Treatment of Fetal Tachycardia With Sotalol: Transplacental Pharmacokinetics and Pharmacodynamics

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OBJECTIVES The aim of this study was to investigate the pharmacokinetics and pharmacodynamics of sotalol in the treatment of fetal tachycardia.

BACKGROUND Maternally administered, intrauterine therapy of fetal tachycardia is dependent on the transplacental passage of the antiarrhythmic agent.

METHODS In a prospective study of patients treated for fetal tachycardia with sotalol, concentrations of sotalol were determined in maternal and umbilical blood and in amniotic fluid, and the relationship between these concentrations and the occurrence of conversion to sinus rhythm was investigated.

RESULTS Eighteen fetal patients were studied, nine with atrial flutter and nine with supraventricular tachycardia. Fourteen were treated with sotalol; 13 converted to sinus rhythm, of whom 2 relapsed. There was one intrauterine death. Four patients were treated with sotalol and digoxin, of whom two were treated successfully. Mean birth weight was 3,266 g. The daily maternal sotalol dose was linearly related to the maternal plasma concentration. The mean fetal/maternal sotalol plasma concentration was 1.1 (range 0.67 to 2.87, SD 0.63), and the mean amniotic fluid/fetal blood ratio of sotalol was 3.2 (range 1.28 to 5.8, SD 1.4). The effectiveness of sotalol therapy could not be extrapolated from maternal blood levels.

CONCLUSIONS Sotalol is a potent antiarrhythmic agent in the treatment of fetal tachycardia. The placental transfer is excellent. Sotalol accumulates in amniotic fluid but not in the fetus itself. Therefore it seems that renal excretion in the fetus is efficient and greater than the oral absorption by fetal swallowing. The maternal blood level is not a reliable predictor of the chances of success of therapy. Sotalol is not associated with fetal growth restriction. (J Am Coll Cardiol 2003; 42:765–70) © 2003 by the American College of Cardiology Foundation

Fetal tachycardia, defined as a heart rate greater than 180 beats/min, is a condition that occurs in approximately 0.4% to 0.6% of all pregnancies (1). The subset of these cases with more sustained periods of tachycardia and higher heart rates is associated with congestive heart failure, fetal hydrops, neurologic morbidity, and intrauterine death (2–5). Most centers have therefore opted for prenatal intervention in the form of maternal pharmacologic treatment (6–18). Its success, however, depends largely on the amount of drug that crosses the placenta, which is subject to the altered maternal pharmacokinetics and pharmacodynamics in pregnancy. Various physiologic changes during pregnancy influence maternal pharmacokinetics. In addition, the fetal plasma concentration is also influenced by changes in the fetus itself. Studies on the maternal-placental-fetal unit are limited for obvious ethical reasons; however, the treatment of fetal tachycardia provides us with a unique opportunity to investigate this matter. In the literature, data on the transplacental passage of sotalol are confined to two small studies and one case report (19–21).

We present a study in which we have prospectively investigated drug levels of sotalol in maternal blood, umbilical cord blood after delivery and amniotic fluid. A correlation between the success or failure of treatment of maternal-fetal pharmacotherapy and blood concentrations in both mother and neonate is presented.

METHODS

Definitions. Fetal tachycardia, defined as a sustained fetal heart rate >180 beats/min, was diagnosed by M-mode echocardiography and subdivided in supraventricular tachycardia (SVT; 1:1 atrioventricular conduction) and atrial flutter (AF; atrial rate >250 beats/min with a fixed or variable atrioventricular block).

Congestive heart failure was diagnosed if fluid accumulation existed in the fetal body, such as pericardial effusion, pleural effusion, ascites, or skin edema. Fetal hydrops was diagnosed if fluid accumulation existed in two or more of these compartments.

