Bispectral Index Dynamics During Propofol Hypnosis Is Similar in Red-Haired and Dark-Haired Subjects

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BACKGROUND: We have previously shown that red hair is associated with increased desflurane requirement for immobility, compared with dark hair. The effect of red hair on IV anesthetic requirement remains unknown. We tested the hypothesis that the propofol concentration in the effect site associated with half maximal electroencephalogram response, Ce50, is at least 50% higher in subjects with red hair.

METHODS: We modeled the propofol concentration versus electroencephalogram response relationship using a 2-step approach in 29 healthy dark- and red-haired volunteers receiving a propofol infusion to produce loss of consciousness. Bispectral Index (BIS) was the measure of drug effect. The parameters of a 3-compartment pharmacokinetic model were fit to measured arterial propofol concentrations. The relationship between effect-site propofol concentration (Ce) and BIS was characterized using a sigmoid Emax model. Model performance and accuracy of the estimated parameters were evaluated using accepted metrics and bootstrap resampling.

RESULTS: The inclusion of hair color as a model covariate did not improve either the pharmacokinetic or the pharmacodynamic model. A separate analysis for the dark- and red-haired subjects estimated a median (95% confidence interval) Ce50BIS of 2.71 μg/mL (2.28–3.36 μg/mL) and 2.57 μg/mL (1.68–3.60 μg/mL), respectively. Body weight was a significant covariate for the Cl1 and V1.

CONCLUSIONS: Red hair phenotype does not affect the pharmacokinetics or pharmacodynamics of propofol. (Anesth Analg 2013;116:319–26)

loss-of-function mutations in the gene encoding the melanocortin-1 receptor (MC1R) are responsible for the hair color and fair skin in the majority of red-heads.1–3 The human MC1R, primarily expressed on the surface of epidermal melanocytes, is an important regulator of intracellular signaling to the melanin biosynthetic pathway that controls pigment formation. The relative proportion of pheomelanin (yellow-red) and eumelanin (dark brown) pigments determines the hair and skin color in the Caucasian population.4 Thus, whereas expression of a normal (wild-type) MC1R is associated with a predominant production of eumelanin (resulting in a high eumelanin-to-pheomelanin ratio) and dark brown hair, the red hair phenotype is the result of increased pheomelanin production due to a loss-of-function mutation in MC1R.5,6 Anesthesiologists share an anecdotal impression that patients with red hair require higher amounts of hypnotics to achieve certain anesthetic end points (e.g., increased dose of propofol for induction to general anesthesia) compared with patients with a different hair color. In agreement with these observations, we have previously shown in healthy volunteers that red hair phenotype was associated with a 19% increase in desflurane requirement for immobility in response to noxious electrical stimulation (i.e., minimum alveolar concentration [MAC])7 and reduced sedation during midazolam administration,7 compared with dark hair. The effects of human MC1R dysfunction on anesthetic requirement for immobility were further supported by the findings that MAC is slightly, but significantly, increased in yellow-coated mice carrying a mutation in MC1R.4 These findings make red hair a distinct phenotype associated with anesthetic requirement in humans with obvious implications for the practice and science of anesthesia.
The effect of red hair on IV anesthetic requirement remains unknown. We thus evaluated the hypnotic effect of propofol using the Bispectral Index (BIS) of the electroencephalogram, a well-validated surrogate measure of hypnosis, in healthy volunteers with dark and red hair. To conform with the anecdotal clinical observations supporting an enhanced propofol dose requirement for redheads, we hypothesized that their effect-site propofol concentration (Ce)50 for BIS will be at least 50% higher compared with dark-haired subjects.

**METHODS**

With approval of the Human Studies Committee at the University of Louisville and written informed consent, we evaluated 29 healthy volunteers with dark or red hair, between April 2005 and March of 2007. Age was restricted to 20 to 45 years.

