Uptake of Halothane by the Foetal Lamb in Utero

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The uptake of halothane by the normal foetus in utero was determined, using the pregnant ewe as an experimental animal model. Six pregnant ewes of 125–135 days gestation were surgically prepared under general anaesthesia. Polyvinyl catheters were placed in the maternal femoral artery and vein and in the foetal femoral artery and vein and the axillary artery. Each animal was allowed to recover for 24–36 hours prior to study. On the day of the experiment a tracheostomy was performed and after a control period, the ewe was anesthetized with 1.5 per cent halothane in oxygen. During each study, maternal and foetal blood pressure were continuously recorded. Simultaneous maternal and foetal arterial halothane concentrations were measured to construct an uptake curve for the foetus. During the study, foetal mean arterial blood pressure fell significantly (27 per cent). There were no significant changes in foetal or maternal pulse rate or acid-base status. Halothane appeared in the foetal blood by two minutes but foetal halothane levels remained significantly lower than maternal for 24 minutes. We conclude that halothane crosses the placenta rapidly and produces a decrease in foetal blood pressure but no change in foetal oxygenation or acid-base status.

Key Words

ANAESTHETICS, VOLATILE: halothane, pharmacokinetics, foetus.

One of the main concerns of using general anaesthesia in obstetrical patients is the effect it may have on the foetus.^{1,2} Several of the general anaesthetic agents have been shown to cross the placenta rapidly³ and prolonged general anaesthesia in the mother results in depression of Apgar scores in the infant.⁴ Certain situations in obstetrics, however, necessitate the use of general anaesthesia. Caesarean Sections where the mother refuses regional anaesthesia, or where regional is contra-indicated, are two examples.

To provide optimum anaesthesia for the mother and avoid depression in the newborn, the placental transfer of anaesthetic agents needs to be understood in more detail. As a first step in this undertaking we have studied the uptake of halothane by the foetus using the pregnant ewe as an animal model.

Method

Six pregnant ewes of 125–135 days gestation (term 150 days) were surgically prepared as follows: under halothane in oxygen anaesthesia with controlled ventilation, polyvinyl catheters were placed in the maternal femoral artery and vein. Through a midline incision the uterus was exposed and a small hysterotomy incision was made. A foetal limb was withdrawn and polyvinyl catheters were placed in the femoral artery and vein and the axillary artery. All incisions were closed and the catheters tunneled subcutaneously to the maternal flank and enclosed in a protective pocket. Each animal was allowed to recover for 24–36 hours prior to a study.

On the day of the study a tracheostomy was performed in the ewe under local anaesthesia. Maternal and foetal mean arterial blood pressure and pulse rate were recorded continuously via the femoral arterial catheters on a Hewlett-Packard multi-channel recorder. Maternal and foetal arterial

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TABLE I Maternal and Foetal Mean Arterial Blood Pressure (MABP) and Pulse Rate Changes expressed as Per Cent Change from Control During Halothane Anaesthesia (1.5 Per Cent Inspired Concentration). (N = 6; Mean $\pm$ S.D.)

		Time (minutes)				
	Control	8	16	32	64	96
<i>Maternal</i>						
MABP	81.3	% -9.2	% -24.7	% -16.8	% -10.0	% -2.4
(Torr)	± 13.2	± 10.3	± 12.5	± 15.4	± 19.4	± 20.3
Pulse Rate	84.5	+18.8	+0.8	-0.9	+2.9	+9.3
(beats/min)	± 9.6	± 20.6	± 5.2	± 5.2	± 26.5	± 31.4
<i>Foetal</i>						
MABP	52.3	-27.1*	-29.2*	-33.0*	-30.7*	-33.9*
(Torr)	± 7.84	± 7.8	± 6.4	± 10.3	± 8.82	± 6.9
Pulse Rate	160.0	+4.1	+4.1	+6.4	-8.2	-4.2
(beats/min)	± 7.35	± 7.8	± 22.8	± 22.0	± 9.3	± 7.1

*p < 0.05

TABLE II Maternal and Foetal Blood Gases and pH Expressed as Absolute Change from Control During Halothane Anaesthesia (1.5 Per Cent Inspired Concentration) (N = 6; Mean $\pm$ S.D.)

