Gastric fluid volume and pH in elective surgical patients: triple prophylaxis is not superior to ranitidine alone

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The effect of oral ranitidine alone was compared with sequentially administered ranitidine, metoclopramide, and sodium citrate on gastric fluid volume and pH in 196 healthy, elective surgical inpatients, each of whom was randomly assigned to one of four groups. Patients in all groups received oral ranitidine 150 mg 2–3 hr before the scheduled time of surgery. Those in Group 1 also received oral metoclopramide 10 mg one hour before surgery, and sodium citrate 0.3 M 30 ml on call to the operating room; Group 2 received sodium citrate but no metoclopramide; Group 3 received metoclopramide but no sodium citrate; Group 4 received ranitidine alone. Following induction of anaesthesia a #18 Salem sump tube was passed into the stomach and all available gastric fluid was aspirated. Volumes were recorded and pH measured. In all groups mean pH was > 5.8, although at least one patient in each group had pH < 2.5. Mean volumes were significantly greater in patients who received citrate (Groups 1 and 2: 22 and 19 ml) than in those in those who did not (Groups 3 and 4: 10 and 8 ml). One patient in Group 2 and one in Group 3 had pH < 2.5 with volume > 25 ml. Our results do not demonstrate any advantage of double or triple prophylaxis over ranitidine alone. The practical difficulty of correctly administering two or even three medications, each at different but exact preoperative intervals, is emphasized.

Nous avons évalué l'effet de la ranitidine employée seule et en combinaison avec du métoclopramide et/ou du citrate de sodium sur le volume et le pH du liquide gastrique de 196 patients randomisés en quatre groupes avant leur intervention chirurgicale élective. Tous prirent 150 mg de ranitidine orale 2–3 hre avant l'intervention. De plus, les patients du Groupe 1 reçurent 10 mg de métoclopramide oral 1 hre avant l'intervention et 30 ml de citrate de sodium 0,3 M au départ pour la salle d'opération ; ceux du groupe 2, que du citrate de sodium et ceux du Groupe 3, que du métoclopramide. Après l'induction de l'anesthésie, nous aspirions le liquide gastrique à l'aide d'un tube de Salem de calibre 18 et en mesurions le volume et le pH. Même si dans tous les groupes, le pH moyen était supérieur à 5,8 il y avait dans chacun d'eux, au moins un patient dont le pH était inférieur à 2,5. Le volume moyen était significativement plus grand chez ceux ayant reçu du citrate (Groupes 1 et 2 : 22 et 19 ml) que chez les autres (Groupe 3 et 4 : 10 et 8 ml). Un patient du Groupe 2 et un autre du Groupe 3 avaient un pH de moins de 2,5 et un volume de plus de 25 ml. Il ne semble donc pas que la double ou triple prophylaxie soit plus efficace que la ranitidine seule. De plus, il est difficile de synchroniser adéquatement la prise de deux ou trois médicaments.

Key words

GASTROINTESTINAL TRACT: antacids, gastric emptying, gastric pH, gastric volume;
PHARMACOLOGY: metoclopramide, ranitidine.

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Preparation of patients for elective surgery includes measures to reduce the risk of pulmonary acid aspiration syndrome. To minimize gastric fluid volume an overnight fast is usually recommended[1,2] although recent studies[3–5] suggest that there is no clinically significant difference in gastric fluid volume in patients who fast from midnight and those who have taken 150 ml of oral fluids 2–3 hr preoperatively. The administration of an histamine H_2 receptor antagonist lowers mean volume and raises pH above 2.5 in most but not all patients.[4,6] Gastric prokinetic drugs such as metoclopramide accelerate gastric emptying and increase lower oesophageal sphincter tone.[7] Oral antacids neutralize gastric acid.[8,9] It has, therefore, been suggested that not only should every surgical patient receive pharmacological prophylaxis[10] but that routine triple prophylaxis using cimetidine or ranitidine, followed by metoclopramide, and then by a clear antacid (sodium citrate) will protect 100 per cent of patients against the hazards of acid aspiration.[11]

The aim of this study was to investigate whether the

TABLE I Randomized groups

Group	*2–3 hr preop*	*1 hr preop*	*15–30 min preop*
1	Ranitidine 150 mg	Metoclopramide 10 mg	Sodium citrate 30 ml
2	Ranitidine 150 mg	—	Sodium citrate 30 ml
3	Ranitidine 150 mg	Metoclopramide	—
4	Ranitidine 150 mg	—	—

addition of metoclopramide and/or sodium citrate is more effective than ranitidine alone in eliminating gastric pH values <2.5 and in minimizing gastric fluid volume in elective surgical patients.

