Clinical Evaluation of Isoflurane

DOSE REQUIREMENTS

MICHAEL K. CAHALAN

THE COMPETENT ADMINISTRATION of an anaesthetic requires an awareness of the inspired concentrations of agent needed to induce and to maintain safe levels of anaesthesia. This study examines the delivered concentrations of isoflurane used in 6,798 clinical anaesthetics given in 165 teaching hospitals. All participating anaesthetists were aware of the published information concerning isoflurane requirements. Such information obviously will influence the perception of patient needs. However, we assumed that the delivered concentrations recorded were those used and required for the conduct of safe anaesthesia.

A wide spectrum existed in adjuvant anaesthetic use, operative procedures, and patient disease. Individual anaesthetists were responsible for the selection of patients and the tailoring of anaesthesia to individual patient's requirements. The results identified factors which predict deviations in patient requirements: these usually agreed with the general fund of information concerning requirements for all inhalation anaesthetics.

However, some of the results did not reveal anticipated cause and effect relationships. The format of this clinical study and the necessity to keep data acquisition forms succinct meant that cause and effect relationships were often unclear. Sometimes it was not clear whether a specific concentration was delivered to achieve a certain effect or that a specific effect occurred and dictated a certain concentration. Clearly the practitioners titrated the dose of isoflurane in response to clinical events and/or their perception of such events.

PREDICTIONS OF ISOFLURANE REQUIREMENTS

Previous studies have shown that the minimum alveolar concentration (MAC) of isoflurane in oxygen which inhibits movement in response to incision in 50 per cent of middle aged patients is 1.15 per cent.[5] If 60 per cent nitrous oxide is used, 0.53 per cent isoflurane is required. MAC progressively decreases with increasing age. Within any given age group the variation in MAC is small, and concentrations 30 per cent higher than the age-adjusted MAC virtually assure immobility.[5]

The delivered concentrations recorded in this study were those delivered from the anaesthetic machine and exceeded alveolar levels by virtue of isoflurane uptake. Fortunately, isoflurane blood solubility is modest (the blood/gas partition coefficient is 1.4) and estimates of alveolar levels from delivered concentrations normally would err by less than 25–30 per cent.[6] However, the anaesthetic concentrations delivered from the machine can be significantly less than inspired concentrations if low flow rates are used and rebreathing occurs. Inflow rates of four to five litres/min or more minimize or prevent rebreathing in most conventional anaesthetic circuits.

We might begin by examining isoflurane requirements predicted from previous studies. A rapid induction requires an alveolar level half again as large as MAC to achieve MAC partial pressures in brain quickly.[6] Further, a 30 per cent excess of the MAC in oxygen may be desired to assure immobility. On induction, isoflurane inspired concentrations are about double alveolar levels at five minutes. Thus our calculated induction dose with 60 per cent nitrous oxide might be:

$$(\text{MAC} + 30 \text{ per cent}) \times (\text{Alveolar-Brain}) \times (\text{Inspired-Alveolar}) = (\text{Induction Dose})$$

which is

$$[0.53 + (0.3)1.15] \times 1.5 \times 2 = 2.63 \text{ per cent}$$

By similar reasoning we can estimate the maintenance dose assuming the same MAC multiple (1.3), no alveolar-to-brain gradient and a 75 per cent equilibration of alveolar and inspired concentrations:

$$[0.53 + (0.3)1.15] \times (1) \times (1.33) = 1.16 \text{ per cent}$$

Such predictions must be adjusted for changes which alter MAC. As noted, MAC is inversely related to age and nitrous oxide concentrations. Depressant drugs such as tranquilizers and narcotics also decrease MAC.[7,8] The intensity of stimulation will affect the MAC if it is not a supra-maximal stimulation. Skin incision may not be a supra-maximal stimulation and thus one might predict that procedures with more intense stimulation (e.g. airway stimulation in EENT surgery) might require greater anaesthetic concentrations. Alternatively, higher concentrations might be indicated in these cases to modulate cardiovascular (pressure, heart rate) or respiratory (coughing) responses to stimulation.

Having made our predictions and having noted the factors which might alter them, let us examine the study material.

