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Research Article

Intravenous Midazolam is Safe during Outpatient Endoscopic Procedures regardless of Concurrent Enzyme-Inhibiting Medications

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Abstract

Study Objective: Intravenous (IV) midazolam is widely used for sedation during brief medical procedures. Existing literature indicates concern for potential excessive sedation or respiratory compromise when midazolam is administered to individuals concurrently taking CYP3A4 enzyme inhibiting medications. The aim of this study was to evaluate the safety of moderate sedation with IV midazolam during outpatient endoscopic procedures in patients taking concurrent CYP3A4 inhibitors.

Design: Retrospective cohort study

Setting: Outpatient endoscopy center at an academic institution between October 2011-December 2014.

Patients: Adult patients (≥ 18 years) receiving IV midazolam during an outpatient endoscopic procedure.

Measurements and main results: Outcome measures included standard intra-operative patient monitoring parameters and post-procedure recovery time. We compared patients taking CYP3A4 inhibitors (inclusion group) to patients without inhibitors (control).Propensity score matching yielded 490 matched patient pairs with noninferiority testing performed. We demonstrated outcome on inferiority of the inclusion group compared to controls (p-value of < 0.025) for comparisons of all intra-operative vital signs. Supplemental oxygen actually was necessitated more frequently by the control group (7.0%vs. 8.5% requiring> 2 liter/minute, $p < 0.001$). Univariate analyses between control group and inclusion group also revealed a tiny but statistically significant difference in total midazolam dose. Finally, we expected and found an increase in post-procedure recovery time for the enzyme-inhibited group compared to patients not taking CYP3A4 inhibitors (76.0 vs. 66.5 minutes) due to reduced midazolam clearance.

Conclusion: IV midazolam can be administered safely during outpatient endoscopic procedures without altering home medication regimen, midazolam dose, or standard dose titration methods in patients taking CYP3A4 inhibiting medications.

INTRODUCTION

Single intravenous (IV) dose or titrated IV bolus midazolam is widely used in combination with other drugs for carefully monitored sedation during brief medical procedures [1]. Orally-administered midazolam is metabolized by cytochrome P450 (CYP) 3A4 isozymes in the gut wall, controlling its bioavailability. Orally and intravenously administered midazolam is metabolized in liver the same (CYP) 3A4 isozymes, dictating its clearance, biologic half life, and duration of action. The CYP 3A4 system is vulnerable to many drug-drug interactions that change oral bioavailability and systemic clearance. Enzyme inhibition increases the bioavailability of oral CYP3A4 substrate medications and decreases the systemic clearance of both oral and intravenous CYP3A4 substrate drugs. Concern has been expressed that patients taking CYP3A4 inhibiting drugs may

experience increases in plasma midazolam concentration and consequent over sedation if midazolam dose is not reduced during endoscopic procedures [2]. In response to concerns about midazolam-associated prolonged sedation, the United States Food and Drug Administration (FDA) asserts that nelfinavir and fosamprenavir actually are contraindicated with either intravenous or oral midazolam, while only oral midazolam is contraindicated with lopinavir-ritonavir, saquinavir-ritonavir and indinavir-tipranavir combinations, as well as with atazanavir and darunavir [3-6]. The concern about toxicity and the FDA contraindication is of profound import to both patients' essential medication regimens and the endoscopists' choice of sedative and midazolam dose.

Oral midazolam is not used in the US for conscious sedation so enzyme inhibition could never increase bioavailability, or effective dose because bioavailability of an IV medication is always 100 percent. Inhibition of a liver enzyme system responsible for clearance of the IV dose however, clearly can prolong the duration of drug effect. Given the frequency with which patients who take a wide variety of enzyme inhibiting medications undergo endoscopic procedures, and considering the potential consequences of either failing to recognize or responding inappropriately to a drug interaction, we believed that a definitive investigation of the issue was essential. While our objective was to directly address previously-published literature concerning enzyme inhibitors and midazolam, it is important to remember that CYP3A4 inhibitors can also change the clearance of many other drugs cleared by CYP3A [7]. Fentanyl for instance, is also a CYP 3A4 substrate frequently given concurrently with midazolam during endoscopic interventions, and the combination of an opiate (fentanyl) with benzodiazepine (midazolam) can result in respiratory compromise [8]. Indeed, existing literature has claimed to identify respiratory compromise and excessive sedation as complications when midazolam is administered to individuals actively taking enzyme-inhibiting medications [9,10]. A recent study evaluated HIV-positive patients taking CYP3A4 inhibiting anti-retroviral drugs, who received IV midazolam for sedation during inpatient bronchoscopy. Compared to HIV patients not taking CYP3A4 inhibitors, the inclusion (enzyme-inhibited) group had severely prolonged sedation that was defined as greater than 90 minutes [10].

These findings and concerns have widely influenced endoscopic practice guidelines in patients taking CYP 3A4 inhibitors. The result has been modification of standard medication-administration protocols to recommend alternative, more expensive, less hemodynamically predictable sedatives in patients taking CYP 3A4 inhibitors. While previous studies appear to have identified over-sedation in enzyme-inhibited patients receiving intravenous midazolam, the pharmacokinetics of single or titrated bolus intravenous midazolam indicate there should be no increased magnitude of midazolam effect in patients receiving CYP3A4 inhibitors. Therefore, the aim of this study was to assess the safety profile of IV midazolam for outpatient endoscopic procedures in a large, real-world cohort of patients already taking commonly prescribed CYP3A4 inhibitors.

