Sedation for Gastrointestinal Endoscopic Procedures in the Elderly: Getting Safer but Still Not Nearly Safe Enough

Lord DA[1], *Bell GD*[1], *Gray A*[2], *Quine A*[3], *Bowles J*[4], *Romaya C*[5], *de la Iglesia B*[1], *Reynolds A*[1], *Rayward-Smith VJ*[1]

Summary

Background

Previously published UK reports showed that excessively large doses of benzodiazepines and opiates were being commonly used to sedate elderly patients for gastrointestinal (GI) endoscopy. This unsafe practice has lead to avoidable morbidity and mortality. We have taken the opportunity provided by recent reports to examine whether GI endoscopy sedation practice in the elderly has improved in the light of this evidence and the publication of guidelines in which specific recommendations on sedation dosage are given.

Methods

Using data mining techniques, we have extracted data on the use of benzodiazepines and opiates from a recent NCEPOD report on deaths following GI therapeutic endoscopy and from unpublished data from six East Anglian hospital GI endoscopy databases. We have compared and contrasted these data with re-analysed data from two previously published large audits of upper and lower GI endoscopy carried out in 1991 and 1998 respectively.

Findings

Midazolam has largely replaced diazepam as the benzodiazepine of first choice and many more procedures are now carried out without sedation. Improvements have occurred in the use of pulse oximetry, supplemental oxygen and continuous intravenous access. Mean doses of benzodiazepines and opiates given for GI endoscopy sedation in the elderly still exceed published guidelines, although doses have fallen significantly since the 1990's. The use of flumazenil, a specific benzodiazepine antagonist, appears to be a good marker of over-sedation and cardiopulmonary complications were more common in patients who were given the drug. In the NCEPOD study of patients who died within 30 days after therapeutic endoscopy, the time between endoscopy and death was significantly shorter in those who received flumazenil. In the East Anglian study, there was a two-fold difference in the average doses of both midazolam and pethidine used by individual endoscopists in elderly patients. Despite the well-known synergism between opioids and benzodiazepines, worryingly, those endoscopists who used the highest average doses of midazolam in elderly patients also tended to be those who administered the largest amounts of pethidine.

Interpretation

Patient safety would be significantly improved if those GI endoscopists who regularly give unnecessarily high doses of sedative and analgesic drugs to elderly patients changed their sedation practice to conform to published guidelines. Regular audit of sedation dosages and reporting of 'near misses' (including flumazenil usage), is recommended.

Introduction

It was well established over 25 years ago that elderly patients are particularly sensitive to the CNS depressant effects of oral benzodiazepines such as diazepam[1], chlordiazepoxide[1], flurazepam[2] and nitrazepam[3]. Although pharmacokinetic differences are undoubtedly

[1] School of Computing Sciences, UEA, Norwich
[2] NCEPOD
[3] Queen Alexandra Hospital, Portsmouth
[4] Royal Free Hospital, London
[5] British Society of Gastroenterology

contributory[4], the evidence suggests that pharmacodynamic factors are much more important[5] when explaining the marked differences in benzodiazepine CNS sensitivity between the young and old. Based on these and other studies[1-5], it has been standard clinical practice in the elderly to prescribe half (or less) of the dose of hypnotics such as nitrazepam and flurazepam that would normally be prescribed to younger patients.

Midazolam has gradually replaced diazepam as the IV sedative of choice for most gastrointestinal (GI) endoscopic procedures[6, 7]. As with orally administered benzodiazepines[1-3, 5], intravenous (IV) midazolam dosage needs to be reduced dramatically in the elderly[8], especially if a bolus technique is employed[9]. IV midazolam and diazepam can both depress respiration and cause marked hypoxia[10, 11]: hence the need for pulse oximetry, supplemental oxygen[12, 13] and the ready availability of the benzodiazepine antagonist, flumazenil[13, 14].

Monitoring and safety guidelines for sedating patients have been issued in the past[13, 15, 16]; particularly in light of a 1991 UK audit of over 14,000 patients undergoing an upper GI endoscopy[17]. The 1991 audit, published in 1995, found that over 100 patients died within 30 days of the procedure. Several of these patients died as a result of being given too large a dose of either IV midazolam or diazepam[17]. Similar cases of sedation-related deaths have been reported elsewhere[18, 19].

Previous guidelines[13, 15, 16] have all stressed the importance of not exceeding the dose of IV benzodiazepine recommended by the manufacturer and of reducing the dose sufficiently in elderly, frail or at-risk patients.

More recent audits of endoscopic procedures such as colonoscopy[20] and Endoscopic Retrograde Cholangiopancreatography (ERCP)[21] have shown improved use of pulse oximeters, supplemental oxygen and indwelling IV cannulae when compared with the earlier report of Quine et al[17]. Despite this, and a small reduction in the mean doses of sedative and analgesic drugs being employed in the more recent audits[20, 21], there have been, once again, a number of reported sedation-related cardiopulmonary deaths in elderly patients. A 2004 report by the National Confidential Enquiry into Patient Outcome and Death (NCEPOD), "Scoping our Practice"[22], found that there had been 1,818 deaths after therapeutic GI endoscopic procedures. NCEPOD advisors judged that the sedation given was inappropriate in 14% of cases, usually because an overdose of benzodiazepine had been administered.

We decided to re-analyse the NCEPOD therapeutic endoscopy data in terms of sedation practice and to compare and contrast the results with

a) the 1991 Upper GI Audit
b) the 1998 Colonoscopy Audit
c) a current six hospital East Anglian Study[23].

