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Recovery from Sevoflurane Anesthesia

A Comparison to Isoflurane and Propofol Anesthesia

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Background: **Sevoflurane has a lower blood:gas partition coefficient than isoflurane, which may cause a more rapid recovery from anesthesia; it also might cause faster emergence times than for propofol-based anesthesia. We evaluated a database that included recovery endpoints from controlled, randomized, prospective studies sponsored by Abbott Laboratories that compared sevoflurane to isoflurane or propofol when extubation was planned immediately after completion of elective surgery in adult patients.**

Methods: **Sevoflurane was compared to isoflurane in eight studies (N = 2,008) and to propofol in three studies (N = 436). Analysis of variance was applied using least squares method mean values to calculate the pooled mean difference in recovery endpoints between primary anesthetics. The effects of patient age and case duration also were determined.**

Results: **Sevoflurane resulted in statistically significant shorter times to emergence (−3.3 min), response to command (−3.1 min), orientation (−4.0 min) and first analgesic (−8.9 min) but not time to eligibility for discharge (−1.7 min) compared to isoflurane (mean difference). Times to recovery endpoints increased with increasing case duration with isoflurane but not with sevoflurane (patients receiving isoflurane took 4–5 min more to emerge and respond to commands and 8.6 min more to achieve orientation during cases longer than 3 hr in duration than those receiving sevoflurane). Patients older than 65 yr had longer times to orientation, but within any age group, orientation was always faster after sevoflurane. There were no differences in recovery times between sevoflurane and propofol.**

Conclusions: **Recovery from sevoflurane was 3–4 min faster than with isoflurane in all age groups, and the difference was magnified in longer-duration surgical cases (> 3 hr). (Key words: Discharge; emergence; orientation; wake-up.)**

IN this decade, two new volatile anesthetics have been introduced into clinical practice: sevoflurane and desflurane. Both are reported to have an improved recovery profile compared to the older volatile anesthetics because of their lower blood:gas solubility.[1–5] However, at equivalent fresh gas-flow rates, sevoflurane and desflurane cost 2–3 times more than equipotent concentrations of isoflurane. Therefore, to justify the increased expense of the newer volatile anesthetics, a clear cost: benefit ratio needs to be shown. Although some of the benefits of the newer volatile anesthetics may be outcome factors other than an improved recovery profile (*e.g.*, reduced hepatitis risk, more stable cardiovascular profile), this research focused on defining the benefit of sevoflurane over isoflurane anesthesia in achieving clinically important recovery endpoints. In addition, we evaluated whether the expected recovery benefit of sevoflurane over isoflurane was influenced by the duration of anesthetic exposure or by the age of the patient. To do this, we accessed the clinical database from Abbott Laboratories (Abbott Park, IL) that comprised Food and Drug Administration phases II and III, controlled patient trials of sevoflurane. More than 2,000 adult patients participated in studies in which they were randomized to sevoflurane or isoflurane and were to be extubated at the completion of elective surgery. We also identified more than 400 adult patients randomized to sevoflurane or propofol anesthesia in three outpatient studies. We evaluated this database to quantify the recovery profile of sevoflurane and propofol.

Materials and Methods

We requested permission to access the clinical database from Abbott Laboratories, which resulted from

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Food and Drug Administration phases II and III clinical trials. These data were presented to the Anesthetic and Life Support Drugs Advisory Committee of the Food and Drug Administration for the registration of sevoflurane in the United States (January, 1995).

Individual studies chosen for inclusion in this analysis used the following protocol guidelines: patients were adults (> 18 yr), patients received an intravenous anesthetic for induction of anesthesia, patients were randomly assigned to receive sevoflurane or either isoflurane or propofol, and tracheal extubation was planned at the completion of surgery. Recovery endpoints (*i.e.*, treatment-effect variables) were defined as follows:

1. Emergence: time from discontinuation of anesthesia delivery (*i.e.*, vaporizer or propofol infusion pump turned off) to opening of eyes;
2. Response to commands: time from discontinuation of anesthesia delivery to correct response to verbal commands (*e.g.*, hand squeeze);
3. Orientation: time from discontinuation of anesthesia delivery to orientation (*e.g.*, stating name and date of birth or current location);
4. First analgesic: time from discontinuation of anesthesia delivery to the patient request for the first postoperative analgesic;
5. Recovery discharge: time from discontinuation of anesthesia delivery to eligibility for discharge from recovery room.

