Anesthesia Requirements for Redheads

Nathan Classon, RN, BSN, SRNA

Adventist University of Health Sciences

Project Mentor: Tom Andrews, MD, JLR Anesthesia Group

Committee Chair: Alescia DeVasher Bethea, PhD, CRNA

Nurse Anesthesia Program, Adventist University of Health Sciences

March 16, 2016

Abstract

As the melanocortin-1 receptor gene was not discovered until 1995, only anecdotal observation supported that redheads had an increased anesthetic requirement. Utilizing relatively recent research, this project aimed to enhance the knowledge regarding the anesthetic requirements for redheads among student registered nurse anesthetists (SRNAs). Interestingly, there was a decided perspectival shift in the opinion of literature reviewed between 2004 and 2015. Earlier studies were supportive of an increased anesthetic requirement of redheads, while more recent studies discouraged such an approach. It is possible that the later studies relied on self-reported hair phenotype, rather than analysis of genetic makeup of the MC1R genotype. Given this, it is plausible that there is a significant difference in the anesthetic requirements of redheads, depending on whether they are homozygous, heterozygous, or compound heterozygous. Therefore, current literature was reviewed, synthesized, and presented simultaneously to two cohorts of SRNAs at Adventist University (ADU). The project's efficacy was determined by comparing the scores of an identical pre- and post-test.

Table of Contents

Abstract……2

Problem……4

Review of Literature..……..5

Project Description…….12

Evaluation Plan……..13

Results and Conclusions……14

References……..16

Appendix A- Informed Consent….……18

Appendix B- Pre-and Post-Test.……....19

Appendix C- Presentation……..21

Problem

Some anesthesia providers have noticed an increase in anesthetic requirements for patients with a red head phenotype. This suggests that in a majority of surgeries for patients of this phenotype, more inhaled anesthetics may be required to elicit the same responses needed to maintain hemodynamic and physiologic stability. Recent research has shown there could be a genetic predisposition for this phenomenon, specifically involving the melanocortin-1 receptor gene (Liem, Lin, Suleman, Doufas, Gregg, Veauthier, Loyd, & Sessler, 2004). Isolating this genetic variation has the potential to make it scientifically possible to more accurately gauge the anesthetic requirement people of this particular phenotype require when undergoing surgery. This is a particularly important safety concern, as intraoperative awareness can occur when patients are emerging from anesthesia, as well as during periods of surgery when anesthetic depths are diminished (Gradwohl, Aranake, Abdallah, McNair, Lin, Fritz, Villafranca, Glick, Jacobsohn, Mashour, & Avidan, 2015). Anesthesia providers should be cognizant of this specific variant, and be able to apply an appropriate approach to the anesthetic management of patients of this particular genotype and phenotype. Such has neither been possible nor applied previously, as providers have relied solely on empirical anecdotal observations to guide clinical decisions. Employing recent research, anesthesia providers should be able to have a more accurate and dependable measurement of safe anesthetic levels for patients that predominantly produce pheomelanin, resulting in red hair, when compared to patients who do not (Liem et al., 2004). Anesthesia providers and instructors have not fully understood the relationship between pheomelanin producing patients and anesthetic requirements until recently (Myles, Buchanan, & Bain, 2012). As a result, Student Registered Nurse Anesthetists (SRNAs) may also have had a superficial understanding of this association.

Review of Literature

While anesthesia providers have relied on such determinants as variability in age and fluctuations in temperature to safely administer inhaled anesthetics for decades, only anecdotal observation of the increased anesthetic requirement for red-haired patients guided their practice (Liem et al., 2004). With a relatively recent isolation of the melanocortin-1 receptor (MC1R) gene, scientists and anesthesia providers are closer to understanding the exact mechanism that causes the potentially decreased sensitivity to inhaled anesthetics, as well as being able to determine the genetic predisposition for other alterations in pharmacokinetics and pharmacodynamics. The MC1R gene is a single member of the large family of melanocortin receptors that possess a myriad of physiologic functions, including immune and inflammatory responses, hypothalamic function, thermoregulation, and exocrine gland function, among others (Myles et al., 2012).

The ability to ascertain quantitative data regarding the chemical composition of red hair is a relatively recent discovery. In fact, differentiation between eumelanin and pheomelanin was first achieved in 1985, and the discovery of the MC1R gene occurred in 1995 (Ito & Wakamatsu, 2011). In order to reliably determine the varying levels of eumelanin and pheomelanin, Ito and Wakamatsu (2011) utilized hydrogen peroxide (H_2O_2) to oxidize differing hair colors, which yielded pyrrole-2,3,5-tricarboxylic acid (PTCA) and thiazole-2,4,5-tricarboxylic acid (TTCA) as markers for eumelanin and pheomelanin, respectively. The hydrogen peroxide oxidation was stated as both simple and reproducible. This allowed them the ability to quantitatively evaluate the chemical composition of black, dark brown, brown, light brown, blonde, and red hair. They discovered that eumelanin levels are quite pronounced in black hair and subsequently decrease in the order described above, yet all hair colors (except red) have a trace, yet constant level of

pheomelanin. They found that the difference in the red hair phenotype is an approximate equal amount of both eumelanin and pheomelanin (Ito & Wakamatsu, 2011). The authors also analyzed the eumelanin/pheomelanin ratios of various hypopigmentary disorders, such as Hermansky-Pudlak syndrome, Menkes disease, proopiomelanocortin deficiency, cystinosis, malnutrition, and trace metal deficiency. This allowed evaluation of the precise effects of each disease on pigmentation.