Our results show that many endoscopists are persisting in using unnecessarily large doses of IV sedative and analgesic drugs in elderly patients with potentially fatal consequences. We make recommendations regarding drug dosage and clinical practice based on these findings.

Patients, Materials and Methods

NCEPOD Therapeutic Endoscopy Report

This report studied 1,818 patients who died in hospital within 30 days of having undergone a therapeutic endoscopic procedure in England, Wales, Northern Ireland, Guernsey, the Isle of Man, the Defence Secondary Care Agency and hospitals within the independent sector. Data was requested for the period of one year from 1st April 2002 to 31st March 2003. These procedures included oesophageal dilatation, oesophageal stent insertion, injection of oesophageal varices, Percutaneous Endoscopic Gastrostomy (PEG), ERCP and a number of lower GI therapies such as polypectomy and colonic stenting. As described in detail in the report[22], the 1,818 patients who died

probably represents about 3 % of the total number of patients undergoing a therapeutic endoscopic procedure during the time of observation. The anonymised database of the original report from NCEPOD was re-analysed by the medical data-mining group from the School of Computing Sciences at the University of East Anglia (UEA).

Upper GI Endoscopy Audit

In the four-month period from February to June 1991 3,956 upper GI endoscopies were performed in the UK by the East Anglian Health Region, (an estimated 5.76 gastroscopies/1000/year) and in the four-month period from April to August 1991, there were 10,193 examinations carried out by the North West Health Region, (8.8/1000/year). The total number of procedures performed was 14,149 of which 13,036 (92%), were diagnostic and the remaining 8% were therapeutic. The audit included a 30-day post endoscopy period to study both morbidity and mortality. The anonymised database used for the original report was provided for our use by the British Society of Gastroenterology (BSG).

Colonoscopy Audit

Over a four-month period in 1998, there were 9,223 colonoscopies carried out in three Regions (North East Thames, East Anglia and West Midlands). As in the upper GI audit, there was a 30-day post colonoscopy period to study both morbidity and mortality. The anonymised database used for the original report was again provided for our use by the BSG.

East Anglian Endoscopy Database Study

The Endoscopy Units of the following hospitals in East Anglia were included in the study: Norfolk and Norwich University Hospital, Cromer Hospital, Queen Elizabeth Hospital at King's Lynn, North Cambridgeshire Hospital at Wisbech, the James Paget Hospital at Great Yarmouth and the Ipswich Hospital. All these units used either Endoscribe or HCNscribe software as their Endoscopy reporting system and database. With the permission of their IT, medical and nursing staff, a member of the medical data-mining group visited the hospital and took a copy of the Endoscribe/HCNscribe database.

The databases from each of the hospitals were pre-processed (correcting data errors, removing incomplete records and validating field entries). The hospitals and individual endoscopists were each given a code and the data was anonymised. The databases were transformed into a new data structure more suited to statistical analysis and data mining[24-26] and then combined into one database. Data from the Upper GI audit, the Colonoscopy audit and the NCEPOD audit were each processed in the same way to allow a truer comparison between the four studies.

Statistical Analysis

For each of the four above databases, we looked at the mean, median and 95% confidence limits around the doses of the different IV sedative and analgesic drugs used in the different patient age groups. We also looked at the pattern of use of the benzodiazepine antagonist, flumazenil as a surrogate marker of a patient having inadvertently been given an excessive dose of either midazolam or diazepam. Analysis was carried out using algorithms in SQL and PL-SQL, Oracle Data Miner and with the Arcus QuickStat statistical software[25].

Results

NCEPOD Therapeutic Endoscopy Report

This report studied 1,818 patients who died in hospital within 30 days of having undergone a therapeutic endoscopic procedure. In 1,326/1,818, or 72.9% of cases, midazolam was used. In 1,294/1,326 or 97.6%, the actual dose of midazolam was recorded. Flumazenil was prescribed in 160/1294 or 12.4% of patients given midazolam where the dosage was known and in 5/32 or 15.6% of cases where the dose of midazolam was not recorded. Diazepam was used in only 69/1,818 or 3.8% of cases. Flumazenil was prescribed in 8/69 or 11.6% of patients given

diazepam. In all but two of the cases having either midazolam or diazepam, the use of flumazenil was unplanned and the indication stated to be to reverse excessive sedation e.g. respiratory depression or loss of verbal contact.

NCEPOD - Dose of Midazolam and Pethidine Used – with and without Flumazenil being required

The mean age of the 160 patients given flumazenil (where the dose of midazolam was recorded) and the 1,134 who did not receive flumazenil was in both cases 78.4 years of age. As shown in Table 1, the mean dose of midazolam was significantly higher in the patients who received flumazenil ($p=0.0034$). Significantly more midazolam patients who required flumazenil also had the opioid pethidine ($p<0.05$) administered in a dose that was significantly higher ($p=0.0074$) than when reversal was not required.

Drug (mg)	Flumazenil Used	Flumazenil Not Used	Significance
Midazolam	4.3 (2.7)	3.7 (2.1)	p=0.0034
Pethidine	46.0 (14.6)	38.0 (13.9)	p=0.0073

Table 1. Mean (SD) dose of midazolam and pethidine used in the NCEPOD study – with and without flumazenil being required.

The mean dose of midazolam varied with the therapeutic GI procedure performed. The mean dose of midazolam used for ERCP patients was, in all age groups, significantly greater ($p<0.001$) than either the therapeutic Upper or PEG group (see table 2). Predictably therefore, flumazenil was required significantly more frequently to reverse the adverse effects of midazolam sedation during or following an ERCP than PEG insertion ($p=0.0052$) or either a GI therapeutic upper ($p=0.0117$) or lower ($p=0.0034$) endoscopic procedure (table 2).