Methods

The study protocol was approved by the University of Calgary Conjoint Ethics Committee. Informed consent was obtained from 203 inpatients, age 18–65 yr, ASA physical status I or II, who were scheduled for elective surgical procedures. Pregnant patients, those taking medication known to affect gastric secretion or motility and those with any known gastro-oesophageal pathology were excluded. Age, sex, weight, and duration of overnight fast were recorded. Patients were then randomly assigned to one of four groups (Table I) using a table of random numbers. All patients received oral ranitidine 150 mg with 150 ml coffee, tea, fruit juice, or water 2–3 hr before the scheduled time of surgery. Those in Group 1 also received oral metoclopramide 10 mg one hour before the scheduled time of surgery, and oral sodium citrate 0.3 M 30 ml when they left the nursing unit for the operating theatre. Patients in Group 2 received sodium citrate but not metoclopramide, those in Group 3 received metoclopramide but not sodium citrate, and those in Group 4 received ranitidine alone. A marker dye, phenol red 50 mg (phenolsulfonphthalein, Sigma Chemicals P4758) was added to the sodium citrate in Groups 1 and 2 to estimate how much of the antacid remained in the stomach at the time of sampling, and to the 150 ml oral fluid in Groups 3 and 4 to distinguish between ingested fluid and gastric secretion in each gastric sample. The phenol red concentration in each sample was measured in alkalinized solution using a Beckman DU-50 spectrophotometer at 560, 520, and 600 nm.[12] The lower limit of detection was 5 $\mu g \cdot ml^{-1}$. Patients received either no premedication or oral diazepam 5–15 mg 90 min preoperatively, according to the preference of the anaesthetist in charge of the case.

Within five minutes following induction of anaesthesia an investigator, who was unaware of the patient's group allocation, passed an 18 FG Salem sump tube into the stomach and confirmed its position by auscultation over the epigastrium for insufflated air. The epigastric region was manually massaged while gastric fluid was aspirated into a 60 ml syringe with the patient in the supine position and with the sampling tube in several locations within the stomach. Residual gastric fluid volume was recorded, and its pH was measured using a Corning 150 pH meter calibrated at 4.0 and 7.0.

Of the 203 patients recruited, 196 completed the protocol. Seven patients were excluded due to cancellation of surgery, or to uncertainty that the sampling tube was within the stomach. Demographic data are given as mean ± standard deviation (SD). Values for medication-induction intervals, residual gastric fluid volume and pH are given as mean ± SD (range). Appropriate intervals for therapeutic effect, from ingestion of medication to induction of anaesthesia, were considered to be: ranitidine >90 min, metoclopramide 45–240 min, sodium citrate <45 min. Tests of significance among groups were performed using one-way analysis of variance for parametric data, and the Kruskal-Wallis test for nonparametric data. Differences were considered statistically significant when $P < 0.05$.

Results

Patients in all four groups were similar in age, weight, and fast since last oral fluid (Table II). There were no statistically significant differences among groups with respect to mean medication-induction intervals for ranitidine, metoclopramide or sodium citrate (Table III). The wide ranges reflect the fact that surgery times are often behind or ahead of those on the printed schedule. The incidence of inappropriate timing of at least one medication was highest with triple prophylaxis and lowest with single prophylaxis (Table IV). Inappropriate timing occurred for ranitidine (<90 min) in five of 196 patients, for metoclopramide (<45 min or >240 min) in 11 of 102 patients, and for citrate (>45 min) in 32 of 98 patients.

