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Association of Ethnicity with the Minimum Alveolar Concentration of Sevoflurane

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Background: **Selective breeding produces animal strains with varying anesthetic sensitivity. It thus seems unlikely that various human ethnicities have identical anesthetic requirements. Therefore, the authors tested the hypothesis that the minimum alveolar concentration of sevoflurane differs significantly as a function of ethnicity.**

Methods: **The authors recruited 90 American Society of Anesthesiologists physical status I and II adult patients belonging to three Jewish ethnic groups: European, Oriental, and Caucasian (from the Caucasus Mountain region). All were scheduled to undergo surgery requiring a skin incision exceeding 3 cm. Without premedication, anesthesia was induced with 6–8% sevoflurane in 100% oxygen, and tracheal intubation was facilitated with succinylcholine. The skin incision was made after a predetermined end-tidal concentration of sevoflurane of 2.0% was maintained for at least 10 min in the first patient in each group. Blinded investigators observed the patient for movement during the subsequent minute. The concentration in the next patient was increased by 0.2% when patients moved, or decreased by the same amount when they did not. Results are presented as means [95% confidence intervals].**

Results: **Morphometric and demographic characteristics were similar among the groups; however, mean arterial pressure was slightly greater in European Jews. Minimum alveolar concentration for sevoflurane was greatest in Caucasian Jews (2.32% [2.27–2.41%]), less in Oriental Jews (2.14% [2.06–2.22%]), and still less in European Jews (1.9% [1.82–1.99%]) ($P < 0.001$).**

Conclusions: **The results suggest that minimum alveolar concentration varies as a function of ethnicity. However, the extent to which confounding characteristics contribute, including lifestyle choices and environmental factors, remains unknown.**

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GENETICALLY determined variations in pharmacokinetics and pharmacodynamics modulate drug responses. For example, the genetic basis for response to volatile anesthetics is apparent from development of an ether-resistant strain of *Drosophila melanogaster* flies[1] and varying anesthetic sensitivities in *Caenorhabditis elegans*.[2–5] Subsequent studies demonstrated that genetic factors are similarly involved in determining volatile anesthetic requirement in rodents[6–8] and cats.[9] However, red hair remains the only phenotype, including sex,[10,11] linked to volatile anesthetic requirement in humans.[12] Red hair results from mutation of the melanocortin-1 receptor and thus has a distinct genetic basis.[13]

Within the human species, ethnic populations possess distinct genetic characteristics, some of which clearly influence drug disposition and dynamics. A recent study,[14] for example, demonstrated a significant difference in the potency and duration of action of rocuronium among surgical patients from three countries: Austria, America (whites), and China (Han Chinese). It would thus be surprising if various ethnic groups displayed identical anesthetic sensitivity. We therefore evaluated the general theory that the minimum alveolar concentration (MAC or P50 for movement in response to skin incision) of sevoflurane differs as a function of the ethnicity. Specifically, we tested the hypothesis that MAC differs significantly among three groups: European Jews, Oriental Jews, and Jews from the Caucasus Mountain region.

Materials and Methods

With approval from the institutional review board at the Edith Wolfson Medical Center (Holon, Israel) and written informed consent from each patient, we enrolled 90 American Society of Anesthesiologists physical status I and II patients. Each was aged between 20 and 60 yr and scheduled to undergo elective surgery with general anesthesia. Both men and women were enrolled, and women were enrolled irrespective of their menstrual cycle stages. We recruited patients scheduled for operations that began with a skin incision at least 3 cm

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in length; in practice, this meant that laparoscopic procedures were excluded. Candidates having a history of chronic pain or taking analgesic or sedative medications were excluded, as were those with a contraindication to inhalation induction of anesthesia. Pregnant women were also excluded. We restricted enrollment to surgeries scheduled between 8 AM and noon to minimize the circadian influence on anesthetic requirement.[15]

