Precision Medicine: Using Patient's Race as a Pragmatic Indicator of Propofol Sensitivity

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Medical Update Lecture

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Disclosures

- *As co-inventor of the Hamilton Max ventilator, Human Patient Simulator (HPS) mannequin and the Temperature Management System cooling football pads, I receive a fraction of the royalties that the University of Florida collects from the licensees*
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Outline

- Ethnicity ≠ Race
- Personalized vs. Precision Medicine (PM)
- Relevance of PM to multi-racial Mauritius
- Concrete Example of Pragmatic Precision Medicine Promoting Safety and Throughput

Ethnicity ≠ Race

- "Ethnicity" is often misused as a politically correct synonym for "Race" in the US (and elsewhere…)
- Ethnicity is based on language, culture, cuisine, NOT genes
  - Speaking French at home makes one of Francophone ethnicity, irrespective of race
  - Asians are of Indian, Chinese, Vietnamese, Korean, etc. ethnicity depending on native language
- Race is based on genes
- Nationality is based on geography/country of residence

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Patient Variability

- No two patients are identical
- Patient variability is the norm rather than the exception
- Personalized medicine (“the right patient with the right drug at the right dose at the right time”*)

*http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf

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Personalized Medicine

- Providing the right patient with the right drug at the right dose at the right time

  More broadly, “personalized medicine” may be thought of as the tailoring of medical treatment to the individual characteristics, needs and preferences of a patient during all stages of care, including prevention, diagnosis, treatment and follow-up.

  http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf

Personalized vs. Precision Medicine

- Personalized medicine can be misconstrued as designing a *unique* treatment for every *single individual* patient, an impractical proposition
- Therefore, the term “Precision Medicine” is recommended over “Personalized Medicine”*

*http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/PersonalizedMedicine/UCM372421.pdf

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Personalized medicine "refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not" (PCAST 2008). This term is now widely used, including in advertisements for commercial products, and it is sometimes misinterpreted as implying that unique treatments can be designed for each individual. For this reason, the Committee thinks that the term "precision medicine" is preferable to "personalized medicine" to convey the meaning intended in this report.

http://www.plengegen.com/wp-content/uploads/4_Toward-Precision-Medicine.pdf

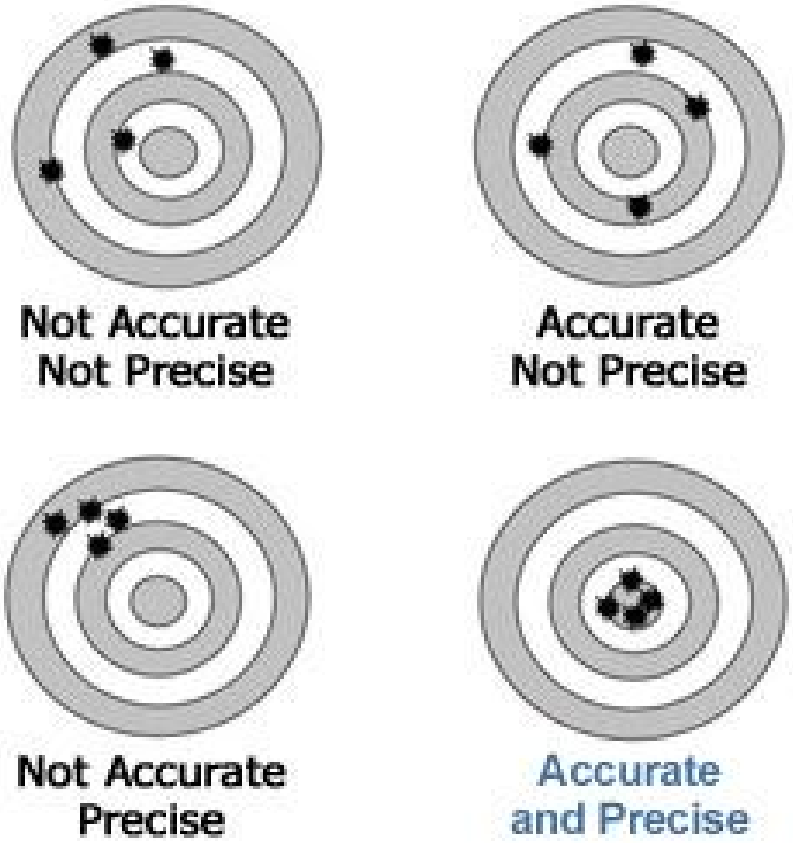
Precision medicine refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease, in the biology and/or prognosis of those diseases they may develop, or in their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not. Although the term “personalized medicine” is also used to convey this meaning, that term is sometimes misinterpreted as implying that unique treatments can be designed for each individual.

