

Clinical Evidence Article

Is isoflurane safer than halothane in equine anaesthesia? Results from a prospective multicentre randomised controlled trial

G. M. JOHNSTON^{†‡}, J. K. EASTMENT^{†§}, P. M. TAYLOR^{†#} and J. L. N. WOOD^{*§}

[†]Department of Clinical Veterinary Medicine, University of Cambridge, Cambridgeshire CB3 0ES and [§]Epidemiology Unit, Animal Health Trust, Lanwades Park, Kentford, Suffolk CB8 7UU, UK.

Keywords: horse; equine; anaesthesia; halothane; isoflurane; perioperative death

Summary

Reasons for performing study: Approximately 1 in 100 horses suffer unexpectedly from anaesthetic-related death. Identification and use of the safest anaesthetic drugs should support this aim. Experimental evidence has suggested that isoflurane should be a safer maintenance agent in equine anaesthesia than halothane.

Hypothesis: The death rate would be reduced in horses being maintained with isoflurane compared to halothane.

Methods: A multicentre randomised controlled trial was undertaken to compare the effects of isoflurane and halothane for maintenance of equine anaesthesia for all types of operation. Data were analysed from 8242 horses in which anaesthesia was maintained with either halothane or isoflurane using mixed effects logistic regression models.

Results: No overall benefit of either drug was detected. However, although not part of the primary hypothesis, data showed that the overall death rate was significantly reduced in horses age 2–5 years with isoflurane and that death from cardiac arrest was also reduced with isoflurane, particularly in high risk cases.

Conclusions and potential relevance: Halothane remains an acceptable anaesthetic for maintenance of anaesthesia in horses, but isoflurane may be safer in the young horse and in high risk cases.

Introduction

It has been recognised for many years that equine anaesthesia carries a high risk of unexpected death; around 1 in 100 horses die from unforeseen causes within 7 days of an anaesthetic (Johnston *et al.* 1995, 2002). This figure compares with 1/10,000 in man (Lunn and Mushin 1982) and 1/600–1000 in dogs or cats (Clarke and Hall 1990; Dyson *et al.* 1998). A large-scale observational study of equine anaesthetic fatalities conducted over 6 years identified several important risk factors for operations other than emergency abdominal surgery (Johnston *et al.* 2002). These

included age, operation type, time of surgery and drugs used for premedication, induction and maintenance of anaesthesia. Inhalational anaesthetic induction and maintenance, night-time and weekend operations and fracture repairs were associated with increased risk. After the first 6 months of life, risk increased with age of horse and was reduced significantly in animals maintained under total i.v. anaesthesia (TIVA) (Johnston *et al.* 2002).

During the original observational study (Johnston *et al.* 2002), the most common agent used for maintenance of anaesthesia was halothane although, in the latter stages of data collection, isoflurane was licensed in the UK as an alternative inhalational anaesthetic agent. Experimental evidence suggested that isoflurane has cardiovascular benefit over halothane (Steffey and Howland 1980; Whitehair *et al.* 1996; Grosenbaugh and Muir 1998; Grubb *et al.* 1999; Rasis *et al.* 2000). However, no significant difference was found in the observational study (Johnston *et al.* 2002) between mortality rate in animals maintained on isoflurane compared to those on halothane (odds ratio [OR] = 1.66, 95% confidence interval [CI] = 0.7–3.6). The observational study of Johnston *et al.* (2002) was not specifically designed to determine the differences in risk associated with the use of these 2 maintenance agents. Indeed, there was some indication that, probably because of experimental evidence, horses perceived as being at higher risk were more likely to be given isoflurane.

It has long been recognised in human and veterinary medicine that differences in the efficacies or safety of 2 or more interventions (including both treatment and prophylactic care) can only be determined using randomised controlled trial methodologies (Pocock 1983), principally due to the problems of observer bias and confounding in observational studies. While randomised controlled trials are now regularly undertaken in human medicine, they are still relatively rare in veterinary medicine (e.g. Morley *et al.* 1999; Littlewood *et al.* 1999).

In the light of numerous reports in the literature showing the range of benefits of isoflurane compared to halothane under laboratory conditions (Steffey and Howland 1980; Whitehair *et al.* 1996; Grosenbaugh and Muir 1998; Grubb *et al.* 1999; Rasis *et al.* 2000), there was a need for a randomised controlled trial to compare

*Author to whom correspondence should be addressed. Present addresses: [‡]Vetstream Ltd, Three Hills Farm, Bartlow, Cambridgeshire CB1 6EN and [#]Taylor Monroe, Downham Market, Ely, Cambridgeshire CB6 2TY, UK.

[Paper received for publication 06.08.03; Accepted 03.10.03]

the 2 anaesthetic agents in equine clinical practice. Isoflurane had an equine product licence in the USA many years before the UK but, despite the high risk of general anaesthesia in equidae and the need to evaluate the real benefit, no randomised controlled trial comparing the 2 volatile agents had been carried out. A number of small, single clinic studies have not shown any clinical benefit of isoflurane (Dunlop *et al.* 1987; Harvey *et al.* 1987; Daunt *et al.* 1992; Ripoll *et al.* 2000). As data on perianaesthetic deaths were becoming available (Johnston 2000), isoflurane was licensed for use in horses in the UK. Therefore, it seemed highly appropriate to undertake a randomised trial of its use in horses.

