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Age-Related Intravenous Induction Dosing In Patients Undergoing Gastrointestinal Surgeries

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ABSTRACT

Background:

It has been shown that elderly patients have decreased anesthetic requirements due to age-related changes in pharmacokinetics, pharmacodynamics and drug sensitivity. Previous work has also shown that anesthetic dosing is often not being rigorously corrected for age.

Purpose:

To determine whether the dosing of intravenous (IV) induction anesthetics in patients undergoing gastrointestinal (GI) surgeries are corrected appropriately for age.

Methods:

We retrospectively reviewed the intraoperative electronic anesthetic records of 1868 adult patients (aged ≥ 18 yrs) receiving general anesthesia for GI surgeries from February 2013 – January 2014. Patients undergoing multiple procedures, those requiring temporary abdominal closure or rapid sequence induction were excluded from this study. Change in mean arterial pressure (MAP) was calculated as the difference between pre- and post-induction MAP. Post-induction MAP was measured within the first 10 minutes of induction. Statistical analysis was done using T-test and one-way ANOVA.

Results:

There was a significant decrease in dosing of fentanyl, propofol and midazolam with increasing age ($p<0.05$). There was a significantly larger drop in MAP following

induction of anesthesia in older patients (ages > 70 yrs) despite the decrease in weight-based dosing ($p<0.01$). Patients aged 70 yrs and under had a mean decrease in MAP of 17.16 ± 19.51 mm Hg, whereas patients over the age of 70 had a mean decrease in MAP of 23.23 ± 25.09 mm Hg. We noted a significant *decrease* in dosing of fentanyl and propofol with increasing ASA class (p-values <0.01). No significant difference in dosing of midazolam was seen based on ASA class ($p=0.47$). For ASA III and IV patients ($n=792$), there was no significant change in dosing of fentanyl based on age.

Conclusion:

The results of this study show that there is a significant age-related decrease in the induction dosing of fentanyl, propofol and midazolam. This change remains significant for propofol after correcting for ASA class. However, the age-corrected doses for these induction anesthetics tend to be either higher, or at the upper limit, of recommended dosing for the elderly patients, which may explain a larger drop in MAP following induction in elderly vs. younger patients.

ACKNOWLEDGEMENTS

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TABLE OF CONTENTS

LITERATURE REVIEW

Epidemiology

The elderly population (those who are 65 years of age and older) is currently the fastest growing portion of the population in the United States. Between 2000 and 2010, the population of those 65 years and over has increased at a faster rate (15.1%) than the total US population (9.7%). According to the 2010 US Census, 40 million people (13%) of the total US population of 309 million people are 65 years and over [1]. In Connecticut, there were over half a million individuals 65 years and older in 2010 and they comprised 14.2% of the total state population [2]. The older population in the US, is projected to double from 36 million in 2003 to 72 million in 2030 and 86.7 million by 2050. The 85 and older group composes a small, but rapidly growing proportion of this older population [3]. This is in part due to increased life expectancies as a result of improving medical care and nutrition. The average life expectancy in the United States has risen from 47.3 years in 1900 to 76.9 years in 2000. A second contributing factor is that many of those in the baby boomer generation began to turn 65yrs in 2011 [3].

This rapidly growing older population has also increased the surgical and anesthesia workload for US hospitals. It is estimated that surgical interventions will be required by more than half of the population older than 65 years, at least once during the remainder of their lives [4]. A study done by Elixhauser et al in 2007 found that there were 15 million operating room (OR) procedures performed in US hospitals that year. They also found that elderly patients underwent these procedures 2 to 3 times more frequently than younger patients [5].

Pathophysiologic changes in the elderly

As the body ages, there are many pathophysiological changes that take place, and many of these changes can affect the pharmacokinetics and pharmacodynamics of commonly used anesthetic drugs. Overall pathophysiological changes result in a decrease in functional reserve in almost all organ systems.

Cardiovascular aging predominantly manifests in increased tissue stiffness and fibrosis, decreased response to beta-receptor stimulation, increased sympathetic nervous system activity and the loss of ischemic preconditioning [6]. The increased tissue stiffness causes the arteries, veins and myocardium to become less compliant, which in turn causes systolic hypertension and ventricular hypertrophy. In response to these changes, the ventricles hypertrophy and become more dependent on adequate end-diastolic atrial filling to maintain cardiac output. A diminished response to beta-receptor stimulation leads to reduced heart rate and contractile response to stimuli such as hypotension, exercise, or exogenous catecholamine administration. This reduction in the heart's ability to increase contractility increases the dependence on the Frank-Starling mechanism to maintain cardiac output, leading to an increase in pre-load and modestly decreased heart rate [6, 7]. It was previously thought that cardiac output decreased in an almost linear manner after the third decade of life [8], however newer longitudinal studies fail to show significant age-associated decline in cardiac output at rest or during exercise in healthy adults between ages 25 and 79 [9].

The most important feature of aging from a respiratory standpoint is the gradual reduction in elastic recoil of the lung tissue due to changes in the arrangement and strength of the elastic fiber network [10]. There is also a gradual decrease in compliance

of the chest wall as the body ages. While the total lung capacity remains the same throughout life, the vital capacity diminishes with age [8, 11]. After the age of 20, vital capacity decreases 20 to 30 ml per year. This is due to the fact that while total lung capacity remains unchanged, there is an increase in the residual volume of 5 to 10% per decade[11]. In addition to these changes in respiratory mechanics, there is a significant decrease in the efficacy of arterial oxygenation in the elderly, which is reflected by an almost linear loss of oxygen partial pressure in the arterial blood after the age of 20 [12], which in part is due to reduced surface area for gas exchange as the integrity of the lung parenchyma is progressively lost with age [13]. The decreased arterial oxygen tension, reduced gas exchange, and increased closing capacity all contribute to increased V/Q mismatch in the elderly [10]. The net effect of these changes results in increased work of breathing and decreased sensitivity to hypoxic and hypercapnic stimuli in the elderly [10]. Structurally, there is a loss of recoil forces that tend to hold small airways open, and this results in a greater number of airways closing at equivalent lung volumes when comparing older patients to their younger counterparts [14]. This puts the older patients at a higher risk for atelectasis and perioperative pulmonary complications.

As the nervous system ages, there is a progressive loss of neuronal tissue, which is reflected in a reduction in the average weight of the brain with age [15]. The volume of the brain declines with age at a rate of about 5% per decade after the age of 40 with the actual rate of decline possibly increasing with age, particularly over the age of 70 [16]. Grey matter decreases faster than white matter from 20 to 50 years of age, however after the age of 50 there is more white matter lost than gray matter with an eventual gray/white matter ratio of 1.55 by the age of 100 [15]. In addition to decrease in nervous tissue

mass, there is a loss of neuronal density, concentration of neurotransmitters, and norepinephrine and dopamine receptors [17]. The brain's choline acetyltransferase levels and muscarinic binding *decrease* with increasing age, as does cholingeric innervation in the caudate nucleus. There are also age-associated *declines* in levels of striatal dopamine uptake sites, dopamine transporters and dopamine levels. Cerebral cortical α_2 and β_2 (but not total β) adrenoreceptors also show an age-associated decrease. Finally, GABA-ergic innervation of the cortex also appears to decline with age [18]. This is particularly important for centrally-acting agents such as propofol and midazolam, which are known to act on GABA receptors. The blood-brain barrier decreases in microvascular density and capillary lumen size, both of which increase its permeability [19].

The kidneys are characterized by a progressive loss of renal mass with aging due to glomerulosclerosis, thickening of the vascular intima, fibrosis of the stoma and chronic infiltration by inflammatory cells. This results in a decline in renal plasma flow and glomerular filtration rate [8, 20]. There is approximately a 7.5 to 8 ml/min decline in GFR per decade[21]. The Baltimore longitudinal study of aging used both cross-sectional and longitudinal data over 10 years, and it reported a decline in creatinine clearance with increasing age. In addition, the longitudinal studies showed that the rate of decline of renal function also increases with age [22]. Newer longitudinal studies using the same population, however reported that 1/3 of all subjects had no decrease in renal function, with a small group with actual increase in clearance rate [23]. Overall, it appears that the majority of elderly patients do exhibit declines in creatinine clearance, but great variability does exist from person to person.

From a metabolic standpoint, there is a decrease in liver volume as individuals approach the end of the 9th decade, however recent studies have shown that there is no significant age-dependent difference in the activity of phase I, phase II or cytochrome p450 metabolism [24-26]. There is a 40% reduction in liver blood flow that occurs as individuals approach the end of the 9th decade [27].

Overall body composition also changes with age. There are relative decreases in total body water and lean body mass, while there is a relative increase in body fat [28]. Decreases in height in older individuals of either gender are almost linear with age whereas decreases in weight occur at different rates in men and women [14, 29].