http://www.plengegen.com/wp-content/uploads/4_Toward-Precision-Medicine.pdf

It should be emphasized that in “Precision Medicine”, the word “precision” is being used in a colloquial sense, to mean both “accurate” and “precise” (in the scientific method, the accuracy of a measurement system is the degree of closeness of measurements of a quantity to that quantity’s actual (true) value whereas the precision of a measurement system, also called reproducibility or repeatability, is the degree to which repeated measurements under unchanged conditions show the same results).

http://www.plengegen.com/wp-content/uploads/4_Toward-Precision-Medicine.pdf

Accuracy and Precision



"Precision" Medicine

White House Precision Medicine Initiative

Doctors have always recognized that every patient is unique, and doctors have always tried to tailor their treatments as best they can to individuals. You can match a blood transfusion to a blood type — that was an important discovery. What if matching a cancer cure to our genetic code was just as easy, just as standard? What if figuring out the right dose of medicine was as simple as taking our temperature?"
- President Obama, January 30, 2015

https://www.whitehouse.gov/precision-medicine

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Existing Examples of Precision Medicine in Mauritius?

- Input from audience, please

Is Precision Medicine Unaffordable for Mauritius?

- Depends….
- Not if Mauritius starts with pragmatic precision medicine that does not require genetic analysis (Example to follow)
- Pragmatic Precision Medicine: Doing what you can with what you have

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Can Mauritius Afford to Ignore Precision Medicine?

- No. Precision medicine relevant to Mauritius
- Patient care: Multi-racial society (different races react differently to some drugs like propofol, opiates)
- Healthcare research: One of the first studies about propofol and race (Ortolani 2004) compared response of Malaysian Indians, Malays and Chinese to Italian Caucasians; Mauritius is similarly multi-racial

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A Concrete Example of Pragmatic Precision Medicine

- Race-Specific Propofol Dosing for Sedation

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How many non-anesthesiologists in the audience?

Propofol sedation

- Patient stays sedated and breathes spontaneously during a painful procedure
  - Loss of Consciousness (LOC); verbal response
- Overdosing of propofol
  - unintended general anesthesia (GA)
  - loss of self-protective reflexes like breathing
  - bad patient outcome, if clinician cannot manage airway, i.e., intubate, during unintended GA

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Propofol sedation

- Patient stays sedated and breathes spontaneously during a painful procedure
  - Loss of Consciousness (LOC); verbal response
  - Loss of Eyelash Reflex (reflex eyelid motion when eyelash is stroked)
- Overdosing of propofol
  - unintended general anesthesia (GA)
  - loss of self-protective reflexes like breathing
  - bad patient outcome, if clinician cannot manage airway, i.e., intubate, during unintended GA

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OAAS (Observer Assessment of Alertness/Sedation) Sedation Score

State	Responsiveness component of OAAS	OAAS Score
Conscious	Responds readily to name spoken in a normal tone	5
	Lethargic response to name spoken in a normal tone.	4
	Responds only after name is spoken loudly or repeatedly or both.	3
Unconscious	Loss of verbal response then Loss of eyelash reflex Responds only after mild prodding or shaking	2
	Does not respond to mild prodding or shaking.	1
	Does not respond to noxious stimulus	0

