SEDATION SOLUTIONS

Conscious Sedation – Moving Away from Intravenous Bolusing

Introduction

The practice of conscious sedation, as it evolved from an alcohol induced state of stupor for primitive amputations, is one of the fastest growing fields in anaesthesia care.

As far as sedation techniques are concerned, we as sedation practitioners tend to get comfortable with one method, e.g. intravenous bolus administration of drugs, and forget about all the other options available to us. Patients are also increasingly well read and informed about all the latest ideas and choices available to them.

It is in view of this that we present a detailed review of the new, forgotten and developing tools, from the simplest through to the most complex, available to the sedation practitioner.

This article cannot be an in-depth discussion but is meant to stimulate sedation practitioners to consider other options in the practice of sedation.

Measurement of Level of Sedation (consciousness)

Before we continue our discussion it is probably prudent to elaborate on a sedation scoring system e.g. observer's assessment of alertness/sedation (OAA/S) scale. The evaluation of the level of sedation, as set out in table 1, is not exactly the one that everybody is familiar with in conscious sedation. However, many studies use this tool to determine the effect of a certain technique on the level of consciousness.

Observation	Score Level
Responds readily to name spoken in a normal tone	5
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
Does not respond to mild prodding or shaking	1

Table 1

The above table was recently modified to include "agitated", a score of 6, and "does not respond to a deep stimulus", a score of 0. It is clear that a patient should be kept above a score of 3 to fall under the definition of conscious sedation.

One can argue about the value of sedation scales, and which scale is the best to evaluate the level of consciousness (LOC) in a subjective way. Maybe personal choice of the sedation practitioner. The University if Michigan Sedation Scale should also be considered to evaluate the LOC as it a validated tool. It is also probably easier to use.

Rebirth of Ancient Remedies

Since Braid coined the term hypnosis in 1841 as a subject centred sedative technique, to distinguish it from mesmerism, which is operator centred, the idea has perplexed humanity ad infinitum. The true value of hypnosis lies probably in the very definition: subject centred.

Hypnosis as a form of self-empowerment is so valuable to the patient, that it has been proven effective in asthma, burns, chronic pain and even some forms of cancer (1). Unfortunately, the literature seems void of good randomised, controlled studies to assess the effectiveness of hypnosis as a sole sedative. However, when used as an adjunct to conscious sedation, hypnosis improved patient satisfaction, decreased discomfort and pain, and reduced the amount of sedatives/hypnotics and opioids used (2).
It has also been used successfully in drug tolerant patients, such as those on chronic opioids for cancer, and to reduce the sedative doses (3). Even post-operative nausea and vomiting seem to benefit from the additive effects of hypnotherapy (4). Not many sedation practitioners are however trained in the art of hypnosis.

One article published by Faymonville et al. deserves special notice. They evaluated whether stress reduction techniques gave the same benefit as true hypnosis. The results were surprising. Not only did the hypnosis group report lower levels of discomfort, pain and PONV, but they also consumed less propofol, presented a better surgical field and had more stable vital parameters (5).

One parameter stands out: the patients in the hypnosis group reported better intraoperative control. A central theme to the efficacy of hypnosis lies in the patient being able to control his or her own sedation. Is patient controlled sedation, as discussed later, not just another form of hypnosis?

Novel Oral Delivery

Transmucosal delivery of drugs to children is one of the most acceptable alternative methods of sedation as there are no needles involved. The only drawback is that the delivery vehicle itself is either unpredictable or unacceptable to the child because of burning on administration of the medication. Consider the bitter taste of midazolam and the poor bioavailability of the intravenous form given orally (6). Unfortunately the oral formulation, Versed syrup (midazolam), is not available everywhere and a liposome encapsulated form is still in early development (Tomoyasu, Yasuda, Maeda, Higuchi, & Miyawaki, 2011).

So which methods are available and acceptable? Midazolam can be mixed in a 1:1 mixture with e.g. strawberry syrup and placed on the anterosuperior aspect of the child's tongue, up to the dose required. This improves acceptability and effectiveness from 59% to 95% (8). One must be careful of mixing midazolam, though, as some researchers who mixed formulations to optimize taste found decreased effectiveness, even as compared to pure oral administration (9). It does, however, hasten the onset of sedation. When comparing transmucosal midazolam to inhalation N_2O, it gives similar results and is much easier to administer (10).

