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A Successful Experience: Safety and Efficiency of Balanced Sedation with Propofol and Remifentanil in Diagnostic Endoscopy

Camilo Blanco A., MD, MSc Edu,[1] Karen Russi G., MD,[2] Diana Chimbi, Enf,[3] Alberto Molano A., MD,[4] Alix Forero, MSc Edu.[5]

1 Gastrointestinal Surgery and Digestive Endoscopy, Master's in Education, Associate Instructor in the Faculty of Education at the Universidad El Bosque and Medical Director at the Videoendoscopy Unit of Restrepo Ltda in Bogotá, Colombia. Email: camiloblancoa@gmail.com
2 Anesthesiologist at the Videoendoscopy Unit of Restrepo Ltda in Bogotá, Colombia
3 Professional Nurse and Epidemiologist, Bogotá, Colombia
4 Anesthesiologist at SEDARTE and the Videoendoscopy Unit of Restrepo Ltda in Bogotá, Colombia
5 Speech Therapist, Master's in Education.

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Abstract

Sedation is an anesthetic technique that is widely used in current digestive endoscopic procedures because of its clear benefits for patients' tolerance and comfort and for the endoscopist. Propofol is the most commonly used drug in monosedation, but balanced regimens using more than one drug are now widely used in diagnostic and therapeutic endoscopy. Balanced sedation using Propofol and Remifentanil allows synergistic potentiation of a sedative with an ultra-short acting opioid which in turn favors decreases of each dose. This is a series of 1,148 patients who underwent diagnostic endoscopy under balanced sedation with average Remifentanil doses of 0.9 mcg/kg of body weight and average Propofol doses of 0.47 mg/kg of body weight. There were no serious adverse events, endoscopists were highly satisfied with the procedures, and costs per drug dose were very low. This is clearly a safe and efficient scheme.

Keywords

Sedation, diagnostic endoscopy, propofol, remifentanil, balanced sedation.

INTRODUCTION

Sedation is the pharmacologically controlled alteration of a patient's state of consciousness to allow procedures that can be bothersome and painful. It ranges from anxiolysis to general anesthesia. (1, 2) The level of depression of the nervous system is a continuum which is not absolutely controllable which can reach deeper levels if specific drugs are used in appropriate doses that are relevant to the complexity of the procedure to be performed. (3)

In diagnostic digestive endoscopy, the main objectives of sedation is to guarantee the tranquility, comfort and cooperation of the patient throughout the procedure. Other secondary objectives are aimed at generating amnesia, reducing or eliminating nausea and even at effectively controlling pain associated with some interventions. (4)

Within the overall process of assuring quality patient care, sedation is considered to contribute to greater precision and accuracy of examinations with decreased levels of the fear associated with these procedures. At the same time, safety must be ensured through prevention, control and management of complications inherent to administration of sedation. These can include hypoxia, hypotension, bradycardia, chest thorax, allergic reactions, oral-tracheal intubation, unscheduled hospitalization and even death. (5)

We began our experience with sedation in 2002 after learning about the various possible schemes for different types of endoscopic procedures. With the participation of an anesthesiologist, we used several schemes for upper digestive endoscopy and lower diagnostic endoscopy. We used single-drug sedation, two drug regimens and three drug regimens with midazolam, fentanyl, propofol, remi-

fentanil and/or ketamine. Our criterion was practical cost efficiency understood as the lowest cost of care and the least time necessary for recovery.

Balanced sedation is understood as the use of more than one anesthetic, sedative or analgesic agent in a proportion that guarantees anxiolysis, sedation, analgesia and amnesia. (7, 8) We present our successful experience, with no significant adverse events, of a series of 1,148 selected patients who underwent diagnostic endoscopy performed by a single endoscopist (Camilo Blanco) with a balanced sedation scheme administered by a single anesthesiologist (Karen Russi). The scheme called for 10 mg/mL of 1% propofol-Profol® and 2 mg 20 µg/mL remifentanil Ultiva® to achieve sedation levels II and III (reduced anxiety and sedated but conscious) according to the classification in Table 1. (4)

MATERIALS AND METHODS

Type of study

This is a retrospective descriptive study of procedures performed at the Videoendoscopy Unit of Restrepo Ltda., an IPS (Institucion Prestadora de Servicios - service provider institution) located in the south central part of the city of Bogotá. Patients underwent diagnostic endoscopy during the period between May 2013 and November 2014. Because this was not an experimental study, it did not require consent for the inclusion of patients in the database. The study was approved by the ethics committee of the unit.

