

Clinical Evaluation of Isoflurane

COMPLICATIONS DURING AND AFTER ANAESTHESIA

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The aim of this study was to quantitate the incidence and to grade the severity of complications during and after isoflurane anaesthesia, and to relate the occurrence of complications to the condition of the patient and to certain interventions. The majority of the patients did not experience any complications, and most complications were minor. However, laryngospasm occurred relatively often in children under 10 years of age.

MATERIALS AND METHODS

This report defines a complication as an incident occurring during the anaesthetic or postoperative period which the responsible anaesthetist considered to be unusual. The anaesthetist was also responsible for categorizing the complications as minor or major and, in his judgment, determined whether the complication was related to the anaesthetic procedure (not necessarily to the anaesthetic agent). Observation periods included: (1) the first 10 minutes of the anaesthetic (induction); (2) the remaining time of the anaesthetic (maintenance); and (3) the time between arrival of the patient in the recovery room and dismissal from the hospital.

In some of the patients, more than one complication was reported for a given period. The statistical significance of the association of a complication with a certain condition or intervention was examined separately for the first, second, or third complication. If the P-values of the Pearson chi square tests for both the first and second complication were less than 0.0005, then the association was considered to be statistically significant. Statistical analyses were done only on the first 5,472 patients, although recording of complications was done on all patients.

RESULTS

General Results (Table 40) – A total of 7,196 patients were studied, but data from only 6,798 patients were included since the information on 398 patients was incomplete. The pa-

tients included 3,677 females (54.1 per cent) and 3,121 males (45.9 per cent). Of these patients 1,589 (23.4 per cent) were smokers and 1,554 (22.9 per cent) were treated for circulatory or respiratory ailments with various drugs; 3,060 patients (44.4 per cent) were classified as ASA status I, 2,263 (32.7 per cent) as ASA II, 1,040 (15.3 per cent) as ASA III, 112 (1.6 per cent) as ASA IV, 1 as ASA V and 322 (4.7 per cent) had emergency procedures; 6,218 patients underwent one, 534 patients two, and 46 more than two surgical procedures. However all patients had only one anaesthetic.

1,735 complications occurred; of these, 1,491 (86.0 per cent) were minor and 231 (13.3 per cent) major. Thirteen deaths were reported (0.7 per cent) (Table 40).

Male and female patients experienced a similar incidence of complications. Approximately one third (30.0 per cent) of the complications occurred during the induction, one third (35.9 per cent) during maintenance, and one third (33.1 per cent) during the postoperative period. Circulatory complications and respiratory complications were as frequent in non-smokers as in smokers in all three periods.

The relative incidence of complications during induction and maintenance but not postoperatively was larger in very young or old patients. Complications also occurred more frequently at very low and very high body weights.

Complications During Induction of Anaesthesia – 92.7 per cent of the patients had no complications. A total of 537 complications occurred and, of these, 90.3 per cent were minor, 9.7 per cent major and no death was reported. Respiratory (46.6 per cent) and circulatory (47.9 per cent) complications were most frequent.

Complications During the Maintenance Period – 91.9 per cent of the patients had no complications. A total of 623 complications were reported and of these 84.1 per cent were minor and 15.2 per cent major. Four patients died. Circulatory complications (76.1 per cent) were more frequent, while respiratory complica-

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TABLE 40
1,735 COMPLICATIONS IN 6,798 PATIENTS

Severity	Induction	Maintenance	Postop
Minor	485	524	482
Major	52	95	84
Death	0	4	9
Total	537 (31.0%)	623 (35.9%)	575 (33.1%)

tions (15.9 per cent) were reported less often. Renal (0.5 per cent), CNS (2.2 per cent), gastrointestinal (1.0 per cent), and miscellaneous unspecified complications (4.3 per cent) constituted the remaining complications.

Complications During the Postoperative Period - 92.7 per cent of the patients had no complications. A total of 575 complications were reported and of those 83.8 per cent were minor and 14.6 per cent major. Nine patients died. Complications related to the respiratory system were most frequent (29.0 per cent). Circulatory complications accounted for 23.7 per cent. Complications related to the gastrointestinal tract (15.3 per cent), central nervous system (17.4 per cent), and miscellaneous unspecified complications (12.3 per cent) occurred at nearly the same frequency, while renal complications were infrequent (2.3 per cent).

Type of Complications - Circulatory (50.0 per cent) and respiratory (29.7 per cent) complications contributed the bulk of reported complications. Unspecified miscellaneous complications (6.6 per cent) and complications related to the central nervous system (7.2 per cent) were much less frequent. Only 5.6 per cent of all complications were related to the gastrointestinal system and 0.9 per cent to the genitourinary system.

Circulatory Complications (Table 41) - Arrhythmias (40.4 per cent), hypotension (33.9 per cent), and hypertension (16.4 per cent) were the most frequently reported circulatory complications (Table 41). About half (50.3 per cent) of the arrhythmias, hypotension (68.4 per cent), and hypertension (49.3 per cent) were considered to be related to anaesthesia.

