

Sole Use of Dexmedetomidine Has Limited Utility for Conscious Sedation during Outpatient Colonoscopy

Przemyslaw Jalowiecki, M.D., Ph.D.,* Robert Rudner, M.D., Ph.D.,† Maciej Gonciarz, M.D., Ph.D.,‡
Piotr Kawecki, M.D., Ph.D.,§ Michal Petelenz, M.D., Ph.D.,|| Piotr Dziurdzik, M.D., Ph.D.§

Background: This study evaluated the ability of dexmedetomidine to provide analgesia and sedation for outpatient colonoscopy, examining outcomes including cardiorespiratory variables, side effects, and discharge readiness.

Methods: Sixty-four patients were randomly assigned to one of three treatment regimens. In group D, patients received 1 $\mu\text{g}/\text{kg}$ dexmedetomidine over 15 min followed by an infusion of 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Group P received meperidine (1 mg/kg) with midazolam (0.05 mg/kg), and group F received fentanyl (0.1–0.2 mg intravenous) on demand. The assessment included measurements of heart rate, blood pressure, oxygen saturation, respiratory rate, quality of sedation/analgesia, and an evaluation of the recovery time.

Results: The study was terminated before the planned 90 patients had been recruited because of adverse events in group D. In all groups, negligible hemoglobin oxygen saturation and respiratory rate variations were observed. In group D, there was a significantly larger decrease in heart rate (to approximately 40 beats/min in 2 of 19 cases) and blood pressure (to less than 50% of the initial value in 4 of 19 patients). Supplemental fentanyl was required in 47% of patients receiving dexmedetomidine to achieve a satisfactory level of analgesia (*vs.* 42.8% of patients in group P and 79.2% of patients in group F). Vertigo (5 patients), nausea/vomiting (5 patients), and ventricular bigeminy (1 patient) were observed only in group D. Time to home readiness was longest in group D (85 ± 74 , 39 ± 21 , and 32 ± 13 min in groups D, P and F, respectively; $P = 0.007$).

Conclusions: The use of dexmedetomidine to provide analgesia/sedation for colonoscopy is limited by distressing side effects, pronounced hemodynamic instability, prolonged recovery, and a complicated administration regimen.

COLONOSCOPY, like many other diagnostic and therapeutic procedures, may be associated with discomfort. Although some patients tolerate colonoscopy without sedation, various techniques are used to limit discomfort and adverse effects. Selection and dosing of sedatives depends on the patient's emotional state, the intensity of pain during examination, foreseeable technical difficulties, the endoscopist's experience, the presence or absence of anesthesia personnel, and hospital-specific procedures.

Conscious sedation is a popular technique for large bowel endoscopy. The combination of an opiate and a

benzodiazepine is known to provide excellent analgesic and sedative conditions during colonoscopy.¹ This method, however, is associated with a risk of side effects, especially respiratory insufficiency. Therefore, pharmacologic agents causing an adequate level of anesthesia or sedation without respiratory depression are of increasing interest to clinicians.

Dexmedetomidine is a highly selective α_2 -adrenoceptor agonist with sedative and analgesic effects.² Compared with clonidine, it is more selective for the α_2 adrenoceptor and acts as a full agonist in most pharmacologic test models. Potentially desirable effects include decreased requirements for other anesthetics and analgesics, a diminished sympathetic response to stress and the potential for cardioprotective effects against myocardial ischemia, and minimal effects on respiration.³⁻⁵ However, sympatholysis also may cause adverse clinical effects, such as hypotension and bradycardia.⁶ Although a primary indication for dexmedetomidine has been the sedation of the critically ill, it can also be used for intraoperative sedation.⁷⁻⁹

This study examined the hypothesis that dexmedetomidine is equally safe and efficacious compared with standard techniques in providing sedation for colonoscopy. We compared its effects on respiration, hemodynamics, analgesia/sedation, and side effects with either meperidine and midazolam or intermittent fentanyl on demand. In addition, because dexmedetomidine has a relatively long elimination half-life (approximately 2 h),¹⁰ we examined its impact on the patient's readiness for home discharge after completing the procedure.

