Effect of Midazolam on Memory During Fiberoptic Gastroscopy Under Conscious Sedation

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Objective: As the fiberoptic gastroscopy using midazolam is being in widespread use, the exact nature of midazolam on memory should be clarified. We intended to examine whether midazolam causes selective anterograde amnesia and what impact it has on other aspects of memory and general cognitive function.

Methods: We recruited healthy subjects undergoing fiberoptic gastroscopy under conscious sedation. At baseline, history taking for retrograde amnesia and the Korean version of the Montreal Cognitive Assessment were performed. A man's name and address were given immediately after intravenous midazolam administration. After gastroscopy, the subjects were asked to recall those items. By the time they had fully recovered consciousness, the same test was repeated along with the Korean version of the Montreal Cognitive Assessment and a test for retrograde amnesia.

Results: A total of 30 subjects were enrolled in this study. Subjects with high-dose midazolam showed lower scores in the immediate and delayed recall of "a man's name and address" compared with those with low-dose midazolam. The midazolam dose was inversely correlated with the delayed recall scores of "a man's name and address." On full recovery of consciousness, the subjects did not exhibit any of anterograde or retrograde amnesia.

Conclusions: These findings suggest that midazolam causes transient selective anterograde amnesia in a dose-dependent manner.

Key Words: Midazolam, anterograde amnesia, gastroscopy, conscious sedation, episodic memory

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Midazolam, a benzodiazepine derivative, is an anxiolytic sedative used in a variety of clinical settings.[1] It is known to be safe, rapid acting, and effective for anxiolysis and sedation.[2] Subjects given midazolam are slightly sedated, but conscious and able to perform various cognitive tasks.[3] They experience transient but dense anterograde amnesia after midazolam injection.[4,5]

Conscious sedation during fiberoptic gastroscopy using midazolam is widely used to increase a patient's tolerance and cooperation.[6] Most patients do not remember the events during gastroscopy under conscious sedation, although not completely. A recent report showed that midazolam induced multiple cognitive impairments at the acute stage and prolonged memory dysfunction 2 hours later only in advanced age patients.[7] Another study demonstrated a midazolam's effect on the working memory function, although it was not as large as those on episodic memory.[4] Whether midazolam causes selective, anterograde, episodic memory dysfunction in a clinical setting has not yet been extensively studied. Neither its dose-dependent effects on memory have been studied. Given the widespread use of midazolam for conscious sedation endoscopy in clinical practice, the exact nature of midazolam should be elucidated.

Our study aimed to investigate the memory impact of midazolam during fiberoptic gastroscopy. We examined whether midazolam causes anterograde amnesia in a dose-dependent manner and whether general cognitive function, retrograde memory, or working memory functions may also be affected after full recovery of consciousness.

METHODS

Study Subjects

This prospective study was conducted in the health promotion center at Asan Medical Center from August to October 2007. Subjects who signed up to undergo fiberoptic gastroscopy for medical checkup were recruited for this study. The exclusion criteria were as follows: those who had recently taken sedative drugs such as benzodiazepine, antihistamines, or opioids that could affect conscious sedation; those with pre-existent memory impairment or dementia; older than 80 years; those unable to respond verbally after midazolam injection; those who refused to give informed consent; or those with Korean version of the Montreal Cognitive Assessment (MoCA-K) scores below 23. This study was approved by our Institutional Review Board and written informed consent was obtained at the time of the patient's enrollment in the study.

Fiberoptic Gastroscopic Procedure

All of the procedures were done in the morning between 9 AM and 12 PM. Standard fiberoptic gastroscopy procedures were done in this study. First, subjects received lidocaine anesthetic spray. In the endoscopy room, all of the subjects received an intravenous midazolam dose ranging from 3.5 mg to 9.5 mg (0.04 mg/kg to 0.11 mg/kg) for conscious sedation and buscopan 20 mg for relief of abdominal pain. Midazolam was initially injected in a dose of 3.5 mg, then 1 to 6 mg of midazolam was additionally given during gastroscopy, if needed, based on the subject's sedation status. After the injection of midazolam, subjects were monitored for their oxygen saturation, heart rate, blood pressure, and respiratory rate. The same fiberoptic gastroscopy device (GIF-Q260; Olympus Optical Co. Ltd, Tokyo, Japan) was used by the same endoscopist with an assistant nurse. Flumazenil 0.5 mg was injected for some of the subjects after gastroscopy to facilitate swift recovery from sedation, according to the doctor's decision. All of the subjects completed the gastroscopy without any significant side effects, such as dyspnea, cardiac arrhythmia, or hypotension.