Inclusion Criteria

With institutional approval, 1,148 consecutive patients attended by a single specialist in gastrointestinal surgery and digestive endoscopy (CB) and only one of the anesthesiologists of the working group (KR) were registered. Patients included had no significant cardiac, pulmonary or metabolic comorbidities, and were classified as Level I or II according to the American Society of Anesthesiology (ASA). (9)

All patients provided informed consent prior to performance of procedures under sedation. This series includes only patients treated on Tuesdays and Saturdays of the week on dates upon which the two main investigators agreed.

Exclusion Criteria

In this institution, patients are not treated at ASA III or IV levels. Patients with known allergies to the drugs used, to eggs or to soybeans, and patients who rejected sedation were excluded.

Objective

The objective of this series was to analyze and show the safety and efficiency of the balanced sedation system using propofol and remifentanil in diagnostic upper digestive endoscopies in an open schedule outpatient setting. Safety was determined by the absence of adverse events associated with sedation. Events considered include hypoxia, hypotension, bradycardia, chest thorax, allergic reactions, orotracheal intubation, unscheduled hospitalization and death.

Efficiency was determined by calculating the cost per patient of the propofol and remifentanil used in the balanced system according to age and body weight in kg. Satisfaction of sedation from the endoscopist's point of view according to a validated scale was also considered.

Conditions of Care

Administration of 3% oxygen with nasal cannula and electrocardiographic and pulse oximetry monitoring, insured that no procedures were conducted with blood oxygen saturation below 90% and blood pressure below 90/70 mm Hg or above 150/95 mm Hg. The balanced mixture was administered by the anesthesiologist in boluses injected manually

Table 1. Classification of sedation levels

Levels of sedation		Patient status	Potential events
I	Awake, alert	Protective reflexes	Excitation, agitation, removal of endoscope
II	Light sedation	Cooperative, eyes open, spontaneous breathing, responds to verbal stimuli	
III	Moderate sedation	Somnolent, eyes closed, responds to tactile stimuli	
IV	Deep sedation	Poor response to vigorous stimuli, muscle hypotonia and loss of reflexes, without spontaneous ventilation, cardiovascular stability	Hypoventilation, hypoxia
V	General anesthesia	Respiratory and cardiovascular reflex suppression, airway obstruction	Apnea, cardiorespiratory arrest

Adapted from: JR Lightdale, Gastroenterological endoscopy. 2nd edition. Venezuela: Amolca; 2012. pp 57-65

with 5 or 10 mL syringes at a rate of approximately 5 mL in 30 seconds. The total amount of the calculated mixture was administered, except when a patient presented early vertical nystagmus, had marked muscle hypotonia or evidence of suppressed ventilation during infusion. During the procedure, the anesthesiologist or assistant nurse checked the patient's response level to verbal stimuli every 15 seconds.

Hypoxia, when the patient's saturation was below 90% for a period greater than 30 seconds and did not correct with jaw hyperextension or vigorous stimulus, was considered to require intervention by the anesthesiologist. Airway control was used if persistent respiratory depression or hypoxia could not be corrected with positive pressure from a manual ventilation device.

Upper endoscopy was performed according to the parameters of systematic endoscopy described by Yao and all included a biopsy according to the Sidney system. (10, 11)

At the end of each examination, the endoscopist assigned a satisfaction score according to the scale: easy procedure for sedation levels II and III, adequate procedure for level IV sedation, and difficult procedure for sedation levels I or V. (12)

After procedures, patients were transferred to a recovery room where they were monitored and by another nursing assistant. They were discharged with the authorization of the anesthesiologist once they had a score of 14 on the Aldrete scale.