MATERIAL AND METHODS

Study design and patient population

The Ohio State University Institutional Review Board approved this retrospective cohort analysis. None of the investigators have any conflicts of interest. A query of the electronic health record (EHR) database was performed for the period October 2011-December 2014. All adult patients at the institution (≥ 18 years of age) who had an outpatient endoscopic procedure and received at least one dose of IV midazolam intra-operatively were included. Patients who received IV midazolam intra-operatively were stratified into either the inclusion group (currently taking CYP3A4 inhibitors) or control group (not taking a concurrent inhibitor) (Figure 1). Propensity score matching then was performed between the two groups to ensure that no statistically significant differences in patient demographics or midazolam doses administered were present. Exclusion criteria included no IV midazolam use, inpatient or emergency room procedures, early procedure termination (i.e. poor colon preparation), utility of monitored anesthesia care, and the presence of a concurrent medication know known to be a CYP3A4 enzyme-inducer.

Data collection

De-identified patient data were extracted through The Ohio State University Medical Center EHR system. This data was subsequently merged with an endoscopic EHR that was able to capture indicators of midazolam effect such as level of consciousness, intra-operative blood pressure, respiratory rate, heart rate, oxygen requirement, oxygen saturation, and post-procedure recovery time. Level of consciousness was objectively assessed using the Richmond Agitation-Sedation Scale (0-4: 0 alert/calm, 1 drowsy, 2 light sedation, 3 moderate sedation, 4 deep sedation). Control patients values were then compared to case (enzyme-inhibited) patients, and the ensuing propensity score matching ultimately paired 490 patients in each group (Figure 1).

Outcomes measures

Intra-operative vital signs, maximum supplemental oxygen requirement, nadir level of consciousness (LOC), and post-procedure recovery time were recorded and analyzed.

Noninferiority study

Our primary hypothesis was that, based upon the pharmacokinetic behavior of single or brief, titrated-to-effect dosing of IV midazolam in the setting of presumed reduced systemic midazolam clearance, magnitude-of-effect outcomes for the inclusion group (patients taking CYP3A4 inhibitors) would not be inferior to (worse than) those in the control group. Noninferiority testing was performed with a significant result ($p < 0.025$) indicating that indeed the inclusion groups' parameters were statistically noninferior to the control groups', an important distinction when interpreting the results section.

Statistical analysis

In order to account for differences in patient characteristics that might affect patient response to or metabolism of midazolam, propensity score matching was used to select inclusion and control patients with balanced characteristics. Propensity scores were estimated using a logistic regression model for probability of CYP3A4 inhibition that included age at procedure, sex, race, BMI, midazolam and fentanyl doses, morbid obesity, and multiple

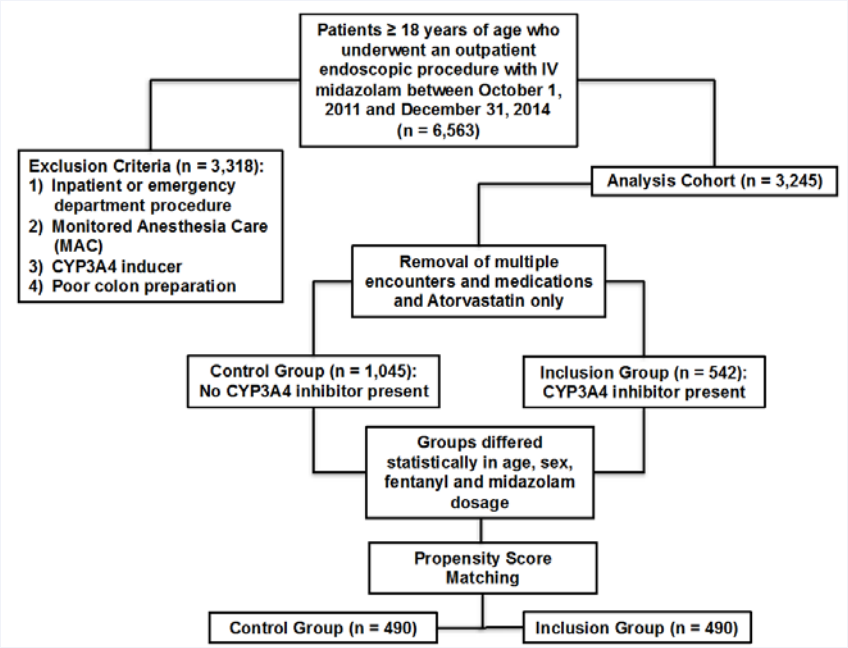

Figure 1 Flowsheet of inclusion and exclusion criteria and of inclusion and control groups after propensity score matching.

co-morbidities. An optimal matching algorithm was used to match inclusion and control patients (vmatch macro) [11], with a caliper of two times the standard error of the logit. Patients not optimally matched within this caliper were excluded.

Demographics and medical conditions were compared between groups accounting for the matching by using paired t-tests for continuous and McNemar tests for categorical variables. Lab values available for the majority of patients were compared by Wilcox on signed rank tests.