Patients. All mothers who were diagnosed with fetal tachycardia at the department of Obstetrics, University Medical Center, Utrecht, from 1999 until 2002 were given a detailed description of the study protocol and consented to enter this study. A maternal history was obtained to exclude preexisting arrhythmias, and a maternal electrocardiogram (ECG) was made to exclude prolonged QT intervals. Sotalol therapy was initiated at either 80 mg twice daily or...
160 mg twice daily, increased to a maximum of 160 mg thrice daily, and the addition of digoxin in the event of conversion to sinus rhythm did not occur (18,22). Patients were regularly scheduled (at least once a week) for control visits to evaluate the fetal heart rhythm and possible signs of congestive heart failure. All deliveries took place at our institution, and neonates were admitted immediately after birth for at least 48 h for observation. Postnatal ECGs were performed in all neonates.

**Blood sampling.** At every prenatal visit, a 5-ml blood sample was drawn from a maternal peripheral vein to measure maternal drug levels. At the time of delivery, 5 ml of maternal blood, 5 ml of blood from the umbilical artery and from the umbilical vein, and whenever possible 10 ml of amniotic fluid was collected.

**Drug analysis.** Sotalol concentrations in plasma and amniotic fluid were determined by a modified ion-pair, reversed-phase, high-performance liquid chromatography method, with ultraviolet detection at 226 nm described by Kärkkäinen (23). The lower limit of quantification was 0.08 mg/l with an intra-day coefficient of variation (CV) of 4.4% at 0.02 mg/l and an inter-day CV of 2.6% at 0.02 mg/l (24).

**Approval.** The study was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht according to the Helsinki protocols.

**RESULTS**

Eighteen women agreed to participate in this study. Details on diagnosis, treatment modalities, and outcome are summarized in Figure 1. Of nine patients with AF, one fetus was hydropic; two of nine fetuses with a SVT had congestive heart failure. Fourteen patients received sotalol as single therapy. Of these 14 patients, 10 converted to sustained sinus rhythm in a mean time to conversion of 46 h (SD 32 h). In one additional patient, two weeks were required to reach sustained sinus rhythm. Two patients, who initially converted to sinus rhythm within 48 h, relapsed into tachycardia after one and five weeks of sinus rhythm, respectively. Because both patients had reached a gestational age of 37+ weeks at that time, a Caesarean section (SC) was performed, rather than increasing the dosage or addition of another antiarrhythmic agent. One nonhydropic fetus with SVT died unexpectedly three days after initiation of therapy with sotalol 160 mg twice daily. Sinus rhythm had not been achieved. The maternal blood level of sotalol was 1.01 mg/l.
which is within the normal range. Autopsy showed significant dilation of the heart and minimal signs of hydrops. No structural abnormalities were present.

In four patients, digoxin was added to the sotalol treatment according to protocol because of persistent fetal tachycardia. In two patients this was successful 24 h and 48 h after the addition of digoxin, respectively. One patient was delivered by SC at 35 weeks and six days, after membranes had ruptured spontaneously, and a prolapsed arm was diagnosed; sinus rhythm had not been achieved despite longstanding multiple drug therapy. The other patient was delivered by SC at 36 weeks and six days because of persistence of tachycardia despite six days of multiple drug treatment.

**Sotalol and digoxin levels.** Maternal sotalol levels measured at the prenatal visits in all patients increased linearly with increasing dose (Fig. 2). Umbilical vein samples were obtained in 12 cases. The relationship between maternal sotalol dosage and umbilical vein concentration is shown in Figure 3. Maternal and fetal blood levels were almost equal, and the mean fetal/maternal sotalol plasma concentration (F/M ratio) was 1.11 (range 0.67 to 2.87, SD 0.63) (Table 1).

Sotalol was measured in amniotic fluid in seven cases. The concentration was higher in amniotic fluid than in fetal cord blood and maternal blood, and the concentration ratios were 3.2 (range 1.28 to 5.8, SD 1.4) and 2.94 (range 1.0 to 6.0, SD 1.6), respectively.