We undertook a randomised controlled comparison of isoflurane and halothane in general equine practice to determine whether or not the use of either drug was associated with a reduced death rate. The study reported here was primarily UK-based, although some US clinics also participated. The study was designed to test the primary hypothesis that the use of isoflurane as a maintenance agent in equine anaesthesia was associated with a 50% reduction in risk of mortality. We were also interested in comparing rates of specific causes of death, particularly as the reported beneficial effects of isoflurane principally involved the cardiovascular system (Steffey and Howland 1978, 1980). This paper reports the results of this trial, which we conducted on 8990 horses. The CONSORT statement (Moher *et al.* 2001) has been followed in reporting the clinical trial.

Materials and methods

Objectives

A prospective randomised controlled comparison of isoflurane and halothane used for maintenance of anaesthesia in equine veterinary practice was performed, sufficient in size to detect a 50% reduction in the perioperative death rate (within 7 days of the anaesthetic) in horses receiving isoflurane. Secondary objectives were to consider specific causes of death as well as perioperative complications.

Design

The study was a prospective, multicentre, randomised controlled trial conducted in a 'convenience' sample of 35 equine surgical clinics in 7 countries. Clinics initially agreed to enter into the trial all equidae intended for any operation under general anaesthesia with inhalational maintenance. Data were collected between May 1997 and September 1999.

Randomisation

Horses were randomised immediately prior to induction of anaesthesia to receive either isoflurane or halothane for maintenance. The study managers provided participating clinics with a series of sequentially numbered opaque sealed envelopes revealing which volatile anaesthetic agent was to be used on each horse. Premedication and induction agents were chosen and recorded by the responsible clinician unless anaesthesia was induced with an inhalational agent, in which case the allocated maintenance agent was used for induction.

Data

Clinics completed one-line diaries for each general anaesthetic episode. Information recorded included the sequential number

(shown on the envelope containing the randomisation information) date, time and type of operation, body position during surgery, including whether this changed, and anonymised codes for the surgeon and anaesthetist. The horse's breed, age, gender and stage of pregnancy (if appropriate) were recorded along with a subjective assessment of anaesthetic risk (low, medium or high) made by the clinician responsible for each case. All drugs used for premedication, induction and maintenance of anaesthesia were recorded using standard abbreviations. Duration of anaesthesia from induction until the vaporiser was switched off was recorded in minutes. Additional treatments recorded included use of nitrous oxide (N₂O), intermittent positive pressure ventilation (IPPV) and whether arterial blood pressure (BP) was monitored. The quality of recovery was assessed and any sedative given during the recovery period was also recorded. Date, time and type or cause of perioperative death or nonfatal complication were recorded for each case.

Case definition

The primary outcome measure (death) was whether or not the horse had died, including being subjected to euthanasia as a result of a perioperative complication within 7 days of induction of anaesthesia. Horses subjected to euthanasia because of severity of the lesion, or due to inoperable problems, were recorded as 'put to sleep' (PTS) and excluded from analyses, as were multiple anaesthetic episodes, subsequent to the first anaesthetic episode, within the 7 day period. The records of all cases classified as 'death' were checked individually by one author (GMJ) and were assigned a specific cause of death on the basis of information provided by the clinicians. Other, nonfatal conditions developing in the same time period were defined as nonfatal perioperative complications.

Study size and trial conduct

Initial sample size estimates, based on the expectation of a death rate of 1% in the halothane group and a 5% significance level, suggested that around 12,000 cases were required to give the study 90% power to detect a 50% reduction of mortality in the isoflurane group (Pocock 1983). The death rate proved to be much higher (1.6%) and the required study size was re-evaluated during the data collection phase. At that time, around 8500 cases, involving 134 deaths, had been recorded which, using the initial assumptions, provided >95% power to test the primary hypothesis. The study was therefore terminated, as sufficient data had been collected to achieve the proposed study power.

Statistical analyses

Data were analysed on an intention to treat basis, treating the outcome of interest as a binary variable, with death = 1 and alive = 0. Following careful univariable and stratified contingency table exploration, in particular considering whether there was clear evidence that use of one agent was associated with reduced risk of death, detailed mixed effects logistic regression (MELR) modelling was performed. All variables associated with outcome ($P < 0.4$) in univariable analyses were tested for inclusion in multivariable models. Initially, terms were retained in models if they were significantly associated with outcome (Wald $P \leq 0.05$) or if they significantly reduced model residual deviance (likelihood

TABLE 1: Distribution of patients between the two randomised groups (all randomised horses n = 8990)

Variable	Halothane		Isoflurane	
	n	%	n	%
<i>Day of operation</i>				
Sunday	187	4	183	4
Monday	574	13	571	13
Tuesday	1006	23	915	21
Wednesday	897	20	886	20
Thursday	858	19	879	20
Friday	641	15	691	16
Saturday	241	5	230	5
<i>Type of practice</i>				
Referral institution	2132	48	2226	51
Referral practice	1835	42	1690	39
Non referral practice	437	10	439	10
<i>Specialism of surgeon</i>				
Mixed	592	13	643	15
Specialist equine	3412	77	3348	77
Missing	400	9	364	8
<i>Age of patient</i>				
Mean (s.d.)	7 (5.4)		7 (7.5)	
<i>Breed</i>				
Thoroughbred	1729	39	1742	40
Warmblood	1935	44	1876	43
Coldblood	227	5	235	5
Pony	416	9	400	9
Other breeds	17	<1	20	<1
Missing	80	2	82	2
<i>Gender</i>				
Gelding	1852	42	1813	42
Female	1598	36	1606	37
Entire male	900	20	884	20
Pregnant female	41	1	40	1
Missing	13	<1	12	<1
<i>Risk</i>				
Low	2810	64	2701	62
Medium	1040	24	1068	25
High	535	12	572	13
Missing	19	<1	14	<1
<i>Operation</i>				
ENT	645	15	686	16
Emergency abdominal	774	18	797	18
Orthopaedic (other)	1659	38	1602	37
Fractures	117	3	110	3
Urogenital	589	13	570	13
Miscellaneous	620	14	590	14
<i>Blood pressure</i>				
No	688	16	656	15
Yes	3697	84	3677	84
Missing	19	<1	22	1