Methods

The general procedures of data collection and analysis were outlined previously. Four values for inspired concentrations were obtained in each case: the highest delivered isoflurane concentration used during induction (HIFLUR 2) and maintenance (HIFLUR 3) and the average concentration delivered during induction (AVGFLUR 2) and maintenance (AVGFLUR 3).

Results

The mean values of HIFLUR 2 and 3 and AVGFLUR 2 and 3 are shown for our study population (Table 10). The "mean patient" was classified ASA I or II and weighed 63.8 kg. She (54 per cent female) received a combination of premedications including a narcotic 57 per cent of the time and a tranquilizer 47 per cent of the time. A barbiturate was used in 77 per cent of the inductions.

Nitrous oxide use was ubiquitous: in 96.8 per cent of inductions and in 97.5 per cent of cases during maintenance. Fresh gas flows exceeding 4.0 litres/min were used in 82.6 per cent of patients during induction and 62.4 per cent during maintenance.

The range of concentrations delivered was large. The exceedingly high values were rare, as one can appreciate from the standard deviations (Table 10), and resulted from cases in which very low flows were used. Utilizing data from patients who received fresh gas flows less than 3 litres/min, a significant correlation was found between fresh gas flow and the delivered isoflurane concentration. No such correlation existed when fresh gas flows of 4 litres/min or more were employed. Indeed, induction was accomplished in 80.4 per cent of all patients within a four-fold range of concentrations (HIFLUR 2 > 0.8 or ≤ 3.2 per cent). Likewise a four-fold range of concentrations maintained anaesthesia in 78.9 per cent (AVGFLUR 3 > 0.4 ≤ 1.60 per cent).

TABLE 10

Delivered Isoflurane (% ATM) (N = 6,798)

	Mean	Standard deviation	Range*
Hiflur 2	2.307	1.726	0–40.0
Avgflur 2	1.693	0.978	0–22.0
Hiflur 3	1.712	0.877	0–18.5
Avgflur 3	1.203	0.593	0–8.8

Hiflur 2–highest isoflurane concentration delivered during induction.

Hiflur 3–highest isoflurane concentration delivered during maintenance.

Avgflur 2–average isoflurane concentration delivered during induction.

Avgflur 3–average isoflurane concentration delivered during maintenance.

*High values were obtained in cases where low flow closed circuits were used.

Clearly we can explain some of the variation by factors known to affect MAC. Results in Table 11 are mean delivered anaesthetic concentrations arbitrarily grouped by age. The inverse correlation with age appears confirmed since adults required significantly less isoflurane than infants or youths. Regressions of age vs delivered concentrations demonstrate significant negative correlations. So few of the patients did not receive nitrous oxide that, despite the potent effect nitrous oxide is likely to have had, we could not demonstrate it; but the effect of the other factors can be seen.

Narcotic premedication, whether given alone or in combination with other drugs, was asso-

TABLE 11

Mean Delivered (% ATM) Isoflurane to Three Age Groups

	Infant	Youth	Adult
	(<1 yr) n = 135	(>1 <20 yr) n = 1197	(>20 yr) n = 5561
Hiflur 2	2.873	2.616	2.252
Avgflur 2	1.850	1.937	1.653
Hiflur 3	1.848	1.866	1.687
Avgflur 3	1.387	1.378	1.163

Symbols as in Table 10.

ciated with lower delivered concentrations of isoflurane. A comparison of patients who received only a narcotic as a premedication with those who received no premedication revealed a significant difference (Table 12). The use of a barbiturate during induction was associated with a lower concentration of delivered isoflurane (Table 13). However, when the effect of the other adjuvant agents was examined during induction and maintenance, no consistent association was evident. For instance, when a narcotic or barbiturate was used during maintenance, generally higher delivered isoflurane concentrations were noted. Whether these drugs were given to suppress a response that might have been interpreted as inadequate anaesthesia, while at the same time delivered isoflurane concentrations were increased, is a question which could not be answered in this study.

As predicted, different procedure sites were associated with different isoflurane concentrations. For example, intracranial surgery required the lowest and EENT surgery the highest – a significant difference (Table 14). Between these extremes the procedure site itself seems to have little predictable association with isoflurane requirements.

Several other factors appeared to alter anaesthetic requirements. Our results indicate a lower delivered concentration of isoflurane was used in patients with ASA status III, IV, or V as against ASA I or II (Table 15), and thus it was no surprise that delivered concentrations were also lower in patients taking any of the current medications or having one or more of the specified diseased systems.