Pharmacodynamic and pharmacokinetic changes in the elderly

Many of the factors related to pharmacokinetics and pharmacodynamics (PK/PD) are altered with aging and have been described above. The net result of these pathophysiologic changes as related to the pharmacology of anesthetic drugs is complex.

From a pharmacokinetic standpoint, there are many factors that contribute to the absorption, distribution, metabolism and excretion of anesthetic drugs, and many of these variables change as people age. Drug absorption is for the most part a passive process and the extent of absorption depends on the absorptive capacity of the small bowel, and this shows little change with increasing age [28]. However, the distribution of drugs is heavily dependent on body composition, which as was mentioned earlier, goes through significant change with age. Relative changes in body fat and lean body mass associated with aging can affect the volume of distribution (Vd) for many drugs. As the percentage of fat content increases, fat-soluble drugs will have a relatively increased Vd, and water-

soluble drugs will have a relatively decreased Vd [14, 28]. Vd is also a determinant of plasma concentration in acute dosing, and therefore is a major determinant in IV induction dosing.

Pharmacokinetics is often described with the three-compartment model (Figure 1). This model consists of a central compartment (V1), a rapidly equilibrating compartment (V2), and a slowly equilibrating compartment (V3) [30]. The central compartment (V1) consists of the central plasma pool. The rapidly equilibrating compartment (V2) consists of the hepatoportal system and to some extent the viscera. The slowly equilibrating compartment (V3) represents tissue such as muscle and fat, where there is decreased perfusion in comparison to V2 [31]. These compartments help to explain the three phases of drug distribution. When a drug is given IV, it goes into V1, and it is followed by a rapid distribution phase where there is rapid movement of the drug from the plasma into the rapidly equilibrating tissues. Often, there is a second slow distribution phase where there is movement of the drug into more slowly equilibrating tissues and return of the drug to the plasma from the rapidly equilibrating tissues. Finally the terminal phase involves drug return from both V2 and V3 back into V1 and is permanently removed by metabolism or excretion [30]. Therefore, increases in the relative fat content with increasing age leads to alterations in duration of drug effect in the elderly due to an increase in V3 [14, 28]. A relative decrease in total body water leads to a decrease in V1, which results in higher peak drug concentrations following boluses or rapid infusions [14, 32].

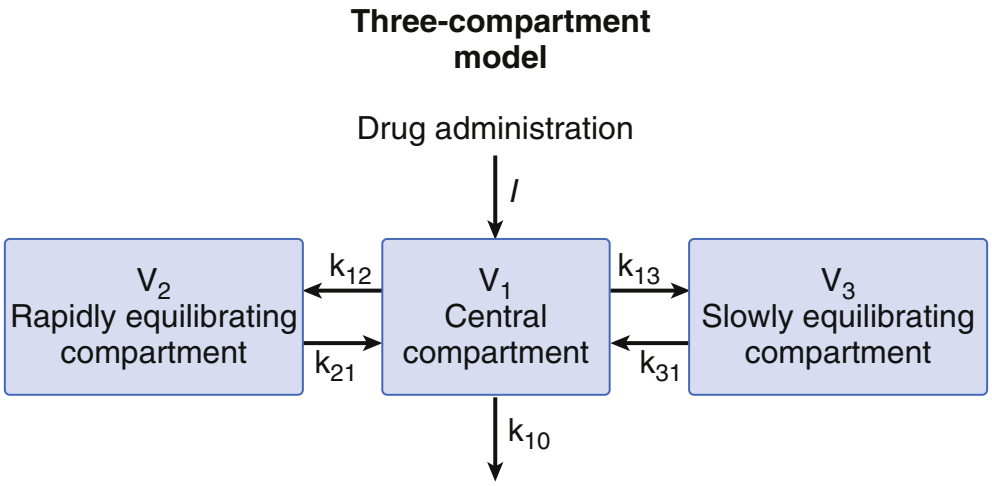

Figure 1. Schematic for the three-compartment model of drug pharmacokinetics [30]

Plasma protein drug binding varies for each individual drug and there are small but significant changes in serum albumin concentrations with aging. This results in increased free drug concentrations in elderly patients [33]. These changes are often not clinically relevant in healthy older patients, however elderly patients often have significant decline in albumin levels with severe illness or malnutrition, which could significantly increase the free plasma concentration of certain drugs [28]. Malnutrition in the elderly is common and has also been shown to be an independent predictor of institutionalization rate [34] and mortality in elderly patients and can be considered a marker of frailty in the elderly. Therefore it is expected to reflect an individual's susceptibility to acute health problems [35].

The rate of drug metabolism and a certain degree of drug elimination are mainly functions of the liver and these processes have been shown to decrease with advancing age [36, 37]. However, recent studies have not shown a significant decrease in liver function or histology [24-26], which suggests that the decreased rate of drug metabolism

in the elderly is not necessarily due to changes in liver function. A novel hypothesis by Le Couteur and Mclean suggests that there is hepatic sinusoid pseudocapillarization associated with aging that results in reduced diffusion and decreased drug metabolism [38]. Decreased blood flow to the liver may also contribute to the reduced rate of drug metabolism in the elderly [27]. Renal clearance of drugs is general reduced in the elderly population [28] due to both physiologic changes to the kidneys and reduced renal blood flow. Therefore, the dose requirements of drugs excreted mainly by the kidney should be reduced in those patients with reduced renal function [28].

Pharmacodynamic differences related to aging can be due to either differences in baseline performance or differences in sensitivity to the drug [39]. Mechanisms thought to contribute to these differences include altered neurotransmitters and/or receptors, hormonal changes, and impaired glucose metabolism or decreased availability of glucose and oxygen in the cerebral vasculature [16]. Drugs may also penetrate the CNS more easily with increasing age. For example, P-glycoprotein is an efflux pump that actively transports some drugs out of the brain and the functional activity of this pump is reduced with aging. This could potentially lead to increased drug exposure to the brain for older patients at given serum concentrations, leading to increased sensitivity to drugs that act on the central nervous system (CNS) [39]. Specific changes to PK/PD with age will vary for each drug based on the unique characteristics of each drug that affect its distribution, metabolism and elimination.

Overall, these changes results in higher peak drug concentrations, increased drug sensitivity, and decreased drug clearance in the elderly. This necessitates reductions in dosing for inhalational and IV anesthetic drugs.

IV induction medications and associated changes in PK/PD in the elderly

Commonly used IV induction medications include propofol, midazolam and fentanyl. All three drugs have increased potency in the elderly [14]. These are a result of both pharmacokinetic and pharmacodynamics changes in the elderly that lead to decreased drug dosing requirements in the elderly. The anesthetic potency of each IV drug can be quantified by its Cp50 value, which is defined as the plasma concentration required to prevent movement response in 50% of patients to surgical stimuli [40].

Propofol is currently the most widely used IV hypnotic that acts on both GABA and NMDA receptors. The brain becomes more sensitive to the effects of propofol with age, and Cp50 for propofol decreases with increasing age [41], with approximately a 30% reduction in a 90 year old patient versus a 30 year old [42]. This is because age influences the inter-compartmental drug distribution of propofol [42] and results in a reduction in systemic clearance, reduction in the size of the rapidly equilibrating compartment (V2) and reduction in inter-compartmental clearance to V2 [14], which would lead to higher plasma concentrations in older patients. Therefore, for a given propofol infusion rate, the plasma concentration in a 75 year old will rise 20-30% higher than in a younger patient. However, if given plasma concentrations are maintained with infusions of propofol, the plasma concentrations will fall faster in the 75 year old versus a 25 year old when the infusion is turned off [42]. Although the plasma concentrations fall more quickly in older patients once drug administration is complete, it often take longer to return to consciousness due to the increased sensitivity to propofol in the elderly [43].

In clinical practice, midazolam is often used immediately before induction of anesthesia to decrease anxiety and induce amnesia[44]. While overall pharmacokinetics do not change with age for midazolam, it does appear that the elderly are more sensitive to it [45, 46]. The Cp50 for midazolam decreases significantly between the ages of 40 and 80 years old, with the Cp50 for 80 year olds being less than 25% of that for 40 year olds [47]. In addition, there is a reduction in the clearance of midazolam by approximately 30% in 80 year olds versus 20 year olds [48]. Overall this results in a significant decrease in the dosing requirements for the elderly. Bell et al., noted a strong relationship between the dose of midazolam used and the subject's age in a cohort of patients undergoing upper GI endoscopy. They found that 7.2% of patients over the age of 70 required more than 5 mg for adequate sedation, while 83% of patients less than 70 years old required more than 5 mg. This correlated to a 75% decrease in dose requirement from age 20 to age 90 [49].