Statistical Methods

Descriptive statistics (mean, standard error, and range) were used to summarize age, duration of anesthesia, and minimum alveolar concentration (MAC) per hour (MAC · h).

Recovery endpoints were analyzed by a mixed-effects analysis of variance, with response equal to anesthetic and study site random. Mean differences and 95% confidence intervals were obtained from the least squares mean values of the model. A statistically significant difference was achieved if the 95% confidence interval of the mean differences (sevoflurane minus isoflurane or propofol) did not include zero.[6]

A mixed-effects analysis of variance model that included the study site as a random effect also was used to evaluate the relations among recovery endpoints, anesthetic, age, and duration of anesthesia subgroups. Preliminary evaluation of the model, including all main and interaction effects, lead to a reduced model containing main effects of anesthetic, case duration, and age and interaction effects of anesthetic × case duration and anesthetic × age. Age was divided into three subgroups of 18 to 34, 35 to 64, and ≥ 65 yr. Duration of anesthesia was divided into three subgroups of less than 1 h, 1 to ≤ 3 h, and 3 to ≤ 5 h.

The incidence of nausea or vomiting was compared using Cochran-Mantel-Haenzsel analysis with stratification by study site. Statistical significance was considered when $P < 0.05$.

Results

A total of 11 studies were compatible with the inclusion criteria. There were eight randomized studies from the database that compared sevoflurane to isoflurane (n = 2,008 patients); three studies comparing sevoflurane to propofol were identified (n = 436 patients). Although individual studies involved randomization, in no study was the investigator blinded to the treatment. Using emergence times as an example, the residual error from the mixed-effect analysis of variance was 44.2, and the estimate of the site variability was 3.7, indicating there was more variability within a study site than between study sites. This uniformity between study sites was consistent with all recovery endpoints. The average patient age, duration of anesthesia, and MAC · h are presented in table 1.

All patients were included in the evaluation of the incidence of nausea and vomiting, however, it was decided that "outliers" be removed from certain other analyses. Two types of outliers were identified: those with prolonged times to extubation and those with prolonged recovery room discharges. Nine patients were excluded from all recovery-event analyses because of a time to extubation that exceeded 80 min; five had received sevoflurane and four had received isoflurane. This cut-off time was arbitrarily chosen from inspection of the data set that indicated usual extubation times (0–25 min) in almost all study participants. A similar inspection of the data set identified a few patients for whom discharge from the recovery room was more than 300 min. There were 29 patients identified with extremely long discharge times; 14 had received sevoflurane and 15 had received isoflurane. The only recovery endpoint excluded from analyses for these 29 patients was the time to discharge, because other endpoints (emergence, orientation, among others) were comparable to the remaining data. Although the reasons for these extended times to discharge are unknown, explanations could be related

Table 1. Descriptive Data for Sevoflurane, Isoflurane, and Propofol Anesthesia

	Sevoflurane	Isoflurane	Sevoflurane	Propofol
n	1168	840	216	220
Age (yr)	43 ± 0.5	42 ± 0.6	37 ± 0.9	36 ± 0.9
Range (yr)	18–93	18–84	18–75	18–71
Duration of anesthesia (min)	122 ± 2.5	112 ± 2.7	75 ± 2.7	75 ± 2.8
Range (min)	8–569	6–546	4–274	11–270
MAC · h	1.2 ± 0.03	1.3 ± 0.04	0.8 ± 0.03	NA
Range (MAC · h)	0.04–7.5	0.04–15.1	0.05–2.7	—
Infusion rate ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	NA	NA	NA	75 ± 1

Data are mean ± SEM.

NA = not applicable.

to an adverse postoperative event after early recovery was achieved or could simply reflect an error in data collection or entry.