	ERCP	PEG	Upper GI	Lower GI
Mean (SD) Midazolam dose	5.1 (2.9)	3.3 (1.5)	3.9 (2.3)	3.2 (1.5)
Significance vs. ERCP (Midazolam)		p<0.0001	p<0.0001	p<0.0001
Number (%) given Flumazenil	35/177 (19.8)	64/566 (11.3)	62/521 (11.9)	1/30 (3.3)
Significance vs. ERCP (Flumazenil)		p=0.0052	p=0.0117	p=0.0034

Table 2. Use of flumazenil in the NCEPOD study. Flumazenil was used significantly more frequently during or after an ERCP than any other procedure.

NCEPOD – Critical Incidents during the Endoscopic Procedure

In all 93% (1,688/1,818) responded to the question relating to critical events. Cardiorespiratory critical incidents during therapeutic endoscopy were relatively frequent. In total, from 73 patients there were nine cardiac arrests, 7 respiratory arrests and 62 reported incidents of clinically significant hypoxia. If a cardiac arrest, respiratory arrest or hypoxic incident was reported then flumazenil was given in significantly more cases than when no such critical episode was reported: 27/73 or 37.0% vs. 125/1,615 or 7.7% ($p<0.0001$).

NCEPOD – Time to Death after the Endoscopic Procedure and the Effect of Having Required Sedation Reversal with Flumazenil

In the NCEPOD database, it was possible to calculate the time in days from the endoscopic procedure to death for 1,789 patients. In this group, there were 173 patients who received flumazenil and 1,616 patients who did not. Those given flumazenil died on average two days earlier than those not given the reversal agent ($p<0.05$).

As shown above, the ERCP group received the largest doses of midazolam and had the highest percentage flumazenil usage. When the ERCP group was considered separately, (see figure 1) the median time to death was on average four days earlier when flumazenil had been used than when it was not required ($p=0.0108$).

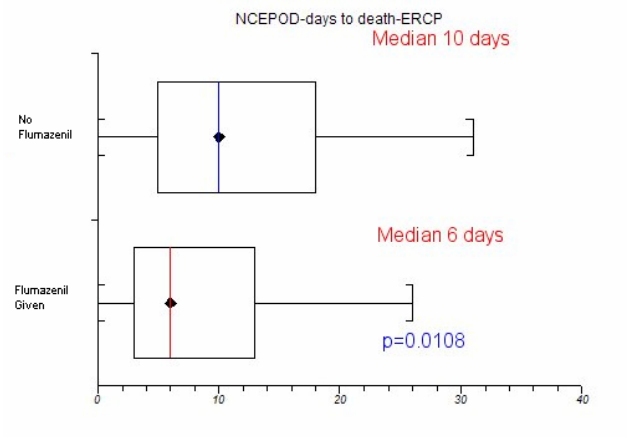

Figure 1. A 'box and whisker' plot shows that patients undergoing an ERCP examination on average died 4 days earlier when flumazenil was required to reverse their midazolam sedation when compared with those whose sedation did not require reversal.

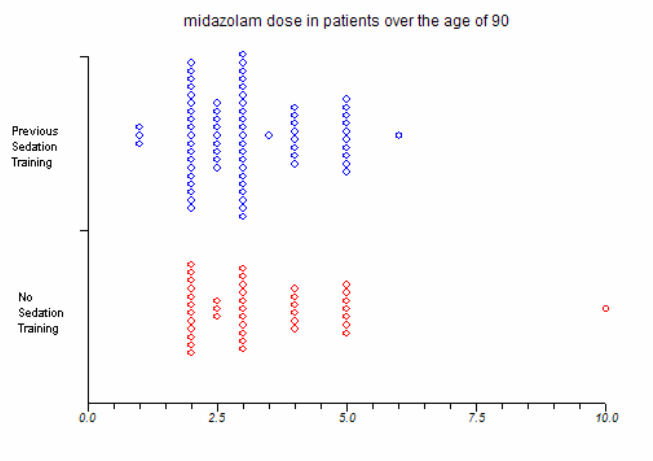

Figure 2. Each data point represents a single dose of midazolam administered by an individual endoscopist to a patient over the age of 90 years. It can be seen that those claiming to have had previous training in sedation techniques (red symbols) used no less sedation than those who had not been specifically trained (blue symbols).

NCEPOD – Effect of Endoscopist's Previous Sedation Training on the Sedation Dose and use of Flumazenil

In all, for 634 of the patients involved in the NCEPOD study, the endoscopist stated that they had had previous training in sedation techniques. While in 1,171 of the patients, the endoscopists conducting the examination indicated they had not received specific training in sedation. There was no difference in either the dose of midazolam (means both 3.8 mg) or pethidine (mean dose of 36.2 mg and 39.2 mg respectively) in the sedation 'trained' and 'untrained' groups. Similarly, flumazenil requirements to reverse excessive sedation were very similar at 67/644 or 10.4% and 109/1172 or 9.3% respectively in the 2 groups. Just how high the doses of midazolam administered were on occasion is illustrated in figure 2. It can be seen that sedation training made no difference to the dose of drug administered to patients over the age of 90.

Upper GI Endoscopy Audit

In East Anglia and the North West, 86% (3,405) and 84% (8,593) of upper GI endoscopies were performed with some form of intravenous sedation plus or minus local anaesthetic. In all, midazolam was used in 52.5% of cases and diazepam (mainly in the form of Diazemuls) was given to 47.5% of patients. At the time of this audit, diazepam was the preferred intravenous sedative in East Anglia (used in 59 % of all patients sedated) whereas in the North West Region more endoscopists favoured midazolam (57% of all patients sedated).