**Correlation between maternal blood levels and success of therapy.** There did not seem to be a correlation between sotalol blood concentrations and the occurrence of conversion to sinus rhythm. The levels at which the drug proved to be effective were only slightly higher than those that did not result in conversion, indicating a large difference in sensitivity to the drug. In three individual patients in which sotalol initially was not effective, an increase in dose from 80 mg twice daily in two patients (blood levels 0.60 and 0.87 mg/l) to 160 mg twice daily (blood levels 1.27 and 1.63 mg/l) and from 160 mg twice daily in one patient (blood level of 0.77 mg/l) to 160 mg thrice daily (blood level of 1.50) was associated with conversion to sinus rhythm, whereas in one case a decrease in dose (from 160 mg twice daily to 80 mg thrice daily) and serum level (1.75 mg/l to 0.6 mg/l) was associated with a relapse of AF.

**Postnatal outcome.** One fetus died in utero, and one infant with a massive hydrops, delivered at 33 weeks and four days, died two days after delivery. Follow-up is available for the other 16 infants, varying from 6 months to 36 months after birth. Eight infants (5 had AF and 3 had SVT) had no rhythm disturbances during the newborn period, and no medication was initiated. None of these patients have developed episodes of tachycardia, and they are currently doing well. Three patients showed AF at birth (two therapy-resistant cases and one relapse), and all required electrical cardioversion to reach sustained sinus rhythm. These three patients are currently doing well and require no
medication. Five patients showed SVT postnatally, of whom two had Wolff-Parkinson-White syndrome, two had persistent junctional reciprocating tachycardia, and one patient showed intermittent periods of SVT of unknown origin. All are doing well on antiarrhythmic therapy, consisting of digoxin in two patients, propranolol in one patient, and a combination of these two agents in two patients. All surviving infants are in good neurologic condition.

Postnatal corrected QT interval (QTc). The mean QTc at the first day of life was 0.41 (range 0.35 to 0.47, SD 0.035), and no relationship with the maternal sotalol dosage or fetal blood level was present.

**Birth weight.** The mean birth weight was 3,266 g (range 960 to 4,280 g, SD 804). All infants were appropriate for dates with one exception. This baby was born at 33 + 4 weeks of gestational age with a birth weight of 960 g, which is below 2.3rd percentile of normal birth weights for this gestational age (25); this infant was only treated for four days, and the low birth weight could therefore not be attributed to the beta-blocking therapy.

**DISCUSSION**

**Choice of drugs.** The choice of sotalol as drug of first choice was based on our previous experience with this drug. As reported in a previous article, sotalol seems to be more efficacious than other drugs in fetal AF (17). In fetal SVT, conversion rates were comparable to that of other studies, but a relatively high mortality rate was present, and we called into question the use of sotalol in fetal SVT. However, after consideration of the data, no statistical difference in mortality was present compared with that of other studies, and therefore, the protocol in nonhydropic SVT remained the same. In fetal SVT complicated by hydrops, we opted for a different strategy as discussed in a previous article (18), consisting of either flecainide orally or digoxin intravenously, as these strategies seemed to be more successful.

**Success of therapy.** In the patients treated with sotalol as a single agent, results were favorable, because 13 of 14 patients converted to sinus rhythm in a relatively short amount of time. Unfortunately, the one patient who went into premature labor did not benefit long enough from sinus
rhythm, as this only lasted for three days and hydrops was still present at the time of delivery. The other two patients who went into relapse clearly profited from in utero therapy as they reached gestational maturity while on therapy. Our choice of delivery by SC at that time, rather than the increase of dosage or the addition of a second antiarrhythmic agent, was based on our opinion that the possible harmful effects of transplacental therapy (adverse effects of mother, and potential proarrhythmic effects for both mother and fetus) outweigh the benefits of further in utero maturation. In the patient who was treated with both sotalol and digoxin in which no conversion was reached at 36 + 6 weeks, the decision to perform a SC was based on the same opinion. The conversion rates of 72% with sotalol, reaching 83% after the addition of digoxin, compare favorably with the results of other treatment protocols using digoxin as the drug of first choice, in which conversion rates of 50% to 71% are reported (8,10–12).

The unexpected intrauterine death, possibly as a result of ventricular fibrillation, raises the possibility of proarrhythmic effects of sotalol in the fetus. Although we have no evidence that this was indeed the cause of death, we think that the possible risk of proarrhythmia should be minimized. Intrauterine therapy should therefore always be weighed against possible adverse effects. As proarrhythmia of sotalol is known to be dose-related (26), low initiation doses are preferable and dosage increases should be stepwise. Close monitoring, especially during the initiation phase, is recommended. In addition, maternal potassium levels and magnesium levels should be monitored regularly and supplemented if necessary.

