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Clinical Efficacy of Oral–Transdermal Clonidine Combinations during the Perioperative Period

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In an attempt to maintain stable levels of an α_2-adrenergic agonist throughout the perioperative period, two different oral–transdermal clonidine dosage regimens were administered according to a randomized, double-blind, placebo-controlled study in patients undergoing abdominal surgery. We determined the clinical efficacy of a high- and a low-dose clonidine regimen on sedation, hemodynamic parameters, anesthesia, and analgesia. The low-dose clonidine group of patients (n = 14) received a 7-cm^2 clonidine transdermal patch (Catapres-TTS® #2), which was supplemented with oral doses of clonidine ~3 $\mu g \cdot kg^{-1}$ on the evening prior to surgery and on the morning of surgery. The high-dose clonidine group (n = 14) received a 10.5-cm^2 clonidine transdermal patch (Catapres-TTS® #3) with oral clonidine ~4.5 $\mu g \cdot kg^{-1}$ at bedtime and 6.0 $\mu g \cdot kg^{-1}$ on the morning of surgery. Placebo-treated (control) patients received the same occlusive patch without active ingredient and oral placebo tablets at bedtime and on the morning of surgery. Preanesthetic medication included midazolam 50 $\mu g \cdot kg^{-1}$ intramuscularly (im). Anesthesia was induced with alfentanil 30 $\mu g \cdot kg^{-1}$ intravenously (iv), thiopental 3 $mg \cdot kg^{-1}$ iv, and vecuronium 0.1 $mg \cdot kg^{-1}$ iv, and was maintained with 70% nitrous oxide in oxygen and a continuous infusion of alfentanil 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Isoflurane was added when the blood pressure exceeded 110% of the patient's prestudy value. For pain relief postoperatively, the patients received morphine, 1–2-mg iv boluses, *via* a patient-controlled analgesia pump. The low-dose clonidine patient group had mean plasma clonidine concentrations that varied from 1.47 $ng \cdot ml^{-1}$ (preoperative) to 1.32 $ng \cdot ml^{-1}$ (postoperative day 2). Patients in the high-dose clonidine group had mean clonidine concentrations that varied from 1.93 $ng \cdot ml^{-1}$ (preoperative) to 1.70 $ng \cdot ml^{-1}$ (postoperative day 2). Patients in the clonidine treatment groups (both high- and low-dose) were more sedated preoperatively, required significantly less volatile anesthetic intraoperatively to maintain hemodynamic stability, and self-administered less morphine for postoperative analgesia. In addition, the hemodynamic parameters were more stable intraoperatively in both clonidine-treated groups. This study demonstrates the utility and efficacy of oral–transdermal clonidine regimens as a perioperative adjunct in the anesthetic management of surgical patients undergoing major abdominal operations. (Key words: Anesthetic technique: transdermal. Clonidine: oral; transdermal. Sympathetic nervous system, α_2-adrenergic agonists: clonidine.)

CLONIDINE, AN IMIDAZOLINE COMPOUND, is a selective agonist for α_2 adrenoceptors with an α_2:α_1 selectivity ratio of approximately 200:1. This centrally active α_2 agonist was introduced more than 2 decades ago for the treatment of hypertension[1]; however, its sedative action was found to be a troubling side effect.[2,3]

The sedative quality of α_2 agonists can be used to advantage in the anesthetic paradigm, since these compounds also possess anxiolytic effects comparable to those reported with benzodiazepine compounds.[4] The addition of clonidine significantly decreases anesthetic requirements for both opioids[5] and volatile agents[6] and minimizes fluctuations in the hemodynamic profile during anesthetic induction.[7] Furthermore, the α_2-adrenergic agonists have long been known for their analgesic properties.[8]

Clonidine has been administered orally,[5] parenterally,[9] intrathecally,[10] and epidurally[11] in the perioperative period. With oral administration of clonidine, the onset of pharmacologic action occurs after 1.5–2 h[12]; the peak plasma concentrations are achieved within 3 h; and the elimination half-life is 8.5 ± 0.9 h (mean ± SEM).[13] More recently, clonidine has been evaluated as a rate-controlled transdermal patch to provide a more sustained effect.[14] The possible advantage of the transdermal route of clonidine administration, by application of a patch to the skin preoperatively, is the perioperative stability of the concentration of the drug. Also, since parenteral preparations of clonidine are not available in the United States, the transdermal preparation is useful in settings in which oral administration is contraindicated.