We enrolled patients representing three different Jewish ethnic groups: European Jews (n = 39), Oriental (Middle Eastern and North African) Jews (n = 36), and Jews from the Caucasus Mountain region (n = 27). Patients born in Israel to parents born outside Israel were allocated to their parents' group (*i.e.*, European Jews). Second-generation patients born in Israel were allocated to the Oriental Jews category. Patients from mixed parents (*i.e.*, European and Oriental) and patients from other ethnic groups were excluded. Table 1 presents the specific ethnic groups and subgroups enrolled in the study. Available and consenting patients were enrolled until the *a priori* total of 90 subjects was reached.

Protocol

Patients were not given preoperative medications but were allowed to continue chronic nonsedative and nonanalgesic treatments (*i.e.*, antihypertensive medications). Routine anesthetic monitors were applied, including a neuromuscular monitor that was positioned to stimulate the ulnar nerve at the wrist. End-tidal sevoflurane concentration was measured through a calibrated Datex-AS-3 monitor (Datex, Helsinki, Finland) with an accuracy of 0.1%.

Anesthesia was induced by inhalation of 6–8% sevoflurane in 100% oxygen. When end-tidal sevoflurane concentration exceeded 4%, succinylcholine was given intravenously, paralysis was confirmed by lack of response to a supramaximal train-of-four stimulus, and the trachea was intubated. The patients' lungs were ventilated with 80% oxygen, balance nitrogen. An esophageal temperature probe was inserted. Forced-air was used to maintain normothermia because MAC for volatile anesthetics decreases by 4–5% per degree Celsius of core hypothermia.[16,17]

Patients were maintained at their assigned end-tidal sevoflurane concentration for at least 10 min before skin incision, with a fresh-gas flow of 3 l/min and a tidal volume of 8–10 ml/kg. End-tidal partial pressure of carbon dioxide was kept near 35 mmHg. Care was taken to avoid stimulating patients until incision. Before skin incision, we confirmed that the patient had recovered a full train-of-four.

The first patient from each group was assigned to an end-tidal sevoflurane concentration of 2%. If this patient moved in response to surgical skin incision within 1 min, the sevoflurane concentration was increased by 0.2% in the subsequent patient of that group. In contrast, the sevoflurane concentration in the subsequent patient in that group was decreased by 0.2% if skin incision did not provoke movement. This paradigm is referred to as the Dixon up-and-down method.[18] Hence, each patient provided a "move" or "no move" response at a specific concentration that was determined by the previous patient's response.

Measurements

Two independent investigators, blinded to the end-tidal concentration of sevoflurane, determined patient response to skin incision (movement or no movement). One investigator observed the patient's arms and head, and the other observed the patient's legs. We covered the vaporizer and end-tidal gas monitor to avoid bias by the observers. A positive response to skin incision was defined by a purposeful movement of one or more extremities or the head.[19] Grimacing and coughing were not considered purposeful responses.

We also recorded the patients' demographic and morphometric characteristics. Mean arterial pressure (measured oscillometrically), heart rate, and esophageal temperature were measured just before skin incision.

Table 1. Countries of Origin for the Included Ethnic Groups

Primary Grouping	European Jews	Oriental Jews	Jews from Caucasus Mountain Region
Countries of origin	Israelis of European origin North and South Americans of European origin	Israelis of Oriental origin Syrians Iraqis Lebanese Yemenites Turks Egyptians Tunisians Algerians Libyans Moroccans	Israelis of Caucasus Mountain origin Jews from Bukhara Azers Afghans Georgians Iranians (including Kurds) Uzbeks

Patients born in Israel to parents born outside Israel were allocated to their parents' group (*i.e.*, European Jews). Second-generation patients born in Israel were allocated to the Oriental Jews category.

Statistical Analysis

The objective of the study was to estimate the MAC (*i.e.*, P50) for each ethnic group and to assess whether the anesthetic requirements of the groups differed significantly. The P50 for a particular group was defined as the concentration of sevoflurane at which there was a 0.50 probability that a person from this group would exhibit movement in response to a surgical skin incision.