For all evaluable studies, the investigator was required to vary the volatile anesthetic concentration to meet the demands of the surgical stimulus. All studies used MAC values of 2.05% for sevoflurane[7] and of 1.15% for isoflurane;[8] four of the studies had significantly lower average-administered MAC for sevoflurane compared to isoflurane using these values. However, when using MAC values of 1.80% for sevoflurane and of 1.17% for isoflurane, as recently suggested by Mapelson,[9] there were no significant differences in anesthetic concentration as a percent of MAC.

Sevoflurane versus *Isoflurane*

Patients were classified as ASA class I, II, or III. They ranged in age from 18 to 93 yr. Induction agents included thiamylal, thiopental, propofol combined with protocol-defined (per kg) doses of midazolam, and fentanyl as adjuncts to induction drugs. The duration of anesthesia was not different between groups and averaged 114.3 min and 119.0 min for sevoflurane and isoflurane, respectively. The average end-tidal concentration of sevoflurane was 1.28%, which corresponds to 0.62 MAC if 2.05% sevoflurane is used for the one MAC value, and 0.71 MAC using a MAC value of 1.8%. Isoflurane had an average end-tidal concentration of 0.85%, which was 0.74 MAC. The MAC levels were not different between anesthetics. Anesthesia was administered in 50–70% nitrous oxide with oxygen balance, with the exception of one study (n = 75), in which anesthesia was administered in 100% oxygen.

Analysis of variance results are summarized in table 2 and indicate small but nevertheless significantly shorter times to early recovery for sevoflurane compared to

Table 2. Recovery from Anesthesia Parameters for Sevoflurane *Versus* Isoflurane and Propofol

	Emergence	Response to Command	Orientation	Time to First Analgesic	Eligibility for PACU Discharge
Sevoflurane *versus* isoflurane					
Sevoflurane	8.2*	9.2*	13.0*	38.5*	99.8
Isoflurane	11.5	12.3	17.0	47.4	101.5
Pooled data					
Mean difference	−3.3	−3.1	−4.0	−8.9	−1.7
Confidence interval	−3.9 to −2.7	−3.9 to −2.3	−5.2 to −2.9	−13.6 to −4.2	−5.6 to 2.3
n (sevo/iso)	1,139/826	729/688	717/687	944/649	1,038/752
Sevoflurane *versus* propofol					
Sevoflurane	9.1	10.1	12.2	57.8	82.8
Propofol	9.9	11.2	13.1	64.3	86.4
Pooled data					
Mean difference	−0.7	−1.2	−0.9	−6.6	−3.6
Confidence interval	−2.0 to 0.5	−2.6 to 0.3	−2.5 to 0.7	−19.9 to 6.8	−12.6 to 5.3
n (sevo/prop)	213/218	213/218	214/216	123/123	211/214

Data are the least squares mean times (min) with the 95% confidence interval. Differences in time are the sevoflurane time minus the isoflurance or propofol time.

* $P < 0.05$, statistical significance achieved within the sevoflurane *versus* isoflurane or sevoflurane *versus* propofol if confidence interval does not include zero.

isoflurane for emergence (3.3 min), response to commands (3.1 min), orientation (4 min), and first postoperative analgesic (8.9 min). There was no difference in the late-recovery endpoint of time to recovery room discharge.

Preliminary analyses of these data indicated a nonsignificant case-duration × age-interaction effect, which implies that there is a consistent pattern of response among case-duration subgroups for each age subgroup and conversely. There was a significant anesthetic × case-duration interaction effect for time to emergence, response to commands, and orientation, implying a different response pattern between sevoflurane and isoflurane among the case-duration groups (fig. 1). Evaluation of the least squares mean indicated no significant differences between sevoflurane and isoflurane anesthetics at case duration times less than 1 hr. In contrast, there were significant differences between sevoflurane and isoflurane in the 1-to-3-hr and the 3-to-5-hr case-duration groups. The least squares mean differences were approximately 4 to 5 min shorter in duration for sevoflurane than for isoflurane for emergence and response to commands and 5.8 and 8.6 min shorter in duration for orientation in the 1-to-3-hr and 3-to-5-hr groups, respectively (fig. 1). There was no significant difference among case-duration groups for time to first postanalgesic, but the case-duration means were significantly different for eligibility for recovery room discharge, with shorter-duration cases associated with faster recovery room discharge (84, 107, and 117 min).

