Sotalol in the Treatment of Fetal Dysrhythmias

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Background—Fetal tachycardia may cause hydrops fetalis and lead to fetal death. No unanimity of opinion exists regarding the optimum treatment. This study evaluates our experience with transplacental sotalol therapy to treat fetal tachycardias in terms of safety and efficacy.

Methods and Results—The charts of 21 patients who were treated with sotalol for fetal tachycardia were reviewed. Ten fetuses had atrial flutter (AF), 10 had supraventricular tachycardia (SVT), and 1 had VT. Hydrops fetalis was present in 9 fetuses. Drug treatment was successful in establishing sinus rhythm in 8 of 10 fetuses with AF and in 6 of 10 fetuses with SVT. The mortality rate in this study was 19% (4 of 21 fetuses; 3 had SVT and 1 had AF); 3 deaths occurred just after the initiation of sotalol therapy, and 1 occurred after a dosage increase. At birth, tachycardia was present in 6 infants. Two patients who converted to sinus rhythm in utero suffered from neurologic pathology postnatally.

Conclusions—Fetal tachycardia is a serious condition in which treatment should be initiated, especially in the presence of hydrops fetalis. The high success rate in fetuses with AF suggests that sotalol should be considered a drug of first choice to treat fetal AF. The low conversion rate and the fact that 3 of the 4 deaths in this study occurred in fetuses with SVT indicate that the risks of sotalol therapy outweigh the benefits in this group and that sotalol should, therefore, be limited in the treatment of fetal SVT. (Circulation. 2000;101:2721-2726.)

Key Words: tachycardia ▪ arrhythmia ▪ maternal-fetal exchange ▪ sotalol ▪ hydrops fetalis

Fetal tachyarrhythmia may cause nonimmune fetal hydrops and lead to fetal morbidity and mortality.1–6 Several protocols for pharmacological therapy to restore sinus rhythm have been proposed.7–18 Digoxin and flecainide are the most commonly used agents in such therapies. Digoxin as a single therapy, however, is not successful in restoring sinus rhythm in all fetuses with atrial flutter (AF) or in hydropic fetuses.8,11–13,19–21 The use of flecainide was called into question after a report regarding the potential proarrhythmic dangers of this drug.9 These data have lead to a continued search for new and possibly better drugs.

Sotalol is a potent β-blocking agent with additional class III antiarrhythmic properties and a mild or absent negative inotropic effect22,23 that has proven to be safe and efficacious in the treatment of tachycardia in adults24–26 and infants.27–30 Sotalol passes the placental barrier rapidly and almost completely.31 On the basis of these findings, we hypothesized that sotalol would be a safe and effective antiarrhythmic agent for the treatment of various forms of tachycardia in fetuses.

Little is known about the effect of sotalol on fetuses. We present a multicenter, retrospective study reviewing our experience with the use of sotalol in the treatment of fetal tachycardia.

Methods

Patients

This retrospective study includes 21 fetal patients who were diagnosed with tachycardia between 1993 and 1999 at the University Hospitals of Utrecht and Nijmegen, the Netherlands, and at Yale-New Haven Children’s Hospital, New Haven, Conn. The patients included in the study had either supraventricular tachycardia (SVT; defined by 1:1 atrioventricular [AV] conduction with a rate of >180 bpm) or AF with a regular atrial rate of >250 bpm with fixed or variable AV block. Ventricular tachycardia (VT) was encountered in 1 patient who will be described separately. Tachycardia was detected during routine prenatal visits, and the patients were subsequently referred for further evaluation. Associated cardiac structural abnormalities and possible definable causes for tachycardia, such as viral infections, were excluded. Hydrops fetalis, a sign of fetal cardiac failure, was diagnosed when ≥2 fluid collections existed in the fetal body, such as pericardial effusion, pleural effusion, ascites, and skin edema, regardless of the amount of effusion present. Fetuses were monitored for 30 minutes and treatment was initiated when, during this whole period, tachycardia was present or a combination of intermittent tachycardia and hydrops fetalis existed.

In Utero Management

Oral maternal drug therapy was chosen because of previous positive experience with this technique.14 Patients received sotalol as their initial mode of therapy to achieve sinus rhythm or rate control because of partial AV block. Before the initiation of sotalol therapy,
preexisting arrhythmias in the mother were excluded. Mothers were interviewed to reveal possible histories of arrhythmic events, and ECGs were performed to evaluate QT interval and to minimize the potential for maternal proarrhythmic events.

