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Fospropofol Disodium for Sedation in Elderly Patients Undergoing Flexible Bronchoscopy

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Abstract

Background—Fospropofol disodium is a water-soluble prodrug of propofol. A subset analysis was undertaken of elderly patients (≥ 65 y) undergoing flexible bronchoscopy, who were part of a larger multicenter, randomized, double-blind study.

Methods—Patients received fentanyl citrate (50 mcg) followed by fospropofol at initial (4.88mg/kg) and supplemental (1.63mg/kg) doses. The primary end point was sedation success (3 consecutive Modified Observer's Assessment of Alertness/Sedation scores of ≤ 4 and procedure completion without alternative sedative or assisted ventilation). Treatment success, time to fully alert, patient and physician satisfaction, and safety/tolerability were also evaluated.

Results—In the elderly patients subset ($n=61$), sedation success was 92%, the mean time to fully alert was 8.0 ± 10.9 min, and memory retention was 72% during recovery, and these were comparable with the younger patients subgroup (age, < 65 y). Sedation-related adverse events occurred in 23% of the elderly and 18% of the younger patients (age, < 65 y) group. Hypoxemia occurred in 26% of the elderly and 18% of the younger patients group, but no escalation of care was required.

Conclusions—Fospropofol provided safe and effective sedation, rapid time to fully alert, and high satisfaction in this elderly subset undergoing flexible bronchoscopy, which was comparable with outcomes in younger patients.

Keywords

bronchoscopy; elderly; fospropofol; sedation

In 2000, worldwide, approximately 605 million people were 60 years or older. By 2050, this number is expected to be close to 2 billion. At that time, seniors will outnumber children, aged 14 years and below, for the first time in history. Accompanying the increased elderly population will be an increased use of healthcare resources. The annual median health care expenditures among those who are > 64 years of age was at least 2-fold greater than 45 to 64-

year-old patients.¹ Bronchoscopy is a common procedure, and the number of bronchoscopies performed will likely increase in the elderly patients by virtue of an aging population and the increased prevalence of lung cancer in the elderly patients.

Despite the potential for an increased rate of complications from bronchoscopy in the elderly patients, results from several studies have shown the risk of complications to be similar among the young and the old patients.²⁻⁶ However, the addition of pharmacologic agents to provide procedural sedation and analgesia could increase the risk of complications among the elderly patients who may be more prone to adverse reactions to these drugs. Thus, it is important to establish the safety of procedural sedation agents that are used for bronchoscopy in the elderly population.

Fospropofol disodium is a water-soluble prodrug of propofol, with a pharmacokinetic and pharmacodynamic profile that differentiates it from propofol lipid emulsion.⁷ Fospropofol is effective, safe, and well tolerated when used for moderate sedation during diagnostic and therapeutic procedures, such as colonoscopy and flexible bronchoscopy.^{8,9} Potentially, fospropofol could be preferred for moderate sedation in an elderly population because it may offer a less variable, more predictable pharmacokinetic and pharmacodynamic profile.⁷ The aim of this study was to evaluate the effect of fospropofol in the elderly patients compared with younger patients undergoing fiberoptic bronchoscopy.

METHODS

This was a subgroup analysis of elderly patients aged ≥ 65 years compared with those < 65 years enrolled in a phase 3, randomized, double-blind, dose-controlled study, who were undergoing flexible bronchoscopy. Detailed methodology was described earlier.⁸ The study was conducted according to good clinical practices, and an institutional review board at each clinical site approved the study protocol. All patients provided oral and written informed consent before enrollment.

Patient Selection

This subgroup analysis included patients from the original study cohort, who were aged ≥ 65 years and had a American Society of Anesthesiologists (ASA) Physical Classification System status of P1 to P4, these being the eligibility criteria for enrollment.

Exclusion criteria included hypersensitivity to any anesthetic or opioid, failure to meet nil per os status, an abnormal, clinically significant electrocardiogram, or participation in an investigational drug study within the previous month. Other exclusion criteria were a Mallampati Classification Score of IV or III and a thyromental distance ≤ 4 cm, or a difficult airway for any other reason as judged by the clinician.