Analysis of the effect of the MC1R gene has not only been human specific, but has also been tested on mice. Xing, Sonner, Eger, Cascio, and Sessler (2004) found similar, although not as remarkable results as Liem et al. (2004). In the Xing et al. (2004) study, mice with dysfunctional MC1R genes (and subsequent changes in coat color) were also found to have an increased minimum alveolar concentration (MAC) requirement. This requirement is used by anesthesia providers to gauge anesthetic depth, as the MAC of an inhaled anesthetic to produce anesthesia, or lack of movement to surgical stimulation in 50% of the population, is inherently useful. At only a 5.5% increase in MAC requirement among mice with the deficient MC1R gene, these results were not as staggering as Liem et al. (2004), albeit significant. This study went further to suspect reasonable contributions to the theory that MC1R gene may indeed cause acute alterations in anesthetic depth, secondary to its action on brain glial cells and neurons of the ventral periaqueductal gray, an area of the central nervous system known to act on nociception (Xing, et al., 2004).

Five years after the discovery of the MC1R gene, Flanagan, Healy, Ray, Philips, Todd, Jackson, Birch-Machin, and Rees (2000) sought to determine the downstream, or pleiotropic, effects of the gene. They analyzed the contribution of MC1R variation in homozygous, compound heterozygotes, and heterozygotes in 273 individuals, with 174 of them from 11 large

kindreds. The authors focused on the likelihood (and shade) of a red head phenotype, and asserted that individuals with homozygous or compound heterozygous (two dysfunctional recessive alleles, but exist at two locations, rather than homozygous, having two dysfunctional recessive alleles at the same loci) were more likely to have bright red hair; in fact, 69% of those with two dysfunctional genes had this phenotype, and the remaining 31% exhibited strawberry blonde or auburn hair. Additionally, the authors noted that those with MC1R variant genes were compromised in their ability to stimulate intracellular cyclic adenosine monophosphate (cAMP), which further encourages production and release of eumelanin.

Liem et al. (2004) tested young women, ranging in age from 18-40, and explains that women's perception of pain has been documented as being different from men. Additionally, menstrual cycles can have an effect on pain perception, such that pain threshold varies dependent upon the phase of the cycle. Therefore, the authors included women in the first 10 days of their menstrual cycle. For the study, no premedication was given that could alter the results. The general anesthetic was initiated using an inhalational induction with sevoflurane, and then subsequently switched over to desflurane. The women were kept normothermic. After a 45-minute equilibration period, testing for movement to painful electrical stimulation began. The independent investigator was blinded to initial desflurane concentrations, where a 0.5% increment between 4.5-7.5% was the initial concentration. If the participant moved to stimulation, the concentration was increased; if the participant did not move, the concentration was decreased. After all testing, the authors noted that participants with red hair (and ostensibly a single dysfunctional gene or two dysfunctional MC1R genes) required a 19% increase in desflurane requirement when compared to black or dark brown-haired women in order to not move to painful stimulation.

The following year, an informative literature review highlighted the influence that pharmacogenetics had and will have on anesthesia (Galley, Mahdy, & Lowes, 2005). Referencing much of the Liem et al. (2004) study, the authors included other aspects of pharmacogenetics such as differing hepatic and enzymatic inducers, ryanodine receptors, opioid receptors, as well as several other mediators involved in both anesthesia specifically and pharmacogenetics generally.

The exact role of the MC1R gene, with specificity to anesthesia, is as of yet unclear. While Liem indicated a clinically significant variation in anesthetic requirements of redheads, other studies have suggested no such categorization should be made (Gradwohl et al., 2015; Myles et al., 2012). At present, while the opinions regarding anesthetic implications are mixed, this capstone project synthesized a compendium of current research and theories, in order to facilitate a scientifically-based, germane understanding regarding the implications that the MC1R gene specifically, and pharmacogenetics generally, have on anesthesia practice.

A review of current literature demonstrated conflicting data regarding the anesthetic requirement for the red head phenotype. Liem et al. (2004) suggested this phenotype can require as much as a 19% increase in anesthetic requirement when compared to brunettes and black-haired women; however, Myles et al. (2012) stated no such assertion can be made. Limitations of Liem et al. (2004) include a small sample size (n = 20), and only women between the ages of 18 and 40 were tested. Myles et al. (2012) included a much larger sample size (n = 468) of both men and women, ranging from 18 to 70 years of age, with exclusion criteria for any patient who did not receive an inhalational general anesthetic, sex-specific surgery, emergency surgery, treatment with lithium, or existence of an underlying neurological condition.

Liem, Joiner, Tsueda, & Sessler (2005) followed up the initial study of inhalational anesthetic requirement to ascertain if red-haired women also were resistant to the effects of local anesthetics, specifically lidocaine. The authors again tested only young women; citing similar rationale from the Liem et al. (2004) study published the year prior. Limitations included a small sample size (n = 60) and exclusion of men. They again found significant differences between the anesthetic requirements of red-haired women when compared to their dark-haired counterparts: redheads were more sensitive to cold pain, both in perception and tolerance. When it came to heat pain, perception between the groups was analogous, but redheads were significantly less tolerant of heat pain. Liposomal lidocaine was also tested in this study, and was compared to the efficacy of subcutaneous injection amongst the two groups of women, redheads and black or dark brown-haired women. Liposomal lidocaine was only slightly less effective in redheads; however, subcutaneous lidocaine was significantly less effective in redheads when compared to subjects with dark hair. Thus, the authors suggested that redhead women had increased anesthetic requirement with both inhalational and local anesthetic when compared to those with dark hair.