The operative procedure and the highest isoflurane concentration used during induction were significantly associated with the occurrence of circulatory complications during induction. Operative procedure, pre-existing circulatory or respiratory diseases, duration of anaesthesia,

TABLE 41
CIRCULATORY COMPLICATIONS IN 6,798 PATIENTS

Complication	Induction	Maintenance	Postop
Arrhythmia	118	188	44
Clotting	1	2	2
Congestive failure	0	4	6
Hypertension	43	56	43
Hypotension	81	187	26
Myocard. infarction	0	1	1
Myocard. ischaemia	4	4	1
Pulmonary embolus	0	1	0
Thrombophlebitis	0	0	1
Other emboli	0	2	1
Other circulatory	10	29	11
Total	257	474	136

and intake of digitalis, beta blockers, or diuretics were significantly associated with the occurrence of circulatory complications during maintenance. Operative procedure, duration of anaesthesia, respiratory or circulatory diseases, and intake of digitalis and beta blockers were significantly associated with occurrence of circulatory complications during the postoperative period.

Respiratory Complications (Table 42) - Unspecified respiratory complications (53.3 per cent), laryngospasm (23.6 per cent), and bronchospasm (11.0 per cent) were the most frequently reported respiratory complications. Most laryngospasm (80.3 per cent) and nearly half of the bronchospasms (49.1 per cent) were believed to be related anaesthesia.

TABLE 42
RESPIRATORY COMPLICATIONS IN 6,798 PATIENTS

Complication	Induction	Maintenance	Postop
Aspiration	3	1	2
Atelectasis	0	1	12
Bronchitis	0	0	1
Bronchospasm	26	22	9
Laryngitis	1	1	4
Pneumonia	0	0	4
Pneumothorax	0	2	2
Tracheitis	0	0	0
Laryngospasm	77	25	20
Sore throat	0	0	28
Other respir. complications	143	47	85
Total	250	99	167

The highest and the average isoflurane concentrations used during induction correlated significantly with the occurrence of respiratory complications during induction. Operative procedure, duration of anaesthesia, respiratory or circulatory diseases, and tracheal intubation during the postoperative period were significantly associated with the occurrence of respiratory complications during the maintenance period. Operative procedure, respiratory or circulatory diseases, intake of digitalis or beta blockers, and tracheal intubation during the postoperative period were significantly associated with the incidence of respiratory complications during the postoperative period.

Central Nervous System Complications – Unspecified complications (41.6 per cent) and prolonged obtundance (27.2 per cent) were the most often reported complications related to the central nervous system. In 23 patients the prolonged obtundance was thought to be related to anaesthesia. Operative procedure was significantly associated with the occurrence of prolonged obtundance during the postoperative period.

Renal Complications – Two instances of oliguria were reported for the maintenance and four for the postoperative period. Anuria occurred twice postoperatively. Renal failure was not reported.

Gastrointestinal Complications (Table 43) – Prolonged nausea and vomiting in the postoperative period occurred in 36 and 22 patients, respectively (Table 43); they tended to be more frequent in female than in male patients. One patient developed hepatitis during the postoperative period. It could not be determined whether the hepatitis was related to the anaesthetic procedure (see below).

Severity of Complications – The severity of

the complications (minor, major, or death) during the maintenance period was significantly related to the operative procedure, average isoflurane concentration using during the maintenance period, postoperative mechanical ventilation, duration of anaesthesia, and ASA status. The severity of complications reported for the postoperative period was also significantly related to the operative procedure, postoperative mechanical ventilation, and ASA status.

DISCUSSION

The most important findings of this study are that the majority of patients did not develop complications; most complications were minor; complications occurred at nearly similar rates during induction, maintenance, and postoperative periods; complications occurred at nearly the same frequency in male and female patients; smokers did not experience more respiratory or circulatory complications; and laryngospasm and bronchospasm occurred relatively frequently, the former particularly in younger patients.

Comments on Limitation of Methodology – It was our purpose to record the incidence of complications during and after isoflurane anaesthesia, and to relate the incidence of complications to the condition of the patient and to the anaesthetic and surgical procedure. We did not propose to compare the rate and severity of complications with isoflurane against rate and severity of complications observed with other anaesthetic agents.

The accuracy of any conclusion from this study depends critically on the accuracy of the information reported by the several hundred participating anaesthetists. The low rate of some of the postoperative complications, as for instance pneumonia (0.06 per cent) and sore throat (0.4 per cent), suggests that some participating anaesthetists understood that complications were to be reported only for the immediate recovery rather than for the total postoperative period.

The definition of an unusual incident (i.e. a complication) was left to the participating anaesthetists. Laryngospasm may have been recorded by some as a reflex activity, by some as a complication, and by others as both. Similarly, some anaesthetists may have considered hypotension or arrhythmias either as a reflex activity or as a complication.