**Protocol**

The volunteers fasted at least 8 hours before the trial. All standard anesthetic monitors including oscillometric blood pressure, electrocardiogram, end-tidal CO2 through nasal prongs, and pulse oximetry (Spo2) were applied to the volunteers. Electrodes to capture the BIS (A-2000 monitor, BIS 3.3 algorithm, system revision 1.07; Aspect Medical Systems, Inc., Newton, MA) were applied to the forehead according to the manufacturer’s instructions. Impedance of the BIS sensors was maintained at <5 kΩ throughout the study period.

A 20-gauge catheter was inserted at the antecubital fossa on the dominant arm for the propofol infusion, and a 20-gauge catheter was inserted into the radial artery of the contralateral arm for blood sampling. Normothermia was maintained with forced-air warming, while volunteers breathed supplemental oxygen via nasal prongs to maintain an Spo2 >92%.

After a 3-minute period of quiet relaxation and baseline BIS recording with eyes closed, 200 mg of propofol (Diprivan 1%; Zeneca Inc., Wilmington, DE) was infused IV over a 10-minute period (AS50 Auto Syringe; Baxter Healthcare Corp., Deerfield, IL). A blank arterial blood sample was obtained before the initiation of the propofol infusion; additional 4-mL arterial samples for propofol determination were obtained at 1, 3, 5, and 10 minutes after the beginning, and at 1, 3, 5, 10, 15, 20, 30, 45, and 60 minutes after the stop of propofol infusion.

**Measurements**

Heart rate from the electrocardiogram, arterial blood pressure, end-tidal pCO2, respiratory rate, and arterial oxygen saturation were recorded every 5 minutes during the study period. BIS values were downloaded during the trial to a laptop PC and saved for offline analysis.

During the propofol infusion and until the volunteers recovered, the level of consciousness was assessed every 10 seconds using the responsiveness (“open your eyes”) component of the Observer’s Assessment of Alertness/Sedation (OAA/S) score. Loss of consciousness (LOC) and recovery of consciousness (ROC) were defined as the first OAA/S score ≤2 (LOC = no response to verbal command) followed by the first OAA/S score >2 (ROC = response to verbal command). The time period spanning between LOC and ROC defined sleep duration in each volunteer. Evaluation of responsiveness was performed by an investigator who was blinded to BIS.

Arterial blood samples for propofol determination were immediately processed and maintained at −70°C until analysis, which was conducted with high-performance liquid chromatography and fluorescence detection assay modified from the method of Plummer. Calibration curves with spiked and extracted plasma passed through the origin and were linear in the calibration range of 0.29 to 29 μg/mL with correlation coefficient values of r² ≥ 0.998. The intraday and interday coefficients of variation were 2.45% and 3.2% for quality-control samples containing 14.5 μg/mL propofol, respectively. The limit of quantitation (S/N = 10) was 30 ng/mL, and the recovery rate ≥95%.

**Data Analysis**

Individual demographic and morphometric data are presented as number of patients or means ± SDs. We used the 2-step approach proposed by Sheiner et al. to model individual subject Ce using the measured arterial propofol concentrations and BIS as a continuous high-resolution measure of drug effect. Accordingly, propofol kinetics was estimated first, followed by calculation of k e (i.e., the rate constant for plasma–effect site equilibration) and the parameters of the concentration versus response model.

**Pharmacokinetics**

The parameters of a 3-compartment pharmacokinetic (PK) model were fit to the data using nonlinear mixed-effect modeling (NONMEM VII, GloboMax LLC, Hanover, MD, operated through PLT Tools graphical interface, version 3.0.2, PLTsoft, San Francisco, CA) with first-order conditional estimation. The propofol infusion regimen was used as input to the model and NONMEM estimated first typical values of the volumes and clearances in the population and subsequently post hoc Bayesian volumes and clearances in each subject. The interindividual variability for estimating the individual post hoc predictions of the volumes and clearances was modeled as a log-normal distribution:

\[
P_i = P_{TV} \times e^{\omega_i},
\]

where \( P_i \) is the parameter value in the \( i \)th subject, \( P_{TV} \) is the typical value of the parameter in the population, and \( \omega_i \) is a random variable with a mean of 0 and a variance of \( \sigma^2 \). Interindividual variability is reported as \( \sigma \), the SD of \( \omega \) in the log domain, which approximates the coefficient of variation (CV) in the standard domain when CV is relatively low (i.e., CV <50%). CV (in %) for the NONMEM estimates was calculated as:

\[
CV = \frac{SD}{TV} \times 100
\]

Residual intraindividual error, \( \varepsilon \), was assumed to be proportional to the prediction (i.e., a constant CV).

