Does halothane anaesthesia decrease the metabolic and endocrine stress responses of newborn infants undergoing operation?

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Abstract

Concern about the side effects of various anaesthetic agents in newborn infants has led to the widespread use of anaesthesia with unsupplemented nitrous oxide and oxygen with muscle relaxants in such patients. To investigate the efficacy of such a regimen 36 neonates undergoing operations were randomised to two groups: one group received anaesthesia with nitrous oxide and curare alone and the other was additionally given halothane. Concentrations of metabolites and hormones were measured before and at the end of operation and at six, 12, and 24 hours after operation and the values compared between the two groups. Neonates given halothane anaesthesia showed decreased hormonal responses to operation, with significant differences between the two groups in the changes in adrenaline, noradrenaline, and cortisol concentrations and the ratio of insulin to glucagon concentration. Changes in blood concentrations of glucose and total ketone bodies and plasma concentrations of non-esterified fatty acids were also decreased in neonates receiving halothane anaesthesia. Neonates given anaesthesia with unsupplemented nitrous oxide showed significantly greater increases in the urinary ratio of 3-methylhistidine to creatinine concentration and their clinical condition was also more unstable during and after operation.

Unless specifically contraindicated potent anaesthesia with halothane or other anaesthetic agents should be given to all neonates undergoing surgical operations as it decreases their stress responses and improves their clinical stability during and after operation.

Introduction

The use of halothane anaesthesia for newborn infants undergoing operation has been controversial. Initially it was recommended widely,¹ although early studies suggested that neonates required a higher concentration to achieve anaesthesia than older children and adults.^{2,3} At these higher concentrations its margin of safety was narrow,^{4,5} so that the combination of nitrous oxide and oxygen and curare became the recommended anaesthetic regimen for newborn babies.⁶ More recently, however, studies have shown that newborn infants were given unnecessarily high concentrations of halothane,⁷ so the complications documented previously may have been the effects of overdosing.

No previous study has examined comprehensively the metabolic and endocrine effects of the currently recommended doses of

halothane or whether potent anaesthesia with halothane confers any advantage over nitrous oxide and curare alone. We found that anaesthesia with fentanyl in preterm neonates decreases their stress responses to operation and may improve the postoperative clinical outcome.⁸ We report here a randomised controlled trial, which was performed concurrently with the trial of fentanyl and was designed to investigate whether the stress responses of neonates given anaesthesia with halothane were any different from those of neonates given conventional anaesthesia with nitrous oxide and curare.

Patients and methods

We obtained written parental consent, after the parents had been fully informed, and the approval of the Central Oxford Research Ethics Committee to study 36 neonates (27 born at term and nine prematurely) undergoing operation (tables I and II). None of the neonates had experienced

TABLE I—Details of neonates studied according to anaesthetic group. Values are means (SEM)

	Group receiving halothane (n=18)	Group not receiving halothane (n=18)
Age at operation (days)	24 (5)	17 (4)
Gestation (weeks)	37 (1)	38 (1)
Birth weight (g)	2800 (300)	2800 (200)
Weight at operation (g)	3100 (300)	2900 (200)
Dextrose infusion (mg/kg/min)	4.8 (0.4)	4.8 (0.2)
Time before operation without food (h)	6.0 (0.4)	6.0 (0.4)
Temperature loss (°C)	0.7 (0.2)	0.8 (0.2)
Dose of tubocurarine chloride (mg/kg)	0.43 (0.06)	0.66 (0.07)*

* $p < 0.025$, Mann-Whitney U test.

TABLE II—Diagnosis and operation performed for 36 neonates studied. Values are numbers of infants

	Group receiving halothane	Group not receiving halothane
Pyloric stenosis; pyloromyotomy	5	4
Inguinal hernia; herniotomy	3	3
Defect of abdominal wall; repair	3	3
Oesophageal atresia; anastomosis and repair	2	2
Diaphragmatic hernia; repair	1	1
Intestinal obstruction; resection and anastomosis	2	1
Imperforate anus (high); colostomy	2	2
Tracheo-oesophageal fistula; gastrostomy		1
Meningomyelocele; closure		1

haemorrhage, trauma, hypothermia, or hypoxia during the 72 hours before operation. Feeds were withheld for six hours before surgery, and an intravenous dextrose infusion was maintained at 4-6 mg/kg/min throughout the period of the study. Blood (1-2 ml) was sampled just before the induction of anaesthesia, at the end of the operation, and at six, 12, and 24 hours after the operation. Intramuscular morphine injections were prescribed after the operations by clinical staff who were unaware of which anaesthetic had been given to the infants; the timing of the injection was such that morphine was not injected during the two hours before blood samples were taken. Urine was collected during the second 12 hours of each of the three days after operation.

