Correspondence

Safe combined intravenous opiate/benzodiazepine sedation for transoesophageal echocardiography

Dear Sirs

The recent article by Manika *et al*.[1] regarding sedation for transoesophageal echocardiography (TEE) recommends a national agreed strategy for TEE sedation that incorporates both an opiate and a benzodiazepine.

The survey data presented show only 6% of the UK hospitals questioned the use of opioids in combination with midazolam, perhaps with good reason. Bailey *et al*.[2] investigated the effects of midazolam and the opiate fentanyl in volunteers. When midazolam alone was used, no significant respiratory effects were seen. Fentanyl alone produced hypoxaemia (saturations <90%) in half of the subjects, but no apnoea. The combination of drugs, however, produced hypoxaemia in 92% and apnoea in 50%. These authors noted that at the time of publication, 78% of deaths associated with midazolam were respiratory in nature, and 57% involved opiate co-administration. They concluded that the combination should only be used if persons skilled in airway management are present.

The Royal College of Anaesthetists working party specifically state: "Combinations of drugs, especially sedatives and opioids, should be employed with particular caution...there may be potentially dangerous synergistic effects when they (opioids) are used in combination with sedatives".[3] The National Patient Safety Agency comment: "Adverse events occur more commonly when drug combinations are used, for example, midazolam with pethidine or other opioid drugs. Such drugs, used in combination, have synergistic effects and, as a result, narrower margins of safety. The use of multiple drugs during conscious sedation presents additional training requirements".[4]

If combination sedation is to be undertaken, then specific recommendations exist. Importantly, the opiate should be given first, with the full effect observed before proceeding.[3,5] The midazolam dose should be adjusted (downwards) when combined with opiate.[4] The author's current protocol dictates the administration of midazolam and/or pethidine, with periodic reassessment and repeated administration as necessary. This implies that the drugs may be co-administered at each time point, and that midazolam may be followed by pethidine. If so, this would be against current expert guidance.

At a time when many units run successful TEE lists without any routine sedation, to recommend a national strategy of combination sedation for TEE may not be justified. Whilst combination sedation may improve tolerability of the procedure, the clear and significant additional risks may not justify this approach. Other strategies to improve tolerability whilst reducing the use of sedative agents, for example with ondansetron,[6] may be preferable.

Yours faithfully

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Dear Sirs,

We read with interest the recent article by Mankia et al.[1] and cannot help but agree with the accompanying editorial by McCormack[7] that the quoted complication rate of 6/151 requiring resuscitation with intravenous fluids and 2/151 requiring benzodiazepine reversal with flumazanil as concerningly high for a proposed *'safe' protocol.*

At our centre we make considerable effort to reassure and calm the patient prior to sedation and then use a simple technique of lidocaine (Xylocaine®) local anaesthetic throat spray followed by 2.5 mg intravenous midazolam – reduced to 1.25 mg at the operator's discretion in elderly patients. After a short period of observation we then intubate in a gentle and controlled manner allowing the patient to guide the pace at which the probe is swallowed. Very occasionally an additional dose of up to 2.5 mg of midazolam is required for anxious patients. We perform the procedure with the patient in the left lateral position with the echo machine behind the patient so the operator can see both the screen and patient at all times. We provide the patient with 2 litres/minute of oxygen via nasal cannula and undertake continuous ECG monitoring. Using this technique, our patients can be monitored closely and because of the low sedative dose many of our patients remain conscious and rousable and sometimes awake throughout the procedure. We find we are able to explain the findings to the patient immediately after the procedure with generally high levels of information retention. This may not be possible if higher sedative doses were used.

We do not use any opiate analgesia. Although Mankia *et al*. rightly state that benzodiazapines lack an analgesic effect, we do provide anaesthetic throat spray and there is no evidence presented by Mankia *et al.* to show that the addition of an opiate produces a better clinical outcome. As they also use a throat spray, the issue, raised by McCormack, regarding suppression of the gag reflex in a sedated patient is not avoided.

Using this technique we have performed 132 procedures over the last two years without the need for use of either intravenous fluids or flumazanil. Despite this, we have only failed to intubate two patients, one of whom

was successfully intubated at a second attempt a week later using the same technique, requiring only our standard midazolam dose. The second patient did not have a further attempt at TOE as it was no longer felt to be clinically necessary. Interestingly, the intubation failure rate from the John Radcliffe group is not quoted by Mankia *et al.*

The mantra we should all be aiming for is to deliver a dose of sedation that is 'As Low As Reasonably Practical (ALARP)'. Good patient communication can dramatically reduce anxiety levels allowing lower doses of benzodiazapines to be used. This, in turn, allows intubation to be performed with the cooperation of the patient, obviating the need for opiates. Success rates from this approach are high and complication rates are minimal and the low doses used and avoidance of long-acting agents, such as pethidine, allow the patient to be safely discharged shortly after the procedure having had an explanation of the results. Whilst a nationally agreed guideline is a laudable aim, the suggested protocol does not seem to provide the answer we are looking for.