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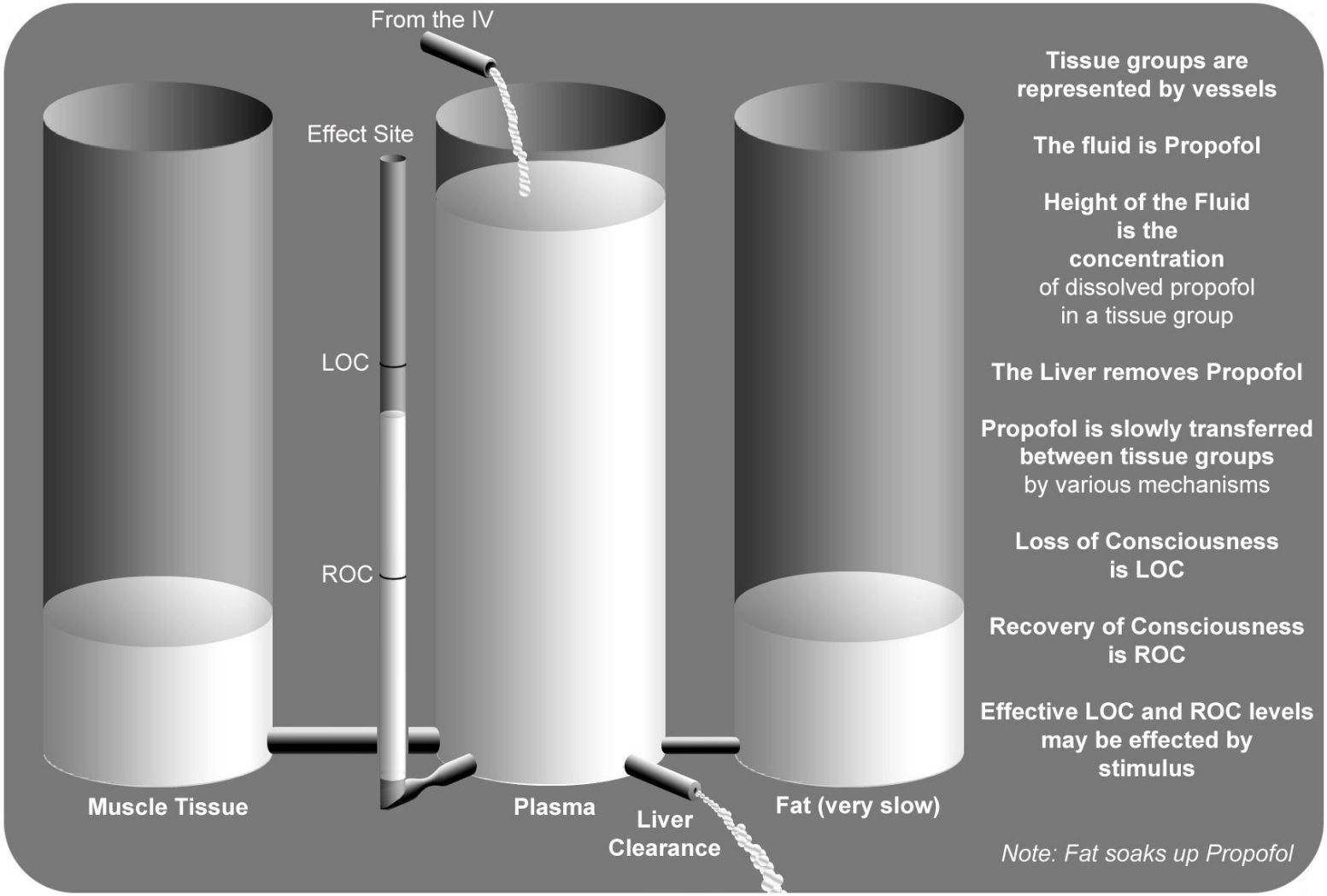
Propofol PK/PD

- PK = PharmacoKinetics – what the body does to the drug
- PD = PharmacoDynamics – what the drug does to the body
- Two-compartment hydraulic analog model
- Propofol PK/PD compartmental model

Effect site concentration



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EC05, EC50, EC95

- Effective Concentration (EC) at which 5%, 50% and 95% of a patient population exhibit a response, e.g., loss of consciousness (LOC; loss of verbal response) or loss of eyelash reflex

Precision Modeling & Simulation

- Modeling subsets of patients, such as those from a given group such as race (or within a race, patients with red hair with increased anesthetic requirements – Liem et al 2004), to reflect unique group characteristics such as PK/PD

Race-Specific Propofol PD

- Puri et al (2011): TCI Diprifusor
- ESC (adapted) EC50 at LOC for Indians (South Asians): 1.88 mcg/ml

Race-Specific Propofol PD

- Natarajan et al (2011): constant infusion of 40 mg/kg/hr propofol
- Mean dose of propofol for loss of verbal response in Blacks and Caucasians was 1.16 and 1.41 mg/kg respectively
- ESC (adapted) EC50 at LOC for Blacks: 2.02 mcg/ml