Analytical methods—Blood concentrations of glucose, lactate, pyruvate,

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acetoacetate, 3-hydroxybutyrate, alanine, and glycerol were measured by specific enzymatic methods⁹; plasma insulin¹⁰ and glucagon¹¹ concentrations by radioimmunoassay techniques; and plasma adrenaline and noradrenaline concentrations by a double isotope radioenzymatic assay.¹² Steroid hormones (aldosterone, corticosterone, 11-deoxycorticosterone, progesterone, 17-hydroxyprogesterone, 11-deoxycortisol, cortisol, and cortisone) were isolated by automated Sephadex LH-20 chromatography and concentrations measured by specific radioimmunoassays.¹³ Concentrations of 3-methylhistidine and creatinine in urine were measured by a fluorometric¹⁴ and Jaffe rate colorimetric method, respectively, with autoanalysers; the molar ratio of the two concentrations was then calculated.

Trial design and analysis—Neonates undergoing operation were randomised to two groups, both of which were given curare (0.4 mg/kg) and 50% nitrous oxide in oxygen; one group was given halothane in addition (1.2% for induction, 0.5–1.0% for maintenance). A schedule for balanced randomisation in blocks was prepared by the National Perinatal Epidemiology Unit, Oxford, which was retained by the unit until the trial was completed. Four index variables were selected to test the hypothesis, and the standardised difference between groups was calculated for each variable on the basis of previous studies and clinical relevance.¹⁵ Using these standardised differences (plasma adrenaline concentration 0.95, plasma noradrenaline concentration 1.00, blood glucose concentration 1.05, and the urinary ratio of 3-methylhistidine to creatinine 0.95) the sample size required to give 80% power to the trial (at $p < 0.05$) was calculated from a standard nomogram.¹⁵ The anaesthetic protocol was deviated from two cases in each randomised group: pancuronium bromide or atracurium besylate was given instead of curare to two neonates in the group receiving halothane, and thiopentone sodium was given to induce anaesthesia in two neonates in the other group. Despite these alterations data from all neonates were included in the statistical analysis. Non-parametric tests were used for statistical comparison of the two study groups. The responses of the neonates were characterised by the changes in the concentration of each hormone or metabolite from its preoperative value. For clarity all data are presented as means (SEM).

Results

Hormonal changes—There was no significant difference between the two groups in any of the plasma hormone concentrations measured before operation. Plasma adrenaline concentrations increased during operation to a greater extent in the group that did not receive halothane ($p < 0.05$); this difference was not maintained postoperatively (fig 1). Noradrenaline concentrations in the group that did not receive halothane were three times higher during operation than those in the group that received halothane ($p < 0.005$), but no significant differences were observed after operation

FIG 1—Comparison of mean (SEM) changes in plasma adrenaline and noradrenaline concentrations between group receiving halothane (●—●) and group not receiving halothane (○—○). * $p < 0.05$, ** $p < 0.005$ By Mann-Whitney U test.

FIG 2—Comparison of mean (SEM) changes in plasma cortisol, insulin, and glucagon concentrations and ratio of insulin to glucagon concentration between group receiving halothane (●—●) and group not receiving halothane (○—○). * $p < 0.05$ By Mann-Whitney U test.