ratio statistic $P \leq 0.05$). However, this approach resulted in 'over-fitted models', with too many terms given the numbers of cases; restricted models are presented which included only variables that were significant and reasonably common in the study population. Models were fitted using PROC LOGISTIC and PROC NL MIXED in SAS (v.8.2)¹. Data from each clinic were regarded as possibly correlated and multilevel regression models, treating the clinic as the highest level in 2-level hierarchical logistic regression models, were used (Snijders and Bosker 1999). Fit of models was evaluated using the Hosmer-Lemeshow statistic (Hosmer and Lemeshow 1989) and evaluation of receiver operating characteristics (ROC) (Greiner *et al.* 2000). We estimated confidence limits around the 'number needed to treat', derived from absolute differences in risk between 2 treatment groups, using the Delta method (Rice 1995).

TABLE 2: Association between maintenance agent and all cause mortality, showing no significant differences between the 2 agents

	Halothane	Isoflurane
Survived	4080 (98.3%)	4028 (98.4%)
Died (cases)	69 (1.7%)	65 (1.6%)
Total	4149	4093

Results

Data from over 11,000 general anaesthetic episodes were collected during the course of the study (Fig 1). However, 1437 horses were withdrawn from the study, mainly from 2 clinics. One clinic declined to randomise any emergency operations and the other had to use an operating facility out of hours which had no choice of vaporiser. Over 800 horses did not receive inhalational maintenance and so were not eligible for the study. A total of 8990 horses were randomised to receive halothane or isoflurane, of which 517 were PTS inoperable and 231 were identified as having more than one operation within the 7 day period and so only the first episode was retained in the analysis. Data were therefore analysed from 8242 horses, 4149 of which were randomised to receive halothane and 4028 to receive isoflurane. In each arm of the study, there were a small number of horses (550, no deaths) which, although randomised to receive one agent, in fact received another. Reasons for this included equipment failure, human error or the need to switch between maintenance agents for clinical reasons. Data were analysed according to intention to treat.

Effectiveness of the randomisation in ensuring balance between the 2 treatment groups in respect of the various factors was evaluated by comparing the distribution of all covariates between the 2 randomised groups (Table 1). With no exceptions, there was an equal distribution (differences <2%), consistent with successful randomisation.

Overall results

A total of 134 deaths were recorded, giving an overall perioperative mortality frequency of 1.6% (95%CI 1.4–1.9%). If colic and other emergency abdominal surgeries were excluded, perioperative mortality within 7 days was 0.9% (95%CI 0.8–1.3%). There was no difference in mortality between the

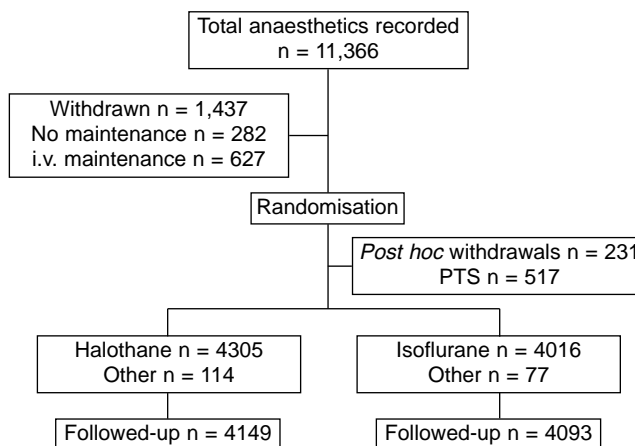


Fig 1: Trial profile, as recommended in the CONSORT statement.

TABLE 3a: Association between maintenance agent and nonfatal perianaesthetic complications, showing no significant differences between groups

	Halothane	Isoflurane
No complication	3961 (97.1%)	3930 (97.6%)
Nonfatal complication (cases)	119 (2.9%)	98 (2.4%)
Total	4080	4028

TABLE 3b: Association between maintenance agent and all cause mortality in horses age 2–5 years, showing significantly reduced risk in isoflurane group

	Halothane	Isoflurane
Survived	1346 (98.5%)	1334 (99.7%)
Died (cases)	21 (1.5%)	4 (0.3%)
Total	1367	1338

2 treatment groups (Table 2; $\chi^2_{1df} = 0.07$, $P = 0.8$), nor in the occurrence of nonfatal perioperative complications (Table 3a; $\chi^2_{1df} = 1.8$, $P = 0.2$).

Stratified analysis suggested that there was significant heterogeneity between different age groups in the risk of death in the isoflurane group. The overall risk of death was similar between isoflurane and halothane in horses of all ages. However, although not part of the primary hypothesis, a significant reduction in the risk of death (Table 3b; $\chi^2_{1df} = 11.3$, $P < 0.001$) was recorded in patients age 2–5 years. A similar significant reduction in nonfatal perioperative complications associated with isoflurane was also seen in this age group (data not shown).