Dosage
The starting dosage used was 80 to 160 mg of sotalol, given orally 2 times a day. The dosage was occasionally increased to a maximum of 160 mg 3 times per day if tachycardia persisted.32 Digoxin was added to the treatment in patients in whom adequate control could not be achieved with sotalol as a single therapy.

Variables included in the study were the following: gestational age at recognition of the tachycardia, heart rate, mechanism of the tachycardia as noted on prenatal M-mode echocardiography, the presence of hydrops, possible structural malformations, in utero therapy and results, maternal adverse effects, gestational age at birth, mode of delivery, Apgar score, mechanism of the tachycardia as noted on postnatal electrocardiography, postnatal therapy, and outcome of these newborns.

The statistical evaluation of the differences in heart rates and time to successful conversion was performed by Student’s test. P<0.05 was considered significant.

Results
The 21 fetuses were divided into 3 groups according to their electrophysiologic mechanism, as noted on prenatal M-mode echocardiography (Figure 1). SVT was present in 10 fetuses; they had heart rates of 200 to 300 bpm (mean, 237 bpm; mean peak fetal heart rate, 260 bpm). AF existed in 10 fetuses; they had atrial rates of 283 to 550 bpm (mean, 383 bpm; mean peak fetal heart rate, 403 bpm) and a variable degree of AV block, which resulted in a slower ventricular heart rate (mean, 193 bpm). VT was seen in 1 fetus. A total of 9 fetuses were hydropic at the time of presentation: 5 had SVT, 3 had AF, and 1 had VT. The mean gestational age at the time of presentation was 31 weeks (SEM, 0.96 weeks).

In Utero Management
Figure 2 shows the mode of therapy and the results. Regardless of the mechanism of tachycardia, all but 1 fetus were initially treated with sotalol.

Nonhydropic Fetuses
Twelve fetuses showed no signs of hydrops at the time of presentation: 5 had SVT and 7 had AF. All 12 fetuses had a gestational age of 21 to 37 weeks and were started on sotalol as a single therapy; 7 converted to normal sinus rhythm, and no further tachycardia was encountered.

Relapses
One patient (aged 21 weeks) who had AF at 300 bpm and 3:1 AV block converted to sinus rhythm on a sotalol dose of 160 mg 2 times per day, but the patient relapsed into flutter after the initial sotalol dosage was diminished to 80 mg of sotalol 3 times per day. This prompted an increase in the sotalol dosage to 80 mg 4 times per day and the addition of digoxin to the drug regimen. Stable sinus rhythm was then achieved, and no further relapses occurred. A second patient (aged 35 weeks) who had SVT at 300 bpm initially reverted to sinus rhythm for 2 weeks, after which a relapse occurred. The original dosage of sotalol had been decreased from 80 mg 3 times a day to 80 mg 2 times a day; it was subsequently increased to 160 mg twice a day. The fetus died in utero 1 day later. Autopsy did not establish a cause of death.

One patient with SVT at 240 bpm did not convert to sinus rhythm, although the heart rate slowed to 210 bpm. Despite a dosage increase from 80 mg 3 times a day to 80 mg 4 times a day, SVT persisted at 210 bpm. After 1 week of unsuccessful treatment, a cesarean section was performed at 37 weeks of gestation. Shortly after birth, the patient was diagnosed with a permanent junctional reciprocating tachycardia. Heart rate persisted at 195 bpm, and intravenous digoxin therapy was initiated. This was followed by conversion to normal sinus rhythm.

The remaining 2 nonhydropic fetuses, both with AF, did not convert to sinus rhythm, and digoxin was added to their treatment. This combination succeeded in restoring sinus rhythm in 1 fetus. In the other patient, sinus rhythm was never achieved, but an atrial rate of 220 bpm and a ventricular rate of 110 bpm was well tolerated. At birth, the ECG showed AF; electrical cardioversion established a normal sinus rhythm of 130 bpm.

Figure 2. Outcome of all fetuses as differentiated by the presence of hydrops and form of therapy. IUD indicates intrauterine death.
In summary, 75% of nonhydropic fetuses were successfully converted to a normal sinus rhythm in a mean period of 7 days (range, 1 to 28 days). In 1 patient, only an adequate block was achieved. Mean gestational age at birth was 39 weeks.

One fetus with SVT at 300 bpm died suddenly after the dosage of sotalol was increased to 160 mg 2 times a day.

