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CLINICAL INVESTIGATIONS

Sedative, analgesic and cognitive effects of clonidine infusions in humans†

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This placebo-controlled, randomized study evaluated, on separate days, the dose–response relationship for 1 h infusions of clonidine 1, 2 and 4 μg kg^{-1} h^{-1}, in eight healthy volunteers aged 22–30 yr. Response end-points included sedation (bispectral index, visual analogue scale and observer assessment of sedation), analgesia to a cold pressor test, memory (recall of word lists), cognitive function (digit symbol substitution test (DSST)), respiratory function (respiratory rate, end-tidal carbon dioxide, oxygen saturation) and haemodynamic stability (heart rate and mean arterial pressure). Clonidine infusions resulted in significant and progressive sedation, but all subjects were easily awoken to perform tests and evaluations. Statistically significant analgesia, memory impairment and reduced performance on the DSST occurred during 4 μg kg^{-1} h^{-1} infusions (resulting in a plasma concentration of 2 ng ml^{-1}. There were no statistically significant changes in cardiorespiratory variables throughout the study.

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Unlike most other sedative drugs, α_2-adrenoceptor agonists are capable of producing both sedation and analgesia and result in little, if any, respiratory change.[1] This combination makes them potentially useful in the postoperative, non-ambulatory setting, especially in high-dependency and intensive care situations. With the development of the new α_2-agonist dexmedetomidine, there has been a resurgence of interest in the use of this class of drugs for sedation purposes.[2 3]

An important difference between clonidine and dexmedetomidine is their elimination half-life, which is nearly four times longer for clonidine than for dexmedetomidine.[4] Therefore, dexmedetomidine is more titratable than clonidine, and recovery is more rapid.[2] However, slower elimination may sometimes be desirable, especially in the intensive care situation, where a more gradual weaning from sedation and analgesia might be desired or beneficial.

Continuous i.v. clonidine has been evaluated for its morphine-sparing effects in treating postoperative pain,[5 6] and in the postoperative period for complete pain control.[5] One notable finding in these studies was a substantial haemodynamic effect (hypotension and bradycardia) coincident with the desired sedative and analgesic effects. In addition, these studies provided little information about the dose–response relationship for analgesia, sedation and haemodynamic effects. The present placebo-controlled study in healthy volunteers evaluated three doses of clonidine that were predicted to have minimal cardiovascular effects, and evaluated several end-points, including sedation, cognitive function, analgesia and cardiorespiratory function.

Methods

With Institutional Review Board approval, eight subjects provided their written consent to participate in the study. Volunteers were 22–30 yr of age, ASA grade I, and of both genders. They were given a brief physical examination,

†This article is accompanied by Editorial I.

along with a urine pregnancy test as appropriate. They were excluded if there was a history of asthma requiring treatment or any contraindication to α_2-adrenoceptor agonists, if their ideal body weight was greater than 20% of normal, or if they were unable to complete psychomotor tests.

Subjects were asked to abstain from alcohol for 24 h and any oral intake for 6 h before the study. Each volunteer participated on four occasions separated by at least 7 days, but not more than 10 days. They were randomized to either placebo or one of three doses of clonidine. Treatments consisted of a loading dose of placebo or clonidine, 1, 2 or 4 $\mu g\ kg^{-1}$, given over a 15 min period and followed by a maintenance infusion of placebo or clonidine, 1, 2, or 4 $\mu g\ kg^{-1}\ h^{-1}$, for a 45 min period. Monitoring involved ECG leads II and V_5 for monitoring heart rate (HR) and cardiac conduction changes, non-invasive oscillometric arterial pressure measurement (mean arterial pressure, MAP), pulse oximetry for oxygen saturation (Sp_{O_2}), and a nasal cannula for end-tidal carbon dioxide monitoring. The depth of hypnosis was monitored with a processed EEG (bispectral index system, BIS; Aspect Medical Systems, Newton, MA, USA). Two i.v. lines were placed in the non-dominant arm, one for infusion of clonidine and the other in a different vein for sampling for plasma clonidine concentration. The dominant hand was used to perform written tests and for immersion into ice water (cold pressor test).

