Minimal and Moderate Sedation

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Content

- Why sedation?
- Current sedation practice
- Guidelines from professional society governing sedation practice
- Pharmacologic properties of sedatives
- Monitoring of patients undergoing sedation
- Clinical data on fospropofol for sedation

Procedural Sedation

- Over 40 million procedures performed each year with moderate sedation
- About 23 millions endoscopic procedures performed annually
- Depending of the intended level of sedation, sedation is performed by trained nurses as well as anesthesia personnel
- Approximately two-thirds of the endoscopic procedural sedation performed by non anesthesia personnel

Importance of Sedation

- Relief of anxiety and fear
- Relief of discomfort
- Increase patient compliance with screening/surveillance guidelines
- Enhance quality of the examination
- Minimize risks and physical injury to the patients
- Improve over experience and satisfaction

Common Sedation Sites

- Colonoscopy
- Bronchoscopy
- Gastroscopy
- cardiac catheterization
- Office based outpatient surgery
- Emergency department

Colonoscopy

- Safe
- Complications can occur
- Majority are cardiopulmonary complications, e.g. over sedation, hypoventilation, aspiration, vasovagal
- CV complication rate: 2-4/1000
- Patients at risk: elderly, morbidly obese

Overview of agents used for minimal to moderate sedation

Characteristics of an Ideal Sedative

- Rapid onset of action allows rapid recovery after discontinuation[1]
- Effective at providing adequate sedation with predictable dose response[1,2]
- Easy to administer[1,3]
- Lack of drug accumulation[1]
- Few adverse effects[1-3]
- Minimal adverse interactions with other drugs[1-3]
- Predictable dose response[2]
- Cost-effective[3]

[1]Ostermann ME, et al. *JAMA.* 2000;283:1451-1459.
[2]Jacobi et al. *Crit Care Med*. 2002;30:119-141.
[3]Dasta JF, et al. *Pharmacother.* 2006;26:798-805.
[4]Nelson LE, et al. *Anesthesiol*. 2003;98:428-436.

Pharmacological Agents in MAC

- Hypnotics
  - Midazolam
  - Propofol
  - Methohexital
  - Ketamine
  - Nitrous oxide
  - Dexmedetomidine
- Analgesics
  - Opioids
    - Fentanyl
    - Meperidine
    - Hydromorphone
    - Morphine
  - Local anesthetics
  - NSAIDS

Current Sedation Practice

- 99% of colonoscopies are performed with sedation
  - 75% with benzodiazepine and opioid
  - 25% with propofol and opioid
    - 93% sedation with propofol performed with the presence of anesthesia professional

Cohen et al. Am J Gastroenterol 2006;101:967-74

Sedation Standard
Drugs Used in Sedation

- Opioid and Benzodiazepine combination
- Benefits
  - 1 + 1 = 4
  - Effective in 85% of patients
  - Reversal drugs available
- Challenges
  - Significant pharmacodynamic variability
  - Drug interactions
  - Potential for respiratory depression

Cohen L. Gastroenterology 2007;133-675-701

Challenges Continued

- Challenges
  - Delayed recovery, not “clear headed”
  - Patients unable to recall postprocedural discussions
  - Potential for nausea and vomiting, drowsiness
  - Duration of effect may persist for more than 24 hours

Jonas DE. AM J Gastroenterol 2007;102;2401-10

Midazolam

- Highly lipophilic
- Onset of action in 1 to 2 minutes
- Offset: rapid redistribution
- $T_{1/2}$= 1.8-6.4 hrs
- Metabolism - hepatic and renal routes
- Prolonged action in elderly, hepatic and renally impaired
- >65 – use half doses

Midazolam

- wide range of midazolam blood levels associated with adequate sedation
- Alcoholics: decreased sensitivity to drug
- Elderly: greater depressant effects
- Stimulatory effects in some patients
- cytochrome P450 (CYP) 3A4 oxidases

Diazepam

- longer half-life
- a greater chance of phlebitis
- has less amnestic properties
- initial bolus of 2.5 to 5.0 mg.
- Incremental doses of 2.5 mg can be given in 3 to 4 minute intervals.