The mean dose of diazepam used for sedation in the two regions was 13.5 mg, (East Anglia) and 14.0 mg, (North West) and for midazolam, the mean dose was 5.7 mg in both regions. The distribution of dosages used in both regions was equally wide; maximum doses of diazepam and midazolam used were 50 mg and 30 mg respectively. The mean dose of both midazolam and diazepam given decreased with advancing age (see table 3), but for each age group the dose given to individual patients varied enormously.

Age Group	Upper GI Audit	Colon Audit	NCEPOD	East Anglian
Under 20	6.7 (3.1)	8.0 (4.0)		4.9 (1.7)
20-29	7.1 (3.1)	6.5 (3.7)		4.7 (1.5)
30-39	6.7 (2.8)	6.3 (4.1)		4.7 (1.4)
40-49	6.7 (2.7)	6.0 (3.2)		4.5 (1.4)
50-59	6.0 (2.5)	5.8 (3.2)	4.0 (n=4)	4.4 (1.4)
60-69	5.4 (2.1)	5.4 (3.0)	2.0 (n=2)	4.0 (1.3)
70-79	4.6 (2.0)	4.9 (2.1)	4.8 (1.9)	3.5 (1.3)
80-89	4.0 (1.9)	4.2 (1.9)	2.7 (0.9)	3.1 (1.2)
90 plus	4.3 (2.4)	3.4 (1.4)	2.7 (0.6)	2.6 (1.0)

Table 3. Mean (SD) dose of midazolam used in patients of different age groups in the four different audits discussed in the present paper.

Upper GI Endoscopy Audit - relationship between the dose of diazepam or Midazolam administered and the use of Flumazenil

Flumazenil was used in 382/11,896 or 3.2% of all cases sedated with either midazolam or diazepam. Patients in the NW Region received flumazenil in 4% of cases compared with 2% in East Anglia. This difference was almost entirely due to the fact that two centres in the NW (who contributed 189 and 92 patients respectively) were at that time using flumazenil routinely in all patients being sedated with midazolam. If these two centres are excluded, then 290/11,513 or 2.5% of sedated patients had flumazenil reversal.

The mean dose of Diazemuls was 18.9 mg when flumazenil was also given compared 13.1 mg when it was not ($p<0.0001$). Excluding the two units where Flumazenil was given routinely to all patients, the mean dose of Midazolam when Flumazenil was also given was 5.8 mg compared to 5.7 mg without ($p=0.172$)

In 1991, many endoscopists in both Regions tended to use the same dose of diazepam or midazolam irrespective of patient age or ASA status. We were thus able to look at the percentage of patients in different age groups receiving a) 10 mg of diazepam b) 20 mg of diazepam or c) 5 mg of midazolam (again excluding the two groups from the NW mentioned above) who subsequently were given flumazenil (see figure 3). It can be seen that flumazenil use was both dose and age-related and increased dramatically after 70 years of age.

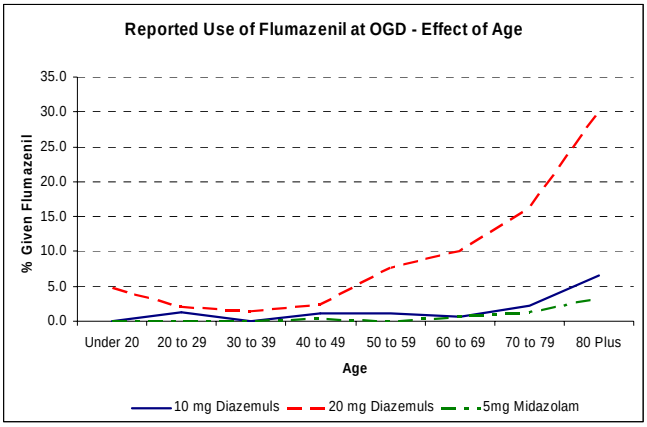

Figure 3. Relationship between the age of patient and reported use of flumazenil when a 10 mg or 20 mg dose of diazemuls or a 5 mg dose of midazolam was given.

1998 Colonoscopy Audit

In this study in three Health Regions carried out over a four-month period in 1998, 73 Endoscopy units prospectively audited their colonoscopic practice plus 30-day morbidity and mortality figures. In all 9,223 colonoscopies were performed. In 94.6%, some form of sedation was used. When sedation was used, midazolam was given in 88.6% of cases and diazepam (as Diazemuls) in 11.4%. The most common was a combination of pethidine and midazolam (57.8% of colonoscopies). The mode dose of midazolam was 5.0 mg (range 0.5 - 20 mg) while that of Diazemuls was 10 mg (range 1.0 - 30 mg). The mode dose of pethidine was 50 mg (range 10 - 100 mg). The mean dose of midazolam was 5.8 mg while that of Diazemuls was 13.2 mg. The mean dose of pethidine was 48.3 mg.

Colonoscopy Audit - Relationship between the Dose of Midazolam given and Flumazenil use

Flumazenil was used in 3.4% of patients. In the vast majority of these cases, this was to reverse excessive benzodiazepine sedation[20]. Although there was a small reduction in the maximum sedation dosages used when compared with the

Quine audit[17], mean dosages for midazolam were very similar. There were still many endoscopists using the same dose of midazolam (most often 5 mg) in all age groups. We were thus able to look at the percentage of patients in different age groups receiving 5 mg of midazolam who subsequently required reversal with flumazenil (see figure 4). It can be seen that, as in the Quine study (see figure 3), flumazenil usage increased markedly after the age of 70 years of age.