Hydropic Fetuses

Eight fetuses were hydropic at the time of presentation (gestational age ranged from 25 to 33 weeks): 5 had SVT and 3 had AF. Sotalol as a single therapy successfully converted cardiac rhythm to sinus rhythm and resolved the hydrops in 2 fetuses. One severely hydropic fetus with SVT at 240 bpm at 29 weeks of gestation was started on 160 mg of sotalol 3 times a day, but the fetus died in utero after 2 days of treatment. Autopsy showed signs of chronic anoxia, and an abnormal accessory myocardial AV connection was seen, suggesting a reentry-tachycardia mechanism.

Another fetus, who had SVT at 260 bpm at 25 weeks of gestation and signs of ascites, was initially treated with multiple drug combinations, including digoxin, flecainide, and propranolol, as well as direct fetal intra-umbilical therapy with adenosine, which was transiently successful for 30 minutes. Tachycardia persisted, and hydrops fetalis worsened; therefore, at 29 weeks of gestation, all previous medication was withdrawn, and sotalol was started at a dosage of 120 mg 2 times a day. The heart rate slowed within 2 days to 210 bpm, with intermittent episodes of sinus rhythm. As hydrops fetalis persisted, the sotalol dosage was gradually increased to 160 mg twice a day. The fetus converted into sinus rhythm, with short runs of tachycardia to 220 bpm. Six days after the start of sotalol therapy and 2 days after the dosage increase, an ultrasound showed no fetal movements and a fetal heart rate of 90 bpm. On prostaglandin, the mother went into labor and gave birth to a stillborn infant. An autopsy was not performed.

In 3 of the remaining 4 fetuses, rhythm control was achieved after the addition of digoxin, with the subsequent resolution of hydrops fetalis. The fourth fetus had an AF rate of 440 bpm with 2:1 AV block. Sotalol was initiated at 80 mg 3 times a day. Because rhythm control was not achieved, digoxin was added to the treatment and the sotalol dosage was increased to 80 mg 4 times per day. Shortly after this change in treatment, the fetus died in utero at 39 weeks of gestation. Autopsy showed severe fetal hydrops, stenosis of the venous duct, and a hypoplastic placenta.

In the hydropic group, 62.5% of fetuses were successfully converted to normal sinus rhythm in a mean period of 7 days, and the hydrops resolved in all of these cases in a period ranging from 2 to 21 days (mean, 14 days). The time to successful conversion to sinus rhythm was equal to that in the nonhydropic group (P = 0.921). Mean gestational age at birth was 35 weeks. Three deaths occurred in the hydropic group, all of which occurred in a period ranging from 2 to 6 days after the initiation of sotalol therapy.

VT

In 1 hydropic fetus, an intermittent tachycardia with a rate of 260 to 280 bpm was diagnosed at the gestational age of 30 weeks. This was erroneously interpreted as SVT, and sotalol therapy was initiated. On this therapy, the tachycardia worsened and became persistent. The echocardiographic appearance of the heart showed a strange, peristaltic-like movement suggesting a torsade de pointes mechanism. Sotalol therapy was withdrawn and replaced with digoxin, which remained unsuccessful. After birth by cesarean section at 31 weeks, this patient proved to have prolonged QT syndrome and uncontrollable periods of ventricular, torsade de pointes tachycardia. Despite extensive and multiform therapy, which eventually included a defibrillation pacemaker, this patient died at 2 years of age of uncontrollable VT and secondary myocardial infarction.

Adverse Effects

In 2 cases, maternal adverse effects were encountered. They were only temporary. One mother experienced nausea, and the other, dizziness and fatigue.

Unfortunately, we did not recognize fetal VT in 1 patient, and the worsening of the fetal tachycardia was probably because of provocation of torsade de pointes in this patient.

SVT Versus AF

Sotalol therapy was successful in 6 of 10 fetuses with SVT and in 8 of 10 fetuses with AF. Treatment was partially effective in 2 fetuses, 1 with AF and 1 with SVT. Drug therapy was effective in 60% of cases of SVT and in 80% of cases of AF. Three deaths in the SVT group and 1 in the AF group were encountered.

Management and Outcome After Birth

Follow-up was possible in 17 cases (4 intrauterine deaths occurred). No rhythm disturbances were seen in 11 of the 17 surviving patients with fetal tachyarrhythmias (65%). Prophylactic drug therapy was administered for 9 months to 1 year in 5 of these 11 patients; 2 patients received sotalol, and the other 3 patients received digoxin. None of these patients have shown recurrent signs of tachycardia, and they are currently doing well.