If redheads are indeed resistant to the effects of local anesthetics, one possible alternative would be to add vasoconstrictors (such as epinephrine), alpha-2 agonists (such as clonidine or dexmedetomidine), or anti-inflammatory agents (such as dexamethasone or ketorolac) to the local anesthetic. This practice was suggested by Opperer, Gerner, & Memtsoudis (2015) in order to synergize the effects of the anesthetic for all patients (not redheads exclusively). Given that the MC1R dysfunction has no documented effect on the alpha receptor specifically, and there is only a tenuous relationship on the inflammatory cascade, adding adjuvants to local anesthetics

has the potential to increase the efficacy of the drug in this particular phenotype, although more research is needed.

Intraoperative awareness is of particular concern germane to this discussion. During both emergence from anesthesia and periods of surgery when less anesthetic requirement is needed, there is a potential for red-haired patients to be at an increased level of consciousness. To this end, a secondary analysis of a prospective trial on intraoperative awareness was utilized by Gradwohl et al. (2015), which maintained that no difference in risk of awareness could be identified between the red hair phenotype and controls. Numerous risk factors for intraoperative awareness included open-heart surgery, pulmonary hypertension, end-stage pulmonary disease, anticipated difficult intubation, and an ejection fraction of <40% (Gradwohl et al., 2015). Additionally, Berger, Mušič, Zakrajšek, & Mekiš (2014) further elucidated the neurobiology of awareness, as well as methods for assessment of the depth of anesthesia.

Increased intraoperative bleeding amongst redheads has also been an anecdotal observation of many anesthesia providers and surgeons. Two studies focused specifically on the coagulation of redheads when compared to individuals with dark hair (Liem, Hollensead, Joiner, & Sessler, 2006; Leebeek, Dehghan, Kruip, Hofman, Uitterlinden, De Wee, Witteman, & De Maat, 2011). Liem et al. (2006) focused on coagulation studies such as prothrombin time (PT), activated partial thromboplastin time (aPTT), international normalized ratio (INR), hemoglobin concentration and platelet count and function (quantitative and qualitative platelet analysis). The authors again only analyzed data from women, citing evidence that MC1R dysfunction mediated female-specific mechanisms of mu-opioid analgesia and other physiologic processes. While redhead participants in this study did report a higher incidence of bruising by history, no significant differences in coagulation or hemoglobin or platelet count or function was found.

As platelet function analysis is known to be less sensitive in detecting decreased levels of von Willebrand factor (VWF), Leebeek et al. (2011) analyzed this factor in a large cohort study of nearly 4000 volunteers. The sample was from older individuals; the participants were 55 years of age and older, primarily Caucasian, and lived in the Netherlands. This focused analysis was a weakness of the study; although no indication was made that markedly different results would be expected from a different cohort of participants with the same hair color (black, brown, blonde, and red). Similar to the Liem et al. (2006) study, any increased bleeding could not be described by a decrease in VWF, as the levels were nearly identical in all hair color groups.

Redheads have also been noted to have a decreased response to benzodiazepines, which are commonly given for preoperative sedation. To ascertain the extent to which this claim is true, Chua, Tsueda, and Doufas (2004) performed a study that analyzed both sedation (via an observer's assessment of alertness/sedation (OAA/S) scale), and later drowsiness (via a visual analog scale (VAS) and bispectral index, an increasingly common assessment tool that monitors depth of anesthesia. For the study, both men and women were included, who were reported as "healthy" (Chua, Tsueda, & Doufas, 2004). A relatively small sample size (n=40) of red (n=20) and non-red (brown or blonde, n=20) participants was used, but the results were significant: participants with red hair were less sedated and less drowsy than their non-red hair counterparts. The participants with red hair were consistently more awake and were able to respond briskly to name calling when compared to those participants with blonde or brown hair. The study suggested that a possible explanation of this phenomenon was the effect that the MC1R gene has on both α-melanocyte-stimulating hormone (α-MSH), adrenal corticotrophic hormone (ACTH), β-endorphin in the pituitary gland, as well as the gastrointestinal tract, placenta, skin, and gonads.

By isolating the MC1R gene, scientists and anesthesia providers are closer to more fully understanding the relationship between genetics and anesthesia. While current evidence indicated the precise mechanism of the MC1R gene and anesthesia is unclear, additional research is needed to support or refute the relationship between people of a red hair phenotype and increased anesthetic requirements.

Project Description

The intent of this capstone project was to provide an educational presentation on the anesthetic requirements of red haired people, the pharmacogenetics of the melanocortin-1 receptor gene and its effects on anesthesia, including local anesthetics, inhaled anesthetics, as well as pain sensitivity and various anesthesia related topics. Informed consent of all participants was gathered (see Appendix A). Delivered to SRNAs attending Adventist University of Health Sciences (ADU), the presentation utilized a pre-test to assess existing subject knowledge. Subsequent post-testing after the presentation assessed if there had been any change in knowledge base. The pre- and post-test used an identical instrument (see Appendix B). The primary goal of this capstone project was to increase the SRNAs' awareness regarding anesthetic requirements of redheads. With the information provided, the intent was that the SRNAs would understand and hence be better prepared to safely administer anesthesia to patients with an MC1R variation.