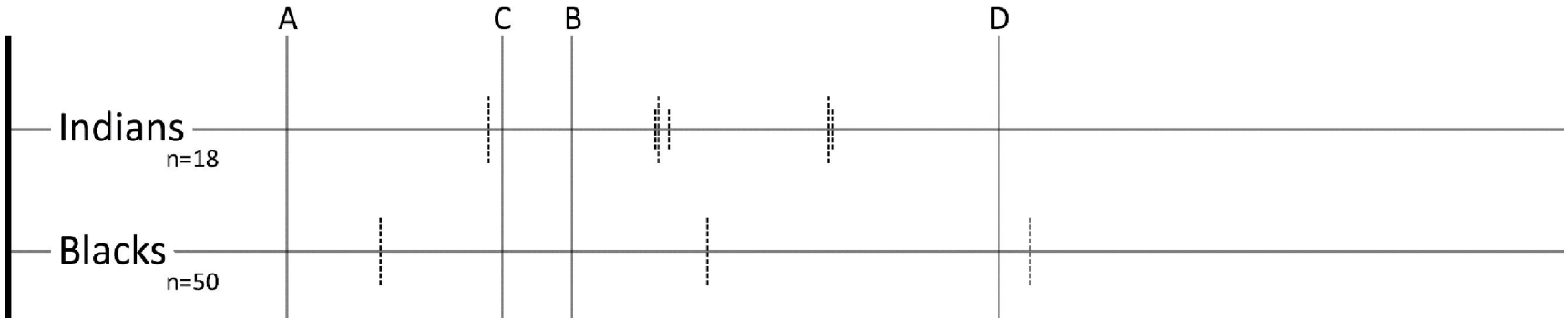
Race-Specific Propofol PD

- Irwin et al (2002): TCI Diprifusor
- ESC EC50 at LOC for Chinese: 2.66 mcg/ml
- Xu et al (2009): TCI (using identical propofol infusion profile used by Milne for Caucasians)
- ESC EC50 at LOC for Chinese (Mainland China): 2.2 mcg/ml

Race-Specific Propofol PD

- Milne et al (2003): TCI Diprifusor
- ESC EC50 at LOC for Caucasians: 2.8 mcg/ml

Race-specific model of propofol-induced LOC



Lampotang et al: Race-Specific Pharmacodynamic Model of Propofol-Induced Loss of Consciousness. Journal of Clinical Pharmacology DOI: 10.1002/jcph.716, 2016

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Patient Safety

Propofol sedation gone wrong

- ".. a case in Florida in 2004 when a patient stopped breathing during breast augmentation surgery and died as a reason... the surgeon personally administered anesthetic drugs, including propofol, and overmedicated the patient."

http://www.surgistrategies.com/news/2005/07/debate-heightens-on-non-anesthesiologists-adminis.aspx

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Date: **March 21, 2002**

Procedure: Breast augmentation
Location: Hollywood, Florida
Anesthesia: Prescribed by surgeon
Anesthesia: Administered by registered nurse
Event: Intraoperative PROPOFOL infusion for sedation progressing to complete cardiac arrest.

Date: **July 29, 2002**

Procedure: Facelift
Location: Hollywood, Florida
Anesthesia; Prescribed by surgeon
Anesthesia: Administered by registered nurse
Event: Introperative PROPOFOL infusion for sedation resulting in respiratory arrest, anoxic brain injury, and subsequent death.

Date: **December 18, 2002**

Procedure: Breast augmentation and liposuction
Location: Miami, Florida
Anesthesia: Prescribed by surgeon
Anesthesia: Administered by certified registered nursing assistant
Event: Intraoperative midazolam, fentanyl, and PROPOFOL for sedation; resulting in respiratory arrest, anoxic brain injury, and death one day later.

Date: **September 25, 2003**

Patient: Julie L. Ayer Rubenzer
Procedure: Breast augmentation
Location: Sarasota, Florida
Anesthesia: Prescribed by surgeon
Anesthesia: Administered by registered nurse
Event: Introperative PROPOFOL for sedation resulting in respiratory arrest, anoxic brain injury, and subsequent death, which received national news media attention.