Opioids

- Fentanyl
  - Synthetic opioid
  - Fast onset
  - 25-50 mcg, total doses <200 mcg
  - Titrate to comfort
- Meperidine
  - 50-100 mg
- Hydromorphone

Pharmacological Antagonists

- Flumazenil
  - For reversing benzodiazepines
  - Does not reverse respiratory depression
  - 0.2 mg boluses up to 3 mg
  - Risk of resedation
- Naloxone
  - Central opioid antagonist
  - Short acting, renarcotization risk
  - 40-100 mcg
  - Risk of pulmonary edema

Continuum of Depth of Sedation

	Minimal sedation (anxiolysis)	Moderate sedation/ analgesia ("conscious sedation")	Deep sedation/ analgesia	General anesthesia
Responsiveness	Normal response to verbal stimulation	Purposeful** response to verbal or tactile stimulation	Purposeful** response following repeated or painful stimulation	Unarousable even with painful stimulus
Airway	Unaffected	No intervention required	Intervention may be required	Intervention often required
Spontaneous ventilation	Unaffected	Adequate	May be inadequate	Frequently inadequate
Cardiovascular function	Unaffected	Usually maintained	Usually maintained	May be impaired

** Reflex withdrawal from a painful stimulus is NOT considered a purposeful response.

http://www.asahq.org/publicationsAndServices/standards/20.pdf, 2004

Standards for procedural monitoring for minimal to moderate sedation

Evaluation of Patients Undergoing Sedation

- History and physical exam
- Review of current medications and allergies
- Assessment of cardiopulmonary status
- Patient instruction – e.g. NPO

Sedation-related risk factors

- Sedation-related risk factors include:
  - significant medical conditions such as extremes of age, severe pulmonary, cardiac, renal or hepatic disease, pregnancy,
  - the abuse of drugs or alcohol
  - uncooperative patients
  - a potentially difficult airway for intubation.

Monitoring

- Patients undergoing endoscopic procedures with moderate or deep sedation must have continuous monitoring before, during, and after the administration of sedatives.
- Standard monitoring
  - heart rate (ECG), blood pressure, respiratory rate, and oxygen saturation

Monitoring for Sedation

- Nurse-Patient interaction
- Sedation Scores – Ramsay, OAAS/S
- Monitors
  - Pulse oximetry
  - ET CO2
  - Depth of sedation monitor: EEG based
    - BIS, Sedline, AEP, Entropy

Observer's Assessment of Alertness/Sedation Scale (OAAS)

Scores	Descriptions
5	**Responds readily to name spoken in normal tone**
4	**Lethargic response to name spoken in normal tone**
3	**Responds only after name is called loudly and/or repeatedly**
2	**Responds only after mild prodding or shaking**
1	**Responds only after painful trapezius squeeze**
0	**No response after painful trapezius squeeze**

Post procedural Management

- Post-procedural monitoring including observation and vital sign monitoring
- Post-procedure written instructions for patients

Guideline statements by ASA, AGA, ASGE, AAAASF, and others professional societies on conscious sedation

Professional Societies Guidelines

- ASA, AGA, ASGE, AAAASF, AANA all have specific guidelines on sedation for endoscopic procedures
- Purpose is to ensure patient safety

What are the national organizations' positions?

- The American Association for the Accreditation of Ambulatory Surgical Facilities (AAAASF) has explicitly taken the position that propofol, unlike other intravenous sedation, may not be administered by a registered nurse.

ASA and AANA

- The joint ASA/ AANA statement on propofol use indicates that, “personnel who administer propofol should be qualified to rescue patients whose level of sedation becomes deeper than initially intended and who enter, if briefly, a state of general anesthesia.”

JCAHO

- The Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requires that clinicians intending to administer deep sedation be qualified to rescue patients from general anesthesia and be competent to manage an unstable cardiovascular system as well as a compromised airway and inadequate oxygenation and ventilation.

AGA, ACG and ASGE

- The American Gastroenterological Association (AGA), the American College of Gastroenterology (ACG), and the American Society for Gastrointestinal Endoscopy (ASGE) issued a joint statement supporting nurse-administered propofol by nonanesthesiologists for endoscopy.