Memory Task

Memory test and history taking for subjects were done by an experienced research psychometrist. At baseline, history taking, including the age, education level, recent medications,

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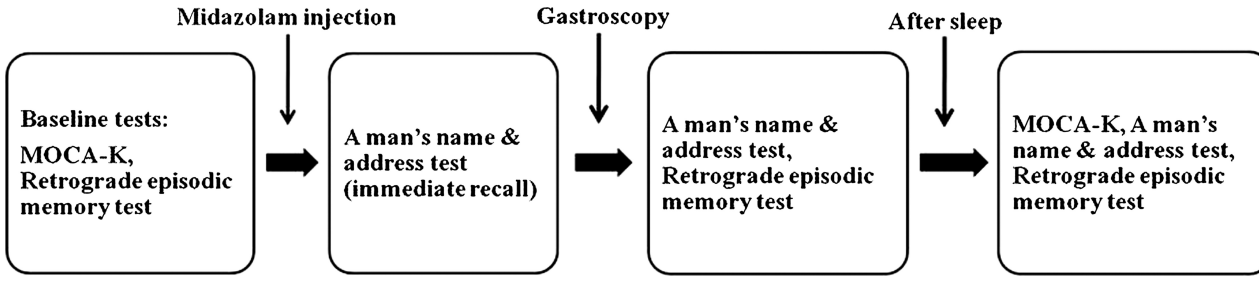

FIGURE 1. Study flow chart.

and comorbidities, was done. Subjects were asked 3 questions: "What did you eat for breakfast?" "What color were your clothes before you changed into a patient gown?" "How did you get here?" The answers were kept for future use of retrograde amnesia testing. The MoCA-K[8] was administered at baseline.

A man's name and address were given immediately after intravenous injection of midazolam for a memory task composed of 6 words including a man's name, age, and address (5 division sections of administrative district: e.g., name-age-prefecture-city-street-apartment). We made a 6-point scale using out of this for the evaluation of episodic memory function. Subjects repeatedly heard a man's name and address until he or she could say it verbatim. Only the first performance was scored. After the gastroscopy was finished, they were asked to recall the man's name and address to assess anterograde amnesia. They were asked once again to do so after full recovery from sedation. They were also asked to answer the 3 questions regarding the episodes in the morning immediately after gastroscopy in order to assess possible retrograde amnesia, What did you eat for breakfast? What color were your clothes before you put changed into a patient gown? and How did you get here? It was scored 3 if they answered everything correctly.

By the time they fully recovered consciousness, the same memory tasks, that is, a man's name and address and remembering the episodes in the morning, were done along with the MoCA-K. In addition, they were asked whether they remembered the episodes during gastroscopy: "What were the gastroscopy instructions from the doctor?" and "Did you feel pain or discomfort during gastroscopy?" If subjects answered correctly, we scored 1 point per question, with a total of 2 points. The study flow chart is shown in Figure 1.

Statistical Analysis

Comparisons of the demographics, memory task score, MoCA-K score, sedated duration, and flumazenil use between a high dose and low dose of midazolam were assessed. Comparisons of the demographics, memory task score, MoCA-K score, sedation duration, and the midazolam dose were also assessed according to the use of flumazenil. Comparisons between the subject groups were done using the Mann-Whitney *U* test. We measured whether the MoCA-K score and a man's name and address score changed significantly using the paired *t* test. Partial correlation coefficients were measured among the outcome variables. Correlations between the midazolam dose and the memory scores were measured after adjustment for age, sex, education level, and flumazenil use. All statistical analyses were performed using SPSS (version 21), and *P* values less than 0.05 were considered statistically significant.

RESULTS

A total of 37 patients were recruited in this study. Among them, 2 were excluded due to excessive sedation after midazolam injection, 1 due to a low MoCA-K score (score of 22), and 4 due to prolonged sedation after gastroscopy preventing the implementation of cognitive testing. Consequently, data from 30 subjects were analyzed.

