

## Effect of pethidine and esmolol on the cardiovascular changes occurring during upper gastrointestinal endoscopy

A.K. Gupta<sup>a,\*</sup>, K.E.A. Nicholson<sup>b</sup>, I.K. Driver<sup>a</sup>, C. Woollard<sup>c</sup>, G.D. Bell<sup>c</sup>

<sup>a</sup>Department of Anaesthesia, Addenbrooke's Hospital, Box 93, Hills Road, Cambridge CB2 2QQ, UK

<sup>b</sup>Department of Anaesthesia, Southampton General Hospital, Tremona Road, Shirley, Southampton SO9 4XY, UK

<sup>c</sup>Department of Gastrointestinal Medicine, The Ipswich Hospital, Heath Road, Ipswich, Suffolk IP4 5PD, UK

Received 15 August 1996; accepted 26 August 1996

### Abstract

The cardiovascular effects of patients undergoing upper GI endoscopy when sedated with midazolam and pethidine, or midazolam and esmolol have been compared. A significant rise in heart rate ( $P < 0.006$ ), systolic blood pressure ( $P < 0.001$ ) and rate pressure product (systolic blood pressure  $\times$  heart rate) ( $P < 0.001$ ) occurred in both the patients receiving midazolam alone and those receiving pethidine in addition to midazolam. There were no significant differences in the peak rises in heart rate, blood pressure and, thus, rate pressure product between these two groups of patients. Those patients receiving a bolus dose of esmolol just prior to oesophagoscopy demonstrated a significantly smaller rate pressure response to oesophageal intubation than those in the first two groups. Copyright © 1996 Elsevier Science B.V.

**Keywords:** Upper gastrointestinal endoscopy; Esmolol; Pethidine; Midazolam

### 1. Introduction

In the USA, most endoscopic procedures are carried out using an opioid analgesic such as pethidine together with a benzodiazepine for sedation [1]. Quine et al. in their recent audit of gastrointestinal endoscopy in two regions in England found that between 10 and 20% of endoscopists routinely use pethidine in addition to midazolam for sedation [2]. This confirmed the findings of Daneshmend et al. in their previous nationwide survey [3]. The combination of an opioid drug with a benzodiazepine can increase the potential for cardiorespiratory events including hypoventilation, respiratory arrest, hypoxaemia, cardiac arrest and death [3–5].

Oesophageal intubation causes a rise in heart rate and blood pressure during upper GI endoscopy, increasing myocardial oxygen demands. Some groups have suggested that pethidine and other opioids may offer advantages over benzodiazepine sedation alone in terms of attenuation of this pressor response [6,7].

We evaluated the effect of pethidine in addition to midazolam on the pressor response to oesophageal intubation and then the effect of a bolus dose of esmolol given just prior to oesophageal intubation. Esmolol is a cardio-selective beta-blocker with an elimination half-life of 9 min when administered intravenously. A number of studies have demonstrated that esmolol can attenuate the pressor response to laryngoscopy and tracheal intubation when given by infusion or bolus dose [8–10]. This profile might be appropriate for a drug used in the endoscopy suite as it is non-sedative with no effect on respiratory drive.

\* Corresponding author.

## 2. Methods

Fifty patients presenting for routine upper gastrointestinal endoscopy were entered into this study, after written informed consent and with local ethical committee approval. Thirty-five patients were randomly allocated into one of two groups prior to their arrival in the endoscopy suite. Group one, the control group, received midazolam sedation alone and group two received pethidine in addition to midazolam as sedation prior to endoscopy. A third group received midazolam followed by esmolol.

Group one patients received a saline bolus as placebo whilst group two patients received an age-related dose of pethidine intravenously (50 mg aged under 70 years and 25 mg aged over 70 years) prior to sedation. All patients received intravenous midazolam for sedation at time zero. Patients under the age of 70 received 5 mg and patients over the age of 70 received 2.5 mg. Two minutes later oesophagoscopy was performed by one endoscopist (GDB) using a Pentax EG 2901 endoscope (time = 120 s).

Subsequently, 15 patients received midazolam at time zero followed, by a bolus dose of esmolol (200 mg) at time = 90 s, i.e. just prior to endoscopy at  $t = 120$  s. Exclusion criteria for this group included (i) asthma, (ii) cardiac failure, (iii) heart block, (iv) resting heart rate < 60 beats per min, (v) resting systolic BP < 100 mmHg, (vi) patients taking beta-blocker medication.