Elderly patients also have an increased sensitivity to opioid analgesics such as fentanyl. As determined by EEG, there is approximately 50% depression in EEG in 85 year olds compared to 20 year olds [50]. Overall pharmacokinetics of fentanyl, however do not appear to change with age [51, 52], and so this would translate clinically to a reduction of doses by one-half to achieve the same effect in older patients. Similar reductions (50% decrease in EEG in 84 year olds compared to 20 year olds) were found in shorter-acting opioids such as remifentanil [53].

Current IV induction anesthetic dosing recommendations in the elderly

Based on the pharmacokinetic and pharmacodynamics changes as discussed above, the current dosing recommendations for elderly patients require reductions from standard adult dosing. Standard induction dosing for propofol in adults is 2-2.5mg/kg, however a dose of 1 mg/kg with premedication and 1.75 mg/kg without premedication is recommended for induction of patients older than 60 years [44, 54]. Induction dosing for midazolam can be up to 0.3 mg/kg in young healthy adults, however a reduction of at least 50% is recommended for patients over the age of 60 [44] . Fentanyl is commonly given in combination with midazolam and propofol during induction at doses starting at 2 mcg/kg. However given that elderly patients are twice as sensitive to opioids, it is recommended that dosing for older patients to start at 1 mcg/kg although there is no consensus on the starting age at which the decreased dosing should be given [55].

Although recommendations exist for IV induction dosing for the elderly, it is not well known if elderly patients are receiving the correct dosing for their age, and whether the current recommendations are sufficient for our growing geriatric population. In addition, we currently lacking in PK/PD data and recommendations for the very elderly patient population (>80 yrs).

Impact of Severity of Illness on Drug Dosing and Clinical Outcomes

Since its formulation in 1941, the American Society of Anesthesiologists' (ASA) physical status classification system was intended to provide a common language to describe patients severity of illness before surgery [56]. ASA I corresponds to a normal healthy patient and ASA IV corresponds to a patient with severe systemic disease that is

a constant threat to life. Further definitions of the ASA classification system are detailed in **Table A**. This classification system has been shown to predict morbidity and mortality in surgical patients [57]. Studies have shown a strong correlation between increasing ASA class and decreasing requirements for induction dosing of propofol [58], which suggests that patients with increased severity of illness require less propofol to induce adequate anesthesia than those without significant disease.

In addition to decreased anesthetic requirements, higher ASA classification (class III/IV) is independently associated with increased 1-year mortality following non-cardiac surgery [59]. Patients with higher ASA classifications have also been shown to have significantly longer hospitalizations for operative fixation of ankle procedures – a 1 point increase in ASA was associated with a 3.42 day increase in average length of stay [60]. The prevalence of intraoperative hypotension is also greater in patients who are ASA III/IV (12.6%) versus ASA I/II (7.7%) [61].

Although the ASA classification system is easily applied and communicated, the system lacks specificity, which leads to inconsistent ratings between anesthesiologists and imprecise clinical interpretation [57]. A meta-analysis of 77 studies looking at correlations between ASA classification and post-operative outcomes showed a pooled sensitivity of 0.74 and a pooled specificity of 0.66. This specificity falls to 0.53 in the studies associated with high-risk surgical procedures [57].

ASA PS	Definition
I	A normal healthy patient
II	A patient with mild systemic disease
III	A patient with severe systemic disease
IV	A patient with severe systemic disease that is a constant threat to life
V	A moribund patient who is not expected to survive without the operation
VI	A declared brain-dead patient whose organs are being removed for donor purposes

Table A. Definitions of the American Society of Anesthesiologists' physical status classification levels

STATEMENT OF PURPOSE

The purpose of this study is to evaluate whether IV induction anesthetics are being appropriately corrected for age and ASA class.

METHODS

Study Design

A retrospective review was conducted for the intraoperative electronic anesthetic records of 1868 adult patients (aged 18 years and older) who had received general anesthesia for GI surgeries at Yale-New Haven Hospital. Only patients who underwent IV induction were considered in this study. GI surgery was defined as any procedure involving the GI tract or gallbladder. Both laparoscopic and open abdominal procedures were included in the study. Endoscopic procedures were not included in the current study.

Patient Selection

2471 adult patients scheduled to undergo GI procedures were identified from February 2013 to January 2014. Patient exclusion criteria are summarized in **Figure 2**. Any patients who did not undergo traditional IV induction for anesthesia were excluded. This included patients who underwent RSI, MAC, inhalational anesthetic induction, epidural anesthesia, or were already intubated on arrival to the OR. Patients who had multiple procedures or required temporary abdominal wall closure were also excluded. The final exclusion criteria involved any patients who were missing data points, such as

height, weight, pre-induction blood pressure, or post-induction blood pressure. 602 patients were excluded and the final cohort size was 1869 patients.

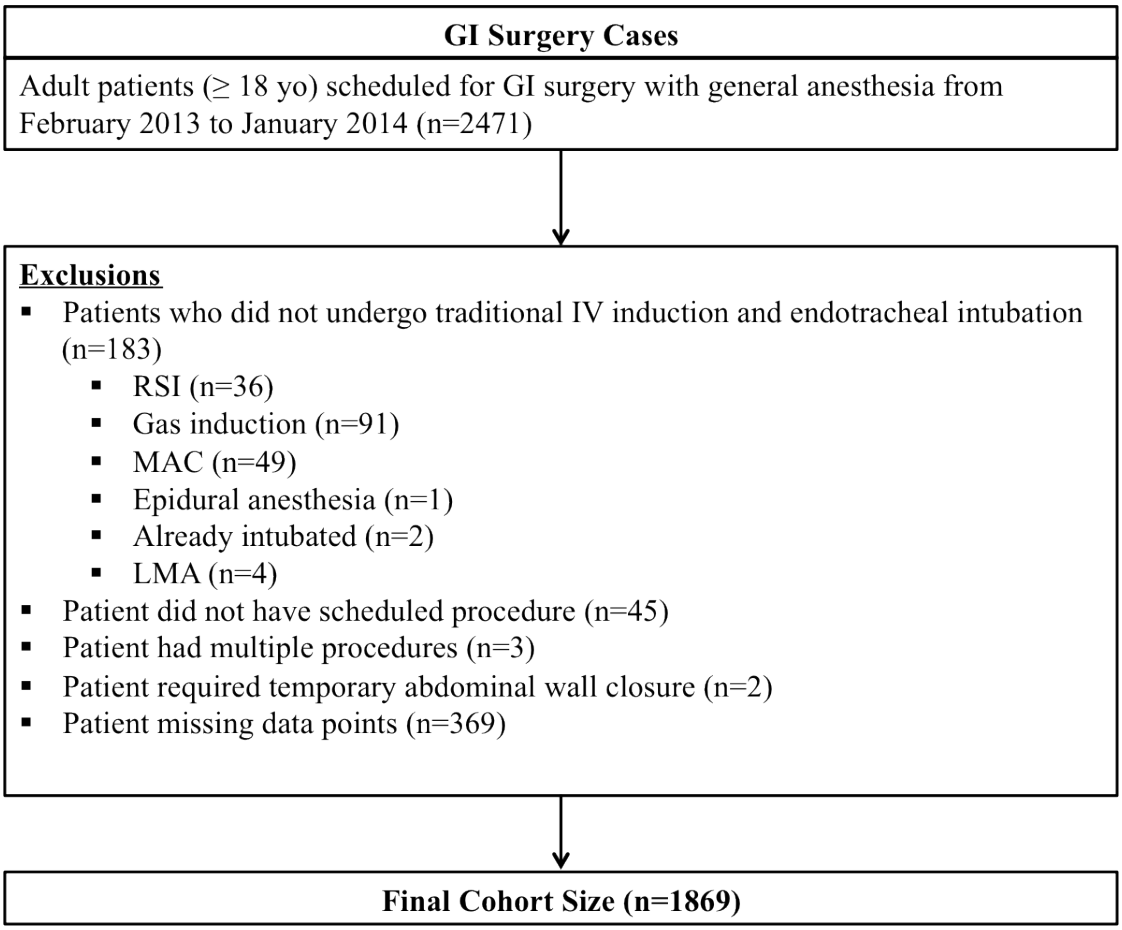

Figure 2. Exclusion flow chart for patient cohort.

Data Collection

Data were extracted from preoperative and intraoperative anesthesia electronic records. Basic patient information included age, gender, height and weight. Body surface area was calculated using the Mosteller equation: BSA (m^2) = (height (cm) x weight(kg) / 3600)^{½} . Ideal body weight was also calculated based on height and gender.

For males, IBW = 50 kg + 2.3 kg for each inch over 5 feet. For females, IBW = 45.5 kg + 2.3 kg for each inch over 5 feet.