This study investigated the plasma concentrations of clonidine delivered *via* an oral–transdermal regimen and compared the effect of two different dosing schemes on preoperative sedation, perioperative hemodynamic variability, and anesthetic and postoperative analgesic requirements in patients undergoing abdominal surgery.

Materials and Methods

After institutional review and approval had been obtained, 45 consenting ASA physical status 1 and 2 patients

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scheduled for elective abdominal surgery were randomly assigned to one of three treatment groups according to a double-blind protocol design. Exclusion criteria included treatment with clonidine, α-methyldopa, β-adrenergic antagonists, tricyclic antidepressants, or opioids, and a history of an allergic reaction to any of the study drugs. In the placebo (control) group, patients received an inert transdermal occlusive patch and an oral placebo tablet, on the night before and 1 h prior to surgery. Patients in the low-dose clonidine group received a 7.0-cm^2 transdermal clonidine patch (Catapres-TTS® #2) and an oral dose of clonidine $\sim 3\ \mu g \cdot kg^{-1}$ at bedtime. On the morning of surgery, patients in the low-dose clonidine group received an additional dose of oral clonidine $\sim 3\ \mu g \cdot kg^{-1}$. Patients assigned to the high-dose clonidine group received a 10.5-cm^2 transdermal patch of clonidine (Catapres-TTS® #3) and oral clonidine $\sim 4.5\ \mu g \cdot kg^{-1}$ the night before surgery. One hour prior to surgery, patients received an additional oral dose of clonidine, $\sim 6\ \mu g \cdot kg^{-1}$. All patients received midazolam 50 $\mu g \cdot kg^{-1}$ intramuscularly 1 h prior to surgery.

Intraoperative monitoring included an intraarterial catheter for systemic blood pressure monitoring, ECG leads V5 and II, mass spectrometry for measurement of inspired and expired gas concentrations, esophageal temperature monitoring, and a pulse oximeter for measurement of hemoglobin oxygen saturation (Sp_{O_2}).

Anesthetic management consisted of alfentanil 30 $\mu g \cdot kg^{-1}$, thiopental 3 $mg \cdot kg^{-1}$, and vecuronium 0.1 $mg \cdot kg^{-1}$ for induction. Anesthesia was maintained with an alfentanil infusion 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and 70% nitrous oxide in oxygen. Neuromuscular blockade was maintained with vecuronium (1–3 mg as required). Isoflurane was administered to maintain the mean arterial pressure within 110% of the patient's preoperative value.

The alfentanil infusion was discontinued 10 min prior to the conclusion of surgery, and the residual neuromuscular blockade was reversed with neostigmine 0.07 $mg \cdot kg^{-1}$ and glycopyrrolate 0.01 $mg \cdot kg^{-1}$ iv. The transdermal patch was removed 48 h postoperatively.

The following assessments were made.

A) Degree of preoperative sedation was determined according to a five-point sedation scale:
   1) alert
   2) drowsy but easily aroused by verbal command to an alert state
   3) sleeping and arousable by verbal command
   4) sleeping not arousable by verbal stimuli, but arousable to a drowsy state by light tactile stimulation
   5) sleeping and difficult to arouse by tactile stimulation

B) Time to awakening from anesthesia was determined as the time from the discontinuation of the nitrous oxide until the time the patient first opened their eyes in response to a verbal command.

C) Intraoperative volatile anesthetic requirements were measured by the amount of isoflurane delivered per hour of surgery. Isoflurane concentration (v/v%) was continuously assessed by mass spectrometry of the expired gas and the area under the concentration *versus* time curve was integrated.

D) Postoperative analgesic requirements were assessed using a patient control analgesic (PCA) delivery system (Abbott LifeCare® pump) which the patient activated to deliver a preset bolus of morphine, 1 $mg \cdot ml^{-1}$. The initial PCA settings were: morphine bolus dose 2 mg at a lockout interval of 10 min with a four hour limit of 40 mg. If analgesia was consistently inadequate after 2 mg bolus doses, the morphine dose was increased by increments of 0.5 mg every ten minutes until adequate analgesia with minimal sedation was achieved. If sedation was excessive after the initial dose of 2 mg, the dose was decreased by 0.2 mg decrements until adequate analgesia without sedation was achieved.