TABLE III—Hormonal and metabolic changes observed at end of operation: 95% confidence intervals

Variable	Group receiving halothane	Group not receiving halothane	Level of significance (p value)
Adrenaline (nmol/l)	-1.43 to 3.15	-0.31 to 3.43	<0.05
Noradrenaline (nmol/l)	-6.02 to 8.12	-3.19 to 9.89	<0.005
Cortisol (nmol/l)	-107 to 953	3 to 1267	<0.05
Insulin (pmol/l)	-82 to 142	-41 to 113	NS
Glucagon (pmol/l)	-3.0 to 6.4	-10.7 to 16.3	NS
Glucose (mmol/l)	0.4 to 10.4	3.9 to 10.1	<0.025
Alanine (mmol/l)	0.02 to 0.10	-0.03 to 0.04	<0.01
Non-esterified fatty acids (mmol/l)	-0.03 to 0.37	0.36 to 1.34	<0.01
Total ketone bodies (mmol/l)	-0.16 to 0.34	-0.08 to 0.54	<0.02

(fig 1). Plasma cortisol concentrations increased during operation in both groups, but this response was significantly greater in the group that did not receive halothane at the end of and at 12 hours after operation ($p < 0.05$ for both) (fig 2). Plasma insulin concentration increased during operation in both groups; this increase was significantly greater six hours after operation in the group that did not receive halothane ($p < 0.05$). Although there were no significant differences in the effects on plasma glucagon concentration between the two groups, the ratio of insulin to glucagon concentration decreased during operation in the group that did not receive halothane and was unaltered in the group that received halothane, with a significant difference at the end of operation ($p < 0.05$) (fig 2). No significant differences were observed between the two groups with regard to changes in the other steroid hormone concentrations measured.

Metabolic changes—Hyperglycaemic responses of neonates in the group not receiving halothane were significantly greater than those in the group receiving halothane at the end of operation ($p < 0.025$), but no differences were observed postoperatively (fig 3). There were no significant differences between the two groups with regard to changes in blood concentrations of lactate, pyruvate, and glycerol and plasma concentrations of triglycerides during or after operation. Concentrations of total ketone bodies increased during operation in the group not receiving halothane and were unchanged in the other group, with a significant difference at the end of operation ($p < 0.02$). Increases in plasma concentrations of non-esterified fatty acids were significantly higher in the group not receiving halothane than in the other group at the end of and six hours after operation ($p < 0.01$ and $p < 0.05$, respectively). Plasma alanine concentration increased during operation in the group receiving halothane and was unchanged in the other group, with significant differences at the end and six hours after operation ($p < 0.01$ and

FIG 3—Comparison of mean (SEM) changes in blood concentrations of glucose, alanine, and total ketone bodies and plasma concentrations of non-esterified fatty acids between group receiving halothane (●—●) and group not receiving halothane (○—○). * $p < 0.05$, ** $p < 0.025$, *** $p < 0.01$ By Mann-Whitney U test.

FIG 4—Comparison of mean (SEM) changes in urinary ratio of 3-methylhistidine to creatinine between group receiving halothane (●—●) and group not receiving halothane (○—○). * $p < 0.05$, ** $p < 0.01$ By Mann-Whitney U test.

$p < 0.02$, respectively) (fig 3). Table III lists the confidence intervals for the hormonal and metabolic changes observed at the end of operation in the two groups.

Urinary nitrogenous constituents—The urinary ratio of 3-methylhistidine to creatinine was similar in the two groups on the day after operation; it increased significantly in the group that received unsupplemented nitrous oxide and curare on the second and third days after operation ($p < 0.05$ and $p < 0.01$, respectively) but was unchanged in the group that received halothane.

Clinical observations—The clinical course of babies in the group not receiving halothane was unstable compared with that of babies in the group

receiving halothane. Before operation the mean (SEM) heart rate was 139 (2) beats/minute in the group that did not receive halothane compared with 149 (3) in the group that did ($p < 0.05$). Infants in the group that did not receive halothane had significantly higher heart rates during surgery, the mean (SEM) maximum heart rate being 204 (4) beats/minute in this group and 174 (3) beats/minute in the other ($p < 0.01$). The mean (SEM) minimum heart rate during operation did not differ significantly between the two groups, being 116 (8) beats/minute in infants who did not receive halothane and 131 (7) beats/minute in those who did. Neonates who did not receive halothane developed respiratory and cardiovascular instability postoperatively (table IV). No complications were observed in 13 of the neonates in the group receiving halothane and in four of those in the group that did not.