After instrumentation and a 10 min rest period, baseline measurements (HR, MAP, Sp_{O_2}, carbon dioxide and BIS) were collected. This was followed by a 5 min rest period, after which resting haemodynamics and end-tidal carbon dioxide were averaged during a 3 min sampling period. There followed the battery of tests to assess sedation, psychomotor performance and memory, and the cold pressor test. After all the baseline measurements and tests had been done, infusions were started with both investigators and subject blinded to the randomization code. Cardio-respiratory parameters were measured at the end of the loading dose (15 min), the end of infusion (60 min) and at 45 and 90 min of recovery, as well as during all cold pressor tests. BIS was recorded every 5 min throughout infusion and recovery. Assessments of sedation (Observer Assessment of Analgesia/Sedation (OAA/S) and a visual analogue scale for sedation ($VAS_{SEDATION}$)) and a self-rating of co-ordination (visual analogue scale for coordination ($VAS_{COORDINATION}$)) were taken at 5, 10 and 15 min during the loading dose and again at 60 min, just before drug termination. Psychomotor (Digital Symbol Substitution Test, DSST), cold pressor and memory tests were performed only at the end of the 60 min infusion period. After drug termination, all tests and assessments were repeated at 45 and 90 min of recovery.

Description of tests

There were three measures of sedation. The first was objective and measured from the processed EEG signal, which indicated the state of hypnosis (BIS). This was recorded continuously and noted at 5 min intervals throughout the study. The second measure was assessment by an independent observer (OAA/S) and was based on categories of responsiveness to verbal stimuli, speech, facial expression and eyes. Finally, visual analogue scales (VAS, scale 0–100) were used to assess sedation and coordination by sliding a movable indicator line between the two end-points of the scale. The subject rated the level of sedation ($VAS_{SEDATION}$) on a scale in which the 0 end represented 'asleep' and 100 represented 'wide awake'; the coordination scale ($VAS_{COORDINATION}$) had the descriptors 'clumsy' at 0 and 'well coordinated' at 100.

Psychomotor performance was tested using a DSST and memory function was determined from a word recall test (MEM). The DSST is a timed test of psychomotor performance (a different test form is given at each time point) with a chart of eight rows of digits in random sequence. There are nine written symbols, each with a corresponding numerical digit. The subject replaces the symbol with its corresponding number. Correct substitutions within a 90 s period were tallied for the score. The MEM test consisted of listening to a series of 16 unrelated words and immediately reciting as many as possible. The MEM test at the 90 min recovery point was different. Subjects did not listen to a new series of words, but rather they were asked to recall as many of the words as possible from the three previous lists, which had been given at baseline, 60 min of infusion and 45 min of recovery. This test is termed the comprehensive memory test (CMEM). In addition to tallying the total number recalled, the number recalled from each list was identified.

The cold pressor test consisted of immersing the subject's hand to the wrist in a constantly agitated ice/water mix for 1 min, and collecting haemodynamic variables and averaging them over the last 15 s of the test. Pain experienced due to the cold exposure was assessed by the subject using a visual analogue scale (VAS_{PAIN}) that had end-points of 'no pain' (0) and 'worst pain imaginable' (100).

Statistics

Data are expressed as mean (SD) except in graphical presentations, where standard error bars are used to reduce clutter. Repeated measures analysis of variance (ReANOVA) was used and *post hoc* analysis was with the Bonferroni test. The CMEM was a single test (not repeated over time), so Student's *t*-test was used to determine differences between groups. Significance was established at $P<0.05$.