There were no significant differences between age groups for time to emergence, response to commands, and eligibility for recovery room discharge (fig. 2). For time to orientation, the 18-to-34, 35-to-64 and ≥65-yr age groups had mean times of 14.5, 14.8, and 17.4 min, respectively. The mean orientation time for the ≥65-yr group was significantly greater than the mean times for the other two age groups and was independent of case duration. For the time to first postoperative analgesic, the mean time for the two younger groups (38.7 min) was significantly less than the mean time for the elderly group (61.2 min).

There was not a significant difference in the incidence of nausea or vomiting between sevoflurane and isoflurane (table 3).

Sevoflurane versus *Propofol*

Patients were American Society of Anesthesiologists class I or II and received propofol for induction of anesthesia. Patient age and case duration of anesthesia

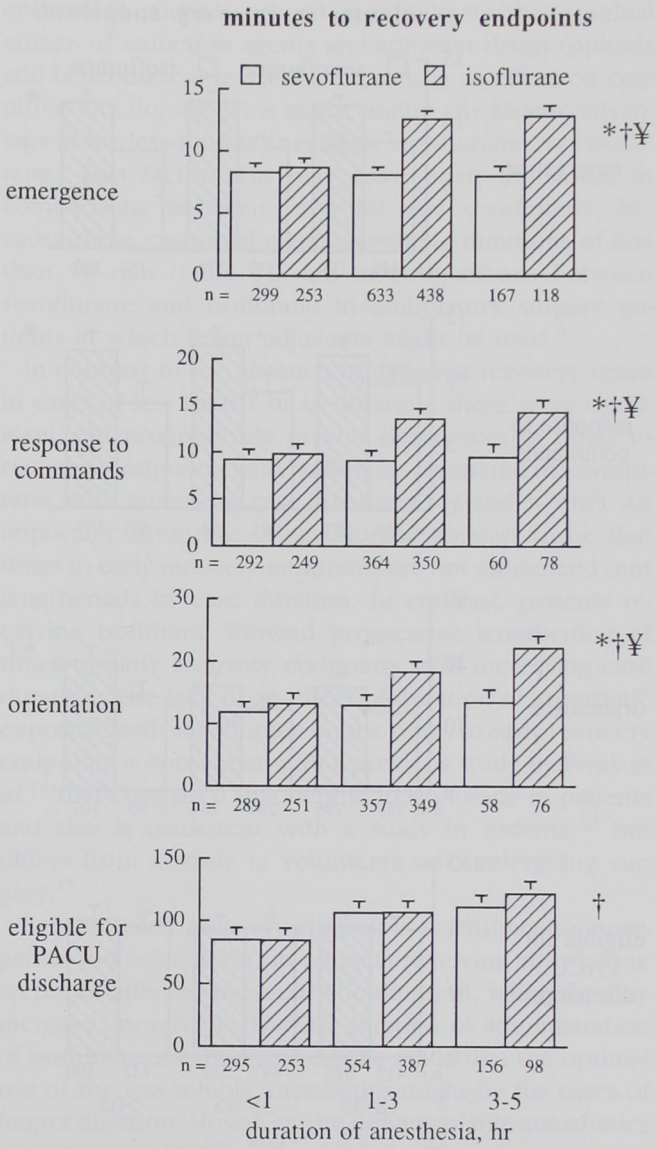

Fig. 1. Analysis of variance results showing times to emergence, responses to commands, orientation, and discharge from recovery according to anesthetic used and duration of anesthesia. Data are shown as mean ± SEM; n = number of patients in each observation. *Significant difference between sevoflurane and isoflurane (significant anesthetic effect); †significant difference with increasing duration of anesthesia; ¥ significant interaction between and anesthetic and duration of anesthesia.