TABLE IV—Postoperative complications according to anaesthetic group. Values are numbers of infants

Complication	Group receiving halothane	Group not receiving halothane
Persistent tachycardia*		8
Increased respiratory support†	2	5
Spontaneous bradycardias	2	6
Poor peripheral circulation		1
Gastric bleeding	1	4
Metabolic acidosis		2
Paralytic ileus		2
Oliguria		2

*Heart rate > 200 beats/min during and after operation in the absence of appreciable blood loss.

†Infants needed increased oxygen or mechanical ventilation.

Discussion

We previously showed appreciable hormonal and metabolic changes in term and preterm neonates subjected to operation with unsupplemented nitrous oxide as the anaesthetic agent, which indicated catabolism and mobilisation of metabolic substrates during and after surgical operations.¹⁶ Such changes may be disadvantageous for newborn infants, who have a precarious metabolic balance and limited metabolic stores; in addition, the metabolic demands for rapid growth and organ maturation are high during the neonatal period. We have also shown that potent anaesthesia with a narcotic agent (fentanyl) in preterm neonates can reduce their stress response to operation.⁸ This trial was designed to determine whether similar effects can be obtained with an inhalational anaesthetic agent and was performed concurrently with the fentanyl trial.

The neonates randomly allocated to the two groups were similar in their characteristics; they received the same clinical management perioperatively and underwent a similar degree of operative stress (table II). The important difference between the two groups was the inclusion of halothane in the anaesthetic regimen of one group. As previously described,^{6,17} neonates in the group not receiving halothane required a significantly higher dose of curare than the neonates whose anaesthesia was supplemented by halothane. Nevertheless, this difference would not affect an investigation of the overall hypothesis as the present trial was designed to compare "a policy of giving halothane and nitrous oxide" with "a policy of giving nitrous oxide alone" (the policy of giving nitrous oxide alone being associated with the use of comparatively larger doses of muscle relaxants).¹⁸

The most prominent difference in the hormonal responses between the two groups was the changes in catecholamine concentrations during operation. Neonates in the group that received unsupplemented nitrous oxide showed changes in adrenaline and noradrenaline concentrations that were two and three times greater than the changes seen in neonates in the group receiving halothane. Potent anaesthesia with halothane was probably responsible for reducing these changes in catecholamine concentrations, as has been observed in animal studies^{19,20} and adult patients.²¹ Similarly, the changes in cortisol concentrations in the group not given halothane were significantly greater than those in the group given

halothane at the end of operation and 12 hours later. A similar though non-randomised study in older infants (mean age 7.3 months) also showed that changes in cortisol concentration were significantly greater in infants given nitrous oxide anaesthesia than in infants given halothane and nitrous oxide.²² That study also included seven neonates given nitrous oxide anaesthesia, and although the magnitude of the changes in plasma cortisol concentrations was similar to that in our study, the changes were not significant owing to the small number of patients studied and wide variation in the data.²² In a recent study significant changes in cortisol concentration were observed in neonates and infants undergoing various operations.²³ These data and our results indicate that changes in cortisol concentration in neonates were greater in magnitude but shorter in duration than those in adult patients undergoing similar operations.²⁴ The metabolic effects of cortisol release may be greater than expected as the proportion of cortisol not bound to protein increases during operation²⁵; this effect may be accentuated by the lower plasma transcortin concentrations in neonates than in adults.²⁶

Plasma insulin concentrations increased in response to operative hyperglycaemia in both groups, but six hours after operation the insulin response was greater in the group that was not given halothane. This difference could have resulted either from the stimulatory effect of the hyperglycaemia, which was significantly greater in the group not receiving halothane, or from the direct inhibition of insulin secretion by halothane anaesthesia.²⁷ The ratio of insulin to glucagon concentration, however, decreased during operation in the group that did not receive halothane, whereas it was unchanged in the group that did. For metabolic regulation, changes in this ratio are of greater importance than changes in the individual hormone concentrations, and its reduction would probably lead to a catabolic milieu during and after operation.²⁸ These differences in the effects on catecholamine and cortisol concentrations and the ratio of insulin to glucagon concentration would probably account for the differences between the two groups in their metabolic responses.