This capstone project was highlighted by an educational presentation, utilizing a PowerPoint presentation and various visual aids to enhance learning. The presentation was delivered simultaneously to two different cohorts of ADU SRNAs (graduating classes of 2016 and 2017) on November 12, 2015. Several aspects of the project's success were determined by

the results and analysis of the pre- and post-tests, which were administered anonymously, with all identifiers removed. Follow up questions and comments were encouraged.

The project intervention included the previously discussed presentation, which ostensibly enhanced the knowledge of ADU SRNAs. Hopefully, the increased knowledge level will ultimately be reflected in improved clinical practice by the SRNAs, specifically when managing the care of patients with an MC1R variation.

Evaluation Plan

The success of this project was evaluated with the utilization of a written assessment, through which, the understanding of the presentation objectives were assessed. The efficacy of the presentation was determined by comparing scores of pre- and post-tests on the topic. The pretest was administered before the presentation, while the posttest followed the presentation. The test assessed topics related to the stated objectives of the presentation, which entailed pharmacogenetics specific to the MC1R gene variation, and anesthetic implications of this specific genotype. The pretest evaluated the present knowledge level of the ADU SRNAs, and the posttest assessed the change in understanding evaluated through test scores.

The statistical analysis of the test results allowed the presenter to assess comparative knowledge before and after the presentation. This analysis enabled the presenter to determine efficacy of the presentation, indicating success of the project. The pre- and post-presentation assessment was delivered without collecting the names of participants, utilizing a numerical identifier. The presenter was able to collect aggregate data and compared scores pre-presentation and post-presentation, with changes noted. This quantitative data was then interpreted utilizing statistical analysis tools, such as a paired t-test.

Results and Conclusions

Two identical tests were administered pre- and post-presentation (Appendix B). A total of 34 SRNAs were able to participate in the testing, which was approximately 10 fewer than expected (an automobile accident on a major thoroughfare prevented many from being able to attend the pre-test and beginning of the presentation, thus were excluded from testing). Test scores increased with a mean score of approximately 3.76 to 9.82 (Table 1). Statistical analysis was completed utilizing a paired-t test in an effort to determine significant outcomes. The result of this test is presented below (Table 2).

Table 1- Paired Samples Statistics

		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Pre-Test	3.7647	34	1.79323	.30754
	Post-Test	9.8235	34	2.28924	.39260

Table 2- Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Pre-Test - Post-Test	-6.05882	2.56953	.44067	-6.95538	-5.16227	-13.749	33	.000

The statistical result proved to be interesting. Given that both the pre- and post-test scores were lower than expected, several possible explanations could exist. First, the test could have been too difficult. Secondly, given that the presentation and test were administered at the end of a clinical week, a certain lack of participation or apathy among the SRNAs could have been explanatory for the lower scores. Finally, the earlier reference to the automobile accident and subsequent traffic could have been emotionally unsettling for those test participants who arrived on time to participate.

This capstone project dovetailed into several captivating and intriguing topics that are both specific to anesthesia as well as generalizable to the whole of health care. First, the idea of "MAC-Ginger": that if necessary anesthetic requirement is in fact increased in redheads, as many experienced providers feel, there are now several supportive studies of such a claim. This anecdotal observation was unable to be supported through research until as recently as 2004. As more research becomes available, more conclusive supportive or discounting information could soon alter the course of opinion. Secondly, as pharmacogenetic testing becomes less expensive and more accessible, the ability of a "genetic iStat" seems more likely. This would give clinicians the ability to dose medications based on a genetic algorithm by way of point-of-care testing, offering a more tailored health care profile and plan. Given that the MC1R variation is isolated to a very specific phenotype, as more information is gleaned about different genotypes, it could soon become possible to dose medications based on genotype rather than a weight-based, body habitus approach. This would be an exciting, refreshing, and more accurate way to deliver medications to every patient health care providers encounter.

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Appendix A

ADU NAP CAPSTONE PROJECT – INFORMED CONSENT

My name is Nathan Classon, and I am an MSNA student in the Nurse Anesthesia Program (NAP) at Adventist University of Health Sciences (ADU). I am doing a Capstone Project called *Anesthesia Requirements for Redheads*. This project is being supervised by Dr. Alescia DeVasher. We would like to invite you to participate in this project. The main purpose of this form is to provide information about the project so you can make a decision about whether you want to participate.

WHAT IS THE PROJECT ABOUT?

The purpose of this project is to provide an educational presentation on the anesthetic requirements of red haired people, the pharmacogenetics of the melanocortin-1 receptor gene and its effects on anesthesia, including local anesthetics, inhaled anesthetics, as well as pain sensitivity and various anesthesia related topics.

WHAT DOES PARTICIPATION IN THIS PROJECT INVOLVE?

If you decide to participate in this project, you will be asked to complete an anonymous pre-assessment, attend a classroom presentation, and then complete an anonymous post-assessment. The assessment will determine the correlation between information acquired during the lecture and SRNAs' knowledge base, which will determine the efficacy of the lecture. Your participation by attendance at the presentation and completion of the survey is anticipated to take approximately 60 minutes.