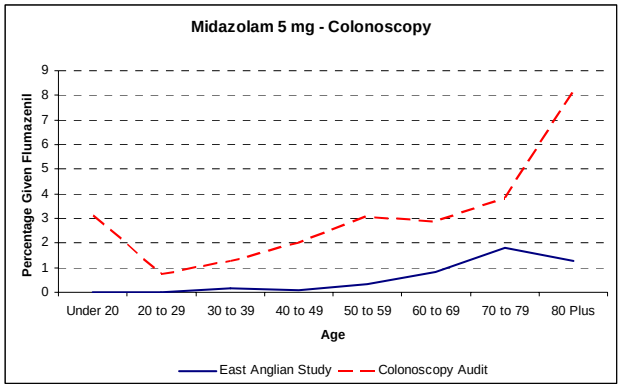

Figure 4. Relationship between the age of patient and reported use of flumazenil when a 5mg dose of midazolam was administered. The graph also shows comparable data from the East Anglian Study.

East Anglian Endoscopy Database Study

The number of Endoscopy reports collected from each hospital and the time-period over which the data was collected is given in table 4. In total, the combined database included 51,609 upper GI endoscopies (of which 4,161 where therapeutic), 2,406 ERCPs, 1,061 PEGs and 19,050 colonoscopies. For upper GI endoscopy, the percentage of patients who had their procedure performed without any IV sedation was 20,138/ 51,609 or 39 %. This figure is significantly greater ($p<0.0001$) than the figure of 1,841/13,737 or 13.4% reported in the 1991 OGD audit of Quine et al[17].

Hospital	Number of Procedures	Period Covered
A	28 184	Feb 2002 – Sep 2004
B	15 957	Mar 2001 – Jun 2004
C	19 913	Jan 2000 – Feb 2005
D	12 855	Jan 2000 – Aug 2005
E	9 908	Jan 2000 – Aug 2005
Total	**86 817**	

Table 4. East Anglian study, Number of procedures and the period covered, by hospital.

Fewer endoscopists were still using diazepam (mainly in the form of Diazemuls). Only 8.9% of all sedated endoscopic procedures were carried out using diazepam. These were mainly performed by just two endoscopists (who contributed 3,354 and 982 cases respectively). The mean (SD) dose of diazepam used in all patients was 9.3 (2.1) mg, while in the case of OGD and colonoscopy it was 9.2 (2.4) mg and 9.4 (1.8) mg respectively. These diazepam doses were significantly less than in the 1991 upper GI and 1998 colonoscopy audits when the figures were 14.0 (11.0) mg and 13.2 (6.8) mg ($p<0.0001$ and $p<0.0001$ respectively). In the case of the 91.1% of sedated patients who were sedated with midazolam, the mean (SD) dose of midazolam used in all patients was 3.9 (1.4) mg, while in the case of OGD and colonoscopy it was 3.8 (1.4) mg and 3.9 (1.3) mg respectively. These doses were significantly less than in the 1991 upper GI and 1998 colonoscopy audits[19], where the comparative figures were 5.6 (2.6) mg and 5.8 (3.1) mg ($p<0.0001$ and $p< 0.0001$ respectively).

The mean doses of midazolam and pethidine used in the different age groups of patients in East Anglia for procedures such as PEG tube placement, ERCP, colonoscopy and therapeutic upper GI Endoscopy are shown in tables 5 to 9. For purposes of comparison, the same tables contain the data calculated from a) the Quine audit of OGD b) the Bowles colonoscopy audit and c) NCEPOD report.

Age Group	Upper GI Audit	Colon Audit	NCEPOD	East Anglian
< 20	50.0 (n=4)	52.4 (18.7)		45.5 (11.8)
20-29	50.0 (13.8)	51.1 (12.6)		48.6 (10.2)
30-39	60.6 (24.0)	50.2 (12.1)		48.4 (10.5)
40-49	54.1 (24.6)	49.4 (12.1)		48.1 (10.8)
50-59	47.5 (12.5)	48.9 (10.1)	50.0 (n=1)	46.6 (10.9)
60-69	47.9 (13.1)	47.8 (9.8)	40.0 (n=1)	44.2 (11.6)
70-79	46.2 (12.6)	46.1 (10.6)	41.7 (11.8)	40.9 (12.5)
80-89	37.8 (14.9)	40.7 (12.5)	35.7 (12.4)	38.7 (12.6)
90 plus	41.3 (13.4)	43.8 (10.8)	20.9 (5.9)	35.1 (12.3)

Table 5. Mean (SD) dose of pethidine used in patients of different age groups in the four different audits discussed in the present paper.

Age Group	Mean (SD) Midazolam		Mean (SD) Pethidine	
	NCEPOD	East Anglian	NCEPOD	East Anglian
Under 20		8.5 (2.2)		55.6 (15.7)
20-29		7.2 (2.6)		54.3 (12.7)
30-39	12.5 (2.5)	7.2 (2.3)	50.0 (n=2)	56.5 (18.9)
40-49		6.2 (2.1)		52.7 (12.9)
50-5	7.4 (3.3)	5.9 (2.2)	41.7 (11.8)	52.6 (13.3)
60-69	6.4 (4.0)	5.4 (1.8)	45.6 (9.6)	50.2 (10.9)
70-79	5.3 (2.5)	4.8 (1.9)	41.9 (11.9)	47.9 (10.9)
80-89	4.4 (2.0)	4.1 (1.4)	33.1 (16.2)	43.9 (11.1)
90 plus	3.7 (1.8)	3.6 (1.2)	33.8 (13.8)	39.0 (12.5)

Table 6. Mean (SD) dose of midazolam and pethidine used in ERCP patients of different age groups in both the East Anglian study and the NCEPOD report.