The study design, the Dixon up-and-down method,[18] has been used in anesthesia for many years. To estimate the P50 from this design, we used the Brownlee adaptation[20] of the Dixon and Mood method.[21] We also used the turning point method introduced by Wetherhill.[22]

In their original work, Dixon and Mood[21] estimate the P50 as the average of the observed concentrations for the entire experiment, including the concentration that would follow the last response. However, they only used data from either the successes or failures (in our study, movements or nonmovements), whichever number was smaller, because the initial observations are not very informative. We use the method of Brownlee[20] and others, who proposed using all the data except for the first observation, from both the successes and failures, including the projected concentration based on the last observed response.

Another valid analysis approach to the up-and-down design is that of Wetherhill,[22] who proposed using only the turning points (peaks and troughs) of the up-and-down experiment to estimate the P50. The concentration halfway between the previous measurement and the peak or trough is the data point used for analysis. Wetherhill *et al.*[22] claim that their method is superior to that of Brownlee because it focuses only on the observations most informative of the true P50, the turning points. This method typically produces somewhat larger SEs than the method of Brownlee and is therefore a bit more conservative.

Ethnicities were compared for each method using analysis of variance and the Tukey-Kramer adjustment for multiple comparisons. For the Brownlee method, we fit a multivariable model including baseline factors that either differed between groups or had at least a moderate relation to the outcome. A multivariable model would not be appropriate for the turning point method because not all of the observations (and so not all of the patients) are used in obtaining the estimator. Confidence intervals (95%) for the P50 of each method, as well as for the difference between ethnicities, were obtained from the analysis of variance model.

We assessed for potential confounders by measuring the association between the available baseline (demographic and laboratory) variables and both ethnic group and concentration, where a confounder would be a variable associated with both the independent variable (ethnic group) and the outcome (end-tidal sevoflurane concentration). Concentration is, of course, directly related to P50, the outcome of interest.

SAS statistical software (Cary, NC) was used for all analyses. The Tukey-Kramer multiple comparison procedure was used to maintain the family-wise significance level at 0.05 for each hypothesis. With sample sizes of n = 39, n = 36, and n = 27 for the European Jews, Oriental Jews, and Jews from the Caucasus Mountain Region, respectively, and given the observed P50 SEs, we had 90% power to detect differences of 10% or more between the P50 of the three groups at the 0.05 significance level, including a Bonferroni correction for multiple comparisons.

Results

Patients were recruited from March 2004 until September 2005. All of the patients finished the study, and there were no adverse events associated with the protocol. Table 2 presents the characteristics of patients and potential confounding factors. The ethnic groups did not differ with respect to age, American Society of Anesthesiologists physical status, core temperature, or heart rate at the time of skin incision. European Jews had more years of study and a greater mean arterial pressure than both Oriental Jews and Jews from the Caucasus Mountain region. None of the variables was associated with end-tidal sevoflurane concentration. Therefore, no baseline variable was found to be a true confounder of the relation between ethnicity and anesthetic concentration.

Raw data from the up-and-down design for each ethnic group is displayed in figure 1. Table 3 reports the estimated P50, 95% confidence interval, and *P* values comparing ethnic groups using the Dixon-Brownlee and the turning point (Wetherhill) methods. The multivariable model results for the Dixon-Brownlee method were similar to the univariable results for that method and included education level, core temperature, and type of surgery.

The Dixon-Brownlee and Wetherhill (turning point) methods provided similar estimates of P50 for each ethnic group. As expected, though, the up-and-down analytic method had a slightly smaller SE, which directly corresponded to narrower estimated confidence intervals (for each group and for the differences between groups) and more significant *P* values comparing groups. All comparisons of P50 for the three ethnic groups were statistically significant using both the up-and-down method and the turning point method, even after the adjustment for multiple comparisons within each method (fig. 2).