The date of surgery, attending surgeon, procedure and ASA class were recorded. Two automated systolic and diastolic blood pressure readings were extracted from the electronic intraoperative anesthesia record for each patient – once prior to any administration of IV medication and once within 10 minutes of induction. Induction was defined as the administration of IV propofol. Mean arterial pressures were calculated using the recorded systolic and diastolic pressures. The doses of propofol, fentanyl and midazolam were extracted from the records and the weight-based dosing was calculated. The presence or absence of post-induction hypotension (defined as post-induction mean arterial pressure of <70 mm Hg or reduction in MAP by 40%) was noted.

Data Analysis

Statistical analysis was done using T-test and one-way ANOVA, with $p < 0.05$ considered significant. Age-based analysis was done with the following age groups: 18 to 30, 31 to 40, 41 to 50, 51 to 60, 61 to 70, 71 to 80, and >80 years old. Changes in the average weight-based dosing of midazolam, fentanyl and propofol with increasing age were analyzed using one-way ANOVA. A subsequent change in the average change in MAP from pre-induction to post-induction was also analyzed using one-way ANOVA. Analysis based on ASA class was also performed using one-way ANOVA.

Comparisons between the average weight-based dosing for elderly patients (defined as >70 years old in this study) versus younger adult patients (18-70 yrs) were made using the student's T-test. Patients were further stratified by ASA class, and

patients were grouped into ASA I/II vs. ASA III/IV (Figure 3). This was done to control for potential changes in dosing based on ASA class. Further analysis was done using the Student's T-test within these stratified groups.

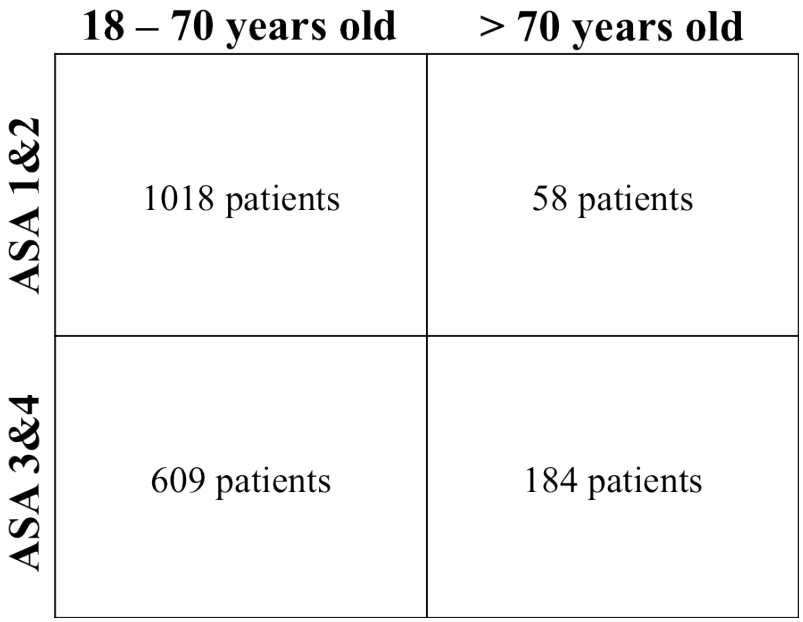

Figure 3. Stratification scheme for both ASA class and age

Distribution of Work

Contact with the Human Investigations Committee of the Yale School of Medicine regarding initial and ongoing study approval was maintained by Shamsuddin Akhtar, MD, of the Department of Anesthesiology at the Yale School of Medicine. The list of potential subjects was compiled by Jia Liu (YSM 2015). Data were collected by Jia Liu. Data analysis was performed by Jia Liu and Shamsuddin Akhtar, MD with assistance from Joseph Heng (YSM 2015).

RESULTS

Patient Characteristics

Of the 1869 patients in the final study cohort, 241 were over the age of 70 (age range 18-93). 55.9% of the patients were female and 44.1% were male. 1076 patients were classified as ASA I/II and 792 patients were classified as ASA III/IV (**Figure 4**). Average height for all patients was 1.68m, average weight was 86.64 kg and average calculated BSA was 2.00 m^2. Procedures included in this cohort were performed by 44 different surgeons, over the course of one year. The types of surgeries undergone by these patients are shown in **Table B.**

Patients were then stratified by age, and patient characteristics for each age group are detailed in **Table C**. There were no significant changes in average height with increasing age. There was a trend of decreasing weight with increasing age starting at age 50. A similar trend in body surface area was also noted starting at age 50. Of note, for patients over the age of 70, only 58 patients were classified as ASA I/II versus 183 patients who were classified as ASA III/IV.

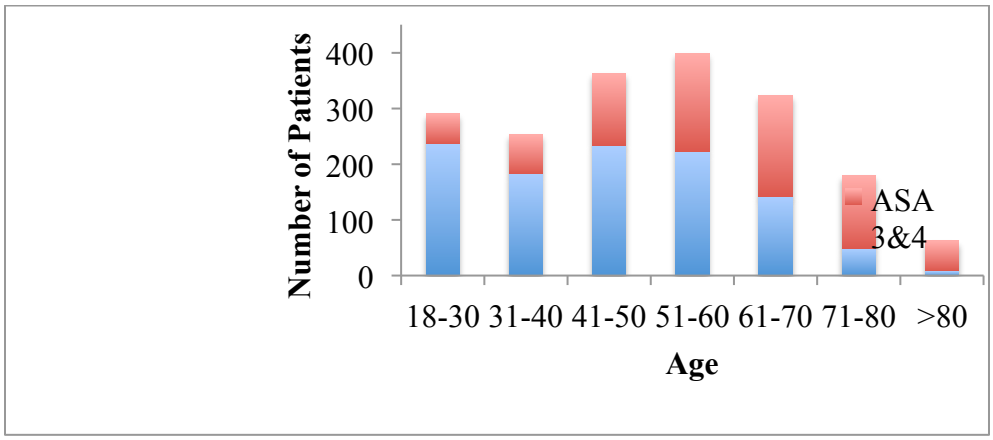

Figure 4. Age and ASA distribution of patients.

Type of GI Surgery	Total Number
Upper GI Surgery	363
Lower GI Surgery	278
Anal/Perianal Surgery	54
Appendectomy	198
Cholecystectomy	436
Hernia Repair	478
Exploratory Laparotomy/Lysis of Adhesions	52
Other	10
Total	1869

Table B. Distribution of surgery type for the study cohort

Age Range (in years)	Total	Female (%)	ASA 1&2 only	ASA 3&4 only	Ratio of ASA 1&2 and 3&4	Height (m)	Weight (kg)	BSA (m^2)
18-30	290	55.5	237	53	4.47	1.69	83.33	1.95
31-40	253	67.6	183	70	2.61	1.68	91.92	2.05
41-50	362	57.2	233	129	1.81	1.68	93.33	2.07
51-60	399	49.4	223	176	1.27	1.70	89.26	2.04
61-70	324	51.2	142	181	0.78	1.69	82.44	1.95
71-80	179	54.7	49	130	0.38	1.67	79.34	1.91
>80 yr	62	70.9	9	53	0.17	1.65	67.59	1.74
Total	1869	55.9	1076	792	1.36	1.68	86.64	2.00

Table C. Patient characteristics various age groups – height, weight and BSA are given as averages.

Age-Related Dosing

There were significant decreases in dosing of fentanyl, propofol and midazolam with increasing age. Average dose of fentanyl for the 18-30 year old age group was 1.41 ± 0.81 mcg/kg and >80 year old age group was 1.21 ± 0.80 mcg/kg. Average dose of propofol for the 18-30 year old age group was 2.48 ± 0.83 mg/kg and >80 year old age group was 1.63 ± 0.59 mg/kg. Average dose of midazolam for the 18-30 year old age group was 0.026 ± 0.16 mg/kg and >80 year old age group was 0.0017 ± 0.0053 mg/kg with the majority of patients receiving *no* midazolam during induction. (**Figure 5).**