Statistical Analysis

The database was cleaned in Excel and processed in the Epi-Info statistical program. Univariate and multivariate analysis was performed. Continuous parameters were presented as measures of central tendency and standard deviation (SD).

RESULTS

Data were collected from 1,148 patients who underwent diagnostic upper digestive endoscopy from May 2013 to November 2014. All procedures were performed with patients under balanced sedation with propofol and remifentanil.

In the total patient sample, 59% were women and 41% were men while in the ASA II group the 68% portion of women was higher. Mean weights were 64 kg for the ASA I group, 68 kg for ASA II patients, and 66 kg for the total series (Table 2).

Seven hundred ninety-three patients (69%) were classified as ASA I. Of these, 83% were between 17 and 59 years of age. Only 4% were younger than 17 years, 11% (n = 90) were between 60 and 74 years and 1% (n = 11) were older than 75 years.

Three hundred fifty-five patients (31%) were classified as ASA II, but unlike the ASA I group, only 51% were between 17 and 59 years old. Proportionally, the 60-74 age group grew to 35% (n = 123), and 14% (n = 50) were older than 75 years (Figure 1 and Table 3).

Table 2. General characteristics

	ASA					
	I		II		Total	
Sex						
Women	440	55%	242	68%	682	59%
Men	353	45%	113	32%	466	41%
Total	793	69%	355	31%	1148	
Weight (kg)						
Mean	64		68		66	

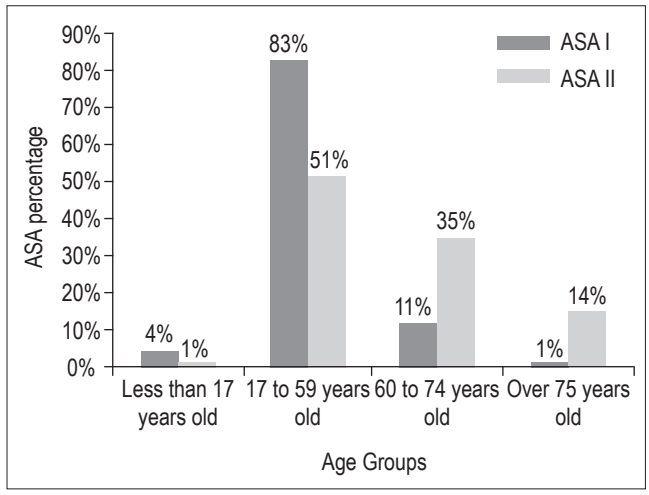

Figure 1. Distribution by age group and ASA classification.

Table 3. Distribution by age groups and ASA classification

General Characteristics	ASA					
	I		II		Total	
Age Groups	N	%	N	%	n	%
Less than 17 years	35	4%	2	1%	37	3%
17 to 59 years	657	83%	180	51%	837	73%
60 to 74 years	90	11%	123	35%	213	19%
More than 75 years	11	1%	50	14%	61	5%
Total	793	69%	355	31%		1148

Doses per kg of weight varied according to age. The average dose of remifentanil given to patients under the age of 17 years was .09 μg (SD ± 0.06 μg), those between 17 and 59 years old were given 0.98 μg (SD ± 0.126 μg). These dosages are in agreement with the general average dose of 1 μg per kg of body weight. It should be noted that the mean dose in elderly patients was decreased to 0.76 μg for patients bet-

ween 60 and 74 years of age (SD ± 0.125 µg) and to 0.71 µg (SD ± 0.126 µg) for patients over 75 years of age.

Average propofol dosage for patients under17 years was 0.57 ± 0.06 mg/kg of weight, and for patients between 17 and 59 years old, the average dosage was 0.49 ± 0.06 mg/kg. These dosages are in accordance with the general average dose per kilogram of weight mentioned. For patients between 60 and 74 years of age, the dose was 0.39 ± 0.06 mg7kg and for patients over 75 years the mean dosage was 0.37 ± 0.06 mg/kg (Figure 2, Table 4).