WHY ARE YOU BEING ASKED TO PARTICIPATE?

You have been invited to participate as part of a convenience sample of students currently enrolled in the ADU NAP. Participation in this project is voluntary. If you choose not to participate or to withdraw from the project, you may do so at any time.

WHAT ARE THE RISKS INVOLVED IN THIS PROJECT?

Although no project is completely risk-free, we don't anticipate that you will be harmed or distressed by participating in this project.

ARE THERE ANY BENEFITS TO PARTICIPATION?

We don't expect any direct benefits to you from participation in this project. The possible indirect benefit of participation in the project is the opportunity to gain knowledge that will guide clinical application and decisions regarding the anesthetic requirements of redheads.

HOW WILL THE INVESTIGATORS PROTECT PARTICIPANTS' CONFIDENTIALITY?

The results of the project will be published, but your name or identity will not be revealed. To maintain confidentiality of assessments, the investigators will conduct this project in such a way to ensure that information is submitted without participants' identification. In order to preserve anonymity, each quiz will use numbers for identification in place of student names. Each student will be provided with a numbered test that will be used for both the pre- and post-test. Thus, the investigators will not have access to any participants' identities.

WILL IT COST ANYTHING OR WILL I GET PAID TO PARTICIPATE IN THE PROJECT?

Your participation will cost approximately 60 minutes of your time, but will require no monetary cost on your part. You will not be paid to participate.

VOLUNTARY CONSENT

By signing this form, you are saying that you have read this form, you understand the risks and benefits of this project, and you know what you are being asked to do. The investigators will be happy to answer any questions you have about the project. If you have any questions, feel free to contact Nathan Classon at nathanclasson@mac.com. If you have concerns about the project process or the investigators, please contact the Nurse Anesthesia Program at (407) 303-9331.

Participant Signature	**Participant Name (PRINTED LEGIBLY)**	**Date**

Appendix B

Pre- and Post-Test

1) **Patients with a red head phenotype require _____ higher concentrations of Desflurane when compared to dark haired patients.**
   a) 11% b) 19% c) 25% d) 38%

2) **People with _____ variance have an increased requirement for local anesthetics.**
   a) CYP450
   b) MC1R
   c) MSHR
   d) Both b and c are correct

3) **Patients with a red head phenotype typically require 25% dose increase in _____.**
   a) beta agonists
   b) beta antagonists
   c) acetylcholinesterase inhibitors
   d) none of the above

4) **People with MC1R variance have an increased requirement for benzodiazepines due to _____.**
   a) α-melanocyte-stimulating hormone (α-MSH)
   b) adrenal corticotropic hormone (ACTH)
   c) a decrease in CYP 450 metabolism
   d) two of the above are correct
   e) there is no increase in benzodiazepine requirements in red heads

5) **The analgesic effect of clonidine has been linked to _____.**
   a) modulation of cytokines, evidenced by reduced postoperative levels of TNF-α in the CSF
   b) reduction of systemic interleukin-6 and CRP
   c) both a) and b) are correct
   d) neither a) nor b) are correct

6) **MC1R is in the family of melanocortin receptor that provides significant homeostatic influence on _____.**
   a) hypothalamic regulation, thermoregulation, and adrenal steroidogenesis
   b) gluconeogenesis, adrenal steroidogenesis, and anterior pituitary function
   c) thermoregulation, estrogen production, and vascular resistance
   d) none of the above

7) **MC1R genes are primarily found _____, and are expressed in _____, which modulates nociception.**
   a) Centrally / glial cells and neurons of the ventral periaqueductal gray
   b) Peripherally / glial cells and neurons of the ventral periaqueductal gray
   c) Centrally / the spinothalamic tract
   d) Peripherally / the spinothalamic tract

8) **Increased surgical bleeding and bruising in patients with a red head phenotype is primarily caused by alterations in:**
   a) decreased von Willebrand factor
   b) increased activated partial thromboplastin time

c) increased prothrombin time
d) two of the above are correct
e) none of the above are correct

9) Which of the following physiologic ratios of eumelanin to pheomelanin manifest as a red head phenotype?
a) greater amounts of eumelanin as compared to pheomelanin
b) greater amounts of pheomelanin as compared to eumelanin
c) similar amounts of pheomelanin as compared to eumelanin
d) this relationship is not important in determining the red head phenotype

10) Most redheads are _____ or _____, meaning that they have _____ variant MC1R allele(s).
a) autosomal dominant / autosomal recessive / one or zero
b) homozygous / compound heterozygous / two
c) heterozygous / compound heterozygous / two
d) Homo sapiens / Homo erectus / at least ten

11) Which specific melanocortin receptors are responsible for the modulation of hyperalgesia, pain, behavior, stress, and food intake?
a) MC1R & MC3R
b) MC1R & MC2R
c) MC2R & MC4R
d) MC3R & MC4R

