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CASE REPORT

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Chronic Shortage of Drugs Revive Older Almost Forgotten Remedies for Office Sedation

Claudio Melloni*

Private practitioner, Consultant in Anesthesia, Italy

***Corresponding author:** Claudio Melloni, Private practitioner, Consultant in Anesthesia, Paolo Costa 16, 40137 Bologna, Italy, Tel: +39 335 309504; E-mail: melloniclaudio@libero.it

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Abstract

205 adult ASA 1&2 patients undergoing dental, plastic, ophtalmological surgery under local anesthesia lasting at least 90 minutes were sedated in a office facility with midazolam 1-2 mg, promazine 7.5-15 mg+meperidine 15-25 mg (modified lytic cocktail); midazolam and fentanyl were used intraoperatively as rescue only because of their chronic shortage. These drug combinations offered good operating conditions consenting fast discharge side effects were modest: 3 patients got nausea, 3 extrapyramidal movements (1 serious), 5 vasovagal reactions, 2 tachycardia, 1 hypotension. No desaturation occurred with a continuous minimal oxygen flow of 0-5-1 lit/min.

It is concluded that these old drug under full monitoring and cautious titration may still find a place in the field of office based sedation.

Abbreviations: CHLORP: Chlorpromazine; FENT: Fentanyl; MEP: Meperidine (or Pethidine); MIDAZ: Midazolam; MORF: Morphine; PROM: Promazine; PROP: Propofol; PONV: Postoperative Nausea and Vomiting

Introduction

In the past years the shortage of very important drugs like propofol, midazolam and fentanyl has caused concern among anesthesiologists in the belief that without these drugs quality of care could have been compromised adding professional dissatisfaction and frustration due to the inability to offer what was perceived as the standard best treatment for the patients.

Moreover the substitution of the aforementioned drugs with others of the same class but with different potency or pharmacokinetics has resulted in harm for lack of familiarity or error [1].

Due to the shortages of midazolam, propofol, fentanyl we were obliged in a office setting to resort to the older longer acting drugs, phenotiazines (PROM-CHLORP) and the opiate (MEP) and (MORF) mixed in one of the many modifications of the lytic cocktail for light/moderate sedation in a variety of surgical procedures done in more than 200 consecutive cases.

Aim of this report is to present our experience showing the technique followed and the problems encountered.

Patients and Methods

The study was performed on adult patients scheduled to undergo light/moderate sedation for a variety of office procedures (dental, plastic, ophtalmology) under local anesthesia from February 2018 to September 2020. Inclusion criteria were age 18 years or older, American Society of Anesthesiologists physical status I or II, surgery lasting at least 90 min. Patients completed a routine lab work up and a 12 leads ECG if older than 65 years; fasted for 6 hours before surgery. Premedication was given in the holding room with diazepam 1mg/10 kg BW (5-8 mg p.os) 20-30 min before their arrival in the operating room. Written informed consent was obtained for all subjects and all completed a written health questionnaire. The day of the operation all patients were evaluated for potential difficult airways with the combination of 6 following tests [2,3]:

-The Mallampati test (original or modified);

-Wilson risk score (including patient's weight, head and neck movement, jaw movement, receding chin, buck teeth);

-Thyromental distance;

- Sternomental distance;

- Mouth opening test;

- Upper lip bite test

Standard monitoring included Noninvasive Blood Pressure (NIBP), Heart Rate (HR), 3 or 5 leads Electrocardiography (ECG), SPO_2, $ETCO_2$ (sidestream), respiratory rate, temperature (Datex cardiocap and Capnomac). An intravenous cannula (22 or 20 g) was

secured in the forearm or hand for administration of fluids (3-5 ml/hr) and medications. All patients breathed oxygen 0.5/1 lit/min through a nasal cannula (Salter labs® divided cannula). Intraoperatively, the patient's level of sedation was assessed using the Ramsay five-level scale [4] maintaining a score between 2-3. The patient's recovery of function after surgery was assessed using the Aldrete score, to whom was added ability of walking, dressing, and orientation to date, place and some elementary calculation. Intraoperative and postoperative pain was assessed by means of a visual analogue scale. Perioperative side effects were also recorded; oxygen desaturation (<90%), brady/tachycardia (<50, >120 bpm). hyper/hypotension (>180, <90 mmHg systolic), pain on injection, disruptive movements, vivid dreams, nausea, and vomiting. Patient data were collected on specially designed sheets every 5 minutes.