Study Procedures

After baseline assessments, patients were randomly assigned to receive the standard treatment with fospropofol of 6.5 mg/kg or 2mg/kg in a 3:2 allocation ratio. This subgroup analysis focused on patients ≥ 65 years of age, who were randomized to the 6.5 mg/kg group (therapeutic dose). Sedation was evaluated during 2 phases—initiation and maintenance. All patients were given supplemental oxygen (4 L/min). All patients received fentanyl citrate (50 mcg). Among this subgroup of patients aged ≥ 65 years of age, the initial dose of fospropofol was reduced by 25% to 4.88mg/kg. If supplemental doses of fospropofol were needed to reach a Modified Observer's Assessment of Alertness/Sedation (MOAA/S) score ≤ 4 (Table 1),¹⁰ the supplemental fospropofol dose (1.63mg/kg) was also reduced by 25% to 1.22mg/kg. Supplemental doses of fospropofol at intervals of ≥ 4 minutes from the preceding dose were 25% of the initial dose [ie, 1.63mg/kg (range, 97.5 to 146mg) for the 6.5 mg/kg

group]. Patients ≥ 65 years of age and/or ASA P4 (or P3 at the discretion of the investigator) had their doses reduced by 25%. The dosage was also limited by lower and upper weight limits of 60 kg and 90 kg, respectively.

Initiation Phase

During the initiation phase, 1 bolus dose and up to 3 supplemental doses of fospropofol were administered to reach a MOAA/S score ≤ 4 . Supplemental doses of fospropofol were given at intervals of ≥ 4 minutes. The procedure began after the first MOAA/S score ≤ 4 . If > 3 supplemental doses of fospropofol were required to achieve MOAA/S scores of ≤ 4 before the beginning of the procedure, the patient was considered for sedation failure and alternative sedative medication was administered.

Maintenance Phase

Supplemental doses of fospropofol could be administered at intervals ≥ 4 minutes for a MOAA/S score of ≥ 4 and showed purposeful movement. One additional 25 mcg dose of fentanyl was allowed for pain. The level of sedation was assessed using the MOAA/S scale every 2 minutes from the first dose of fospropofol until the patient was determined to be fully alert. Alternative sedative medication could be administered only for sedation failure.

Study End Points

Sedation success was defined as 3 consecutive MOAA/S scores ≤ 4 after fospropofol administration and completion of the procedure without requiring either alternative sedative or manual/mechanical ventilation. Treatment success was defined as completion of the procedure without requiring either alternative sedative or mechanical/manual ventilation. Other end points included the proportion of patients willing to be retreated with fospropofol and who did not recall being awake during the procedure, the proportion of patients requiring supplemental doses of fentanyl, the number of supplemental fospropofol doses that were administered, time to sedation, and the MOAA/S scores.

Physician satisfaction scores were collected at the end of the initiation phase and at the end of the procedure. Ready for discharge was defined as a score ≥ 9 on the Aldrete¹¹ discharge scale. At ready for discharge, patients rated their experience (ie, recall of insertion and/or removal of the bronchoscope), level of satisfaction, and comfort during the bronchoscopy. A 10-point Likert scale (1=dissatisfied; 10=highly satisfied) was used to assess both patient and physician satisfaction.

Safety and Tolerability

Treatment-related adverse events (TRAEs) were analyzed for frequency, severity, relationship to treatment, and outcome. The events were considered to be severe if they interfered with the daily functioning of the patient or if in the judgment of the investigator; the symptom was of significant intensity. Sedation-related AEs (SRAEs) included apnea (lack of spontaneous breathing > 30 sec), hypoxemia (oxygen saturation $< 90\%$ for > 30 sec), hypotension (systolic blood pressure < 90 mm Hg and requiring medical intervention), and bradycardia (heart rate < 50 beats/min and requiring medical intervention).