E) Plasma clonidine concentrations were determined using a radioimmunoassay method[15] on blood sampled on the day of surgery (at the start of the operation), and subsequently on the first and second postoperative days. The sensitivity of this assay was 0.1 $ng \cdot ml^{-1}$ with a coefficient of variation of $\leq 15\%$.

F) Plasma alfentanil concentrations were determined using a standard radioimmunoassay technique[16] on blood samples collected just prior to discontinuation of the infusion. The sensitivity of this assay was 1.0 $ng \cdot ml$ with a coefficient of variation of $\leq 6\%$.

G) Perioperative complications were recorded (e.g. heart block, postoperative hypotension, contact dermatitis, rebound hypertension).

Parametric data were analyzed by analysis of variance (ANOVA) and subsequently by the unpaired t test with Bonferroni corrections for multiple comparisons. Nonparametric data (sedative scale) were analyzed with the Mann-Whitney U tests. A P value <0.05 was required to achieve statistical significance.

Results

Of the original 45 patients enrolled in this study, two patients were withdrawn (one from each of the clonidine treatment groups) because a decision was made during surgery to mechanically ventilate the lungs of these patients postoperatively. Of the remaining patients, there were no significant differences between groups with respect to age, gender, weight, ASA physical status, intraoperative fluid requirements, duration of surgery, or estimated blood loss (table 1) . Similar doses of thiopental,

TABLE 1. Patient Demographic Data

	Placebo	Clonidine	
		Low	High
n	15	14	14
Age (yr)	57 ± 16	66 ± 10	60 ± 7
Sex (M/F)	12/3	12/2	13/1
Weight (kg)	73 ± 13	79 ± 13	81 ± 11
ASA physical status			
1	2	3	0
2	13	11	14
Fluids (l)			
Crystalloid	4.4 ± 2.2	3.6 ± 2.0	3.6 ± 1.5
Blood	1.1 ± 1.9	0.9 ± 1.0	0.8 ± 0.8
Colloid	0.3 ± 0.5	0.2 ± 0.4	0.3 ± 0.3
Surgical duration (min)	205 ± 76	207 ± 90	199 ± 81
EBL (l)	1.7 ± 2.2	1.5 ± 1.1	1.4 ± 1.1

Mean ± SD.

TABLE 3. Effects of Clonidine

	Placebo	Clonidine	
		Low (n = 14)	High (n = 14)
Sedation (arbitrary scale)	1.8 ± 1.0	3.4 ± 0.9*	3.4 ± 1.3*
Isoflurane requirement (% v/v time integrated)	0.30 ± 0.24	0.11 ± 0.14*	0.08 ± 0.11*
Time to awakening (min)	11 ± 12	6 ± 5	5 ± 7
Morphine requirements (mg per 48 h)	102 ± 51	51 ± 29*	63 ± 47*
Plasma alfentanil (ng/ml)	84 ± 27	134 ± 37*	133 ± 53*

All values are mean ± SD.
* Significantly different from placebo.

alfentanil and vecuronium were administered to all three treatment groups. In the low-dose clonidine group, the mean plasma clonidine concentrations varied between 1.47 $ng \cdot ml^{-1}$ immediately preoperatively to 1.21 $ng \cdot ml^{-1}$ on postoperative day 1 (table 2). In the high-dose clonidine group, the mean plasma clonidine concentrations varied between 1.93 $ng \cdot ml^{-1}$ preoperatively to a low of 1.70 $ng \cdot ml^{-1}$ on postoperative day 1 (table 2).

Patients in both the low- and the high-dose clonidine groups were significantly more sedated than were those in the placebo group on arrival in the operating room (table 3) and required less supplemental isoflurane (table 3). However, there were no significant differences in the times to awakening in the three groups of patients (table 3). Both of the clonidine treatment groups had significantly lower mean arterial pressures before induction and had attenuated blood pressure responses to laryngoscopy and intubation. The high-dose clonidine group also had lower mean arterial pressures in the postanesthesia care unit (PACU) (fig. 1). Patients in the clonidine treatment groups had significantly lower heart rates at each time period measured, including preinduction, postinduction at the time of intubation, and arrival in the PACU (fig. 2). Placebo patients also had more variation in heart rate during surgery (fig. 3). PCA morphine requirements were significantly lower in the first 48 h in both clonidine treatment groups (table 3) than in the placebo group. Although similar total amounts of alfentanil were administered during the operations, plasma alfentanil concentrations were greater in the clonidine treatment groups at the end of surgery than in the placebo group (table 3).