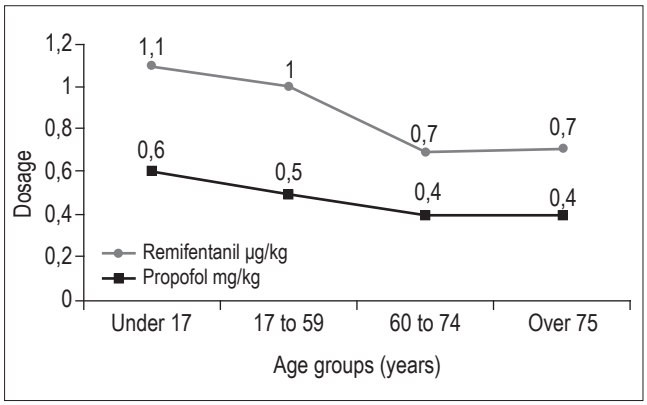

Figure 2. Ideal dose per kg of weight by age group.

Ninety-four percent (n = 1084) of the sedation levels achieved were in ideal levels II and III. Three percent (n = 34) were in level IV, and patients required vigorous stimulation to maintain ventilation. Only 2% (n = 28) reached level V sedation. All of these were due to hypoxemia that required positive pressure. Only one patient required oral-tracheal intubation which was done under relaxation with succinylcholine. This was necessitated by a laryngeal spasm, a condition that, according to the patient's history, had previously presented spontaneously during episodes of coughing. There were no events of hypotension, anaphylaxis, bradycardia or death in this series. This was especially due to rapid intervention with ventilation support for patients at sedation levels IV and V (Table 5).

The gastroenterologist's perceptions of satisfaction indicated that, under sedation, endoscopy was an easy procedure in 94% (n = 1084) of these cases which are related to sedation levels II and III. He considered that the procedure could be performed adequately in 3% (n = 34), the same number of patients with sedation level IV. Three percent of the procedures (n = 30) were perceived to be difficult. These included patients who were agitated, who struggled, and/or those attempted to remove the endoscope during the initial step of the procedure. Also included are those who had nausea and those who did not recover ventilation with vigorous stimulus and required ventilation assistance directed by the anesthesiologist. Once spontaneous ventilation was restored, endoscopy was be completed in all patients, including the patient who required intubation (Table 6).

The average per patient drug cost was sixty-six cents in US dollars or COP 2,006: COP 861 for propofol and COP 1,145 for remifentanil dollars. This calculation uses an exchange rate of USD 1.00 = COP 3,000, mean patient weight of 66 kg, and a mixture of 0.5 mg/kg propofol and 1 µg/kg remifentanil. It also uses the drug costs in Colombia as of October 2016 which were COP 261 for 10 mg of propofol and COP$ 347.14 for 20 µg of remifentanil (Table 7).

DISCUSSION

Various studies that have compared endoscopy with sedation to endoscopy without sedation have found that the latter provides greater tolerance for the patient and better acceptance of a repetition of the procedure. (13, 14) Thus, we consider sedation to be an integral component of modern endoscopic procedures since the development of different techniques of sedation has allowed for better tolerance and has reduced anxiety, pain and unpleasant memories associated with prolonged periods of intervention as in endoscopic retrograde cholangiopancreatography [ERCP] and endoscopic ultrasonography [UES]) and in cases for which it is necessary to repeat the examination to follow up on patient pathologies, as in the case of patients at risk for cancer. (15, 16)

The ideal sedation scheme should have quick onset of sedative and analgesic action, with easy control of the desired level of sedation, rapid disappearance of the sedative effect and, therefore, rapid recovery. All of this is needed to maintain adequate safety for the patient. (17)

Tabla 4. Dosis por kg de peso y por grupos de edad

	Dose per kg of body weight			
Age groups	Less than 17 years	17 to 59 years	60 to 74 years	More than 75 years
Remifentanil, mean µg/kg ± SD	1.09 ± 0.06	0.98 ± 0.126	0.76 ± 0.125	0.71 ± 0.126
Propofol, mean mg/kg ± SD	0.57 ± 0.06	0.49 ± 0.06	0.39 ± 0.06	0.37 ± 0.06
Total Patients: 1,148				

