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Remifentanil Use in the ICU: A Health Economic Viewpoint

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Due to its unique pharmacokinetic profile, remifentanil may lead to improved clinical outcomes and cost-savings in the Intensive Care Unit (ICU).

Abstract

Unlike other opioids, remifentanil is quickly metabolised to an inactive metabolite by non-specific esterases. It does not accumulate and has a very short context-sensitive half-life. Furthermore, the level of analgesia can be quickly increased to prevent additional pain associated with ICU procedures. The unique pharmacokinetic profile of remifentanil enables optimised sedation, better neurological assessment and faster post-infusion respiratory function recovery. Furthermore, the rapid and predictable offset of effects allows patients to be weaned and extubated faster. Decreasing time on mechanical ventilation may also minimise the risk of ventilator-associated morbidity. Although remifentanil is a more expensive option, it is inappropriate to consider health economics by comparing the net costs of drugs alone. Resource utilisation and attributable health effects must be taken into account to calculate the incremental net costs and effects. At this time, there are no published economic evaluations on the use of remifentanil in the ICU. However, several studies show that remifentanil can substantially decrease the length of ICU and hospital stay, so that its use may be cost-effective or even costsaving, depending on the setting, country and perspective.

Introduction

A combination of sedation and analgesia is often required in critically ill patients, since they experience pain, anxiety, agitation and confusion, mostly related to painful procedures. One of the major reasons for patients being admitted to the ICU is the need for mechanical ventilation. Since 2002, remifentanil has been approved for the provision of analgesia in mechanically ventilated adult ICU patients by the European Medicines Agency. This paper summarises the available evidence on the use of remifentanil in the ICU from a health economic viewpoint.

Pharmacokinetic Profile

Remifentanil can be distinguished from other opioids by its unique pharmacokinetic profile. Non-specific blood and tissue esterases rapidly metabolise remifentanil to a clinically inactive compound. As a result, remifentanil does not accumulate and its contextsensitive half-life is about 3-5 min, independent of the infusion duration (Egan et al. 1993; Kapila et al. 1995; Malbrain et al. 2004; Westmorland et al. 1993). Additionally, remifentanil also has a rapid onset of action (1 min) reaching steady state concentrations. The pharmacokinetics of remifentanil do not change in patients with hepatic (Navapurkar et al. 1998) or renal impairment (Breen et al. 2004; Pitsiu et al. 2004). In comparison, traditional opioids may lead to accumulation, unpredictable metabolism, active metabolites and prolongation of effect with increased duration of infusion.

Clinical Advantages of Remifentanil in the ICU

Clinical Advantages

Based on its unique pharmacological properties, remifentanil has both potential advantages and disadvantages. I discuss first the potential benefits.

Remifentanil provides rapid, reliable and easily titratable analgesia and patient comfort. The level of analgesia can be quickly increased to cover additional pain caused by ICU procedures. Remifentanil enables an optimised sedation, often without the need for hypnotics (e.g. propofol). As a

result, the possible negative effects, especially of over sedation (respiratory depression, hypotension, bradycardia, immunosupression, venous stasis, increased time on the ventilator, increased time in the ICU, failure to recognise cerebral insult, possible cognitive dysfunction (Ramsay 2000)) and the associated costs can be minimised. The prevention of over sedation allows patients to be awake or easily awakened within the ICU. This enables improved communication and thus optimised neurological/analgesic assessment and patient co-operation during ICU procedures, which in turn can decrease the need for expensive diagnostics such as brain CT (Wilhelm et al. 2004). Optimised sedation and rapid, predictable offset of effect allow patients to be weaned and extubated more quickly (Wilhelm 2004). Decreasing time on mechanical ventilation maynot only reduce ICU and hospital stay (Wilhelm 2004), but also minimise the risk of ventilator-associated morbidity, such as airway trauma or pneumonia (Cook et al. 1998). Several studies investigating the use of remifentanil in an open-label manner have shown that weaning and extubation times are substantially reduced (Karabinis et al. 2004; Malbrain et al. 2004; Matthey et al. 2004; Matthey et al. 2004). Dahaba showed this effect even in a double blind study (Dahaba et al. 2004).

Clinical Disadvantages

Compared to other opioids there is only one clinical problem with the use of remifentanil and this can easily be solved. Owing to the rapid offset, the anaesthetist must plan the patient's analgesic requirements before remifentanil is discontinued. For some patients high dosages may also be necessary, possibly due to the phenomenon of opioid tolerance, which can occur with all opioids. Remifentanil, like other opioids, should be used with caution in patients with pre-existing sinus node dysfunction and/or arrhythmias, as it can cause bradycardia. When given in combination with anti-hypertensive drugs or to patients with severely depressed cardiac function, remifentanil should not be titrated above 0.25 mg/kg/min. In these patients the combination of remifentanil with midazolam may be preferable to propofol.

Health Economics

Based on the above listed pharmacokinetic properties and clinical advantages, it is clear that the use of remifentanil has the potential to become the first choice agent for sedation and analgesia in the ICU.

As remifentanil is more expensive than other opioids its use may be anticipated to result in increased net hospital costs. However, the average remifentanil concentration required in the ICU is much lower than in the operating theatre (0.10-0.15 µg/kg/min versus 0.25µg/kg/min) (Dahaba et al. 2004; Muellejans et al. 2004). Table 1 lists the costs in a Belgian hospital for different treatment regimes at different doses for a hypothetical patient weighing 70kg. Remifentanil can also reduce the expense of hypnotics, as it has a hypnotic sparing effect. Consideration of drug costs alone is inappropriate because it doesn't take into account the changes in other cost types. A full economic evaluation, i.e. a cost-effectiveness analysis, is necessary to estimate the net costs and effects. Firstly, the resource utilisation and health effects of a remifentanil regime and of an appropriately comparable regime need to be measured in detail and evaluated from a specific perspective (e.g. hospital, insurance or society). Secondly, the rendered costs and effects of the two regimes should be subtracted from each other to obtain the incremental net costs and effects. Dividing the gained net costs by the net effects produces the incremental cost-effectiveness ratio. Potential savings with remifentanil are likely to be gained by reducing the length of ICU and hospital stay and decreasing the risk for costly complications (pneumonia and antibiotics use). Optimised sedation may also lead to savings due to the prevention of diagnostic and medical procedures. Furthermore, the use of remifentanil could potentially result in improved health effects, decreasing the risks associated with over sedation, especially with long-term ventilation, which in turn may minimise the risks for negative sequelae.

Although economic evaluations are increasingly common in the critical care literature, such evaluations face several challenges and the reported approaches to their conduct are not standardized (American Thoracic Society 2002). At this time there is no published economic evaluation for the use of remifentanil in the ICU. Clearly, it will depend on the country and setting whether the use of remifentanil and the associated changes in hospital resource utilisation results in net costs or net savings to the specific payer, such as the hospital (Welte et al. 2004).

Conclusions

Owing to its unique pharmacokinetics, remifentanil has the potential to decrease the time on mechanical ventilation and the length of stay in the ICU and the hospital, and to minimise the use of expensive diagnostics. The cost-effectiveness of remifentanil in the ICU remains to be determined. For this purpose, a full economic evaluation from a specific perspective is necessary, to identify the incremental net costs and effects of remifentanil use compared to an appropriately comparable treatment.

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