A noninferiority testing strategy was employed with noninferiority margins set a priori: a margin of 10% of the control group mean for the difference in means continuous outcomes (i.e. nadir systolic blood pressure (SBP) 115.2 mmHg x 0.1 margin of 11.52 mmHg) (Figure 2) and a margin of 5% for difference in percentages for dichotomous outcomes (i.e. maximum oxygen requirement > 2L). Once margins were specifically determined based on the a priori criteria, the difference in group means and the corresponding 95% confidence interval were obtained. P-values were obtained using one-sided tests evaluated at the $\alpha = 0.025$ significance level as recommended in Piaggio et al. [12]. Differences in continuous variables were tested by one-sided t-tests and risk differences for dichotomous variables utilized Farrington-Manning confidence intervals [13]. A p-value less than 0.025 indicates a non-inferiority conclusion and corresponds to a 95% confidence interval for the difference completely within the noninferiority margin. For the recovery time outcome standard tests for differences (paired t-tests for continuous variables and Fisher's exact test for categorical variables) were also performed as follow-up tests.

The noninferiority testing approach was appropriate to the hypotheses. In order to make a strong conclusion of noninferiority, a noninferiority test must be used and the null hypothesis of inferiority must be rejected with a significant p-value. The approach of using "traditional" tests for comparing differences, and then concluding equivalence or noninferiority if the p-values are non-significant actually would have been erroneous. The tests could easily be non-significant due to lack of power from an inadequate sample size. To reach a conclusion of actual noninferiority (outcomes not worse than), positive evidence reflected in a significant noninferiority test result is required rather than simply the lack of evidence of a difference from traditional tests [14,15].

Secondary analyses included comparing outcomes for two subgroups: inclusion group versus controls stratified by colonoscopy or EGD and inclusion patients taking HIV medications versus controls. The comparisons were performed by noninferiority test in the same manner as the primary outcomes. Midazolam dose and fentanyl dose are also reported for these subgroups.

RESULTS

The initial univariate analysis identified small but statistically significant differences in age, sex, fentanyl and midazolam doses between the inclusion group and the control group. Subsequent propensity score matching eliminated differences by pairing 490 patients each from inclusion and control group with no statistically significant in age, sex, race, BMI, co-morbidities, midazolam dose, or fentanyl dose (Supplemental Table 1). Additionally, there was no statistical difference between the groups in the lab values serum creatinine, INR, or total bilirubin. Table 1 outlines the breakdown of all inclusion drugs utilized in this study and delineates them into strong, moderate, and weak inhibitors. By using a well-documented classification system, we performed multiple analyses based on inhibitor strength.

Noninferiority testing for all inhibitor strengths

It is important to note that in an noninferiority study, a

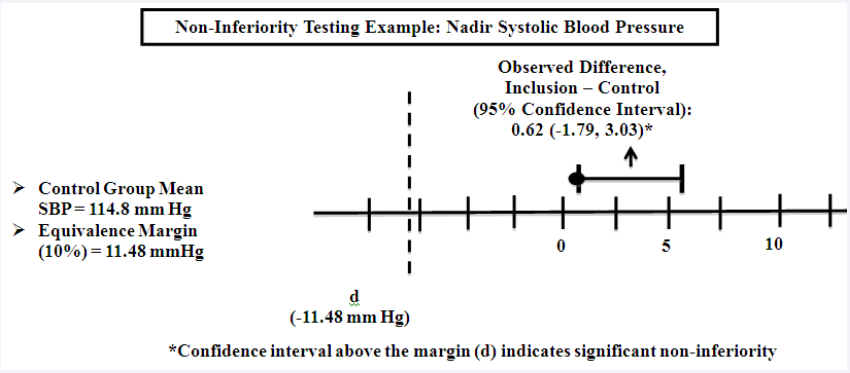

Figure 2 Illustration of noninferiority testing between inclusion and control systolic blood pressures. A confidence interval within the noninferiority margin indicates significant the inclusion group is not inferior to the controls.

statistically significant p-value (p <0.025 in the current study) is indicative of noninferiority (outcome no worse than) as the underlying premise is to show current therapy (CPY3A4 inhibitors) is not inferior (i.e. equal or superior) to patients receiving no CYP3A4 inhibitor (Figure 2). Outcome measures of interest included intra-operative vital signs (SBP, heart rate, respiration rate, oxygen saturation, supplemental oxygen requirement, and level of consciousness) and post-procedural recovery time (Table 2). The noninferiority tests resulted in conclusions of significant noninferiority of the inclusion group relative to controls for intra-operative vital signs including maximum HR (84.9 vs. 84.0, p < 0.001), maximum respiratory rate (30.0 vs. 30.8, p < 0.001), nadir oxygen saturation < 93% (15.6% vs. 18.0%, p = 0.001), maximum oxygen requirement> 2 L (7.0% vs. 8.5%, p < 0.001), and nadir level of consciousness > 1 (48.2% vs. 50.6%, p = 0.01). Furthermore, there was clearly an expected increase in post-procedure recovery time for the inclusion group (76.0 vs. 66.5 minutes, noninferiority p =0.79; paired t-test p = 0.006 indicated significant group differences).