Model fit was assessed by visual inspection of plots of the observed (measured) versus predicted plasma propofol concentration (Cp), linear regression, and calculation of the median prediction error (MDPE) and median absolute prediction error (MDAPE). First, prediction error was estimated for each blood sample as percentage of the predicted concentration.
\[
PE = \frac{C_{\text{meas}} - C_{\text{pred}}}{C_{\text{pred}}} \times 100
\]

where \(C_{\text{meas}}\) and \(C_{\text{pred}}\) are the measured and predicted propofol \(Cp\), respectively. Prediction error, MDPE, and MDAPE were calculated twice: first using the \(Cp\) predicted from the population PK model and second using the individual post hoc Bayesian estimates of \(Cp\).

Bootstrap analysis\(^\text{16}\) was used to estimate 95% confidence intervals (CIs) for each PK parameter by randomly sampling a new dataset from the volunteers’ data, with replacement, and then repeating NONMEM estimation of the final model 500 times. According to the percentile method,\(^\text{16}\) a 95% CI was calculated from the bootstrap results as the interval from the parameter value at the 2.5% rank to the parameter value at the 97.5% rank.

Covariates were assessed for potential inclusion into the final model based on their regression against the individual post hoc estimates of the PK parameters using general additive modeling.\(^\text{17,18}\) We targeted covariates for potential inclusion to the model based on their relationship with parameters’ interindividual variability (\(\eta\)). This relationship was assessed by visual inspection, as well as Pearson correlation analysis, a statistical tool embedded in PLT Tools. The final model was also tested for a hair color (dark versus red) covariate effect on \(C\), retained in the final model. If >1 covariate were significant, \(P < 0.01\) with 1 degree of freedom), and this covariate was calculated from the bootstrap results as the interval from the parameter value at the 2.5% rank to the parameter value at the 97.5% rank.

Results

All recruited volunteers (\(N = 29, 16\) with dark and 13 with red hair color) completed the study. Table 1 presents individual and average demographic and morphometric characteristics.

Cardiorespiratory physiology remained within normal limits during and after the propofol infusion. A total of 406 arterial blood samples (including 29 blank samples) were obtained from the volunteers for the determination of plasma propofol concentration. The samples at the first minute after initiating the propofol infusion in volunteers 3 and 9, as well as the sample obtained at 5 minutes after the end of infusion in volunteer 28, revealed a drug concentration below our quantitation limit of 30 ng/mL; these concentration values were not included in the PK analysis. Therefore, 374 propofol concentration values were used for the determination of the PK model. All the PK data and relevant morphometrics have been uploaded to the Open TCI site (http://opentci.org/doku.php?id=data:propofol:propofol#doufas_redhead_study).

Table 1. Demographics of the Dark- and Red-Haired Volunteers

<table>
<thead>
<tr>
<th>Gender, male/female</th>
<th>Age (y)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Body mass index (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dark (n = 16)</td>
<td>10/6</td>
<td>27 ± 5</td>
<td>72 ± 10</td>
<td>172 ± 8</td>
</tr>
<tr>
<td>Red (n = 13)</td>
<td>6/7</td>
<td>28 ± 5</td>
<td>74 ± 15</td>
<td>168 ± 11</td>
</tr>
</tbody>
</table>

Group results presented as number of patients or mean ± SD.
Propofol Hypnosis in Red-Haired Subjects

Propofol Hypnosis in Red-Haired Subjects

in the model, sequentially for the central clearance (CL1) and central volume (V1), significantly (P < 0.01) improved the basic model. The upper panel in Figure 2 shows the performance of the final PK model as a function of time. Assessment of the hair color covariate effect for all the PK parameters did not result in a model with either a lower −2LL or a better fit (i.e., a lower MDAPE value).

