PHARMACOLOGY OF CONSCIOUS SEDATION

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Introduction

The use of locoregional anesthesia for a variety of surgical procedures is increasing as it provides not only satisfactory operating conditions and good intra- and postoperative analgesia, but also has advantages in terms of health economics. Also some surgical procedures which in the past have required general anesthesia and open operation can now be carried out percutaneously under local anesthesia. In order to improve patient acceptability, comfort and reduce stress, it is common practice to provide some form of sedation during such procedures. Ideally during sedation, the patient should be relaxed, comfortable and cooperative throughout the procedure. In practice, achieving this ideal may be the most challenging aspect of anesthesia. Increasingly, procedures which were once undertaken as open surgical operations can now be achieved by less non-invasive techniques under locoregional anesthesia and sedation. These factors have led to an increase in the requirements for conscious sedation.

Sedative agents

An ideal sedative agent should produce a rapid and smooth onset of action and allow easy control of the level and duration of sedation. It must have rapid offset and recovery without rebound or emergence effects to enable rapid discharge from the recovery area and hospital. Of the currently available drugs propofol and midazolam are the two must suitable agents with midazolam being particularly popular with non-anesthetists. However, the pharmacokinetics properties and recovery characteristics of propofol make it potentially better suited for short-term sedation. Although both drugs achieve a rapid peak blood concentration after a bolus dose, there is considerable delay to peak clinical effect with midazolam compared to propofol. In practice this means there is more potential for dose stacking and eventual overdose with midazolam, this is supported by available studies comparing the 2 drugs[1].

TCI for sedation

The problem with propofol particularly for the non-anesthetist is its short duration of action requiring repeated bolus dosing or complex infusion regiments. An alternative approach to the delivery of this drug is the use of a target controlled infusion (TCI)[2]. TCI uses a pharmacokinetic model of propofol to provide an infusion profile designed to achieve and maintain any select target blood concentration. In this way the physician can easily titrate the target blood concentration up or down in order to achieve the desired level of sedation. Skipsey et al. used TCI to provide sedation for orthopedic procedures under spinal anesthesia[3]. They concluded that the system provided good quality sedation with the patients remaining within the target sedation score range 87% of the time with little over sedation. The median target concentration for this group was 0.9 μg/ml with a range of 0.15-2.6 μg/ml. Church et al. used TCI infusions for sedation in patients undergoing gastroscopy. In this study an initial target of 1.5 μg/ml was selected and increased by 0.5 μg/ml increments every 30 seconds until the patient's speech became slurred. The median target concentration of propofol in the group was 2.5 μg/ml with a range of 1.5-4 μg/ml[4]. The higher targets required in the later group are explained by the increased level of surgical stimulation in this group. As can be seen from the range of target values in these 2 studies, there is considerable intra-individual variation in propofol requirements, thus it is not possible to predict in advance the target blood or effect site concentration any patient will require for adequate sedation. it is therefore necessary to titrate the TCI blood concentra-

tion to the desired effect in the patient. Although TCI allows rapid titration of the blood concentration of propofol, the clinical effect of the drug is delayed, and can be represented by a theoretical effect site concentration. Thus the physician needs to be aware of this delay in order to avoid potential overdosing by increasing the target concentration before the effect site concentration has had time to equilibrate.