Discussion

We conducted this prospective trial to determine whether ethnicity affects the sensitivity of the MAC

Table 2. Characteristics of Patients and Potential Confounding Factors of Each Ethnicity

Factor	European Jews, n = 39	Oriental Jews, n = 36	Jews from Caucasus Mountain Region, n = 27	*P* Value*
Education, yr	13.1 (2.1)	11.6 (1.7)	11.4 (2.1)	<0.001‡§
Age, yr	41 (9)	36 (9)	40 (12)	0.11
Mean arterial pressure at skin incision, mmHg	86 (10)	78 (12)	78 (11)	0.002‡§
Heart rate at skin incision, beats/min	79 (16)	74 (15)	74 (13)	0.30
Core temperature at skin incision, °C	36.2 (0.4)	36.1 (0.4)	36.3 (0.5)	0.06
Female sex	20 (51.3%)	16 (44.4%)	14 (51.9%)	0.79†
American Society of Anesthesiologists physical status				
I	30 (76.9%)	29 (80.6%)	22 (84.6%)	0.75†
II	9 (23.1%)	7 (19.4%)	4 (15.4%)	
Smoker	14 (35.9%)	18 (50.0%)	11 (42.3%)	0.47†
Type of surgery				
Abdominal	11 (28.2%)	6 (17.6%)	7 (29.2%)	0.47†
Orthopedic	20 (51.3%)	20 (58.8%)	10 (41.7%)	
Other	8 (20.5%)	8 (23.5%)	7 (29.2%)	

Data are mean (SD) for continuous and number of patients (%) for categorical factors.

* Analysis of variance, unless otherwise specified. † Chi-square. ‡ Significant overall at $P < 0.05$. § European > Oriental, Caucasus Mountain (Tukey test).