In interpreting the data from the study, one

TABLE 43
GASTROINTESTINAL AND OTHER MISCELLANEOUS
COMPLICATIONS IN 6,798 PATIENTS

Complication	Induction	Maintenance	Postop
Hepatitis	0	0	1
Ileus	0	1	2
Prol. nausea	0	0	36
Prol. vomiting	0	0	22
Other GI	3	5	27
Other miscell.	16	27	71
Total	19	33	159

must keep in mind that the decision of the anaesthetist linking a complication to the anaesthetic procedure was partly subjective. Furthermore, no attempt was made in this study to distinguish between the responsibility of isoflurane and that of other aspects of the anaesthetic procedure.

Within these limitations, the results of the study reflect the rate of complications during isoflurane anaesthesia and the relation of these complications to the condition of the patient and to certain interventions. However, at the time of this study most anaesthetists were relatively unfamiliar with the use of isoflurane and hence some complications may decline with more experience.

Circulatory Complications – During induction of anaesthesia, arrhythmias were reported as a complication nearly twice as often (3.0 vs 1.3 per cent), hypotension more than three times as often (2.7 vs 0.8 per cent), and hypertension nine times as often (1.8 vs 0.2 per cent) in patients with pre-existing circulatory disease than in patients without circulatory disease. These complications were also more frequent in patients with circulatory than without circulatory disease during the maintenance, {arrhythmias (5.2 vs 2.2 per cent), hypotension (7.4 vs 1.8 per cent), hypertension (2.6 vs 0.3 per cent)} and postoperative period {arrhythmias (2.1 vs 0.2 per cent), hypotension (2.2 vs 0.2 per cent), hypertension (0.9 vs 0.2 per cent)}. Since isoflurane produces peripheral vasodilation, arterial hypotension during the induction or maintenance of anaesthesia might have been expected. It is surprising, however, that the occurrence of arterial hypertension was frequently thought to be related to the anaesthetic procedure.

Respiratory Complications – Unspecified respiratory complications which probably included coughing, sneezing, and the occurrence of secretions were most frequently reported. Laryngospasm was relatively frequent in children under the age of 10 years. Its incidence was significantly associated with the inspired isoflurane concentrations used during induction and may be related to the pungency of isoflurane. Further studies will show whether the incidence of laryngospasm can be reduced by more carefully titrating the inspired concentration of isoflurane during induction.

Other Complications – Previous studies in animals and man demonstrated little or no adverse effect of isoflurane on the liver, which is

perhaps related to its minimal biotransformation. In this study one case of hepatitis was observed. It occurred in an obese female who had a cholecystectomy for acute cholecystitis. The hepatitis was considered to be minor and the patient recovered. Although the recording the postoperative complications may not have included the entire duration of hospitalization, we believe from our experience that any other case of postoperative hepatitis would most likely have been brought to the attention of the anaesthetists by the surgeons. The incidence of 0.015 per cent of hepatitis in this study compares with an incidence of 0.010 per cent of massive hepatic necrosis and of 0.023 per cent of intermediate hepatic necrosis reported in the National Halothane Study.⁴¹ Only extensive experience with isoflurane can establish its effect on liver function.

Seizures were reported in nine instances as complications and twice were considered to be related to the anaesthetic. The cause of these seizures was uncertain, but there was no significant association between the seizures and the isoflurane concentrations used. Convulsive activity has not been observed in previous studies on animals and man, but the isomer of isoflurane (enflurane) can produce convulsive activity. Further studies of the association between seizures and isoflurane are indicated.

The cause of the oliguria and anuria were also uncertain; no significant association existed between the occurrence of renal complications and isoflurane concentrations used, but in one instance oliguria was thought to be related to the anaesthetic procedure. Further studies on the renal effect of isoflurane are indicated. Previous studies on animals and man have shown no adverse renal effects.

Death Occurring During and After Isoflurane Anaesthesia – No deaths were reported for the induction period. The four patients who died during maintenance were elderly (51 to 77 years) with multiple system disease. Three of these four patients had cardiac surgery and the other an intra-abdominal procedure. There was no relationship between the concentration of isoflurane and the death. In all four cases the deaths were not considered to be related to the anaesthetic procedure. The nine patients who died in the postoperative period died of a variety of problems (sepsis, bleeding, pulmonary oedema, left ventricular rupture, and cardiac arrest). Overall, the incidence of death (0.19 per cent) was

considerably less than that reported in the National Halothane Study (1.93 per cent).⁴¹

SUMMARY

Approximately 90 per cent of the patients had no complications. Most of the 1,735 complica-

tions were minor and presented no significant problem to the patient.

It is suggested that isoflurane appears to be a safe anaesthetic agent in a wide variety of clinical settings. However, as with any drug, its ultimate safety will be determined only after extensive use.