Bolus tocolysis: Treatment of preterm labor with pulsatile administration of a β-adrenergic agonist

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The treatment of premature labor with β-adrenergic substances is complicated by side effects. Although most human control mechanisms are pulsatile, therapy is usually administered continuously. We designed a microprocessor-controlled pump to allow pulsatile tocolytic infusion, hoping to reduce the total dose and thus the side effects. In 33 patients pulsatile bolus tocolysis was compared with continuous tocolysis in a control group of 38 patients. Bolus tocolysis required considerably less β-sympathomimetic agent for comparable therapeutic success (median dosage 3.0 versus 15.9 mg, $p < 0.001$). Duration of therapy under bolus tocolysis was also significantly shorter ($p < 0.05$). Birth weight was higher after bolus tocolysis (median 3070 versus 2580 gm, $p = 0.05$). Additional indicators favored bolus tocolysis but were not statistically significant: a longer gestational period, fewer infants weighing <2500 gm, and a lower incidence of respiratory distress syndrome. Pulmonary edema occurred in one patient during continuous tocolysis. (Am J Obstet Gynecol 1989;160:713-7.)

Key words: Preterm labor, β-sympathomimetic agent, pulsatile infusion, bolus tocolysis

Stimulation of β-adrenergic receptors by β-adrenergic receptor agonists inhibits contractions of smooth muscles. These substances are widely used in the treatment of preterm labor. They allow prolongation of gestation[1] but cause side effects; the most serious is pulmonary edema.[2] One approach to minimize the side effects is to reduce the dose and duration of therapy. Because the physiologic stimulation of the myometrium is probably pulsatile, we designed a device for pulsatile intravenous administration of β-adrenergic receptor agonists (bolus tocolysis).

Continuous intravenous infusion has been used for many years for the administration of β-mimetics; various protocols have been developed for the initiation, maintenance, and termination of therapy. We tested bolus administration and continuous infusion using the dosage schedule that is customary in our institution. The two regimens were compared for their effects on dosage, duration of therapy, prolongation of gestation, total dose of drug required, length of therapy, and effect on maternal and fetal heart rates.

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Material and methods

A commercially available syringe pump was modified by replacing the electronic components with a microprocessor system, which allows the intravenous delivery of a preset dose at a high infusion rate and the programming of the time interval between two bolus applications. The bolus dose in units of 20 μl and the time interval in minutes are set by means of thumb wheel switches on the front of the pump. One bolus unit is delivered within approximately 1.8 seconds. The microprocessor system continuously controls the status of the pump. An alarm is sounded by any defect or by an unauthorized altering of the dosage parameters.*

Fenoterol† was chosen as the β-sympathomimetic agent because we have had many years of experience with this drug. Compared with other β-sympathomimetics in use (e.g., ritodrine or salbutamol), fenoterol has a short half-life. The syringe was filled with 50 ml of undiluted fenoterol and 1000 IU of heparin. Fenoterol is manufactured in a concentration of 50 μg/ml. One bolus unit of 20 μl corresponds to 1 μg fenoterol.

Diagnosis of premature labor was based on documentation by external tocography of three or more uterine contractions in 30 minutes. Intravenous tocolytic therapy was used when gestational age was >24

*An infusion pump suitable for pulsatile bolus medication is available from Braun AG, D-3508 Melsungen, Federal Republic of Germany.

†Partusisten, Boehringer Ingelheim, Federal Republic of Germany, is currently not available in the United States.

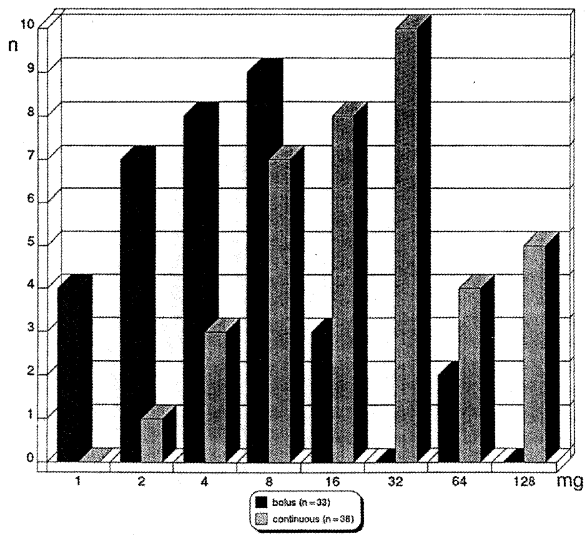

Fig. 1. Distributions of total fenoterol doses administered as continuous or bolus tocolysis.