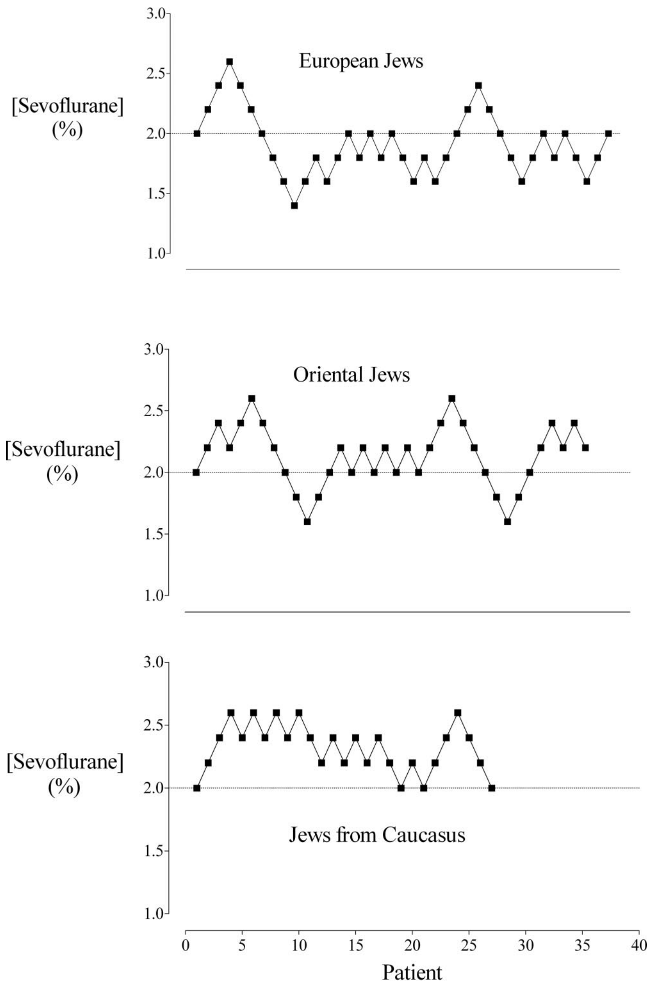

Fig. 1. Individual starting sevoflurane concentrations for each ethnic group using the Dixon up-and-down method. According to the Dixon-Brownlee analytic method, the estimated P50 (95% confidence interval) was 1.91 (1.83–1.98) for European, 2.14 (2.07–2.22) for Oriental, and 2.34 (2.25–2.43) for Caucasus Jews. The *horizontal line* denotes the starting sevoflurane concentration of 2.0%. European Jews were born or had parents born in Europe, Oriental Jews were of Middle Eastern or North African origin, and Caucasus Jews were from the Caucasus Mountain region.

(P50) of sevoflurane. Our results indicate that Jews from the Caucasus Mountain region were more resistant to sevoflurane, in terms of movement at skin incision, than were Jews of European and Oriental origin. In fact, the Jews from the Caucasus required, on average, 24% more sevoflurane to prevent movement in response to skin incision than those of European origin. We are not aware of any previous studies in which MAC was directly compared among various ethnicities in the context of a single study. However, numerous investigators have determined MAC for various anesthetics, each evaluating different local populations. For example, sevoflurane has been extensively studied in both Western and Asian populations, and there is a hint that MAC may be slightly (*i.e.*, approximately 10%) less in Asian than in Western subjects; for details, see the table in a review by Eger.[16]

The maximum difference in MAC that we observed was between the European Jews (1.88%) and Jews from the Caucasus Mountain region (2.34%). This 24% increase, while highly statistically significant, is possibly of marginal clinical consequence, although immigrants from the Caucasus Mountain region might be more likely to remember events during anesthesia if given the same amount of sevoflurane as Oriental Jews. The importance of the finding, though, is that it confirms our theory that anesthetic sensitivity varies as a function of ethnicity. It is likely that other populations demonstrate both higher and lower sensitivities than observed in our three ethnic groups.

Ethnicity has also been shown to determine pain perception, analgesic requirement, and response to muscle relaxants.[23–25] Houghton *et al.*[25,26] concluded that ethnicity affected recovery from suxamethonium and from anesthesia, with Europeans recovering faster than Asians. The same authors also found that although the elimination half-life of alfentanil in Chinese and Nepalese patients were both significantly shorter than that of

Table 3. P50 and Jewish Ethnicities: Analysis Results

Method	Ethnicity			Differences between Ethnicities		
	European (E), n = 39	Oriental (O), n = 36	Jews from Caucasus Mountain Region (C), n = 27	E minus O	E minus C	C minus O
Dixon-Brownlee: univariable	1.91 (1.83 to 1.98)	2.14 (2.07 to 2.22)	2.34 (2.25 to 2.43)	−0.24 (−0.36 to −0.12)*	−0.44 (−0.55 to −0.33)*	0.20 (0.09 to 0.31)‡
Dixon-Brownlee: multivariable	1.88 (1.79 to 1.96)	2.13 (2.05 to 2.22)	2.34 (2.24 to 2.44)	−0.26 (−0.40 to −0.11)*	−0.46 (−0.62 to 0.31)*	0.21 (0.06 to 0.36)†
Wetherhill (turning point method)	1.86 (1.76 to 1.95) n = 18	2.15 (2.05 to 2.25) n = 16	2.36 (2.26 to 2.46) n = 17	−0.29 (−0.47 to −0.12)*	−0.50 (−0.67 to −0.33)*	0.21 (0.03 to 0.38)§

Data are estimated P50 concentrations as percent (95% confidence interval).

Significant after Tukey-Kramer multiple comparison procedure: * $P < 0.001$; † $P = 0.004$; ‡ $P = 0.005$; § $P = 0.016$.