- Mild to moderate sedation
  - Non anesthesiology personnel
- Deep sedation and general anesthesia
  - Anesthesia personnel

Approved Drugs for Monitored Anesthesia Care

Propofol

- highly lipophilic
- Large Vd
- Triphasic distribution
  - Rapid redistribution – 2-3 min
  - Metabolism
  - Slow elimination from adipose tissues

Advanatges of Propofol

- Rapid onset
- Rapid offset
- Optimal sedation level
- Antiemetic

Propofol Metabolism

- Eliminated as sulfate and/or glucuronide conjugates in the urine
- Less than 0.3% excreted as the parent compound
- Extra hepatic metabolism
- Hepatic and renal dysfunction do not significantly alter the pharmacokinetics of propofol
- Elderly – lower Vd and lower clearance, lower doses needed

Caution on sedation

- Sedation is a continuum
- rapid, profound changes in sedative depth
- non-anesthesia personnel who administer propofol should be qualified to **rescue** patients from deeper level of sedation
- education and training to manage the potential medical complications of sedation/anesthesia

Adverse Effects of Propofol

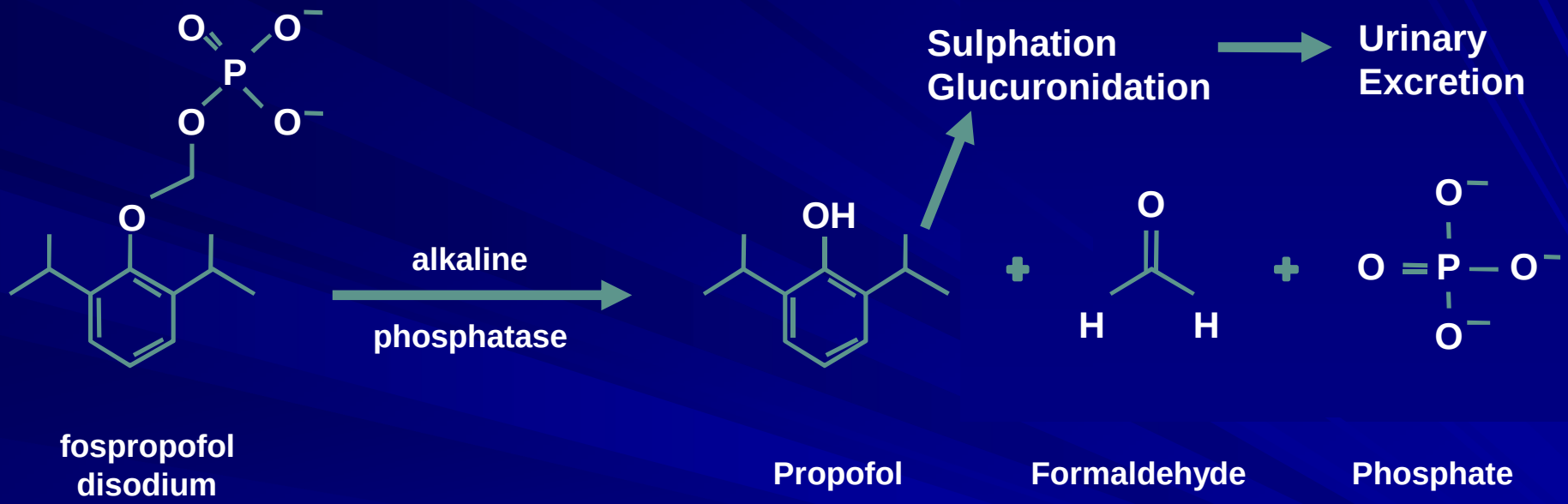
- IV injection site pain
- Hypotension especially in hypovolemia
- Hypoxia
- Microbial contamination
- lipidemia > 3 days of infusion
- Green discoloration of the urine

Pharmacodynamics and pharmacokinetics of fospropofol

Fospropofol

- new sedative/hypnotic agent
- Fospropofol – water soluble prodrug of propofol
- Developed in an attempt to reduce the disadvantages of the lipid emulsion of propofol
- enzymatic action of alkaline phosphatases in the vascular endothelium

Fospropofol Disodium Metabolism (Enzymatic Liberation of Propofol)