Materials and Methods

This prospective, randomized, single-blind study was conducted with a population of patients undergoing ambulatory elective colonoscopy. The study was approved by the Ethical Committee of the Silesian University School of Medicine (Katowice, Poland), and written, informed consent was obtained from all of the participants. We intended to enroll 90 patients, but the study was interrupted before the planned number of patients had been recruited because of adverse events (described in the Results section).

A total of 64 adult patients (aged 18–60 yr; American Society of Anesthesiologists physical status I and II) were studied. The exclusion criteria were as follows: pregnancy, history of colon surgery, psychiatric or emotional disorder, chronic use of or addiction to opiates or seda-

* Professor and Chairman, † Assistant Professor, § Senior Lecturer, Department of Anesthesiology and Intensive Therapy, ‡ Associate Professor, || Assistant Professor, Department of Internal Medicine.

Received from the Department of Anesthesiology and Intensive Therapy and the Department of Internal Medicine, Silesian University School of Medicine, Katowice, Poland. Submitted for publication January 6, 2005. Accepted for publication April 29, 2005. Support was provided solely from institutional and/or departmental sources.

Address reprint requests to Dr. Rudner: Department of Anesthesiology and Intensive Therapy, Silesian University School of Medicine, Wojewodzki Szpital Specjalistyczny im. Sw. Barbary, Pl. Medyków 1, 41-200 Sosnowiec, Poland. Address electronic mail to: rrudner@mp.pl. Individual article reprints may be purchased through the Journal Web site, www.anesthesiology.org.

tives, previous adverse reactions to any medication used in this study, and pain unrelated to the gastrointestinal tract.

A computer-generated randomization list was used to assign patients to one of three study groups. In the first group (group D, $n = 19$) patients received conscious sedation with an intravenous infusion of 1 $\mu\text{g}/\text{kg}$ dexmedetomidine (Precedex[®]; Abbott Laboratories, North Chicago, IL) administered *via* a syringe infusion pump (Terufusion TE-312[®]; Terumo, Tokyo, Japan) over a 15-min period before colonoscopy, followed by an infusion of 0.2 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$. Drug infusion was discontinued if one of the following adverse events was observed: apnea lasting longer than 30 s, hemoglobin oxygen saturation (Spo_2) lower than 90%, decrease of heart rate (HR) below 50 beats/min, mean arterial pressure (MAP) below 70% of its initial value, and sedation that made verbal contact with the patient impossible.

In the second study group (group P, $n = 21$), patients received 1 mg/kg intravenous meperidine (Dolargan[®]; Chinoin, Budapest, Hungary) and 0.05 mg/kg intravenous midazolam (Sopodorm[®]; Solco-Basel, Basel, Switzerland) before the colonoscopy.

In the third study group (group F, $n = 24$), the patients were not sedated before the procedure but were given 0.1–0.2 mg intravenous fentanyl (Fentanyl[®]; Polfa-Warsaw, Warsaw, Poland) in response to pain. Oxygen was delivered by Venturi facemask (fraction of inspired oxygen = 0.35) to all patients throughout the procedure. A jaw thrust maneuver was applied to the patients if necessary. All colonoscopies were performed by the same experienced endoscopist with a video colonoscope (EC 3840 FK2; Pentax Corp., Tokyo, Japan). Sedation and monitoring were performed by the same anesthesiologist in all cases.

The following parameters were measured continuously and recorded every minute: HR, MAP, Spo_2 , and respiratory rate (DASH 3000[®] monitor; GE Marquette Medical Systems, Milwaukee, WI). The recorded data were analyzed and averaged over the following time intervals: baseline—at least 3 min before the first drug administration or starting colonoscopy; colonoscopy—during colonoscopy; and postprocedure—from the end of the colonoscopy to the time at which a score of 10 points on the Modified Post Anesthesia Discharge Scoring System (MPADSS) scale was reached (table 1).¹¹

The quality of analgesia was assessed using the 11-point (0–10) Numerical Pain Rating Scale (NRS),¹² in which 0 represents no pain at all and 10 represents the worst pain imaginable. If the patient reported pain exceeding 6 on the NRS, intravenous fentanyl in doses of 0.1 mg was administered.