Fentanyl, an opioid, is available in a lollipop form, which in itself is probably the best vehicle for a child. Oral transmucosal fentanyl (OTFC) is safe and effective for sedation and analgesia of children during painful procedures (11). It unfortunately has a high incidence of PONV and can result in respiratory depression. It should be carefully used in the out of hospital setting.

Ketamine was also recently released in a transmucosal lollipop form. When compared to oral midazolam for premedication, results were mixed, with some researchers finding no benefit (12) and others claim effectiveness (13). In theory this should be the "miracle cure" to all conscious sedation ailments, but we could not find a single article that describes the use of ketamine lozenges for sedation.

Subcutaneous Dissociative Conscious Sedation

Javid et al. did ground-breaking work in using subanaesthetic doses of ketamine via subcutaneous injection, in combination with a narcotic, for procedures as invasive as laparoscopic peritoneal dialysis catheter placement (14), and compromised airway management for mediastinal masses (15). They then decided to try this form of sedation for more conventional procedures requiring conscious sedation.

Prominent features of subcutaneous dissociative conscious sedation (sDCS) are: the ability to maintain the airway with spontaneous ventilation, cooperation between the surgeon and sedation practitioner, and prominent amnesia.

Patients in their study were randomly assigned to receive either ketamine s.c. 0.6mg/kg in the anterior aspect of the forearm, propofol 50µg/kg/min or midazolam 0.015mg/kg i.v.

The study shows that pain scores and opioid consumption was significantly less in the sDCS group, and no patients desaturated. Only 3.3% of patients needed additional fentanyl in the sDCS group, as compared to 33.3% and 36.6% in the propofol and midazolam groups respectively. Patient satisfaction in the propofol and sDCS groups was 100% with no recall in all of the cases. Endoscopist satisfaction was 93% when sDCS was used, compared to 70% in the propofol, and 33.3% in the midazolam groups (16). Only one patient had a recovery time of more than 20 minutes.

This way of the administration of sedative/analgesic drugs is probably one of the most exciting new ideas in the administration of drugs for conscious sedation. The safety and ease of its use makes it ideal for short painful procedures outside of the operating theatre, without the need to set up intricate pumps and using large doses of possible respiratory depressants.

Target Controlled Infusions

To be able to accurately predict the plasma or effect site concentrations of drugs, without tedious measurements and gross estimation, has made TCI one of the most popular methods of intravenous drug delivery. After the pioneering work of Schwilden in 1981 (17) and March et al.'s meticulous methodology in 1991 (18), Diprifusor was released as the first commercially available TCI.

Target controlled infusions use mathematical models based on multicompartment pharmacokinetics to predict probable effect or plasma drug concentrations. This gives the user the ability to control the level of sedation more accurately and with greater ease, even in the paediatric population (19), without having to time and adjust infusion rates throughout. Unfortunately, this is not the holy grail of sedation practise.

Pharmacokinetics

The first and probably most important concept to understand is that of context-sensitive half-life. During the initial stages of an infusion, the contributions of distribution to the second and third compartments can decrease a drug's plasma concentration by almost half, whereas during a long infusion where equilibrium has

been reached, reduction of plasma concentration is dependent on the interplay between redistribution and elimination (Hughes, Glass, & Jacobs, 1992). During intermediate infusions, this will fall somewhere in between these two extremes. The halving time is known as context sensitive half-time, where the context is the duration of infusion (Hill, 2004). This, in turn, is dependent on the volume of distribution (V_D) and redistribution rate constants. Examples of context sensitive half-times are presented in figure 1.
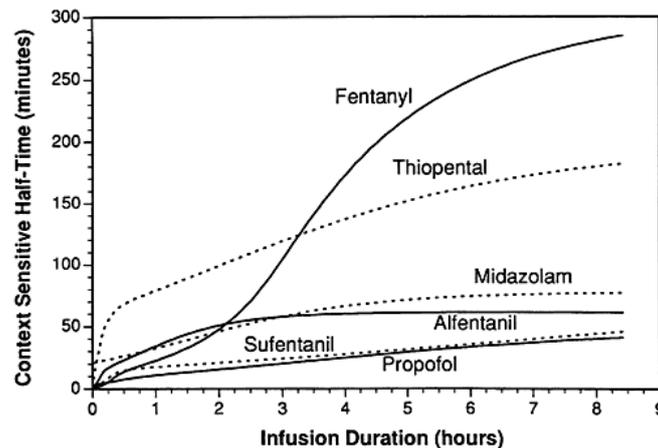