On arrival in the endoscopy suite, all patients had a pulse oximeter applied to the right index finger and a continuous non-invasive blood pressure monitor (Finapres, 2300e) applied to the right middle finger. Baseline measurements of heart rate, systolic, diastolic and mean arterial blood pressure together with oxygen saturation were recorded continuously for 2 min prior to giving sedation. All the patients routinely received supplemental oxygen via nasal cannulae at 2 l per min.

During the procedure heart rate, systolic, diastolic and mean arterial blood pressures were continuously recorded by the Finapres monitor. Rate pressure product (RPP) was calculated as systolic blood pressure  $\times$  heart rate. The measured variables were averaged over 30-s epochs and downloaded onto computer for later analysis. Continuous monitoring ceased approximately 1 min after completion of the procedure. The patients were transferred to recovery for routine monitoring.

Comparison between the groups were made using analysis of variance and Student's  $t$ -test with a  $P$  value < 0.05 taken as being statistically significant.

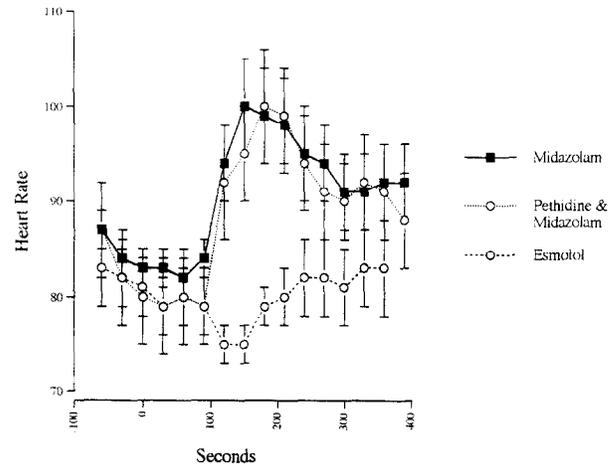


Fig. 1. Upper gastrointestinal endoscopy using midazolam sedation, pethidine and midazolam sedation, or esmolol and midazolam sedation. Effect on heart rate (mean  $\pm$  S.E.M.).

## 3. Results

Two patients were excluded from the study because data failed to download onto the computer. There were no significant differences in age or sex between group one and group two patients. There were no significant differences in baseline resting values of heart rate, systolic BP or RPP between group one and group two patients.

Our results show a significant rise in heart rate ( $P < 0.006$ ), systolic BP ( $P < 0.001$ ) and RPP ( $P < 0.001$ ) on oesophageal intubation in both group one and group two patients (Figs. 1–3). There were no significant differences between the peak values of heart rate, systolic BP or RPP on oesophageal intubation between groups one (midazolam alone) and two (pethidine and midazolam). The peak values occurred at 150 s and within 1 min of oesophagoscopy.

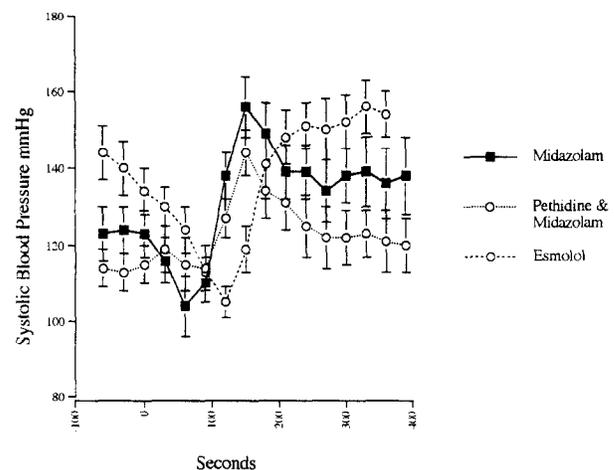


Fig. 2. Upper gastrointestinal endoscopy using midazolam sedation, pethidine and midazolam sedation, or esmolol and midazolam sedation. Effect on systolic blood pressure (mean  $\pm$  S.E.M.).

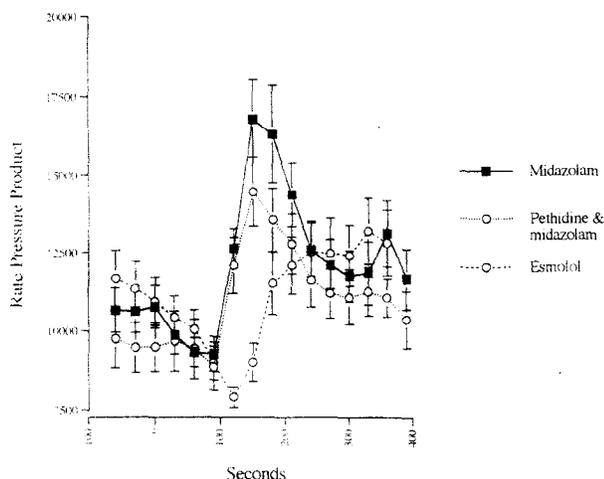


Fig. 3. Upper gastrointestinal endoscopy using midazolam sedation, pethidine and midazolam sedation, or esmolol and midazolam sedation. Effect on rate pressure product (mean  $\pm$  S.E.M.).