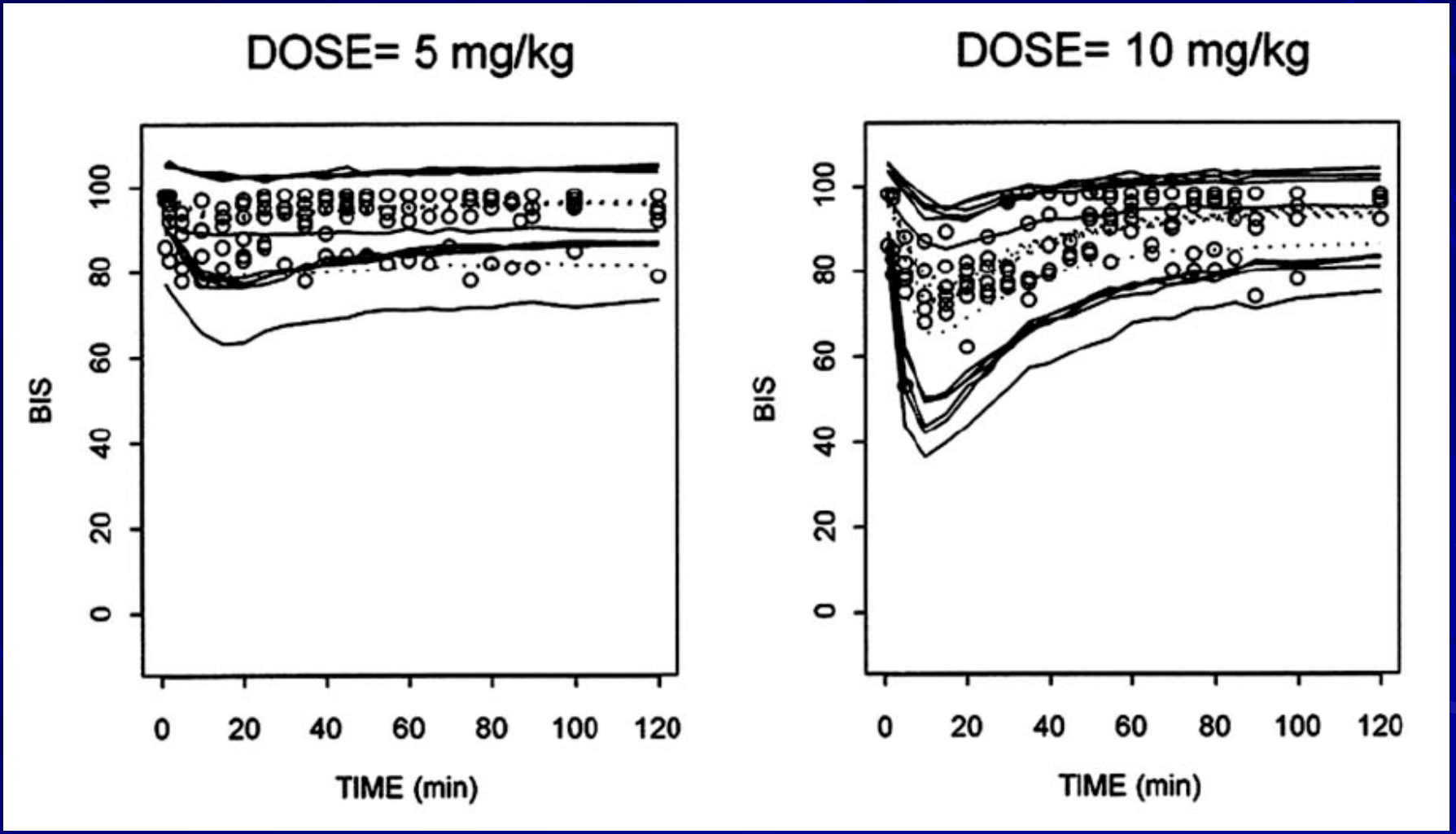
- Water-soluble prodrug of propofol with differentiated PK/PD
- Alkaline phosphatase is widely distributed in body
- Fospropofol disodium is rapidly and completely metabolized

Fechner J, et al. *Anesthesiology.* 2003;99:303-1313.