		Time (minutes)				
	Control	8	16	32	64	96
<i>Maternal</i>						
pO ₂ (Torr)	414	426	409	403	411	403
	± 25.7	± 9.6	± 73.9	± 75.9	± 31.9	± 32.6
pCO ₂ (Torr)	28.1	27.2	21.6	21.1	26.4	28.4
	± 6.4	± 3.4	± 6.1	± 5.9	± 9.8	± 5.9
pH (Units)	7.50	7.51	7.54	7.60	7.53	7.48
	± 0.10	± 0.05	± 0.20	± 0.12	± 0.05	± 0.07
H ⁺ nanomoles/L	31.6	30.9	34.6	25.1	29.5	33.1
	± 0.79	± 0.89	± 0.63	± 0.76	± 0.89	± 0.85
B. E.	-1.1	+0.3	+0.6	+1.8	+0.8	+1.0
	± 2.9	± 2.5	± 1.2	± 2.5	± 2.9	± 2.7
<i>Foetal</i>						
pO ₂ (Torr)	22.0	21.6	21.6	17.7	20.5	21.7
	± 4.2	± 3.4	± 2.9	± 2.7	± 3.4	± 5.4
pCO ₂ (Torr)	44.1	45.2	40.7	39.6	41.7	50.6
	± 5.8	± 8.8	± 6.6	± 4.9	± 8.8	± 13.2
pH (Units)	7.29	7.31	7.33	7.37	7.34	7.27
	± 0.04	± 0.06	± 0.06	± 0.04	± 0.12	± 0.12
H ⁺ nanomoles/L	51.2	48.9	46.7	42.6	45.7	53.7
	± 0.91	± 0.87	± 0.87	± 0.91	± 0.76	± 0.76
B. E.	-4.3	-3.7	-0.6	-0.8	-1.7	-4.4
	± 3.4	± 3.8	± 8.3	± 2.4	± 2.9	± 6.4

blood gases and pH were measured every 15 minutes on a Corning blood gas analyser.

Each study began with a 30-minute control period with the ewe breathing 100 per cent oxygen. This insured stability of the preparation. Then

halothane, at a constant inspired concentration of 1.5 per cent, was introduced into the maternal breathing circuit. The inspired concentration was monitored on a Beckman infrared analyser.

Maternal and foetal arterial concentration of

TABLE III Maternal and Foetal Halothane Levels During Administration of Halothane at a Fixed Inspired Concentration of 1.5 Per Cent (N = 6; Mean $\pm$ S.D.)

	Time									
	0 min	2 min	4 min	8 min	16 min	24 min	32 min	48 min	64 min	96 min
Maternal arterial concentration Mg/L	0	43.4 ± 18.0	53.0 ± 13.8	92.0 ± 40.5	119.7 ± 40.5	125.2 ± 27.8	141.6 ± 60.5	162.7 ± 69.5	162.8 ± 62.2	168.2 ± 64.5
Foetal concentration Mg/L	0	13.8* ± 6.5	20.2* ± 6.8	35.5* ± 10.2	64.3* ± 11.8	80.0* ± 19.5	88.4 ± 18.5	104.5 ± 24.7	121.4 ± 34.5	111.2 ± 25.3

*p < 0.05

halothane were measured at 2, 4, 8, 16, 32, 48, 64, and 96 minutes of anaesthesia. Maternal samples were drawn from the femoral artery and foetal samples from the axillary artery. The samples were analysed by gas chromatography.⁵

The data for mean arterial blood pressure, pulse rate, pH, and blood gases were analysed by one-way analysis of variance. The unpaired t test was used for maternal and foetal arterial halothane concentrations. A p value of less than 0.5 was considered significant.⁶

Results

Maternal mean arterial blood pressure (MABP) (Table I) tended to decline during the first 24 minutes of the study but the values were not significantly different from control. There was no significant change in pulse rate. Foetal MABP fell significantly, by 27 per cent after eight minutes of halothane anaesthesia and remained decreased throughout the remainder of the study. There was no significant change in pulse rate.