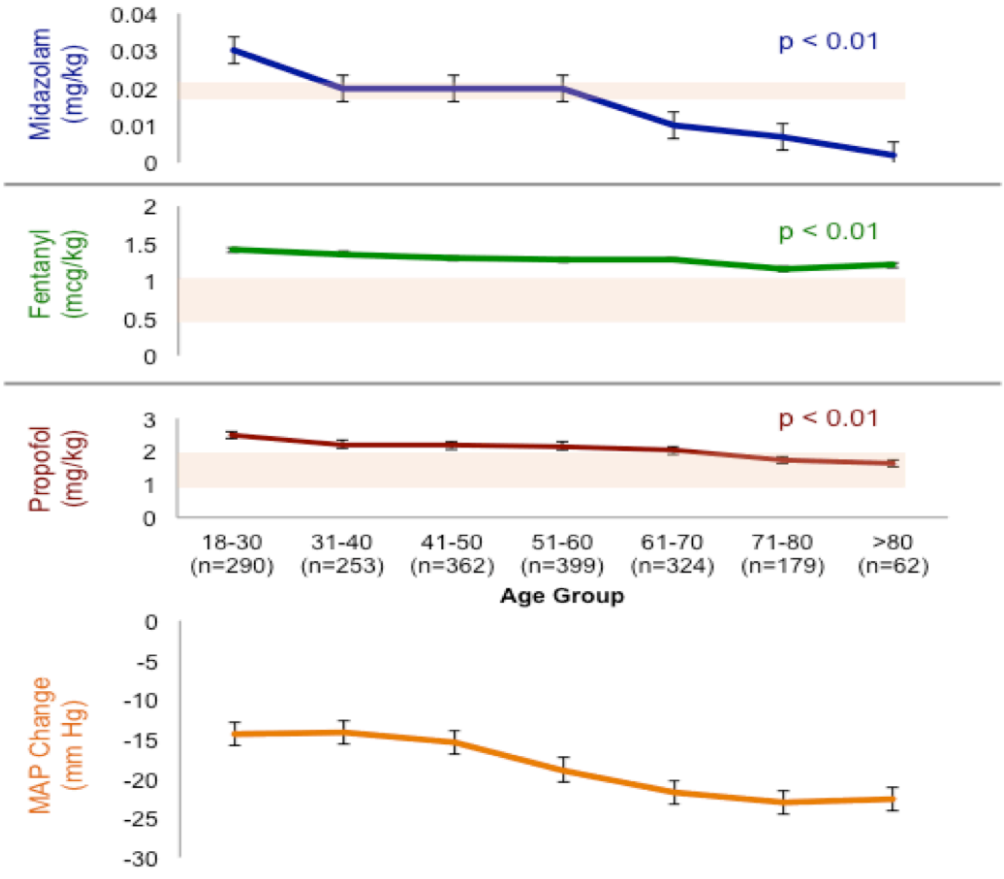

Figure 5. Average weight-based doses of different induction anesthetics and post-induction changes in mean arterial pressure are represented for different age groups.

Standard error bars are included. Translucent shaded bars reflect recommended dosing ranges for the elderly. P-values were calculated using one-way ANOVA, with $p<0.05$ considered significant.

Pharmacodynamic effect

There was a significantly larger drop in MAP following induction in older patients (>70 years old) despite the decrease in weight-based dosing (**Figure 5**). Patients aged 70 and under had an average decrease in MAP of 17.16 ± 19.51 mm Hg (median 23.33 mm Hg) following IV induction, whereas patients over the age of 70 years had an average decrease in MAP of 23.23 ± 25.09 mm Hg (median 17.33 mm Hg) following IV induction. There was also a trend in the average MAP following induction, with larger decreases with increasing age from age 40 and older. Over 30% of patients over the age of 60 years experienced post-induction hypotension, and there was a similar percentage of patients aged 18 to 30 years old who also experienced post-induction hypotension (**Table D**).

Age Range (in years)	Number of Patients with Post-Induction Hypotension	Percentage of Patients with Post-Induction Hypotension (%)
18-30	95/290	32.7
31-40	66/253	26.1
41-50	78/362	21.5
51-60	83/399	20.1
61-70	104/324	32.1
71-80	65/179	36.3
>80	23/62	37.1
Total	514/1869	27.5

Table D. Patients within each age group found to have post-induction hypotension

Dosing Related to ASA Class

We noted a significant decrease in dosing of fentanyl and propofol with increasing ASA class (p-values < 0.01). Fentanyl dosing decreased from an average of 1.39 ± 0.71 mcg/kg for ASA-I to an average of 1.04 ± 0.94 mcg/kg for ASA-IV. Propofol dosing decreased from an average of 2.63 ± 0.79 mg/kg for ASA-I to 1.57 ± 0.59 mg/kg for ASA-IV. There was no significant difference in dosing of midazolam based on ASA

class (p=0.47) with an average dosing of 0.019 ± 0.013 mg/kg in ASA 1 and 0.0047 ± 0.0097 mg/kg in ASA 4 patients. **Figure 6**

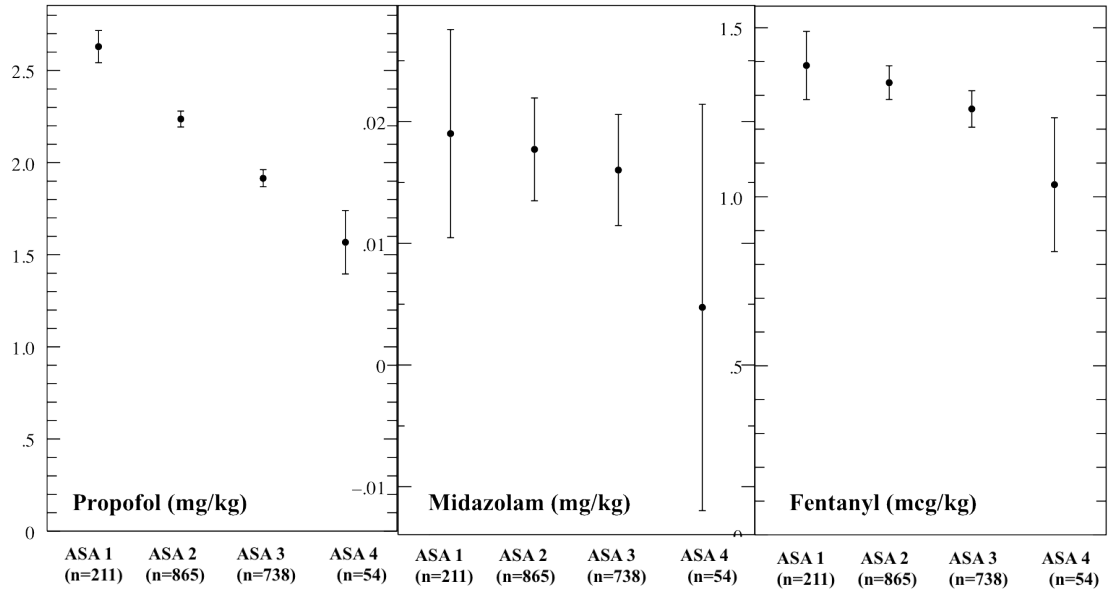

Figure 6. Average weight-based doses of different induction anesthetics stratified by ASA class.

Age-Related Dosing Stratified by ASA Class

When stratified by ASA class, the decreased dosing for older patients (>70 years old) continued to be significant for both midazolam and propofol within each ASA class stratification (p-values <0.01). However, when stratified by ASA class, the age-based change in dosing for fentanyl was no longer significant (p=0.06 for ASA I/II, p=0.15 for ASA III/IV). **Table E**

	Age 18-70 [n=1628]	Age > 70 [n=241]	P-value
Midazolam (mcg/kg)			
All Pts	0.018	0.006	<0.01
ASA I/II	0.018	0.008	<0.01
ASA III/IV	0.018	0.005	<0.01
Fentanyl (mcg/kg)			
All Pts	1.30	1.18	<0.01
ASA I/II	1.36	1.17	0.06
ASA III/IV	1.27	1.17	0.15
Propofol (mg/kg)			
All Pts	2.20	1.70	<0.01
ASA I/II	2.34	1.88	<0.01
ASA III/IV	1.96	1.65	<0.01

Table E. Dosing differences for IV induction anesthetics stratified by age and ASA class. ASA I/II (n=1076), ASA III/IV (n=793). $p<0.05$ considered significant.

DISCUSSION

Age-Related IV Induction Dosing

It is well known that elderly patients require 20-50% less for IV induction dosing than younger patients. Propofol doses are often reduced by as much as 50% and the

initial doses of opioids should also be reduced by approximately 50% [44, 55]. The goal of our study was to investigate whether practitioners are generally following these recommendations by reducing IV induction dosing for the elderly. However, even with our growing elderly population, there is very little data for the very elderly (>80 yr). For example, there are 21 previously published datasets on propofol pharmacokinetics, and the pooled data contains 660 patients total, however only 6 of those patients are over the age of 80 [62].

Based on our current cohort, there were significant reductions in the average IV induction dosing of propofol, midazolam and fentanyl with increasing age. When comparing the 18-30 year old age group and the >80 year old age group, there was a 14% reduction in fentanyl dosing, a 34% reduction in propofol dosing, and a 93% reduction in midazolam dosing. While these reductions in dosing were significant, the dose reductions for propofol were still in the upper limit of the recommended dosing range for the elderly. The dose reductions for fentanyl were higher than the recommended dosing of 0.5-1 mcg/kg, and our study patients received on average more than 1 mcg/kg.