Patients receiving esmolol (group three) had a significantly higher resting systolic BP than the other two groups. These patients had no significant change in heart rate throughout the procedure (Fig. 1). Systolic blood pressure fell significantly following sedation and esmolol administration ( $P < 0.01$ ) however, diastolic BP did not fall significantly. There was no significant rise in systolic BP over baseline levels in those patients receiving esmolol (Fig. 2). RPP fell significantly following esmolol administration ( $P < 0.01$ ). The peak rise in RPP occurred at  $t = 330$  s and was not significant (Fig. 3).

#### 4. Discussion

This study demonstrated that pethidine in combination with midazolam has no significant effect on heart rate, systolic BP or RPP when compared to midazolam alone. These results supported the results of our previous study which showed that midazolam has no effect on the cardiovascular changes occurring during upper GI endoscopy. The addition of pethidine increases the potential for hypoventilation and hypercapnia and may lead to hypoxia. This may be of significance in the elderly, the obese or those suffering from ischaemic heart disease. Murphy et al. demonstrated that cardiac arrhythmias are concurrent with desaturation and that desaturation occurs most frequently at oesophageal intubation [13]. This coincides with peak rises in blood pressure and heart rate.

Using continuous non-invasive blood pressure monitoring, we previously demonstrated that the rise in RPP was comparable in magnitude to the rise in RPP that occurs on tracheal intubation under general anaesthesia (unpublished data). Numerous studies have investigated

the attenuation of the pressor response to tracheal intubation because of its association with myocardial ischaemia.

The effect of esmolol given as a bolus and an infusion has been investigated [8–10]. Esmolol appears to blunt, but not abolish the cardiovascular response to tracheal intubation, having its main effect on reducing stress induced tachycardia. We have similarly shown that esmolol has a significant effect on the cardiovascular changes occurring during upper GI endoscopy and its most significant effect is on reducing the tachycardia associated with oesophageal intubation although the effect on RPP is also significant.

A 200-mg dose of esmolol was chosen as this dose has been shown to provide adequate haemodynamic control after tracheal intubation [9]. The timing of the dose would seem to be important, in that the maximal effect with a significant fall in systolic blood pressure occurred within the first minute and therefore a bolus dose just prior to intubation is the most appropriate timing.

Esmolol has a short half-life (9 min) and this was manifest by peaks in heart rate, systolic blood pressure and rate pressure product occurring 4 min after its administration, suggesting that its effects were wearing off.

Although systolic blood pressure and heart rate fell prior to oesophageal intubation, diastolic BP was maintained. This suggests that despite a fall in systolic BP, coronary artery filling may be preserved and thus myocardial oxygen balance optimum. Esmolol has no respiratory depressant effects. Oxygen saturation was not affected.

Upper gastrointestinal endoscopy induces a rise in blood pressure and heart rate on oesophageal intubation and has been associated with a fall in arterial oxygen saturation [6,7,11,12]. Increasing myocardial oxygen demands at a time of reduced supply may be detrimental to some patients. It is recognised that the combination of a benzodiazepine with an opioid can increase the risk of adverse cardiorespiratory events [3–5].

Kinoshita et al. recognised the importance of the pressor response to oesophagoscopy and advocated the use of intravenous pethidine for sedation during upper GI endoscopy [6]. They found that pethidine increased the tolerance of the patients to the procedure (over topical local anaesthesia alone) and attenuated the rise in systolic blood pressure and heart rate. This is in direct contrast to our study. We monitored patients continuously throughout the procedure and although the patients in both studies achieved similar peak rises in heart rate and systolic blood pressure, we were not able to demonstrate that pethidine in addition to midazolam prevented a significant rise in HR or BP on oesophagoscopy. The patients in the control and study

groups received topical local anaesthetic spray whereas the patients in our study all received midazolam sedation. In a previous study we had demonstrated no differences in cardiovascular changes in patients receiving topical local anaesthetic spray compared to patients receiving these doses of midazolam for sedation (unpublished data). The doses of midazolam used in our study had previously been found to produce a dysarthric and drowsy patient, who was still able to cooperate and in whom oesophageal intubation was easy and well tolerated. This was based on a study of 800 consecutive cases using bolus doses in this unit [14].