did not differ between propofol and sevoflurane groups (table 1). The end-tidal concentration of sevoflurane was 1.4% (~ 0.7 MAC); the average rate of infusion of propofol for maintenance of anesthesia was 75 $\mu g \cdot kg^{-1} \cdot min^{-1}$. There were no obvious outliers in the sevoflurane-*versus*-propofol database for tracheal extubation times or times to discharge from recovery room, such as

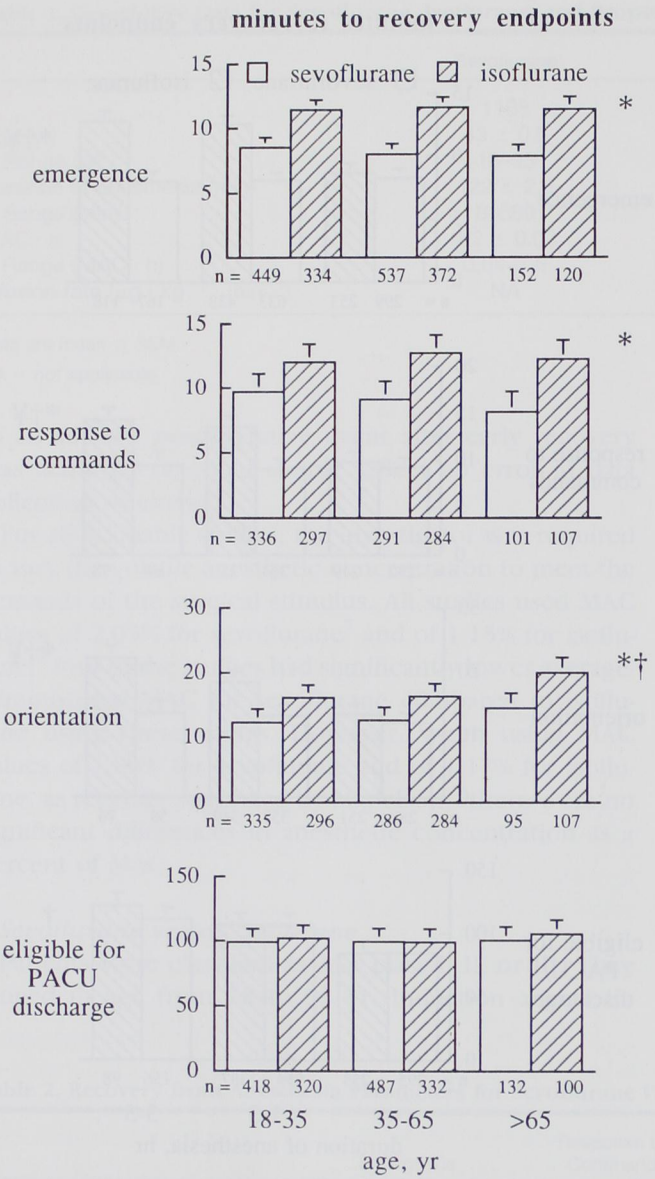

Fig. 2. Analysis of variance results showing times to emergence, responses to commands, orientation, and discharge from recovery. Data are shown as mean ± SEM; n = number of patients in each observation. *Significant difference between sevoflurane and isoflurane (significant anesthetic effect); †significant difference with increasing age.

there were in the isoflurane-*versus*-sevoflurane database. There were no statistical differences between sevoflurane and propofol for the recovery endpoints (table 2) or for nausea and vomiting (table 3).

Discussion

The results indicate that, in the general patient population undergoing elective surgery, small but significant differences exist in early recovery endpoints between sevoflurane and isoflurane anesthesia. In patients anesthetized with sevoflurane, emergence from anesthesia occurred an average of 3.3 min earlier, and orientation occurred 4 min earlier than in patients anesthetized with isoflurane. There were no significant differences in recovery endpoints when comparing sevoflurane to propofol anesthesia, and there were no significant differences between sevoflurane and isoflurane anesthesia in the times to eligibility for discharge from the recovery room.

Because we had access to the individual patient files from the database, we were able to perform additional analyses to determine the effects of age and case duration on recovery endpoints in patients receiving sevoflurane and isoflurane. We could not perform these analyses to compare sevoflurane and propofol because of limited numbers of patients older than 65 yr (n = 6 sevoflurane, n = 8 propofol) and similar limitations in the sample size for cases longer in duration than 3 hr (n = 4 sevoflurane, n = 5 propofol).