When stratified by ASA class, there was also a significant reduction in IV induction dosing of propofol and fentanyl with increasing ASA class. Given the higher percentage of patients with higher ASA classes (III&IV) in older patients, this suggests that some component of the overall reduction in IV induction dosing could be in part due to overall severity of illness of the patient and pre-existing comorbidities present in older patients rather than age itself. It has been shown that for patients undergoing ambulatory GI procedures that practitioners are more likely to adjust for ASA class than age [63]. To delineate the whether dosing reductions in this study were due to age or ASA class, the

study cohort was stratified by ASA class before age-based analysis was done. The cohort was divided into ASA I/II (those who are healthy and with well-controlled disease) vs. ASA III/IV (those who have significant or poorly controlled disease) and then stratified by age. Once controlled for ASA class, there continued to be a significant decrease in dosing for both midazolam and propofol with increasing age, suggesting that significant dose reductions seen in this study are in fact based on age in addition to those reductions seen in association with increasing ASA class. However, there was no significant change in dosing of fentanyl based on age once stratified by ASA class. This suggests that the reduction in dosing we noted in the unstratified age-based analysis was likely due to the increased proportion of ASA III/IV patients in the older age groups rather than actual changes in dosing based on age.

Once stratified by ASA class, those patients with higher ASA classifications over the age of 70 years still had doses of propofol that were in the upper limit of recommended dosing and doses of fentanyl that were above those recommended for the elderly. This suggests that even those older patients with the most significant disease burden are receiving more IV induction anesthetic than necessary, especially when considering that these reductions in dosing were still associated with significant post-induction blood pressure decreases.

Post-induction hemodynamic changes

We noticed greater post-induction hemodynamic changes in MAP with increasing age despite the decreased dosing in IV anesthetic. We noted an age-dependent increase in the degree of post-induction hypotension. Propofol and midazolam and known to

have hemodynamic effects that result in decreases in arterial blood pressure [44], and co-administration of these two drugs has a synergistic effect [64]. Fentanyl, when used as the sole or primary induction agent, has been shown to result in hemodynamic stability throughout the perioperative period [55]. However studies have shown that when used in combination with propofol, opioids reduce the plasma propofol concentration required for loss of consciousness [65, 66]. Specifically, alfentanil has been shown to enhance the depressant effects of propofol on systolic blood pressure. Hemodynamic stability therefore does not appear to be improved with combinations of propofol and alfentanil [66]. Studies combining midazolam, propofol and fentanyl show a synergistic effect of these drugs, which reflected by significant reductions in propofol dose requirement when adding midazolam pre-treatment to a standard propofol and fentanyl induction. This synergistic effect appeared to be even more significant in the older age group (>60 yr). There was also a trend where the treatment group that did not receive midazolam tended to maintain systolic blood pressure more effectively than the treatment group that received all three drugs, although this effect was not statistically significant [67]. While this study did not determine each induction agent's individual effect on blood pressure, the post-induction hemodynamic changes seen in this study are likely in part due to the synergistic action of the induction agents used, and this effect is likely more significant in the elderly.

Older patients are known to show more hypotension and greater lability during anesthesia than young adults [6, 68, 69]. It is also well known that induction of anesthesia by bolus administration of propofol can produce significant hypotension [70-72]. There is evidence that hypotension and hypertension during general anesthesia are

independently associated with adverse outcomes in patients having both non-cardiac and cardiac surgery [59, 61, 73, 74]. While the consequences of post-induction hypotension are not yet entirely known, a study by Reich et al noted in a retrospective review that 9% of their patients experienced severe hypotension 0 to 10 minutes post-induction of general anesthesia. The patients with post-induction hypotension were more likely to experience prolonged postoperative stays and/or death than those patients without post-induction hypotension. The proportion of those adverse events in patients with hypotension at any time during the first 10 minutes following induction was 13.3%, versus 8.6% in patients without hypotension, during this post-induction period [61]. A prospective cohort study by Monk et al also showed that 1-year mortality risk was increased with longer duration of intraoperative hypotension. There was a 0.36 % increase in mortality risk per minute when the mean arterial pressure was below 80 mm Hg in patients with intraoperative hypotension [59]. More recently, Walsh et al found that patients with intraoperative hypotension where the mean arterial pressure fell below 55 mmHg had an increased risk for both acute kidney injury and myocardial injury. Even short durations (1 to 5 minutes) of hypotension were associated with an increased risk for these adverse outcomes, however the risk increased with increased duration of intraoperative hypotension [74].

The elderly population is especially at risk for post-induction hypotension given the pathophysiological changes associated with aging. There is decreased baroreceptor sensitivity with increasing age, which impairs the ability to buffer short-term changes in blood pressure. Decreased responsiveness to β-adrenoreceptors and the renin-angiotensin-aldosterone system stimulation also increases the risk for hypotension in

older patients [10]. Given the increased risk of both morbidity and mortality associated with even short durations of post-induction hypotension, careful management of IV induction dosing and hemodynamics in the elderly could improve the postoperative outcomes for these patients.

While the average mean arterial pressures reflected an increase in the degree of post-induction hypotension in older patients, there were large standard deviations associated with these pressures. This reflects the degree of pathophysiological variability and pharmacological variability in regards to individual response to varying IV induction agents. This could in part be due to the tremendous variability in physical status of elderly patients [54], it could also be due to the variability across different anesthesia providers.

Data on rate of drug administration are missing in this retrospective review. The assumption in this study is that induction doses are given as bolus injections rather than steady infusions. Studies have shown that while bolus administration of drugs such as propofol commonly produce significant hypotension following induction [71, 72], induction with a slow infusion (0.75 mg/kg/min) with propofol at total doses of approximately 1.6 mg/kg does not significantly decrease blood pressure in the elderly (defined as 65 to 85 yrs by Chan et al), and it does not require significantly longer to achieve loss of consciousness [70]. It is likely that this reduction in the infusion rate attenuates the peak drug concentration and thus has a lesser effect on the hemodynamics.

Study Limitations

A major limitation to this study is the retrospective nature of the review. We were constrained to the data that were collected by the clinicians, though automated, at the time. Therefore our dosing data were entirely reliant on the documentation in the electronic medical record. Knowing that the induction of anesthesia is often a busy time for the anesthesia staff, it is quite possible that the documentation is done after the fact. This could result in modest variation between actual time of induction and the documented time of induction. We also do not have data on fluid therapy, positional changes, mildly stimulating procedures (such as urinary bladder catheterization) or any other factors that could have influenced blood pressure.

In the current study, we did not exclude patients if the post-induction blood pressure measurement was taken after intubation. Tachycardia and hypertension are well-documented complications associated with laryngoscopy and tracheal intubation [75, 76], and typical pressor response can include a 40-50% increase in blood pressure, a 20% increase in heart rate and an elevation in both plasma epinephrine and norepinephrine [77]. It is very likely that for a proportion of the patients in this study cohort with noted post-induction increases in blood pressure, this increase in blood pressure was due to the pressor response associated with tracheal intubation. While elderly patients (65-80 yr) have been shown to have a decreased chronotropic response to intubation, there have been no documented age-related differences in the effect of laryngoscopy and tracheal intubation on mean arterial pressure [78, 79]. Therefore, while the pressor response associated with tracheal intubation likely attenuated the magnitude of post-induction hypotension noted in the overall study, it is not likely to have

significantly affected the age-related differences in post-induction blood pressure that were seen in this study.

Like the vast majority of age-related studies, the current study is cross-sectional and the age-related differences inferred here are based on comparisons of mean values between the various age groups. This assumes that mean differences observed between age groups reflect the change that occurs in an individual with the passage of time, which may not always be valid. Cross-sectional studies can often confound time-related factors of age and birth cohort effects [39] For example, generational differences in regards to things such as environmental exposures and access to healthcare could be confounding the age-related effects seen in this study. There may also be certain selective mortality biases in a cross-sectional study because the individuals in the oldest cohort have survived to reach old age. Ideally, longitudinal studies provide the best data on the effects of aging, however it would be difficult to obtain longitudinal data on the effects of IV induction anesthetics as that would require a patient cohort that would require regular invasive procedures that require general anesthesia.

The data collection for this study was done at one institution, and therefore the overall generalizability of the study is somewhat limited. Further studies utilizing large databases or multi-center studies would be beneficial to confirm the results obtained at this institution, and it would improve the generalizability of the study results. However, previous studies at other institutions have given similar results, which is reassuring that the results of this study are not institution-specific [80, 81].