Ishido et al. advocated the use of fentanyl in addition to topical local anaesthetic spray to attenuate the endoscopy induced rise in RPP. As previously explained, our control group of patients received midazolam sedation rather than topical local anaesthetic spray. In contrast to their patients, our control group of patients achieved far higher increases in RPP over baseline levels and the addition of an opioid drug did not prevent significant rises in RPP on intubation. In our previous study, we monitored patients receiving topical local anaesthetic spray and these patients also achieved far higher increases in RPP over baseline levels. It is possible that these brief but dramatic rises in RPP are not observed when monitoring is intermittent.

The addition of pethidine to midazolam increases the risks of respiratory depression. Pethidine has a relatively long half-life compared to esmolol and may prolong recovery, particularly in the elderly. We could not demonstrate that pethidine has any beneficial effect on reducing the pressor responses to oesophagoscopy when used together with midazolam for sedation. These factors implicate pethidine as an unsuitable and potentially dangerous adjunct to midazolam for sedation for upper GI endoscopy. There is no advantage to this combination.

The number of patients in this study is small and definitive conclusions cannot be drawn. However, these initial observations do suggest that esmolol is a useful drug during upper GI endoscopy, and pethidine is less suitable to control cardiovascular changes due to oesophagoscopy. In view of the high morbidity and cardiorespiratory complications associated with this procedure, esmolol may be beneficial in patients, particularly where the balance of oxygen supply and demand

is critical. No adverse events were recorded with the dose used in this study.

## References

- [1] Arrowsmith JB, Gerstman BB, Fleischer DE, Benjamin SB. Results from the American Society for Gastrointestinal Endoscopy/US Food and Drug Administration Collaborative Study on complication rates and drug use during gastrointestinal endoscopy. *Gastrointest Endosc* 1991;19:421–427.
- [2] Quine MA, Bell GD, McCloy RF, Charlton JE, Devlin HB, Hopkins A. A prospective audit of upper gastrointestinal endoscopy in two regions of England. *Gut* 1995;36:462–467.
- [3] Daneshmend TK, Bell GD, Logan RFA. Sedation for upper gastrointestinal endoscopy. *Gut* 1991;32:12–15.
- [4] Murray AW, Morran CG, Kenny GNC, Anderson JR. Arterial oxygen saturation during upper gastrointestinal endoscopy: the effects of midazolam/pethidine combination. *Gut* 1990;31:270–273.
- [5] Zsigmond KE, Flynn K, Martinez OA. Diazepam and Meperidine on arterial blood gases in healthy volunteers. *J Clin Pharmacol* 1974;14:377–381.
- [6] Kinoshita Y, Ishido S, Nishiyama K, Kitajima N, Itoh T, Inatome T, Inoh T, Fukuzaki H, Chiba T. Arterial oxygen saturation, blood pressure and pulse rate during upper gastrointestinal endoscopy: influence of sedation and age. *J Clin Gastroenterol* 1991;13:656–660.
- [7] Ishido S, Kinoshita Y, Kitajima N, Nishiyama K, Tojo M, Yano T, Inatome T, Fukuzaki H, Chiba T. Fentanyl for sedation during upper gastrointestinal endoscopy. *Gastrointest Endosc* 1992;38:689–692.
- [8] Ebert JP, Pearson JD, Gelman S, Harris C, Bradley EL. Circulatory responses to laryngoscopy. The comparative effects of placebo, fentanyl and esmolol. *Can J Anaesth* 1989;136:301–306.
- [9] Sheppard S, Eagle CJ, Strunin L. A bolus dose of esmolol attenuates tachycardia and hypertension after tracheal intubation. *Can J Anaesth* 1990;37:202–258.
- [10] Vucevic M, Purdy GM, Ellis FR. Esmolol hydrochloride for management of the cardiovascular stress responses to laryngoscopy and tracheal intubation. *Br J Anaesth* 1992;68:529–530.
- [11] Jones G. Oxygen saturation during upper gastrointestinal endoscopy. *Br J Anaesth* 1986;58:807.
- [12] Fujita R, Kumura F. Arrhythmia and ischaemic changes of the heart induced by gastric endoscopic procedures. *Am J Gastroenterol* 1975;64:44–48.
- [13] Murray AW, Morran CG, Kenny GNC, Macfarlane P, Anderson JR. Examination of cardiorespiratory changes during upper gastrointestinal endoscopy. *Anaesthesia* 1991;146:181–184.
- [14] Smith MR, Bell GD, Quine MA, Spencer GM, Morden AE, Jones JG. Small bolus injections of intravenous midazolam for upper gastrointestinal endoscopy: a study of 800 consecutive cases. *Br J Clin Pharm* 1993;36:573–578.