Characteristics of the subjects are shown in Table 1. The mean age was 45.5 years, ranging from 22 to 67 years. The mean dose of midazolam was 0.07 mg/kg. The time to be taken for gastroscopy procedure ranged from 5 to 14 minutes (mean duration: 8.2 ± 2.05 minutes). The time to full recovery of consciousness took 58.9 ± 21.47 minutes after gastroscopy. Most

TABLE 1. Subjects Characteristics and Results of Memory Tasks

Characteristics	Minimum	Maximum	Mean ± SD
Age, y	22	67	45.5 ± 9.99
Education, y	11	18	15.0 ± 2.39
Midazolam dose, mg/kg	0.04	0.11	0.07 ± 0.019
Gastroscopy time, min	5	14	8.2 ± 2.05
Sedation time, min	21	102	58.9 ± 21.47
MoCA-K (baseline)	23	30	27.1 ± 1.57
MoCA-K (final)	23	30	27.7 ± 1.64
Immediate recall after midazolam injection*	1	6	4.0 ± 1.43
Delayed recall after gastroscopy*	0	6	2.2 ± 1.90
Delayed recall after sedation*	0	6	2.4 ± 1.94

Data were expressed as Mean ± SD.

*A man's name and address memory task score on a scale of 0 to 6.

TABLE 2. Comparison of Subjects on a High-Dose and a Low-Dose Midazolam Group

Variables	Low Dose (<0.08 mg/kg) N = 21	High Dose (≥0.08 mg/kg) N = 9	*P*
Age, y	46.1 ± 9.99	44.1 ± 10.45	0.627
Male, n	14	3	0.123
Education, y	15.0 ± 2.65	15.1 ± 1.76	0.808
Flumazenil injected, n	14	8	0.374
Gastroscopy time, min	8.0 ± 1.80	8.9 ± 2.52	0.163
Sedation time, min	62.2 ± 23.01	51.1 ± 15.80	0.198
MoCA-K (baseline)	27.1 ± 1.42	26.9 ± 1.67	0.796
MoCA-K (final)	27.8 ± 1.44	27.6 ± 2.13	0.704
Immediate recall after midazolam injection*	4.3 ± 1.35	3.2 ± 1.39	0.039
Delayed recall after gastroscopy*	2.6 ± 1.94	1.2 ± 1.48	0.073
Delayed recall after sedation*	2.9 ± 2.01	1.3 ± 1.32	0.047

Data were expressed as Mean ± SD.

*A man's name and address memory task score on a scale of 0 to 6.

of the subjects, except for 4 individuals, did not remember the episodes (2 episodes: 1 for the instructions from the doctor and 1 for the feeling of discomfort) during gastroscopy. Only 3 remembered both, whereas 1 subject remembered only the instructions from the doctor during gastroscopy. On the other hand, all subjects remembered the 3 episodes in the morning before midazolam injection.

The MoCA-K scores increased slightly but significantly after the termination of sedation, compared with those at baseline (mean 0.67 ± 1.35 increase, $P = 0.011$). The delayed recall test score in the MoCA-K also increased approximately 1 ± 0.79 point, which was statistically significant. On the other hand, scores of the memory task, "a man's name and address," dropped significantly, with the difference of 1.8 ± 1.92 between the start of midazolam injection and completion of the gastroscopy ($P < 0.001$). The score decreased 1.6 ± 1.63 between the midazolam injection and the termination of sedation ($P < 0.001$). However, there was no significant difference in the scores between these two ($P = 0.269$).

We divided individuals into 2 groups according to the midazolam dose, with a dose of 0.08 mg/kg or more being the high-dose group (N = 9) and a dose of 0.07 mg/kg or less being the low-dose group (N = 21). The subjects in the 2 groups did not show any differences in their characteristics (Table 2). Subjects in the high-dose group showed lower scores in their immediate and delayed recall in the "a man's name and address" test (Table 2). There were much more lower-scored subjects (from 0 to 3) in the high-dose group, whereas there were much more higher-scored subjects (from 4 to 6) (up to 40%) in the low-dose group (Fig. 2).