Recommendations and Future Directions

This study is one of the many suggesting that older patients are routinely given more IV anesthetic than is recommended for their age [63, 80-82]. While dose reductions noted in this study are within the recommended range for older patients, the fact that these doses were still associated with significant drop in mean arterial pressure suggests that further dose reductions may be required for older patients. With the increasing population of patients over the age of 65 years, it may be necessary to look at age as a continuous variable when considering anesthetic drug dosing in older patients rather than treating "adult" versus "elderly" patients. This study noted that post-induction decline in mean arterial pressure were greater with increasing age, suggesting that our current drug dosing recommendations for the elderly may not be sufficient. Very little is known about the pharmacodynamics differences in those aged >85 years old [39], and this is one of the fastest growing populations in the United States [3]. There are data showing that adequate levels of anesthesia can be provided with doses of propofol as low as 0.82 mg/kg for both bolus and infusion dosing [83].

Further study in this very elderly population (>85 yr) would be helpful to delineate the PK/PD differences in this population beyond what has been studied for those patients over the age of 65. Titrated dosing with commonly used IV induction agents in addition to blinded EEG monitoring will help to determine whether the PK/PD changes in the very elderly are different in comparison to the data previously discussed regarding patients over the age of 65. While this study did show a progressively increasing hemodynamic response to IV induction agents with increasing age, it has been

well established that hemodynamic variables are not predictive of hypnotic depth [59]. Therefore, adequate depth of anesthesia must be established with either intraoperative EEG or BIS monitoring before the dosing of IV anesthetics can be lowered when trying to maintain hemodynamic stability in these patients.

Until there are more detailed studies looking at the pharmacokinetic and pharmacodynamics differences in adults >85 years old, perhaps it would be beneficial for there to be progressive dose reductions with increasing age for older patients to prevent perioperative complications such as post-induction hypotension and improve hemodynamic stability for older patients in the operating room.

REFERENCES

1. Werner, C.A., *U.S. Census Bureau: 2010 Census Briefs - The Older Population: 2010.* US Dept of Health and Human Services, 2011.
2. Howden, L.M. and J.A. Meyer, *U.S. Census Bureau: 2010 Census Briefs - Age and Sex Composition: 2010.* US Dept of Health and Human Services, 2011.
3. He, W., et al., *U.S. Census Bureau, Current population reports - 65+ in the United States: 2005.* US Dept of Health and Human Services, 2005.
4. Veering, B.T., *Management of anaesthesia in elderly patients.* Curr Opin Anaesthesiol, 1999. **12**(3): p. 333-336.
5. Elixhauser, A. and R.M. Andrews, *Profile of Inpatient Operating Room Procedures in US Hospitals in 2007.* Arch Surg, 2010. **145**(12): p. 1201-1208.
6. Rooke, G.A., *Cardiovascular aging and anesthetic implications.* Journal of Cardiothoracic and Vascular Anesthesia, 2003. **17**(4): p. 512-523.
7. Fleg, J.L., *Alterations in cardiovascular structure and function with advancing age.* Am J Cardiol, 1986. **57**(5): p. 33C-44C.
8. Tonner, P.H., J. Kampen, and J. Scholz, *Pathophysiological changes in the elderly.* Best Pract Res Clin Anaesthesiol, 2003. **17**(2): p. 163-177.
9. R.J., R., et al., *Exercise cardiac output is maintained with advancing age in healthy human subjects: cardiac dilatation and increased stroke volume compensate for a diminished heart rate.* Circulation, 1984. **69**(2): p. 203-213.
10. Corcoran, T.B. and S. Hillyard, *Cardiopulmonary aspects of anaesthesia for the elderly.* Best Pract Res Clin Anaesthesiol, 2011. **25**(3): p. 329-54.
11. Sprung, J., O. Gajic, and D.O. Warner, *Review article: age-related alterations in respiratory function - anesthetic considerations.* Can J Anaesth, 2006. **53**(12): p. 1244-1257.

12. Wahba, W.M., *Body build and preoperative arterial oxygen tension.* Can Anaesth Soc J, 1975. **22**(6): p. 653-658.
13. Auerbach, O., E.C. Hammond, and L. Garfinkel, *Thickening of walls of arterioles and small arteries in relation to age and smoking habits.* N Eng J Med, 1968. **278**(18): p. 980-984.
14. Sadean, M.R. and P.S. Glass, *Pharmacokinetics in the elderly.* Best Pract Res Clin Anaesthesiol, 2003. **17**(2): p. 191-205.
15. Brody, H., *The aging brain.* Acta Neurol Scand, 1992. **Suppl 137**: p. 40-44.
16. Peters, R., *Ageing and the brain.* Postgrad Med J, 2006. **82**(964): p. 84-8.
17. Kanonidou, Z. and G. Karystianou, *Anesthesia for the elderly.* Hippokratia, 2007. **11**(4): p. 175-177.
18. Mrak, R.E., W.S.T. Griffin, and D.I. Graham, *Aging-associated changes in human brain.* J Neuropathol Exp Neurol, 1997. **56**(12): p. 1269-1275.
19. Strom, C., L.S. Rasmussen, and F.E. Sieber, *Should general anaesthesia be avoided in the elderly?* Anaesthesia, 2014. **69 Suppl 1**: p. 35-44.
20. Fliser, D., et al., *Renal functional reserve in healthy elderly subjects.* J Am Soc Nephrol, 1993. **3**(1371-1377).
21. Muhlberg, W. and D. Platt, *Age-dependent changes of the kidneys: pharmacological implications.* Gerontology, 1999(45): p. 243-253.
22. Rowe, J.W., et al., *The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study.* J Gerontol, 2976. **31**(2): p. 155-163.
23. Lindeman, R.D., J.D. Tobin, and N.W. Shock, *Longitudinal studies on the rate of decline in renal function with age.* J Am Geriatr Soc, 1985. **33**(4): p. 278-285.
24. Herd, B., et al., *The effect of age on glucoronidation and sulphation of paracetamol by human liver fractions.* Br J Clin Pharmac, 1991. **32**: p. 768-770.
25. Schmucker, D.L., et al., *Effects of age and gender on in vitro properties of human liver microsomal monooxygenases.* Clin Pharmacol Ther, 1990. **48**(4): p. 365-374.
26. Wynne, H.A., et al., *The effect of age upon the affinity of microscomal mono-oxygenase enzymes for substrate in human liver.* Age Ageing, 1988. **17**(6): p. 401-405.
27. Wynne, H.A., et al., *The effect of age upon liver volume and apparent liver blood flow in healthy man.* Hepatology, 1989. **9**(2): p. 297-301.
28. Cusack, B.J., *Pharmacokinetics in older persons.* Am J Geriatr Pharmacother, 2004. **2**(4): p. 274-302.
29. Fulop, T., et al., *Body composition in elderly people II: comparison of measured and predicted body composition in healthy elderly subjects.* Gerontology, 1985. **31**(3): p. 150-157.
30. Kim, T.K., S. Obara, and K.B. Johnson, *Basic Principles of Pharmacology*, in *Miller's Anesthesia, Eighth Edition*, R. Miller, Editor. 2015, Saunders: Philadelphia, PA.
31. Gibaldi, M. and S. Feldman, *Pharmacokinetic Basis for the Influence of Route of Administration on the Area Under the Plasma Concentration-Time Curve.* J Pharm Sci, 1969. **58**(12): p. 1477-1480.
32. Norris, A.H., T. Lundy, and N.W. Shock, *Trends in selected indices of body composition in men between ages 30 and 80 years.* Ann N Y Acad Sci, 1963. **110**: p. 623-639.