Study Protocol

After arrival in the operating room and after baseline values had been obtained, all patients received midazolam 1-2 mg. The mixture of meperidine/promazine (2:1) (15/7.5-25/12.5) mg was infused within 10 min diluted in 100 ml of normal saline; once achieved the desired sedation state (Ramsay score 2-3) patients were given 7-8 mg/kg of lidocaine 0.2 %+epinephrine 1:200.000 in 250-500 ml of normal saline (Plastic surgery) or 4% articaine or 2% mepivacaine for alveolar dental block with or without maxillary/mandibular block (dental cases). Cataract patients received eye drops; peribulbar block for vitrectomy. Surgery started after having ascertained the validity of the local anesthesia, usually after 5-10 min in dentistry and 30 min in plastics.

Top ups doses of analgesics (mep/promaz mixture 0.5 ml , fent 25 microgr ,morph 1-2 mg) and/or local anesthetics were administered during the procedure when patients experienced pain (visual analogue scale score >4), Midaz 0.5-1 mg boluses were administered for sedation. At the end of surgery, all patients received ketorolac 30 mg and dexamethasone 4 mg intravenously. All patients (except 1) were discharged 3 hours after surgery (Table 1).

Clonidine 45-60 microgr was used for hypertension (defined as >180 systolic or >95 diastolic); atropine 0.5/0.6 mg for bradycardia defined as HR<50 min. Vasovagal reactions were treated with atropine (0.5 mg)+ephedrine (5-10 mg)+crystalloids (100-200 ml bolus)+supplemental O_2+adoption of the Trendelenburg position; in case of nausea alone haloperidol 0.4/0.5 mg *i.v.*

Postoperative analgesia was provided with ketorolac (20-30 mg) and /or paracetamol (1000-1500 mg), by mouth.

All patients (except 1) were discharged home with an accompanying adult within 3 hours after the completion of surgery.

Discussion

The phenothiazines as a class were among the most widely used drugs in medical practice in the management of patients with serious psychiatric illnesses until the mid 90". They exhibited also a wide spectrum of clinically useful properties including antiemetic, antinausea, antihistaminic effects plus the ability to potentiate the general anesthetics, sedatives and analgesics; as a consequence every anesthesiologist trained in the years 1970-1990 had to become expert in the administration of at least a couple of these drugs, generally PROM (Phenergan, Fargan, etc) and CHLORP (Largactil, Thorazine, etc.) as preanesthetics and sedatives, with the aim to reduce the need for surgical anesthetics [5]. Many drugs of this group are stiil in use today in veterinary anesthesia [6]; moreover they may see possible applications in many other areas of medicine, in the treatment of neurodegenerative disease [7] and as antiviral, anticancer, antiprotozoal drugs [8].

Nowadays phenothiazines are still used as general purpose antinausea and antiemetics [9] but in general they are limited to the treatment of psychosis and are virtually disappeared from the pharmacopeia of anesthesia because the unwanted effects of extrapyramidal motor disturbances and the occurrence of prolonged drowsiness and sedation. However some of their effects dependent from the blockage of a variety of receptors particularly acetylcholine (muscarinic), histamine (H1), noradrenaline (alpha) and 5HT could be exploited to success even in the difficult environment of office anesthesia. As a matter of fact only 1.5% of our patients got nausea (and the vast majority were considered at high risk for PONV): in only 3 cases we added droperidol and none actually vomited. The choice of adding another neuroleptic agent in this context could not have been the best option considering the possibility of enhancement of Extrapyramidal Side Effects (EPS) and would not be repeated in the future.

Acute Extrapyramidal Syndromes (EPS), including dystonia, parkinsonism, and akathisia, are associated with the use of virtually all neuroleptic agents. They may be alleviated by reducing the neuroleptic dosage, switching to a lower potency drug, or administering an adjunctive agent such as an anticholinergic, amantadine, benzodiazepine, or β-blocker. Akathisia may be only partly dispelled by anticholinergics; alternatives are β-blockers, benzodiazepines, and clonidine [10,11].

The treatment of choice of EPS consists of antiparkinson drugs, but these are not available in the OR's or offices and we were unable to find references about the intraoperative acute therapy of these side effects; scopolamine [12], clonidine, diazepam, β-blockers were mentioned by many authors, but none used in the context of an intraoperative period; these last 2 options appear the most feasible in the surgical environment. Numerous references mention anticholinergics and antiadrenergics by mouth as useful in the treatment of EPS benztropine (dosage range, 0.5-8 mg/d), trihexyphenidyl (1-15 mg/d), procyclidine (7.5-20 mg/d), biperiden (2-8 mg/d), and orphenadrine (100-400 mg/d), propranolol and clonidine, but a Cochrane review failed to support them [13,14].