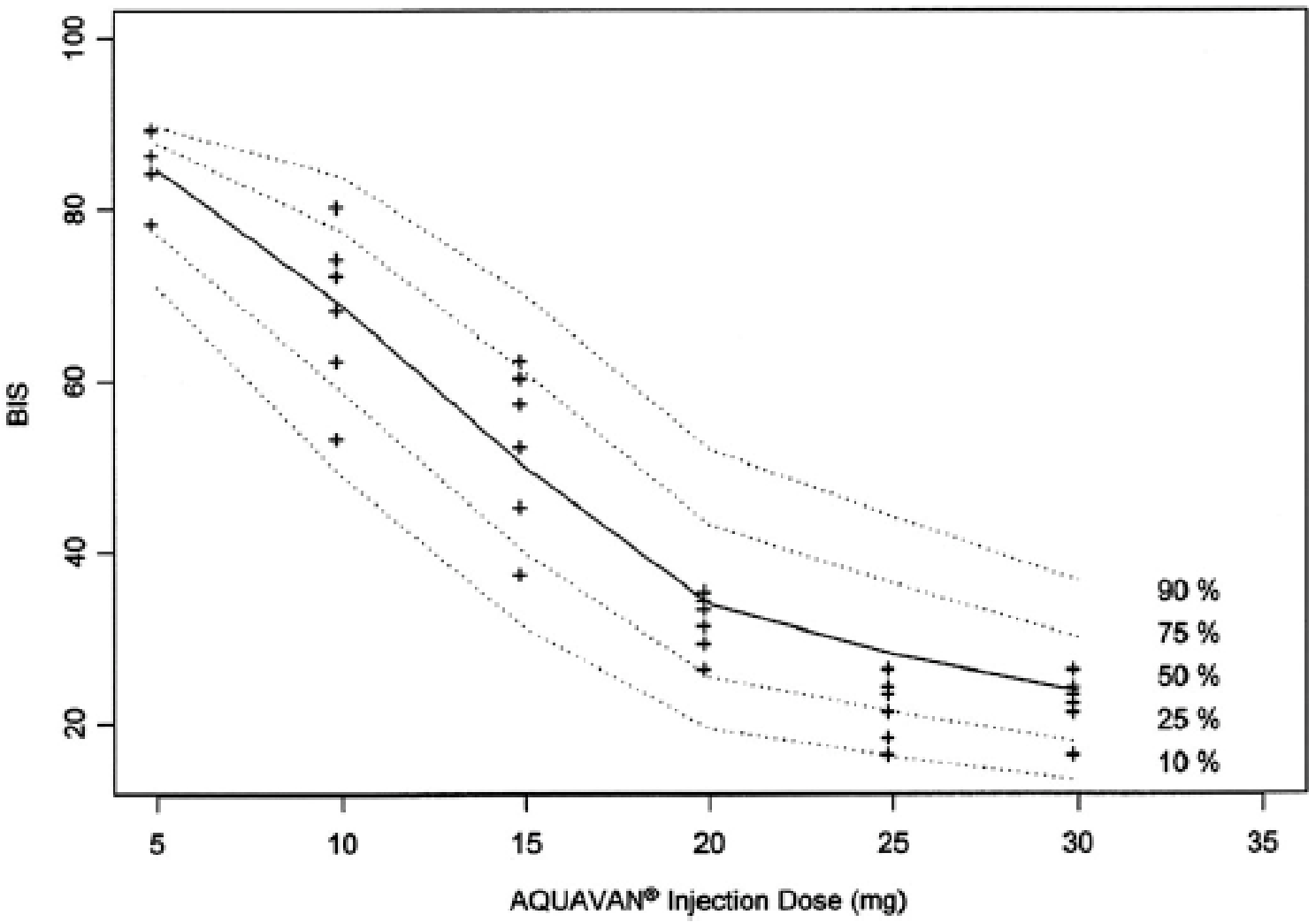
Fospropofol - PK and PD

- Non-linear, 6 compartments with an effect site compartment
- longer half-life, larger Vd, and a delayed onset of action compared with propofol
- lower peak concentrations and more prolonged plasma concentrations
- No pain on injection in the arm
- Parasthesia and itching in the perineal region

Fospropofol PD – Single bolus and BIS Levels



Fospropofol Doses and BIS Levels



Clinical profiles of fospropofol

Dose titration

- The solution for a steep concentration-response relationship
  - Administer small fractions of initial dose
- Phase II/III studies for Aquavan do nicely follow this guideline
  - Fospropofol 6.5 mg/kg as initial dose followed by ¼ of this dose (1.6 mg/min) every 4 minutes up to a maximum of 3 repeat doses
  - 'Sedation failure' rate of approximately 20%
  - At least 15 minutes would be required to reach 'sedation failure' decision