Table 5. Sedation levels achieved according to ASA

Sedation levels	ASA					
	I		II		Total	
	n	%	n	%	n	%
I	2	0%	0	0%	2	0%
II-III	752	95%	332	94%	1084	94%
IV	25	3%	9	3%	34	3%
V	14	2%	14	4%	28	2%

Table 6. Satisfaction of the endoscopist and relationship to ASA

Satisfaction of endoscopist	ASA I		ASA II		Total	
Adequate	25	3%	9	3%	34	3%
Easy	752	95%	332	94%	1084	94%
Difficult	16	2%	14	4%	30	3%
Total	793	69%	355	31%	1148	100%

Table 7. Average drug costs in Colombian pesos and US dollars for a 66 kg patient at ideal doses

Drug	Average cost per patient	
	COP	US
Remifentanil	1,145	0.38
Propofol	846	0.28
Total	2006	0.66

Safety

Sedation's safety profile is based on the fact that the team working together on the endoscopic procedure has clearly defined the level of sedation to be reached understanding sedation as a continuum from anxiolysis to general anesthesia that is not completely controllable. The level sought is determined primarily by the type of procedure to be performed, but factors inherent to the patient must also be considered. (1, 18) Under mild to moderate levels of sedation in which the patient is conscious, the patient can respond to simple or soft verbal or tactile commands to increase the frequency or depth of breathing, suppress swallowing, or keep limbs immobile. (19) At the same time cardiorespiratory functioning and protective reflexes which suppresses nausea and improve patient cooperation are maintained. (4)

On the one hand, the risks associated with sedation require that all personnel involved, anesthesiologists and others, have the training and knowledge needed for detection and reversal of unwanted or unnecessary sedation for the type of procedure being performed. This should include training in basic and advanced vital support. It is particularly important that the physician in charge of sedation be exclusively responsible for administration and monitoring. (16) Other safety features have to do with equipment and accessories such as the oxygen source, a suction pump independent of the endoscope, basic and advanced respiratory management equipment, secretion aspiration probes, masks, a positive pressure device, a laryngoscope, and endotracheal tubes. Another necessary safety measure is guaranteeing that drugs for reversal of drugs used and drugs for management of allergies and advanced cardiopulmonary resuscitation are on hand. All of this is in addition to the normal requirements for monitoring equipment for blood pressure (BP), heart rate (RF), pulse oximetry, electrocardiography and possibly capnography, plus a recovery room with monitoring, oxygen source and suction and personnel specifically in charge of this area. (20, 21)

On the other hand, despite the regulations that require that when propofol is administered alone it should be done by anesthesiologists, there are multiple reviews and consensuses that support its safety and efficiency when used by adequately trained physicians and nurses. (22, 23) For example, in a series 646,080 patients, only 11 tracheal intubations were required, no permanent neurological damage occurred, and there were only four deaths which occurred in patients with significant comorbidities and were not strictly attributable to sedation. (24) Other authors have concluded that traditional sedation with benzodiazepines and opioids results in a lower mortality rates than does propofol, and an index similar to that presented in general anesthesia performed by anesthesiologists. (17) They also conclude that sedation administered by non-anesthesiologists may even have higher levels of safety in patients at ASA Levels over III provided that the person administering sedation is exclusively dedicated to managing and controlling sedation. (25-27)

Nevertheless, our institution chose to have an anesthesiologist participate in procedures and to incur the additional cost involved because of the safety an anesthesiologist provides when this procures level II or III of conscious sedation. This is so because of the confidence in his/her knowledge of resuscitation, medications, dosages and injection rates that can lead the patient into deeper levels of sedation which might generate greater risks than sedation administered by non-anesthesiologists.

Knowledge of various sedation techniques and selection of the most appropriate technique according to the experience of the endoscopy group, the procedure to be performed, the ASA classification, the patient's expectations, and available medications are important. (28) At the time of this series in 2013 and 2014, there was no obligation for the administrator of sedation to be a professional other

than the endoscopist. This was subsequently decreed in Colombia in 2014. (29)

Efficiency

In the field of digestive endoscopy, analysis of efficiency or cost-effectiveness is very difficult since many factors are involved in calculations, and a scheme or model can be enormously efficient in one scenario, but a total failure in another.