Risk factors for deaths from all causes

Mixed effects logistic regression models were developed as described. Significant variables included in the final model included age, anaesthetic risk, operation type and an interaction between age of horse and maintenance agent (Table 4). The distribution of patients between different levels of the covariates is also shown in Table 4. The final model fit the data reasonably well (HL statistic, $P = 0.55$) and the ROC curves indicated that the model had reasonable discriminatory ability. We also fitted models in which we replaced clinic with surgeon or anaesthetist as the random term and found no difference between the different models (results not shown).

The model suggested that, even though there was no overall difference between halothane and isoflurane (Table 1), isoflurane was associated with significantly lower mortality in horses age 2–5 years, having adjusted for confounding variables. The adjusted odds ratio associated with isoflurane use in this age group was 0.18 (95%CI 0.06–0.50). Risk of death was increased in fracture and emergency abdominal surgery and was lowest with ear, nose and throat (ENT) or urogenital surgery. Comparing age groups, risk was lowest in yearlings. The output from the model suggested that, for every 208 horses age 2–5 years anaesthetised (95%CI 63–353), one less would die if isoflurane were used rather than halothane.

Causes of death

The main cause of death was cardiac arrest (43/134), with fractures in recovery accounting for a further 31/134 (Table 5). Horses were classified as having died from cardiac arrest if the responsible

TABLE 4: Final mixed effects logistic regression model of the risk of all cause mortality

	Alive	Dead	β	s.e. β	P	OR	95%CI
<i>Intercept</i>			-5.77	0.73			
<i>Risk</i>							<0.007
Low risk	5250	41				1.00	
Medium risk	1865	38	0.83	0.25	0.001	2.28	1.4–3.7
High risk	738	53	1.84	0.32	<0.001	6.34	3.4–11.9
<i>Treatment</i>							
Halothane	3955	68				1.00	
Isoflurane	3898	64	0.01	1.00	0.9	1.01	0.1–7.3
<i>Operation type</i>							<0.001
ENT/urogenital/misc	3482	26				1.00	
Emergency abdominal	1080	59	0.90	0.3	0.002	2.48	1.4–4.5
Fracture	204	9	1.57	0.4	<0.001	4.80	2.2–10.6
Other orthopaedic	3087	38	0.57	0.3	0.03	1.77	1.06–2.90
<i>Age group</i>							0.7
Foal	586	13	0.89	0.8	0.3	2.40	0.5–12.4
Yearling	577	4				1.00	
2–5 years	2670	25	0.63	0.7	0.4	1.87	0.4–8.1
≥6 years	4020	90	0.53	0.7	0.5	1.69	0.4–7.1
<i>Treatment x age (years)</i>							0.009
Treatment x age = foal	311	7	-0.12	1.2	0.9	0.89	0.08–8.60
Treatment x age = 2–5	1330	4	-1.75	1.2	0.1	0.17	0.02–1.70
Treatment x age = 6+	1984	51	0.30	1.0	0.8	1.34	0.2–10.0
Random effects variance			0.09	0.09	0.29		

TABLE 5: Specific causes of perianaesthetic death in horses enrolled in the study

	Halothane	Isoflurane	Total	%
Cardiac	30	13	43	32
Fracture	16	15	31	23
Myopathy	6	4	10	7
Respiratory	2	4	6	4
Abdominal	7	10	17	13
CNS/SCM	-	5	5	4
Other	8	14	22	16
Total	69	65	134	100

CNS = Central nervous system; SCM = Spinal cord malacia.

clinician reported that they suffered from either true cardiac arrest, fatal arrhythmia or circulatory failure leading to ventricular standstill. Myopathy was also a common complication type ($n = 67$) when nonfatal complications were also considered, even though only 15% ($n = 10$) of these cases were fatal. More detailed analyses are presented for cardiac-associated mortality and myopathy; lack of anaesthetic deaths precluded such analyses of other specific causes.

Cardiac-related mortality: Cardiac arrest was the most common specific cause of death and was also of specific interest, given observed experimental effects of isoflurane. Use of isoflurane was associated in both univariable (Table 6; $\chi^2_{1df=1} = 6.47$, $P = 0.01$) and multivariable analyses (Table 7) with a significantly reduced risk of cardiac-related mortality, compared to halothane. The fit of this model to the data was satisfactory (HL $P = 0.37$). In multivariable analyses, the clinical 'risk' status of the horse prior to surgery (positively) and routine blood pressure monitoring (negatively) were also significantly associated with the risk of cardiac-related mortality.

Myopathy: In contrast to many other causes of death or complication (e.g. cardiac-related mortality), myopathy was not

TABLE 6: The association between cardiac-related mortality and treatment, showing a significantly reduced risk in isoflurane group

	Halothane	Isoflurane
Survived	4080 (99.3%)	4029 (99.7%)
Cardiac death	30 (0.7%)	13 (0.3%)
Total	4110	4042

TABLE 7: Final mixed effects logistic regression model of the risk of cardiac-related perianaesthetic death

	Alive	Dead	β	s.e. β	P	OR	95%CI
<i>Intercept</i>			-5.18	0.46			
<i>Risk</i>					<0.001		
Low risk	5377	8				1.0	
Medium risk	1915	9	1.43	0.50	0.004	4.2	1.6–11.2
High risk	761	25	3.76	0.46	<0.001	42.9	17.6–105.0
<i>Treatment</i>							
Halothane	4054	29				1.0	
Isoflurane	3999	13	-0.82	0.34	0.02	0.4	0.2–0.8
<i>Blood pressure monitoring</i>							
BP not monitored	1269	13				1.0	
BP monitored	6784	29	-1.92	0.41	<0.001	0.1	0.06–0.30
Random effects variance			0.79	0.53	0.15		

seen until after anaesthesia and surgery were finished. Therefore, it was possible to consider duration of operation for this outcome. In the final myopathy model (Table 8), both duration of operation and body position during surgery were associated significantly with risk. The fit of the model to the data was good (HL $P = 0.80$). Operations lasting over 90 mins carried an increased risk and it was also significantly more common in horses in lateral recumbency. There were no significant treatment (isoflurane vs. halothane) effects.