Age Group	NCEPOD - PEG	East Anglian - PEG
Under 20		4.4 (3.0)
20-29	3.5 (0.5)	3.9 (1.1)
30-39	3.9 (0.9)	4.3 (1.3)
40-49	4.3 (3.2)	5.0 (2.0)
50-59	5.2 (1.8)	4.1 (1.6)
60-69	3.5 (1.2)	3.8 (1.4)
70-79	3.3 (1.4)	3.4 (1.3)
80-89	3.0 (1.3)	2.9 (0.9)
90 plus	2.9 (1.0)	2.4 (0.9)

Table 7. Mean (SD) dose of midazolam used in PEG patients of different age groups in both the East Anglian audit and the NCEPOD report.

Age group	NCEPOD	East Anglian	Colon Audit
Under 20		5.0 (1.6)	8.0 (4.0)
20-29		4.6 (1.5)	6.5 (3.7)
30-39		4.5 (1.3)	6.3 (4.1)
40-49		4.4 (1.3)	6.0 (3.2)
50-59	4.0 (n=4)	4.2 (1.2)	5.8 (3.2)
60-69	2.0 (n=2)	3.9 (1.2)	5.4 (3.0)
70-79	4.8 (1.9)	3.5 (1.2)	4.9 (2.1)
80-89	2.7 (0.9)	3.1 (1.2)	4.2 (1.9)
90 plus	2.7 (0.6)	2.6 (0.8)	3.4 (1.4)

Table 8. Mean (SD) dose of midazolam used in colonoscopy in patients of different age groups in the East Anglian study, colonoscopy audits and the NCEPOD report.

Age group	NCEPOD	East Anglian	Colon Audit
Under 20		46.3 (10.8)	52.4 (18.7)
20-29		48.7 (9.7)	51.1 (12.6)
30-39		48.1 (9.9)	50.2 (12.1)
40-49		47.9 (10.5)	49.4 (12.1)
50-59	50.0 (n=1)	46.3 (10.8)	48.9 (10.1)
60-69	40.0 (n=1)	43.8 (11.4)	47.8 (9.8)
70-79	41.7 (11.8)	40.5 (12.3)	46.1 (10.6)
80-89	35.7 (12.4)	37.3 (12.6)	40.7 (12.5)
90 plus	20.9 (5.9)	32.3 (11.2)	43.8 (10.8)

Table 9. Mean (SD) dose of pethidine used in colonoscopy in patients of different age groups in the East Anglian study, colonoscopy audits and the NCEPOD report.

East Anglian Study - relationship between the dose of midazolam administered and the use of flumazenil

In the 49,681/86,817 patients, who were sedated with midazolam for any procedure, the overall percentage recorded as subsequently being given flumazenil was 0.8%. The figures for upper GI endoscopy, PEG insertion, ERCP and colonoscopy were 0.9%, 3.2%, 1.8% and 0.6% respectively. In all patients given exactly 5mg of midazolam, the relationship between age and percentage recorded as having been given flumazenil is shown in figure 5.

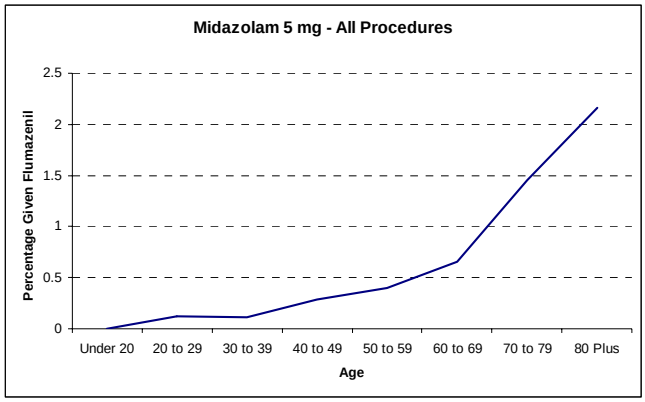

Figure 5. Relationship between the age of patient and reported use of flumazenil when a 5mg dose of midazolam was administered for any procedure.

East Anglian Study – Individual endoscopist's variation in average dose of midazolam and pethidine prescribed in patients over the age of 70 years

We noted a 2.0 - 2.5 fold variation in the mean dose of both midazolam and pethidine being used by different individual endoscopists to sedate their elderly patients. These differences were particularly marked in the case of patients undergoing colonoscopy. Typical results from hospital A and B are shown in figures 6 and 7.

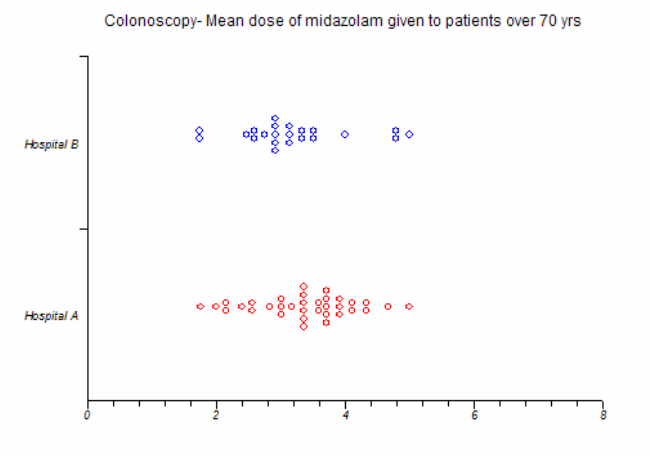

Figure 6. Shows a 2.5 fold variation in the dosage of midazolam that a patient over the age of 70 can expect to receive depending on which endoscopist administers the sedation. Each data point represents the average dose of midazolam in mg given to patients over the age of 70 years by different individual endoscopists in either hospital A (red symbols) or hospital B (blue symbols).