The scheme presented here has been successful for our institution, but its initial implementation generated an increase in costs in four main areas:

- Medications including propofol, remifentanil, naloxone, medications for resuscitation and oxygen
- Disposable materials including syringes, venous catheters, plugs, endotracheal tubes, suction cannulas and oxygen cannulas
- Equipment, especially monitoring systems
- Additional staff and training including anesthesiologists and nurses

Various publications have shown that sedation contributes to more complete and better quality examinations and to reduction of repeat procedures. This efficiency partially compensates for the expenses above while increased patient tolerance and satisfaction generates long term social preferences in regard to the attention received. (17)

Other parameters that have been used as measures of the efficiency of sedation systems are recovery time (from the end of the procedure to achievement of a minimum of 10 Aldrete scale), induction of sedation (time from the first injection to the beginning of sedation), quality of sedation (evaluated by endoscopists, nurses and patients, with measurement at the end of the procedure), and complications related to the procedure. (33)

In this series, the quality of sedation during endoscopy was measured according to the endoscopist's perception using a 3-level scale for the general procedure of easy, adequate and difficult. These levels refer to what the endoscopist felt were levels of patient cooperation, absence of nausea or retching, adequate maintenance of ventilation without intervention, absence of pain, acceptable level of amnesia and expression of patient satisfaction.

For the endoscopist, overall procedures were easy (94%, associated with sedation levels II and III). Adequate only accounted for 3% for sedation levels I and IV. These were cases in which either additional doses of drugs, vigorous stimulation or both were required and in which the continuity of endoscopy was momentarily interrupted without the need for removing the endoscope. Difficult cases also accounted for 3%. These were associated with Level V sedation that required interruption of the examination, ventilation assistance with a positive pressure device, and in one case with oral-tracheal intubation. Once spontaneous ventilation had recovered, the endoscope was reintroduced. (12)

Propofol and Remifentanil

Our combined unpublished experience includes more than 60,000 endoscopies under sedation. We have used different injection techniques including with infusion pumps, continuous drips, and blouses. Moreover, we have used several different single drug sedation schemes using diazepam, midazolam, fentanyl or propofol. However, in 2004, we began to use propofol-balanced sedation as originally described by Cohen et al. for moderate sedation. (8) In this regimen, balanced sedation combines small incremental doses of propofol with small doses of benzodiazepines and opioids. They can even be initially administered by a physician who is not an anesthesiologist. (30) The synergistic action of drugs in conscious sedation reduces the total dose of propofol below that required in monosedation and reduces the risk of cardiovascular complications related to its use. (31, 32) Combined use with opiates or benzodiazepines aims to achieve adequate sleepiness, amnesia and analgesia. (33)

It should be mentioned that the advent of propofol allowed us to change from the earlier previous balanced sedation scheme of benzodiazepine-opioid (midazolam with remifentanil). In that scheme respiratory depressions occurred very frequently, and their duration was longer. This has been described in other studies in which deep sedation occurred with this combination in 85% of patients who underwent examinations with endoscopic ultrasound or ERCP, 60% of those who underwent upper digestive endoscopy, and 45% of those who had colonoscopies. (34, 35) The advantage of that scheme was that the strong amnesiac effect of the benzodiazepine meant that patients had no unpleasant memories of the procedure whether it only reached Level I sedation or whether it required vigorous stimuli or ventilation assistance.