Table 2. Pharmacokinetics of Propofol Estimated with NONMEM Using Data from All Volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TV</th>
<th>SD</th>
<th>CV</th>
<th>Covariate effects</th>
<th>500 bootstraps, median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 (L)</td>
<td>5.54</td>
<td>0.0004</td>
<td>&lt;1</td>
<td>0.1 + (wt − 71.7) × 0.08</td>
<td>5.57 (4.89–6.38)</td>
</tr>
<tr>
<td>V1 (L)</td>
<td>6.18</td>
<td>0.0001</td>
<td>&lt;1</td>
<td>0.1 + (wt − 71.7) × 0.08</td>
<td>6.14 (4.3–10.6)</td>
</tr>
<tr>
<td>V1 (L)</td>
<td>71.4</td>
<td>0.20</td>
<td>0.28</td>
<td>0.1 + (wt − 71.7) × 0.03</td>
<td>72.7 (49.7–323)</td>
</tr>
<tr>
<td>CL1 (L/h)</td>
<td>2.64</td>
<td>0.17</td>
<td>6.4</td>
<td>0.1 + (wt − 71.7) × 0.03</td>
<td>2.61 (1.69–2.88)</td>
</tr>
<tr>
<td>CL1 (L/h)</td>
<td>1.17</td>
<td>0.0004</td>
<td>&lt;1</td>
<td>0.1 + (wt − 71.7) × 0.03</td>
<td>1.17 (0.94–1.48)</td>
</tr>
<tr>
<td>CL1 (L/h)</td>
<td>1.35</td>
<td>0.28</td>
<td>20.7</td>
<td>0.1 + (wt − 71.7) × 0.03</td>
<td>1.38 (1.18–2.16)</td>
</tr>
</tbody>
</table>

Model performance

- MDPEpop/MDAPEpop (%) = −4/23, −3/21, −4/21 (−5, −4)/(21, 22)
- MDPEindiv/MDAPEindiv (%) = 2/11, 2/11, 2/11 (2, 3)/(10, 11)
- Objective function value = −707.53, −718.48, −728.71 (−732.2, −729.42)

Standard deviation (SD) for the NONMEM parameter estimates was calculated as the square root of the variance $\omega^2$, whereas the coefficient variation (CV) was expressed in %. Model performance was evaluated based on the reduction in the minimum objective function value, as well as the median prediction error (MDPE) and median absolute prediction error (MDAPE) of the model before and after inclusion of the covariate effects. Inclusion of weight (wt) as a covariate effect for the central clearance (CL1) and central volume (V1) significantly (denoted in blue) improved the model. Inclusion of hair color as a covariate for all pharmacokinetic (PK) parameters did not significantly improve the model. TV stands for typical (mean) value; $\propto$ denotes the relationship between a PK parameter and its covariate.

Pharmacodynamics

Figure 1 (lower panel) presents the time course of BIS during and after the propofol infusion in dark- and red-haired subjects, as well as indicators for the LOC and ROC end points. Table 3 presents the parameters of the PD model for propofol as these were estimated by NONMEM using the post hoc individual estimates of the PK model from all volunteers and BIS. Assessment of the hair color covariate effect for Ce50_BIS did not significantly improve the basic model. The lower panel in Figure 2 shows the performance of the final PD model as a function of time.

Separate PD model fits for dark- and red-haired subjects (Table 4) estimated a median (95% CI) for Ce50_BIS of 2.71 (2.28–3.36) and 2.57 (1.68–3.60), respectively. As indicated by the overlapping 95% CI (produced by bootstrapped reanalysis of the data), none of these parameters, including the model predictions for propofol CeLOC and CeROC, differed between the 2 groups (Fig. 3).

No significant correlation was shown between sleep duration and both the propofol Ce50_BIS and the dose of the drug that each subject received calculated in mg/kg body weight (Fig. 4).

