

Safety of cimetidine in obstetric patients¹

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Introduction

There are a number of maternal deaths each year associated with anaesthesia and particularly with the acid pulmonary aspiration (Mendelson's) syndrome. Obstetric patients are particularly at risk because of the potentially large gastric residue of pH below 2.5 (Teabeaut 1952, Taylor & Pryse-Davies 1966).

In 1946 Mendelson, an American cardiologist, published his report on 66 obstetric patients who inhaled gastric contents during the administration of nitrous oxide-oxygen and ether anaesthesia. He described in 40 of these patients the syndrome named after him, prominent features of which are development of an asthmatic-like wheeze, signs of hypoxia, a degree of pulmonary oedema and patchy radiographic changes in the lungs.

Although Mendelson did not report any deaths in these patients, the syndrome has made a major contribution to the maternal death rate in recent years. The 1970-72 report on confidential enquiries into maternal deaths in England and Wales cited 16 deaths associated with inhalation of stomach contents. Fourteen of these were due to Mendelson's syndrome, 3 of the patients having been given Magnesium Trisilicate Mixture (BPC). The more recent report of 1973-75 indicated no improvement in mortality: it recorded 13 deaths, all of patients who had received antacid (Scott 1978).

Teabeaut (1952) showed that a pH below 2.5 was particularly dangerous and that reactions became progressively less severe above this pH. Roberts & Shirley (1974) consider 25 ml may be enough to produce lung damage, although in clinical practice it is difficult to know how much or how little may have been responsible.

There are perhaps two broad approaches which attempt to prevent acid damage to the lungs. One can either attempt to prevent vomitus or regurgitated material reaching the lung or one can attempt to prevent such material damaging the lung if it is aspirated. Fasting is the simplest and most obvious approach but in the obstetric emergency, where gastric emptying is delayed, this is not practical. Emptying the stomach by nasogastric tube or the use of apomorphine are not without their hazards, apart from being objectionable to the patient. In 1961 Sellick described the use of cricoid pressure to occlude the oesophagus at its upper end, but this can make tracheal intubation more difficult.

Attention has turned to preventing lung damage if aspiration should occur. From 1966 onwards the routine use of an oral alkali, such as Magnesium Trisilicate Mixture (BPC), has been advocated (Taylor & Pryse-Davies 1966, Crawford 1971, Moir 1976). A typical regime would be 15 ml administered 2-hourly throughout labour with a 30 ml additional dose prior to induction of anaesthesia. The gastric acidity would be markedly reduced by the neutralizing effect of the alkali. However, the reports already referred to above show that Mendelson's syndrome and death can occur in patients treated thus.

A new approach, which has recently been found of interest, is the use of cimetidine to reduce gastric acidity (Dobb 1978, Husemeyer *et al.* 1978). Cimetidine is a specific competitive histamine H₂-receptor antagonist, without significant interaction at catecholamine β-receptors, histamine H₁ receptors or muscarinic receptors (Parsons 1977). Its principal action is inhibition of gastric acid secretion. This effect is on basal acid secretion as well as either histamine or pentagastrin stimulated secretion. It is widely used, therefore, in conditions

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where a reduction of gastric acid secretion is likely to be of benefit, such as peptic ulceration and reflux oesophagitis.

Histamine H₂ receptors are also found in the myometrium of the uterus, although no significant effects were found in animal reproductive studies (Leslie & Walker 1977). Histamine has a relaxant effect on the uterus, mediated by histamine H₂ receptor, and Blyth (1973) investigated the effect of blocking these receptors in the rat uterus. The possibility that histamine has a direct effect on the contractile elements of the uterus is not supported by his results, the effect being independent of membrane polarization.

This study was designed, therefore, to assess the safety of using cimetidine during labour, with particular reference to uterine tone and the effect on the fetus. The protocol was approved by the local ethical committee. In addition a study was designed to assess the cardiovascular effects of cimetidine in man. This was carried out on patients in an intensive care unit (*see Samuel & Dundee, p 898*).

