Midazolam causes less sedation in volunteers with red hair

[Le midazolam cause moins de sédation chez des volontaires aux cheveux roux]

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Purpose: We studied sedation, cognition, and mood during midazolam infusion in volunteers with red and non-red (blond or brown) hair, to test the hypothesis that patients with red hair may require more drugs to attain desired levels of sedation.

Methods: Twenty red and 19 non-red hair subjects were studied in a randomized, placebo-controlled cross-over design. Subjects were studied during placebo and midazolam at 30 ng·mL^{-1} target effect site concentration. Sedation was assessed using the observer's assessment of alertness/sedation (OAA/S) scale, the drowsiness visual analogue scale (VAS), and the bispectral index; cognition was assessed using the Repeatable Battery for Assessment of Neuropsychological Status; and mood was assessed using the bipolar form of the Profile of Mood States (POMS).

Results: Red hair volunteers showed significantly higher OAA/S ($P < 0.01$) and lower drowsiness VAS ($P < 0.05$) scores compared to non-red hair subjects during midazolam infusion. Visuospatial score was significantly higher in subjects with red compared to non-red hair during placebo and midazolam trials. Delayed memory score was significantly higher during midazolam infusion in subjects with red compared to non-red hair. There were no group differences in POMS during either trials.

Conclusion: Midazolam appears to cause significantly less sedation and cognitive impairment in red haired subjects.

Objectif : *Étudier la sédation, la fonction cognitive et l'humeur pendant une perfusion de midazolam chez des volontaires aux cheveux roux et non roux (blonds ou châtains) pour tester l'hypothèse voulant que chez les patients aux cheveux roux, il faut de plus grandes quantités de médicaments pour obtenir les niveaux de sédation désirés.*

Méthode : *Vingt sujets roux et 19 non roux ont participé à l'étude randomisée, croisée et contrôlée contre placebo. L'expérimentation a eu lieu pendant que la concentration cible au site effecteur était de 30 ng·mL^{-1} de midazolam ou de placebo. La sédation a été notée avec l'évaluation par un observateur de l'échelle d'attention/sédation (EOA/S), l'échelle visuelle analogique de somnolence (EVA) et l'index bispectral ; la fonction cognitive par la Batterie de tests répétables de l'évaluation de l'état neuropsychologique et l'humeur par la forme bipolaire du Profile of Mood States (POMS).*

Résultats : *Avec le midazolam, les volontaires roux, comparés aux non roux, ont présenté des scores significativement plus élevés à l'échelle d'EOA/S ($P < 0,01$) et moins de somnolence à l'EVA ($P < 0,05$). Le score visuospatial a été significativement plus élevé chez les sujets roux sous placebo ou midazolam. Le score de mémoire différée a été significativement plus élevé avec le midazolam chez les sujets roux. Les scores au POMS n'ont présenté aucune différence intergroupe pendant une épreuve ou l'autre.*

Conclusion : *Le midazolam semble causer moins de sédation et d'altération de la fonction cognitive chez les sujets aux cheveux roux.*

ANECDOTAL descriptions exist that subjects with red hair may faint easily and are difficult to anesthetize.[1] A mail survey of anesthesiologists[A] has shown that red-haired patients are perceived to have a propensity for drug hypersensitivity, airway difficulties, hemodynamic instability, dysrrhythmias, combativeness and confusion at anesthesia emergence, nausea/vomiting, and bleeding. Our clinical observations suggest that patients with red hair may also require more drugs to attain desired levels of sedation.

A *Algarra NN, Foust JA, Green SM, Hardy AE, Hendrix SR.* Perception of certified registered nurse anesthetists in Georgia regarding anesthesia morbidity in patients with red hair. Houston: University of Texas Health Science Center, School of Nursing, 1994: 1–5.

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We therefore evaluated the hypothesis that subjects with red hair are more resistant to sedative drugs than are subjects with non-red hair. To this end, sedation, cognition, and mood were studied at a light sedation with midazolam in healthy volunteers with red and non-red hair.

Methods

After approval by the Human Studies Committee of the University of Louisville and written informed consent, we studied 40 healthy volunteers of both genders with red ($n = 20$) and non-red hair (blond or brown, $n = 20$) using a randomized, placebo-controlled, and crossover design. Both investigators and volunteers were blinded with respect to the treatment but not to hair colour. Exclusion criteria were: 1) hair dyed red; 2) age less than 18 and more than 40 yr; 3) education less than eight years; 4) vulnerability to psychosis (screened by the Bell Realty Testing Inventory);[2] 5) history of psychological counselling; 6) psychiatric disease; 7) chemical substance abuse; 8) use of drugs that affect central nervous system function; 9) chronic pain; 10) obesity defined by a body mass index ≥ 30.0, and/or 11) presence of acute or chronic diseases.