One patient had oscillating rotations of the lower legs lasting for about 60 minutes; she was unaware of the movements and had to be tied up in order to complete the procedure.

Intravenous diphenhydramine has been used in case of phenothiazine poisoning: note that no instance of apnea was recorded on these 48 cases [15] confirming the sparing effects on respiration.

The combination of the sedative and antiemetic effects of promethazine with the analgesia offered by MEP was described long time ago [16] and followed the pioneering work done by the French physician H Laborit [17]. The lytic cocktail, a mixture of MEP, CHLORP and PROM, gained popular acceptance in the 60' used mainly for premedication in anesthesia and surgery. Many modifications of the original mix were adopted during the ensuing years and many anesthesiologists modified the mixture according to their needs; as a matter of fact the combination used in this paper results from the mixture of 100 mg of MEP with 50 mg of PROM, i.e. MEP 1/PROM 0.5 ratio, for instance 1 mg of MEP/0.5 mg of PROM. From the practical point of view 1 ampul of MEP (100 mg) and 1 ampul of Prom (50 mg) are injected in a bottle of normal saline (100 ml), from whom 15-25 ml are withdrawn to be once again injected in another 100 ml bottle of normal saline to be infused *i.v.* in 10 minutes.

Table 1: Drugs used in surgical procedures and their side effects

Procedures	Number	
Face lift	9	
Blepharoplasty	37	
Dental (wisdom teeth,sinus lift,multiple implants….)	81	
Breast augmentation	38	
Liposuction (thighs, hips buttocks, abdomen waist, upper arms, back, chin and neck)	36	
Cataract	2	
Vitrect	1	
Otoplasty	1	
Gynecomastia	3	
Mini Abdominoplasty	12	
Combined surgeries	19	
Nose reshaping	2	
Drugs	**Number**	**Dose**
Mep+Prom initial	all	15/7.5-25/12.5 mg
Fent top up	83	25-50 microgr
Morf top up	27	1-2 mg
Mep+Promaz top up	4	5/2.5 mg
Chlorp top up	10	4-8 mg
Midaz initial	all	1-2 mg
Midaz top up	68	0.5-1 mg
Clonidine	6	45-60 microgr
Side Effects	**Number**	**Note**
Vasovagal reactions	5	
Nausea	3	
Extrapiramidal movements	3	1 severe,requesting forced immobilization
Respiratory depression	1	Chin lift 10 min.
Unpleasant sensations	1	During initial infusion;too quick???
Hypotension	1	
Tachycardia requiring treatment		
3		

MEP (Pethidine, Demerol) also is a veteran drug introduced before the IInd world war but still widely used today as an analgesic ; a statistical national survey in Taiwan [18] Identified 500.000 prescription/year between 2002-2007.

MEP is widely used for sedation/analgesia for gastroenterological sedation and often by non anesthesiologists: a nationwide survey in Spain found widespread usage [19,20].

The drug has the added benefit of being very useful in the prevention and treatment of postoperative shivering [21-23].

MEP is also popular as an analgesic during labor with a long record of a safety at low dosages [24].

The use of the lytic cocktal (called DPT) lost however slowly its role thanks to the appearance of newer drug, with better receptor targeting, faster onset and recovery [25,26].

Tachycardia was noted in many cases, but responsibility for the cocktail could be established only in 2 patients, since it appeared immediately following the priming infusion of the drugs; afterwards the epinephrine added to the local anesthesia could have been contributory to the increase in HR, due to the beta stimulation in healthy hearts. Two patients received a small amount of sotalol to control a very fast HR (>150 bpm); the HR decreased to 110-120/min, abating slowly in the following minutes.

The most serious side effect was the appearance of sudden episodes of vasovagal reactions; the incidence of this complication has been 1.5% (3 patients) (1 during LA infiltration for gynecomastia and 2 50-80 min in the course of the plastic surgery procedure). The occurrence is similar to that encountered in interventional injection procedures done under X-ray guidance (2.6%) [27]: other centers reported lower rates of vasovagal reactions (<1%) in a large series of facet joint nerve blocks [28]; other seresi on interventional pain procedures reported a lower incidence (1%) [29].