Methods

A total of 20 patients were studied (Table 1) from one obstetric unit where routine measurement of intrauterine pressure and fetal scalp electrode monitoring during labour is advocated. Patients being monitored thus were given a full explanation of the study, and verbal permission to give cimetidine and draw blood samples was obtained. Obstetric management of the labour and deliveries was at the discretion of the obstetrician in charge. In most cases oxytocin infusions were used.

When labour was established, as indicated by evidence of progress in the first stage of labour with regular contractions, a bolus injection of 200 mg cimetidine was given over 30 seconds. The times between injection and delivery are grouped in Table 2. All the patients were continuously observed for one hour by the author and subsequently by a midwife. Fetal heart rate and maternal intrauterine pressure were measured with a Sonicaid FM3 or FM3R monitor until delivery.

Table 1. Details of cases studied

Average age (years)	26.1 ± 1.1
Average term weight (kg)	73.7 ± 2.0
Primigravida	4●
Parity 1	10
Parity 2 and 3	6
Birth weight (g)	2925-4470

● 2 forceps deliveries, 1 caesarian section

Table 2. Time between intravenous cimetidine 200 mg injection and delivery

	Injection to delivery (hours)			
	<1	1-3	3-8	13
No. of patients	5	9●	5●	1■

● 1 forceps delivery
 ■ Caesarian section

Blood samples (5 ml) were obtained before injection of cimetidine, at delivery and between 2 and 20 hours after delivery. An infant mixed cord blood sample (5 ml) was taken at delivery and a heel-prick sample (0.5 ml) taken to correspond to the maternal post-delivery sample. All these were stored at -20°C as heparinized whole blood for subsequent cimetidine estimations.

Records were kept of the progress of labour and maternal blood loss was measured by collecting blood and clots from the waterproof sheeting. A paediatrician examined the babies at delivery and 24 hours later. The Apgar score was given by allotting 0, 1 or 2 points to heart rate, respiratory effort, muscle tone and reflex irritability (Crawford *et al.* 1973). Colour was not included as it is considered an unreliable parameter.

Results

Cimetidine 200 mg intravenously did not change the pattern of uterine contractions or the course of labour in primigravida or parous patients. The durations of the labours and the degree of blood loss (Table 3) are within the limits of normality (Crawford 1978). There was

no evidence of prolongation of first or second stage of labour or need for intervention for delivery which could be attributed to this drug (Table 4). None of the patients had more than the normally expected blood loss in the puerperium. No transfusions or infusions were necessary.

Table 3. Labour summary

	Primigravida	Parity 1	Parity 2 and 3
1st stage (hours): Average	14	4.5	3.75
Range	7-26	1-11	2-6
2nd stage (min): Average	57	22	20
Range	20-95	15-50	5-25
3rd stage (min): Average	7	7	6
Range	5-10	5-15	5-15
Blood loss (ml): Average	283	266	250
Range	150-500	100-700	50-400

Table 4. Apgar scores at one minute

Score	No. of infants	Comment
5	3	1 forceps delivery—delay 2nd stage of labour 1 umbilical cord around neck
6	8	1 caesarian section—failure to progress in labour 1 loss of beat to beat variation—abnormal placenta 1 forceps delivery—maternal distress 1 infant had transposition of great vessels—died 50 hours
7	8	
8	1	

Figures 1 and 2 show the trace of the fetal heart rate (upper) and uterine tone (lower) in a typical patient before (Figure 1) and after (Figure 2) injection of cimetidine. There was no change in the pattern or strength of contraction and the fetal heart did not show any alterations in rate or pattern. However one of the 20 patients had several bouts of loss of 'beat to beat' variation lasting 5-10 minutes both before and after cimetidine (Table 4).