Results

Eight healthy subjects (four men and four women aged 22–30 yr) were enrolled. The eight subjects had a mean weight of 71 kg (range 50–84 kg) and a mean height of

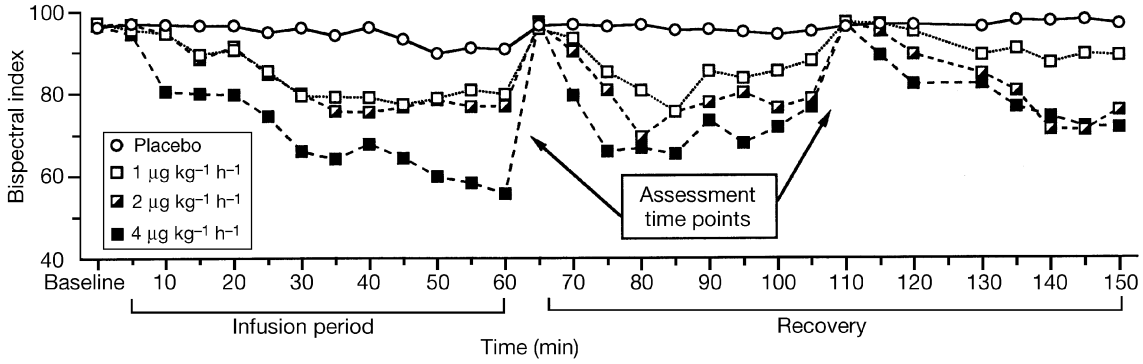

Fig 1 Group results (means) of bispectral index (BIS) numbers recorded every 5 min during the 60 min infusion and 90 min recovery periods in eight volunteers.

165 cm (range 146–180 cm). Mean (SD) plasma clonidine concentrations achieved at 15 and 60 min respectively of each 1 h of clonidine infusion were 0.34 (0.1) and 0.25 (0.1) ng ml^{-1} for 1 μg kg^{-1} h^{-1}, 0.81 (0.4) and 0.84 (0.2) ng ml^{-1} for 2 μg kg^{-1} h^{-1}, and 2.0 (0.9) and 1.96 (0.5) ng ml^{-1} for 4 μg kg^{-1} h^{-1}.

Sedation assessment

All three doses of clonidine produced significant sedation (BIS) compared with placebo (Figs 1 and 2). There was increasing sedation with increasing dose, but the BIS was unable to differentiate between 1 and 2 μg kg^{-1} h^{-1}. After the 60 min infusion, the BIS number had decreased by 6, 17, 21 and 62% in placebo, 1, 2 and 4 μg kg^{-1} h^{-1}. At 90 min recovery from clonidine 1 μg kg^{-1} h^{-1}, the BIS had returned to baseline concentrations, but 90 min after the 2 and 4 μg kg^{-1} h^{-1} infusions there were still significant concentrations of sedation based on BIS. The OAA/S gave essentially identical results to the BIS during both infusion and recovery. Only slightly different results from the $VAS_{SEDATION}$ tests were noted; a 23, 57, 60 and 84% reduction in score was recorded at the 60 min infusion time point for the four groups respectively. This test did not provide a statistically significant difference between placebo and clonidine 1 μg kg^{-1} h^{-1}, though it did show a difference between placebo and clonidine 2 and 4 μg kg^{-1} h^{-1} and a similar recovery profile to the BIS and OAA/S.

Cognitive function and coordination

Although immediate memory recall decreased after the 60 min infusion by 12, 25, 25 and 45% in the four groups respectively, the only significant difference was noted in the placebo versus clonidine 4 μg kg^{-1} h^{-1} comparison (Fig. 3). The CMEM of total recall of the three previous word lists, given at 90 min recovery, indicated that the 4 μg kg^{-1} h^{-1} dose significantly impaired recall of the list heard after the 60 min infusion compared with placebo (33% recall after placebo; 7% recall after clonidine 4 μg kg^{-1} h^{-1}). Recall of the list given at the 45 min recovery period was not