The evaluation of the quality of sedation was based on a five-point Observer's Assessment of Alertness/Sedation Scale.¹³ The level of recovery from anesthesia and the return of psychomotor fitness were studied using the

Table 1. Modified Post Anesthesia Discharge Scoring System*

| Category | Description | Score |
|-------------------|-------------------------------------|-------|
| Vital signs | Within 20% of preoperative value | 2 |
| | Within 20–40% of preoperative value | 1 |
| Ambulation | Within 40% of preoperative value | 0 |
| | Steady gait/no dizziness | 2 |
| | With assistance | 1 |
| Nausea/vomiting | None/dizziness | 0 |
| | Minimal | 2 |
| | Moderate | 1 |
| Pain | Severe | 0 |
| | Minimal | 2 |
| | Moderate | 1 |
| Surgical bleeding | Severe | 0 |
| | Minimal | 2 |
| | Moderate | 1 |
| | Severe | 0 |

* See reference 11.

MPADSS scale (table 1). The duration of colonoscopy and the time from the end of the procedure to the moment of scoring 9 and 10 on the MPADSS scale were measured. The discharge criteria required that the patients be awake and alert with stable vital signs, be able to ambulate without assistance, and be free of side effects (*i.e.*, a score of 10 on the MPADSS scale).

Administration of any medication apart from the study protocol and occurrences of complications and side effects (strong vertigo, nausea, vomiting) were recorded. In case of serious adverse events, the study protocol provided for hospital admission to an observation ward for minimum of 12 h. Patients were also asked about their willingness to undergo a repeat procedure with the same sedation regimen in the future if required.

Statistical Analysis

Results were expressed as numbers of occurrences, percentages, and mean \pm SD for continuous variables. In some cases, the data were presented as percent changes for clarity. Categorical data were analyzed using the chi-square test with a Yates correction or Fisher exact test, where appropriate. NRS scores were not normally distributed and were compared between groups using a nonparametric Kruskal-Wallis test. The differences in continuous parameters such as patient characteristics, preoperative data, time intervals, and amounts of supplemental fentanyl were analyzed using one-way analysis of variance. Repeated-measures analysis of variance was used to test for the difference between groups in HR, MAP, respiratory rate, and Spo_2 over time. Correction with *post hoc* tests (Bonferroni method) was used because repeated measurements of a single variable were tested over time. A *P* value of less than 0.05 was considered significant. Statistical analyses were performed using Statistica for Windows version 6.0 software (StatSoft, Tulsa, OK).

Table 2. Patient Demographics and Preoperative Data

| Parameters | Group D (n = 19) | Group P (n = 21) | Group F (n = 24) | P Value |
|-----------------------|---------------------|---------------------|---------------------|---------|
| Women | 11 (58%) | 12 (57%) | 14 (58%) | > 0.78* |
| ASA II | 14 (74%) | 16 (76%) | 18 (75%) | > 0.80* |
| Age, yr | 52 ± 8.4 | 57 ± 9.5 | 55 ± 9.9 | 0.37† |
| Weight, kg | 66.8 ± 13.7 | 70.7 ± 16 | 76.5 ± 20 | 0.18† |
| MAP, mmHg | 101.4 ± 16.7 | 103.4 ± 17.9 | 100.2 ± 15.8 | 0.82† |
| HR, min ⁻¹ | 82 ± 16 | 79 ± 14 | 89 ± 18 | 0.19† |
| Spo ₂ , %‡ | 99 ± 0.7 | 99 ± 1.1 | 99 ± 0.9 | 0.91† |
| RR, min ⁻¹ | 19 ± 1.9 | 20 ± 1.6 | 19 ± 1.8 | 0.37† |

Data are presented as n (%) or mean ± SD.