The hyperglycaemia observed in both groups of neonates at the end of operation was probably precipitated by release of adrenaline during the operation and potentiated by the changes in glucagon and cortisol concentrations.¹⁵⁻²⁹ Also, differences in the hyperglycaemic response between the two groups may be explained by the significantly greater increases in plasma adrenaline and cortisol concentrations in the group that did not receive halothane as well as the decrease in the ratio of insulin to glucagon concentration. A greater albeit similar suppression of the hyperglycaemic response to operation was observed in preterm babies given anaesthesia with fentanyl.⁸

Blood lactate and pyruvate concentrations increased during operation in both groups probably because of glycogenolysis in skeletal muscle stimulated by adrenaline and increased glycolysis in injured tissues.³⁰ Alternatively, a decreased rate of gluconeogenesis in liver cells³¹ or a decreased hepatic blood flow during halothane anaesthesia³² may contribute to an accumulation of gluconeogenic substrates. If these experimental findings apply to newborn infants gluconeogenesis may be inhibited by halothane either directly or indirectly by a decrease in hepatic blood flow, which would explain the slower disappearance of gluconeogenic substrates after operation in the group receiving halothane. These effects seemed transient as gluconeogenic substrate concentrations had reverted to pre-operative values by six hours after operation.

Plasma concentrations of non-esterified fatty acids increased substantially during operation in the group receiving unsupplemented nitrous oxide and remained high six hours postoperatively, whereas only a marginal response was observed in the group receiving halothane. These responses indicate a greater degree of lipolysis, probably mediated by the considerable release of catecholamines and decrease in the ratio of insulin to glucagon concentration during operation in the group that did not receive halothane. Concentrations of total ketone bodies were also increased in this group, which may be related to the greater changes in catecholamine and glucagon concentrations in these neonates.³³ We investigated breakdown of endogenous protein by measuring the

urinary ratio of 3-methylhistidine to creatinine, which increased significantly in the group receiving unsupplemented nitrous oxide and was unchanged in the group receiving halothane. Although changes in this ratio may not specifically represent breakdown of skeletal muscle, its increase is associated with a negative nitrogen balance, weight loss, and poor clinical condition in newborn infants.³⁴

Although neonates in the group receiving halothane had a significantly higher heart rate before operation, the heart rate increased considerably during the operation in the other group, possibly because of release of catecholamines. The clinical condition of the neonates in the group that did not receive halothane was also more unstable than that in the other group (table IV).

Further clinical implications arise from our study. It is believed widely that perception, discrimination, and localisation of pain may not be developed in newborn babies, mainly because of the lack of myelination in their central nervous systems. Neuroanatomical data from the collaborative perinatal project (of the National Institute of Neurological and Communicative Disorders and Stroke show conclusively, however, that the nerve tracts associated with nociception are fully myelinated up to the thalamus by 31 weeks of gestation and up to the cerebral cortex by 37 weeks.³⁵ This and other traditional arguments for the lack of perception of pain in neonates can be refuted: neuroanatomical evidence and the observed metabolic responses indicate that noxious stimuli are transmitted centrally and hence may be perceived.³⁶ Our studies show that anaesthesia with nitrous oxide and oxygen alone is less satisfactory in reducing the metabolic and endocrine stresses of operation than anaesthesia with nitrous oxide and oxygen supplemented by potent agents.¹⁵⁻¹⁶ We advocate such supplements for all neonatal anaesthesia unless there are specific contraindications to their use. We further suggest that the effectiveness of analgesia and anaesthesia, particularly in paralysed and ventilated neonates, can be established only by measuring the circulating concentrations of metabolic fuels and hormones.

In conclusion, our study has confirmed previous observations that newborn infants show substantial metabolic and endocrine stress responses to operation. On the basis of preselected criteria our randomised trial has rejected the hypothesis that halothane anaesthesia does not alter the hormonal and metabolic stress responses of newborn infants subjected to operation. We recommend that greater attention should be paid to using effective analgesia and anaesthesia in newborn infants undergoing not only operations but other invasive medical procedures during intensive care. Clearly, the therapeutic management of painful experiences in neonates and children is an important topic for future research.

