Bronchoscopy
Section A

Diphenhydramine as an Adjunct to Moderate Sedation in Outpatient Flexible Bronchoscopy

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Abstract

Background Diphenhydramine is commonly used to decrease sedative usage in outpatient bronchoscopy, however, data to support this practice is lacking. Methods We conducted a single-center retrospective analysis of all outpatient bronchoscopies from November 2013 to February 2016. Each subject that was included had two bronchoscopies: no diphenhydramine used (control) versus diphenhydramine used (intervention). The primary objective was to determine if diphenhydramine administration decreases total midazolam usage. Additionally, we explored potential medication cost savings. Results Of 1164 patients with greater than 1 outpatient bronchoscopy, 61 unique subjects fulfilled the primary inclusion criteria resulting in 122 procedures. The mean dose of diphenhydramine was 38.3±15.12 mg. Procedure time was 22.9±16 mins in the intervention group and 23.2±17.8 mins in the control group (p= 0.907). Mean opiate dose administered was 5.6±2.6 mg versus 6.2±2.4 mg in the intervention and control group, respectively (p= 0.113). Mean midazolam dose was 8.4 ± 3.2 mg in intervention group and 10.2±3.8 mg in control group (difference: -1.795 mg, p= 0.005). In a multivariate analysis, mean midazolam use remained lower in the diphenhydramine group after adjusting for age, procedure time and opiates used, (difference -1.29±3.53 mg, p= .004). There was no significant difference for the total cost of medication between the control and the diphenhydramine group ($6.21±2.70 vs. $6.23±2.53, p= .968). Conclusions Intravenous administration of diphenhydramine during outpatient bronchoscopy resulted in a small but statistically significant reduction in midazolam usage with no notable cost advantage.

Keywords: Sedation, bronchoscopy

1. Introduction

Moderate sedation is a common practice in outpatient bronchoscopy. 1,2 It has been shown to safely shorten procedure times and improve patient experience. 3 4 However, sedation practices in bronchoscopic procedures, including the use of diphenhydramine, vary between institutions 2,5-7 . Diphenhydramine exert a sedative and hypnotic effect by antagonizing central nervous system histamine H1 receptors8,9 and it may also mitigate opioid-related respiratory depression.10 Because of this properties, it's use has been described in multiple procedures including gastrointestinal endoscopies11,12, dental procedures13 ,cardiac catheterization14 and bronchoscopy. 15-19 The anticholinergic properties of diphenhydramine may decrease cough and secretions in bronchoscopy9,20 however the more potent anticholinergic agent, atropine, failed to demonstrate these benefits in a randomized clinical trial 21. Though used in bronchoscopy primarily to reduce complications related to cumulative sedative dosages16,17,22,23, to our knowledge, no analytical studies have evaluated patient-related outcomes of diphenhydramine use in flexible bronchoscopy and guidelines in bronchoscopy have not endorsed its use24,25 With this in mind, the primary objective of this study was to determine whether diphenhydramine administration would decrease the need for other sedative medications during outpatient flexible bronchoscopy. We specifically wanted to assess whether diphenhydramine decreases the total dose of benzodiazepine and opioid administered thereby providing cost savings. In addition, we sought to determine if diphenhydramine use has an impact on procedure-related complications.

2. Methods

2.1. Patients

All outpatient bronchoscopies at Henry Ford Hospital from November 2013 to February 2016 were retrospectively reviewed after the approval of our institutional review board (IRB#10248). During this period, a combination of physician preference, expected procedure duration, and patient factors led to a decision as to whether or not diphenhydramine was employed as an adjunctive agent during bronchoscopy. Adult patients were selected for the study if they had at least 2 outpatient bronchoscopies during which there was differential use of diphenhydramine. So, each patient had at least one bronchoscopy with no diphenhydramine used (labeled as the control procedure) and one bronchoscopy in which diphenhydramine was used (labeled as the intervention procedure). Thus, each patient served as his/her own control. If there were more than 3 bronchoscopies for a patient, the most recent pair (control versus intervention) were selected. Bronchoscopies done as in-patient were excluded. Baseline characteristics collected at the time of each bronchoscopy included age, body mass index, outpatient use of alcohol, current ongoing use of benzodiazepines, opiates, antidepressants and anti-psychotics. The outpatient medications were grouped based on their class (e.g. opiates included morphine and other synthetic narcotics).

2.2. Bronchoscopy

The procedure time was measured from the time of the "critical pause" to the bronchoscope's withdrawal past the nose or mouth. Mean procedure time was determined for each group. All bronchoscopic procedures were aggregated based on procedure group types (i.e., airway examination only, transbronchial biopsy, endobronchial ultrasound, etc.) and their mean times were calculated.

