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Double-blind evaluation of ritodrine sustained release for oral maintenance of tocolysis after active preterm labour

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Objective To evaluate the effect of ritodrine sustained release capsules for maintaining uterine quiescence after successful treatment of active preterm labour.

Design Multicentre placebo-controlled trial.

Setting Five teaching hospitals in the Netherlands.

Participants Women ($n = 95$) at less than 35 weeks of gestation in whom active preterm labour had been stopped with intravenous ritodrine.

Interventions Women received either two 40 mg ritodrine sustained release capsules ($n = 50$) or identical placebo capsules ($n = 45$) three times a day for seven days.

Results The proportion of women who received another course of active treatment was significantly smaller with the sustained release than with placebo (1 of 50 *versus* 11 of 45: $P = 0{\cdot}003$) as was the number delivering because of preterm labour during treatment (0 of 50 *versus* 4 of 45: $P = 0{\cdot}04$). There were no other significant differences between the two groups.

Conclusions Maintenance treatment with ritodrine sustained release capsules after arrest of preterm labour reduces the risk of recurrences of preterm labour that necessitate treatment or precipitate delivery.

INTRODUCTION

There is some evidence from controlled studies that inhibition of preterm labour with betamimetics is more likely to be effective when intravenous treatment is followed by oral maintenance than when it is not. That evidence is weak, however, and spread across three small studies not all of which used the same betamimetic agent[1–3]. Among them they only showed fewer relapses and longer relapse free intervals, but no reduction in the incidence of preterm birth[4,5]. These not particularly impressive effects required the frequent intake of a large number of tablets to compensate for the low bioavailability and short half-lives of oral betamimetics[6].

The use of ritodrine in a sustained release formulation permits the limitation of betamimetic intake to three times a day while obtaining plasma levels that parallel the lower range of effective intravenous treatment[7] with few side effects[7,8]. We wished to examine whether the use of this sustained release preparation would be sufficiently effective in reducing recurrences of preterm labour to warrant its use in clinical practice.

METHODS

A placebo-controlled comparison of ritodrine sustained release capsules for maintaining uterine quiescence after arrest of preterm labour was conducted with ethical approval at five Dutch teaching hospitals. Women recruited for the study were those who had participated in a randomized comparison of two schedules of intravenous ritodrine administration, described elsewhere[9], and in whom this had resulted in the arrest of active preterm labour. Of the 143 women in whom preterm labour had been stopped with either one of two ritodrine schedules, 18 were not eligible because they had received indomethacin ($n = 6$), had ruptured membranes ($n = 2$), had experienced severe side effects during intravenous treatment ($n = 4$), or were beyond 34 weeks of gestation ($n = 6$)[9]. Of the 125 women who were eligible, 30

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Table 1. Baseline characteristics of women participating in the oral maintenance trial.

Characteristics	Ritodrine $n = 50$	Placebo $n = 45$	P
Age (years)	29·0 (5·2)	28·7 (5·0)	0·80[1]
Duration of pregnancy at trial entry (days)	219 (14)	219 (16)	0·84[1]
Multiple pregnancy			0·006[2]
Twins	7	—	
Triplets	1	—	
Tocolytic index (ref. 20)	2·8 (0·9)	3·0 (1·1)	0·57[3]
Bishop score	4·0 (1·8)	4·2 (1·7)	0·64[3]
Intravenous ritodrine treatment schedule prior to trial entry			0·59[4]
Loading dose	25	25	
Incremental dose	25	20	
Total duration (days)	4·1 (3·2)	3·9 (2·2)	0·80[5]
Intravenous treatment until tapering off			
Duration (hours)	45 (15)	55 (33)	0·37[5]
Dose of ritodrine (mg)	433 (410)	434 (368)	0·86[5]

Values are n or mean with SD in parentheses.
Statistical tests: [1] t test, [2] Fisher exact, [3] Cochran-Mantel-Haenszel, [4] χ^2 test, [5] Wilcoxon.

did not participate in the present study: 16 because they received active treatment without blinding; eight because of transfer to a nonparticipating hospital or lack of consent; and six for reasons that were not documented. Thus, 95 women participated in the trial; 50 of them had originally received the loading and 45 the incremental dose schedule of intravenous treatment[9] (Table 1).

It had been estimated that with an anticipated $> 90\%$ success rate of the active treatment a sample of 100 women would have 80% power to detect a 20% difference in the frequency of successful maintenance between the active treatment and placebo (two-tailed $\alpha = 0{\cdot}05$). Success was defined as no delivery and no administration of a new course of active tocolytic treatment (intravenous tocolysis) during the seven days of maintenance.

At the start of maintenance treatment, all women had been on an intravenous dose of 50 μg/min ritodrine for 12 to 24 h following successful arrest of contractions. Maintenance consisted of either two 40 mg ritodrine-sustained release capsules or two identical placebo capsules three times a day for seven days supplied in block-randomised, pharmacy-coded drug boxes. The protocol recommended bedrest for the first 48 h and hospitalisation for the duration of the seven-day maintenance treatment. A new episode of intravenous treatment was prescribed with the same regimen that the woman had received previously if active labour recurred before 34 weeks of gestation. Maintenance treatment was to be stopped in the event of severe side effects, intrauterine infection, fetal distress, recurrent preterm labour requiring intravenous treatment or leading to delivery, or after seven days. Other tocolytic agents were not used.

The main outcome parameters were administration of another course of intravenous tocolysis and delivery during the seven days of maintenance treatment. Additional predefined outcomes were: number of deliveries before 35 and 37 weeks and the presence of side effects irrespective of whether or not these prompted arrest of treatment.

