Clinical Evaluation of Isoflurane

DISCUSSION

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The aims of this study were to conduct a clinical evaluation of isoflurane in a variety of clinical settings and to determine the demographic descriptors of a sample population of patients undergoing surgical operations during isoflurane anaesthesia. There were five general objectives:

(a) What patient and anaesthetic factors affect the changes in pulse rate and blood pressure associated with isoflurane?

(b) What are the clinical requirements as highest and average concentrations of isoflurane in a broad population of patients and what factors determine the level used?

(c) What patient and anaesthetic factors predispose to the occurrence of arrhythmias (atrial, nodal, ventricular)?

(d) What factors predispose to the occurrence of reflex activities?

(e) What complications occur during and after operation and what factors predispose to their occurrence whether related to isoflurane or not?

The design of the study was a single cohort design since all patients had isoflurane as a criterion for inclusion. Serious and lengthy consideration was given at the outset to inclusion of comparative groups having other inhalational anaesthetics. Despite the value of such comparison, the validity of comparing the clinical effects of the new agent isoflurane in an open manner with other more familiar agents, such as halothane or enflurane, was judged by the panel to carry the risk of bias in addition to the probable learning phenomenon during its early use. Therefore the decision was made by the authors that the initial screening should address the five broad questions outlined above, but should also include an investigation of any temporal changes in the way isoflurane was used or patients included as the study progressed, by examining successive cohorts of approximately 1,000 patients. Since the normal patient population undergoing surgical operations was to a large extent unknown and since it was assumed that this could vary within each institution depending on specialised services (for example paediatric, cardiovascular, neurosurgical and so on) consideration was given to selecting institutions which, when added together, would provide as broad a population of patients as possible. This provided a unique opportunity to examine patterns of practice as well as to assess the clinical effects of isoflurane in numerous but varied teaching hospitals throughout North America.

The Association of Canadian University Departments of Anaesthesia (ACUDA) was asked to cooperate in the multi-center study and the physician/investigator panel was formed through this organization, with representation reflecting special expertise. It was further agreed by Ohio Medical Products Inc. that, despite full approval from the Federal Drug Administration in The United States and the Health Protection Branch of Health and Welfare Canada for general release in 1980, prior to the study, final widespread release would be delayed until the panel had reviewed the results of the study and given its approval. This was done in April 1981 and isoflurane has been available for general use since then.

In addition to providing valuable information on the clinical effects of isoflurane, this study has provided demographic information which was not previously available on such a large scale. The patient characteristics which have been examined have been referred to in previous sections and indicate geographic differences in the relative incidences of disease, procedures, current medications, and the various drugs used during anaesthesia. Further, there were significant variations between institutions, even within sample regions, which reflected the particular patient population as well as patterns of practice.

The information on the relationships between body size (weight, height, and surface area) and age factors, pulse rate and blood pressure before and during anaesthesia provides a clinically useful set of predictors. Similarly, the dependence of some of the clinical effects of isoflurane on those factors, such as reflex activities, war-

rents further study in comparison to other inhalational agents.

The results of this study indicate that the five general aims of the study have been met. On average, there was an increase in pulse rate at induction to six per cent above awake values which fell to three per cent above awake values during maintenance. Blood pressure on average decreased to seven per cent below awake values at induction and decreased further during maintenance to 12 per cent below awake values. The extent to which pulse rate increased and blood pressure decreased depended on age and body size. Thus pulse rate increased to a lesser extent with age while blood pressure decreased to a greater extent. Preoperative pulse rate and blood pressure were found to significantly influence the values occurring during isoflurane anaesthesia and varied with age. The variability around the means for each age group was greater for pulse rate in the patients under 10 years and for blood pressure in patients over 60 years both before and during isoflurane anaesthesia, although the only significant predictors of lability of pulse rate and blood pressure were the respective preoperative values. The studies of Homi, et al[28] indicate that blood pressure decreased linearly with increasing concentration of isoflurane while pulse rate increased but was not related to the blood level of isoflurane. In the present study, there were positive correlations for pulse during induction and maintenance against highest and average isoflurane concentration during induction and average isoflurane concentration during maintenance, respectively (see Table 25). However a negative correlation was found between change in blood pressure and average isoflurane concentration during maintenance. These findings tend to contradict those previously published[28] and deserve further study.