Yours faithfully

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Dear Sirs,

Mankia *et al*.[1] are to be congratulated for introducing a sedation protocol for transoesophageal echocardiography (TEE) in their institution[1]. They also call for a national strategy for TEE sedation that incorporates both an opiate and benzodiazepine. This call for a national guidelines for TEE is echoed in the accompanying editorial by McCormack,[7] who rightly points out that TEE is similar to upper GI endoscopy, and that the British Society of Gastroenterologists (BSG) have published a great deal of guidance for its members; initially in 1991, the latest iteration relating to the elderly in 2006.[8] It has been a source of amazement to those responsible for sedation by non-anaesthetists in individual Trusts, as a result of the Academy of Medical Royal Colleges (AoMRC) report published in 2001,[9] that whilst the specialist societies, or Colleges of all of the other specialty groups who carry out sedation, chest physicians, radiologists, gastroenterologists, and ophthalmic surgeons have produced guidelines for their members, this is not the case for cardiologists. It is time they caught up.

Having said that, we are surprised at the protocol devised by the Oxford group. As McCormack points out, the suggested maxima for doses of midazolam and pethidine are inordinately high. We are also surprised that pethidine was chosen as the opioid of choice, as it is relatively long acting, and not particularly efficacious. Perhaps this was because it was often used by gastroenterologists in the past in the belief it relaxed the sphincter of Oddi. Practice is changing, and in the BSG's latest survey of endoscopic retrograde cholangiopancreatography (ERCP) practice, pethidine was used in only 56% of units in England. Moreover, both the BSG and AoMRC guidance state that if an opioid is to be used that this should be administered first and allowed to take effect prior to administration of a benzodiazepine.

Finally, a comment about risk. There is a plethora of papers, such as by Mankia *et al*., in which small groups of patients are subjected to sedation techniques 'successfully'. The 'rule of three' demonstrates that this technique, described in 151 patients, allows us to say with 95% certainty only that the absolute mortality of the technique = 3/151, i.e. less than or equal to 1 in 50[10,11]. Clearly, therefore, this small study demonstrates nothing clinically, but rightly highlights the desperate need that cardiologists have for national guidance on sedation in their practice from the British Cardiovascular Society and the British Society of Echocardiography.

Yours faithfully

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The authors reply

We read with interest the responses to our article[1] and are pleased that there is a general consensus about the need for guideline-led transoesophageal echocardiography (TEE) sedation practice. The responses also demonstrate some centres are leading the way in providing such an approach. Nevertheless, a major aim of our study was to investigate current sedation practice for TEE over the whole of the UK and the results suggest these responses are not entirely representative of wider practice.

Our protocol was offered as an example of a local solution and the responses offer some important modifications that would allow progress towards more widely applicable guidance. As the median total midazolam dose administered in our cohort was 2 mg - which also reflects the doses used by Wynn and Somauroo - our upper limit of a potential maximum dose of 10 mg midazolam and 75 mg pethidine could quite reasonably be modified. Consistent with the suggestion of Hunter and Lyne, a lower maximum dose of 5 mg midazolam and 50 mg pethidine, as advised by the British Society of Gastroenterology (BSG) for endoscopy,[12] might be appropriate. We also acknowledge that provision of an initial dose of opiod without further titration would bring it closer in line with other guidelines. Furthermore, there is varied opinion on the opiod of choice, such that fentanyl may be more acceptable in some centres. Wynn and Somauroo make a vital point regarding the importance of patient reassurance and we agree that there may be value in explicitly stating this within a guideline.

We would suggest Irwin may be being overly cautious in arguing against the combination of opiod and benzodiazepine. The combination is used successfully in many other procedures and its analgesic effect helps simplify intubation and improves the patient's experience. Our decision to continue use of this combination was, in part, guided by a patient experience survey that we performed as part of the study. This demonstrated a significantly higher patient satisfaction score in those who had also received pethidine. We acknowledge that several patients required benzodiazepine reversal

with flumazenil during the period of data collection. The rate of reversal agent and IV fluid use within our unit has been markedly lower since the initial guideline introduction phase and the protocol has been successfully used in well over 500 TEEs. Therefore, we think this may reflect practice during adoption of new guidelines by operators who were not yet fully familiar with the protocol.

We thank the authors for the responses and hope, in combination with our article, these prompt a wider discussion about the importance of TEE-specific sedation guidelines.

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