Fig 1 (22)

As can clearly be seen, some drugs have an unpredictable and prolonged context sensitive half-time, such as fentanyl and thiopental. It is because of this that only a select list of drugs are preferred for conscious sedation (see later).

Ketamine, a drug which has become extremely popular for sedation, has a context-sensitive half-time which increases dramatically after 30 minutes. This has lead to concerns amongst sedation practitioners that if the drug is used as an infusion for more than 90 mintes accumulation may occur. This may influence the recovery characteristics of patients after sedation.

Secondly, one must consider the site, plasma vs. effect site, one wishes to target. In early TCI's the only setting available was the plasma concentration. This presented a problem, as there was hysteresis between the plasma concentration and clinical effect (23). This was caused by a temporal delay in equilibration at the effect site. Subsequently infusion pumps were programmed to increase the initial bolus of the

drug, to compensate for the effect site first order rate constant k_{eo}. Effect site is determined by time to peak effect, as it is impossible to measure concentrations directly (Minto, Schnider, Gregg, Henthorn, & Shafer, 2003). This was proven to be accurate during levels of moderate (conscious) and deep sedation, using the bispectral index (Yeganeh, Roshani, Almasi, & Jamshidi, 2010), a more objective way of measuring the LOC.

Furthermore, the incidence of recall at effect site concentrations above 1.5µg/ml was low enough to disregard the use of the bispectral index during surgery. It is thus always recommended to use effect site concentration.

Propofol

So how do we make sense of all the pharmacokinetic models? The biggest confusion comes from the propofol models, designed by Schnider and Marsh. Barakat et al compared the accuracy of these models as it specifically relates to sedation. They found that the Marsh model corresponds more accurately with Observer Assessment of Alertness/Sedation (OAAS) scores (a subjective sedation scoring system), as well as the bispectral Index (an objective way of measuring the level of consciousness) in healthy volunteers (26).

One other potential pitfall with the Schnider model is the use in morbidly obese patients. As the calculations for k_{10} is adjusted for lean body mass, weight and height, the maths generate paradoxical values in the morbidly obese, resulting in excessive increases in maintenance values (23). This is also an advantage, as the lean body weight calculation makes the Schnider model safer to use in elderly individuals, who has a lower lean body mass and central compartment. The Schnider model calculates the central compartment of a 70kg male to be 4.27L, whereas the Marsh model calculates it as 15.9L (27). Hopefully the problem will be solved soon, by replacing the James formula with the Janmahasatian formula for lean body mass, as TCI was more accurate at these extremes of weight.

This is seldom a problem in conscious sedation, as morbid obesity and extremes of age usually disqualify the patients for out of hospital procedures. It is also important to note that the two different TCI models use different methods of calculating the effect site, with potential differences in concentration.

When using TCI sedation in children, two models are available for use. Both the Kataria and Paedfusor models were recently validated in children (28). There are, however, still weight and age limits to these models, having only proved accurate

between 3 and 16 years, and above 15kg. TCI in children below 1 year becomes very inaccurate, because of immature hepatic glucuronidation (Wilson G. , 2010). The Short model shows promise in this regard (Sepúlveda, et al., 2011).

Propofol a non-opioid, non-barbiturate, sedative/hypnotic agent remains extremely popular for sedation both as boluses and for intravenous infusion. The drug has a rapid onset and short duration of action (half life of 4.4min, children 9min) due to rapid equilibration between the blood and the brain. There is quick redistribution of the drug to peripheral tissues.
Propofol has a rapid metabolic clearance from the blood with excellent recovery characteristics.