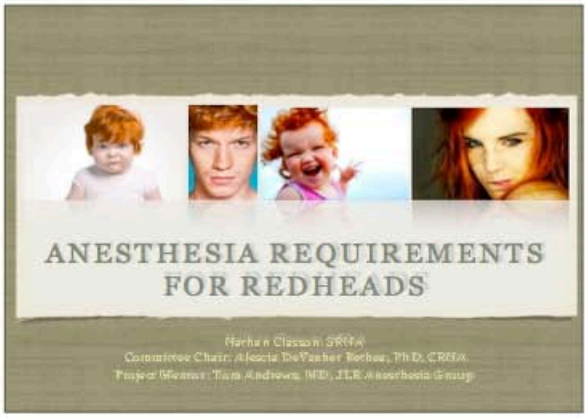
12) A possible theory is that MC1R dysfunction ____ production of primary ligands, melanocortins including α-melanocyte-stimulating hormone, which stimulates other melanocortin receptors, including the _____ receptor that modulates cold and mechanical allodynia.
a) down-regulates / melanocortin-3
b) down-regulates / melanocortin-4
c) up-regulates / melanocortin-3
d) up-regulates / melanocortin-4

13) Redhead women are _____ to _____, but show no difference in baseline _____ thresholds.
a) less sensitive / electrical pain / thermal pain
b) more sensitive / electrical pain / thermal pain
c) more sensitive / thermal pain / electrical pain
d) less sensitive / thermal pain / electrical pain

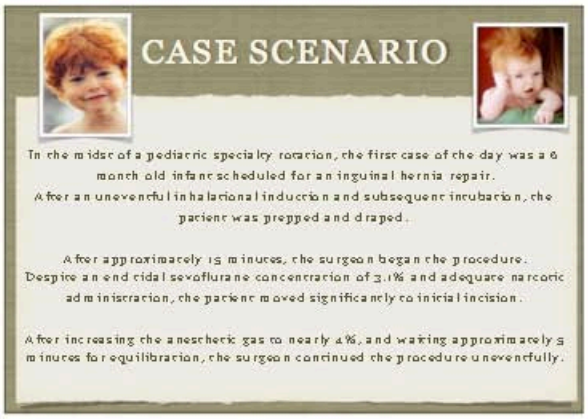
14) Redheads are _____ to the _____ effects of lidocaine.
a) more sensitive / analgesic
b) more resistant / analgesic
c) more sensitive / antiarrhythmic
d) more resistant / antiarrhythmic

15) The following parameters could be significantly altered in patients with a redhead phenotype:
a) post-operative recovery time
b) pain
c) quality of recovery
d) more than one of the above are correct

Appendix C


ANESTHESIA REQUIREMENTS FOR REDHEADS
Nathan Classon, SRNA
Committee Chair: Alecia DeVasher Bethea, Ph.D, CRNA
Project Mentor: Tom Andrews, MD, ILR Anesthesia Group


OBJECTIVES
· Identify at risk populations
· Review current literature, both supporting and disputing the claim that several aspects of anesthesia are altered in redheads
· Discuss current and future anesthetic implications
· Raise awareness for Student Registered Nurse Anesthetists attending Adventist University


CASE SCENARIO
In the midst of a pediatric specialty rotation, the first case of the day was a 6 month old infant scheduled for an inguinal hernia repair.
After an uneventful inhalational induction and subsequent incubation, the patient was prepped and draped.
After approximately 15 minutes, the surgeon began the procedure. Despite an end tidal sevoflurane concentration of 3.1% and adequate narcotic administration, the patient moved significantly to initial incision.
After increasing the anesthetic gas to nearly 4%, and waiting approximately 5 minutes for equilibration, the surgeon continued the procedure uneventfully.

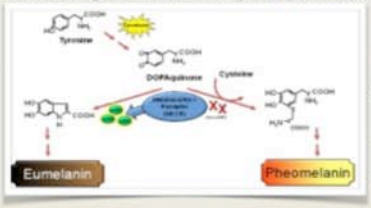

TO WHICH TYPE OF REDHEADS DO I REFER??


IMPACT OF HAIR COLOR
· Hair color is one of the most conspicuous phenotypes of humans
· Hair color ranges from black, dark brown, brown, light brown, and blonde to red, with a myriad of hues in each category
· Hair color has tremendous societal and cosmetic impact
· Diversity of hair color arises primarily from the quantity and ratio of two types of pigment: black to brown eumelanin, and reddish brown to yellow pheomelanin


THE SCIENCE BEHIND RED HAIR

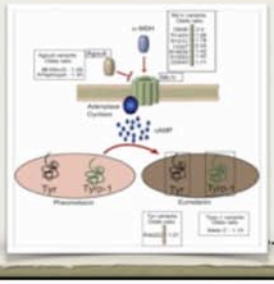
THE SCIENCE BEHIND RED HAIR

Another picture interpreting the interaction of a functional ~~and~~ non-functional MC1R (also called **melanocyte-stimulating hormone receptor (MSHR)**...

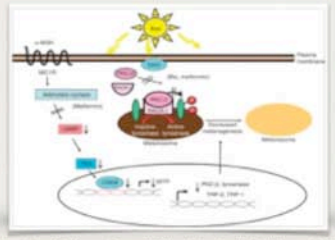


THE SCIENCE BEHIND RED HAIR

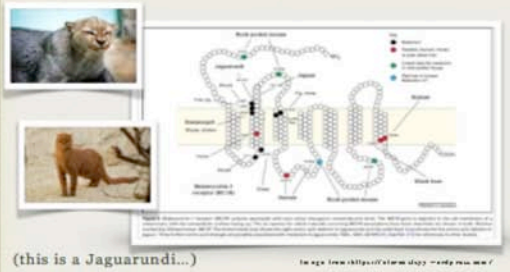
And another...