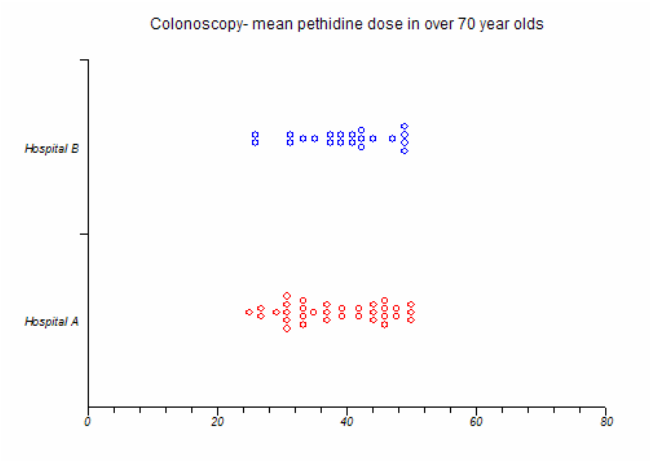

Figure 7. Shows a two-fold variation in the dosage of pethidine that a patient over the age of 70 can expect to receive depending on which endoscopist administers the sedation. Each data point represents the average dose of pethidine in mg given to patients over the age of 70 years by different individual endoscopists in either hospital A (red symbols) or hospital B (blue symbols).

In order to see if those colonoscopists who were using a relatively large average dose of midazolam were compensating by using a smaller dose of pethidine (or vice versa), we correlated each colonoscopists mean dose of midazolam with their mean dose of pethidine in the over 70 year old group. As can be seen from the example data from one large hospital shown in figure 8, the

results showed just the opposite. Those endoscopists using larger mean dosages of midazolam were also frequently the same endoscopists who administered relatively high doses of pethidine (p=0.0135).

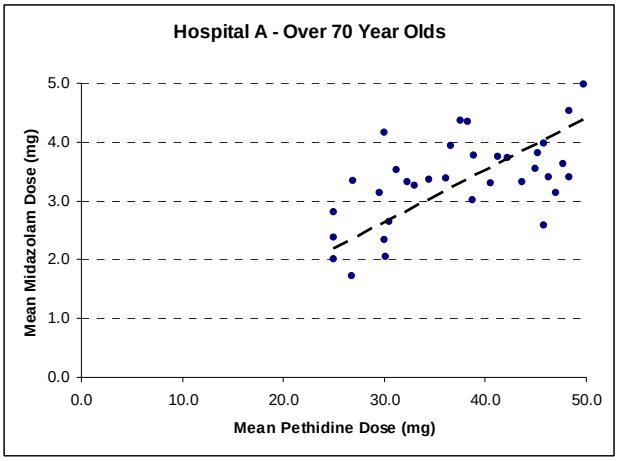

Figure 8. Hospital A - Shows the relationship between the mean midazolam dose and the mean pethidine dose given by individual endoscopists (who performed at least ten procedures) to patients over the age of 70 years of age.

Discussion

As the NPSA (National Patient Safety Association) points out, the medical profession is notoriously slow to learn from its mistakes and 'near misses'[27]. A new report from the National Audit Office(NAO) entitled 'A safer place for patients: learning to improve patient safety'[28] accepts that there is significant under-reporting of deaths and serious incidents within the NHS. The NAO estimates that 22% of incidents, many of which are medication errors, still go unreported and agrees with the NPSA that 'near misses' are rarely acted upon[28].

NCEPOD Study

Our results taken from the NCEPOD report clearly show that, if elderly patients are given an IV benzodiazepine in the sort of doses that are more appropriate for fit young adults, then their safety is endangered. In the NCEPOD study, the benzodiazepine antagonist flumazenil was almost entirely given to attempt to reverse an overdose situation. In those patients who were given an IV dose of a benzodiazepine, midazolam was used in 95% of cases while diazepam was employed in just 5% of patients. Detailed analysis therefore was concentrated on midazolam usage. The mean dose of midazolam given when flumazenil was required was significantly higher than that when reversal was not needed. Predictably, bearing in mind the well-known synergism between benzodiazepines and opioids[29], flumazenil was also required significantly more frequently when midazolam was combined with pethidine.

Patients who needed to have their midazolam reversed were more likely to a) have a critical event such as significant hypoxia leading in certain cases to cardiopulmonary arrest during their endoscopy and b) die on average two days earlier than comparable patients not requiring flumazenil. It was of interest that the patients undergoing an ERCP examination:

i) had the largest doses of sedation
ii) required flumazenil significantly more frequently that other groups
iii) died, on average, four days earlier when reversal was required

It has previously been shown that, as for oral benzodiazepines[1-5], elderly patients require only a fraction of the dose of midazolam needed by fit young adults[11]. Most endoscopists in the UK administering IV sedative plus or minus an analgesic drug use a bolus injection over a few seconds rather than the more correct slow titration method. In this situation, even more dramatic reductions in dosage are required[9, 30].