2.3 *Medications*

The total and mean doses (milligrams) of benzodiazepines and opiates were determined for each group. Opioid doses were converted to morphine-equivalent doses for uniform comparison. The timing of diphenhydramine administration with reference to the first midazolam dose was also computed. As the use of diphenhydramine varied according to the bronchscoscopist performing the procedure, the physician performing the procedure was also included in all analyses. Doses of other medications used as adjuncts during the procedure were also recorded..

2.4 Complications

Each procedure encounter was reviewed for any naloxone or flumazenil usage. Charts were evaluated for any admission in the 24-hour period after the procedure and any procedural hypotension. Hypotension was defined as systolic blood pressure of less than 90mmHg taken 2 consecutive times (re-checked immediately) at any point during the procedure..

2.5 Cost for medications

The average wholesale price of each vial of medications used in our bronchoscopy suite was used to compute the mean costs of medications used in the control and diphenhydramine groups. As a practical approach, if another vial was opened, the cost of that particular vial was added to the total cost even though part of it was wasted.

2.6 Statistical analysis

To determine study size for this investigation, we evaluated prior research by Tu et al who found that diphenhydramine use in colonoscopy decreased midazolam dose by 0.55 mg. However, in their study, the average midazolam used was only around 3-4 mg.11 Our bronchoscopic procedures average midazolam usage was estimated to be 10mg (roughly between 8-12 mg). Using these data, we calculated that we would require 60 subjects to have 80% power to detect a reduction in midazolam dose of more than 2 mg, using an alpha of 0.05. In our analyses, variables with dichotomous outcomes were compared using McNemar's test. Differences on continuous variables between the groups was determined using Paired t-test. Conditional logistic regression was used to compare use of diphenhydramine between bronchoscopists. A multivariate model was applied to determine the difference in midazolam use between the two groups after adjusting for age, duration of procedure and total morphine equivalent dose administered. Categorical variables were presented as frequencies and percentages, and continuous variables as mean and standard deviation. Cost analysis was performed using the average wholesale price (AWP) of the vials used for the procedures. Additionally, the cost for ondansetron, meperidine, naloxone and flumazenil was computed if they were used. Cost for procedure related admission and nursing monitoring was not included in this study.

3. Results

Of the 1164 patients with greater than 1 outpatient bronchoscopies in the study period, there were 61 unique subjects that fulfilled the primary inclusion criteria resulting in 122 procedures (Figure 1). The patients were predominantly female (56%) and their characteristics (Body mass index, age, alcohol use and outpatient medication use) at the time of each bronchoscopy were similar (Table 1). Four patients did not have their weight or height recorded; therefore, no BMI was computed. These subjects were the same 4 patients in both groups. There was no difference on outpatient medications use between the group (Table 1).

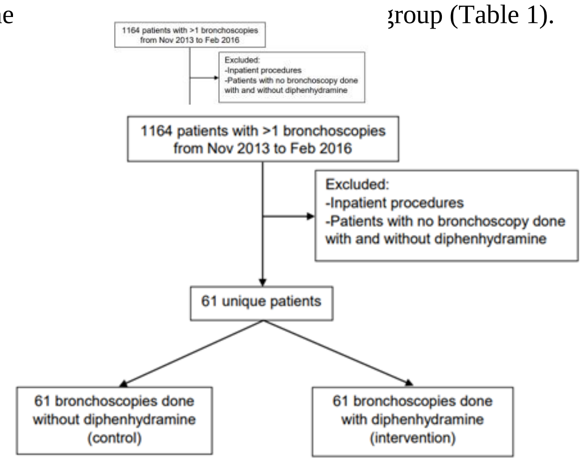

Figure 1. Flow diagram of patient selection

regards to use of diphenhydramine (Table 3).