DISCUSSION

Using the 2-step approach proposed by Sheiner et al.13 and BIS, as a continuous measure of hypnotic drug effect, we...
found that the hypnotic effect of propofol does not differ between volunteers with dark and red hair.

We have previously shown that red-haired subjects required more drug to achieve desflurane-induced immobility and midazolam-induced sedation and amnesia compared with dark-haired volunteers. However, MC1R loss-of-function mutation in mice and humans was associated with reduced sensitivity to experimental noxious stimuli and enhancement of opioid analgesia. Furthermore, whereas red-haired subjects were more sensitive to noxious cold and heat, they were more resistant than dark-haired volunteers to the local anesthetic effect of lidocaine. Differences in the methodology might account for some of the contradictory findings in these studies. However, the involvement of numerous, seemingly diverse, end points supports the influence of MC1R mutation on a central nervous system (CNS) agency with widespread regulatory activities, including function of the autonomic nervous system.

We have previously demonstrated a difference in the MAC\text{immobility} of desflurane between subjects with red and dark hair, using nonparametric unpaired testing (Mann-Whitney U test). Herein, we use mixed-effect modeling, which is a more sensitive method to test for covariate effects because it uses all of the data to test the statistical hypothesis, with appropriate weighting for the certainty of the finding in each subject. A Mann-Whitney U test assumes equal certainty of the finding in every subject, which is probably not the case. That does not invalidate our previous study, because even though we used a weaker statistical test, it was still adequate to demonstrate a difference. However, we need to recognize the fact that the anesthetic end points examined in these

![Figure 2. Observed/measured propofol concentration (Cp) (upper panel) and Bispectral Index (BIS) (lower panel) for the population (left) and the individual post hoc (right) model fits, as a function of time. Performance metrics for the respective models (i.e., median prediction error [MDPE] and median absolute prediction error [MDAPE]) are also indicated. The color of lines discriminates between the 2 different hair color groups (i.e., dark and red).](image-url)

<table>
<thead>
<tr>
<th>Table 3. Pharmacodynamics of Propofol Estimated with NONMEM Using Data from All Volunteers</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Final pharmacodynamic model</th>
<th>Parameter</th>
<th>TV</th>
<th>SD</th>
<th>CV</th>
<th>500 bootstraps, median (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ce50 (μg/mL)</td>
<td>2.82</td>
<td>0.46</td>
<td>17</td>
<td>2.75 (2.20–3.35)</td>
<td></td>
</tr>
<tr>
<td>Gamma (γ)</td>
<td>2.48</td>
<td>0.65</td>
<td>26</td>
<td>2.48 (1.90–3.65)</td>
<td></td>
</tr>
<tr>
<td>E0 (BIS)</td>
<td>95</td>
<td>0.1</td>
<td>0.1</td>
<td>95 (93–98)</td>
<td></td>
</tr>
<tr>
<td>Emax (BIS)</td>
<td>0.5</td>
<td>4.3</td>
<td>871</td>
<td>1 (0–9)</td>
<td></td>
</tr>
<tr>
<td>ke0 (min(^{-1}))</td>
<td>0.20</td>
<td>0.5</td>
<td>250</td>
<td>0.2 (0.16–0.24)</td>
<td></td>
</tr>
<tr>
<td>CeLOC (μg/mL)</td>
<td>1.90</td>
<td>0.51</td>
<td>27</td>
<td>1.88 (1.32–2.58)</td>
<td></td>
</tr>
<tr>
<td>CeROC (μg/mL)</td>
<td>1.71</td>
<td>0.44</td>
<td>26</td>
<td>1.74 (1.11–2.46)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Model performance</th>
<th>Basic model</th>
<th>+ (Ce50 ∝ hair color)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDPEpop/MDAPEpop (%)</td>
<td>3/6</td>
<td>2/6</td>
</tr>
<tr>
<td>MDPEindiv/MDAPEindiv (%)</td>
<td>0/3</td>
<td>0/3</td>
</tr>
<tr>
<td>Objective function value</td>
<td>14,035</td>
<td>14,034</td>
</tr>
</tbody>
</table>