Sample size

Sample size was based on two primary end-points, observer's assessment of alertness/sedation (OAA/S)[3] and the bispectral index (BIS) of the electroencephalogram (EEG). We assumed baseline values of OAA/S and BIS to be 5 and 95 to 99, respectively and a 20% reduction in these values to be clinically meaningful. From the data in our previous study,[4] sample size was 18 for OAA/S and 20 for BIS with $\alpha = 0.25$ (two tests) and a power of 0.9.

Protocol

Each subject was tested twice approximately two weeks apart. Subjects were randomly assigned to computer generated numbers to receive either midazolam or placebo during the first trial and the alternative treatment during the second trial. All trials were scheduled to begin at 9:00 a.m. A Harvard pump 22™ (Harvard Apparatus, Holliston MA, USA) was used to target a midazolam effect site concentration of 30 $ng \cdot mL^{-1}$. The pump was controlled by version 4/98 of the Stanpump program (Steven L. Shafer, M.D., Stanford University) using the pharmacokinetic data of Greenblatt *et al.*[5] For placebo, normal saline was infused with the pump similarly set. Volunteers sat in a reclining chair in a quiet study room for approximately 15 min. An antecubital vein was cannulated with a 20-gauge catheter for the drug infusion. Electrocardiogram, heart rate (HR), respiratory rate (RR), and arterial oxygen saturation (SaO_2) were monitored continuously. Blood pressure (BP) was monitored every 15 min. Sedation, cognition, and mood were assessed before (baseline) and 20 min after the beginning of the infusion.

Measurements

A detailed medical/surgical history was taken with a particular focus on any unusual perianesthetic event. BP, HR, RR, and SaO_2 were recorded every 15 min. RR was measured using a nasal cannula (Salter Style™ Salter Labs, Arvin, CA, USA) and a capnograph.

Sedation was assessed using the OAA/S, the drowsiness visual analogue scale (VAS, 0–100), and the BIS using a Monitor Model A-2000™ (Aspect Medical Systems, Inc., Natick, MA, USA). The mean values of 60 epochs recorded immediately before assessment of OAA/S and the drowsiness VAS scores were used for analysis.

Cognitive function was assessed using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS™ Randolph C: RBANS manual; Psychological Corporation, San Antonio, Harcourt Brace & Co., 1998).[6] Each of the five domains of RBANS consists of two to four subtests. Immediate memory was assessed by a ten-word list (range, 0–40) and story memory (0–24). Visuospatial/constructional ability was assessed by a figure copy (0–20) and line orientation (0–20). Language was assessed by picture naming (0–10) and semantic fluency (0–40). Attention was evaluated by digit span (0–16) and digit-symbol substitution (0–89). Delayed memory was evaluated by a ten-word list recall (0–10), the list recognition (0–20), a story recall (0–12), and figure recall (0–12). The subtest score was converted by z-score transformation. An index score for a domain was obtained by transforming the sum of subtest z-scores to a scale with a mean (SD) of 100 (15). The total scale of index scores (i.e., global assessment of cognitive function) was obtained similarly by transforming the sum of index scores that contribute to the total composite to a scale with a mean ± SD, of 100 ± 15 (40–160).

Mood was assessed using the bipolar form of the Profile of Mood States (McNair DM, Lorr M, Doppleman LF. EdITS manual for the profile of mood states; San Diego: Educational and Industrial Testing Service, 1992).[7] Each of the six mood states in the test (i.e., composed-anxious, agreeable-hostile, elated-depressed, confident-unsure, energetic-tired, and clear-headed-confused) is composed of 12 adjective scales, of which one pole represents the positive aspect of the dimension while the other pole refers to the negative

TABLE I Demographics and morphometrics in volunteers with red and non-red hair

	Non-red hair (n = 19)	*Red hair (n = 20)*
Age (yr)	28 ± 7	29 ± 6
Body height (cm)	173 ± 7	173 ± 8
Body weight (kg)	76 ± 11	73 ± 11
Race (Caucasian/Asian)	18/1	20/0
Body mass index (kg·m^2)	26 ± 4	25 ± 3
Sex (male/female)	3/7	11/10
Education (yr)	16 ± 2	17 ± 3
Perianesthetic history (subjects/ surgeries/events)§	14/29/0†	15/28/7‡
Vagovasal reaction at vein cannulation¶	1 (5.3%)	5 (23.8%)¶
Total midazolam dose (mg)	4.5 ± 0.7	4.4 ± 0.7

*One subject did not show for the second session; †Fourteen subjects had 29 surgeries. There were no unusual events in this group. ‡Fifteen subjects had 28 surgeries. Seven of 15 subjects developed unusual anesthetic events. ¶One of five subjects who fainted withdrew from the study. One more red-haired volunteers was enrolled. The incidence of fainting was five out of 21 red-haired volunteers.