Table IA. Size of bolus for tocolysis

	Weight of patient		
	<61 kg	*61 to 79 kg*	*>79 kg*
Bolus size (μg)	3	4	5

and <35 weeks. The pelvic score was documented before onset of therapy but had no influence on patient selection. Patients who had received any previous tocolytic therapy were excluded from the study. The total of 87 patients were divided into a study group receiving bolus tocolysis and a control group receiving tocolysis with conventional continuous infusion. Patients were alternately allocated to the study and control group at the time of hospitalization.

Because most of the parameters did not distribute normally, the analyses are as median, minimum, and maximum instead of mean and SD. Differences in central tendencies were tested by the nonparametric U test of Wilcoxon, Mann, and Whitney. Comparisons of relative frequencies were carried out by the χ^2 test. The presence of statistical significance was accepted at p values ≤ 0.05.

Continuous tocolysis was started with 2 μg/min of fenoterol by means of an automatic drop counter. During the first 2 hours the infusion rate was titrated against uterine activity as recorded by external monitoring of uterine activity. When there were fewer than two contractions per 30 minutes, dosage was reduced; if there were more than two contractions, dosage was increased. Increases or reductions were made in increments of 0.5 μg/min. The maintenance dose was adjusted daily according to the record of uterine activity. Whenever the patient complained of increasing frequency or intensity of contractions, uterine activity was recorded and dosage was increased as required. The infusion was stopped when there were fewer than three contractions per hour.

Table IB. Therapy schedule of bolus tocolysis

	Time interval (min)
At beginning	3
At diminishing labor	6
After 12 hr (if possible)	12
After 24 hr (if possible)	24
After 48 hr (if possible)	End of intravenous tocolysis

In bolus tocolysis the bolus size (3 to 5 μg) was determined according to the patient's weight (Table IA). At the beginning of treatment a bolus was given every 3 minutes (Table IB). This dose is equivalent to the starter dose in continuous tocolysis. Uterine activity was externally monitored as for continuous tocolysis. If contractions continued at a rate of more than two per 30 minutes, the bolus dose was increased up to a maximum of 7 μg at 2-minute intervals. As soon as uterine activity decreased, intervals between boluses were doubled. After 12 hours, bolus intervals were extended to 12 minutes if the frequency and intensity of contractions had not increased. After another 24 hours, the bolus interval was extended to 24 minutes. If contractions disappeared or fell below the physiologic range, the infusion was stopped.

To increase or lower the dose, the same criteria of uterine activity were applied as for continuous tocolysis. A 30-minute recording was obtained twice daily for all patients. Tocolysis was considered unsuccessful when delivery could not be delayed for at least 48 hours.

In both groups treatment was continued in most patients with 5 μg fenoterol orally five times a day. Patients on a regimen of oral maintenance were discharged.

Maternal heart rate was determined daily at 7 AM by pulse counting. Fetal heart rate was also determined daily as a 15-minute average from the heart rate tracing of the cardiotocogram. From the individual values, the median for both maternal and fetal heart rates was calculated for day 1, day 2, etc., until day 7 of treatment or as long as intravenous therapy was maintained.

Results

Ten of the 43 patients treated with bolus tocolysis were excluded from further analysis. In two cases therapy was discontinued because of infection of the fetal membranes. In one case of abruptio placentae, severe fetal bradycardia necessitated cesarean section. In seven cases errors in protocol were found (with patients

Table II. Obstetric factors at entry to the study

	Bolus tocolysis (n = 33)			*Continuous tocolysis (n = 38)*			
	Median	*Minimum*	*Maximum*	*Median*	*Minimum*	*Maximum*	*Significance*
Age (yr)	27	19	42	26.5	16	44	NS
Parity	1	1	5	1	1	3	NS
Gravidity	2	1	9	2	1	5	NS
Bishop score*	4	1	11	4	1	12	NS
Gestational age (days)*	216	174	242	212.5	171	245	NS

*At beginning of tocolysis.

Table III. Obstetric factors related to treatment

	Bolus tocolysis (n = 33)			*Continuous tocolysis (n = 38)*			
	Median	*Minimum*	*Maximum*	*Median*	*Minimum*	*Maximum*	*Significance*
Duration of tocolysis (days)	4	0*	42	6	1	40	$p < 0.05$
Gestational age at delivery (days)	265	218	293	253.5	191	292	NS
Prolongation of gestation (days)	45.5	0*	116	27	3	80	NS
Total dosage (mg)	3.0	0.3	62.3	15.9	2.0	114.5	$p < 0.001$
Dosage per day (mg)	0.85	0.24	2.71	2.79	1.19	4.42	$p < 0.001$
Tocolysis failure (delivery within 48 hr after start of therapy)		$n = 2$			$n = 4$		NS

*Seven hours.

above or below the acceptable gestational age or, because the patients had been previously treated with β-sympathomimetics, three patients were changed to continuous tocolysis).