Analysis

The modified intent-to-treat population included all randomized patients who received ≥ 1 dose of fospropofol and had ≥ 1 postdose clinical assessment. The safety population included randomized patients who received ≥ 1 dose of fospropofol. The number and proportion of patients achieving the primary and secondary end points were calculated. The Fisher exact test was used to compare proportions and a *t* test was used to compare mean values for the 2

treatment groups. Wilcoxon rank sum test was used to compare satisfaction scores. A *P* value <0.05 was considered to be significant.

RESULTS

The original study enrolled 252 patients; 150 patients were randomized to treatment with fospropofol of 6.5 mg/kg. Of 150 patients who were randomized to fospropofol of 6.5 mg/kg, 61 were at least 65 years of age and comprised the elderly patients subgroup. One patient was randomized to fospropofol of 6.5 mg/kg but received fospropofol of 2.0mg/kg. This patient was included in the 6.5 mg/kg group for analysis. Baseline demographic and clinical characteristics showed that patients in the elderly and young patient subgroups were comparable (Table 2). The median age was 72 years in the elderly patients subgroup and 56 years in the young patients subgroup. A few patients in the elderly patients subgroup were ≥ 90 kg (21.4% vs 32.6%), and more patients in the elderly patients subgroup were ASA P3/4 (54% vs 40%). Otherwise, the elderly and young patient subgroups were comparable at baseline.

Efficacy

Sedation success and treatment success rates exceeded 85% in all groups and were numerically higher in the elderly patients subgroup, although no significant differences were observed between elderly and young patient subgroups (Fig. 1).

For other efficacy end points, no significant differences were observed between elderly and young patient subgroups for MOAA/S scores, recall of being awake, supplemental analgesic or sedative doses or mean time to fully alert, and to discharge (Table 3). A higher proportion of elderly than young patients had memory retention during recovery (72.0% vs 58.4%), although this difference was not significant. More patients in the younger versus the elderly group required at least 1 alternative sedative medication at any time during the procedure [10 (11.2%) vs 2 (3.3%)].

Overall mean (SD) patient satisfaction scores were 9.7 ± 0.7 in the elderly versus 9.4 ± 1.1 in the young patients group ($P=0.7$). Mean (SD) comfort level scores during the procedure were 9.4 ± 1.6 in the elderly and 9.4 ± 1.3 in the young patients group. The proportion of patients willing to be treated with fospropofol again was 93.4% in the elderly and 94.4% in the young patients group.

Mean physician satisfaction scores with fospropofol during the initiation phase were 8.6 ± 1.8 in the elderly and 7.6 ± 2.7 in the young patients group ($P=0.04$), and at the end of the procedure were 8.4 ± 1.8 in the elderly and 8.2 ± 2.6 in the young patients group ($P=0.68$). During the initiation phase, physicians rated overall satisfaction as a score of 9 or 10 for 64% of the elderly versus 49% of the young patients group ($P<0.05$).

Safety/Tolerability

The most common TRAEs were paresthesia, pruritus, hypotension, and hypoxia (Table 4). The incidence of paresthesia was lower and the incidence of hypoxia was higher in the elderly patients subgroup than the young patients subgroup, but the differences were not significant.

SRAEs occurred in 14 (23%) patients in the elderly subgroup and in 16 (18%) patients in the younger age group; however, this difference was not significant. In the elderly subgroup, 12 patients experienced 13 cases of hypoxia and 2 patients experienced an episode of hypotension (Table 5). One event (hypoxia) was judged to be severe, 6 moderate, and 8 of mild intensity. Events in 5 patients were considered to be definitely related to treatment and

possibly or probably related in an additional 5 patients. All SRAEs resolved, and none were considered to be serious adverse events.

Airway assistance was required in 16 patients in each subgroup. In the elderly patients subgroup, airway assistance consisted of administering oxygen to all 16 patients; 4 of the 16 patients also required additional maneuvers including suction, chin lift, bag-mask ventilation, or tactile and verbal stimulation.