Standard deviation (SD) NONMEM parameter estimates were calculated as the square root of the variance \(\sigma^2\), whereas the coefficient variation (CV) was expressed in %. Inclusion of hair color as a covariate for the Ce50 did not result in a significant improvement of the basic model, based on the objective function. TV stands for typical (mean) value; ∝ denotes the relationship between a pharmacodynamic parameter and its covariate; median prediction error (MDPE). CI = confidence interval; BIS = Bispectral Index; LOC = loss of consciousness; ROC = recovery of consciousness.
26,27 via 

romodulators with documented excitatory effects on the α-melanocyte stimulating hormones, which are potent neutral melanocortins such as the adrenocorticotropic and MC1R may lead to a compensatory up-regulation of cen-

recovery (CeROC) of consciousness. BIS = Bispectral Index.

Figure 3. Median values and 95% confidence intervals (CIs) (determined by bootstrap resampling analysis) for the propofol Ce50 BIS, as well as the propofol effect-site concentration at loss (Ce LOC) and recovery (CeROC) of consciousness. BIS = Bispectral Index.

2 studies; (immobility versus hypnosis), as well as the mechanisms governing these end points, are fundamentally different.22

Although expression of MC1R has been demonstrated in neurons that are dispersed in the periaqueductal gray of rat and human brains,23 as well as in human glial cells,24,25 the nervous system is not a major site of MC1R occurrence. How could it be possible for a mutation in a receptor that is normally expressed on epidermal melanocytes to affect behavioral end points originating in the nervous system? Red-hair MC1R variants may mediate the observed anes-

thetic effect and the associated bootstrap resam-

pling analysis showed with high confidence that the values of Ce50 BIS in the 2 hair color groups were almost identical and quite similar to those we7,11 and others14–39 have previ-

ously estimated in general population samples with compa-

rable demographics. Using hair color as a covariate did not improve performance of the propofol pharmacology model, and separate analysis of the dark- and red-haired subjects also resulted in overlapping estimates for Ce50 BIS. In addition, loss and recovery of consciousness, based on a behavioral scale of sedation, occurred at similar propofol Ce in the 2 groups; these CeROC levels were comparable to those estimated in previous studies involving healthy volunteers.41,42

Table 4. Pharmacodynamic Model Fits for the Dark- and Red-Haired Volunteers, Separately

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dark</th>
<th>Red</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TV</td>
<td>SD</td>
</tr>
<tr>
<td>Ce50 (μg/mL)</td>
<td>2.65</td>
<td>0.24</td>
</tr>
<tr>
<td>Gamma (%)</td>
<td>2.43</td>
<td>0.61</td>
</tr>
<tr>
<td>E0 (BIS)</td>
<td>95</td>
<td>0.1</td>
</tr>
<tr>
<td>Emax (BIS)</td>
<td>3.5</td>
<td>2.6</td>
</tr>
<tr>
<td>kloc (min−1)</td>
<td>0.19</td>
<td>0.21</td>
</tr>
<tr>
<td>CeLOC (μg/mL)</td>
<td>1.90</td>
<td>0.48</td>
</tr>
<tr>
<td>CeROC (μg/mL)</td>
<td>1.90</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Model performance

<table>
<thead>
<tr>
<th>MDPEperc/MDAPEperc (%)</th>
<th>3/6</th>
<th>2/7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective function value</td>
<td>8236</td>
<td>5731</td>
</tr>
</tbody>
</table>

MDPEperc = median prediction error, MDAPEperc = median absolute prediction error, TV = total variance, SD = standard deviation, CV = coefficient variation, Ce50 = propofol concentration at 50% loss of consciousness, CeLOC = propofol concentration at loss of consciousness, CeROC = propofol concentration at recovery of consciousness. All Ce values were determined by bootstrap resampling analysis (500 bootstraps) for the population and individual post hoc fits of the data. Bootstrap resampling analysis was used to estimate the median (95% confidence intervals) for the pharmacodynamic model parameters. CI = confidence interval; BIS = Bispectral Index; LOC = loss of consciousness; ROC = recovery of consciousness.