TABLE II Patient characteristics. Values are mean ± SD

Group	*n*	*Age (yr)*	*Weight (kg)*	*Fast (hr)*
1	46	40 ± 13	74 ± 16	3.1 ± 0.9
2	50	41 ± 13	73 ± 13	3.0 ± 1.0
3	51	40 ± 13	72 ± 13	3.2 ± 1.0
4	49	39 ± 14	75 ± 16	2.9 ± 1.0

TABLE III Preoperative medication intervals (minutes). Values mean ± SD (range)

Group	*Ranitidine*	*Metoclopromide*	*Citrate*
1 (RMC)	187 ± 54 (35–340)	88 ± 44 (15–240)	44 ± 24 (10–165)
2 (R--C)	178 ± 62 (65–400)	—	42 ± 17 (10–90)
2 (RM--)	189 ± 61 (60–390)	101 ± 51 (35–300)	—
4 (R----)	178 ± 47 (95–285)	—	—

TABLE IV Inappropriate medication-induction intervals.* Number (%) of patients in whom at least one interval was incorrect

Group	*Patients*	*(%)*
1 (RMC)	21	(44)
2 (R--C)	19	(37)
3 (RM--)	6	(12)
4 (R----)	0	(0)

*Intervals for optimal therapeutic effect: ranitidine >90 min, meto clopramide 45–240 min, sodium citrate <45 min.

Gastric fluid volume and pH are shown in Table V and in Figures 1–4. Volumes in Groups 1 and 2 were significantly higher than in Groups 3 and 4 ($P < 0.0001$). There were no significant differences among groups either in pH values or in the number of patients with gastric pH < 2.5 or the number with pH < 2.5 and volume >25 ml (Table VI). Of the ten patients with gastric pH < 2.5 all received ranitidine as scheduled; one received ranitidine alone, six received metoclopramide as scheduled, and four received sodium citrate although in three cases it was given more than 45 min before induction of anaesthesia. Medication-induction intervals for patients with pH > 2.5 were similarly variable. There were no statistically significant differences for volume or pH between premedicated and unpremedicated patients within groups.

Mean phenol red retrieval values of 19 and 17 per cent for Groups 1 and 2 respectively indicated that these percentages of ingested sodium citrate were still in the stomach at the time of sampling. The wide range (0–76 per cent) of values did not correlate with the medication-induction interval. In Groups 3 and 4 phenol red (which was given with 150 ml oral fluid 2–3 hr preoperatively) was detected in only two samples. This indicated that, in all the remaining patients, emptying of ingested fluid was complete.

TABLE V Results: volume and pH. Values are mean ± SD (ranged)

Group	*Volume (ml)*	*pH*
1 (RMC)	22 ± 20 (0–68)*	6.31 ± 1.46 (2.12–8.10)
1 (R--C)	19 ± 16 (0–58)*	5.83 ± 1.33 (1.61–8.27)
1 (RM--)	10 ± 15 (0–80)	6.09 ± 1.82 (1.78–8.93)
4 (R----)	8 ± 10 (0–40)	5.86 ± 1.73 (1.74–8.61)

*$P < 0.0001$ versus Groups 3 and 4.

Discussion

The H_2-receptor antagonists, which decrease gastric acid secretion, are commonly prescribed for obstetrical patients, the morbidly obese, and others who are considered to be at high risk of regurgitation and aspiration of gastric contents during anaesthesia.[13] Cimetidine and ranitidine cause a clinically significant increase in pH although a small percentage of patients still have a pH < 2.5.[14] A single oral dose of ranitidine 150 mg produces peak plasma levels at 1–3 hr, and therapeutic plasma levels for 8–12 hr,[15] so that operative delays are not important.

Metoclopramide is a dopaminergic antagonist which increases peristalsis and relaxes the pylorus. It has no clinically important effect on gastric fluid pH.[7] Peak plasma levels occur 30–75 min afer oral metoclopramide 10 mg.[16] However, there is such a wide variation of bioavailability that its efficacy by this route is questionable.[17] In our study comparison of volume and phenol red retrieval between Groups 1 and 2, and between Groups 3 and 4, suggest that metoclopramide had no consistent effect on volume.

Sodium citrate is a non-particulate antacid which increases gastric pH rapidly. When 30 ml of 0.3 M solution was administered shortly before induction of anaesthesia it raised gastric pH above 2.5 in 87 per cent of patients,[9] but with an increase in gastric fluid volume. The medication-induction interval and the rate of gastric emptying are important because the therapeutic effect of sodium citrate depends upon its continuing presence in the stomach.[18] In our study the addition of sodium citrate, with or without metoclopromide, almost doubled gastric fluid volume without guaranteeing pH > 2.5.