Noninferiority testing for moderate and severe strength inhibitors

Weak enzyme inhibitors were excluded in subsequent analyses and the inclusion cohort was further stratified based on inhibitor strength (moderate or strong enzyme inhibition). Table 3 outlines noninferiority testing for both moderate and strong inhibitors versus the control population. Here we show noninferiority for nearly all intra-operative vitals including maximum HR (85.2 vs. 83.8, p < 0.001), respiratory rate (29.5 vs. 30.4, p < 0.001), maximum oxygen requirement (6.2% vs. 8.3%, p < 0.001), and nadir level of consciousness (47.9% vs. 51.8%, p = 0.007). Nadir oxygen saturation just missed a noninferiority conclusion at the α = 0.025 significance level (16.2% vs. 16.2%, p = 0.03). As for the full set of inclusion drugs, recovery time was significantly longer for patients taking strong or moderate inhibitors compared to controls (paired t-test p = 0.027).

Our next analysis compared only patients taking strong inhibitors with control individuals because strong enzyme inhibitors reduce drug clearance most and are most likely to cause changes the effect of a target drug. Again, we found noninferiority for nadir SBP, maximum heart rate, maximum respiratory rate, nadir oxygen saturation, maximum oxygen requirement, and nadir level of consciousness (ps< 0.025, Table 4). Noninferiority was not concluded for recovery time (70.6 vs. 71.0, p = 0.88).

Of note, we attempted to perform an analysis of patients taking multiple inclusion drugs; however, only 30 patients were concurrently taking more than one CYP3A4 inhibitor.

HIV population

Patients in this study took combinations of nine different HIV medications classified as CYP3A4 inhibitors. Because previous literature has identified HIV patients as of particular concern for clinically-significant interactions with midazolam, we performed a sub-analysis on this population (n = 56) compared to controls (n = 1045) and found noninferiority for all outcomes except nadir oxygen saturation (12.5% vs. 16.2%, p = 0.06) favoring the inclusion group, and nadir level of consciousness (55.4% vs. 52.5%, p = 0.38), slightly deeper in the inclusion group, and recovery time (74.1 vs. 71.0 minutes, p = 0.29), which was clearly longer in the includion group (Supplemental Table 2). Of note, 35 out of 56 patients (62.5%) were taking multiple HIV medications at time of procedure.

Colonoscopy vs. Esophagogastroduodenoscopy

Outcomes were subsequently separated by procedure type, colonoscopy versus EGD, to determine any possible influence of the type of endoscopic intervention on the results (Supplementary Table 3). ERCP, EUS, push enteroscopy, and flexible sigmoidoscopy were not included in this sub-analysis. In terms of EGD procedures, the inclusion group (n = 422) compared to the control group (n = 373) showed statistically noninferior findings for SBP, HR, and maximum oxygen requirement (4.9% vs. 4.5%, p = 0.01). Interestingly, statistical noninferiority was not concluded for nadir oxygen saturation (14.2% vs. 12.1%, p = 0.16) or maximum respiratory rate (29.3 vs. 28.1, p = 0.11). Of note, it is not possible to form conclusions regarding recovery time for the EGD group given the small sample size (3 inclusion patients vs. 8 control patients). When looking at colonoscopies alone, the inclusion group (283 patients) compared to the control group (649 patients) showed noninferiority for SBP, HR, and respiratory rate (ps< 0.001), nadir oxygen requirement (56.3% vs. 57.3%, p = 0.003), and maximum oxygen requirement (7.3% vs 10.4%, p <0.001). Finally, nadir level of consciousness (58.0% vs. 57.3%, p = 0.11) and recovery time (75.2 vs. 70.5 minutes, p = 0.22) did not result in conclusions of noninferiority.

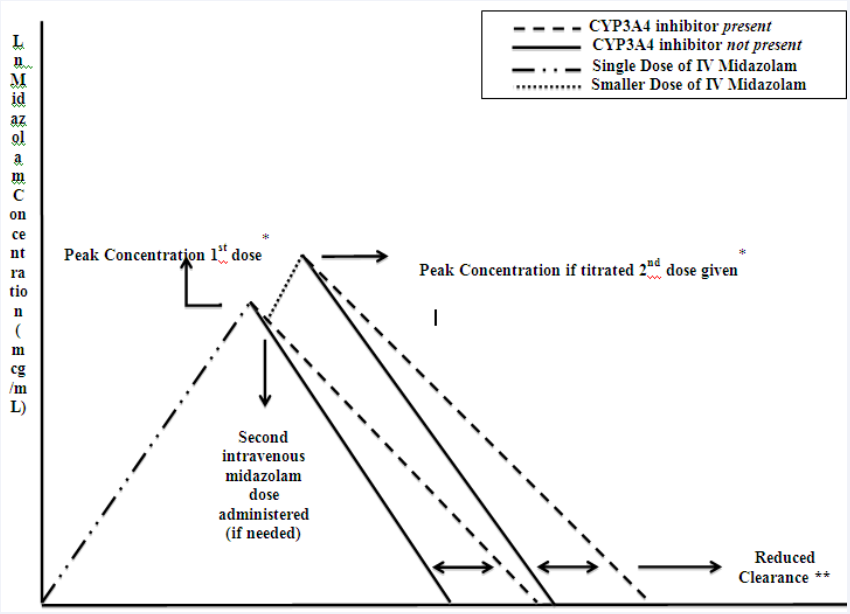

Figure 3 IV Midazolam pharmacokinetics showing how peak concentration influences intra-operative outcomes and reduced clearance influences post-procedural outcomes. *Peak concentrations influence intensity of sedation **Clearance influences elimination and determines duration of sedation.