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ONE HUNDRED YEARS AGO

It is a question of much interest and importance whether the great material progress of the present century has been accompanied by any corresponding moral advance. That we have made immense strides in wealth and luxury, in scientific and industrial development, in all the arts and inventions that contribute to ease and comfort, is a commonplace and unquestionable statement. It is more open to debate whether the tone of public morality has risen, and whether vice and crime have undergone any notable diminution. There are not wanting those who regard the growth of great cities—that striking and essential feature of modern civilisation—as conducive to moral degeneracy, and preach a reversion to simple modes of life as a necessary condition of the preservation of a high tone of national character. Much of the argument on this subject is conducted by those who prefer vague declamation to scientific induction, and hence the question has been obscured by rhetorical exaggeration, and often argued with a notable disregard of fact. Let us briefly consider the subject, and, shunning hypotheses however attractive, look strictly to evidence that is incontrovertible.

In proof that the material progress of the century has had a correlative moral advance, we can point to a diminished and steadily declining consumption of intoxicants, and to a notable improvement in the views generally held upon the liquor question. In the last century drunkenness was not regarded as a degrading vice, and hardly constituted a detraction from the character of the fine gentleman. Now the drunkard is held to be scarcely fit for decent society, and even the tippler is rightly viewed as one to be sedulously shunned. Not less encouraging is the altered tone of public opinion regarding such cruel and demoralising pastimes as pugilism and cock-fighting. These are still, no doubt, practised, but scarcely a voice is now raised in their defence.

A welcome addition to the statistics of public morals is afforded by Sir Edmund Du Cane in an article upon Crime and Criminals published some time ago in *Murray's Magazine*. Taking the year of the Queen's accession and that of her Jubilee as a basis for comparison, he is able to point to a highly satisfactory, and, indeed, surprising, diminution in crime. In spite of the fact that the population has almost doubled during this period, we find that the convicts of all classes in the year 1887 were only about one-fifth of their number in 1837. If we compare the sentences to transportation in 1837 with those to penal servitude in 1887, the contrast is only a little less encouraging, the figures being for the former year 3,785, and for the latter 910. The number of executions in 1837 (including those carried out in the colonies) Sir E. Du Cane puts at 46, while for the five years ending 1886 the average was only 14. In addition to these statistical facts, he points out that highway robbery, once very common, is now practically unknown, and that

smuggling, from being one of the most frequent, has become one of the rarest of offences. Surely the most confirmed pessimist or the most persistent *laudator temporis acti* can hardly study such facts and continue to deny to this age the credit of growth in morals.

While facts such as the above are beyond dispute, their explanation is more open to casuistry. Sir Edmund assigns the chief credit to the efforts made by benevolent societies to aid discharged prisoners in obtaining honest work, to the beneficial influence of reformatories and industrial schools, and to the gradual spread of education. We have no doubt all these causes, and others, have been in operation. In spite of occasional discouraging signs, we believe that this age has been one of great moral and religious progress all along the line, and that a great advance is constantly being made towards those

Sweeter manners, purer laws,

of which the Laureate sings. How far the work of the churches and of benevolent societies has co-operated with wise legislation and private philanthropic efforts it is not our province to seek to determine, but the general conclusion remains certain.

As regards the most efficient means of dealing with crime *per se*, two points require to be kept in view, namely, that the natural tendency of blind social forces, unless wisely counteracted, is to keep criminal the man who has once fallen into crime, and to cause the offspring of criminals themselves to drift into a criminal life. Of the two problems, the preservation of the young from their threatened evil destiny is undoubtedly much the easier of solution. Hence, the great importance of reformatories and industrial schools, which tend to divert the current of crime at its very source. Heredity is, doubtless, strong, and the children of thieves and vagabonds come into the world heavily handicapped; but there is no reason to doubt that due restraint timely employed, proper education, and the opening up of honourable careers, have been, and are, most efficient means for cutting off the supplies from the criminal market.

The reform of the hardened criminal is a more difficult matter, but without going into other matters, it is certainly essential that we should not regard the man who has once fallen into crime as hopelessly depraved, and that we should afford him the chance of reformation. Such is the aim of the various charitable organisations, which recognise that society has not done its duty to the criminal when it has merely punished him, however deservedly, and that after punishment comes the not less imperative duty of opening up the way to a return to honesty and purity of life.

(*British Medical Journal* 1888;i:543)