Six of 44 patients treated with continuous tocolysis were eliminated (therapy was discontinued in one case because of infection of fetal membranes, in one case because of preeclampsia, and in one case the mother had severe tachycardia and palpitations. One patient developed pulmonary edema and two women were above or below the preset gestational age).

There were no statistical differences with respect to age, parity, and gravidity between the two groups. At the start of therapy, the cervical condition and gestational age were found to be comparable (Table II). In the study group 29 of 33 patients and 37 of 38 control patients were delivered in the Department of Obstetrics, University of Zürich. Only one case of rehospitalization because of premature contractions was registered in the control group.

The total amount of fenoterol administered with bolus tocolysis was only one fifth of that used in continuous tocolysis ($p < 0.001$, Table III). The frequency distribution of the total dose is shown in Fig. 1. The lower total dose with bolus tocolysis was achieved by a smaller dose per unit of time and a significantly shorter duration of treatment (Figs. 2 and 3, Table III). Dosage with bolus tocolysis could be reduced in the majority of patients during the first 2 hours. Dosage reduction was not possible in most patients in the continuous infusion group until 16 to 32 hours after the start of treatment (Fig. 4).

Maternal heart rate (counted once a day) showed a faster decline in the bolus group. This is an expression of the more rapid reduction in the dosage in this group, but the difference in response of maternal heart rate did not reach statistical significance. Fetal heart rate changes showed no difference.

A longer gestational period was achieved with bolus tocolysis although this difference did not reach statistical significance. The mean prolongation in the bolus group was 46 days compared with 27 days in the continuous infusion group. Bolus tocolysis failed in two cases and continuous tocolysis failed in four cases (Table III). There was also a higher median birth weight in the bolus group, which is consistent with the longer gestation; this difference was statistically significant (Table IV). There was no difference in the Apgar scores. There were eight infants with birth weights <2500 gm in the bolus group and 16 in the continuous

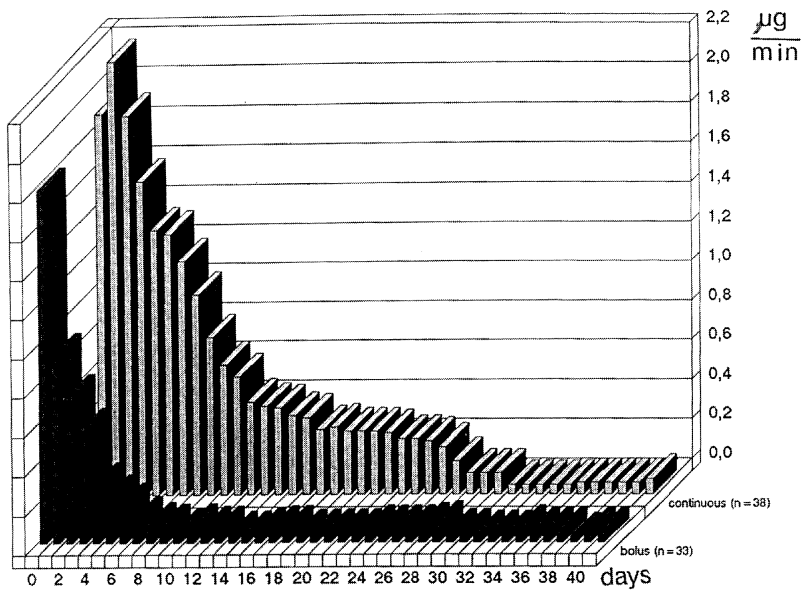

Fig. 2. Fenoterol doses per time unit in relation to duration of therapy.

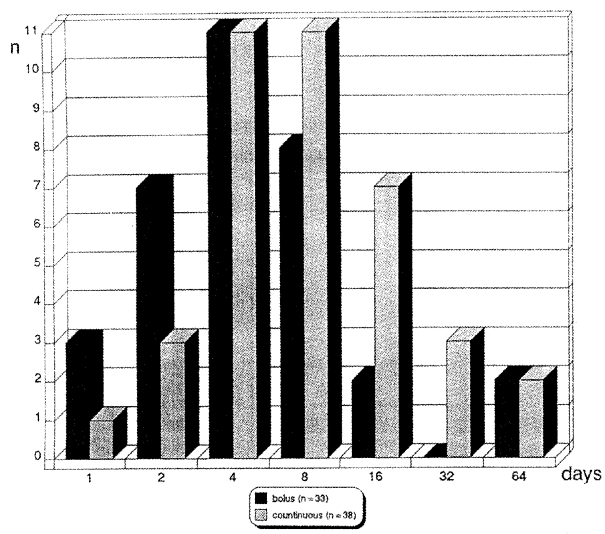

Fig. 3. Duration of therapy in continuous and bolus tocolysis groups.

