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Pain relief with low-dose intravenous clonidine in a child with severe burns

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Abstract The case of an 11-year-old boy who suffered second and third degree burns to 78% of his body is reported. The large doses of morphine used as analgesia resulted in severe side effects: ventilatory dependence, impairment of gastrointestinal function and psychological disturbance. Intravenous lignocaine was added without benefit. The addition of low-dose intravenous clonidine, however, precipitated a dramatic reduction in morphine consumption with an attendant improvement in ventilatory, gastrointestinal and psychological functions.

Key words Burns · Pain · Analgesia
Morphine · Lignocaine · Clonidine

Case history

An 11-year-old (35-kg) boy was doused with petrol and set alight. He sustained second and third degree burns to 78% of his body. On admission to hospital he was intubated and ventilated using the synchronised intermittent mandatory ventilation (SIMV) and the pressure support mode of a Siemens 300 ventilator. Morphine and midazolam infusions were started to provide sedation and analgesia. On the evening following resuscitation, escharotomies were performed and dressings were changed every 2–3 days thereafter. Wound debridement began on day 25, and the first skin grafting was performed on day 39.

Following an initial period of stability, the patient's clinical condition began to deteriorate on day 4. He started to manifest systemic signs of sepsis: tachycardia, pyrexia, leucocytosis and progressive hypoxia. Organ failure ensued, primarily affecting the respiratory and renal systems. Treatment included broad spectrum antibiotics, as well as dopamine and vecuronium infusions.

By day 9 the patient's gas exchange had improved sufficiently to allow cessation of vecuronium infusion. However, the high dose of morphine required to provide adequate analgesia resulted in a number of serious side-effects. The primary problem was impaired gastrointestinal motility with consequent nausea, constipation and poor tolerance of enteral feeding, resulting in poor nutritional status. Bouts of extreme agitation, sweating, anxiety and nightmares were also prevalent at this time.

In an attempt to reduce morphine consumption, an intravenous lignocaine infusion was begun on day 11. The initial dose was 0.3 $mg\,kg^{-1}\,h^{-1}$; this was gradually increased to 1.2 $mg\,kg^{-1}h^{-1}$. While there was an initial reduction in morphine consumption, this unfortunately was not sustained. Failure to successfully wean the morphine infusion resulted in a corresponding failure to wean from the ventilator.

Following debridement there was an abrupt, if anticipated, rise in morphine requirements. Therefore, clonidine was introduced intravenously at a rate of 7.5 μg every 4 hours. This rate was increased to 10 μg the following day without adversely affecting haemodynamic parameters. At this point, morphine consumption was equivalent to 525 mg/day. Subsequent to the introduction of clonidine, morphine requirements diminished from 15 $mg\,kg^{-1}\,day^{-1}$ to 1.4 $mg\,kg^{-1}day^{-1}$, despite frequent operative interventions. This expedited ventilatory weaning and permitted successful extubation within 7 days (Fig. 1).

Coupled with this enhanced respiratory drive was an improved tolerance of enteral feeding. The addition of clonidine facilitated analgesia at a higher level of consciousness and abolished the psychological disturbances, thereby improving the patient's cooperation with nursing staff and physiotherapy.

Discussion

Patients with severe burns suffer intense pain, particularly during dressing of wounds. Currently, there is no established satisfactory alternative to potent opioid

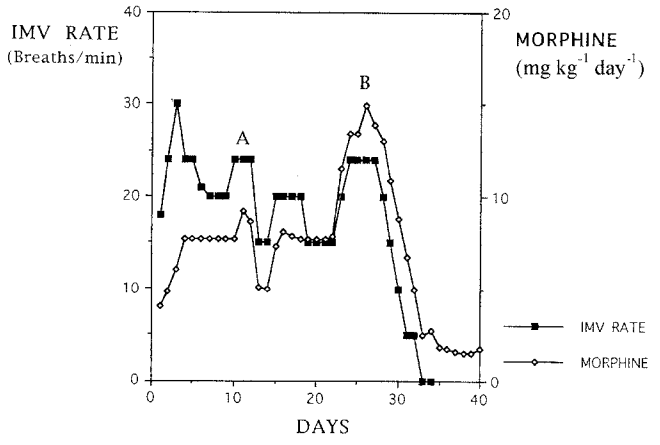

Fig. 1 Morphine consumption and ventilation rate over time. *A* lignocaine infusion started; *B* clonidine introduced

analgesics. These high doses of opiates produce numerous adverse effects, several of which were exhibited by our patient: failure to wean, difficulty with enteral feeding, constipation and psychological disturbance. The first strategy we employed to try to reduce morphine consumption was the addition of a lignocaine infusion. Intravenous local anaesthetic infusions have been shown to reduce post-operative pain and to inhibit the algesia of burns [1]. In the cases described by Johnson et al., where patients had suffered 10–30% burns, lignocaine was the sole analgesic agent used. Unfortunately, however, it failed to have the same impact in this case.