The advantages of propofol (2,6-diisopropylphenol) come from the fact that it is a very short-lived hypnotic agent with a rapid onset of action (usually between 30 and 60 seconds), a short recovery time (between 4 and 8 minutes), minimal analgesic effect and very good amnesia. It degrades in the first hepatic passage, its effects quickly terminate, and patients rapidly return to consciousness. It is highly lipophilic and rapidly crosses the blood-brain barrier but is contraindicated in patients who are allergic to eggs or soy since the most common presentation is an emulsion containing 10% soybean oil, 2.25% glycerol and 1.2% egg lecithin even though evidence that does not validate this contraindication has appeared recently. It is a cate-

gory B drug in pregnancy and should be used with caution during breastfeeding. (4)

These characteristics have made increased its use throughout the world in the last decade since it provides safety to comparable traditional sedation with benzodiazepines and opiates, (2, 14, 36, 37) and its ease of reaching deeper levels of sedation is dose-dependent which makes it a real alternative for both short-term and long-term endoscopic procedures (ERCP or UES). (38) However, its potential for inducing greater depths of sedation together with the absence of a specific antagonist has led to the norms described above that restrict its use. (4, 17) This has generated a perception of the risks that in the US has caused endoscopists to become reluctant to use propofol. (38).

On the other hand, remifentanil is a fast acting opioid whose effects begin 30 seconds after administration and which has short duration of action with a half-life of 8 to 10 minutes. For this reason, termination of its action is predictable. Its analgesic potency is similar to fentanyl, and it is 20 to 30 times more potent than alfentanil, but its duration of action is much shorter than either of the other two because it is rapidly metabolized by non-specific blood esterase and other tissues. (39) Its use in high doses causes loss of consciousness and is associated with chest wall and muscular rigidity. (40) In elderly patients doses should be reduced by 50% because onset of action may be prolonged, and the half-life may be increased. For obese patients, the dose should be calculated on the basis of the body mass index (BMI). Its effects at the cardiovascular level can be hypotension and bradycardia, and when associated with propofol it can reduce BP by 17% -23%. Nevertheless, it generally provides for good hemodynamic stability. The respiratory depression it can produce is dose dependent. Its clearance is not altered when there is hepatic or plasma cholinesterase dysfunction, but its main metabolite is elevated in patients with renal insufficiency although this has no clinical influence because its potency is low. In addition to being used as an analgesic during induction of anesthesia, it is an alternative in propofol-balanced sedation. Increases of the dose can cause chest wall rigidity glottal closure when it is administered quickly. For this reason administration through slow titration is suggested. It is not recommended for use in pregnant or breast feeding women or in children under two years old. Up to 9% of patients may have muscle stiffness, but this is reduced to 1% when used in conjunction with a potent hypnotic or muscle relaxant, either with general anesthesia or through continuous infusion. (34, 39, 41, 42)

As mentioned above, there is no specific antagonist for propofol available at this time. For remifentanil, the competitive antagonist is naloxone which should be administered intravenously to reverse the adverse effects described above. The fact that it may produce catecholamine release, tachyarrhythmia and even sudden death in patients with underlying heart disease should be taken into account. It can also cause withdrawal syndromes in narcotic -dependent patients. (4) We did not need to use pharmacological reversion in this series of patients since the most frequent event was respiratory depression at V sedation level which only required adequate patient ventilation assistance in periods of no longer than two minutes.

Balanced Sedation

There is currently sufficient evidence to demonstrate that propofol, alone or in combination with an opiate, is the drug of choice for endoscopic procedures. In the balanced sedation scheme, it is possible to reduce the dose while achieving the same hypnotic effect. Similarly, in balanced sedation the most favorable opioid for is remifentanil because of its pharmacokinetic and pharmacodynamic profile given the rapid elimination mentioned previously. Nevertheless, its potency provides only a narrow therapeutic margin that requires controlled administration by an anesthesiologist. (17)

Several studies of pancreatobiliary endoscopic procedures have compared monosedation regimens with propofol to balanced regimens. They report that the dose for intravenous (IV) 30 second bolus induction of 0.5 mg to 1.0 mg/kg of weight followed by repeated doses of 10 to 20 mg (or 0.25 mg/kg) to maintain adequate sedation according to the desired level and risk profile of the patient. Average total doses should be 185 mg, (33, 34) but this should be reduced to 106 mg when the propofol is balanced with midazolam or meperidine, (7) and to 117 mg to 175 mg in the remifentanil-ketamine balanced regimen. (34)