26,27 via MC2R and MC4R. In particular, MC4R has been involved in mediating stress-induced anxiety-like behavior28,29 and hyperalgesia30,31 in several animal models.

It is possible that MC1R mutations decrease people’s ability to cope with stress, thus provoking anxiety. We have shown that MC1R gene variants and red hair color were associated with increased dental care–related anxiety and fear of dental pain.32 This is an important finding because high preoperative anxiety was associated with increased propofol requirements for both induction and maintenance of anesthesia,33 and the determination of sedation threshold has been used in the past for quantifying tension in psychiatric patients.34 Along these lines, acute or chronic exposure to stress could exaggerate subsequent pain experiences in humans,35 and the effect of stress on pain perception could be predicted from baseline autonomic tone.36 It is thus possible that the effect of red hair genotype on the anesthetic requirement and/or pain perception is determined to a certain degree by the efficiency of a person’s coping strategy in the presence of a potentially threatening stimulus such as a pending surgical or dental procedure.

Although we cannot exclude the possibility of a small difference between dark- and red-haired subjects regarding the propofol hypnotic effect, it is fairly unlikely that this difference is large enough to trigger a clinical observation supporting existing anecdotal impressions. Modeling of the propofol BIS effect and the associated bootstrap resampling analysis showed with high confidence that the values of Ce50 BIS in the 2 hair color groups were almost identical and quite similar to those we7,11 and others14–39 have previ-

ously estimated in general population samples with compa-

rable demographics. Using hair color as a covariate did not improve performance of the propofol pharmacology model, and separate analysis of the dark- and red-haired subjects also resulted in overlapping estimates for Ce50 BIS. In addition, loss and recovery of consciousness, based on a behavioral scale of sedation, occurred at similar propofol Ce in the 2 groups; these CeROC levels were comparable to those estimated in previous studies involving healthy volunteers.41,42
The sampling scheme in our study was not optimized to fully characterize the kinetics of propofol; nonetheless, our estimation for the $V_\infty$, the main determinant of the plasma–effect site kinetics, was highly accurate and similar to previous reports. In fact, our estimation for the $k_0$ (0.20 min$^{-1}$; bootstrap resampling analysis: 0.20 [95% CI: 0.16–0.24]) confirms our previous findings ($k_o = 0.17$ min$^{-1}$) in volunteers with a comparable morphometric map. In addition, although our fixed-dose propofol regimen precluded the achievement of a consistently low BIS (Emax) in all volunteers (especially the heavier ones), it resulted in BIS <40 in most of them, thus providing enough confidence to our estimation of the Ce50BIS parameter.

A limitation of our study is that we did not investigate the MC1R genotype in our volunteers. However, a genotype analysis in our previous study confirmed that all red-haired volunteers carried at least one variant MC1R allele and that 9 of 10 harbored 2 such alleles, which is consistent with the reports of larger genetic investigations. In contrast, 5 of 10 dark-haired volunteers harbored a single mutant allele, and the remaining 5 showed consensus MC1R alleles.

In conclusion, using arterial plasma sampling for propofol determination and BIS, we showed that red hair phenotype is not associated with altered propofol pharmacology and a high resistance to the hypnotic effect of the drug. Anecdotal impressions among anesthesiologists that propofol requirements are increased in redheads thus seem unsubstantiated.

**RECUSE NOTE**

Dr. Steven L. Shafer is the Editor-in-Chief of the Journal. This manuscript was handled by Dr. Tony Gin, Section Editor for Anesthetic Clinical Pharmacology, and Dr. Shafer was not involved in any way with the editorial process or decision.

**DISCLOSURES**

Name: Anthony G. Doufas, MD, PhD.  
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.  
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**Figure 4.** Pearson correlation ($r$ [95% confidence interval]) of sleep duration with the individual Ce50BIS values (left panel) and the propofol dose (right panel) each of the subjects received, calculated in milligrams/kilogram. Colored markers discriminate between the 2 different hair color groups (i.e., dark and red).
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