DISCUSSION

This is the first prospective study to provide data on the effectiveness, safety, tolerability, and satisfaction of fospropofol with bronchoscopy in an elderly population. All bronchoscopies were performed by board-certified pulmonologists without the presence of an anesthesiologist. The outcomes with fospropofol were comparable in the elderly and young patient groups. No significant differences were noted for sedation and treatment success, but also for other outcomes including time to awake, supplemental doses, MOAA/S score, and patient and physician satisfaction. These results confirm that the modified 6.5 mg/kg dose reduced by 25% in the elderly population produced a comparable level of sedation and comparable tolerability as was observed in the younger population. Fospropofol achieved a high level of satisfaction among both physicians and patients in both the elderly and young patient groups.

The proportion of patients requiring airway assistance was 8% higher, and the occurrence of SRAEs was 5% higher in the elderly patients subgroup compared with the younger patients group. This is not an unexpected finding in an elderly population that typically has comorbid illnesses, including chronic pulmonary disease, which can complicate bronchoscopy. Other researchers have observed a higher rate of adverse events in elderly patients undergoing bronchoscopy.¹² Despite the higher incidence of SRAEs and airway assistance, no patient required an elevated level of care for either of these types of events.

Flexible bronchoscopy is widely acknowledged to be safe and well tolerated among the elderly population. Early retrospective studies found no increase in morbidity or mortality and a rate of complications that was comparable with younger populations.⁴⁻⁶ More recent studies have confirmed the safety of bronchoscopy in the elderly population. Among 358 patients undergoing fiberoptic bronchoscopy, including 165 (46%) patients who were at least 70 years of age, increasing age was not a limiting factor for undergoing bronchoscopy.³ A retrospective study evaluated bronchoscopy among 436 consecutive patients, which included 191 patients who were at least 75 years of age.² Indications and safety/tolerability did not differ between groups that were above and below 75 years of age. Thus, bronchoscopy should not be withheld or contraindicated solely on the basis of advanced age alone.

Bronchoscopy is usually performed with accompanying sedation to improve patient tolerability, to make the procedure easier for the bronchoscopist to obtain diagnostic material or perform a therapy, and to make the patient more willing to accept a repeat procedure if needed.¹³ Sedation during bronchoscopy should be limited or used with extreme caution in patients with severe chronic obstructive pulmonary disease who have an increased risk of an adverse response. Although amnesia may be important for patient acceptance of bronchoscopy,^{14,15} there are no studies that directly compare sedative drugs in doses sufficient to produce complete amnesia with lower doses producing a lesser degree of sedation.

A prospective study evaluated flexible bronchoscopy in a university hospital among 1358 adults, including 219 (16%) adults aged 70 years or older.¹² Mean doses of midazolam and

fentanyl for sedation decreased with increasing age ($P<0.001$). The overall risk of adverse events increased with increasing age ($P<0.01$). Hypotension and pneumothorax occurred more often in those aged >70 years and <40 years. This study concluded that elderly patients tolerated bronchoscopy well. Overall, adverse events were rare. Premedication with temazepam and lidocaine was compared with alfentanil alone in patients aged 75 years or older, who were undergoing bronchoscopy.¹⁶ Overall, the procedure was well tolerated with both regimens. Thus, the value of administering sedative and analgesic medication during the procedure has been reported in a few studies, although data with propofol and other drugs are lacking.

Midazolam, perhaps the most commonly used drug for sedation during bronchoscopy, is a water-soluble benzodiazepine with an elimination half-life of approximately 2 hours and is generally preferred to diazepam. Midazolam has a rapid onset and brief duration of action. Less than 10% of the population exhibit prolonged effects due to impaired metabolism.¹⁷ Many investigators have used a dose of 0.07mg/kg midazolam before bronchoscopy. However, adequate sedation cannot be assured by a single dose.¹⁸ Thus, incremental dosing with midazolam over a range from 0.07 to 0.67mg/kg, achieves improved tolerance of bronchoscopy, induces amnesia, and improves patient satisfaction with repeat bronchoscopy.¹⁵

Propofol is an emulsion formulation that is suitable for the induction and maintenance of anesthesia. In randomized controlled studies, propofol produces adequate sedation with a rapid onset and duration of action and may offer advantages over midazolam and diazepam/alfentanil in combination.¹⁹⁻²² The average sedative dose of propofol, administered during bronchoscopy, in 1 study was 155mg, equivalent to an anesthetic induction dose.¹⁹ Propofol offers advantages over other sedative agents, but requires both expertise and experience in administering this drug.