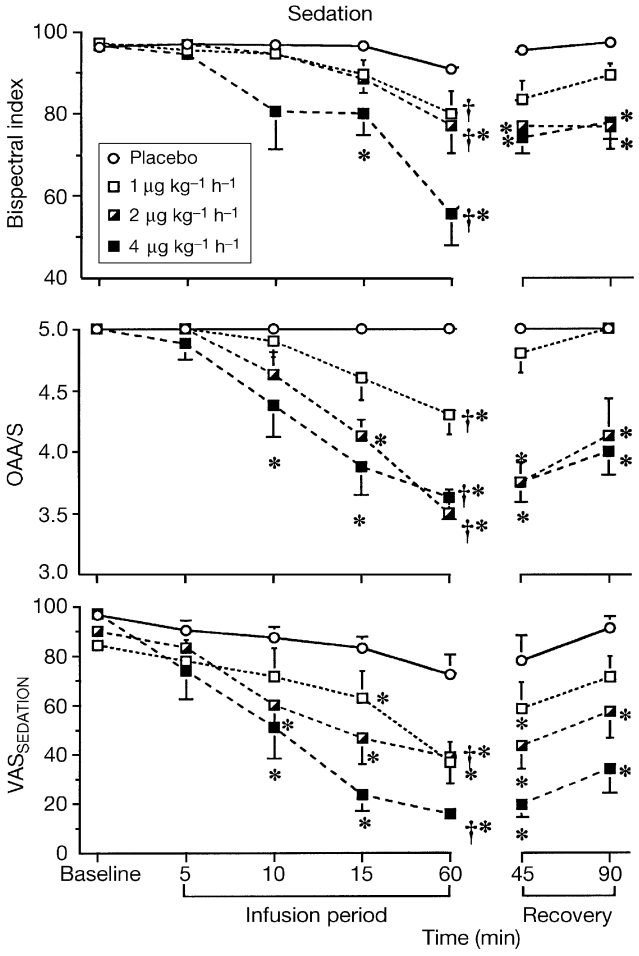

Fig 2 Results of sedation tests indicate that there were progressive increases in sedation with increasing dose of clonidine. There were significant differences by ReANOVA (†) compared with placebo for the 2 and 4 μg kg^{-1} h^{-1} doses for all tests of sedation. In addition, specific time points were compared with baseline with Bonferroni *post hoc* analysis *$P<0.05$.

significantly impaired after clonidine infusion (Fig. 3). During placebo, recall increased from baseline so that the most words were recalled from the most recent list. This