Table 1: Breakdown of all inclusion drugs (n=542 patients).

Inclusion Drug [a]	Number of Patients
Strong Inhibitors (121)	
CLARITHROMYCIN	50
RITONAVIR	35
DARUNAVIR	23
ITRACONAZOLE	8
LOPINAVIR-RITONAVIR	3
KETOCONAZOLE	2
Moderate Inhibitors (341)	
DILTIAZEM	142
FLUCONAZOLE	131
VERAPAMIL	49
ERYTHROMYCIN	19
Weak Inhibitors (136)	
CYCLOSPORINE	37
RANOLAZINE	26
OLANZAPINE	13
ATAZANAVIR	13
FLUVOXAMINE	11
AMLODIPINE	10
SIMEPREVIR	8
EFAVIRENZ	4
VORICONAZOLE	4
POSACONAZOLE	3
FOSAMPRENAVIR	2
OLANZAPINE-FLUOXETINE	2
BOCEPREVIR	1
EZETIMIBE-ATORVASTATIN	1
TELAPREVIR	1

a: Patients with multiple inclusion drugs counted once for each drug

Midazolam and fentanyl dosing in sub-analysis groups

Because the sub-analysis groups (procedure type, multiple inclusion drugs, and HIV medications) were not propensity score matched, there were small absolute differences in midazolam and fentanyl dosages; however, we believe it is highly unlikely that the very few microgram difference in doses between groups resulted in either measurably deeper or detectably prolonged sedation in the inclusion group.

DISCUSSION

In this study we utilized noninferiority testing to definitively demonstrate that IV midazolam can be safely used with or without fentanyl in patients who are actively taking CYP3A4 inhibitors during brief outpatient endoscopic procedures ,and that no adjustment to home medications or standard midazolam titration methods are necessary. These results are in contrast to prior findings that suggest patients taking concurrent CYP3A4 inhibitors experienced more severely-depressed level of conscious [9,10]. Our findings are distinguishable from previous studies because we selectively focused on outpatient endoscopic procedures. This allowed us to eliminate the many confounding factors involved in hospitalizations that could influence both intra-operative outcomes such as sepsis-induced tachycardia or pneumonia related oxygen requirement and post-procedural outcomes including transportation delaying reported recovery time.

Midazolam is metabolized to functionally inactive metabolites by both gut and liver cytochrome P450 3A4 enzymatic activity [16]. The FDA has appropriately recommended against using oral midazolam in the setting of several CYP3A4 inhibitors including atazanavir, darunavir, and ritnonavir as its bioavailability could be substantially increased [3-5]. When gut wall CYP3A4 activity is strongly inhibited, orally administered midazolam exposure

Table 2: Propensity matched outcomes by inclusion status with noninferiority for all inhibitors.

Outcome	Inclusion Group (n=490)	Control Group (n=490)	Noninferiority Margin[a]	Observed difference in means or proportions [inclusion-control]	Noninferiority
Nadir SBP, mean (95% CI)	115.3 (113.6, 117.0)	114.8 (113.2, 116.3)	-11.48	0.62 (-1.79, 3.03)	<0.001
Maximum heart rate, mean (95% CI)	84.9 (83.4, 86.4)	84.0 (82.6, 85.5)	8.4	0.82 (-1.33, 2.97)	<0.001
Minimum heart rate, mean (95% CI)	68.5 (67.3, 69.7)	67.5 (66.4, 68.6)	-6.75	0.97 (-0.63, 2.57)	<0.001
Maximum respiratory rate, mean (95% CI)	30.0 (28.7, 31.3)	30.8 (29.3, 32.2)	3.08	-0.71 (-2.64, 1.22)	<0.001
Nadir oxygen saturation, <93	76/488 (15.6%)	88 /488	5%	-2.50%	0.001
Maximum oxygen requirement, >2L	28/400 (7.0%)	34/400	5%	-1.50%	<0.001
Nadir level of consciousness(max score), >1	235/488 (48.2%)	247/488 (50.6%)	5%	-2.50%	0.01
Recovery time (scope out to recovery care complete), minutes, mean (95% CI)	76.0 (70.4, 81.5) [c]	66.5 (62.6, 70.4) [c]	6.65	9.45 (2.70, 16.21)	0.79 [d]

a: Noninferiority margin: 10% of control group mean for continuous outcomes; 5% difference in proportions for dichotomous outcomes.
b: A significant result ($p < 0.025$) yields the conclusion that the inclusion group is not inferior to the control group for this outcome.
c: n=150 matched pairs
d: standard test for differences indicates significant difference, $p = 0.006$

Table 3: Propensity matched outcomes by inclusion status with noninferiorityfor moderate and strong inhibitors.