We therefore propose a new dosage scheme with an initiation dose of 80 mg of sotalol twice daily, stepwise increased with 80 mg per three days to a maximum of 160 mg thrice daily. Digoxin may be added as a second-line drug. This protocol has our preference in the treatment of fetal AF, either with or without hydrops. We have no definite preference for either sotalol or digoxin in the treatment of nonhydropic fetal SVT. In fetal SVT complicated by hydrops, other strategies seem to be more successful.

**Dosage and maternal blood levels.** Despite high oral sotalol dosages, all maternal blood levels remained below the “toxic” level of 2.5 mg/l (at which marked QTc prolongation is noted). This is probably the result of the increased blood volume and renal clearance in pregnant women. This is important, as maternal adverse effects and the risk of torsade de pointes tachycardia (as a result of QTc prolongation) are dose-related. The F/M ratio of 1.11 shows that the fetus also stays below the “toxic” level.

**Fetal/maternal ratio of plasma concentration.** Sotalol passes the placenta easily and completely, as can be concluded from the mean F/M ratio of 1.11. This result is similar to that reported by O’Hare et al. (19), though it differs from the lower ratio found in the study of Erkkola et al. (20), although this could be explained by the nature of the study in which only a single dose was administered 3 h before delivery. The ratio of 1.11 compares favorably with the F/M ratios of other commonly used drugs in fetal tachycardia. Apparently sotalol does not accumulate in the fetus, which implies that the excretion of sotalol by the fetal kidney is efficient close to term. The adequate renal excretion may explain the relatively high concentration of sotalol in amniotic fluid. The high amniotic fluid/umbilical venous blood ratio combined with an almost 1:1 relationship of fetal and maternal blood and the swallowing of amniotic fluid by the fetus implies that the elimination rate of sotalol is greater than the oral reabsorption.

**Correlation of maternal blood level and success of therapy.** Although in individual cases the maternal dosage of sotalol was related to the success of therapy, statistically a strong relationship between the maternal blood level and the success of therapy was not shown. The therapy-resistant cases required either electrical cardioversion or multiple drug therapy, which suggests that the success of therapy may be more related to the type of arrhythmia.

The maternal blood levels do, however, strongly relate to the fetal blood level and could thus be valuable in preventing exposure of the fetus to toxic levels.

**Postnatal QTc.** The QTc interval at the first day of life is of potential interest, as repolarization may still be under the influence of the class III antiarrhythmic properties of sotalol. The effects of sotalol on the neonatal QTc interval may be extrapolated to the fetal situation, although measurement of the fetal QT interval by fetal magnetocardiography in future studies may be more reliable. The mean QTc in our patients is somewhat higher than reported in previous studies (27,28); however, it remains below 0.44, at which point a lengthened QTc is diagnosed. The effects of sotalol on repolarization in the dosages used in this study are therefore, in our opinion, limited and do not reach “toxic” limits.

**Birth weight.** Some beta-blockers, such as propranolol, have been associated with intrauterine growth retardation (29). All but one of our patients had birth weights within the normal range, even though in several cases this treatment was continued throughout the whole third trimester. Therefore, it seems unlikely that sotalol induces fetal growth restriction.

**CONCLUSIONS**

We conclude that sotalol is a potent antiarrhythmic agent in the treatment of fetal tachycardia, especially in fetal AF (with or without hydrops). Sotalol passes the placenta quickly and reaches a steady-state level almost identical to the maternal plasma level. Maternal blood levels can therefore be used as an indicator of the fetal blood levels. Sotalol accumulates in amniotic fluid but not in the fetus itself, indicating that renal excretion is efficient, and implying that the elimination rate of sotalol exceeds oral absorption in term fetuses. Maternal blood levels are not a reliable
predictor of the chances of success of therapy. Sotalol is not associated with fetal growth restriction.

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