* Chi-square test. † Analysis of variance. ‡ Oxygen by Venturi facemask (fraction of inspired oxygen = 0.35).

ASA = American Society of Anesthesiologists physical status; group D = dexmedetomidine group; group F = fentanyl group; group P = meperidine-midazolam group; HR = heart rate; MAP = mean arterial pressure; RR = respiratory rate; Spo₂ = hemoglobin oxygen saturation.

Results

The study groups were comparable regarding demographic characteristics, indications for colonoscopy, initial vital signs, and American Society of Anesthesiologists physical status (table 2). In all patients, endoscopy was completed. Because of adverse events in group D, enrollment was halted after 64 subjects. In all groups, negligible Spo₂ and respiratory rate variations were observed (fig. 1). A jaw thrust maneuver had to be applied in 6 of the cases (29%) in group P. This was not required in groups D and F.

In group D, significantly larger HR and MAP decreases were observed during and after colonoscopy as compared with groups F and P (fig. 1). In group D, the postcolonoscopy MAP values were on average 26% lower than baseline (*vs.* 14% in group P and 3% in group F). Blood pressure decreased to approximately 50% of the initial value in four cases in group D. One of these patients was taking perindopril because of hypertension.

Fig. 1. Mean values of mean arterial pressure (MAP, in mmHg), heart rate (HR, in beats/min), respiratory rate (RR, in respirations/min), and hemoglobin oxygen saturation (Spo₂, as a percentage), determined at different stages of the study. Baseline = at least 3 min before the first drug administration or starting colonoscopy; colonoscopy = during colonoscopy; postprocedure = from the end of the colonoscopy until the patient was fully conscious and registered parameters returned to baseline ±20%; group D = dexmedetomidine group; group F = fentanyl group; group P = meperidine-midazolam group. Vertical lines represent SDs. * *P* < 0.05 after correction by Bonferroni method.

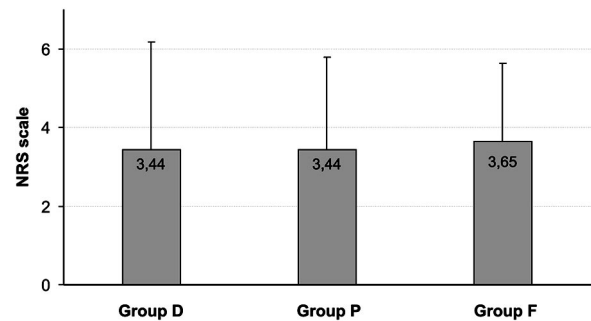
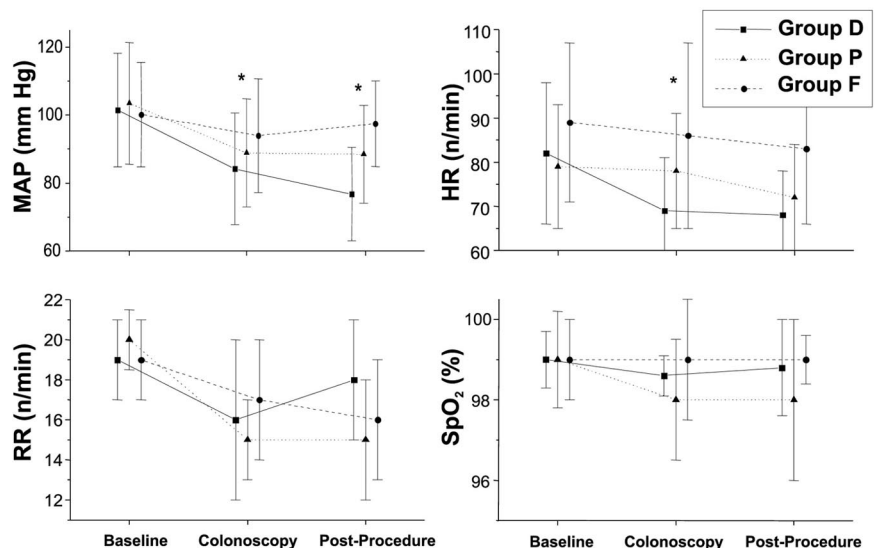


Fig. 2. Comparison of the intensity of pain, according to the Numerical Pain Rating Scale (NRS) in the study groups. Data are presented as mean and SD; vertical lines represent SDs. Group D = dexmedetomidine group; group F = fentanyl group; group P = meperidine-midazolam group. *P* > 0.05.