THE SCIENCE BEHIND RED HAIR

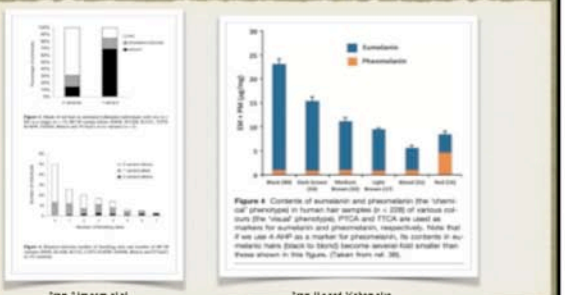


THE SCIENCE BEHIND RED HAIR



(this is a Jaguarundi...)

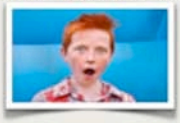
THE SCIENCE BEHIND RED HAIR



THE SCIENCE BEHIND RED HAIR

That's nice, but...

What do the melanocortin receptors do?

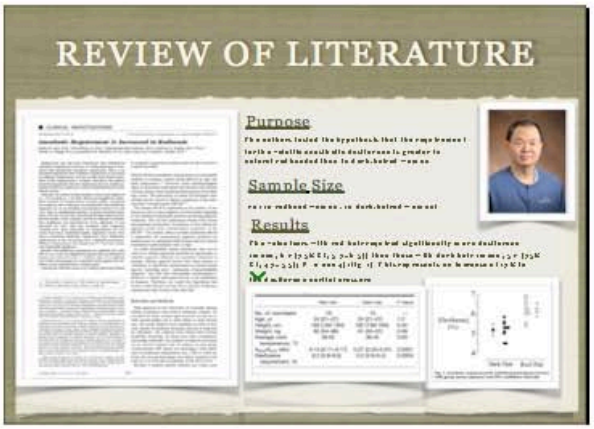


Melanocortin receptors are actively involved in **adrenocortical steroidogenesis, immune and inflammatory responses, hypothalamic regulation of food intake, body weight, exocrine gland function and thermoregulation.**

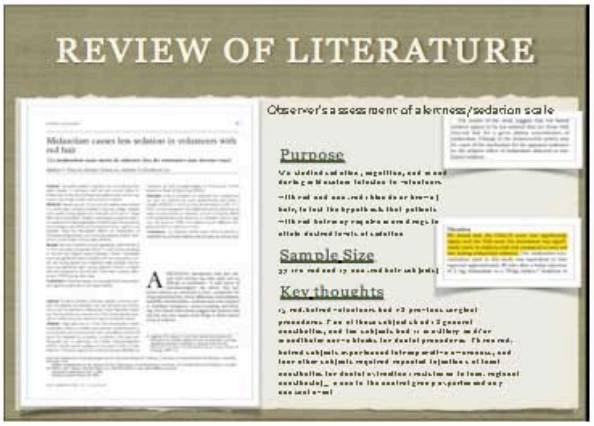

THE SCIENCE BEHIND RED HAIR


THE SCIENCE BEHIND RED HAIR
Also nice, but...
What DON'T the melanocortin receptors do??
Melanocortin receptors have nothing to do with beta agonists, beta antagonists, or acetylcholinesterase inhibitors...


REVIEW OF LITERATURE
Purpose
Sample Size
Key thoughts


REVIEW OF LITERATURE
Purpose
Sample Size
Results


REVIEW OF LITERATURE
Sample Size
Major Findings
Key thoughts


REVIEW OF LITERATURE
Observer's assessment of alertness/sedation scale
Purpose
Sample Size
Key thoughts

REVIEW OF LITERATURE

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

The take away? Increased benzodiazepine requirement in patients with MC1R variant is primarily due to the effect of the α-melanocyte-stimulating hormone (α-MSH) and adrenal corticotrophic hormone (ACTH)...