Vasovagal reactions occur frequently in other environments; for instance the incidence was reported at 5% during femoral arterial sheath removal [30]; other authors reported that vasovagal reactions were common, but that no serious adverse reactions occurred [31] while other claimed to reduce the incidence of reactions with a change in the technique [32].

We treated the reaction very aggressively as described above in order to minimize the potential sequelae; all subjective symptoms and clinical signs disappeared in the course of a few minutes as checked by the speeding up of the measurements of HR, BP and questioning of patients.

We defined very low level of SaO_2 (90%) as a threshold limit for desaturation even though in many studies in the dental literature (and not limited to dentistry) the safety limit has been posted at 94% [33]. As a matter of fact the steepness of the oxyhemoglobin curve indicates a dangerously low level of PaO_2 at 90% saturation, but no desaturation occurred in our patients thanks to low flow oxygen (0.5-1 lt/min).

Desaturation could be a serious problem when oxygen could not be used because the danger of fire associated with the procedure, i.e laser resurfacing of the face; here opinions differ regarding the technique to be used, continuous infusion *vs.* intermittent, midazolam, fentanyl with or without propofol etc; very often the case series are small like [34] (15 pts!!) and therefore conclusion highly biased.

Luckily no patient undergoing surgery on the face desaturated in the absence of oxygen; anyhow since we were not using lasers a flow of O_2 could have been used in the proximity of the nose/mouth of the patient in case of need without disturbance to the surgeon.

From these experiences we believe that the lytic cocktail alone+midaz careful titration is a valid technique for maintaining a safe range of oxygen saturation in the absence of oxygen supplementation, keeping in mind that we were dealing with patients in good shape.

Conclusion

Careful titration of sedatives and analgesics is of paramount importance for the success of office base surgery. The drugs used should possess intrinsic safety, devoid of dangerous side effects and offer favourable pharmacokinetic/pharmacodynamic profiles well suited to the non operating room practice, even although MEP and PROM are far from ideal drugs to be considered in this setting, they may still deserve a place under well controlled conditions. The priming with these drugs allowed surgery to proceed safely with a minimal dosage of the precious MIDAZ and FENT, these last drugs used more as rescue rather than corner stones.