Since IV anesthetics such as hypnotics, opioids and benzodiazepines are known to combine synergistically and are associated to potentiate each other, (43, 44) balancing seeks to achieve their desired effects with the lowest possible doses. The association of remifentanil with propofol for endoscopic examinations, using lumbar punctures for pediatric patients, has been reported to allow extremely rapid recovery with very short durations of effects. (45) Also, remifentanil doses of 0.3 μg/kg and propofol doses of 1 mL/3 seconds reduces pain at the propofol injection site by up to 11% with a reduction in total propofol dose from 2.07 mg/kg (in monosedation) to 1.19 mg/kg (ranges between 0.51 to 1.91 mg/kg) when used in a remifentanil-balanced regimen at the dose described above of 0.3 μg/kg. (46)

Accordingly, the balanced propofol and remifentanil sedation scheme for diagnostic endoscopy fulfills ideal drug characteristics of fast connection with the site of effect, reduced accumulation in the body, rapid elimination, pharmacodynamic effects such as early hypnosis,

moderate to profound sedation, rapid and efficient control of autonomic responses, rapid return of consciousness and greater predictability of effects. This gives it a great margin of safety and prevents adverse effects. (46)

Remifentanil is a better choice than fentanyl or alfentanil because the duration of their effect may extend too far into the recovery period making them undesirable or efficient in short procedures such as diagnostic digestive endoscopies. (47)

Results of a study by Hayes in 2008 showed that by increasing the dose of remifentanil to 1.5 μg/kg and reducing the dose of propofol to 2 mg/kg, the duration of apnea increased, but the recovery time was reduced. (45) In turn, by reducing remifentanil to 0.5 μg/kg and increasing propofol to 4 mg/kg, the apnea time was reduced, but the recovery period increased. We opted for the first alternative of higher doses of remifentanil than of propofol and achieved shorter recovery times with a lower proportion of patients requiring vigorous stimulation and/or ventilation assistance (3% IV sedation and 2% V sedation). However, we were always clear about, and aware of, the potential for depressed ventilation from the two interacting drugs based on the principle of the asymmetric interaction curve proposed by Fidler. (48) We decided to use the lowest required doses of remifentanil and propofol (Figure 2) according to our experience at that time and, as can be seen, these were safe for patients.

An effect that was not quantified in this series, but which has been perceived and described in other studies, was reduction of pain at the site of venipuncture. Although the most common presentation of propofol is in emulsion, its application causes pain and even phlebitis, especially if the injection is in small peripheral veins. The administration of low doses of remifentanil a few seconds earlier effectively decreases pain. (49-51).

Limitations of the series

As in any series of cases, there are no comparison groups for results from other doses of the same drugs, although it is clear that extremely young and extremely old patients require different doses due to obvious differences in drug sensitivity. Nor are recovery times, discharge times and measurement of patient satisfaction included. This was obviated by the as yet unpublished results of our telephone follow-up surveys of patients that reported satisfaction levels of over 95% for the process including sedation.

CONCLUSIONS

1. Balanced sedation is a safe scheme when administered by a physician other than the endoscopists. In this series, administration by an anesthesiologist was obligatory given the institution's restriction on the use of propofol.
2. Potentiation of drug combinations allows significant reductions of doses required, even to levels below those found in this series.
3. Dose reduction facilitates (but does not ensure) levels of conscious sedation (II and III) for diagnostic upper endoscopy procedures.
4. The total cost of drugs in balanced sedation is very low, but it should be borne in mind that overall costs of assembling a sedation care system can be very significant. This is especially true for monitoring equipment and the anesthesiologist's fees. However, in the medium term the overall results can be highly efficient.
5. Despite the safety of regimen the presented, it should not be forgotten that sedation can be a continuum from alertness to general anesthesia. Consequently, every measure needed for monitoring patients and training the team involved in the procedure must be taken. Expertise in airway rescue, adherence to checklists, theoretical training and clinical practice with a mandatory minimum number of patients are absolutely necessary for rescue and recovery of patients who reach unexpectedly deep sedation levels.

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