Maternal and foetal blood gases and pH are shown in Table II. There were no significant changes in any of these parameters during the study.

Maternal and foetal arterial halothane concentrations expressed as mg/L are shown in Table III, and graphically as vol.% in Figure 1. Halothane was present in the foetal blood by two minutes but the concentration was significantly lower than maternal for 24 minutes. By 32 minutes, although mean foetal arterial concentrations were lower than maternal, there was no statistically significant difference.

Discussion

Despite a significant fall in foetal MABP during the study, foetal oxygenation and acid-base status

FIGURE 1 Maternal and foetal arterial halothane levels during administration of halothane at an inspired concentration of 1.5 per cent for 96 minutes (N = 6; Mean $\pm$ S.E.)

remained unchanged from the control values. The normal foetal lamb appears to tolerate halothane anaesthesia well.

Halothane rapidly crosses the placenta but equilibrium with the maternal arterial concentrations is not reached until after 24 minutes of anaesthesia. There are several possible explanations for the delay in reaching equilibrium.

First, shunting of blood on both the maternal and foetal sides of the placenta might result in lower foetal concentrations of halothane. This could be considered analogous to V/Q abnormalities in the lung.

Second, the placenta is a very active metabolic organ and uptake of halothane may be considerable. The trophoblastic cells interposed between maternal and foetal blood may act as a large reservoir for halothane.

Third, the measurement of the foetal arterial concentration was from the axillary artery to reflect

levels of halothane going to the foetal brain. Foetal blood coming from the placenta via the umbilical vein traverses the liver prior to entering the arterial system. Uptake of halothane by foetal liver in guinea pigs⁷ has been shown to be extremely high. Uptake by the liver may, in part, account for the lower arterial levels which we found in the arterial blood of the foetal lamb.

Despite the time delay in reaching equilibrium between maternal and foetal arterial halothane concentrations, the foetus is affected by even low levels of halothane. The fall in foetal MABP was significant by eight minutes. This did not impair oxygenation or acid-base status in the normal foetal lamb but this degree of hypotension in a stressed foetus might have deleterious effects. The effects of halothane on the stressed foetus are currently being examined in our laboratory.

Conclusion

In the normal foetal lamb in utero, low levels of halothane produce a significant fall in MABP but no change in pulse rate, oxygenation, or acid-base status. Halothane appears in the foetal circulation within two minutes but equilibrium is not reached until after 24 minutes of halothane anaesthesia.

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Résumé

La résorption d'halotane chez le fœtus normal in utero a été mise en évidence avec notre expérience chez la brebis gravide. Six brebis gravides de 125–135 jours en gestation ont été préparées pour l'opération chirurgicale avec l'anesthésie générale. On a placé des cathéters dans l'artère et la veine fémorales maternelles ainsi que dans l'artère fémorale du fœtus et l'artère axillaire. Chaque brebis pouvait récupérer de 24 à 36 heures avant notre expérience. Le jour de l'expérience, on effectua une trachéotomie et après la période de contrôle, la brebis fut anesthésiée avec 1.5 pour cent d'halotane contenu dans l'oxygène. Pendant la durée de notre étude, la tension artérielle maternelle et celle du fœtus furent mesurées continuellement. Les concentrations simultanées d'halotane du débit artériel maternel et fœtal ont été mesurées afin d'obtenir une courbe de résorption du fœtus. Durant le cours de notre expérience, la tension artérielle moyenne du fœtus baissa de façon significative (27 pour cent). Il n'y a pas eu de changements significatifs de la fréquence du pouls chez la brebis et le fœtus ni de l'équilibre acido-basique. L'halotane passe dans le sang fœtal en deux minutes mais le niveau d'halotane reste significativement plus bas que celui de la brebis. Nous concluons donc que l'halotane passe rapidement dans le placenta et engendre une baisse de la tension artérielle du fœtus. Cependant, on n'observe pas de changements dans l'oxygénation du fœtus ni de l'équilibre acido-basique.