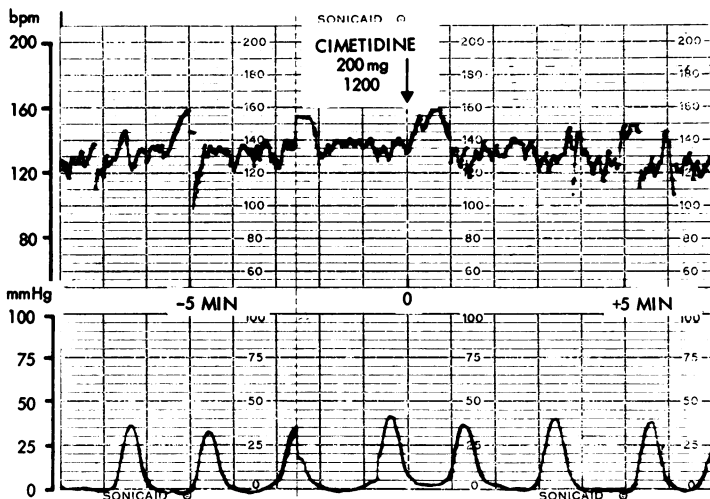


Figure 1. Trace of fetal heart rate and intrauterine pressure 5 minutes before and after intravenous injection of cimetidine 200 mg

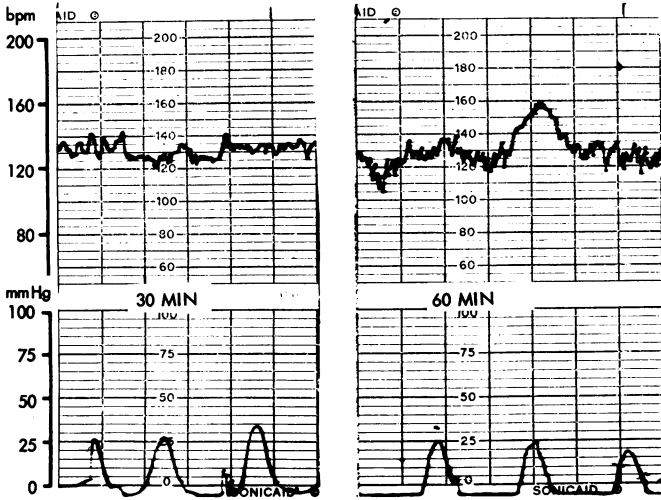


Figure 2. Trace of fetal heart rate and intrauterine pressure 30 and 60 minutes after intravenous injection of cimetidine 200 mg

Apgar scores given by the paediatrician are shown in Table 4. Most of the lower scores were associated with obstetric problems and none of the babies, except one who had transposition of the great vessels, showed any signs of ill effects. All the Apgar scores at 5 minutes were above 7.

Blood levels: Table 5 shows that there was a large scatter in fetal-maternal cimetidine levels at delivery. This could be partly accounted for by the variation in injection to delivery times.

Table 5. Maternal and infant cord blood cimetidine levels ($\mu\text{g/ml}$) at delivery with C/M ratio

Patient	Age (years)	Weight (kg)	Height (cm)	Time from injection (min)	Cimetidine levels ($\mu\text{g/ml}$)		Ratio C/M
					Mother (M)	Cord (C)	
1	25	82	158	185	ND	0.12	—
2	19	74	163	780	0.12	ND	—
3	29	85	162	70	1.14	0.16	0.14
4	26	65	158	435	0.08	ND	—
5	23	64	152	130	0.34	0.12	0.35
6	20	62	158	40	9.65	0.77	0.08
7	32	75	159	125	1.18	0.05	0.04
8	27	65	161	430	0.16	0.05	0.31
9	27	83	164	160	0.57	0.23	0.40
10	25	64	154	50	2.18	0.26	0.12
11	25	95	173	120	1.91	0.41	0.21
12	29	79	168	5	12.19	1.22	0.10
13	18	66	152	265	0.36	0.12	0.33
14	28	85	173	100	0.39	0.24	0.61
15	19	76	168	285	0.24	0.26	1.08
16	26	66	156	60	1.23	0.84	0.68
17	38	80	172	440	0.80	0.16	0.20
18	23	68	157	105	0.91	0.73	0.80
19	31	70	162	55	2.47	1.08	0.44
20	32	70	164	190	0.49	0.35	0.71

ND = none detected

In 12 patients post-delivery samples were obtained (Table 6). These show that, except in one mother and baby (patient 14) and one other baby (patient 13), cimetidine is not detectable after 19 hours from injection. Comparing the infant 'heel-prick' sample with that at birth indicates that a fall in cimetidine levels from birth occurred in all cases except one (patient 14). The fall was not as great as that found in the mothers.