Anaesthetic drugs and premedication were found to affect the overall pulse and blood pressure response to isoflurane. When no premedication was given pulse rate increased by 10.8 per cent and blood pressure decreased by six per cent at induction, compared to an increase of 10.6 per cent in pulse rate and decrease of eight per cent in blood pressure for the most frequently used premedication of anticholinergic, tranquilizer, and narcotic. When isoflurane alone in oxygen and nitrous oxide was used for anaesthesia, pulse rate increased by 14.6 per cent and blood pressure decreased by 6.8 per cent during induction, whereas when a barbiturate was also used at induction (75 per cent of cases) pulse rate increased by 6.9 per cent and blood pressure decreased by 7.5 per cent.

The lack of effect on pulse rate by dose of pancuronium and on blood pressure by dose of tubocurarine was rather surprising in view of the widely known effects of these muscle relaxants. The doses used, however, clearly support the synergism of isoflurane in terms of muscle blockade which has been reported by others.[27,28,34] This potentiation of neuromuscular blockade with drugs such as succinylcholine, tubocurarine or pancuronium was not associated with difficulty of reversal or with a higher incidence of post-anaesthetic respiratory problems. The negative correlation between pulse rate and fluid therapy and positive correlation between blood pressure and fluid therapy were expected (Table 31) and depended to a large extent on procedure site (cf Table 5). Major vascular and intra-abdominal procedures were associated with greater blood loss and more fluid therapy.

The lack of any change in pulse rate in patients with either circulatory or respiratory disease was of particular interest. In these patients blood pressure fell to a greater degree, but both preoperative values and those during maintenance were higher than the control group with no disease. This supports the findings of previous studies[13,14] which indicate that isoflurane conveys a degree of stability which may be an advantage in the patient at risk because of cardiovascular disease.

Arrhythmias were very infrequent in this study. There were significant correlations for preoperative atrial and ventricular arrhythmias with ASA status, age, and preoperative blood pressure. New atrial and ventricular arrhythmias increased with the maximum blood pressure during anaesthesia. In normal healthy patients (80 per cent of cases) the overall incidence of preoperative arrhythmias was less than 2.5 per cent and was unchanged in patients with normal blood pressures under anaesthesia. This confirms the studies of others[27,28,34] which point to a much greater stability of heart rhythm with isoflurane compared to other agents. In the New Drug Application for isoflurane[10], preoperative ventricular arrhythmias were present in 1.8 per cent of 602 patients while the incidence of preoperative arrhythmias was 1.6 per cent for 554 patients given halothane. No change in

incidence of ventricular arrhythmias was found for isoflurane but increased to 6.1 per cent with halothane.

The concentrations of isoflurane which were used in the present study were very close to those predicted from previous studies[10] making allowance for the need for greater concentrations than the MAC value alone (see Table 17) in the clinical setting. The average concentration used at induction was 1.69 per cent and during maintenance was 1.2 per cent. A greater concentration was required in younger patients, tending to confirm the work of Gregory et al[48] for halothane and Stevens et al[5] for isoflurane, although in the latter study no patients under 20 years of age were included. The close similarity between the age dependence of MAC values for halothane and isoflurane in the adult where, for 20 year old patients, MAC values were 0.84 and 1.27 respectively, resulted in the ratio of these values being unaltered with increasing age. On this basis, one could have predicted an average clinical requirement of about 1.5 per cent for isoflurane in patients under one year of age. The average concentration found during maintenance was 1.4 per cent. This implies a lower value than indicated for halothane[48] or, more likely, indicates a measure of caution in the way isoflurane was used in the present study.

The overall incidence of reflex activities was rather low in each of the listed types. These were for the most part similar to the only other large scale study of isoflurane.[10] Some differences were found, however. Cough, laryngospasm and bronchospasm were more frequent, while breath holding was no different and nausea in the postoperative period was much less frequent. The incidence of breath holding, laryngospasm and cough increased with the concentration of isoflurane used at induction. In the usual range of concentrations of less than 2.5 per cent, fewer than 3.5 per cent of patients exhibited laryngospasm, and this compares to 2.4 per cent in the NDA study.[10] A number of factors were found to decrease these irritant responses at induction; for example, narcotic either as premedication or at induction reduced the relative risk of coughing, while age reduced the relative risk of laryngospasm. On the other hand, smokers and those with respiratory disease had a higher incidence of respiratory irritant responses.