A relapse of tachycardia was seen in 6 of the 17 cases (35%). Two patients had AF and 3 had SVT. The child with VT had recurrent VT after birth. Two patients were successfully treated with sotalol, 1 patient was treated with digoxin, and 1 patient received a combination of sotalol and digoxin. The fifth patient had AF and was electrically cardioverted to restore sinus rhythm.; sotalol was also administered. All newborns were treated until the age of 1 year.

Morbidity

Two patients with fetal hydrops had significant neurological morbidity immediately after birth. One had SVT and was treated with sotalol, the second had AF and was treated with sotalol and digoxin. Before conversion to persistent sinus rhythm was achieved, these patients experienced intermittent episodes of tachycardia with long-lasting periods of normal sinus rhythm. These episodes lasted 10 and 21 days, respectively, at the gestational ages of 29 and 25 weeks, respectively. Although control of the tachycardia was achieved and these babies were born with good Apgar scores, their post-
natal evaluation showed neurologic pathology; this was due to intracranial hemorrhage in one and cerebral hypoxic ischemia in the other.33

Discussion
Fetal tachycardia can lead to fetal heart failure and death. This has led us to treat tachycardic fetuses prenatally, although others have been reluctant to treat certain forms of tachycardia.44 The patients described in this study were treated on the basis of the existence of longstanding or sustained tachycardia, with or without fetal hydrops.

Choice of Drugs
Sotalol was the drug of first choice in this study. Although previously used agents such as digoxin and flecainide have proven to be successful in most patients, various reports led us to search for alternative and hopefully better drugs. High maternal serum digoxin levels are required to reach therapeutic levels in the fetus, because this drug has slow and only partial transplacental transfer in the presence of hydrops fetalis.19–21 Digoxin as a single therapy has had limited success in the treatment of AF.8,13 The use of flecainide remains controversial due to the report by Allan et al of a fetal death that was possibly induced by flecainide; however, Frohn-Mulder et al12 remain very positive on the use of this drug.

The safety and efficacy of sotalol has been well established in adults, children, and infants.22–30 A negative inotropic effect, which might be expected, has not been found in isolated cardiac tissue. On the contrary, sotalol may even increase contractility slightly because its class III antiarrhythmic properties, which prolong the action potential, may increase time the for calcium influx.22,23 The use of digoxin as second-line drug was motivated by the fact that digoxin, besides its antiarrhythmic properties, may have a positive inotropic effect on the compromised function of the fetal heart.

Recently, however, a study was published in which the risk of proarrhythmic events seemed to be higher in the pediatric age group than in adults and close monitoring by ECG was recommended during the initiation of sotalol therapy in children.27 The most serious potential adverse effect of sotalol, the development of maternal torsade de pointes/ventricular fibrillation, deserves serious consideration. To minimize this risk the possible presence of prolonged maternal QT intervals must be excluded before the initiation of sotalol therapy. In addition, a thorough and in-depth maternal history should be performed to detect previously existing arrhythmias. While on therapy, the maternal ECG should be regularly evaluated for changes in QT interval.

Mechanism of Tachycardia
The efficacy of sotalol as a single therapy was 40% in the SVT group; in the AF group, 50% reverted to sinus rhythm. After the addition of digoxin, another 20% in the SVT group and 30% in the AF group reverted to sinus rhythm. The fact that this study was performed retrospectively hampered our ability to elucidate the relationship between the action mechanism of sotalol and the success rates. Perhaps this would have been possible in a prospective, randomized study.

The conversion rate in the SVT group (60%) is dissatisfying when compared with the rates of other studies, which are as high as 88%.11 The relatively low conversion rate in this study suggests that sotalol is probably not the optimal drug of first choice for the treatment of fetal SVT. Moreover, the fact that 3 of the 4 fetal deaths occurred in fetuses with SVT indicates that the use of sotalol should be restricted to those cases in which other treatment options have failed.

The rate of success in the AF group (80%) compares favorably with previous studies, which have shown success rates ranging from 50% to 66%.11,13 One of 10 fetuses with AF died in utero, probably due to a combination of severe congestive heart failure, stenosis of the venous duct, and a hypoplastic placenta. The low postnatal recurrence rate (10%) also favors sotalol therapy. The high success rate and the low recurrence rate indicate that sotalol could, in our opinion, be considered a drug of first choice in the treatment of fetal AF, possibly with digoxin as a second-line drug.