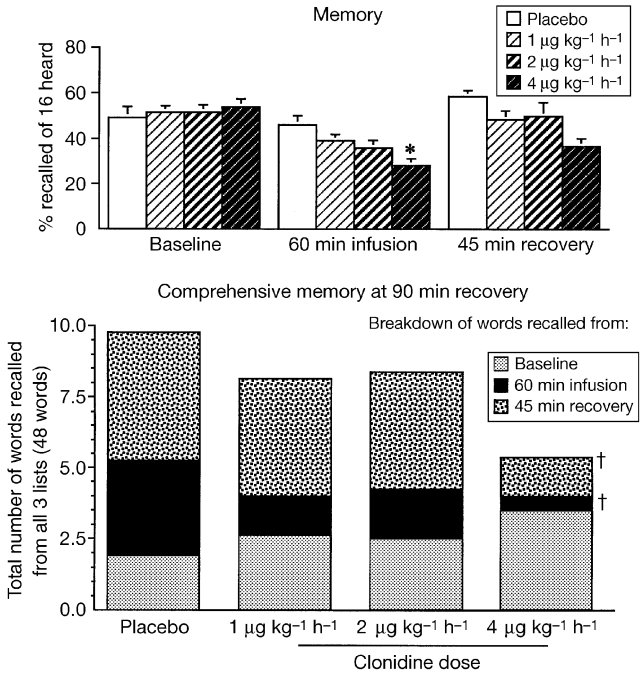

Fig 3 (Upper graph) Percentages of words recalled in the three 16-word memory tests given at baseline, after 60 min of infusion and 45 min into recovery. Only the clonidine 4 μg kg^{-1} h^{-1} infusion resulted in significant impairment in memory. *p<0.05 compared to placebo. (Lower graph) The 90 min recovery comprehensive memory test, in which subjects were asked to recall as many of the words as possible from the lists presented previously. The total number of recalled words and the list from which the word originated are shown. The total number of words recalled was greatest in the placebo group, whose recall increased from baseline, so that the most words were recalled from the most recent list. This progression did not persist in the clonidine groups, primarily because of the volunteers' inability to recall words presented during the infusion periods. This was particularly true during the 4 μg kg^{-1} h^{-1} infusion, when only two (of 16) words were recalled. †P<0.05 compared to placebo.

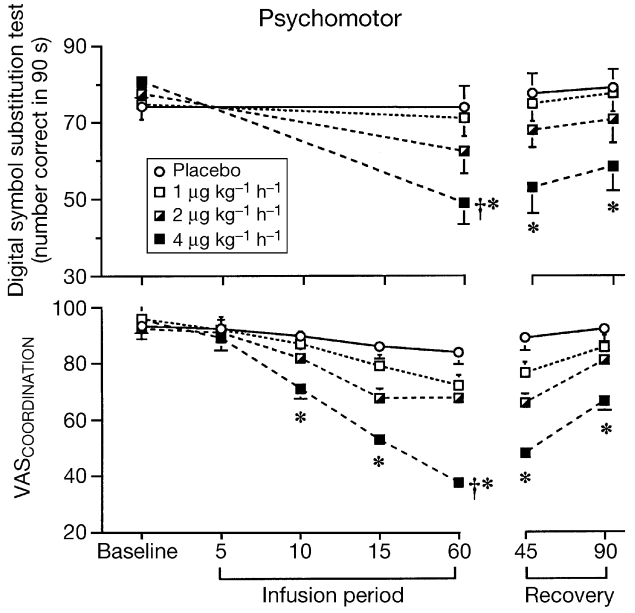

Fig 4 Visual analogue scale (VAS) for coordination, as evaluated by the volunteers, and the 90 s timed digital symbol substitution test (DSST). Significant impairment was found in the clonidine 4 μg kg^{-1} h^{-1} group, but no significant changes were seen in the other groups. †Results of ReANOVA; *comparison of specific time points from baseline responses (P<0.05).

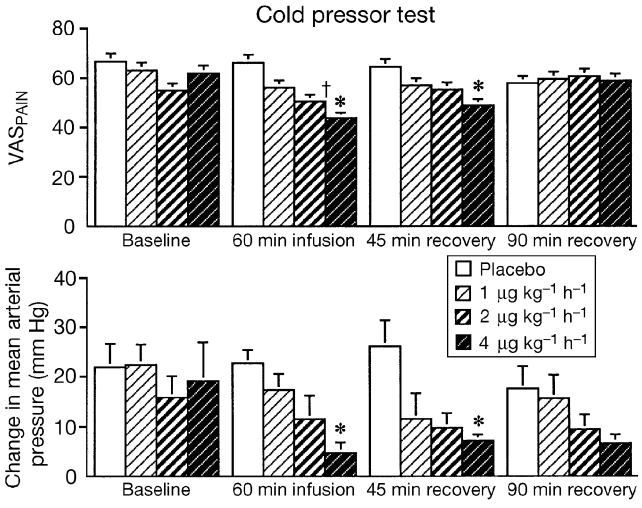

Fig 5 With increasing doses of clonidine, there was a trend for the cold pressor test to elicit smaller increases in mean arterial blood pressure and pain scores. Significance was achieved, in terms of reduction in blood pressure and the pain response, at the 4 μg kg^{-1} h^{-1} infusion rate (*P<0.05). The attenuation of the arterial pressure response and the pain response persisted through 45 min of recovery. †Significant difference between groups.

pattern was not observed in the clonidine infusion groups. There was no evidence of retrograde amnesia, as the recall of the baseline list (presented before infusion) was not different between the placebo and clonidine infusions groups.