Table 6. Maternal and infant heel prick cimetidine levels ($\mu\text{g/ml}$) at various times from delivery

Patient	Time from delivery (hours)	Time from injection (hours)	Cimetidine levels ($\mu\text{g/ml}$)		Ratio I/M
			Mother (M)	Infant (I)	
7	18	20	ND	ND	—
8	12	19	ND	ND	—
9	19	22	ND	ND	—
10	21	22	ND	ND	—
12	19	19	ND	ND	—
13	18	22	ND	0.25	—
14	18	20	0.06	0.20	3.33
15	14	19	ND	ND	—
16	4	5	<0.05	<0.05	—
18	2	4	0.37	0.70	1.89
19	2	3	0.74	1.0	1.35
20	2	5	0.16	<0.05	—

ND = none detected

Discussion

The normal pattern for labour has been divided into three stages. During the first stage of labour the cervix effaces and progressively dilates with each uterine contraction until full dilatation is reached. This, the longest phase of labour, is usually longer in the primigravida as, in fact, are all the stages. The second stage of labour, parturition, combines maternal effort and uterine contractions to expel the baby from the uterus. The 'birth' of the placenta follows, after a brief delay, thus forming the third and final stage of labour.

During this study cimetidine did not have a significant effect on the contractility of the uterus during any of the three stages of labour or in the immediate post-delivery period, when it is important that good uterine tone is present to minimize blood loss. Blocking histamine H_2 receptors in the rat uterus did not affect the contractility of the myometrium (Blyth 1973). It would seem that the same holds for the human myometrium, or else cimetidine in the doses used in this study was insufficient to effect a blockade.

Fetal scalp electrode monitoring is now a recognized procedure in the obstetric management of labour. The normal fetal heart rate should be 120–160 beats per minute, with no change during contractions of the uterus and a normal 'beat to beat' variation of greater than 5 beats/min (Filshie 1974). All these criteria were observed in each of the 20 patients except for occasional loss of the 'beat to beat' variation in one patient. As this patient had an abnormal placenta and the changes were seen before as well as after the cimetidine injection, it would seem reasonable to suggest that cimetidine has no significant effects on the fetus. This can be further supported by Apgar scores at birth.

Cimetidine crosses the placenta and the variation in the levels found in the mothers and babies at birth merely reflects the variation in time intervals from injection. The numbers of infants in this study with detectable amounts of cimetidine found in the post-delivery sample are insufficient for conclusive comment. However there is in most cases a fall in cimetidine levels after birth. In one patient (13) there was a rise in the infant cimetidine plasma levels after birth which is difficult to explain. A larger number of 'early' samplings will be necessary to elucidate these findings and this work is presently being done. The small volume of blood obtained at a heel-prick sampling may also have a bearing on the accuracy of the analysis.

These findings suggest that further studies of cimetidine in obstetric patients would be safe in so far as labour and the birth of a healthy baby are concerned. It should be pointed out that cimetidine given as it was in this study will not affect the pH of gastric juices already in the stomach. Perhaps a suitable regime for oral cimetidine, with or without metoclopramide, will put Mendelson's syndrome into the history books and out of current literature and statistics.

Summary

Cimetidine has been suggested as a new approach to the prevention of the acid pulmonary aspiration syndrome in obstetric anaesthesia. In 20 patients in labour cimetidine 200 mg intravenously did not prolong labour or alter the pattern or strength of uterine contractions. The fetal heart rate did not show any alteration in rate or pattern and it was confirmed that cimetidine crosses the placenta. These findings suggest that further studies of cimetidine in obstetric patients would be safe.

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