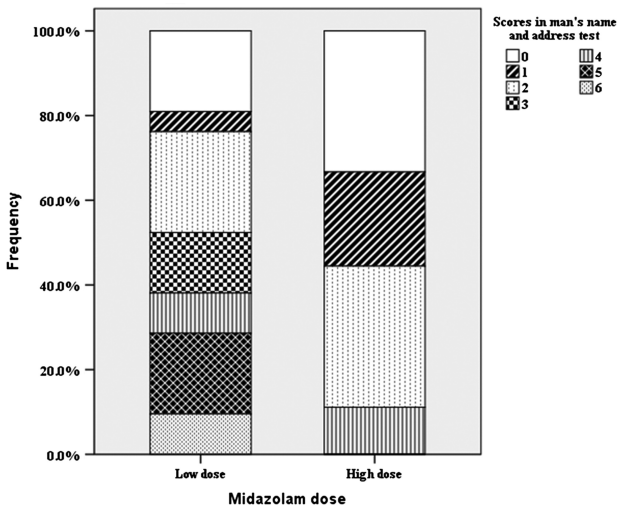

FIGURE 2. Performance of "a man's name and address" memory task according to the midazolam dose.

Subjects who received intravenous flumazenil after gastroscopy did not differ from those who did not with regard to their sedation time, final MoCA-K scores, and memory task scores (Table 3).

Finally, correlations among the variables were measured. The midazolam dose were significantly related to the delayed recall scores of "a man's name and address" ($P = 0.014$, $r = -0.476$ on after the gastroscopy task; $P = 0.015$, $r = -0.473$ on after sedation) and the immediate recall scores ($P = 0.034$, $r = -0.417$), although not to the baseline or final MoCA-K scores ($P > 0.05$) after adjustment for age, sex, education, and flumazenil injection status (Table 4). The midazolam dose was inversely correlated with the delayed recall scores of "a man's name and address" after gastroscopy, even after correction for age, sex, education, flumazenil injection status, and the immediate recall scores ($P < 0.05$, $r = -0.398$, Table 4).

DISCUSSION

Our study showed that subjects who had received a midazolam injection for gastroscopy did not remember the events during gastroscopy except a few, which shows anterograde amnesia of episodic memory. On the other hand, there was no subject who showed retrograde amnesia of episodic memory or a decline in their general cognitive function after the procedure. The MoCA-K scores representing general cognitive function, on the contrary, increased, perhaps due to the learning effect. Another interesting finding is that midazolam induced selective anterograde amnesia in a dose-dependent manner. A midazolam dose greater than 0.08 mg/kg brought about lower scores in both the immediate and the delayed recall tests compared with a low (<0.08 mg/kg) dose of midazolam. Moreover, the midazolam dose continued to show a significant correlation with the delayed recall scores even after correction for age, sex, education, flumazenil status, and immediate recall scores.

TABLE 3. Comparison of Subjects According to the Flumazenil Injection Status

Variables	Flumazenil (−) N = 8	Flumazenil (+) N = 22	*P*
Age, y	43.8 ± 10.58	46.1 ± 9.95	0.572
Male, n	4	13	0.698
Education, y	14.9 ± 2.80	15.1 ± 2.29	0.860
Midazolam dose, mg/kg	0.065 ± 0.020	0.070 ± 0.019	0.511
Gastroscopy time, min	8.0 ± 1.77	8.3 ± 2.17	0.531
Sedation time, min	62.1 ± 28.09	57.7 ± 19.18	0.905
MoCA-K (baseline)	27.1 ± 1.55	27.1 ± 1.62	0.751
MoCA-K (final)	27.5 ± 1.60	27.8 ± 1.68	0.666
Immediate recall after midazolam injection*	3.9 ± 1.73	4.0 ± 1.35	0.836
Delayed recall after gastroscopy*	2.5 ± 2.07	2.1 ± 1.86	0.583
Delayed recall after sedation*	2.5 ± 2.27	2.4 ± 1.87	0.868

Data were expressed as Mean ± SD.

*A man's name and address memory task score on a scale of 0 to 6.