Date: **April 13, 2004**

Location: Jacksonville, Florida
Anesthesia: Prescribed by surgeon
Anesthesia: Administered by certified registered nursing assistant
Procedure: Liposuction
Event: Introperative PROPOFOL infusion for sedation resulting in respiratory and cardiac arrest five hours after the procedure while still in the doctor's office; and, subsequently, resulting death.

Date: **April 13, 2004**

Location: Lakeland, Florida
Anesthesia: Prescribed by surgeon
Anesthesia : Administered by certified registered nursing assistant
Procedure: Photocoagulation/virectomy
Event: Intraoperative PROPOFOL boluses for sedation resulting in respiratory arrest with failure to intubate airway. Anoxic brain injury and death occurred one week later.

Propofol sedation gone wrong

Needs Assessment Study

Participant Demographics

- 23 males and 14 females participated (13 faculty, 10 residents, 8 nurse anesthetists, 3 fellows, 3 anesthesiology assistants)
- Age ranged from 28-68 (38.6±10.1) years
- Experience delivering propofol sedation ranged from 1-20 (6.8±5.8) years.

- Video

Preliminary Analysis

	Loading dose (mg/kg; range, mean ± SD)	Total propofol administered (mg/kg; range, mean ± SD)	LOC duration (s; range, mean ± SD)	Time to recovery (s; range, mean ± SD)
Caucasian	0.27 - 1.71 0.77 ± 0.31	1.16 – 2.77 1.95 ± 0.41	0 - 318 147 ± 85	269 - 701 444 ± 101
Black	0.25 - 1.71 0.79 ± 0.28	1.08 – 3.1 1.59 ± 0.41	0 - 367 191 ± 81	260 - 1090 538 ± 177
Indian	0.29 – 1.71 0.80 ± 0.32	1.51 – 2.6 1.63 ± 0.42	26 – 338 207 ± 68	338 - 1115 522 ± 154

Preliminary Analysis

- Between patient races, there was a significant difference in:
  - LOC duration ($p=0.014$)
  - total propofol consumption ($p<0.0001$)
  - time to fully conscious ($p<0.0036$)
- but no significant difference in
  - loading doses ($p=0.58$)

Preliminary Analysis

- On average, Caucasians spent significantly less time over-sedated than Blacks ($p=0.0003$) and Indians ($p=0.005$)
- The total propofol consumption of Caucasians was significantly higher than for Indians ($p=0.0002$) and Blacks ($p<0.0001$)

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Preliminary Analysis

- The time from removal of the endoscope (end of procedure) for the patient to become fully conscious (OAAS 5) was significantly shorter for the Caucasian patient compared to Blacks ($p<0.004$) and Indians ($p=0.01$)

Preliminary Conclusions

- Loading dose data indicate a formulaic approach and a general lack of awareness of racial differences in propofol response in anesthesia provider participants
- There was no significant difference between the loading dose in the questionnaire administered before the simulation and the loading dose used in the simulation

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Preliminary Conclusions

- Lower total propofol amount administered to Blacks and Indians indicative of titration to effect as the simulated patients responded/did not respond according to race-specific pharmacodynamics

Preliminary Conclusions

- Longer durations of LOC and time to awakening of Blacks and Indians indicate that titration was insufficient to counteract the initial formulaic loading dose
- Suggesting that loading doses, in addition to weight, should also take race into consideration, as an example of patient-centered anesthesia

My personal “experiential” learning

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North America

DIPRIVAN- propofol injection, emulsion
AstraZeneca Pharmaceuticals LP

DIPRIVAN®
(*propofol*) Injectable Emulsion
FOR IV ADMINISTRATION

DESCRIPTION

DIPRIVAN (propofol) Injectable Emulsion is a sterile, nonpyrogenic emulsion containing 10 mg/mL of propofol suitable for intravenous administration. Propofol is chemically described as 2,6-diisopropylphenol and has a molecular weight of 178.27. The structural and molecular formulas are:

Clinical Trials

Anesthesia and Monitored Anesthesia Care (MAC) Sedation

DIPRIVAN Injectable Emulsion was compared to intravenous and inhalational anesthetic or sedative agents in 91 trials involving a total of 5,135 patients. Of these, 3,354 received DIPRIVAN Injectable Emulsion and comprised the overall safety database for anesthesia and MAC sedation. Fifty-five of these trials, 20 for anesthesia induction and 35 for induction and maintenance of anesthesia or MAC sedation, were carried out in the US or Canada and provided the basis for dosage recommendations and the adverse event profile during anesthesia or MAC sedation.