Fospropofol Sedation Success during Colonoscopy

Cohen LB. ***Alimentary Pharmacology & Therapeutics*** 27 **(7), 597-608.**

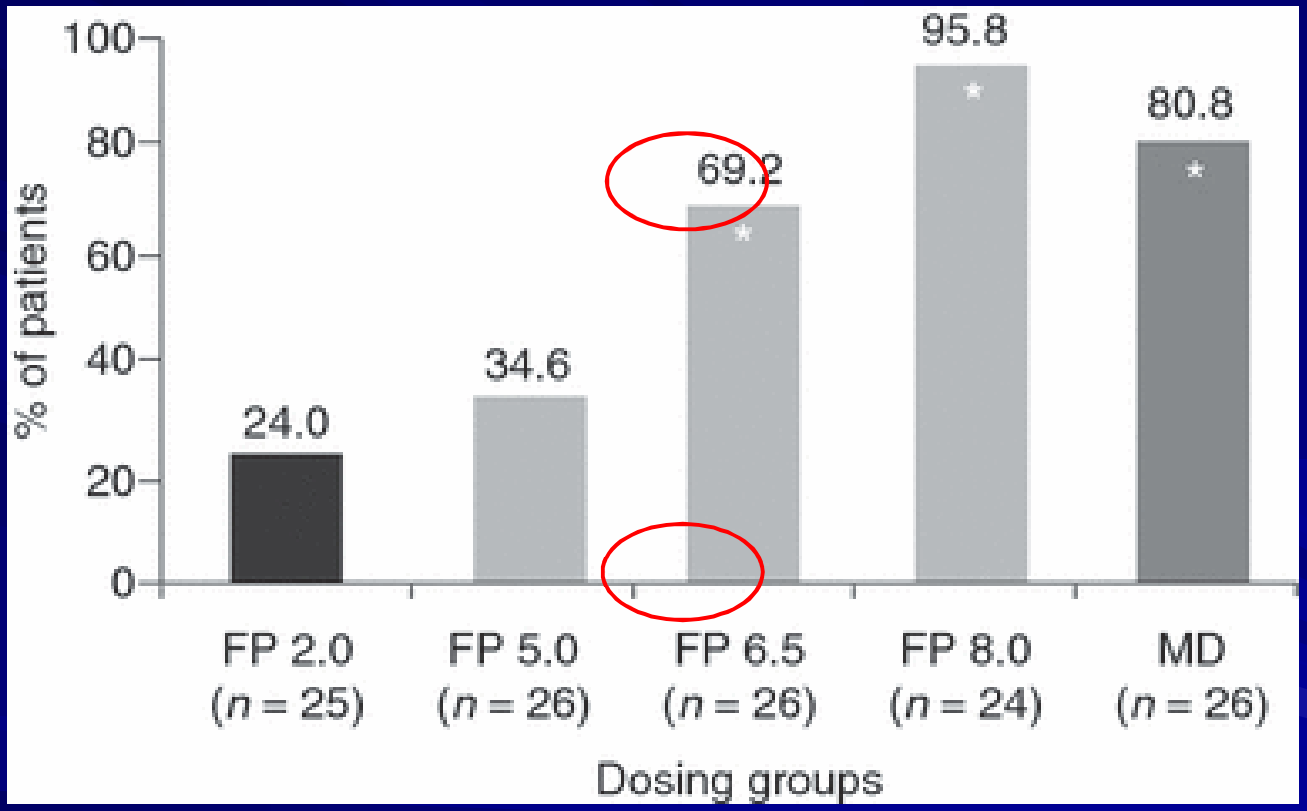


Figure 1. Sedation success. The primary end point of this study was sedation success, where a highly significant dose-dependent trend was observed across fospropofol dosing groups in the modified intent-to-treat population ($P < 0.001$ by Cochran–Armitage trend test). The sedation success rates were 24%, 35%, 69% and 96% in the FP 2.0, FP 5.0, FP 6.5 and FP 8.0 groups respectively. *$P < 0.05$ vs. FP 2.0 and FP 5.0.