References

1. Institute for Safe Medication Practices (2012) A Shortage of Everything Except Errors: Harm Associated With Drug Shortages.
2. Laborit H, Leger L (1950) Utilisation d'un antihistaminique de synthèse en thérapeutique pré, per, et post-opératoire. Presse Med 58: 492.
3. Roth D, Pace NL, Lee A, Hovhannisyan K, Warenits A, et al. (2018) Airway physical examination tests for detection of difficult airway management in apparently normal adult patients. Cochrane Database Syst Rev 5: CD008874.
4. Ramsay MA, Savege TM, Simpson BR, Goodwin R (1974) Controlled sedation with alpaxalone-alphadolone. Br Med J 2: 656-659.
5. Stoelting RK (1999) Pharmacology and Physiology in Anesthetic Practice. In: Drugs used for psychopharmacologic therapy. 3rd Edition, Lippincott-Raven 370-373.
6. Ringer SK (2012) Chemical Restraint for Standing Surgery. In: Equine Surgery. 4th Edition, Elsevier.
7. Varga B, Csonka A, Csonka A, Molnar J, Aamaral L, et al. (2017) Possible Biological and Clinical Applications of Phenothiazines. Anticancer Res 37: 5983-5993.
8. Dastidar SG, Kristiansen JE, Molnar J, Amaral L (2013) Role of Phenothiazines and Structurally Similar Compounds of Plant Origin in the Fight against Infections by Drug Resistant Bacteria. Antibiotics (Basel) 2: 58-72.
9. Brunton LL, Chabner BA, Knollmann BC (2011) Goodman & Gillman's The pharmacological basis of therapeutics. 12th Edition, McGraw Hill 1343.
10. Tonda ME, Guthrie SK (1994) Treatment of acute neuroleptic-induced movement disorders. Pharmacotherapy 14: 543-560.
11. Holloman LC, Marder SR (1997) Management of acute extrapyramidal effects induced by antipsychotic drugs. Am J Health Syst Pharm 54: 2461-2477.
12. Lampignano D, Sharma TR (2016) Scopolamine for Management of Extrapyramidal Side Effects as a Result of Antipsychotic Medication Use: A Case Report and Brief Review of the Literature. Prim Care Companion CNS Disord 18: 10.
13. Lima AR, Bacalcthuk J, Barnes TRE, Soares-Weiser K (2004) Central action beta-blockers *versus* placebo for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev 224: CD001946.
14. Lima AR, Weiser KV, Bacaltchuk J, Barnes TRE (2004) Anticholinergics for neuroleptic-induced acute akathisia. Cochrane Database Syst Rev 1: CD003727.
15. Barry D, Meyskens FL Jr, Becker CE (1973) Phenothiazine poisoning-A review of 48 cases. Calif Med 118: 1-5.
16. Hopkins DAB, Hunter D, Jones CM (1957) Promethazine and petidine in anesthesia. Anesthesia 12: 276.
17. Henri L (1951) L'anesthésie facilitée par les synergies médicamenteuses/Henri Laborit. Paris: Masson et Cie, Editeurs 1: 120.
18. Hsueh-Hsing P, Chung-Yi L, Tso-Chou L, Ju-O W, Shung-Tai H, et al. (2012) Trends and characteristics of pethidine use in Taiwan: a six-year-long survey. Clinics 67: 749-755.
19. Rembacken BJ, Axon AT (1995) The role of pethidine in sedation for colonoscopy. Endoscopy 27: 244-247.
20. Baudet J, Borque P, Borja E, Alarcón-Fernández O, Sánchez-del-Río A, et al. (2009) Use of sedation in gastrointestinal endoscopy: a nationwide survey in Spain. Eur J Gastroenterol Hepatol 21: 882-888.
21. Alfonsi P (2001) Postanaesthetic shivering. Epidemiology, pathophysiology and approaches to prevention and management. Minerva Anestesiol 69: 438-442.
22. Tsai YC, Chu KS (2001) A comparison of tramadol, amitriptyline, and meperidine for postepidural anesthetic shivering in parturients. Anesth Analg 93: 1288-1292.
23. Roy J, Girard M, Drolet P (2004) Intrathecal meperidine decreases shivering during cesarean delivery under spinal anesthesia. Anesth Analg 98: 230-234.
24. Nunes RR, Colares PGB, Montenegro JP (2017) Is Pethidine Safe during Labor? Systematic Review. Rev Bras Ginecol Obstet 39: 686-691.
25. Snodgrass WR, Dodge WF (1989) Lytic/"DPT" cocktail: time for rational and safe alternatives. Pediatr Clin North Am 36: 1285-1291.
26. Auden SM, Sobczyk WL, Solinger RE, Goldsmith LJ (2000) Oral ketamine/midazolam is superior to intramuscular meperidine, promethazine, and chlorpromazine for pediatric cardiac catheterization. Anesth Analg 90: 299-305.
27. Kennedy DJ, Schneider B, Casey E, Rittenberg J, Conrad B, et al. (2013) Vasovagal rates in fluoroscopically guided interventional procedures: a study of over 8,000 injections. Pain Med 14: 1854-1859.

28. Manchikanti L, Malla Y, Wargo BW, Cash KA, Pampati V, et al. (2012) Complications of fluoroscopically directed facet joint nerve blocks: a prospective evaluation of 7,500 episodes with 43,000 nerve blocks. Pain Physician 15: E143-E150.

29. Carr CM, Plastaras CT, Pingree MJ, Smuck M, Maus TP, et al. (2016) Immediate Adverse Events in Interventional Pain Procedures: A Multi-Institutional Study. Pain Med 17: 2155-2161.

30. Ang CK, Leung DYC, Lo S, French JK, Juergens CP (2007) Effect of local anesthesia and intravenous sedation on pain perception and vasovagal reactions during femoral arterial sheath removal after percutaneous coronary intervention. Int J Cardiol 116: 321-326.

31. Weinschenk S, Hollmann MW, Strowitzki T (2016) New perineal injection technique for pudendal nerve infiltration in diagnostic and therapeutic procedures. Gynecol Obstet 293: 805-813.

32. Cicinelli E, Schonauer LM, Barba B, Tartagni M, Luisi D, et al. (2003) Tolerability and cardiovascular complications of outpatient diagnostic minihysteroscopy compared with conventional hysteroscopy. J Am Assoc Gynecol Laparosc 10: 399-402.

33. Nagels AJ, Bridgman JB, Bell SE, Chrisp DJ (2014) Propofol-remifentanil TCI sedation for oral surgery. N Z Dent J 110: 85-89.

34. Cillo Jr JE, Finn R (2005) Moderate intravenous sedation for office-based full face laser resurfacing using a continuous infusion propofol pump. J Oral Maxillofac Surg 63: 903-907.