Ketamine

As the newcomer to the arena of TCI, ketamine still has a long way to go towards the ideal pharmacokinetic model. However, as this drug has a central and fundamental role to play in conscious sedation, it is necessary to discuss the current thoughts on the matter. Based on the work done by Domino et al, most pharmacokinetic calculations are done with the following values: V_1 0.063L/kg^{-1} and k_{10} of 0.438 (31). The performance of these was shown to be clinically acceptable, but it had poor predictive value and underestimated plasma concentrations at the end of an infusion (32). The Clements model showed more accurate predictions as measured biochemically and is currently the recommended model for ketamine TCI (33) (34).

Ketamine is nowadays commonly used in combination with propofol as ketofol for sedation and analgesia. The two drugs are either used in combination with each other in the same syringe, or independently, the one following the other. It is a debate which ratio is the best for a quick recovery after sedation.

It is suggested that the 1:10 ratio (ketamine 20mg, propofol 200mg) be used for TCI for procedures not longer than 90 minutes. Accumulation of ketamine may be an issue with longer procedures if the rate of infusion is not reduced; it is recommended that propofol only can then be used for sedation for longer procedures.

Opioids

When painful procedures are performed it may be necessary to augment the primary sedatives with an opioid even if local/regional anaesthesia is used. The three short-acting opioids available for TCI are: sufentanil (Gepts Model), alfentanil (Scott Model), and remifentanil. As can be seen in fig 1, all of these have context sensitive half-times of less than 50min at maximum duration, but for the duration of sedation (typically less than an hour), sufentanil is the one best suited as it will give a much faster recovery.
In a study during which patients were kept under conscious sedation for plastic surgery, it was found that the addition of sufentanil to propofol improved sedation scores, as measured by OAAS (35). Unfortunately 20% of patients presented with depressed respiration, which makes this a challenging technique for out of hospital sedation. Some studies however say sufentanil is the drug of choice for in hospital conscious sedation, e.g. during colonoscopy, as it gives results similar to dexmedetomidine, and superior to both midazolam and meperidine (36).

Even though remifentanil is not recommended for conscious sedation for the out of hospital setting, it has extremely favourable pharmacokinetics. When one compares its context -sensitive half- time to that of any other opioids, it makes much more sense to use it. Consider: remifentanil plasma concentration decreased to 50% in just 3min, even after 3hours of continuous infusion (37).
 Compare this to alfentanil which has a context sensitive half time of 47min. Should rescue be needed, the rapid elimination will shorten the effect. The pharmacokinetic profile is also unaffected by renal or hepatic disease. It has a lower protein binding than sufentanil and propofol.
 Byun et al showed that at TCI concentrations of 3ng/ml and less, using the Minto model, patients showed acceptable levels of sedation and no side effects (38). Spontaneous ventilation was found to occur at plasma levels of 4-5ng/ml, and even if respiratory depression occurs, return of spontaneous ventilation is rapid and with little variability when the infusion is stopped (39). Even the advantage of effect site versus plasma targeting is abolished for remifentanil, because of its unique pharmacokinetic profile. During an awake fibreoptic intubation (extrapolated to flexible bronchoscopy) remifentanil provided better conditions than propofol, at the price of higher recall (40).

Should we use remifentanil as part of our sedation practices out of hospital? The answer is no as all international sedation guidelines do not support its use outside the hospital environment. Inside the hospital, yes. When used in children it should be used with great care. Children have a very high parasympathetic drive, which makes them especially sensitive to bradycardia during remifentanil use (41).

Remifentanil use gives faster discharge times, but at the price of an estimated incidence of 5% of apnoea, needing positive pressure ventilation (42).

The short-acting opioids demonstrate pharmacokinetc/pharmacodynamic profiles associated with rapid onset and offset making them excellent drugs for sedation and analgesia. Onset of action with alfentanil and remifentanil occurs within 0.96 min and 1.6 min respectively; those of fentanil and sufentanil 6.6 min and 6.2 min respectively.

Remifentanil has the shortest context-sensitive half-time. Fentanil quickly becomes context-sensitive.