Our results that confirm that selective anterograde amnesia in normal subjects might be explained as follows. Midazolam is known to cause amnesia by facilitating the action of γ-amino butyric acid (GABA)[9] by increasing the frequency of the channel opening and decreasing the cholinergic function, especially in the hippocampus.[10] The GABA is an inhibitory neurotransmitter of the brain. Binding of benzodiazepines at the $GABA_A$ receptors results in a potentially inhibitory action on the neural circuit.[11] Midazolam increases the binding of GABA to $GABA_A$ receptors which are prevalent in the hippocampus where they are thought to cause amnestic effects.[12,13] The GABA reduces the long-term potentiation for episodic memory in the hippocampus, impairing encoding process of memory.[14] Consequently, the effects of benzodiazepine on memory are mainly anterograde, with retrograde memory intact.[15]

Immediate recall, representing working memory function, might be vulnerable to the midazolam effect. Although midazolam works primarily on the hippocampus, there is evidence that the prefrontal cortex can also be affected by midazolam[16] which is known to be an anatomical substrate of working memory. Our results keep in line with those of a previously published report showing the effect of midazolam on short-term/working memory processes, although the effect was reported to be less than that of midazolam on the episodic memory function.

In addition, a high dose of midazolam showed worse functioning of both episodic memory and working memory, according to our study results. Anterograde amnesia might be partially mediated by its effect on working memory dysfunction indexed by the repetition task as the encoding process is affected by the working memory process.[17] However, the midazolam's effect on delayed episodic memory was persistently strong even after adjustment for age, sex, education, flumazenil effect, and working memory function. Moreover, the amnesia was not caused solely by the general effects of sedation because low scores on the episodic memory task (a man's name and address) remained even after the termination of sedation. On the other hand, at the time of full recovery of consciousness, MoCA-K total scores and delayed recall scores increased compared to the baseline, suggesting that general cognitive function and episodic memory were not affected, and anterograde amnesia during gastroscopy was selective and transitory.

There was no significant difference between the flumazenil-injected group and the noninjected group in the recall score for the procedure. Flumazenil is an imidazobenzodiazepine derivative which antagonizes the benzodiazepine effects by binding to GABA-benzodiazepine receptors. It is widely used to reverse benzodiazepine-induced sedation, including conscious sedation during gastroscopy.[18] However, similar to our results, a previous study reported that flumazenil does not reduce or interfere with midazolam's sedative or amnestic effects.[18] The effect of flumazenil on the episodic memory function might require further studies as we did not randomize our study subjects.

TABLE 4. Correlation Analyses Between Patients Characteristics and Cognitive Measures

	Baseline MoCA		Final MoCA		Immediate Recall		Delayed Recall (After Gastroscopy)		Delayed Recall (After Sedation)	
Variables	r	*P*	r	*P*	r	*P*	r	*P*	r	*P*
Age	−0.156	0.448	−0.087	0.674	−0.297	0.140	−0.253	0.212	−0.307	0.127
Sex	0.229	0.261	0.422	0.032	−0.480	0.013	0.168	0.412	−0.085	0.681
Education	0.530	0.005	0.463	0.017	0.014	0.946	0.124	0.547	−0.076	0.712
Midazolam dose/kg	−0.309	0.124	−0.358	0.072	−0.417	0.034	−0.476	0.014	−0.473	0.015
Flumazenil use	−0.009	0.965	0.185	0.365	0.058	0.777	0.007	0.973	0.105	0.610

r = Values of Pearson's correlation coefficient; partial correlation coefficient analysis was done for measuring correlations between variables; Correlations of variables were adjusted by other factors (e.g., correlations between midazolam dose/kg and cognitive outcomes were adjusted by age, sex, education, and flumazenil use), and the correlations between midazolam dose/kg and delayed recall (after gastroscopy) scores remained significant after additionally adjusting by immediate recall scores.

Our study has some limitations. First, because we only did immediate recall of "a man's name and address" test for working memory, our results should be cautiously interpreted in the context of working memory. Given the small amount of time allowed for testing at the time of short-acting midazolam injection, we were limited in how much we could do with cognitive testing. Second, the memory tasks using "a man's name and address" were done differently during the time interval between the immediate and the delayed recall tests because the gastroscopy duration and sedation time varied from one subject to another. Therefore, these differences may have contributed to the effect of midazolam on memory tasks in our subjects. Lastly, the decision on whether or not to use flumazenil was made by the endoscopist on a case-by-case basis and was not randomized. Further studies with more strict protocol and randomization may be required. This study dealt with normal, rather young subjects and, thus, cannot be generalized to other populations. The effect of midazolam on cognitive function in the elderly individuals, particularly those with cognitive decline or Alzheimer's disease would be of great interest and concern considering the growing number of those people who might undergo sedation endoscopy.