Forbes suggested recently that pancuronium decreases MAC independently of its paralytic action.[9] Our results support this conclusion, since both pancuronium and curare dosages have significant negative correlations with the dose of isoflurane. Of interest is the absence of such a correlation with succinylcholine which may have greater difficulty entering the central nervous system.

One surprising result is that men in all age groups consistently required more isoflurane than women (Table 16). Only the youth group is shown in the Table 16 because within this group the differences approach or reach statistical

TABLE 12

DELIVERED ISOFLURANE (% ATM) THE EFFECT OF NARCOTIC PREMEDICATION

	No premed n = 1380	Narcotic alone n = 447	P
Hiflur 2	2.396	2.107	0.001
Avgflur 2	1.774	1.649	0.089
Hiflur 3	1.731	1.610	0.070
Avgflur 3	1.289	1.154	0.0001

Symbols as in Table 10.

TABLE 13

DELIVERED ISOFLURANE REQUIREMENTS EFFECT OF BARBITURATE ADMINISTERED DURING INDUCTION

	No IV drugs n = 1142	Only barb. n = 4407	P
Hiflur 2	2.707	2.374	0.0001
Avgflur 2	1.945	1.757	0.0001
Hiflur 3	1.847	1.756	0.012
Avgflur 3	1.310	1.217	0.0001

Symbols as in Table 10.

TABLE 14

DELIVERED ISOFLURANE (% ATM) THE EFFECT OF PROCEDURE SITE

	Intracranial n = 106	EENT n = 832	P
Hiflur 3	1.431	1.913	0.0001
Avgflur 3	0.872	1.417	0.0001

Symbols as in Table 10.

TABLE 15

DELIVERED ISOFLURANE (% ATM) THE EFFECT OF ASA STATUS

	ASA I or II n = 5521	ASA III, IV, or V n = 1277	P
Hiflur 2	2.377	2.087	<0.001
Avgflur 2	1.757	1.470	<0.001
Hiflur 3	1.730	1.674	0.096
Avgflur 3	1.236	1.054	<0.001

Symbols as in Table 10.

TABLE 16

DELIVERED ISOFLURANE (% ATM) THE EFFECT OF GENDER (YOUTH GROUP)

	Female n = 533	Male n = 644	P
Hiflur 2	2.529	2.687	0.078
Avgflur 2	1.880	1.983	0.077
Hiflur 3	1.747	1.962	0.0001
Avgflur 3	1.322	1.424	0.010

Symbols as in Table 10.

TABLE 17

COMPARISON OF AVERAGE DELIVERED ISOFLURANE REQUIREMENTS (% ATM)

	Induction	Maintenance
Predictions*	2.63	1.16
NDA Study	2.70	1.37
This Study	2.313	1.203

*See introduction to this section. Values at induction are highest values while those during maintenance are average values.

significance. However, in both the infant and adult group similar trends were evident.

CONCLUSION

The isoflurane concentrations used in this study during maintenance are very close to the predicted values and to the values demonstrated in the NDA study[10] (Table 17). A range of concentrations from 0.4 to 3.2 per cent delivered in 50–70 per cent nitrous oxide induced and maintained anaesthesia in most patients. When low flow or closed systems were used, extensive rebreathing required delivery of much higher concentrations.

Age, premedication drugs (particularly narcotics), and higher ASA status all were associated with lower delivered isoflurane concentrations. Patients who received barbiturates during induction received lower isoflurane doses. Patients undergoing EENT surgery received more isoflurane than most other patients, particularly those undergoing intracranial surgery who had the lowest requirements. The use of non-depolarizing relaxants was also associated with lower concentrations of isoflurane.

Surprisingly, males consistently received more isoflurane than females, a finding not previously demonstrated for inhalational anaesthetics. However the difference is too small to be of clinical significance.

DISCUSSION

None of these factors altering anaesthetic requirement operated independently. No *a priori* attempt has been made to test the isolated effect of a specific factor on isoflurane requirement. The 6,798 anaesthetic cases were conducted with a view only to producing optimal clinical results in the individual patient. It is within this setting that we have defined the clinical requirements of isoflurane. Because of this fact, these data should be used with great care in constructing cause and effect relationships or to predict outcomes.