Clonidine is an alpha-2 receptor agonist, which acts by inhibiting adenylate cyclase, resulting in a reduction in intracellular cyclic adenosine monophosphate (cAMP). It may effect potassium channels by causing a hyperpolarisation of membranes, as well as suppressing calcium influx into nerve terminals. Although in many countries clonidine is licensed only as an antihypertensive agent, its profile in anaesthesia is increasing. A large number of studies have been undertaken to evaluate its place in the treatment of adult patients; its role in both paediatric anaesthesia and intensive care, however, remains relatively uninvestigated. To date the main use of clonidine in paediatric medical practice has been in the treatment of neuroendocrine and psychiatric disorders [2].

Clonidine possesses many attributes that make it an attractive adjuvant in the treatment of pain in the critically ill. It provides sedation and anxiolysis by directly affecting the *locus coeruleus* [3]. Antinociception is mediated at three levels: peripheral, spinal and supraspinal. Alpha-2 adrenergic agonists have been found to decrease oedema and pain behaviour in animal models of peripheral tissue inflammation. The modulation at brain and brainstem level is achieved by activation of inhibitory descending pathways to the spinal cord. However, the primary analgesic effect appears to be due to a reduction in substance P release and the hyperpolarisation of dorsal horn neurons [4]. Coadministration of opioids and alpha-2 agonists for post-operative pain results in a substantial decrease in opioid dosage without adversely affecting the quality of analgesia [4].

The dose of clonidine used in this case (0.2–0.3 μg/kg four hourly) was substantially lower than that used in other clinical trials. Depending on the route of administration, the dose in these studies varied from approximately 1–9 μg/kg [5, 6]. The continuing colonisation of wounds by *Streptococcus faecalis* and methicillin-resistant *Staphylococcus aureus* (MRSA) and the large uncovered surface area created the potential for the development of sepsis. We therefore felt that it would be unwise, given the inherent cardiovascular activity of clonidine and the possible re-emergence of sepsis, to use large doses of clonidine. Since the analgesic action of clonidine appears to be dose related [6], we incrementally increased the dose until adequate analgesia was achieved at a lower level of morphine consumption. A dose as low as 0.3 μg/kg appeared to be effective in this case.

Clonidine may result in a minor depression of the respiratory drive. However, this effect is inconsequential when compared to that of morphine, there being no synergistic action on ventilation between the two drugs [7]. In fact, the addition of perioperative clonidine facilitated weaning from ventilation in patients who had undergone coronary artery bypass grafting [8].

Clonidine also has recognised effects on renal function. It induces a diuresis in animals, while in humans it inhibits both the release and renal tubular action of antidiuretic hormone (ADH). It may increase the glomerular filtration rate and secretion of atrionaturetic peptide (ANP), while effecting a decrease in plasma renin levels [9, 11].

In the case described here, clonidine provided obvious benefits in the areas of sedation, analgesia and ventilation. It also facilitated a rapid reduction in the morphine dosage without precipitating withdrawal symptoms. This is not surprising, as it is a well-recognised treatment for the prevention of the sympathetic overactivity characteristic of withdrawal from opiate addiction [10]. This treatment also reduced the incidence of vivid dreams in our patient, again not unexpectedly, since clonidine has been shown to control hallucinations associated with delirium tremens [11].

The major side-effects of clonidine are hypotension and bradycardia induced by a "resetting" of the

sympathetic nervous system. However, there appears to be a preservation of sympathetic responsiveness [8], as shown in a recent study in children where a single intravenous bolus of clonidine 2.5 μg/kg resulted in relative haemodynamic stability [12].

In conclusion, low-dose intravenous clonidine allowed optimisation of our analgesic regimen while minimising side-effects. Because of the limited anaesthetic experience with alpha-2 agonists in children, clonidine intervention was begun late in this case. The positive results achieved in this patient should encourage further exploration of its use in paediatric intensive care units.

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