We were unable to identify significant differences from placebo in DSST performance during the 60 min infusion test except at clonidine 4 μg kg^{-1} h^{-1} (Fig. 4). Decreases in the DSST at 60 min in the placebo and clonidine 1, 2 and 4 μg kg^{-1} h^{-1} infusion groups were 0, 5, 21 and 40% respectively. When compared with the respective baseline tests, the DSST performance was significantly changed in the 4 μg kg^{-1} h^{-1} group after the 60 min infusion and throughout recovery. The volunteer's assessment of co-ordination on a VAS paralleled the DSST impairment at the 4 μg kg^{-1} h^{-1} dose.

Cold pressor test

Compared with placebo, VAS_{PAIN} during cold pressor test decreased progressively from baseline with increasing clonidine infusion doses but was significant only at 4 μg kg^{-1} h^{-1} (Fig. 5). In addition, clonidine 4 μg kg^{-1} h^{-1} produced significantly more analgesia than 2 μg kg^{-1} h^{-1}. There was a 29% decrease in pain score during the 4 μg kg^{-1} h^{-1} infusion, but no analgesia was retained in

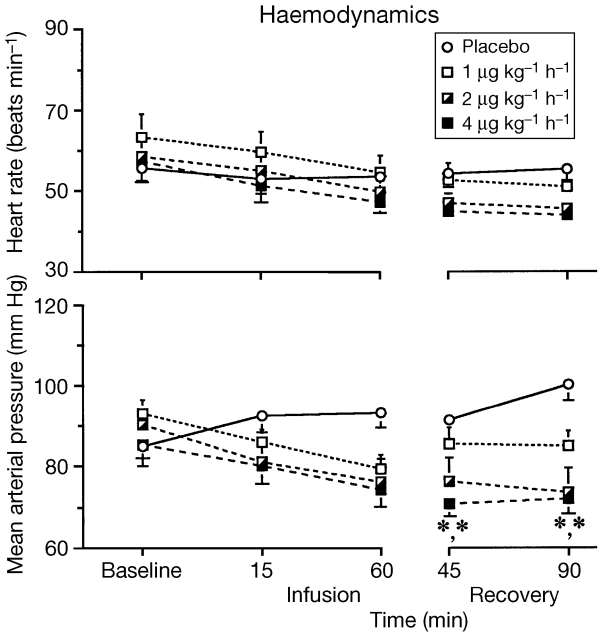

Fig 6 The haemodynamic responses to infusion of clonidine and placebo. The data suggest that clonidine lowered arterial pressure whereas placebo raised it, but statistically significant differences were not achieved between groups during the infusion periods. Similarly, heart rate showed no significant changes over time compared with baseline. $*P<0.05$ compared to baseline.

the recovery period. The MAP response during the cold pressor test after the 60 min infusion increased by 4% in placebo but decreased by 23, 31 and 74% during clonidine 1, 2 and 4 μg kg^{-1} h^{-1} infusions respectively. This decreased response was significant in the 4 μg kg^{-1} h^{-1} group and had recovered by the 90 min recovery.