A combination of a benzodiazepine and narcotic has been widely used for sedation during bronchoscopy and combines the amnesic effects of a benzodiazepine with the analgesic and antitussive effects of a narcotic.^{23,24} Unfortunately, a benzodiazepine and a narcotic analgesic may be associated with more arterial desaturation and CO₂ retention than when using midazolam alone.²⁵ Morphine is commonly used, but synthetic shorter-acting narcotics may be preferred. The combination of nalbuphine (0.2mg/kg) and midazolam (0.05mg/kg) produced slightly higher CO₂ levels than midazolam alone.²⁴ The synthetic, potent, and short-acting narcotic, alfentanil of 0.05 to 1.0mg, when used alone achieves equivalent levels of sedation to midazolam but with greater antitussive effects.²⁵

Limitations of this analysis are that it represents a post hoc analysis of a randomized controlled trial; however, the elderly patients subgroup was a planned subgroup analysis of the original study. As this was a subgroup analysis, a relatively small sample size may have limited statistical comparisons. These results also provided no comparison of fospropofol with usual care for sedation, which is typically midazolam and fentanyl, or with the use of bronchoscopy without sedation. Another limitation is that despite the focus of the study and inclusion criteria, a few ASA P4 patients and few patients >80 years of age were included, so that these results may not apply to these populations. Strengths of this analysis are that data were obtained from a prospective, multicenter, randomized, controlled trial in a relatively sick population in which all types of patients were accepted for enrollment. Future studies should consider a larger cohort of elderly patients and potentially include a comparison with usual care.

In summary, as the population ages more elderly patients will undergo bronchoscopy. Caution should be taken when performing this procedure in the elderly patients, as patients

are likely to have a higher prevalence of comorbid diseases. Fospropofol is promising as a sedative agent in bronchoscopy for an elderly population with comorbid illness. Future studies of bronchoscopy in the elderly population should concentrate on comparison of differing regimens, differing dose adjustments, and differing monitoring options to assure patient safety while ensuring successful completion of the procedure.

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FIGURE 1.
Proportion of patients in the elderly and young patient subgroups who achieved sedation and treatment success.

Table 1Modified Observer's Assessment of Alertness/Sedation Scale¹⁰

Responsiveness	Score
Responds readily to name spoken in normal tone	5 (Alert)
Lethargic response to name spoken in normal tone	4
Responds only after name is called loudly and/or repeatedly	3
Responds only after mild prodding or shaking	2
Responds only after painful trapezius squeeze	1
Does not respond to painful trapezius squeeze	0

TABLE 2

Baseline Demographic and Clinical Characteristics of Elderly and Young Patient Subgroups

	≥65y (n=61)	<65y (n=89)	P*
Age (y)			
Mean (SD)	72.4 (5.1)	52.8 (9.8)	
Median	72	56	
Range	65-83	25-64	
Sex, n (%)			0.5073
Female	24 (39.3)	40 (44.9)	
Male	37 (60.7)	49 (55.1)	
ASA status, n (%)			0.2691
P1	3 (4.9)	4 (4.5)	
P2	25 (41.0)	49 (55.0)	
P3	28 (45.9)	33 (37.1)	
P4	5 (8.2)	3 (3.4)	
Race, n (%)			0.0516
White	57 (93.4)	73 (82.0)	
Black/other	4 (6.6)	16 (18.0)	
Weight (kg), n (%)			0.2118
<60	10 (16.3)	17 (19.1)	
60 to <90	38 (62.3)	43 (48.3)	
≥90	13 (21.4)	29 (32.6)	

* Fisher exact test.

ASA indicates American Society of Anesthesiologists.