Fospropofol Sedation during Colonoscopy - Outcomes

Parameter	Fospropofol				Midazolam (n = 26)
	FP 2.0 (n = 25)	FP 5.0 (n = 26)	FP 6.5 (n = 26)	FP 8.0 (n = 24)	
Treatment success, n (%)	9 (36)	11 (42)	21 (81)*	23 (96)†	23 (89)†
Time to sedation, mean (±s.d.; min)	12.4 (±5.0)	11.0 (±6.9)	6.5 (±4.5)	4.7 (±2.4)	5.0 (±4.2)
Received alternative sedative, n (%)	16 (64)	15 (58)	5 (19)	1 (4)	2 (8)
Number of supplemental doses of sedative, mean (±s.d.)	2.4 (±1.3)	2.3 (±1.2)	2.1 (±1.2)	1.3 (±1.2)	3.3 (±1.7)
Number of supplemental doses of fentanyl, mean (±s.d.)	1.0 (±0.7)	0.9 (±0.7)	0.7 (±0.7)	0.5 (±0.6)	0.6 (±0.6)
Time to ready for discharge from the end of the procedure, mean (±s.d.; min)	15.0 (±19.6)	7.8 (±10.5)	9.1 (±7.8)	14.2 (±13.4)	10.2 (±14.1)

P-value not significant except where indicated: * P = 0.002 vs. fospropofol 2 mg/kg; † P < 0.001 vs. fospropofol 2 mg/kg.

Patients and Physicians Satisfaction

Table 5. Patient and doctor ratings of success (modified intent-to-treat)

Parameter	Fospropofol				Overall *P*-value among fospropofol groups	Midazolam (n = 26)
	FP 2.0 (n = 25)	FP 5.0 (n = 26)	FP 6.5 (n = 26)	FP 8.0 (n = 24)		
Patient satisfaction						
Patient overall satisfaction rated as high (9–10; %)	72.0	84.0	92.3	79.2	0.2793	69.2
Percent of patients remembering being awake	58.3	52.0	42.3	33.3	0.3356	65.4
Percent who would be treated with this sedative again	80.0	84.0	96.2	91.7	0.2832	100
Doctor satisfaction						
Doctor overall satisfaction rated as high (9–10; %)	8.0	11.5	26.9	50.0	0.0028	11.5
Believe patient was adequately sedated	32.0	38.5	80.8	83.3	<0.001	65.4
Percent who would use this sedative again	24.0	57.7	92.3	83.3	<0.001	76.9

Fospropofol for Colonoscopy-Adverse Events

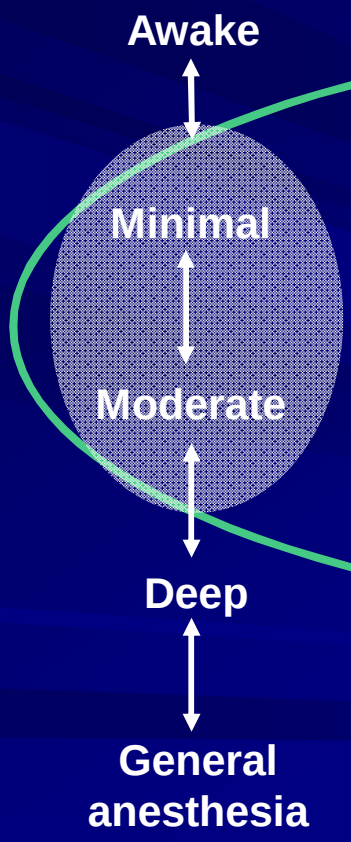
Parameter, *n* (%)	Fospropofol					Midazolam (*n* = 26)
	FP 2.0 (*n* = 27)	FP 5.0 (*n* = 26)	FP 6.5 (*n* = 25)	FP 8.0 (*n* = 23)	All fospropofol groups (*n* = 101)	
Treatment-emergent AEs	22 (82)	22 (85)	24 (96)	17 (74)	85 (84)	16 (62)
TRAEs	14 (52)	19 (73)	19 (76)	10 (44)	62 (61)	2 (8)
Paraesthesia*	13 (48)	15 (58)	14 (56)	7 (30)	49 (49)	1 (4)
Pruritus†	1 (4)	3 (12)	2 (8)	3 (13)	9 (9)	0
Hypotension	0	1 (4)	1 (4)	0	2 (2)	0
Hypoxaemia	0	0	2 (8)	0	2 (2)	0
Abdominal pain	0	0	0	1 (4)	1 (1)	0
AE-related discontinuation of procedure	0	0	0	0	0	1 (4)
Sedation-related AEs‡	0	1 (4)	3 (12)	0	4 (4)	0
Hypotension	0	1 (4)	1 (4)	0	2 (2)	0
Hypoxaemia	0	0	2 (8)	0	2 (2)	0