Statistical analysis was by χ^2 test, Fisher's exact test for expected numbers below 5, and confidence interval analysis[10]. A two-tailed P value $< 0{\cdot}05$ was considered to be stastically significant.

RESULTS

Only one of the women (2%) who received ritodrine-sustained release capsules underwent a new intravenous infusion, compared with 10 of those (22·2%) who received placebo capsules, a difference that is highly significant ($\chi^2 = 7{\cdot}6$, $P = 0{\cdot}006$; Table 2). One woman (after loading dose allocated to placebo) did not comply with maintenance treatment and was given indomethacin. A further placebo-treated woman had a recurrence of preterm labour deemed to be beyond rescue; she delivered without re-infusion. All but one of the re-infusions occurred within the first three days of stopping intravenous treatment and three of the women (all in the placebo group; Table 2) delivered despite re-infusion. There was also a statistically significant difference in the number of women delivering because of recurrent preterm labour during treatment (0 *versus* 4; Fisher's exact test, $P = 0{\cdot}04$), but not in the total

Table 2. Outcome characteristics with the two maintenance treatments

Outcome	Ritodrine ($n = 50$)	Placebo ($n = 45$)	Difference (%) and 95% confidence interval
New active treatment	1	11	−22·4 (−35·6 to −9·3)
Intravenous ritodrine	1	10*	−20·2 (−33·0 to −7·5)
Indomethacin	0	1†	−2·2 (−6·5 to 2·1)
Delivered			
Within 7 days	1**	4	−6·9 (−16·1 to 2·3)
Before 35 weeks	2	6	−9·3 (−20·7 to 2·0)
Before 37 weeks	16	13	3·1 (−15·4 to 21·6)
Discharged from hospital			
Within 5 days	10	8	2·2 (−13·5 to 18·0)
Within 7 days	20	19	−2·2 (−22·0 to 17·6)
Not before delivery	3	7	−9·6 (−22·0 to 2·9)
Treatment stopped due to side effects	1	0	2·0 (−1·9 to 5·9)
Side effects			
Headache	1	0	2·0 (−1·9 to 5·9)
Hypertension	0	1	−2·2 (−6·5 to 2·1)
Tremor	2	0	4·0 (−1·4 to 9·4)
Vomiting	1	0	2·0 (−1·9 to 5·9)
Neurological problems	0	1	−2·2 (−6·5 to 2·1)
Fetal and neonatal deaths	1	0	2·0 (−1·9 to 5·9)

* Of whom 3 delivered within 7 days and below 34 weeks.
** Caesarean section because of vaginal bleeding in the absence of contractions.
† Lack of compliance with maintenance treatment.

number of deliveries during treatment (Table 2). There were no other statistically significant differences between the groups; neither in duration of hospitalisation, gestational age at delivery or incidence of side effects (Table 2). In only one woman (in the ritodrine group) treatment was stopped because of side effects (headache; Table 2).

There was one case of abruption four days after stopping placebo treatment and one death: an unexplained intrauterine death of a mature infant two months after the end of the trial (ritodrine group) and a further 27 days of open oral ritodrine treatment. Except for this death and one mother who could not be traced after moving to another city, all mothers and infants were well at follow up in the postneonatal period.

DISCUSSION

Although virtually all controlled trials of beta-mimetic agents in the treatment of preterm labour have incorporated an episode of maintenance treatment[11,12], there is divergence of opinion between countries and individual obstetricians on whether maintenance treatment is worthwhile after arrest of active preterm labour[13,14]. There are many reasons for this, not the least of which is lack of evidence that such treatment reduces the preterm birth rate[4,5]. Other reasons relate to a wide range of potential, albeit mainly hypothetical effects of prolonged exposure of fetal beta-adrenergic receptors to betamimetic agents[13]. Still others reflect concepts, such as down-regulation of β-adrenergic receptors[15,16] that may limit the utility of long-term tocolysis, or beliefs that tocolytic treatments are symptomatic in nature and thence superfluous when symptoms are no longer present. These many persuasions gain a great deal of impetus from the limited bioavailability of betamimetics after oral administration and the short half-lives which require tablets to be taken at frequent intervals throughout the day and night, if pharmacological credibility is to be sustained[3,6,8,13]. Yet, many clinicians feel something incongruous in waking a woman, who is finally asleep after the uterus has been subdued, merely to maintain the *status quo* so that she can sleep again.

Oral preparations of ritodrine have a bioavailability of about 30%[7,17] and they must be taken 6 times a day in order to maintain reasonable plasma levels[18]. It has been argued that the low efficacy of the medication is often due to inadequate plasma levels[6]. With the sustained release capsules three doses of 80 mg a day are sufficient to obtain plasma levels that are equivalent to those obtained with an intravenous infusion of 50 μg/min ritodrine without serious side effects[7,19]. The fact that only one of 95 women in our study failed to comply with the prescribed maintenance of three doses a day suggests that this treatment is

much easier to tolerate than the usual schedules that require around the clock administration.

Our study now clearly demonstrates that sustaining uterine relaxation with this regimen of ritodrine maintenance reduces the likelihood that women will require another course of intravenous treatment. There is now also evidence that this treatment is more likely to delay delivery for at least seven days than no maintenance treatment. These conclusions gain further credence from the fact that there were significantly more multiple pregnancies in the ritodrine than in the placebo arm of the trial. Both effects can be clinically worthwhile especially when considered in terms of the hazards and maternal discomfort arising from each new course of intravenous betamimetic treatment, as well as the cost of re-admission and hospitalisation of women with recurrent preterm labour.

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