TABLE 3

Secondary Efficacy End Points for Elderly and Young Age Groups

Outcome	Fospropofol ≥65y (n=61)	Fospropofol <65y (n=89)	P
Mean (SD) MOAA/S score during procedure	3.3 ± 0.8	3.5 ± 0.8	0.135 [*]
Patients with a MOAA/S score of 0 or 1, n (%)	11 (18.0)	14 (15.7)	0.824 [†]
No recall of being awake during procedure, n (%)	50 (82.0)	75 (84.3)	0.824 [†]
Memory retention during recovery, n (%)	44 (72.0)	52 (58.4)	0.118 [†]
Required supplemental fentanyl, n (%)	9 (14.8)	16 (18.0)	0.661 [†]
Mean (SD) number of supplemental fospropofol doses	1.46 ± 1.36	1.88 ± 1.86	0.134 [*]
Required no supplemental fospropofol doses, n (%)	14 (23)	24 (27)	0.355 [†]
Mean (SD) time to fully alert (min)	8.0 ± 10.9	7.9 ± 9.2	0.952 [*]
Mean (SD) time to discharge (min)	10.4 ± 11.6	12.4 ± 11.2	0.291 [*]
Willing to receive fospropofol again, n (%)	57 (93.4)	84 (94.4)	1.000 [†]

* Student *t* test.

[†] Fisher exact test.

MOAA/S indicates Modified Observer's Assessment of Alertness/Sedation.

TABLE 4

Treatment-related Adverse Events Occurring in the Elderly and Young Patient Subgroups

Adverse Event	No. (%) of Patients	
	Elderly ≥65y (n=61)	Young <65y (n=89)
Any event	36 (59.0)	69 (77.5)
Chest discomfort	0	2 (2.2)
Dysgeusia	0	2 (2.2)
Hypotension	4 (6.5)	6 (6.7)
Hypoxia	8 (13.1)	8 (9.0)
Nausea	0	2 (2.2)
Paresthesia	26 (42.5)	49 (55.1)
Procedural pain	1 (1.6)	2 (2.2)
Pruritus	8 (13.1)	14 (15.7)
Sinus headache	1 (1.6)	1 (1.1)
Sneezing	1 (1.6)	1 (1.1)

TABLE 5

Description of Sedation-related Adverse Events in the Elderly Patient Subgroup

Patient	Age (y)	ASA Status	Ongoing Respiratory Conditions	Relative Time to Onset (min)	Duration (min)	Severity/Related	Airway Assistance or Concomitant Medication	Modified OAA/S
1	75	P3	Asbestosis	15	66	Moderate/definite	No	4
2	66	P2	Emphysema	17	1315	Moderate/possible	No	2
3	70	P2	COPD Lung mass	8	368	Mild/probable	Verbal stimulation, suction, increased O ₂ flow	4
4	69	P3	COPD, asthma, hemoptysis, and lung cancer	9	103	Mild/definite	Increased O ₂ flow	5
				12	324	Mild/definite	Increased O ₂ flow	3
5	77	P3	COPD, lung mass, and pneumonia	17	240	Moderate/No	Chin lift, increased O ₂ flow	4
6	68	P3	lung mass	14	180	Mild/No	Increased O ₂ flow	3
7	67	P3	COPD	25	180	Mild/No	Increased O ₂ flow	3
8	82	P2	COPD, asthma, and sleep apnea	12	623	Moderate/definite	Increased O ₂ flow	3
9	73	P3	COPD, asthma, and sleep apnea	12	58	Moderate/definite	Increased O ₂ flow	3
10	80	P2	COPD	10	604	Moderate/definite	Increased O ₂ flow	4
11	78	P3	COPD, hypoxemia, and pneumonia	9	7260	Severe/probable	Increased O ₂ flow, manual ventilation (bag valve mask)	3
12	65	P3	COPD	14	60	Mild/possible	Increased O ₂ flow	1
13	76	P3	Lung mass	89	638	Mild/No	Face mask (100% O ₂)	5
14	69	P4	COPD hypoxemia	17	1680	Mild/probable	Increased O ₂ flow, tactile/verbal stimulation	3

COPD indicates chronic obstructive pulmonary disease; MOAA/S, Modified Observer's Assessment of Alertness/Sedation.