Dexmedetomidine

Dexmedetomidine, a highly selective α_2-agonist, has recently received some attention in the field of TCI. During conscious sedation for awake fibreoptic nasotracheal intubation, dexmedetomidine TCI provided similar intubating conditions to propofol TCI, but with fewer cardiovascular and respiratory side effects (43). It is not, however, licensed for use outside of the ICU and surgical theaters. It is not indicated for use outside the hospital environment. There are probably cheaper and more reliable options available, especially in paediatrics. Heard et al. believe that dexmedetomidine is less reliable than previously shown for paediatric MRI scans (44).

In the following table suggested effect site concentrations for the drugs discussed above are summarised.

Drug	Effect Site concentrations
Propofol	0.5-1.0 µg/ml
Remifentanil	1-2 ng/ml
Sufentanil	0.01 ng/ml
Ketamine	To be announced

Table 2

Closed Loop Sedation

Very little has been written about this subject during conscious sedation, but as far as novel approaches to sedation goes, this is as novel as it comes. The concept of a closed loop system is that the module will adjust infusion rate according to a pre-set level of sedation or anaesthesia. This means that the programming will monitor a

given objective parameter, such as the Bispectral Analysis and re-program the pharmacokinetic model to effect. During colonoscopy in healthy volunteers the performance of one of these systems was found to be excellent, with exact sedation criteria (drowsy but rousable), high patient and surgeon satisfaction rates and quick awakenings (45). In a further study during minor surgery, it was found that propofol under closed loop conditions, targeting effect site concentrations, give better accuracy and adequate anaesthesia (46). Another method of monitoring response is by somatosensory evoked potentials, and this has also been deemed a feasible method of controlling the loop (47).

This is probably the future of sedation and anaesthesia as a whole, finally affording the intravenous anaesthetics the comfort and safety that MAC and end-tidal control have given the vapours.

Patient Controlled Sedation

After the astounding success of patient controlled analgesia (PCS), researchers started focussing on other ways to put control of treatment back into the hands of those that are in our care. This follows the principle that the patient can decide how deeply he wants to be sedated to be comfortable, within safe boundaries. Some of the research will be discussed and common techniques used by sedation practitioners highlighted.

Patient controlled sedation consists of three basic settings or variables; the drug(s) one can administer, the dosage that is delivered per demand, and the lock out period between subsequent dosages. This gives the patient complete control of his level of sedation, as well as the ability to adjust the level, as the environment or stimulus demands.

Entonox can be considered as a very primitive, yet effective form of PCS. As a matter of fact, Entonox was first described for use in the out of hospital setting, because of its great safety profile and effectiveness (48). This mixture of 50% N_2O in oxygen is an extremely effective sedative and analgesic, especially during minor dental procedures, and other areas where local analgesia can be supplemented. Is it effective on its own? Orbes found that it is, unfortunately, less effective than midazolam plus meperidine for colonoscopy, but gives a very rapid recovery (49). More recently, a technique was described where a patient inhales Entonox until the caecum was reached, and as needed after that. This approach gave satisfaction ratings and pain scores which was comparable to PCS with TCI propofol (50).

The technique to use PCS effectively is still under much discussion. Even the lock-out periods is an area of debate, as this influences patient safety and possibly recovery time. Consider the following: In a study where patients were given

midazolam, one group could administer 0.1mg per dose, with no lock out period, whereas the other received 1mg per dose with 1minute lock-out. Both groups ended up with similar sedation profiles and no difference could be found in the amount of drug received (51). The same results were found when a 1minute and 3 minute lock-out period was used, but in this study, patient satisfaction was lower in the 3 minute group (52).

Lastly, the issue of the doses given at "induction" is also still an area of debate. Should big doses be used for loading, demand or both? Researchers in Japan took on this very question and found that when using propofol, ketamine and fentanyl for PCS it was best to give a large loading dose. This can be followed by smaller on-demand doses (53). A small loading dose increased the total dose given, as patients demanded more, whereas both large loading and demand doses resulted in over-sedation.

Propofol is probably almost essential in PCS, because of its unique pharmacokinetic profile that leads to a short onset and duration of action, and quick recovery of a patient. It also tends to give less nausea and vomiting, reduces the need for other drugs and improves patient satisfaction, when compared to e.g. remifentanil alone (54). When compared to midazolam and an opioid, propofol and an opioid are superior with regards to recovery time (55). The biggest setback with both of the previous studies is the increased incidence of desaturation and need for rescue.