Cardiorespiratory effects

We found small but not statistically significant differences in the MAP response to clonidine compared with placebo (Fig. 6). After the 60 min infusion, MAP had increased by 10% in the placebo group and decreased by 15, 22 and 13% in the clonidine 1, 2 and 4 μg kg^{-1} h^{-1} groups respectively. In the recovery period, MAP was significantly reduced from baseline concentrations in the 2 and 4 μg kg^{-1} h^{-1} infusion groups. This reduction was still 15–24% below baseline at the 90 min recovery time point. The heart rate decreases of 2, 13, 15 and 18% observed during the infusions and recovery in placebo and clonidine 1, 2 and 4 μg kg^{-1} h^{-1} respectively were not significant and were similar. Respiratory rate (mean 13 b.p.m.), end-tidal carbon dioxide concentration (mean 36 mm Hg) and oxygen saturation (mean 99%) did not change in any group during the course of the study. For example, end-tidal carbon dioxide at baseline, after 1 h of clonidine and after 90 min of recovery for placebo was 39 (1), 39 (2) and 39 (2) mm Hg respectively, and for clonidine 4 μg kg^{-1} h^{-1} it was 37 (1), 38 (2) and 37 (2) mm Hg. Furthermore, haemoglobin oxygen saturation was similar at the same time points (placebo, 99 (1), 99 (1), 99 (1); clonidine 4 μg kg^{-1} h^{-1}, 99 (1), 98 (1), 99 (1)).

Discussion

The present study documents dose-dependent sedation by i.v. infusion of clonidine. Analgesia, suppression of the arterial pressure response to the cold pressor test, memory impairment and significant decreases in psychomotor performance were observed only when clonidine was infused at 4 μg kg^{-1} h^{-1}, and were associated with plasma concentrations of 2 ng ml^{-1}. However, our study was of only eight volunteers and thus of relatively low power. Although MAP and heart rate tended to decrease during clonidine infusions, these changes were not significant.

With the recent development of the highly specific α_2-agonist dexmedetomidine, there has been renewed interest in this class of drug for use in the perioperative period.[2 3 7–9] These drugs offer both analgesia and sedation with little if any impairment of respiratory function—a combination that could be useful in the postoperative or ICU setting.[5] In addition, dexmedetomidine[2] and clonidine (on the basis of this study investigating infusions of duration 1 h) have the interesting property that they allow quick and easy arousal from sedation. This enabled the subjects (and presumably patients) to answer questions and to participate in testing. Clonidine has been investigated extensively for its analgesic and anaesthetic sparing qualities, but its long elimination half-life of 8.5 h[4] makes its use for continuous i.v. sedation and analgesia difficult, and there is no consensus on appropriate dose regimens.

Rat studies have shown MAC (minimum alveolar concentration) reduction in this class of drugs to be mediated by central α_2-adrenoceptors alone, without involvement of opioid and adenosine receptors.[10] MAC reduction from clonidine is reported to be 40% in humans.[11] Because of the incomplete MAC-sparing effects of clonidine, care must be taken when it is used as an adjuvant during anaesthesia, to ensure a depth that is adequate to avoid awareness.

Responses to very high i.v. doses of clonidine have been described. One study in postsurgical patients used 8 μg kg^{-1} i.v. (which produced plasma clonidine concentrations of 2.5 ng ml^{-1}) followed by patient-controlled clonidine analgesia, and found this regimen to be associated with considerable and increasing sedation over the 600 min period of the study.[1] This dose also produced a significant fall in blood pressure (>25 mm Hg). In an effort to avoid unnecessary haemodynamic effects, the present study examined lower doses of clonidine.

Clonidine doses up to 4–5 μg kg^{-1} have been investigated frequently, though primarily for their anaesthetic-sparing effects in the intraoperative period and for their opioid-sparing effects in the postoperative period. Oral premedication with 5 μg kg^{-1} has been used successfully to improve

intraoperative haemodynamic stability and reduce anaesthetic[11] and opioid requirements.[2] A pre-emptive dose of 4–5 μg kg^{-1} i.v. followed by infusion (plasma concentration approx. 1.7 ng ml^{-1}) has also been shown to have a morphine-sparing effect for postoperative analgesia.[5 13] Several studies used similar dosing of clonidine to reduce morphine requirements and reported that sedation with clonidine was not greater than that of the morphine control.[5 6] The present study achieved plasma concentrations above 1.5 ng ml^{-1} during the 4 μg kg^{-1} h^{-1} infusion, which was associated with analgesia and good sedation that was easily overcome by calling the patient's name in a normal or loud voice. The lower plasma concentrations studied in this protocol did not result in significant analgesia, but did provide easy arousal from sedation without impairing cognitive function.