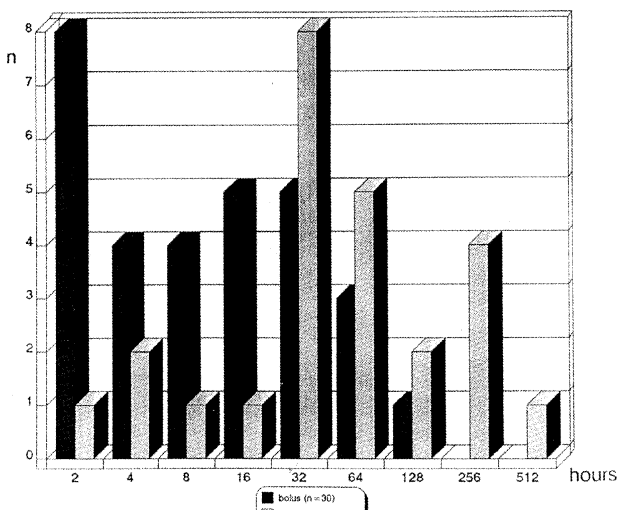

Fig. 4. Time intervals between start of therapy and first dose reduction. Reduction was not possible in nine patients receiving continuous tocolysis and in one patient treated with bolus tocolysis.

infusion group. Two infants in the bolus group and eight infants in the group treated with continuous infusion developed respiratory distress syndrome. Both differences favored bolus tocolysis but were not statistically significant (Table IV).

After completion of continuous or bolus tocolysis, some patients were continued on a regimen of oral fenoterol therapy as prescribed by their physicians. Medication was continued in 14 cases in the study group and 22 in the control group; there was no statistical difference between these two groups.

Comment

Treatment of preterm labor with pulsatile tocolysis proved to be at least as successful in prolonging gestation as the usual procedure of continuous infusion. The results were obtained with a considerably lower total dosage of β-sympathomimetic agonist. Additional advantages were realized for the patients treated by pulsatile tocolysis: reduced length of therapy for the mother, a longer gestation period and increased me-

Table IV. Condition of newborn infant

	Bolus tocolysis (n = 33)			*Continuous tocolysis (n = 38)*			
	Median	*Minimum*	*Maximum*	*Median*	*Minimum*	*Maximum*	*Significance*
Birth weight (gm)	3070	1330	3720	2580	840	3680	$p = 0.05$
Apgar score at 1 min	8	2	9	8	1	9	NS
Apgar score at 5 min	9	6	10	9	6	10	NS
Apgar score at 10 min	9.5	7	10	9	5	10	NS
Birth weight <2500 gm		$n = 8$			$n = 16$		NS
Respiratory distress syndrome		$n = 2$			$n = 8$		NS

dian birth weight, fewer infants weighing <2500 gm, and a lower incidence of respiratory distress syndrome.

The noted differences did not all achieve statistical significance, probably because of the relatively small number of patients in the study. However, none of the investigated parameters negates the concept of bolus tocolysis.

One of the control women among those women who eventually were delivered at the university hospital of Zürich required rehospitalization. There were no rehospitalizations in the study group. Similar data are not available for women who were delivered in other hospitals.

Serum concentrations of fenoterol were not determined in this study. It is likely that significant fluctuations in serum concentrations were achieved by bolus administration, particularly with the longer intervals between boluses. This question is currently being studied in the Department of Obstetrics at the University of Zürich.

Several experimental observations support the concept of increased effectiveness of intermittent administration of β-adrenergic receptor agonists. Myometrial cells reduce their production of cyclic adenosine monophosphate in response to continuous stimulation by β-adrenergic receptor agonists,[3, 4] and there is a decrease in the number of receptors.[5] Spontaneous contractions of human myometrium are more effectively inhibited by the intermittent administration of isoproterenol.[6] This inhibitory effect is produced by short-acting β-sympathomimetic substances.[7] Fenoterol has a half-life of 22 minutes and is included in this group of agonists.[8]

The nature of this study did not permit a double-blind design; thus it is not possible to exclude an unintended bias. The results, however, demonstrate that the described bolus regimen presents distinct advantages over the customary continuous infusion approach to tocolysis.

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