Outcome	Inclusion Group (n=386)	Control Group (n=386)	Noninferiority Margin[a]	Observed difference in means or proportions [inclusion-control]	Noninferiority
Nadir SBP, mean (95% CI)	115.8 (113.9, 117.7)	114.5 (112.7, 116.3)	-11.45	1.36 (-1.36, 4.08)	<0.001
Maximum heart rate, mean (95% CI)	85.2 (83.5, 87.0)	83.8 (82.2, 85.4)	8.38	1.44 (-1.03, 3.91)	<0.001
Minimum heart rate, mean (95% CI)	68.4 (67.1, 69.7)	67.1 (65.9, 68.3)	-6.71	1.25 (-0.58, 3.08)	<0.001
Maximum respiratory rate, mean (95% CI)	29.5 (28.1, 30.9)	30.4 (29.0, 31.9)	3.04	-0.87 (-2.93, 1.19)	<0.001
Nadir oxygen saturation, <93	62/384	62/384	5%	0.00%	0.03
Maximum oxygen requirement, >2L	20/308 (6.5%)	26/308 (8.4%)	5%	-2.00%	<0.001
Nadir level of consciousness	184/384(47.9%)	199/384	5%	-3.90%	0.007
Recovery time (scope out to recovery care complete), minutes, mean (95% CI)	76.7 (70.6, 82.8)[c]	68.0 (63.3, 72.6)[c]	6.8	8.7 (1.0, 16.4)	0.31 [d]

a: Noninferiority margin: 10% of control group mean for continuous outcomes; 5% difference in proportions for dichotomous outcomes.
b: A significant result ($p < 0.025$) yields the conclusion that the inclusion group is not inferior to the control group for this outcome.
c: n=121 matched pairs
d: standard test for differences indicates significant difference, $p = 0.027$

increases as much as 16-fold, owing to diminishment of gut wall enzymes that prevent systemic drug absorption (bioavailability) in addition to diminished systemic drug clearance via liver enzymes. On the other hand, when midazolam is administered intravenously to individuals whose CYP3A4 activity is inhibited, midazolam total exposure increases only 5-fold because the contribution of gut-wall metabolism has been bypassed [3]. Of note, this 5-fold increased exposure is entirely attributable to prolonged elimination (clearance) caused by the presence of CYP3A4 inhibitors. This situation results in prolonged duration of drug effect without any increase in magnitude of drug effect. Figure 3 illustrates how concurrent CYP3A4 inhibition influences IV midazolam peak concentration (intra-operative depth of sedation) and half-life (post-procedural duration of sedation) after both single and multiple IV doses titrated carefully to effect and then discontinued.

Intra-operative outcomes including procedural vital signs, level of consciousness, and oxygen requirement were compared in the propensity-matched groups. From a pharmacodynamic standpoint, the peak drug concentration will have the most significant influence magnitude of drug effect and hence, on these outcomes measures. Higher peak drug concentrations cause augmented drug effect and/or side effects, with low concentrations resulting in potentially inadequate drug effect as well as lack of adverse effects. In a brief procedure situation, drug dose is titrated to peak effect which, in the case of midazolam, is sedation. When sedation is adequate, further doses are not given. If sedation is inadequate, further, small bolus doses are administered until the desired magnitude of effect is achieved; endoscopists titrate intravenous midazolam to effect and then do not administer more. It is important to emphasize that if midazolam were administered orally, increased bioavailability would be a tremendous concern if taken with an enzyme inhibitor. If midazolam, administered to a patient taking an enzyme inhibitor is given on a scheduled basis, or by continuous infusion, accumulation and dangerous over-sedation would absolutely occur in patients taking concurrent CYP 3A4 inhibitors.

Another important aspect of moderate sedation is the utility of fentanyl in the setting of midazolam. Previous literature has documented that the synergy of utilizing a benzodiazepine and opioid has resulted in increased incidence of hypoxemia and apnea [8]. Moreover, similar to midazolam the mechanism of systemic clearance of fentanyl is also through the CYP3A4 pathway. Our analysis was performed to propensity match both midazolam and fentanyl between the inclusion and control groups, allowing us to also comment on fentanyl utility in endoscopic interventions. Our results suggest that even when combining multiple intravenous sedative agents, no excessive drug effect should occur even in an enzyme-inhibited patient.

An expected finding of our study was that post-procedure recovery time was not determined to be statistically noninferior for the inclusion group; rather, recovery time was significantly longer in the inclusion group. CYP3A4 inhibitors are expected to prolong the duration of pharmacologic effect, which is consistent with the inclusion arm having longer post-procedure recovery time. However, our results do not suggest clinical ramifications on patients who certainly experienced prolongations of plasma midazolam half-life.

Our results also included outcome analysis for 56 HIV-positive patients actively taking protease inhibitors. This sub-analysis was performed to ensure our findings could be directly correlated to existing literature. An inclusion population of 56 HIV-positive patients was similar to previous studies with 51 and 70 HIV-positive patients in their inclusion arms, respectively [9,10]. Our results indicate noninferiority in nearly all parameters for HIV-positive patients taking protease inhibitors concurrent with receiving IV midazolam. The exceptions were nadir oxygen saturation (12.5% vs. 16.2%), nadir level of consciousness (55.4% vs. 52.5%) and recovery time (74.1 vs. 71.0 minutes). Although there was not sufficient evidence to conclude noninferiority for these three outcomes, the minor clinical differences observed between groups should not warrant changes in practice guidelines.

This study had several limitations. This is a retrospective study and carries inherent possibility of confounding variables including inaccurate medication history at the time of endoscopy. Furthermore, our sub-analyses (restricting to strong/moderate and strong only inhibitors, procedure type, and HIV medication) were limited by sample size and future adequately powered studies are warranted to establish noninferiority in outcomes. We also cannot exclude variation in results from previous studies due to endoscopic procedures performed in a controlled

Table 4: Propensity matched outcomes by inclusion status with noninferiority for strong inhibitors.