Table 1. Patient Characteristics

	Control (n=61)	*Diphenhydramine (n=61)*	P value
Age (years), mean ± SD	56.77 ± 13.57	57 ± 13.54	0.034
Body mass index (kg/m2), mean ± SD	31.56 ± 9.16	32.5±8.24	0.096
Alcohol use, N (%)	16(26.2)	17 (27.9)	1.00
Benzodiazepine use, N (%)	22 (36.1)	23 (37.7)	1.00
Opioid use, N(%)	42 (68.9)	40 (65.6)	0.727
Antidepressant use, N (%)	20 (32.8)	16 (26.2)	0.125
Antipsychotic use, N (%)	2 (3.3)	2 (3.3)	1.00

3.1. Bronchoscopic procedures

The distribution of each procedure type between the diphenhydramine group and the control group is shown in Table 2. All bronchoscopies had an airway examination performed. Sole airway examinations were done in 52 procedures (42.6%). The remainder were distributed in procedure types that involved multiple combinations of biopsy with or without the use of ultrasound, bronchial wash or brush and balloon dilatation. There was no difference between the diphenhydramine group and the control group in the frequency of a procedure type (Table 2). The mean procedure time was same in both groups (23.2 ± 17.8 minutes in control group vs. 22.9 ± 16.3 minutes in diphenhydramine group, p=0.907). The mean time interval between the two bronchoscopies was 206.1 ± 189 days. Three bronchoscopists performed 92% of the procedures. The remainder were distributed among 6 pulmonologists. There was no significant difference between the groups with

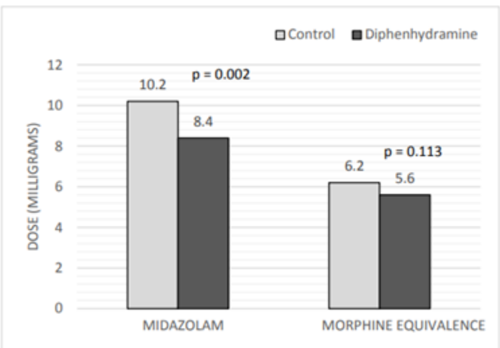

Figure 2. Difference in mean midazolam and morphine dose requirement

3.2 Medication Dosages and Timing

All patient received midazolam as the preferred procedural benzodiazepine. The diphenhydramine group required 1.795 mg less midazolam which was a 17.6% dose reduction (8.4 ± 3.2mg vs. 10.2 ± 3.8 mg, p =0.002) (Figure 2). There was no significant difference in the morphine equivalence dose used between the 2 groups (5.6 ± 2.5 mg vs. 6.2 ± 2.4 mg, p = 0.113) (Figure 2). In a multivariate model, after adjusting for age, procedure time and morphine equivalence, the mean midazolam dose was lower in the diphenhydramine group in comparison to the control group (difference -1.29 ± 3.53 mg, p = 0.004). Most patients received either a 25 mg or 50 mg dose of diphenhydramine. The mean dose used of diphenhydramine was 38.3 ± 15.1 mg. On average, diphenhydramine was administered 12.3 ± 23.3 minutes before to the first dose of benzodiazepine. . Three subjects in the diphenhydramine group received 50 mg of meperidine while no subject received meperidine in the control group. Interestingly, the mean midazolam used in this subgroup who received meperidine was higher compared to the subgroup who had not received meperidine (11.33±1.15 mg vs 8.27±3.20 mg). There were 7 patients who received ondansetron: 5 in the diphenhydramine group and 2 in the control group with a mean dose of 3.1 ± 1.1 mg. 1

3.3 Complications

There were no hypotensive episodes in either group and none received naloxone or flumazenil during their outpatient bronchoscopy. Three patients were admitted within 24 hours in the diphenhydramine group and 5 in the control group (p = 0.717). Table 4 describes the cause of admission in those patients. Medication Cost analysis The mean cost difference of midazolam was $-0.66 ($3.50 ± 1.17 vs $4.16 ± 1.24, p= 0.002) in favor of the diphenhydramine group. However, after accounting for the cost of diphenhydramine, the control and intervention group had similar expenses ($6.20 ± $2.69 vs. $6.07 ± $2.30, p = 0.74). There were no additional cost difference when meperidine and ondansetron were added (control $6.21 ± $2.70 vs. intervention $6.23 ± $2.53, p = 0.97) (Table 5).

4. Discussion

Sedative dose reduction in bronchoscopy is important because complications from procedural sedation are typically dose and agent dependent.26 Moreover, bronchoscopy uses a higher average doses of benzodiazepine relative to gastrointestinal procedures (5- 10 mg IV of midazolam compared to only 3-5 mg IV in GI endoscopic procedure). 4,11,12,27 Our study demonstrated a significant decrease of 18% (1.8 mg, P = .005) in total midazolam dose with diphenhydramine use in outpatient flexible bronchoscopy. Though there was a concern for potentially deeper and longer sedation in the intervention group because of diphenhydramine’s long half-life, none received flumazenil or naloxone during any of the encounters. Similar dose reduction was noted in a randomized double-blind placebo-controlled trial of 258 colonoscopy patients that demonstrated a significant decrease of procedural midazolam (13.7%) and meperidine (10.1%) doses with diphenhydramine pre-medication with no effects on procedural/recovery time and complication rates. 11 A more recent randomized trial of 200 colonoscopy patients, however, demonstrated that diphenhydramine is a poor substitute for midazolam if additional sedation is required.12 As opioids tend to reduce the total doses of other sedatives18,26 and as the length of the procedures ultimately influence the total sedative dose, we adjusted for both factors. Age was also adjusted because it was statistically different in both groups. The significant reduction of total midazolam dose was persistent (difference of 1.29 mg, p= 0.004) after these adjustments. While the