In contrast, the maximum change in MAP did not exceed 35% in group P and 30% in group F. Similarly, in group D, the postcolonoscopy mean HR was 17% lower as compared with preprocedure value readings (*vs.* 9% in group P and 7% in group F). In two cases from group D (one with mild ischemic heart disease treated with pentaerythritol and trimetazidine), HR decreased from 77 and 86 beats/min to 40 beats/min. In the other study groups, the minimum HR was not lower than 50 beats/min. In four cases in group D, bradycardia was treated with atropine.

The lowest Observer's Assessment of Alertness/Sedation Scale score during the study was 3 points in all groups. The NRS score was not different among the study groups (*P* = 0.951; fig. 2). The average use of supplemental fentanyl in cases of inadequate analgesia was 0.04 ± 0.05 mg in group P, which was significantly lower than that in group D (0.1 ± 0.1 mg) and group F (0.18 ± 0.1 mg) (*P* = 0.0005). Fentanyl was administered in 9 cases in both groups D and P and to 19 patients in group F. Vertigo and nausea, followed by vomiting treated with ondansetron, occurred in 5 cases

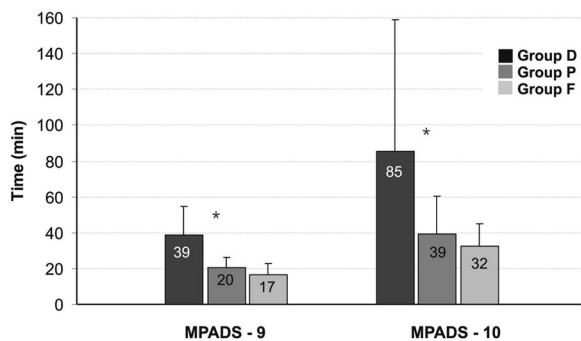


Fig. 3. Time intervals from the end of colonoscopy until scores of 9 or 10 were reached in the Modified Post Anesthesia Discharge Scoring System (MPADSS). Data are presented as mean and SD; vertical lines represent SDs. MPADSS-9 = end of procedure until 9 points on MPADSS; MPADSS-10 = end of procedure until 10 points in MPADSS. * $P < 0.01$.

in group D. No vertigo or nausea was observed in groups P and F.

The average duration of colonoscopy in group D (13 ± 8.6 min) was significantly longer than in groups P (9 ± 4.8 min) and F (8 ± 4.7 min) ($P = 0.0038$). In group D, the time required to reach home discharge readiness (10 points on the MPADSS scale) was significantly longer (85 ± 74 min) compared with the other groups (39 ± 21 min for group P and 32 ± 13 min for group F; $P = 0.007$; fig. 3). Group D patients were delayed in achieving MPADSS scores of both 9 and 10 (*i.e.*, ready for discharge to home) compared with the other groups (fig. 3). Discharge was delayed in group D patients because of the following factors: prolonged drowsiness (six cases), dizziness (two cases), nausea/vomiting (three cases), low blood pressure (two cases).

According to the study protocol, three patients from group D were admitted to the hospital for 12-h observation because of safety concerns. One patient, with no previous history of cardiac disease or symptomatic arrhythmia, experienced ventricular bigeminy with symptoms of chest pressure, blood pressure of 80/50 mmHg, and near-syncope. Two other patients (one with an American Society of Anesthesiologists physical status of I and one with an American Society of Anesthesiologists physical status of II due to diabetes) experienced profound hypotension accompanied by sustained nausea and vomiting that was resistant to ondansetron therapy. Oxygen *via* facemask, intravenous fluid therapy, and ephedrine was implemented.