A limitation of this research is that only healthy volunteers were studied with short-duration infusions and we cannot be certain that these findings translate to the patient population in pain or stressful settings. However, our findings seem to be consistent with patient studies in which patients received i.v. clonidine during the perioperative period.

The present study attempted to assess the depth of hypnosis using a processed EEG monitor. The BIS monitor provided an objective assessment of sedation and proved to be a sensitive correlate of dose. BIS findings were supported by the subjective, observer-assessed OAA/S measurement, so that bispectral analysis of EEG may be a useful assessment tool when using α_2-agonists. α_2-Agonists behave differently from other sedatives, seemingly producing something closer to sleep, as we recorded BIS numbers in the 30 s in a few volunteers, during which the infusion rate was 4 μg kg^{-1} h^{-1}, and yet we were able to awaken them immediately to BIS numbers above 90 to perform tests. During general anaesthesia (or i.v. sedation with common drugs such as propofol and opioid/benzodiazepine combinations), BIS scores as low as this would be taken to indicate deep sedation or hypnosis and immediate waking would not be possible.[14] Consistent with our previous study using dexmedetomidine, a rapid increase in the level of consciousness sufficient to perform neurocognitive tests is a unique characteristic of α_2-agonist sedation.[2]

Clonidine has a low ratio of α_2 to α_1 activity in the rat brain (220:1),[15] and this might result in some α_1-receptor side-effects. In fact, i.v. boluses of clonidine can cause transient hypertension, and both α_2- and α_1-receptor agonism on vascular smooth muscle has been implicated.[16 17] However, transient hypertension has not been seen in patients undergoing spinal surgery and receiving i.v. clonidine (5 μg kg^{-1} followed by an infusion).[5] In fact, significant decreases in MAP were noted and were associated with increased cumulative fluid volume in the postoperative period.[5] In the present study, which used young healthy volunteers, cardiovascular changes were small. A recent study in a similar volunteer population with low-dose clonidine supports our findings.[18] These volunteer studies support the hypothesis of De Kock and colleagues that clonidine produces analgesia at doses lower than those required to cause significant hypotension,[13] and extend this hypothesis by demonstrating significant sedation without analgesia when using clonidine at lower doses. However, we cannot rule out the possibility that the presumed lower sympathetic tone in volunteers not in pain from surgery might contribute to the smaller decreases in arterial pressure noted in this protocol.

A limitation of this study is the short (1 h) duration of infusion of clonidine and the possibility that a steady state was not achieved. Although plasma concentrations of clonidine after the 15 min load and at the 60 min time point were identical for each infusion group, the effect site concentration may not have been equilibrated. The two lower infusion rates of clonidine were more likely to have achieved a steady state, based on stable BIS recordings during the last 15 min of the 1 h infusion. However, the 4 μg kg^{-1} h^{-1} infusion resulted in decreasing BIS values (at 45, 50, 55 and 60 min the average BIS was 64, 60, 58 and 56 respectively), suggesting that the effect sites had not achieved steady state.

The respiratory effects of clonidine have been much debated,[19–22] but the consensus appears to be that it is associated with little respiratory depression, and this study would confirm that. α_2-Adrenoceptor agonists, although found throughout the brainstem, are not thought to have a specific role in central respiratory control.[23] One potential respiratory problem with this class of drugs lies in the fact that they dry the mucous membranes. After the 4 μg kg^{-1} h^{-1} dose, volunteers consistently complained of a dry mouth. The drying of secretions suggests there might be a potential for effects on respiratory function through increased mucous viscosity and, consequently, plugging. If this class of drugs is to be used for postoperative sedation, this potential will have to be evaluated.

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