dose reduction was small, this could be important in the geriatric population. The elderly tend to be more sensitive to sedatives because of reduced hepatic metabolism, decreased renal function and

reduced tissue and blood esterases.28 In fact, the current guideline for flexible bronchoscopy recommend modifying initial and subsequent doses of sedatives for patients who were 70 or older.25 However, it should also be kept in mind that diphenhydramine has a longer half-life in the elderly and that they may be more sensitive to its anticholinergic properties. 29 Our study population appeared relatively younger (mean 56.89 years) and the potential impact in the elderly was not explored in this study. With the decreased total midazolam use in the diphenhydramine group, we expected a lower total cost of medication for patients who received diphenhydramine as demonstrated by Tu et. al.11 However, there were no cost differences between groups after accounting for the cost of diphenhydramine. This was likely a result of the small incremental cost of the opioids added to the cost of diphenhydramine ultimately negating the small difference of $0.66 in midazolam cost saving. It was difficult to assess the unexpected admission rates related to bronchoscopy because of low event rates. Several studies used hypoxia as a complication of sedation in bronchoscopy with varying definitions (saturations usage.

Table 2. Type of Bronchoscopic Procedures and Procedure Duration

	Control (n= 61)	Diphenhydramine (n=61)	P value
Procedure time (min), mean ± SD	23.17±17.79	22.93±16.3	0.907
Procedure type			
Airway examination only	27 (44.3)	25 (41)	0.727
TBBX + bronchoalveolar lavage	14 (23)	15 (24.6)	1.00
Endobronchial biopsy	5 (8.2)	3 (4.9) .	0.688
EBUS TBNA	5 (8.2)	7 (11.5)	0.688
EBUS + periph brush+ wash	5 (8.2)	1 (1.6)	0.125
Peripheral EBUS TBBX+ brush+	1 (1.6)	5 (8.2) .	0.125
Balloon dilatation	4 (6.6)	4 (6.6)	1.00

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Supplemental Tables

Table 3. Use of Diphenhydramine per Bronchoscopist

	B1*	B2*	B3*	Others*
No Diphenhydramine (N=61)	17 (43.6)	15 (51.7)	21 (51.2)	9 (69.2)
Diphenhydramine (N=61)	22 (56.4)	14 (48.3)	20(49.8)	4 (30.8)

*N (%); conditional logistics regression, $p = 0.40$

Table 4. Complication Events and Admissions

	No Diphenhydramine (n= 61)	Diphenhydramine (n=61)
Reasons for admission*	1. Reported diarrhea prior to procedure- lung transplant patient 2. Bronchoscopic diagnosis of pneumonia - lung transplant patient 3. More complex airway stenosis than anticipated 4. Confirmed post-surgical tracheal anastomotic compromise 5. Persistent tachycardia	1. Post-procedure fever 2. Respiratory syncytial virus on bronchoalveolar lavage - lung transplant patient 3. Post-procedure fever

*Primary reasons for admission on chart review.

Table 5. Medication Cost Analysis

Medication (AWP per vial)*	Control	Diphenhydramine	*P* value
Midazolam (5mg/5ml), $1.67/vial	$4.16 ± 1.24	$3.50 ± 1.17	.002
Opioids[#] (fentanyl + morphine)	$2.08 ± 0.36	$2.09 ± 0.17	.860
Diphenhydramine (50 mg/ml), $0.82/vial	0	$0.83 ± 0.11	-
Meperidine (100 mg/ml), $1.64/vial	0	$0.08 ± 0.36	-
Ondansetron (4 mg/2 ml), $0.56/vial	$0.02 ± 0.10	$0.05 ± 0.15	.260
Total cost ($)	$6.21 ± 2.70	$6.23 ± 2.53	.968

*Average wholesale price (AWP) for our institution.

#AWP for morphine (10 mg/ml) was $2.26/vial and for fentanyl (100 mcg/2 ml) was $1.92/vial