One patient in group F (4.5%) and four patients in group D (22.2%) stated that they would decline the same treatment during future colonoscopies, whereas in group P, all patients stated they would opt for the same pain treatment procedure.

Discussion

Methods used to assure patient comfort during painful and embarrassing diagnostic procedures, such as

colonoscopy, should focus on effective pain relief, safety, lack of recall of unpleasant aspects of the procedure, and, finally, on rapid patient recovery and readiness for home discharge.

The results of this study indicate that all techniques studied provided adequate pain relief in patients during colonoscopy. The level of analgesia was similar in all study groups, and the NRS score was less than 4. This result compares favorably with the analgesic effects of other commonly used methods of analgesia during colonoscopy.^{14,15} Unfortunately, in 47% of cases, adequate pain relief in patients receiving dexmedetomidine could be achieved only with supplemental fentanyl. Reports suggest that dexmedetomidine can produce general anesthesia when administered in high doses that are often associated with bradycardia, hypotension, and prolonged recovery.¹⁶

The impetus for exploring the use of dexmedetomidine during ambulatory colonoscopy was the possibility that adequate sedation could be provided with minimal respiratory depression.^{9,17} This study confirmed the lack of clinically significant respiratory effects, including apnea, hypoxemia, or airway obstruction.

It has been suggested that dexmedetomidine may have favorable hemodynamic properties in patients with moderate hypertension and with coronary heart disease.^{3,4} We found that a dose sufficient to produce sedation caused a statistically significant decrease in arterial blood pressure and bradycardia during colonoscopy. These reactions were more profound than those observed in the other study groups. Vasovagal reactions have been reported in 0.8% of unsedated patients undergoing colonoscopy as a consequence of stretching of the colon and mesenteric attachments from looping of the instrument shaft.¹⁸ It is possible that dexmedetomidine may have exacerbated these vagal effects.¹⁹ In our study, pronounced bradycardia and hypotension was relatively common in patients receiving dexmedetomidine. Hemodynamic instability was also observed after the procedure. Similar hemodynamic effects can be observed in patients sedated with dexmedetomidine in the intensive care unit and may represent a significant limitation in the clinical use of this agent.^{20,21} Pronounced hypotension and bradycardia of sufficient severity to necessitate intensive medical interventions and prolonged observation occurred in 3 of 19 patients receiving dexmedetomidine and was the reason for prematurely halting study enrollment.

Another important and frequently discussed factor influencing the general evaluation of ambulatory practice is rapid home discharge. In this study, the times to discharge readiness were significantly longer when dexmedetomidine was used, in some patients requiring several hours. This observation reflects the pharmacokinetic properties of dexmedetomidine, which has an elimination half time of approximately 2 h.¹⁰ The most

frequent reasons for delay in reaching the target MPADSS score in this group included variations in arterial pressure and HR exceeding 20–40% of baseline, prolonged sleepiness, weakness, and nausea. The increased frequency of the adverse events in patients receiving dexmedetomidine can only be partially explained by the use of supplemental opiate because fentanyl was administered in cases of inadequate analgesia in all three study groups.

In the current investigation, the duration of the procedure was significantly longer in patients receiving dexmedetomidine therapy as compared with the other study groups. The adequacy of sedation affects both the technical aspects and the duration of colonoscopy.²² Dexmedetomidine may also inhibit intestinal transit,²³ which could cause technical difficulties with colonoscopy. The study protocol was not designed to assess the satisfaction of the endoscopist.

In conclusion, in patients undergoing colonoscopy, dexmedetomidine provides a relatively satisfactory level of analgesia and sedation without clinically notable adverse respiratory effects. However, compared with commonly used sedation regimens, dexmedetomidine is associated with the frequent requirement for supplemental fentanyl, sometimes profound hypotension and bradycardia, and prolonged recovery time. These side effects may limit its usefulness for this indication.