We grouped the sevoflurane-*versus*-isoflurane database into patients aged 18 to 34, 35 to 64, and ≥ 65 yr of age. Preliminary analyses of these data indicated a nonsignificant case-duration × age-interaction effect, which implied there was a consistent pattern of response among case-duration subgroups for each age subgroup and conversely. We then compared recovery endpoints as a function of age and case duration of anesthesia. Several outcomes of these analyses appear to be unique. First, mean times to early recovery endpoints were significantly shorter in duration after sevoflurane than after isoflurane anesthesia for each of these recovery endpoints and were consistent among each age group. Secondly, with either anesthetic, the time to emergence from anesthesia (eye opening) and time to response to command (squeeze hand) were not influenced by increasing patient age. In contrast, time to orientation

Table 3. Incidence of Nausea and Vomiting after Sevoflurane, Isoflurane, and Propofol Anesthesia

	Sevoflurane *versus* Isoflurane		Sevoflurane *versus* Propofol	
	Sevoflurane	Isoflurane	Sevoflurane	Propofol
n	1,168	840	216	220
Nausea	593 (51)	418 (50)	93 (43)	81 (37)
Vomiting	276 (24)	211 (25)	48 (22)	36 (16)
Nausea or Vomiting	593 (51)	418 (50)	104 (48)	87 (40)

Data are shown as number (%) of patients. There were no statistically significant differences in the incidence of nausea or vomiting (all $P > 0.05$).

(state name and date of birth) and time to first analgesic were delayed in elderly patients compared to patients younger than 65 yr of age, regardless of anesthetic. Lastly, times to late recovery (discharge) were not increased with age. The reason that emergence from general anesthesia with a volatile anesthetic was not longer in duration in the elderly patients than in the younger patients may be two-fold. The blood:gas partition coefficient of sevoflurane does not vary with age,[10] and the awakening concentrations of sevoflurane and isoflurane decrease similarly with increasing age, such that the ratios of MAC to the awakening concentration for sevoflurane and isoflurane are similar.[11] The demonstration that time to orientation in elderly patients was delayed is consistent with clinical observations and may be caused by an interplay of the volatile anesthetics with cognitive functioning in elderly patients.

When evaluating the effects of duration of anesthesia on recovery endpoints, several interesting outcomes were noted. First, in cases less than 1 hr in duration, there were no differences between sevoflurane and isoflurane in any recovery endpoint. This contrasts to a recent publication summarizing the results of a multicenter study of sevoflurane *versus* isoflurane in ambulatory anesthesia in which case durations averaged 38–46 min.[3] The authors showed a 2-min faster time to emergence and a 3-min faster time to orientation with sevoflurane. Because the range of case durations was from 7 to 207 min, it is possible that including cases that lasted for more than 1 hr helped to achieve a statistical difference. It seems more likely that after short-duration anesthetic exposures, a minimal difference in recovery would exist between any of the volatile anesthetics because there would be little time to saturate tissue groups. This was pointed out by Eger *et al.*[12] in a study in rodents in which the kinetic advantages of the less-soluble anesthetics, sevoflurane and desflurane, were more difficult to show after anesthetic exposures of less than 1 hr compared to anesthetic exposures more than 1 hr. It also has been shown in rodents that the differences in times to recovery endpoints between anesthetics are smaller when low concentrations of the anesthetics are used. In the current study, the average concentration of sevoflurane and isoflurane was only 0.7 MAC.