33. Wallace, S.M. and R.K. Verbeeck, *Plasma protein binding of drugs in the elderly.* Clin Pharmacokinet, 1987. **12**(1): p. 41-72.
34. De Buyser, S.L., et al., *A multicomponent approach to identify predictors of hospital outcomes in older in-patients: a multicentre, observational study.* PLoS One, 2014. **9**(12): p. e115413.
35. Incalzi, R.A., et al., *The interaction between age and comorbidity contributes to predicting the mortality of geriatric patients in the acute-care hospital.* J Intern Med, 1997. **242**: p. 291-298.
36. Herrlinger, C. and U. Klotz, *Drug metabolism and drug interactions in the elderly.* Best Pract Res Clin Gastroenterol, 2001. **15**(6): p. 897-918.
37. Kinirons, M.T. and M.S. O'Mahony, *Drug metabolism and ageing.* Br J Clin Pharmacol, 2004. **57**(5): p. 540-4.
38. Le Couteur, D.G., et al., *Pseudocapillarization and associated energy limitation in the aged rat liver.* Hepatology, 2001. **33**(3): p. 537-43.
39. Bowie, M.W. and P.W. Slattum, *Pharmacodynamics in older adults: a review.* Am J Geriatr Pharmacother, 2007. **5**(3): p. 263-303.
40. Weber, U., et al., *Intravenous lidocaine increases the depth of anaesthesia of propofol for skin incision - a randomised controlled trial.* Acta Anaesthesiol Scand, 2015.
41. Kazama, T., et al., *Optimal propofol plasma concentration during upper gastrointestinal endoscopy in young, midde-aged and elderly patients.* Anesthesiology, 2000. **93**(3): p. 662-669.
42. Schnider, T.W., et al., *The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers.* Anesthesiology, 1998. **88**(5): p. 1170-1182.
43. Schnider, T.W., et al., *The influence of age on propofol pharmacodynamics.* Anesthesiology, 1999. **90**: p. 1502-1516.
44. Vuyk, J., E. Sitsen, and M. Reekers, *Intravenous Anesthetics*, in *Miller's Anesthesia, Eigth Edition*, R. Miller, Editor. 2015, Saunders: Philadelphia, PA.
45. Albrecht, S., et al., *The effect of age on the pharmacokinetics and pharmacodynamics of midazolam.* Clinical Pharmacology & Therapeutics, 1999. **65**(6): p. 630-639.
46. Platten, H.P., et al., *Pharmacokinetics and the pharmacodynamic action of midazolam in young and elderly patients undergoing tooth extraction.* Clin Pharmacol Ther, 1998. **63**(5): p. 552-560.
47. Jacobs, J.R., et al., *Aging increasing pharmacodynamic sensitivity to the hypnotic effects of midazolam.* Anesth Analg, 1995. **80**(1): p. 143-148.
48. Maitre, P.O., et al., *A three-step approach combining Bayesian regression and NONMEM population analysis: application to midazolam.* J Pharmacokinet Biopharm, 1991. **19**(4): p. 377-384.
49. Bell, G.D., et al., *Intravenous midazolam for upper GI endoscopy: A study of 800 consecutive cases relating dose to age and sex of patient.* Br J Clin Pharmac, 1987. **23**: p. 241-243.
50. Scott, J.C., K.V. Ponganis, and D.R. Stanski, *EEG quantification of narcotic effect: the comparative pharmacodynamics of fentanyl and alfentanil.* Anesthesiology, 1985. **62**(3): p. 234-241.

51. Scott, J.C. and D.R. Stanski, *Decreased fentanyl and alfentanil dose requirements with age: a simultaneous pharmacokinetic and pharmacodynamic evaluation.* J Pharmacol Exp Ther, 1987. **240**(1): p. 159-166.
52. Singleton, M.A., J.I. Rosen, and D.M. Fisher, *Pharmacokinetics of fentanyl in the elderly.* Br J Anaesth, 1988. **60**(6): p. 619-622.
53. Minto, C.F., et al., *Influence of age and gender on the pharmacodynamics of remifentanil.* Anesthesiology, 1997. **86**: p. 10-23.
54. Schafer, S.L., *The pharmacology of anesthetic drugs in elderly patients.* Anesthesiol Clin North America, 2000. **18**(1): p. 1-29.
55. Fukuda, K., *Opioid Analgesics*, in *Miller's Anesthesia, Eighth Edition*, R. Miller, Editor. 2015, Saunders: Philadelphia, PA.
56. Koo, C.Y., et al., *A Meta-analysis of the Predictive Accuracy of Postoperative Mortality Using the American Society of Anesthesiologists' Physical Status Classification System.* World J Surg, 2015. **39**(1): p. 88-103.
57. Davenport, D.L., et al., *National Surgical Quality Improvement Program (NSQIP) risk factors can be used to validate American Society of Anesthesiologists Physical Status Classification (ASA PS) levels.* Ann Surg, 2006. **243**(5): p. 636-41; discussion 641-4.
58. McCleane, G.J., D.F. Fogarty, and C.H. Watters, *Factors that influence the induction dose of propofol.* Anaesthesia, 1991. **46**: p. 59-61.
59. Monk, T.G., et al., *Anesthetic management and one-year mortality after noncardiac surgery.* Anesth Analg, 2005. **100**(1): p. 4-10.
60. McDonald, M.R., et al., *Predictive factors of hospital length of stay in patients with operatively treated ankle fractures.* J Orthop Traumatol, 2014. **15**(4): p. 255-8.
61. Reich, D.L., et al., *Predictors of hypotension after induction of general anesthesia.* Anesth Analg, 2005. **101**(3): p. 622-8, table of contents.
62. Eleveld, D.J., et al., *A general purpose pharmacokinetic model for propofol.* Anesth Analg, 2014. **118**(6): p. 1221-37.
63. Bing, V.Z.J., J. Heng, and S. Akhtar, *Anesthetic induction dosing in patients undergoing ambulatory gastrointestinal procedures: are we overdosing the elderly*, in *Anesthesiology 2014 Annual Meeting*. 2014: New Orleans, LA.
64. McClune, S., et al., *Synergistic interaction between midazolam and propofol.* Br J Anaesth, 1992. **69**: p. 240-245.
65. Smith, C., et al., *The interaction of fentanyl on the cp50 of propofol for loss of consciousness and skin incision.* Anesthesiology, 1994. **81**: p. 820-828.
66. Vuyk, J., et al., *Pharmacodynamic interaction between propofol and alfentanil when given for induction of anesthesia.* Anesthesiology, 1996. **84**: p. 288-299.
67. Cressey, D.M., et al., *Effect of Midazolam pretreatment on induction dose requirements of propofol in combination with fentanyl in younger and older adults.* Anaesthesia, 2001. **56**(108-113).
68. Folkow, B. and A. Svanborg, *Physiology of cardiovascular aging.* Physiol Rev, 1993. **73**(4): p. 725-764.
69. Forrest, J.B., et al., *Multicenter study of general anesthesia III: predictors of severe perioperative adverse outcomes.* Anesthesiology, 1992. **76**(1): p. 3-15.

70. Chan, V.W.S. and F.F. Chung, *Propofol infusion for induction and maintenance of anesthesia in elderly partients: recovery and hemodynamic profiles.* J Clin Anesth, 1996. **8**: p. 317-323.
71. Claeys, M.A., E. Gepts, and F. Camu, *Hameodynamic changes during anaesthesia induced and maintained with propofol.* Br J Anaesth, 1988. **60**(3-9).
72. McCollum, J.S. and J.W. Dundee, *Comparison of induction characteristics of four intravenous anaesthetic agents.* Anaesthesia, 1986. **41**(10): p. 995-1000.
73. Jain, U., et al., *Electrocardiographic and hemodynamic changes and their association with myocardial infarction during coronary artery byass surgery: a multicenter study.* Anesthesiology, 1997. **86**(3): p. 576-591.
74. Walsh, M., et al., *Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery.* Anesthesiology, 2013. **119**(3): p. 507-515.
75. Prys-Roberts, C., et al., *Studies on anaesthesia in relation to hypertension II: Haemodynamic consequences of induction and endotracheal intubation.* Br J Anaesth, 1998. **80**: p. 106-122.
76. Channaiah, V.B., et al., *Attenuation of Hemodynamic Response to Laryngoscopy and Endotracheal Intubation with Pre Induction IV Fentanyl Versus Combination of IV Fentanyl and Sub Lingual Nitroglycerin Spray.* Med Arch, 2014. **68**(5): p. 339-44.
77. Safavi, M., A. Honarmand, and N. Azari, *Attenuation of the Pressor Response to Tracheal Intubation in Severe Preeclampsia: Relative Efficacies of Nitroglycerine Infusion, Sublingual Nifedipine, and Intravenous Hydralazine.* Anesthesiology and Pain Medicine, 2011. **1**(2).
78. Bullington, J., et al., *The effect of advancing age on the sympathetic response to laryngoscopy and tracheal intubation.* Anesth Analg, 1989. **68**: p. 603-608.
79. Ismail, S., S.I. Azam, and F.A. Khan, *Effect of age on haemodynamic response to tracheal intubation. A comparison of young, middle-aged and elderly patients.* Anaesth Intensive Care, 2002. **30**: p. 608-614.
80. Phillips, A.T., et al. *Propofol induction and aging: are we routinely overdosing our patients, and with what effect?* in *American Geriatrics Society Annual Scientific Meeting*. 2012. Seattle, WA.
81. Sullivan, S.E., et al., *Induction doses for geriatric patients, do we routinely overdose our patients?*, in *Anesthesiology 2003 Annual Meeting*. 2003: San Francisco, CA.
82. Heng, J., G. Rodriguez, and S. Akhtar, *Intravenous induction dosing in the elderly: need for improvement*, in *Anesthesiology 2014 Annual Meeting*. 2014: New Orleans, LA.
83. Peacock, J.E., et al., *Infusion of propofol to identify smallest effective doses for induction of anaesthesia in young and elderly patients.* Br J Anaesth, 1992. **69**(4): p. 363-367.