TABLE II Sedation during placebo and midazolam in red and non-red hair subjects

		Red hair	*Non-red hair*	*P*
OAA/S	Placebo	5.0 (0.0)	5.0 (1.0)	NS
	Midazolam	5.0 (0.0)	4.0 (2.0)	0.004
Drowsiness VAS	Placebo	0 (5)	0 (3)	NS
	Midazolam	42 (54)	67 (47)	0.034
BIS	Placebo	97 (3)	97 (4)	NS
	Midazolam	85 (13)	80 (9)	NS

OAA/S = observer's assessment of alertness/sedation; Drowsiness VAS = drowsiness visual analogue scale; BIS = bispectral index; NS = non-significant. Data are presented as medians (interquartile range). Differences in sedation scores during infusion were tested using the Mann-Whitney test.

aspect. Each adjective was rated by a four-point scale. The total score (i.e., the sum of positive items and negative items plus a constant of 18 for each of the mood states; 0–36) was transformed into a T-scale with a mean ± SD value of 50 ± 10.

Data analysis

Two-factor analysis of covariance was used for between-groups analysis of vital signs, RBANS scores, and mood scores. Analysis of covariance adjusted for any disparity between groups at baseline. Red hair subjects were compared with non-red hair subjects at baseline and infusion, during the placebo and midazolam trial. Differences between baseline and infusion during midazolam infusion were analyzed by paired t-test with Sidak adjustment for multiple comparisons. The OAA/S score, drowsiness VAS, and BIS were analyzed using the Mann-Whitney test. Data are presented as means ± standard deviations, unless otherwise indicated. $P < 0.05$ was considered to be statistically significant. Post hoc power analysis for comparisons between groups during midazolam infusion was performed on cognitive and mood data.

Results

Demographic and morphometric data are summarized in Table I. One woman with red hair who fainted at vein cannulation withdrew from the study. One more volunteer was recruited for the red-hair group. One subject with non-red hair failed to appear for the second session. The study was completed in 20 red-haired subjects and 19 non-red haired subjects (i.e., two with blond hair, 16 with brown hair, and one with black hair). Age, gender, body height, body weight, body mass index, racial composition, and education level were comparable between the groups.

Anesthetic history showed that 15 red-haired volunteers had 28 previous surgical procedures. Ten of these subjects had 18 general anesthetics, and ten subjects had 11 maxillary and/or mandibular nerve blocks for dental procedures. Three red-haired subjects experienced intraoperative awareness, and four other subjects required repeated injections of local anesthetics for dental extraction (resistance to loco-regional anesthesia). Fourteen non-red haired volunteers had 29 surgical procedures. Eleven of these subjects had 24 general anesthetics, and five had five regional blocks for dental procedures, without experiencing any unusual event. Thus, the incidence of unusual perianesthetic events was significantly higher in subjects with red hair. Five red-haired subjects fainted on puncture of an antecubital vein (vasovagal reaction). One subject with non-red hair fainted. The incidence of fainting was not different between the groups.

Data for the OAA/S, drowsiness VAS, and BIS scores were not normally distributed and are presented as medians with interquartile ranges (Table II). The OAA/S score was significantly higher in subjects with red hair during midazolam infusion ($P < 0.005$). The drowsiness VAS score was significantly lower in subjects with red hair ($P < 0.05$). BIS values were not different between groups.

Midazolam significantly impaired total RBANS score, immediate and delayed memory, visuospatial activity, and attention in both groups ($P < 0.05$; Table III). The visuospatial score was significantly higher in subjects with red compared to non-red hair both during placebo and midazolam. Delayed memory and