Europeans, mean plasma concentrations did not differ significantly at the time of recovery of spontaneous ventilation.[23] A study of postoperative morphine consumption revealed that there were significant differences in the dose of analgesics administered to black, Hispanic, and white patients.[27]

Other studies, though, did not identify ethnic differences in the sensitivity to analgesics.[28] Furthermore, investigators have suggested that differences in sensitivity are probably related to factors other than ethnicity.[29] Aun *et al.*,[23] for example, showed that alfentanil had a similar analgesic effect when administered during general anesthesia in both European and Asian patients, although the recovery was slower in Asian patients. Hispanic patients were less likely to receive analgesic in the emergency ward than were non-Hispanics.[30] One problem with many such studies is the difficulty in correctly establishing the true ethnicity of the study subjects. To minimize this problem, we excluded patients who had parents from different ethnicities.

We used both Dixon-Brownlee[20] and Wetherhill turning point[22] analyses. As expected, the estimated SEs using the Dixon-Brownlee method were somewhat narrower than those derived from the turning point analysis. However, the P50 values were nearly identical with each method, and therefore, the conclusions were identical with each analysis method.

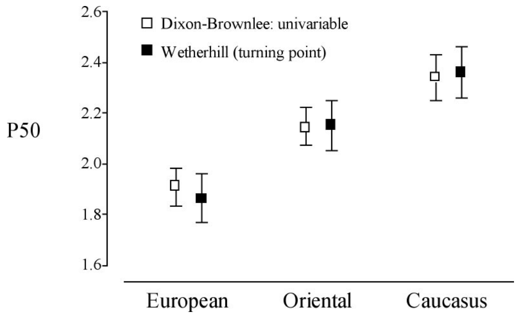

Fig. 2. Sevoflurane P50 shown by Jewish Ethnicity and analytic method (Dixon-Brownlee or Wetherhill). Data are presented as estimated P50 and 95% confidence intervals. All group P50s differed significantly with each method. European Jews were born or had parents born in Europe, Oriental Jews were of Middle Eastern or North African origin, and Caucasus Jews were from the Caucasus Mountain region.

The MAC of inhalational anesthetics decreases with age, owing to age-related pharmacodynamic differences.[31] MAC is also affected by hormonal changes; for example, women in early pregnancy have a lower MAC for isoflurane and enflurane.[32] However, none of our patients were pregnant. We evaluated potential confounding factors to the extent possible; no factors likely to influence anesthetic requirement were found to be associated with either ethnicity or concentration. In particular, sex, core temperature, smoking, American Society of Anesthesiologists physical status, and age were similar among the three groups. The effect of education and the cultural background of the patient and treating staff were also potential confounding factors.[33] The number of years of study was greater in our European group, but this was not found to be a confounding factor in our analysis. Although they were included in the multivariable model, the relation between ethnicity and P50 was not affected by the number of years of study, body temperature, or surgery type.

We nonetheless caution that unmeasured potential confounding factors may have contributed substantially to the differences we observed. Potential unmeasured confounders include diet, drug use (including alcohol), and environmental factors. It is impossible from our data to determine the extent to which one or more of these factors contributed to part or all of the observed differences in anesthetic requirement among the three ethnic groups we evaluated.

A substantial limitation of our study is that it was impossible for us to precisely define the exact geographic and ethnic background of each participant. Genetic studies, presumably involving far greater numbers of patients, will be required to precisely identify the effects of ethnicity on anesthetic sensitivity. Currently, we do not know what genetic variations might underlie the differences in the MAC values. It nonetheless seems likely that the amount of anesthetic required depends on the genetic makeup of individual patients. However, definitive proof awaits future genetic studies.

In conclusion, our results indicate that the P50 sevoflurane concentration needed to stop movement in response to skin incision (MAC) varies in three ethnic groups. Jews from the Caucasus Mountain region had the largest MAC, Oriental Jews had a middle value, and European Jews had the smallest. However, the extent to which confounding characteristics contribute, including lifestyle choices and environmental factors, remains unknown.

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