The BSG, in its most recent guidelines on sedation and safety published in Sept 2003, made recommendations regarding dosage of midazolam and pethidine[16]. In the case of patients over the age of 70 years, the BSG suggests an average dose of no more than 2 mg of midazolam while in a fit young adult a dose of 5 mg might be more appropriate. Should an opioid such as pethidine be required, as it frequently is for procedures such as ERCP or colonoscopy, then the BSG recommends

that the opioid be given first and then the benzodiazepine given slowly and cautiously[16]. In the case of pethidine, the BSG has suggested an average dose of no more than 25 mg in a patient over the age of 70 years of age and no more than 50 mg for a fit young adult.
Bearing in mind the fact that the mean age of patients in the NCEPOD Therapeutic Endoscopy study was 78.4 years and that some 80% were classed as being ASA grade 3, the doses of midazolam and pethidine given to many patients (table 1 and figure 2) were clearly excessive.

Upper GI Endoscopy and Colonoscopy Audits

Comparing the two audits shows a significant improvement over time in terms of reduction in mean diazepam but not midazolam drug dosage. There was also a marked increase in the use of such measures as pulse oximeters, supplemental oxygen and indwelling IV cannulae. The fact that the procedure related mortality, 1:2,000 for upper GI endoscopy and 1:1,500 for colonoscopy, was not improved was disappointing.

Over 100 of the 14,000 patients in the upper GI audit died within 30 days of the procedure. While only seven cases were considered definitely procedure-related, it may be that many of the post procedure myocardial infarctions, cerebro-vascular accidents and aspiration pneumonia cases were also causally related. Of the 11 pneumonias, 6 cerebro-vascular accidents and 19 myocardial infarctions, 24/36, some two-thirds, of these complications occurred within seven days of the procedure. Similarly, in the case of the colonoscopy audit, of the 10 deaths occurring within 30 days of the procedure, some six elderly patients died from cardio-pulmonary complications. In several of these, excessive doses of sedation may again have had a part to play in the patient's final demise.

Revisiting the two databases has allowed us to examine the relationship between benzodiazepine dosage and CNS depression using flumazenil administration as a surrogate marker of increasing sensitivity to the drugs in the elderly. The shape of the curves shown in figure 3 with a rapid rise in the incidence of side effects in the over 70 year old age group are remarkably similar to those reported by Greenblatt et al back in 1977[2]. As in that earlier study, we have shown that there are clear dose and age related effects associated with giving unnecessarily large doses of IV benzodiazepines to elderly patients.

East Anglian Study

Diazepam, in the form of diazemuls, is now only rarely employed by endoscopists in East Anglia with only 3.5% of endoscopists still regularly using it. Unlike the situation in 1991, midazolam is now the preferred benzodiazepine by the overwhelming majority of endoscopists. Many more patients are now asking to have their upper GI endoscopies performed without using any IV sedation than was the case 15 years ago. Furthermore, as shown in tables 5 to 9, the doses of midazolam and pethidine currently in use are certainly significantly less than those used in 1991 or even 1998. Many elderly patients having both diagnostic as well as therapeutic procedures, however, are still being given doses of sedative and analgesic drugs that are well in excess of BSG guidelines[16]. Since these doses are of similar size to those used in the NCEPOD study of 2002-03, the implication has to be that sedation-related cardiopulmonary complications remain more common than is generally recognised.

The East Anglian study showed that the dose of either midazolam or pethidine that an individual patient is given still appears, in many cases, to depend as much on the endoscopist performing the procedure as either the age or ASA status of the patient. As illustrated in figures 6 and 7, patients over the age of 70 are still regularly being given twice or more of the BSG recommended dosage of midazolam and pethidine. Furthermore many endoscopists are either unaware of, or choose to ignore, the known synergism between benzodiazepines and opioids[29] and use excessive doses of both agents (see figure 8).

Flumazenil was used in 3.4% of patients in the upper GI audit, 3.5% of patients in the colonoscopy audit and 7% of patients in the most recent (and yet largely unpublished) ERCP audit[21]. All these percentages are considerably lower than the reported use of flumazenil in the NCEPOD study where the overall figure of 12% rose to almost 20% in the case of the ERCP group (table 2). These differences might relate, in part, to the fact that so many of the patients in the NCEPOD study were on average more frail and elderly than those in the other audits.

In the East Anglian study, the overall figure for flumazenil use was 0.8% of those sedated with midazolam. This is almost certainly a gross underestimate of the true current use of flumazenil in UK endoscopy units, since any reversal that is carried out after the patient leaves the endoscopy unit (or is returned to the ward) would not normally be recorded on the endoscopy database. The shape of the curve relating a 5 mg dose of midazolam to age and flumazenil use, however, is very similar, if much lower, than that generated from properly conducted prospective audits with 30-day morbidity and mortality data (see figures 4 and 5). Monitoring the use of flumazenil might be one way of prospectively looking at a hospital's sedation practice, but in the case of an endoscopy unit, this would need to include collecting information on any doses given after leaving the unit as well as those given during or immediately after the procedure.

Conclusions

In patients as ill, frail and complicated as those in the NCEPOD therapeutic endoscopy study, it is always very difficult to decide how large a part the sedation-related cardio-pulmonary complications played in any individual patient's final demise. Based on our detailed study of both the NCEPOD report as well as other relevant databases discussed in the present paper, we can certainly conclude that elderly and/or frail patients' lives and safety are still being put at risk unnecessarily, by the common practice of not reducing sedation/analgesia dosage sufficiently to allow for their advanced age and co-morbidity. We strongly recommend that endoscopists adhere to the BSG 2003 guidelines on sedation dosage[16] and welcome the NPSA's recent suggested changes to NHS sedation practice[31] which are, in part, a response to the finding of the present study.

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