Discussion

The results from this study have demonstrated the feasibility of conducting large multicentre randomised controlled studies in veterinary practice to evaluate and compare different treatments. Such investigations are commonly undertaken in human medicine and surgery (Moher *et al.* 2001). The success of our investigation supports the general conclusions of Morley *et al.* (1999) in this regard, following their successful conduct of a blinded randomised study of the efficacy of an equine influenza vaccine in North America. There is a need for far more rigorous scrutiny of the treatments used in veterinary medicine than is currently undertaken.

The study was reasonably free from misclassification errors and other biases. Considerable care was taken in classification of the deaths as either deaths or put to sleep (PTS). Each was checked with the clinicians involved whenever there was any question, leading to confidence that all deaths were identified. It was rather more difficult, in the absence of *post mortem* examination reports, to be sure of the precise cause of death, particularly in the case of cardiac deaths. However, when considering specific causes in these analyses, a classification system broad enough to ensure reasonable accuracy was used. It is more likely that there was greater misclassification of the nonfatal problems.

TABLE 8: Final mixed effects logistic regression model of the risk of myopathy

	Unaff.	Aff.	β	s.e. β	P	OR	95%CI
<i>Intercept</i>			-6.7	0.7			
<i>Duration</i>					<0.001		
≤45 mins	1295	3				1.0	
45≤90 mins	3315	6	-0.23	0.7	0.7	0.8	0.2–3.2
>90 mins	2668	54	2.27	0.6	<0.001	9.7	2.9–31.7
<i>Body position</i>					<0.001		
Dorsal - nonabdominal	2584	13				1.0	
Dorsal - abdominal	947	10	0.25	0.4	0.6	1.3	0.6–3.0
Left and right lateral	3128	37	0.84	0.3	0.01	2.3	1.2–4.4
Other - moved	619	3	-0.08	0.7	0.9	0.9	0.3–3.4
Random effects variance			0.31	0.3	0.31		

Unaff. = Unaffected; Aff. = Affected.

The clinics in this study were not selected at random, but were a carefully selected 'convenience' sample, in order to ensure maximal data quality. They represented a range from primary equine practices through to tertiary referral clinics. The majority were selected on the basis of having been highly reliable at recording data in previous observational studies (Johnston *et al.* 2002). It was impossible to blind the anaesthetists to the treatment, because the volatile anaesthetic had to be administered from an agent-specific vaporiser. It was also not feasible to control the drugs used for premedication and induction. In any case, the objective of the study was to assess the effect of the volatile agents as they were normally used in practice. Nevertheless, the study was robust, as the end point (alive or dead at 7 days) was objective, resistant to false recording. The effects of premedication and induction treatments were assessed during statistical analyses and found not to alter the conclusions. Compliance with the randomisation protocol was carefully monitored by checking that the volatile agent recorded by the clinic was the same as that allocated in the randomisation protocol. Although it is possible that the order of operations recorded was altered to suit individual preference, this is unlikely, as data collection, recording and communication was generally of very high quality. The conclusion that compliance was high was consistent with the uniform distribution of covariates between the 2 treatments.

We used a standard approach to analyse the data collected in this study, although we had to exclude some variables in our analyses of overall mortality due to the model becoming overparameterised. In particular, we did not include terms for the other drugs used in anaesthesia, monitoring of blood pressure (which had been associated with reduced risk) and the use of intermittent positive pressure ventilation (associated with increased risk). The terms in the model presented were not affected by their inclusion, their parameter estimates being altered only by small fractions.

Although the primary purpose of the study was to determine whether or not isoflurane was associated with reduced risks, several other results from the regression modelling threw light on overall mortality and specific complications. These results confirm those of Johnston *et al.* (1995, 2002), in demonstrating that cardiac arrest, fractures in recovery and myopathy are the most common perioperative complications. It should be noted that fracture in recovery, responsible for nearly a quarter of all deaths, was not restricted to horses following fracture repair, but was distributed across all operation types.

The primary hypothesis was rejected in that use of isoflurane was not associated with an overall reduced risk of perioperative

mortality in horses. This is the main conclusion from the study. However, there was some heterogeneity of effects between different age groups, and isoflurane use was associated with a significantly reduced risk of death in horses age 2–5 years. Although this result might reflect chance variation, this is less likely, as horses with nonfatal complications (necessarily a group independent of those that died) were also significantly reduced in this age/treatment group.

In contrast to the lack of differences between the 2 agents on overall mortality, use of isoflurane was associated with around a 60% reduction in cardiac-associated mortality compared to halothane (95%CI 20–80%). This result was consistent with the results from experimental studies which demonstrated less cardiovascular depression from isoflurane than from halothane in equine anaesthesia (Steffey and Howland 1980; Whitehair *et al.* 1996; Grosenbaugh and Muir 1998; Grubb *et al.* 1999; Raisis *et al.* 2000). Despite the fact that cardiac problems were the most common cause of death (Table 5), the cardiovascular benefits of isoflurane were matched by small, nonsignificant increases in risk with other causes of death, particularly those associated with disease of the CNS, resulting in a similar overall death rate. There is a perception among anaesthetists that recovery from isoflurane is more agitated and potentially violent than after halothane (Taylor and Watkins 1984; Matthews *et al.* 1998; Donaldson *et al.* 2000) and some clinicians therefore select halothane for fracture repair, where a smooth recovery is particularly important. The reasons underlying these other differences were not clear, but could not be attributed to a higher fracture rate in recovery following isoflurane anaesthesia (Table 5). There is therefore no evidence from the data presented here that the risk of fractures, the most likely disastrous result of a violent recovery, is higher after isoflurane than after halothane. Deaths associated with a central nervous system abnormality appear more likely.