Outcome	Inclusion Group (n=87)	Control Group (n=87)	Noninferiority Margin[a]	Observed difference in means or proportions [inclusion-control]	Noninferiority
Nadir SBP, mean (95% CI)	111.1 (107.9, 114.4)	114.2 (110.5, 118.0)	-11.42	-3.09 (-8.29, 2.10)	0.001
Maximum heart rate, mean (95% CI)	84.7 (81.2, 88.3)	82.9 (79.7, 86.1)	8.29	1.66 (-3.67, 7.00)	0.008
Minimum heart rate, mean (95% CI)	68.1 (65.8, 70.4)	67.5 (64.8, 70.2)	-6.75	0.48 (-3.17, 4.12)	<0.001
Maximum respiratory rate, mean (95% CI)	26.6 (24.5, 28.7)	29.8 (26.9, 32.7)	2.98	-3.13 (-7.05, 0.79)	0.001
Nadir oxygen saturation, <93	Nov-86	17/86	5%	-7.00%	0.018
Maximum oxygen requirement, >2L	0/69 (0%)	4/69 (5.8%)	5%	-5.80%	0.002
Nadir level of consciousness	39/86	47/86 (54.7%)	5%	-10.50%	0.021
Recovery time (scope out to recovery care complete), minutes, mean (95% CI)	70.6 (60.0, 81.1)[c]	71.0 (61.1, 81.0)[c]	7.1	-0.5 (-13.5, 12.5)	0.88

a: Noninferiority margin: 10% of control group mean for continuous outcomes; 5% difference in proportions for dichotomous outcomes.
b: A significant result ($p < 0.025$) yields the conclusion that the inclusion group is not inferior to the control group for this outcome.
c: n=27 matched pairs

outpatient setting versus inpatient hospitalization. A prospective study will be required to address these issues.

In conclusion, we utilized noninferiority testing to show that safety outcomes using IV midazolam with concurrent CYP3A4 inhibitor therapy are not inferior compared to patients not actively taking CYP3A4 inhibitors. Our results indicate that IV midazolam can be used in the setting of CYP3A4 inhibitors during outpatient endoscopic procedures.

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Supplemental Table 1: Propensity score matched demographics, medical conditions, and lab results.

Characteristic	Inclusion Group (n=490)	Control Group	p-value
Age	55.2 (14.1)	55.6 (13.3)	0.65
Sex, Female	265 (54%)	275 (56%)	
Race			0.59
White	361 (74%)	355 (72%)	
Black	103 (21%)	117 (24%)	
Asian	8 (2%)	8 (2%)	
Other	18 (4%)	10 (2%)	
BMI	29.9 (7.8)	29.9 (7.7)	0.94
Morbid Obesity	52 (11%)	54 (11%)	0.84
Cirrhosis	78 (16%)	74 (15%)	0.66
Chronic Hep B	0 (0%)	0 (0%)	1
Chronic Hep C	30 (6%)	33 (7%)	0.68
Acute Hepatitis	12 (2%)	12 (2%)	1
CHF	47 (10%)	46 (9%)	0.91
CAD	88 (18%)	93 (19%)	0.68
MI	28 (6%)	22 (4%)	0.38
COPD	65 (13%)	63 (13%)	0.84
Asthma	80 (16%)	80 (16%)	1
Home O_2	11 (2%)	12 (2%)	0.83
Hx of Alcohol Abuse	14 (3%)	10 (2%)	0.35
Dementia	4 (1%)	4 (1%)	1
Alzheimer's Disease	4 (1%)	5 (1%)	0.74
Midazolam dose (mg)	5.08 (1.97)	5.12 (1.85)	0.75
Fentanyl dose (mcg)	116.0 (44.3)	116.1 (43.5)	0.96
Total bilirubin[a]	0.6 (0.4-0.9) n=418	0.6 (0.5-0.9) n=429	0.55
INR[a]	1.1 (1.0-1.2) n=336	1.1 (1.0-1.2) n=331	0.12
Serum Creatinine[a]	0.90 (0.73-1.12) n=455	0.87 (0.73-1.03) n=464	0.09

a: median (interquartile range)
Mean (SD) or n(%) unless otherwise noted. Continuous variables compared by paired t-test, except for lab results which were tested by Wilcoxon signed rank test; categorical variables were compared by McNemar test for paired data

Supplemental Table 2: Outcomes for inclusion cohort concurrently on HIV medication versus controls with noninferiority.

Outcome	HIV Medication (n=56)	Controls (n=1045)	Noninferiority Margin [a]	Observed difference in means or percentages [inclusion-control]	Noninferiority
Nadir SBP, mean (95% CI)	113.2 (109.1, 117.3)	114.8 (113.7, 115.9)	-11.48	-1.53 (-6.39, 3.32)	<0.001
Maximum heart rate, mean (95% CI)	82.6 (78.6, 86.7)	84.0 (83.1, 85.0)	8.4	-1.39 (-5.70, 2.92)	<0.001
Minimum heart rate, mean (95% CI)	66.9 (63.6, 70.1)	67.3 (66.6, 68.1)	-6.73	-0.44 (-3.76, 2.87)	<0.001
Maximum respiratory rate, mean (95% CI)	25.4 (22.5, 28.2)	30.7 (29.7, 31.6)	3.07	-5.30 (-9.48, 1.12)	<0.001
Nadir oxygen saturation, <93	7 (12.5%)	169 (16.2%)	5%	-3.7% (-14.5%, 7.2%)	0.06
Maximum oxygen requirement, >2	1/51 (2.0%)	76/931 (8.2%)	5%	-6.2% (-11.0%,	0.009
Nadir level of consciousness, >1	31 (55.4%)	548 (52.5%)	5%	2.9% (-10.5%, 16.3%)	0.38
Recovery time (scope out to recovery care complete), minutes, mean (95% CI)	74.1 (59.5, 88.7) [c]	71.0 (68.1, 73.9)[d]	7.1	3.1 (-11.1, 17.3)	0.29
Midazolam and Fentanyl Dosing					
Midazolam dose, mean (95% CI)	4.94 (4.51, 5.37)	5.06 (4.95, 5.17)			
Fentanyl dose, mean (95% CI)	122.3 (112.5, 132.2)	118.8 (116.1, 121.5)			