TABLE VI Number of patients "at risk"

Group	*n*	*Vol > 25 ml*	*pH < 2.5*	*Vol > 25 ml and pH < 2.5*
1 (RMC)	46	15	3	0
2 (R--C)	50	14	2	1
3 (RM--)	51	4	3	0
4 (R----)	49	5	2	1

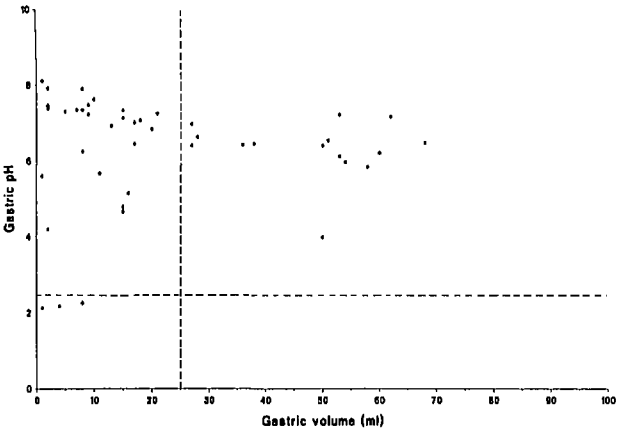

FIGURE 1 Group 1: gastric pH and volume in patients who received ranitidine, metoclopramide, and sodium citrate.

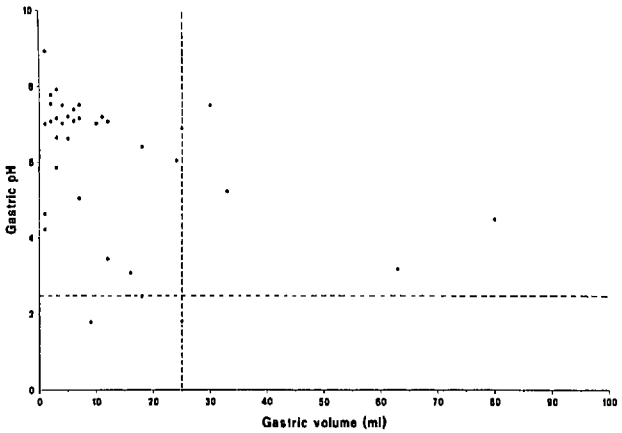

FIGURE 3 Group 3: gastric pH and volume in patients who received ranitidine and metoclopramide.

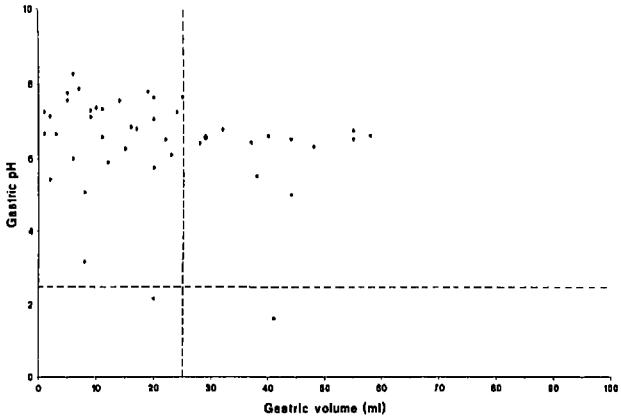

FIGURE 2 Group 2: gastric pH and volume in patients who received ranitidine and sodium citrate.

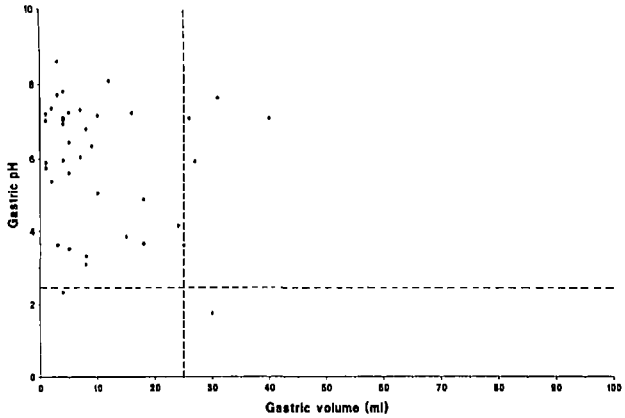

FIGURE 4 Group 4: gastric pH and volume in patients who received ranitidine alone.