The results suggested that horses determined to be most 'at risk' prior to surgery were significantly more likely to die (overall mortality) and to die from a cardiovascular problem. The weakness of this result was that clear criteria, such as the American Society of Anesthesiologists (ASA) grades physical status classification (Thurmon *et al.* 1996), were not provided on which clinicians could base their assessments of risk status, and it is not known when the clinicians decided and recorded the ASA status of each patient. However, evaluation of 'risk status' is normally done preoperatively to aid the choice of premedication and induction agent. The results certainly suggest that clinical evaluation was valuable in identifying horses at particularly increased risk of dying or suffering cardiac arrest. Preoperative identification of risky animals may allow increased resources to be used in these animals.

It has been recognised for some time that long duration of surgery is associated with perioperative complications (Johnston *et al.* 1995, 2002). This is clearly evident in relation to myopathy, where operations greater than 90 mins in length were around 10 times more likely to result in myopathy (Table 8). As horses tended to suffer cardiac complications (the most common cause of death) in the early stages of the operations (Johnston *et al.* 1996), we were unable to consider time of operation in the overall or cardiac-specific analyses. The other variable associated with risk of myopathy was body position, with horses kept in lateral recumbency being at highest risk. Myopathy develops as a result of inadequate muscle perfusion occurring during anaesthesia, as a result of low arterial blood pressure and cardiac output combined with high intracompartmental pressures in dependent limb muscle

(Grandy *et al.* 1987; Lindsay *et al.* 1989). Prolonged anaesthesia simply means that ischaemia is present for longer, a factor known to predispose to greater muscle damage (Hargens *et al.* 1981). Lateral recumbency probably leads to greater localised compression in muscles essential for the act of standing up and walking, compared with dorsal recumbency (Lindsay *et al.* 1985; White and Suarez 1986). Euthanasia due to myopathy is more likely to be necessary when muscles necessary for standing are damaged (Taylor and Clarke 1999). Lateral recumbency is associated with greater compression of muscles such as the triceps group, whereas dorsal recumbency compresses the gluteal muscles. While the former are essential for standing up, damage to the latter may not prevent a horse from reaching its feet and staying upright. Although our results suggest that lateral recumbency is more likely than dorsal recumbency to result in any myopathy, it is possible that milder, nonfatal myopathy (which made up the majority of cases) may simply have been more evident in the horses damaged through being in lateral recumbency. Reduced odds of myopathy were not observed in horses where arterial blood pressure (BP) was monitored. Data were not collected to assess whether inotropes were given if hypotension was detected, and validity of the belief that inotropic support to prevent hypotension reduces the risk of myopathy cannot be ascertained from this study.

Risk of cardiac mortality was reduced in horses having their blood pressure monitored. Routine BP monitoring was performed in some clinics but in others this was not commonly carried out and may have been reserved for high-risk patients, which could theoretically have biased the association in the opposite direction to the observed results. The value of routine BP monitoring is that it may simply mean that closer attention is paid to the cardiovascular system and early warning of volatile agent overdose is given. Routine monitoring may also have allowed supportive measures, such as dobutamine infusion, to be given (Donaldson 1988), thereby reducing the chances of circulatory failure.

There is a general perception among anaesthetists that isoflurane is the better anaesthetic maintenance agent for the high-risk cases, such as those undergoing colic surgery. This is largely because isoflurane depresses myocardial function and cardiac output less than halothane (Steffey and Howland 1980; Grosenbaugh and Muir 1998; Raisis *et al.* 2000). The reduced risk of death from cardiac arrest associated with the use of isoflurane and the increased risk of both cardiac-associated and overall mortality in high risk patients support this view, even though we were unable to demonstrate any specific benefits of isoflurane in high-risk patients. The more rapid recovery from isoflurane compared with halothane (Matthews *et al.* 1992; Whitehair *et al.* 1993; Donaldson *et al.* 2000; Ripoll *et al.* 2000) may also be beneficial, as the depressant effects abate more quickly.

A further reason that isoflurane may be chosen over halothane for maintenance of anaesthesia is the effect on the clinicians' wellbeing. Some 20% of inhaled halothane is metabolised in the liver and the metabolites may be harmful (Elliott and Strunin 1993). Less than 2% of isoflurane is metabolised, and the potential for production of harmful metabolites from inhalation of volatile anaesthetics in operating staff from atmospheric contamination is therefore considerably less with isoflurane than halothane. There may also be inherent differences between the toxicity of the parent compounds, but these have not been well characterised.

In conclusion, the data presented in this paper do not demonstrate that isoflurane is safer than halothane for anaesthetic

maintenance. If personal preference is to use either agent, on grounds of safety for the clinician or perceived appropriateness for a particular case, both can be justified. There may be some specific benefit in the use of isoflurane in young horses and when cardiac compromise is present.

Acknowledgements

We are very grateful to The Wellcome Trust who funded GMJ as a Training Fellow in Clinical Epidemiology to carry out this study. Thanks are also due to Mark Binns of Mallinckrodt Veterinary (marketing both halothane and isoflurane) who generously supplied and fitted isoflurane vaporisers to participating UK clinics and supplied subsidised supplies of both agents for the duration of the study. Dr William Henley (AHT) provided confidence intervals around number needed to treat. The Horserace Betting Levy Board provided funding for James Wood.