References

1. Wong RCK: The menu of endoscopic sedation: All-you-can-eat, combination set, a la carte, alternative cuisine, or go hungry. *Endoscopy* 2001; 54:122–6
2. Aantaa R, Scheinin M: Alpha-2-adrenergic agents in anaesthesia. *Acta Anaesthesiol Scand* 1993; 37:1–16
3. Kamibayashi T, Maze M: Clinical uses of alpha₂-adrenergic agonists. *ANESTHESIOLOGY* 2000; 93:1345–9
4. Taittonen MT, Kirvelä OA, Aantaa R, Kanto JH: Effect of clonidine and dexmedetomidine premedication on perioperative oxygen consumption and haemodynamic state. *Br J Anaesth* 1997; 78:400–6
5. Wijesundera DN, Naik JS, Beattie WS: Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: A meta-analysis. *Am J Med* 2003; 114:742–52
6. Bloor BC, Ward DS, Belleville JP, Maze M: Effects of IV dexmedetomidine in humans: II. Hemodynamic changes. *Anesthesiology* 1992; 77:1134–42
7. Venn M, Newman J, Grounds M: A phase II study to evaluate the efficacy of dexmedetomidine for sedation in the medical intensive care unit. *Intensive Care Med* 2003; 29:201–7
8. Arain SR, Ebert TJ: The efficacy, side effects, and recovery characteristics of dexmedetomidine versus propofol when used for intraoperative sedation. *Anesth Analg* 2002; 95:461–6
9. Scher CS, Gitlin MC: Dexmedetomidine and low-dose ketamine provide adequate sedation for awake fiberoptic intubation. *Can J Anaesth* 2003; 50:607–10
10. Bhana N, Goa KL, McClellan KJ: Dexmedetomidine. *Drugs* 2000; 59:263–8
11. Chung F: Practical issues in outpatient anaesthesia: Discharge criteria—A new trend. *Can J Anaesth* 1995; 42:1056–9
12. Chapman CR, Casey KL, Dubner R, Foley KM, Gracely RH, Reading AE: Pain measurement: An overview. *Pain* 1985; 22:1–31
13. Chernik DA, Gillings D, Laine H: Validity and reliability of the Observer's Assessment of Alertness/Sedation scale: Study with intravenous midazolam. *J Clin Psychopharmacol* 1990; 10:244–5
14. Forbes GM, Collins BJ: Nitrous oxide for colonoscopy: A randomized controlled study. *Gastrointest Endosc* 2000; 51:271–7
15. Greilich PE, Virella CD, Rich JM, Kurada M, Roberts K, Waren JF, Harford WV: Remifentanyl versus meperidine for monitored anesthesia care: A comparison study in older patients undergoing ambulatory colonoscopy. *Anesth Analg* 2001; 92:80–4
16. Ramsay MAE, Luterma DL: Dexmedetomidine as a total intravenous anesthetic agent. *ANESTHESIOLOGY* 2004; 101:787–9
17. Venn RM, Hell J, Grounds RM: Respiratory effects of dexmedetomidine in the surgical patient requiring intensive care. *Crit Care* 2000; 4:302–8
18. Eckardt VF, Kanzler G, Schmitt T, Eckardt AJ, Bernard G: Complications and adverse effects of colonoscopy with selective sedation. *Gastrointest Endosc* 1999; 49:560–5
19. Talke P, Richardson CA, Scheinin M, Fisher DM: Postoperative pharmacokinetics and sympatholytic effects of dexmedetomidine. *Anesth Analg* 1997; 85:1136–42
20. Venn RM, Bryant A, Hall GM, Grounds RM: Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. *Br J Anaesth* 2001; 86:650–6
21. Drummond G: Dexmedetomidine may be effective, but is it safe? *Br J Anaesth* 2002; 88:454–5
22. Kim WH, Cho YJ, Park JY, Min PK, Kang JK, Park IS: Factors affecting insertion time and patient discomfort during colonoscopy. *Gastrointest Endosc* 2000; 52:600–5
23. Asai T, Mapleson WW, Power I: Interactive effect of morphine and dexmedetomidine on gastric emptying and gastrointestinal transit in the rat. *Br J Anaesth* 1998; 80:63–7