Combined prophylactic regimes have not yielded consistent results. Cimetidine was as effective alone as in combination with metoclopramide,[19] and ranitidine was as effective alone as in combination with metoclopramide in normal patients[20] and in the morbidly obese.[21] However, in another study the addition of metoclopramide reduced gastric fluid volume and increased pH.[22] Of 50 healthy women who received oral ranitidine 150 mg on the evening before and oral ranitidine with metoclopramide 10 mg on the morning of surgery, none had a residual gastric fluid volume greater than 30 ml or pH < 2.5.[23]

Scheduled and actual times of surgery rarely coincide. In our study induction of anaesthesia was often later, but sometimes earlier, than the scheduled time, and medication-induction intervals for the three drugs were frequently different from those intended. We have no reason to believe that our surgeons are either better or worse at keeping to schedule than those in other hospitals. If the intervals are too short there is insufficient time for ranitidine and metoclopramide to be absorbed and to exert their effects. If they are too long the effects of metoclopramide and sodium citrate may have dissipated. The maximum benefit of sequential administration of prophylactic medications may only be seen when the intervals can be accurately controlled, and our results demonstrate how difficult it is to achieve this in clinical practice, especially for metoclopramide and sodium citrate. Administration of metoclopramide did not appear to offer any benefit. The interval for sodium citrate exceeded 45 min in nearly one-third of patients in Groups 1 and 2, but only one of these was at "high risk"[24] (volume > 25 ml and pH < 2.5), the same incidence as in Groups 3 and 4 whose patients did not receive citrate. Ranitidine alone was effective in achieving gastric fluid volume < 25 ml

with pH > 2.5 in more than 95 per cent of patients, and additional medications did not give 100 per cent success. Our measurement of gastric fluid volume by blind aspiration underestimates the total volume in each patient. However, a similar error would occur in all groups and inter-group comparisons are therefore valid.

Healthy, elective patients do not benefit from prolonged (overnight) fasting versus 150 ml clear oral fluid 2–3 hr preoperatively whether they receive ranitidine prophylaxis[4,6] or not.[3–5] Olsson *et al.* showed that fatal, or even severe, pulmonary complications following aspiration of gastric contents are rare,[25] and that almost all cases occur in patients who were undergoing emergency surgery, especially in obstetric cases, and in those with difficult airways, or oesophageal or gastric pathology. Many factors contribute to pulmonary complications, and the acid aspiration (Mendelson's) syndrome accounts for only a small minority.[26] Although there is good evidence that pharmacological prophylaxis reduces volume and acidity of gastric fluid, there is no evidence that its use reduces anaesthetic morbidity or mortality from pulmonary aspiration.[12,27] We doubt that routine prophylaxis is justified for all elective patients, and believe that it should be reserved for those with factors which suggest increased risk of aspiration of gastric contents. These factors include increased gastric fluid volume (obstetrical patients and the grossly obese), symptoms of gastro-oesophageal reflux, and anticipated difficult airway management.

Triple prophylaxis is time-consuming and its routine prescription for every patient would significantly increase the nursing workload. Mistiming will always be common because of unforeseen changes in surgical schedules. Our findings demonstrate that no regime guarantees safety, and that a single oral dose of ranitidine 150 mg 2–3 hr preoperatively is as clinically effective as triple prophylaxis.

Acknowledgements

The authors thank Glaxo Canada Inc. who provided funding for this study; Mr. David Kirk for laboratory analyses; and nursing, anaesthesia, and surgical colleagues in Foothills Hospital, Calgary, for their cooperation.

References

1 *Atkinson RS, Rushman GB, Lee JA.* A Synopsis of Anaesthesia. 10th ed. Bristol: Wright 1987: 112.

2 *Orkin FK.* Selection. *In*: Wetchler BV (Ed.). Anesthesia for Ambulatory Surgery. Philadelphia: Lippincott, 1985; 77–123.

3 *Hutchinson A, Maltby JR, Reid CRG.* Gastric fluid volume and pH in elective inpatients. Part I: coffee or orange juice versus overnight fast. Can J Anaesth 1988; 1: 12–5.

4 *Maltby JR, Sutherland AD, Sale JP, Shaffer EA.* Preoperative oral fluids: is a five-hour fast justified prior to elective surgery? Anesth Analg 1986; 65: 1112–6.