We are very grateful to all veterinary and nursing staff in the participating clinics, without whom this work would not have been possible: **Belgium:** Faculteit Diergeneeskunde, Merelbeke; Belgium Dierenkliniek de Bosdreef, Equine Hospital, Moerbeke-Waas. **Brazil:** Faculty of Veterinary Medicine and Zootechny, UNESP, Botucatu; DCCRA, Curso de Medicina Veterinária, FOA, Araçatuba. **Greece:** University of Thessaloniki, St Voutyra. **Holland:** Dierenkliniek 'De Postwagen', Venlo. **Switzerland:** Veterinär-Chirurgische Klinik d Univ Zch, Zurich; Klinik für Nutztiere und Pferde Abt. Anaesthesie, Berne. **UK:** Tortington Centre, Arundel; Endell Veterinary Group, Salisbury; Fellowes Farm Equine Clinic, Huntingdon; Walmsley and Partners, The Liphook Equine Veterinary Hospital; University of Glasgow Veterinary School, Glasgow; Fyrnwy Equine Clinics, Llanymenech; Kearns and Rea, Tewkesbury; Straight Mile Farm, Wokingham; Stirk and Haizelden, Ripon; The Animal Health Trust, Newmarket; Priory Veterinary Surgery, Reigate; The Ashbrook Equine Hospital, Knutsford; J. Hird and Partners, Halifax; Bushy Equine Clinic, Berkeley; Royal (Dick) School of Veterinary Studies, Edinburgh; Bell Equine Veterinary Centre, Maidstone; Beaufort Cottage Equine Hospital, Newmarket; Willesley Equine Clinic, Tetbury; Chine House Veterinary Group, Sibleby; Philip Leverhulme Large Animal Hospital, Liverpool; University of Bristol, Langford; Cinder Hill Equine Veterinary Clinic, Haywards Heath; Wilson McWilliam and Partners, Nantwich; Rainbow Farm, Malton; Department of Clinical Veterinary Medicine, University of Cambridge. **USA:** Marion duPont Scott Equine Medical Center, Leesburg; College of Veterinary Medicine, University of Missouri-Columbia.

Manufacturer's address

¹SAS, Cary, North Carolina, USA.