Hydropic Versus Nonhydropic Fetuses
Hydropic fetuses carry a higher risk of an adverse outcome than nonhydropic fetuses.5,8,33 Although our results suggest that hydropic fetuses can be treated successfully by the maternal administration of sotalol and/or digoxin, they also indicate, in accordance with other reports,35 that there is a high mortality risk in these patients (3 of 8 hydropic fetuses; 37.5%). In those cases in which conversion to sinus rhythm was achieved (5 of 8 hydropic fetuses; 62.5%), the hydrops resolved in a period of 2 to 21 days (mean, 14 days), which is a shorter period than that of previous reports.36

The time to the successful restoration of sinus rhythm was equal in both groups (nonhydropic and hydropic; P = 0.921) of fetuses treated with sotalol, which underscores the drug’s effectiveness, especially in the hydropic fetus.

Postpartum Medication
No unanimity of opinion exists regarding the need for neonatal prophylaxis in patients who do not have persistent or recurrent arrhythmias. Although 11 live-born patients showed no signs of postpartum relapse of the tachycardia, only 7 did not receive any further therapy and are currently doing well, which suggests that postnatal prophylactic medication might not be necessary. A relapse of tachycardia occurred in 6 patients; they received sotalol and/or digoxin prophylaxis for a year, after which it was discontinued, without recurrence of symptoms. Remarkably, 2 of these relapsing patients showed neurological damage (described under Morbidity), which suggests the presence of a therapy-resistant tachycardia. The patient who had torsade the pointes VT died after 2 years of unsuccessful therapy.

Morbidity
Fetal tachycardia has a good prognosis when conversion to sinus rhythm is attained in utero: 82% of all live-born children in this study are alive and well. However, 2 of our hydropic patients suffered from neurologic pathology postnatally. In both of these patients, the time from actual
Sotalol and the combination of sotalol and digoxin were very successful in the AF group, with a conversion rate as high as 80% and the advantage of a low recurrence rate. Therefore, sotalol should be considered as a valuable treatment option for fetal AF.

The low conversion rate and the fact that 3 of 4 deaths occurred in fetuses with SVT indicate that the use of sotalol to treat fetal SVT may be limited. Sotalol can cause proarrhythmic events in the fetus and, although there is no proof, sotalol may have contributed to the mortality rate. This calls into question whether sotalol should be used as a first-line drug to treat fetal SVT, because several other anti-arrhythmic protocols have shown variable success rates without comparable mortality rates. The evidently present risks should be weighed against the limited benefits of sotalol therapy for fetal SVT. It is our belief that the use of sotalol should be restricted to cases with fetal AF and those cases of fetal SVT in which other treatment options have failed.

Mortality

The Table shows the mortality rates of studies performed throughout the past 13 years. Mortality in this study was 4 of 21 fetuses, which is high compared with these previous studies. Because the autopsies did not establish the cause of death in any of our patients, there is a possibility that proarrhythmic events at higher sotalol doses may have caused these deaths. All intrauterine deaths occurred within 1 week after the initiation of sotalol therapy or a dosage increase to a daily dosage of ≥320 mg/day. It is in these periods that sotalol may cause proarrhythmic events. The incidence of proarrhythmic side effects of sotalol in the treatment of pediatric patients varies from 0% to 22%, but the proarrhythmic impact of sotalol may be more pronounced in the immature fetal heart than in adult hearts.

The study of Houyel et al. showed that sotalol causes a significantly greater prolongation of the corrected QT interval in the neonatal heart than in adult hearts. In our fetus with VT, torsades de pointes was confirmed by ECG after birth. This fetus provided evidence that sotalol can cause proarrhythmic events in the immature fetal heart. Therefore, if one opts for sotalol treatment, low initiation doses of 80 mg 2 times per day are preferable, and dosage increases should be stepwise and weighed against possible adverse effects. Close monitoring during the initiation of therapy and dosage increases is recommended.

Conclusions

Fetal arrhythmias present serious conditions in which treatment is necessary, especially in the presence of hydrops. Sotalol and the combination of sotalol and digoxin were very successful in the AF group, with a conversion rate as high as 80% and the advantage of a low recurrence rate. Therefore, sotalol should be considered as a valuable treatment option for fetal AF.

The low conversion rate and the fact that 3 of 4 deaths occurred in fetuses with SVT indicate that the use of sotalol to treat fetal SVT may be limited. Sotalol can cause proarrhythmic events in the fetus and, although there is no proof, sotalol may have contributed to the mortality rate. This calls into question whether sotalol should be used as a first-line drug to treat fetal SVT, because several other anti-arrhythmic protocols have shown variable success rates without comparable mortality rates. The evidently present risks should be weighed against the limited benefits of sotalol therapy for fetal SVT. It is our belief that the use of sotalol should be restricted to cases with fetal AF and those cases of fetal SVT in which other treatment options have failed.

References


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