Induction of General Anesthesia

Adult Patients: Most adult patients under 55 years of age and classified ASA I/II require 2 to 2.5 mg/kg of DIPRIVAN Injectable Emulsion for induction when unpremedicated or when premedicated with oral benzodiazepines or intramuscular opioids. For induction, DIPRIVAN Injectable Emulsion should be titrated (approximately 40 mg every 10 seconds) against the response of the patient until the clinical signs show the onset of anesthesia. As with other sedative-hypnotic agents, the amount of intravenous opioid and/or benzodiazepine premedication will influence the response of the patient to an induction dose of DIPRIVAN Injectable Emulsion.

India

FOR THE USE ONLY OF ANANAESTHETIST ATTACHED TO HOSPITALS, INSTITUTIONS OR NURSING HOMES

PROPOFOL INJECTION B.P. 1%

क्रिटीफॉल
Critifol 1%

COMPOSITION :
Each ml contains :
Propofol B.P. ..... 10 mg
In a vehicle containing Soybean oil U.S.P., Glycerin I.P., Purified Egg Lecithin and Water for Injection I.P.

Critifol 1% (Propofol Inj. B.P.) is an intravenous anaesthetic which is chemically unrelated to other anaesthetics. Induction of anaesthetic with **Critifol 1%** (Propofol Inj. B.P.) is rapid, and maintenance can be achieved by continuous infusion, with either nitrous oxide or opioids used to provide analgesia. **Critifol 1%** (Propofol Inj. B.P.) injection is white, oil in water isotonic emulsion for intravenous injection containing 10 mg Propofol per 1 ml.

DOSAGE AND ADMINISTRATION :
1. Induction of general anaesthesia :
(a) Adults :
In unpremedicated and in premedicated patients, it is recommended that **Critifol 1%** (Propofol Inj. B.P.) should be titrated [approximately 2 ml (20 mg) every 10 seconds in an average healthy adult) against the response of the patient until the clinical signs show the onset of anaesthesia. Most adult patients aged less than 55 years are likely to require 2.0 to 2.5 mg/kg of **Critifol 1%** (Propofol Inj. B.P.). Over this age, the requirement will generally be less. In patients of ASA Grades 3 and 4, lower rates of administration should be used (approximately 1 ml (10 mg) every 10 seconds).

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Preliminary recommendation

- As an example of pragmatic precision medicine, include patient race as a consideration when selecting the loading dose of propofol for procedural sedation

Preliminary recommendation

- Race-specific loading dose of propofol for sedation is pragmatic precision medicine and pragmatic precision anesthesia
- **Systems** approach to safety and preventing over-sedation based on readily observable racial characteristics of a patient and known inter-racial differences without knowing how an actual patient of a given race will respond.

Model-Driven Simulators

- Current model-driven simulators do not model (a) inter-patient variability or (b) inter-racial variability
- Current PK/PD models are based on studies performed in countries with predominantly Caucasian populations

Mannequins in different skin tones

http://www.laerdal.info/files/software/New_ETHNIC-556.pdf

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Timely words of caution

- Medicine: "First, do no harm"
- APSF (Anesthesia Patient Safety Foundation): "That no patient be harmed by anesthesia"
- Simulation: "No negative teaching"
- Diversity in patient simulators welcome but must be more than skin deep only
- Where appropriate, underpinning models must be made race-specific

Portable scenarios for sharing

- Cultural considerations when transferring simulation-based scenarios and curricula, especially for affective skills training
- PK/PD considerations when transferring/sharing scenarios that use drugs known to have race-specific PK/PD

Point of care web page for mobile phones – no wifi or cell needed

- Desktop sim exe
- http://vam.anest.ufl.edu/websims/propofolsim/mobile/

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Collaboration

- Welcome collaboration or interest in additional PM research, e.g., opiates

Parting comments

- Race-Specific ≠ Racist
  - It is not about race, but patient safety and quality of care
- Equality ≠ Similarity
  - Equal access to healthcare does not mean cookie cutter, one size fits all medical care
  - Recognizing and celebrating our individuality and differences
- Quality of care is not necessarily incompatible with quantity (throughput)

Questions/Contact info

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