Fospropofol for Bronchoscopy

Parameters	Fospropofol Groups	
	2 mg/kg (n = 102)	6.5 mg/kg (n = 150)
Patient ratings		
Remembers being awake during scope insertion	47 (46.5)	19 (12.7)
Remembers being awake during procedure	45 (44.6)	25 (16.7)†
Remembers having scope removed	40 (39.6)	16 (10.7)
Agrees to use sedative again	79 (78.2)	141 (94.6)†
Overall satisfaction with entire procedure‡		
1–5	8 (7.9)	1 (0.7)
6–8	22 (21.8)	21 (14.1)
9–10	71 (70.3)	127 (85.2)
Overall comfort level during procedure§		
1–5	11 (10.9)	7 (4.7)
6–8	24 (23.8)	13 (8.7)
9–10	66 (65.3)	130 (86.7)

Use of fospropofol for other procedures requiring minimal to moderate sedation

Modified Observer's Assessment of Alertness/Sedation Scale (MOAA/S)



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

Chernik DA, et al. *J Clin Psychopharmacol.* 1990;10:244-251.
ASA Practice Guidelines. *Anesthesiology*. 2002;96:1004-1017.

Procedure Types and Duration

Procedure	Fospropofol 6.5 mg/kg	Duration of Procedure (min)		
	Patients, n (%) N = 123	Median	Min	Max
Esophagogastroduodenoscopy	27 (22)	4	2	25
Arthroscopy	22 (17.9)	17.5	12	26
Hysteroscopy	21 (17.1)	12	3	31
Bunionectomy	18 (14.6)	43.5	26	105
Transesophageal echocardiogram	13 (10.6)	14	4	26
Ureteroscopy	10 (8.1)	12	8	32
Lithotripsy	8 (6.5)	29.5	24	56
Dilatation & Curettage	3 (2.4)	8	7	26
Arteriovenous fistula	1 (0.8)	45	---	---

Adverse Events

- Majority of adverse events (AEs) were mild to moderate
- Serious AEs (n = 4)
  - n=2 atrial septal defect, n=1 apnea and cardiac arrest, n=1 increased ammonia and hepatic encephalopathy
- Treatment-related AEs
  - Most common were perineal paresthesias (53.7%) and pruritus (26.0%)
- Sedation-related AEs (5 patients, 4.1%)
  - Hypoxemia (n=1, <1min and managed with verbal stimulation and chin lift)
  - Hypotension (n=4, occurred during the dosing and recovery periods)
  - Bradycardia (n=1 concurrently with hypotension and managed with atropine)
- No deaths reported and no procedure discontinued due to adverse event

Hepatic and Renal Impairment

- 20/123 (16%) patients had previous or existing hepatic disease (minimal – severe)
- 5/123 (4%) patients had severe renal impairment (creatinine clearance 11-36 mL/min)
- Adverse event rates were similar to overall population
  - Treatment-related AEs were similar to other patients (paresthesia 50%, pruritus 30%)
- No sedation-related adverse events reported

Package Insert for Fospropofol Similar to Propofol

"For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injectable Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure."

Future

- Better pharmacological agents
  - Better sedatives and analgesics
- Better delivery system
  - Patient-controlled sedation
- Better monitoring system
  - Closed-loop control

Conclusions I

- Sedation ensures that patients are comfortable when undergoing minor medical and surgical procedures
- Constant monitoring of patients during sedation ensures safety and a good outcome
- Practitioners caring for patients under sedation should be properly educated on the pharmacology of the drugs used during sedation as well as how to combine hypnotics and analgesics

Conclusions II

- Minimum and moderate sedation can be safely performed by sedation nurses under the supervision of the physician
- Deep sedation should be cared for by medical personnel with the appropriate training and appropriate monitoring technology
- Propofol and fospropfol are efficacious and safe when administered by medical personnel with the appropriate training and appropriate monitoring technology.

Conclusions III

- Even if moderate sedation is intended, patients receiving propofol or fospropofol should receive care consistent with that required for deep sedation.
- This means that the clinician administering propofol or fospropofol must be competent to recognize a state of general anesthesia and rescue a patient experiencing any of the complications of general anesthesia.