As with reflex activities, the incidence of complications was rather low. More than 90 per cent of patients had no complications and in those that did, almost 90 per cent of the complications were judged minor by the anaesthetist. The most frequent systems involved were circulatory and respiratory, with 867 and 516 respectively, together accounting for 80 per cent of all complications. Postoperative circulatory complications amounted to about two per cent compared to 4.2 per cent in the NDA study.[10] This latter study reported a similar incidence following halothane, suggesting that neither drug predisposes to circulatory complications. The most frequent circulatory complications during or after isoflurane were arrhythmias (5 per cent) and hypotension (4.3 per cent), while the most common respiratory complications were miscellaneous (4.1 per cent), laryngospasm (1.8 per cent) and bronchospasm (0.8 per cent). The presence of pre-existing circulatory or respiratory disease greatly influenced the risk of these complications as did ASA status and age. Although 13 patients died after isoflurane anaesthetics, none of these deaths were judged to be related to either surgery or anaesthesia and, in general, occurred in elderly patients undergoing major vascular operations. This death rate (0.19 per cent) for the present isoflurane study compares with 0.2 per cent in the NDA study[10] for isoflurane and 0.63 per cent for halothane. Since no deaths were associated with the anaesthetic agent per se in any of these studies, these likely reflect an expected proportion of patients dying of unrelated causes.

The conclusions which can be drawn from the present clinical evaluation of isoflurane are that it can be used in a great variety of clinical settings for all types of procedures, on patients of all ages, with an acceptable margin of efficacy and safety and is compatible with all drugs used in anaesthetic practice. Note, however, that its use in the present study excluded obstetrics. There may also be special areas where it offers greater advantages, as suggested throughout the report; however, these would have to be challenged in a randomized controlled study with other agents before such a definitive statement could be substantiated.

There are limitations to a study of this type which does require some comment. The obvious limitation of using a single cohort has already been referred to and the lack of a comparative group could be viewed as a major limit to the usefulness of the study. However, the gathering of the type of information sought by the study, together with the design of multiple subgroups,

allowed considerable evaluation of factors which might have had relevance to specific outcomes. To have done all of these statistical manoeuvres in the absence of any background information for several agents would have been extremely time consuming, with considerable risk of generating a plethora of data in support of the null hypothesis in most instances. The results of this study will enable any future controlled study with other agents to focus on those factors now known or suspected to be important predictors of individual patient response. Further, much new information of an epidemiologic nature was made available which should prove of value for workers in many areas outside anaesthesia.

Perhaps the most serious question relates to the reliability of the data collection. As mentioned, 40 per cent of the forms originally submitted had errors which required correction or clarification and, despite considerable effort to ensure completeness of patient data, 398 forms had irresolvable omissions. These were scrutinized for all outcomes and submitted to the global analysis to ensure that they were no different from the 6,798 cases submitted for complete analysis. Thus the recovery rate of complete forms was 95 per cent which, for a study of this size and given the large number of institutions involved is, in our view, an acceptable response. The extent to which various monitors omitted complications throughout the hospital stay of the patient is unknown, but we suspect that there may have been complications which were not reported if they occurred after the patient left the recovery room. For example, in such a large group of patients, one might have expected more than 12 instances of atelectasis in 6,798 patients having general anaesthesia or more than two patients with ileus when there were 1,590 intra-abdominal procedures. Similarly, only 28 instances of sore throat were reported in 5,126 patients who had tracheal intubation. Nevertheless, apart from this caveat regarding accurate recording of complications we are reasonably confident, given the multiple logic checks that were made and the cross variance analysis between institutions and within institutions, that the remaining data base was accurate. The fact that a number of the outcomes were very close to previous studies tends to confirm this view. It is also likely that reporting of complications in the immediate recovery period was accurate.

Appropriate safeguards were taken in the computer protocol and in the interpretation of the results to avoid the pitfalls of single cohort studies, where cause and effect is difficult to define accurately. Each author has repeatedly expressed the view that where a particular association seems likely, considerable caution should be exercised in drawing any firm conclusion unless these could be substantiated. Where conclusions or findings are firmly stated, we believe the evidence entirely supports them.

Finally, one should recognise the benefit to the community of academic anaesthesia of such a joint effort in the evaluation of a new anaesthetic agent before it becomes generally available. The participation of such a large number of the teaching hospitals in North America, with almost every University department represented, was not without its problems; but one hopes it may set a precedent for future collaboration.

Summary

A clinical evaluation of isoflurane was carried out, using a standardized data collection form, on 6,798 patients in 165 University teaching hospitals in North America. The results of this study identified a number of patient related factors such as age, body size, presence of disease, and current drug therapy, as well as anaesthetic related factors such as isoflurane concentration, anaesthetic drugs, and manoeuvres which significantly influenced the clinical response to isoflurane. In addition, numerous demographic relationships have been established which were previously unavailable. The conclusions of the study based on these findings are that isoflurane has an acceptable margin of efficacy and safety and can be used in a wide spectrum of clinical situations. A number of possible specific advantages are suggested which warrant further comparative study.