TABLE III Cognitive function in red and non-red hair subjects

		Placebo		*Midazolam*		
		Baseline	*Infusion*	*Baseline*	*Infusion*	*Power*
Memory (I)	Red	118.1 (4.1)	106.9 (3.5)	109.2 (3.9)	74.2 (4.5)†	0.33
	Non-red	120.6 (4.9)	110.0 (4.2)	109.3 (4.7)	66.5 (5.5)†	
Visuospatial	Red	103.0 (3.9)‡	100.3 (4.3)‡	101.0 (4.6)‡	90.3 (4.3)†‡	0.84
	Non-red	91.1 (4.7)	89.6 (5.2)	85.6 (5.5)	73.9 (5.1)†	
Language	Red	97.4 (3.3)	106.2 (3.0)	100.8 (4.2)	98.9 (2.9)	0.12
	Non-red	106.3 (4.0)	105.2 (3.6)	99.4 (5.1)	98.6 (3.5)	
Attention	Red	101.3 (3.3)	101.1 (2.5)	95.6 (3.8)	81.4 (3.4)†	0.06
	Non-red	98.9 (4.0)	100.3 (3.0)	97.2 (4.6)	80.9 (4.1)†	
Memory (D)	Red	111.1 (2.8)	105.6 (3.6)‡	107.2 (3.1)‡	62.4 (4.8)†‡	0.85
	Non-red	106.1 (3.3)	98.2 (4.3)	96.7 (3.8)	45.8 (5.8)†	
Total scale	Red	108.9 (3.8)	105.0 (3.1)	104.2 (4.0)‡	76.9 (3.3)†‡	0.63
	Non-red	106.4 (4.6)	100.9 (3.7)	92.9 (4.8)	66.4 (3.9)†	

Memory (I) = immediate memory; memory (D) = delayed memory. Data are presented as means (standard errors). †$P < 0.05$, infusion *vs* baseline during midazolam trial. ‡$P < 0.05$, red *vs* non-red hair groups. Power indicates post hoc analysis of power of finding a group difference during midazolam infusion.

TABLE IV Mood in red and non-red hair subjects

		Placebo		*Midazolam*		
		Baseline	*Infusion*	*Baseline*	*Infusion*	*Power*
Composed	Red	64.8 (1.9)	67.4 (2.3)	61.6 (2.0)	63.4 (1.6)	0.08
	Non-red	63.3 (2.3)	64.8 (2.8)	66.0 (2.4)	64.4 (2.0)	
Agreeable	Red	63.7 (2.3)	63.0 (2.5)	59.1 (2.5)	60.3 (2.7)	0.05
	Non-red	62.0 (2.7)	63.3 (2.8)	62.3 (2.8)	59.8 (3.1)	
Elated	Red	58.2 (2.3)	60.4 (2.6)	56.4 (1.8)	54.4 (2.1)	0.19
	Non-red	60.2 (2.7)	59.3 (3.1)	62.5 (2.2)	57.2 (2.5)	
Confident	Red	59.8 (1.7)	60.4 (2.3)	58.5 (2.2)	55.0 (2.5)	0.26
	Non-red	59.7 (2.1)	61.3 (2.8)	61.8 (2.6)	49.9 (3.0)†	
Energetic	Red	56.7 (2.6)	59.1 (2.8)	55.9 (2.3)	45.5 (2.3)†	0.19
	Non-red	59.4 (3.1)	60.8 (3.3)	58.7 (2.8)	42.3 (2.8)†	
Clearheaded	Red	65.7 (2.1)	64.4 (2.0)	61.8 (2.0)	57.8 (2.8)	0.26
	Non-red	63.2 (2.5)	66.3 (2.3)	64.8 (2.3)	52.3 (3.4)†	

Data are presented as means (standard errors). †$P < 0.05$, infusion *vs* baseline during midazolam trial. Power indicates post hoc analysis of power of finding a group difference during midazolam infusion.

total RBANS scores were significantly higher in red hair compared to non-red hair subjects during midazolam infusion.

There were no significant differences between the groups in mood states during the placebo or midazolam trials. Post-hoc analysis demonstrated a power between 0.05 and 0.26 (Table IV).

Discussion

We found that the OAA/S score was significantly higher and the VAS score for drowsiness was significantly lower in subjects with red compared to non-red hair during midazolam infusion. The midazolam concentration used in this study was equivalent to that expected approximately 30 min after a bolus injection of 2 mg midazolam in a 70-kg subject.[4] Sedation in non-red haired volunteers was similar to that previously observed by our group at the plasma concentration of 30 $ng \cdot mL^{-1}$.[8] Drowsiness was moderate to severe, and response to name calling was lethargic during the midazolam infusion, while, in red-haired volunteers, drowsiness was less (i.e., mild to moderate), and response to name calling during the infusion was brisk.