References

- Clarke, K.W. and Hall, L.W. (1990) A survey of anaesthesia in small animal practice: AVA/BSAVA report. *J. Ass. vet. Anaesth. G.B. Ireland* **17**, 4-10.
- Daunt, D.A., Steffey, E.P., Pascoe, J.R., Willits, N. and Daels, P.F. (1992) Actions of isoflurane and halothane in pregnant mares. *J. Am. vet. med. Ass.* **201**, 1367-1374.
- Donaldson, L.L. (1988) Retrospective assessment of dobutamine therapy for hypotension in anesthetized horses. *Vet. Surg.* **17**, 53-57.
- Donaldson, L.L., Dunlop, G.S., Holland, M.S. and Burton, B.A. (2000) The recovery of horses from inhalant anesthesia: a comparison of halothane and isoflurane. *Vet. Surg.* **29**, 92-101.
- Dunlop, C.I., Steffey E.P., Miller, M.F. and Woliner, M.J. (1987) Temporal effects of halothane and isoflurane in laterally recumbent ventilated male horses. *Am. J. vet. Res.* **48**, 1250-1255.
- Dyson, D.H., Maxie, M.G. and Schnurr, D. (1998) Morbidity and mortality associated with anesthetic management in small animal veterinary practice in Ontario. *J. Am. anim. Hosp. Ass.* **34**, 325-335.
- Elliott, R.H. and Strunin, L. (1993) Hepatotoxicity of volatile anaesthetics. *Br. J. Anaesth.* **70**, 339-348.
- Grandy, J.L., Steffy, E.P., Hodgson, D.S. and Woliner, M.J. (1987) Arterial hypotension and the development of postanesthetic myopathy in halothane-anesthetized horses. *Am. J. vet. Res.* **48**, 192-197.
- Greiner, M., Pfeiffer, D. and Smith, R.D. (2000) Principles and practical application of the receiver-operating characteristic analysis for diagnostic tests. *Prev. vet. Med.* **45**, 23-41.
- Grosenbaugh, D.A. and Muir, W.W. (1998) Cardiorespiratory effects of sevoflurane, isoflurane and halothane anesthesia in horses. *Am. J. vet. Res.* **59**, 101-106.
- Grubb, T.L., Benson, G.J., Foreman, J.H., Constable, P.D., Thurmon, J.C., Olson, W.O., Tranquilli, W.J. and Davis, L.E. (1999) Hemodynamic effects of ionized calcium in horses anesthetized with halothane or isoflurane. *Am. J. vet. Res.* **60**, 1430-1435.
- Hargens, A.R., Schmidt, D.A., Evans, K.L., Gonsalves, M.R., Cologne, J.B., Garfin, S.R., Mubarak, S.J., Hagan, P.L. and Akeson, W.H. (1981) Quantitation of skeletal-muscle necrosis in a model compartment syndrome. *J. Bone Joint Surg. Am.* **63**, 631-636.
- Harvey, R.C., Gleed, R.D., Matthews, N.S., Tyner, C.L., Erb, H.N. and Short, C.E. (1987) Isoflurane anesthesia for equine colic surgery. Comparison with halothane anesthesia. *Vet. Surg.* **16**, 184-188.
- Hosmer, D.W. and Lemeshow, S. (1989) *Applied Logistic Regression*, John Wiley, New York.
- Johnston, G.M. (2000) *CEPEF: A Prospective Multicentre Cohort Study of Equine Perioperative Mortality*. PhD Thesis, University of Cambridge.
- Johnston, G.M., Taylor, P.M., Holmes, M.A. and Wood, J.L.N. (1995) Confidential enquiry of perioperative equine fatalities (CEPEF-1): preliminary results. *Equine vet. J.* **27**, 193-200.
- Johnston, G.M., Eastment, J.K., Taylor, P.M. and Wood, J.L.N. (2002) The confidential enquiry into perioperative equine fatalities (CEPEF): mortality results of Phases 1 and 2. *Vet. Anaesth. Analg.* **29**, 159-170.
- Johnston, G.M., Taylor, P.M., McGee, M.A., Wood, J.L.N. and Holmes, M.A. (1996) The confidential enquiry into perioperative equine fatalities (CEPEF-1). Survival curves. *Vet. Surg.* **25**, 182.
- Lindsay, W.A., Pascoe, P.J., Mcdonell, W.N. and Burgess M.L. (1985) Effect of protective padding on forelimb intracompartmental muscle pressures in anesthetized horses. *Am. J. vet. Res.* **46**, 688-691.
- Lindsay, W.A., Robinson, G.M., Brunson, D.B. and Majors, L.J. (1989) Induction of equine postanesthetic myositis after halothane-induced hypotension. *Am. J. vet. Res.* **50**, 404-410.
- Littlewood, J.D., Lakhani, K.H., Paterson, S., Wood, J.L.N. and Chanter, N. (1999) Clindamycin hydrochloride and clavulanate-amoxicillin in the treatment of canine superficial pyoderma. *Vet. Rec.* **144**, 662-665.
- Lunn, J.N. and Mushin, W.W. (1982) *Mortality Associated with Anaesthesia*, Nuffield Provincial Hospitals Trust, London.
- Matthews, N.S., Miller, S.M., Hartsfield, S.M. and Slater, M.R. (1992) Comparison of recoveries from halothane vs isoflurane anesthesia in horses. *J. Am. vet. med. Ass.* **201**, 559-563.
- Matthews, N.S., Hartsfield, S.M., Mercer, D., Bebeau M.H. and MacKenthun, A. (1998) Recovery from sevoflurane anesthesia in horses: comparison to isoflurane and effect of postmedication with xylazine. *Vet. Surg.* **27**, 480-485.
- Moher, D., Schulz, K.F. and Altman, D.G. (2001) The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomised trials. *Lancet* **357**, 1191-1194.
- Morley, P.S., Townsend H.G.G., Bogdan, J.R. and Haines, D.M. (1999) Efficacy of a commercial vaccine for preventing disease caused by influenza virus infection in horses. *J. Am. vet. med. Ass.* **215**, 61-66.
- Pocock, S.J. (1983) *Clinical Trials: A Practical Approach*, John Wiley and Sons Ltd., Chichester.
- Raisis, A.L., Young, L.E., Blissitt, K.J., Brearley, J.C., Meire, H.B., Taylor, P.M. and Lekeux, P. (2000) A comparison of the haemodynamic effects of isoflurane and halothane anaesthesia in horses. *Equine vet. J.* **32**, 318-326.
- Rice, J.A. (1995) *Mathematical Statistics and Data Analysis*, 2nd edn., Duxbury Press, Belmont California. pp 149-154.
- Ripoll, S.V., White, K.L. and Taylor, P.M. (2000) Halothane vs. isoflurane in horses: a retrospective study of 132 cases in a randomised controlled trial. In:

- Proceedings of the Association of Veterinary Anaesthetists Spring Conference*, Cambridge, UK.
- Snijders, T.A.B. and Bosker, R.J. (1999) *Multilevel Analysis: An Introduction to Basic and Advanced Multilevel Modelling*, Sage Publications Ltd., London.
- Steffey, E.P. and Howland, D. Jr. (1978) Cardiovascular effects of halothane in the horse. *Am. J. vet. Res.* **39**, 611-615.
- Steffey, E.P. and Howland, D. Jr. (1980) Comparison of circulatory and respiratory effects of isoflurane and halothane anesthesia in horses. *Am. J. vet. Res.* **41**, 821-825.
- Taylor, P.M. and Watkins, S.B. (1984) Isoflurane in the horse. *J. Ass. vet. Anaesth.* **12**, 191-194.
- Taylor, P.M. and Clarke, K.W. (1999) *Handbook of Equine Anaesthesia*, W.B. Saunders Co., London.
- Thurmon, J.C., Tranquilli, W.J. and Benson, G.J. (1996) *Veterinary Anesthesia*, 3rd edn., Williams and Wilkins, Maryland. p 22.
- White, N.A. and Suarez, M. (1986) Change in triceps muscle intracompartmental pressure with repositioning and padding of the lowermost thoracic limb of the horse. *Am. J. vet. Res.* **47**, 2257-2260.
- Whitehair, K.J., Steffey, E.P., Willits, N.H. and Woliner, M.J. (1993) Recovery of horses from inhalation anesthesia. *Am. J. vet. Res.* **54**, 1693-1702.
- Whitehair, K.J., Steffey, E.P., Woliner, M.J. and Willits, N.H. (1996) Effects of inhalation anesthetic agents on response of horses to three hours of hypoxemia. *Am. J. vet. Res.* **57**, 351-360.