Propofol administration is associated with a dose-dependent risk of respiratory depression, a risk that is heightened with concomitant opioid use. This can be problematic for the clinician wishing to provide analgesia with opioids as propofol has no intrinsic analgesic properties.

The complimentary drugs are still a matter of choice, but some do fare better than others. Ketamine appears to be superior to opioids when used during "invasive" procedures probably because of the amnestic effect. Amnesia can occur in up to 20% more patients when using ketamine, as compared to alfentanil, for instance (56). It also gave a much more stable sedation, with almost no drop in systolic blood pressure. Unfortunately it did not decrease the incidence of desaturation, as compared to propofol alone, although it did decrease the dose of propofol received (57).

It is claimed by various studies that when we combine ketamine and propofol (ketofol) we need less propofol, and then a lower incidence of respiratory-related adverse events, and we provide analgesia.

Lee et al. took the great success of patient controlled sedation, especially patient satisfaction, one step further. In a randomized controlled trial, they proved that relaxing music, combined with a propofol-alfentanil sedation regime, reduced the

amount of PCS used dramatically and improved acceptance and satisfaction (58). Interestingly, video distraction methods did not prove to be as successful in reducing sedative use, but the addition of music did. Pain scores are also decreased by these methods (59). This technique was even shown to work in children going for electroencephalography, with comparable results to chloral hydrate.

Does this mean the end of sedation practitioners? Murdoch et al. did a study on healthy volunteers, where they tried to assess the safety of this system. Of the 10 subjects, two became over sedated, one with loss of eyelid reflex (60). The conclusion was made that this can only be done under the direct supervision of an anaesthetist or sedation practitioner.

A suggested technique would be as follows: the patient will receive a bolus dose of Propofol/Ketamine 0.25mg/kg i.v. He will then be allowed to administer 1ml boluses of a Propofol/Ketamine combination of 5mg/ml demand setting, with either a short lock-out or no lock-out period. Should the procedure prove to be very painful and no local anaesthesia can be given, alfentanil can be supplemented as needed, with very careful monitoring of ventilation and saturation. It is up to the discretion of the sedation practitioner as to whether a premedication should be administered, e.g. midazolam 0.5 - 1mg. The on demand ketamine can be omitted, but a larger bolus, i.e. 0.3mg/kg can be given at the start of the procedure (61). This regime will give very good sedation to almost all patients for almost any procedure. It does run a high risk of desaturation problems, so the patient must be carefully monitored.

Future Developments

Transdermal Applicators

Following suite on the nicotine patch and transdermal oestrogen, sedation practitioners could also benefit from this easy to utilize organ: the skin. Surgical anaesthesia is induced with the use of a patch containing an opioid, a α_2-agonist and an amnestic agent such as midazolam or ketamine. Anaesthesia will theoretically be reversed by removal of the patch and application of a second patch, containing naloxone and a α_2-agonist (62). If this invention works, it is easy to surmise that it could also be applied to the field of conscious sedation.
Sedation practitioners already use an EMLA® patch to anaesthetise the skin for cannulation purposes.

Nebulisation

The lungs have long been known as one of the biggest available areas for drug administration. One very effective way of utilizing this route is by nebulization, where fluid particles are administered via a face mask. McCormick et al. proved that midazolam given via nebulization has the potential to be an effective and safe route of sedation. Unfortunately their study was too small to give any indication of the possible dose to use (63).

Conclusion

Leonard Sweet said "What is the difference between a living thing and a dead thing? In the medical world, a clinical definition of death is a body that does not change. Change is life. Stagnation is death. If you don't change, you die. It's that simple. It's that scary."

It is very clear from the discussion above that there is a legion of possibilities available to us as sedation practitioners and it would be sad to stick to one, comfortable, regime. Research in sedative techniques is on-going and we are entering a very exciting era. However, the research is also still very scanty and of a pilot nature at the very best. We need to explore and develop new and innovative ways to make a very unpleasant time of a patient's life, more comfortable and if at all possible, a wonderful experience.

We want to acknowledge the contribution of Dr Edwin Marshall with this article.

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