REVIEW OF LITERATURE

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Purpose

Major Findings

REVIEW OF LITERATURE

Purpose

Sample Size

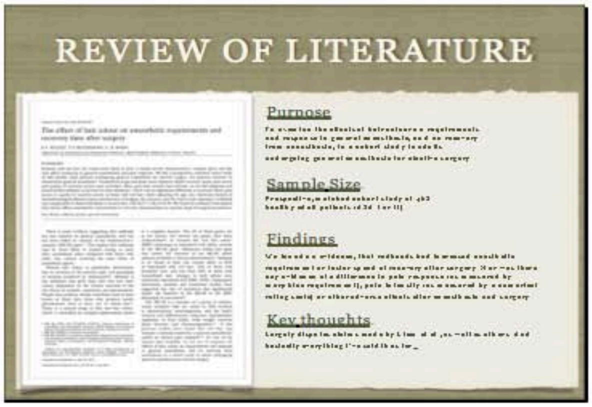
Key thoughts

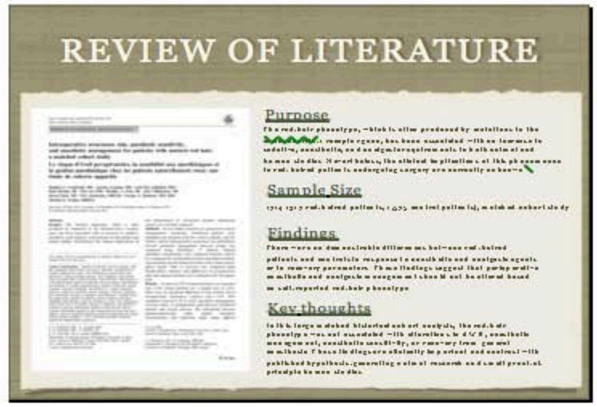
REVIEW OF LITERATURE

Purpose

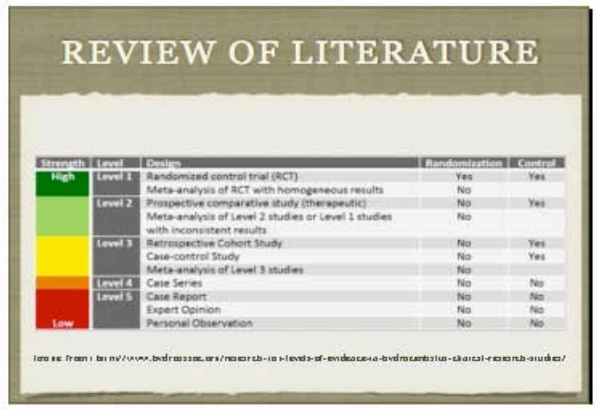
Findings

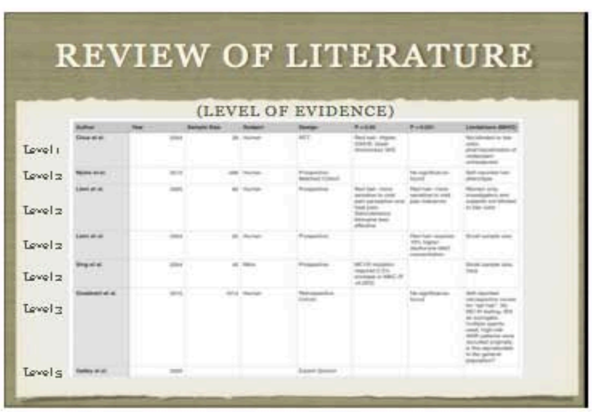
Key thoughts

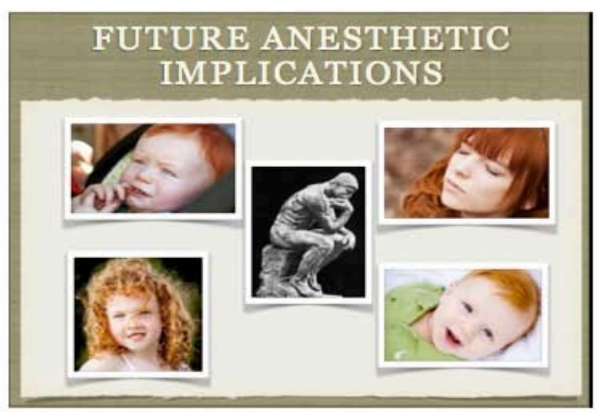

REVIEW OF LITERATURE
Purpose
Sample Size
Findings
Key thoughts


REVIEW OF LITERATURE
Purpose
Sample Size
Findings
Key thoughts


REVIEW OF LITERATURE


REVIEW OF LITERATURE
Strength
Level
Design
Randomization
Control
High
Level 1
Randomized control trial (RCT) Yes Yes
Meta-analysis of RCT with homogeneous results No
Level 2
Prospective comparative study (therapeutic) No Yes
Meta-analysis of Level 2 studies or Level 1 studies with inconsistent results No
Level 3
Retrospective Cohort Study No Yes
Case-control Study No Yes
Meta-analysis of Level 3 studies No
Level 4
Case Series No No
Level 5
Case Report No No
Expert Opinion No No
Personal Observation No No
Low


REVIEW OF LITERATURE
(LEVEL OF EVIDENCE)
Level 1
Level 2
Level 2
Level 2
Level 2
Level 3
Level 5


FUTURE ANESTHETIC IMPLICATIONS

FUTURE ANESTHETIC IMPLICATIONS

Genetic iStat???

- It is possible that in a short amount of time (years?) we would be able to more accurately tailor anesthetic (and a myriad of other pharmacological interventions) levels specific to a given genotype. This presentation and information has primarily focused on *one gene* ~~purely~~ specific to *one phenotype*, who represent approximately 5% of the global population. What if we find more genetic variability that effects 20, 30, or even 90% of the population???

FUTURE ANESTHETIC IMPLICATIONS

MAC-Ginger...

If it is in fact true that redheads require more anesthetic, be it inhalational or local, or greater benzodiazepine requirement, the astute clinician could take a "mental MAC-Ginger" approach, such that:

MAC of Sevoflurane	MAC-Ginger of Sevoflurane	MAC-BAR of Sevoflurane
2.0%	2.38%	2.6%

(MAC-BAR-Ginger 3.094%!!)

MAC of Desflurane	MAC-Ginger of Desflurane	MAC-BAR of Desflurane
6.0%	7.14%	7.8%

QUESTIONS??

REFERENCES

[illegible]

REFERENCES

[illegible]

REFERENCES

[illegible]


ED SAYS "THANKS FOR LISTENING"...
Sure Nathan... whatever...