Patient controlled sedation

A number of researchers have allowed patients to self-administer sedative drugs Patient Controlled Sedation (PCS), in a manner analogous to patient controlled analgesia; this appears to be strongly preferred by patients[5]. The technique involves the patient self-administering a sedative agent to the point at which they are satisfied with the level of sedation. Such an approach has the potential to overcome the pharmacodynamic variation between individual patients. PCS appears to be safe and acceptable to patients, surgeons and anesthetists. Over the past decade more than 30 studies of patient controlled sedation have been published. Two methods of administration of sedative agents for PCS have been used. Most studies describe the use of a modified Patient Controlled Analgesia (PCA) pump which delivers a set amount of bolus sedative agent with or without a lockout time. More recent studies have described the use of a modified TCI device with the patient being able to increase the target concentration for sedation by pressing the demand button. All studies in this field describe satisfactory results with PCS and report a high degree of patient satisfaction. However, all studies involved supervision by an anesthetics and few studies have reported any objectively measurable benefits. Osborne argues that careful monitoring by the anesthetist is mandatory and the use of monitored PCS substantially increases the anesthetist responsibility[6]. This begs the question: does monitored PCS represent an improvement over anesthetist controlled sedation and can the delivery system be made safe enough to be used without anesthetist supervision? The PCS technique referred to as Patient Maintained Sedation (PMC), combines the benefits of Target Controlled Infusion (TCI) with patient controlled feed back to produce safe intra-operative sedation[7]. In this study, 36 un-premedicated patients, undergoing surgery under regional anesthesia, were recruited. An intravenous propofol infusion was started at a target plasma level of 1.0 μg/ml. The patient was then able to increase the target propofol concentration in 0.2 μg/ml increments by pressing a demand button. There was a lockout interval of 2 min and a maximum permissible target concentration 3 μg/ml. The patient was then given control of the handset and was able to increase the propofol target concentration in 0.2 μg/ml increments by pushing twice within 1 second on a demand button. For the first 20 minutes of use if there were no demands made in any 6 minute period, the system decreased the concentration by 0.2 μg/ml, there after it decreased after 12 min without demand and every 12 min thereafter until the baseline target concentration of 0.2 μg/ml was reached. In the study optimum sedation was provided a median target concentration of 0.8-0.9 μg/ml. The investigators observed that there was no cardiovacscular instability and little over-sedation. Respiratory rate decreased with the onset of sedation and the lowest recorded rate was 10 breath/min. There were no instances of airway obstruction requiring intervention. However, 8 patients required supplementary nasal oxygen supplementation therapy because of oxygen saturation readings below 92% and oxygen supplementation improved the saturation in all cases. Recovery was rapid following the cessation of the infusion and there were no delays in discharge from recovery room. This technique combines the benefits of TCI with patient controlled feedback and produces safe intraoperative sedation during loco-regional anesthesia with rapid recovery and high patient satisfaction.

Some potential difficulties with PCS have been raised, including the question of whether patients can adequately judge their sedation needs while already sedated. The clinical experience obtained to date, however suggests that this technique is effective and highly ac-

ceptable to patients. It accommodates wide variations in sedation requirements between patients and allows patients to receive the level of sedation that they want. Patients also derive psychological benefit from this method of control by being able to modify anticipated unpleasant stimuli.

Effect site controlled PMS

It may be appreciated from the above that the sedation effect of propofol is related more closely to the calculated effect site concentration than the blood concentration. It would therefore be preferable to target the effect site rather than the blood concentration with a TCI system. The technology to do this is available, but not currently regulatory approved. Figure 2 shows a comparison of effect site and blood targeted TCI. The effect site system allows the effect site to rise to its target value more rapidly without the risk of overshoot. Such a system with patient control added would allow patients to achieve a given level of sedation more rapidly with a shorter lockout period with little risk of over-sedation. Effect site targeted TCI with patient control to provide self administered sedation has been used in volunteers. The system was set with an increment of 0.1 μg/ml and lockout time of 1 minute. Volunteers were asked to try to anesthetize themselves with the system. No subject lost their airway or desaturated below 90 % although all patients were given supplementary oxygen via a nasal cannula. This new method of delivery has the potential to be the most effective safe and responsive method of sedation and requires further study.

Summary

Propofol is a safe and effective alternative to midazolam for providing conscious sedation. The use of TCI facilitates the delivery of propofol and provides effective titration of sedation. Patient controlled sedation using propofol provides many benefits and gives a high degree of patient satisfaction. The combination of patient control TCI and effect site controlled TCI (with remifentanil too) offer exciting new prospects for sedation and warrant further investigation.

References

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