5 *McGrady EM, Macdonald AG.* Effect of preoperative administration of water on gastric volume and pH. Br J Anaesth 1988; 60: 803–5.

6 *Maltby JR, Reid CRG, Hutchinson A.* Gastric fluid volume and pH in elective inpatients. Part II: coffee or orange juice with ranitidine. Can J Anaesth 1988; 35: 16–9.

7 *Harrington RA, Hamilton CW, Brogden RW, Linkewich JA, Romankiewicz JA, Heel RC.* Metoclopramide – an updated review of its pharmacological properties and clinical use. Drugs 1983; 25: 451–94.

8 *Veigas OJ, Ravindran RS, Stoops CA.* Duration of action of sodium citrate as an antacid. Anesth Analg 1982; 61: 624.

9 *Foulkes E, Jenkins LC.* A comparative evaluation of cimetidine and sodium citrate to decrease gastric acidity: effectiveness at the time of induction of anaesthesia. Can Anaesth Soc J 1981; 28: 29–38.

10 *Ostneimer GW.* Comment in: Aspiration of gastric contents. *In*: Miller RD, Kirby RR, Ostheimer GW, Roizen MF, Stoelting RK (Eds.). Year Book of Anesthesia 1987. Chicago: Year Book Medical Publishers 1987: 322–3.

11 *Ostheimer GW.* Prolonged fluid fasting: a commentary. Wellcome Trends in Anesthesiology 1987; 5: 7.

12 *Schedl HP.* Use of polyethylene glycol and phenol red as unabsorbed indicators for intestinal absorption studies in man. Gut 1960; 9: 237–42.

13 *Hardy J-F.* Large volume gastro-esophageal reflux: a rationale for risk reduction in the perioperative period. Can J Anaesth 1988; 35: 162–73.

14 *Durrant JM, Strunin L.* Comparative trial of the effect of ranitidine and cimetidine on gastric secretion in fasting inpatients at induction of anaesthesia. Can Anaesth Soc J 1982; 29: 446–51.

15 *Zeldis JR, Friedman LS, Isselbacher KJ.* Ranitidine: a new H_2 receptor antagonist. N Eng J Med 1983; 309: 1368–73.

16 *Ross-Lee LM, Eadie MJ, Hooper WD, Bochner F.* Single dose pharmacokinetics of metoclopramide. Eur J Clin Pharmacol 1981; 20: 465–71.

17 *Bateman DN, Davies DS.* Pharmacokinetics of metoclopramide. Lancet 1979; i: 166.

18 *O'Sullivan G, Bullingham RES.* Radio pills for measurement of duration of action of sodium citrate. Anesth Analg 1983; 62: 368–9.

19 *Pandit SK, Kothary SP, Pandit UA, Mirakhur RK.* Premedication with cimetidine and metoclopramide. Anaesthesia 1986; 41: 486–92.

20 *Manchikanti L, Colliver JA, Marrero TC, Roush JR.* Ranitidine and metoclopramide for prophylaxis of aspiration pneumonitis in elective surgery. Anesth Analg 1984; 63: 903–10.
21 *Lam AM, Grace DM, Manninen PH.* The effects of cimetidine and ranitidine with and without metoclopramide on gastric volume and pH in morbidly obese patients. Can Anaesth Soc J 1986; 33: 773–9.
22 *Gipson SL, Stovall TG, Elkins TE, Crumrine RS.* Pharmacologic reduction of the risk of aspiration. South Med J 1986; 79: 1356–8.
23 *Pond W, Lindsey R, Cowan J.* Preoperative ranitidine and metoclopramide. Anesth Analg 1987; 66: 1202.
24 *Roberts RB, Shirley MA.* Reducing the risk of aspiration during Cesarean section. Anesth Analg 1974; 53: 859–68.
25 *Olsson GL, Hallen B, Hambraeus-Jonzon K.* Aspiration during anaesthesia: a computer-aided study of 185,358 anaesthetics. Acta Anaesthesiol Scand 1986; 30: 84–92.
26 *Atkinson RS, Rushman GB, Lee JA.* A Synopsis of Anaesthesia. 10th ed., Bristol: Wright 1987: 321–5.
27 *Hamilton WK.* Does a legalistic approach to anaesthesia benefit the patient? Ann R Coll Surg Engl 1988: 70: 352–6.