a: Noninferiority margin: 10% of control group mean for continuous outcomes; 5% difference in percentages for dichotomous outcomes.
b: A significant result ($p < 0.025$) yields the conclusion that the inclusion group is not inferior to the control group for this outcome.
c: n = 19 , d: n = 450

Supplemental Table 3: Outcomes for inclusion cohort versus controls with noninferiority separately for EGD and Colonoscopy.

EGD Outcome	Inclusion (n=246)	Control (n=373)	Nonifer Margin [a]	Observed difference in means or percentages [inclusion-control]	Noninfer
Nadir SBP, mean (95% CI)	119.3 (116.8, 121.8)	120.0 (118.1, 121.9)	-12	-0.68 (-3.78, 2.42)	<0.001
Maximum heart rate, mean (95% CI)	89.2 (86.8, 91.5)	88.2 (86.4, 90.0)	8.82	0.96 (-1.92, 3.84)	<0.001
Minimum heart rate, mean (95% CI)	70.6 (68.9, 72.3)	69.3 (68.1, 70.6)	-6.93	1.27 (-0.80, 3.22)	<0.001
Maximum respiratory rate, mean (95% CI)	29.3 (27.5, 31.2)	28.1 (26.5, 29.6)	2.8	1.26 (-1.16, 3.69)	0.11
Nadir oxygen saturation, <93	35 (14.2%)	45 (12.1%)	5%	2.2% (-3.1%, 6.5%)	0.16
Maximum oxygen requirement, >2	11/225 (4.9%)	15/335 (4.5%)	5%	0.4% (-3.2%, 4.0%)	0.01
Nadir level of consciousness (max score), >1	90/246 (36.6%)	164/372 (44.1%)	5%		0.001
Recovery time (scope out to recovery care complete), minutes, mean (95% CI)	89.0 (49.0, 129.0) [c]	82.8 (68.9, 96.6) [d]	8.28	6.2 (-19.0, 31.5)	0.43
Midazolam and Fentanyl Dosing					
Midazolam dose, mean (95% CI)	4.84 (4.59, 5.09)	4.88 (4.69, 5.06)			
Fentanyl dose, mean (95% CI)	111.1 (105.5, 116.7)	113.5 (109.0, 118.0)			
Colonoscopy Outcome	**Inclusion (n=283)**	**Controls (n=649)**	**Noninfer Margin [a]**	**Observed difference in means or percentages [inclusion-control] (95% CI)**	**Noninfer p-value b**
Nadir SBP, mean (95% CI)	113.2 (11.1, 115.3)	111.6 (111.3, 112.9)	-11.16	1.61 (-0.82, 4.03)	<0.001
Maximum heart rate, mean (95% CI)	81.1 (79.4, 82.7)	81.5 (80.4, 82.7)	8.15	-0.45 (-2.50, 1.59)	<0.001
Minimum heart rate, mean (95% CI)	66.4 (65.0, 67.9)	66.2 (65.3, 67.1)	-6.62	0.26 (-1.45, 1.98)	<0.001
Maximum respiratory rate, mean (95% CI)	30.0 (28.3, 31.6)	32.3 (31.0, 33.5)	3.23	-2.33(-4.49, -0.16)	<0.001
Nadir oxygen saturation, <93	45 (15.9%)	122 (18.8%)	5%	-2.9% (-8.0%, 2.2%)	0.003
Maximum oxygen requirement, >2	19/261 (7.3%)	60/579 (10.4%)	5%	-3.1% (-7.0%, 0.8%)	<0.001
Nadir level of consciousness (max score), >1	164 (58.0%)	372 (57.3%)	5%	0.6% (-6.3%, 7.6%)	0.11
Recovery time (scope out to recovery care complete), minutes, mean (95% CI)	75.2 (69.6, 80.8) [e]	70.5 (67.6, 73.4) [f]	7.05	4.7 (-1.3, 10.6)	0.22
Midazolam and Fentanyl Dosing					
Midazolam dose, mean (95% CI)	5.31 (5.08, 5.54)	5.15 (5.02, 5.28)			
Fentanyl dose, mean (95% CI)	119.8 (114.7, 124.9)	121.3 (117.9, 124.6)			

a: Noninferiority margin: 10% of control group mean for continuous outcomes; 5% difference in percentages for dichotomous outcomes.
b: A significant result ($p < 0.025$) yields the conclusion that the inclusion group is not inferior to the control group for this outcome.
c: n = 3 d: n = 8e:n = 146 f: n = 216