CONCLUSIONS

In conclusion, our study results show that midazolam causes transient selective anterograde amnesia in a dose-dependent manner in the setting of sedation endoscopy. Midazolam dose shows a significant correlation with the delayed recall scores even after correction for age, sex, education, flumazenil status, and immediate recall scores. On the other hand, there was no subject who showed retrograde amnesia or a decline in their general cognitive function after the procedure.

REFERENCES

1. Merritt P, Hirshman E, Zamani S, et al. Episodic representations support early semantic learning: evidence from midazolam induced amnesia. *Brain Cogn* 2006;61:219–223.
2. Uygur-Bayramiçli O, Dabak R, Kuzucuoglu T, et al. Sedation with intranasal midazolam in adults undergoing upper gastrointestinal endoscopy. *J Clin Gastroenterol* 2002;35:133–137.
3. Merritt P, Hirshman E, Hsu J, et al. Metamemory without the memory: are people aware of midazolam-induced amnesia? *Psychopharmacology (Berl)* 2005;177:336–343.
4. Fisher J, Hirshman E, Henthorn T, et al. Midazolam amnesia and short-term/working memory processes. *Conscious Cogn* 2006;15:54–63.
5. Hirshman E, Passannante A, Arndt J. Midazolam amnesia and conceptual processing in implicit memory. *J Exp Psychol Gen* 2001;130:453–465.
6. Lee SY, Son HJ, Lee JM, et al. Identification of factors that influence conscious sedation in gastrointestinal endoscopy. *J Korean Med Sci* 2004; 19:536–540.
7. Hsu YH, Lin FS, Yang CC, et al. Evident cognitive impairments in seemingly recovered patients after midazolam-based light sedation during diagnostic endoscopy. *J Formos Med Assoc* doi: 10.1016/j.jfma. Accessed July 18, 2013.
8. Lee JY, Lee DW, Cho SJ, et al. Brief screening for mild cognitive impairment in elderly outpatient clinic: validation of the Korean version of the Montreal Cognitive Assessment. *J Geriatr Psychiatry Neurol* 2008;21: 104–110.
9. Evers AS, Maze M. *Anesthetic pharmacology: Physiologic principles and clinical practice*. Philadelphia: Churchill Livingstone, 2004.
10. Ghouri AF, Ruiz MA, White PF. Effect of flumazenil on recovery after midazolam and propofol sedation. *Anesthesiology* 1994;81:333–339.
11. Timić T, Joksimović S, Milić M, et al. Midazolam impairs acquisition and retrieval, but not consolidation of reference memory in the Morris water maze. *Behav Brain Res* 2013;241:198–205.
12. Kobayashi S, Fujito Y, Matsuyama K, et al. Differential effects of midazolam on inhibitory postsynaptic currents in CA1 pyramidal cells and dentate gyrus granule cells of rat hippocampal slices. *Brain Res* 2004;1003: 176–182.
13. Kobayashi S, Fujito Y, Matsuyama K, et al. Comparison of midazolam effects on inhibitory postsynaptic currents in hippocampal CA3 with those in CA1. *Neuroreport* 2005;16:1003–1007.
14. Bliss TV, Collingridge GL. A synaptic model of memory: long-term potentiation in the hippocampus. *Nature* 1993;361:31–39.
15. Saari TI, Uusi-Oukari M, Ahonen J, et al. Enhancement of GABAergic activity: neuropharmacological effects of benzodiazepines and therapeutic use in anesthesiology. *Pharmacol Rev* 2011;63:243–267.
16. Hirshman E, Fisher J, Henthorn T, et al. Midazolam amnesia and retrieval from semantic memory: developing methods to test theories of implicit memory. *Brain Cogn* 2003;53:427–432.
17. Raaijmakers JG, Shiffrin RM. Search of associative memory. *Psychol Rev* 1981;88:93–134.
18. Chudnofsky CR. Safety and efficacy of flumazenil in reversing conscious sedation in the emergency department. Emergency Medicine Conscious Sedation Study Group. *Acad Emerg Med* 1997;4:944–950.