Proopiomelanocortin (POMC) is synthesized and cleaved into peptides that include α-melanocyte-stimulating hormone (α-MSH), adrenal corticotrophic hormone (ACTH), and ß-endorphine in the pituitary gland, gastrointestinal tract, gonads, placenta, and skin.[9] Neuropeptides, ACTH and α-MSH, are potent modulators of cognitive function and neurobehavioural activities in animals and humans.[10,11] The peptides

consistently enhance selective attention and stimulus processing with a visual (but not an auditory) discrimination learning procedure. The peptides produce higher EEG frequencies in humans that are consistent with a generalized arousal response and a disinhibition of central nervous system-activating mechanisms.[12,13] The EEG signs of focusing attention have been reported in occipital leads overlying the primary visual cortex, and visual evoked potentials are consistent with increased attention.[14] Human subjects, when treated with these peptides, performed significantly better than control subjects in visual memory, digit-symbol substitution test (i.e., visual-motor learning), and continuous performance task.[15] Sandman *et al.*[16] reported that, although the peptides actually raised perceptual threshold of stimuli, once these stimuli were perceived, visual discrimination was significantly facilitated. Thus, it has been postulated that ACTH/α-MSH exert their predominant effect on attention rather than memory processes (attentional hypothesis).[16,17] However, reported effects of those peptides on human attention have been inconsistent and at best marginal.[18,19]

The mechanism for the significant resistance to sedation observed in our red-haird volunteers during midazolam infusion is not clear. MSH and ACTH equipotently act on melanocortin receptor-1 (MC1-R), initiating melanogenesis.[9] Of the allelic variants of the MC1-R gene identified in humans, three particular variants, Arg 151Cys, Arg160Trp, and Asp294His, are the most frequently encountered loss of function mutations.[20] These variants result in an increase in the pheomelanin/eumelanin ratio in the skin and hair, and are associated with red hair, fair skin, and poor tanning ability.[9] The mechanisms controlling production of α-MSH have not been clarified, but most pituitary functions are controlled by negative feedback systems. End-organ failure (e.g., loss of function mutations) leads to an increase in the level of hormones. Thus, it may be assumed that MC1-R dysfunction may activate a putative feedback system and increase central α-MSH levels, conferring resistance to midazolam-induced sedation.

Midazolam impaired cognitive function and affected mood, as it has been reported previously.[4,8,10,21] Interestingly, visuospatial/constructional ability was significantly higher in subjects with red compared to non-red hair at all phases (i.e., baseline and infusion) of the study both during placebo and midazolam trials. The heightened visuospatial activity observed in this study is comparable to the enhanced selective attention and stimulus processing with visual learning procedure shown in subjects treated with α-MSH and ACTH.[12–17] We also found that delayed memory score was less impaired in subjects with red compared to non-red hair. This finding is also consistent with the previous results[16] showing heightened attention and subsequent facilitation of visual discrimination in subjects receiving α-MSH and ACTH. It is, thus, possible that the significant differences found in visuospatial activity and delayed memory between groups might be due to higher central levels of α-MSH in red-haired subjects.

The incidence of fainting spells at cannulation of a vein in the sitting position was higher in red (5/21) than in non-red haired volunteers (1/19). The incidence appears to be consistent with perceived vascular instability during anesthesia[A] and the view that subjects with red hair tend to faint easily.[1] The effects of melanocortins on cardiovascular function have recently been reviewed.[22] A putative change in the dynamics of central α-MSH activity may be the underlying mechanism for the perceived association between red hair colour and vascular instability or fainting spells in red hair subjects.[A] Unusual perianesthetic events (i.e., awareness during general anesthesia and resistance to maxillary and mandibular block for dental procedures) were more frequent in subjects with red than non-red hair. These events appear to be consistent with the observations that subjects with red hair may require more inhaled anesthetics for a given level of anesthetics[23] and subjects with red hair are more sensitive to noxious stimuli.[24]

The amount of midazolam used during the study was comparable between subjects with red and non-red hair. However, since plasma levels of midazolam were not measured, a possibility that our findings were due to phamacokinetic differences between subjects with red and non-red hair could not be excluded. The investigators were not blinded with respect to hair colour. Even though efforts had been made to blind the study by covering subjects' hair, the investigators were still able to identify red hair subjects from the skin appearance. The OAA/S and drowsiness VAS scores used in this study are fairly subjective tools for assessment of sedation/sleepiness and the existence of bias can not be excluded.

The results of the study suggest that red haired subjects appear to be less sedated than are those with non-red hair for a given plasma concentration of midazolam. Change in the melanocortin system may be a part of the mechanism for the apparent resistance to the sedative effect of midazolam observed in red-haired subjects.

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