural course of all forms of arrhythmia in utero is lacking. Nevertheless, before prenatal treatment was attempted atrial tachycardias were associated with hydrops, intrauterine death, and prematurity.¹² Our rationale for treating all cases of atrial tachycardia diagnosed prenatally is to prevent or reverse cardiac failure. The inevitable progression of

all cases from non-hydrops to hydrops is not proved. Nevertheless, progression did occur in three cases in this series. The possibility that the presence or absence of cardiac failure prenatally depends on the type of arrhythmia and the heart rate is not supported by our data, as we found no difference between the hydropsic and non-hydropsic groups in either of these features. A factor which may be important is the duration of the arrhythmia and its intermittent nature. Three fetuses were in sinus rhythm at the initial examination after referral for fetal hydrops. All were found to have a tachycardia at a later examination. Two are not included in this series, as they were sent back to the referring hospital before the diagnosis of intermittent tachycardia was made and were therefore not treated by us. The possibility of an intermittent tachycardia as a cause of fetal hydrops must be considered and the mother admitted for fetal heart rate monitoring. Doppler cardiocography is unreliable and misleading for this and we have used phonocardiography¹³ for prolonged (12-24 hour) recording.

Based on experience we treat all hydropsic fetuses with the mothers as inpatients. Non-hydropsic fetuses may be treated in the outpatient department and delivered safely in local centres once conversion has been achieved. We chose digoxin as the most practicable treatment because of its known safety in pregnancy. Verapamil was added in refractory cases for its additive effect with digoxin. There appeared to be no maternal or fetal morbidity attributable to treatment. We achieved conversion to sinus rhythm in 14 of 22 patients overall, and in a further three partial control was achieved. These results are comparable with other series.^{8,11} In three of five cases in which control was not achieved delivery took place less than a week after the start of antiarrhythmic drugs, before adequate treatment could be given. A further case in this group was not treated fully according to our regimen because of poor maternal compliance.

Sequential maternal serum drug concentrations during treatment coupled with cord blood sampling has allowed us to begin to understand placental transfer of these drugs. Many workers have reported failure of digoxin and verapamil and have tried various other drugs, such as procainamide, quinidine, and amiodarone.⁶⁻⁸ We, however, find that high doses given for two to three weeks are necessary to achieve rhythm control, particularly in hydropsic fetuses. Our results of fetal blood sampling from the umbilical cord under ultrasound control and of cord blood sampling at delivery compared with simultaneous maternal sampling indicate that placental transfer of digoxin is around 40% and of verapamil of the order of 10-20%.

With the exception of the one case which progressed from the non-hydropsic to the hydropsic group, analysis of the outcome in the non-hydropsic group does not show a clear advantage to the fetus of successful treatment. All 11 cases were delivered at term irrespective of rhythm control in utero. In all three cases in which complete control had not been achieved prenatally, however, difficulty was experienced in gaining control postnatally.

All the patients in the hydropsic group required both digoxin and verapamil and, on average, a longer duration of treatment to achieve conversion. In this group where control was achieved reversal of the ascites took many days or even weeks after return to sinus rhythm. Mortality and morbidity occurred whether control, partial control, or no control was achieved. It appears that prolongation of gestation occurred after successful treatment. The absence of a control group of untreated cases does not allow us to conclude that treatment caused this delay in delivery. Nevertheless, our results suggest that premature delivery, whether spontaneous or induced, should be

avoided. Our one experience with direct fetal treatment was not successful, and possibly a longer duration of transplacental treatment would have been more appropriate.

In our series the Wolff-Parkinson-White syndrome as the underlying cause of the tachycardia was found in three of the 22 infants who had a postnatal electrocardiogram.

In summary pathological atrial tachycardias are a potential cause of non-immune hydrops. As these rhythm disturbances may be intermittent, this diagnosis should be considered in all cases of fetal hydrops even if the tachycardia is not present at the initial examination. It is not possible to predict which of the non-hydrotic fetuses will progress to become hydropic. We therefore believe that an attempt at transplacental treatment is valid in all cases. Our results show that maternal transplacental treatment is both safe and effective and may avert preterm delivery and its attendant morbidity.

DJM was on secondment from University College Hospital. LDA and DCC were supported by the British Heart Foundation and MJT by the British Heart Foundation and the Joseph Levy Foundation.

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(Accepted 2 March 1988)

The serotonin type 3 receptor antagonist BRL 43694 and nausea and vomiting induced by cisplatin

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In most patients receiving cisplatin nausea and vomiting are observed one to six hours after the drug is given and last for up to 10 days¹; currently available antiemetics show limited efficacy. At conventional doses metoclopramide is inactive, but at high doses it is effective against the vomiting induced by cisplatin, although extrapyramidal reactions are observed.² At these doses metoclopramide competitively blocks serotonin type 3 receptors.³ Selective serotonin type 3 receptor antagonists exhibit potent antiemetic activity in ferrets and recently GR 38032F was shown to be effective in patients receiving mildly emetic drugs,

none of whom received cisplatin.⁴ We report the efficacy and tolerance of the new serotonin type 3 receptor antagonist BRL 43694⁵ in patients receiving cisplatin.

Patients, methods, and results

Cisplatin was given intravenously over 30 minutes, followed by BRL 43694 given by intravenous infusion in 250 ml 0.9% saline over 30 minutes. The first five patients received concurrent dexamethasone 4 mg four times a day, but as the infusions of BRL 43694 were noticeably effective BRL 43694 was subsequently infused on its own. After finishing treatment patients were hydrated for 24 hours. The number of episodes of vomiting and dry retching were recorded before the infusion and at one, four, six, eight, and 24 hours after it. In addition, severity of nausea was subjectively assessed with both global four point severity scores (before the infusion and at four and 24 hours after it) and 10 cm visual analogue scores (before the infusion and at one, four, and six hours after it), which were analysed with a paired Wilcoxon signed rank test.

Eighteen male and four female patients were studied (mean age 47.4 (SD 13) years), 13 of whom had

Details of treatment of 22 patients receiving BRL 43694 as antiemetic for control of nausea and vomiting induced by cisplatin

Case No	BRL 43694 (µg/kg)	Cisplatin (mg/m ²)	Other cytotoxics given	Nausea		No of vomiting episodes	Other antiemetics given
				Grade	Time of onset (h)		
1	10	50	Bleomycin, methotrexate	3	12	7	Yes
2	10	50	None	4	4	6	Yes
3*	20	50	Ifosfamide	3	12	None	Yes
4	20	50	Doxorubicin		None	None	No
5*	20	60	Hydroxyurea, bleomycin		None	None	No
6*	30	20	Etoposide		None	None	No
7	30	50	Mitomycin	2	12	3	No
8*	30	75	None		None	5	No
9*	40	40	Doxorubicin, hydroxyurea, bleomycin		None	None	No
10*	40	40	Ifosfamide, vincristine		None	None	No
11	40	50	None	2	6	1	Yes
12*	40	50	None	2	6	2	Yes
13*	40	60	Doxorubicin, hydroxyurea, bleomycin	3	12	5	Yes
14*	40	60	Doxorubicin, hydroxyurea, bleomycin		None	None	No
15	40	75	None	2	18	3	Yes
16*	40	75	None	4	4	2	Yes
17	40	75	None		None	None	No
18*	40	75	None		None	None	No
19*	40	75	Mitozantrone		None	None	No
20	40	75	None		None	None	No
21*	40	75	None		None	None	No
22	40	100	Fluorouracil	2	16	2	Yes

*Patient had previous chemotherapy.