The difficulty in showing a more rapid recovery with sevoflurane after short durations of anesthesia also may be explained, in part, by the identical alveolar elimination of sevoflurane and isoflurane after short-duration exposures in volunteers.[13] Another possible explanation for the absence of differences in recovery times in shorter-duration surgical procedures could be that residual effects of induction agents and adjuvant drugs (opioids and benzodiazepines) still are exerting an effect on cognitive functioning. This might nullify any kinetic advantage of the less-soluble anesthetic sevoflurane over isoflurane. This factor also may have been influential in comparisons between propofol and sevoflurane, because these cases had mean anesthetic durations of less than 90 min (table 1), and in comparisons between sevoflurane and isoflurane in ambulatory surgery patients in which fewer adjuvants might be used.[3]

In contrast to the absence of different recovery times in cases of less than 1 hr in duration, there were significant and progressively greater differences in times to recovery endpoints with isoflurane compared to sevoflurane, with increasing case duration (1–3 and 3–5 hr). An important advantage of sevoflurane appears to be that times to early recovery endpoints are not influenced (not lengthened) by case duration. In contrast, patients receiving isoflurane showed progressive lengthening of times to early recovery endpoints with increasing case duration. The lack of an effect of duration of anesthetic exposure with sevoflurane on the times to early recovery endpoints is consistent with a previous study by Frink *et al.*[14] that compared sevoflurane to isoflurane in patients and also is consistent with a study in rodents,[12] but differs from a study in volunteers not undergoing surgery.[15]

Because early recovery endpoints (*e.g.*, times to emergence and orientation) in patients receiving sevoflurane were not affected by anesthetic duration, whereas, they increased progressively with duration of administration of isoflurane, an argument can be made that the optimal use of the less-soluble anesthetics might be for cases of longer duration. However, the newer volatile anesthetics cost more per MAC per hour than isoflurane, making this argument less tenable because of hesitation to use a more costly volatile anesthetic in longer-duration cases. One needs to consider whether a savings of indirect costs, such as operating room time or personnel costs, can be achieved if the less-soluble anesthetics are used in the longer-duration cases or whether similar recovery benefits of sevoflurane could be realized in longer-duration cases by using isoflurane throughout most of the procedure and switching to sevoflurane near the completion of surgery.

The absence of differences between the recovery times in patients receiving either sevoflurane or propofol is at variance with two published multicenter studies[16,17] in which early recovery endpoints were achieved

1–3 min faster after sevoflurane than after propofol. However, the current data are consistent with several similar studies that compared recovery end-points between desflurane and propofol anesthetics.[5,18–20] In addition, a meta-analysis of multiple studies of recovery after desflurane and propofol anesthesia showed no statistical differences in times to recovery endpoints. As stated previously, we cannot rule out the influence of other residual drug effects in anesthetic cases of short duration. Interestingly, the current study was unable to show the commonly reported benefit of propofol over volatile anesthetics on the incidence of nausea and vomiting.[21] One needs to consider that the use of narcotics in the recovery room at a time distant from propofol administration might have obscured the antiemetic effects of propofol.[21]

One limitation of this and all previous studies of emergence from anesthesia has been the standard requirement that the anesthetic concentration be kept at "surgical depth" until the last suture or the dressing is in place. Although this permits precise timing of the recovery endpoints, it does not reflect the typical clinical use of these primary anesthetics. Despite the lower blood:gas solubility of sevoflurane compared with isoflurane and the statistical result of a 3–4 min faster time to recovery with sevoflurane, the average time to emergence with sevoflurane still was 8 min. More typically, primary anesthetics are titrated downward near the completion of surgery, and this approach often results in wake-up and extubation occurring at or near the time of the placement of the last suture or wound dressings.

In summary, postanesthesia recovery times in adult patients were similar between sevoflurane and propofol, but times to early recovery endpoints were significantly shorter in duration (3–4 min) for patients receiving sevoflurane than for those receiving isoflurane. These small differences were magnified in cases in which anesthetic exposures exceeded 3 hr. Finally, aging did not influence (prolong) most early-recovery events, except for time to orientation. Regardless of choice of volatile anesthetic, there were longer times to orientation in patients older than 65 yr of age compared with younger patients; but within any age group, time to orientation was always faster after sevoflurane anesthesia.

Appendix 1

Much of the data summarized in the current report have subsequently been published as smaller, separate articles. Of the 2,008 patients randomized to sevoflurane and isoflurane, 10 studies have been published that summarize data from 1,737 patients.[2–4,14,22–25]‖ For the studies comparing sevoflurane to propofol, three publications have been identified that provide data from 434 patients.[26,27]#

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