The frequency of complications did not vary significantly among the three groups of patients. Specifically, none of the patients treated with the transdermal patch developed contact dermatitis or rebound hypertension after removal of the patch. Postural hypotension and/or bradycardic episodes requiring pressor or anticholinergic treatment occurred in two patients in the low-dose clonidine, one patient in the high-dose clonidine, and one patient in the placebo group. In each case, the bradycardic patients responded to treatment with one or two doses of glycopyrrolate 0.2 mg iv, and the hypotensive patient was successfully resuscitated with ephedrine 5.0 mg iv.

TABLE 2. Plasma Clonidine Concentrations

Dose	Preoperative	Postoperative Day	
		1	2
Low	1.47 ± 0.66	1.21 ± 0.55	1.32 ± 0.53
High	1.93 ± 0.76	1.70 ± 0.41	1.83 ± 0.38

All values are mean ± SD (nanograms per milliliter).

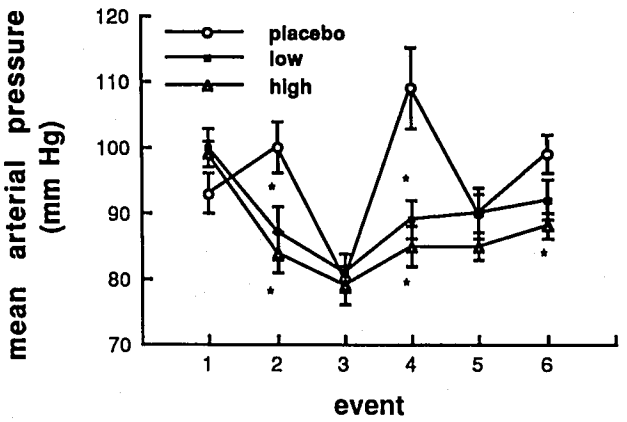

FIG. 1. Perioperative blood pressure. The highest mean arterial blood pressure at defined perioperative events are depicted for low- and high-dose clonidine-treated and for placebo-treated patients. The numbered events are as follows: 1 = ward; 2 = preinduction; 3 = postinduction; 4 = intubation; 5 = intraoperative; and 6 = postanesthesia care unit. Data were analyzed by ANOVA and subsequently by the unpaired *t* test with Bonferroni corrections for multiple comparisons. *Significantly different from placebo.

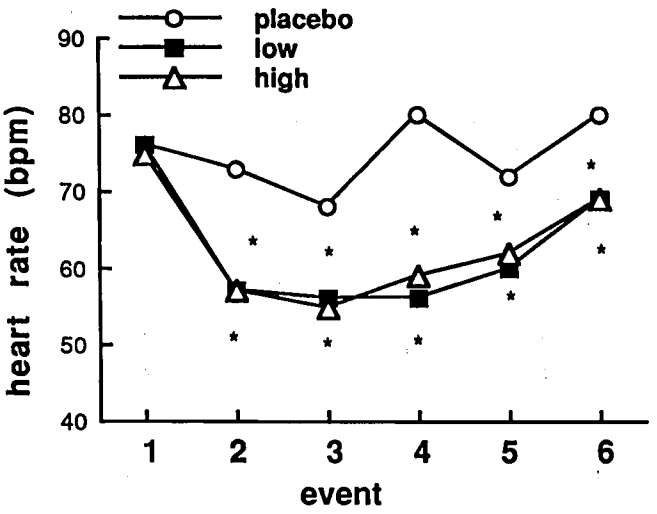

FIG. 2. Perioperative heart rate. The highest heart rate at defined perioperative events are depicted for low- and high-dose clonidine-treated and for placebo-treated patients. The numbered events are as follows: 1 = ward; 2 = preinduction; 3 = postinduction; 4 = intubation; 5 = intraoperative; and 6 = postanesthesia care unit. Data were analyzed by ANOVA and subsequently by the unpaired *t* test with Bonferroni corrections for multiple comparisons. *Significantly different from placebo.

Discussion

The two clonidine treatment regimens provided stable plasma concentrations of clonidine throughout the perioperative period (table 2) . These values are similar to those seen in hypertensive patients chronically treated with the same size patches.[17] Although patients in the high-dose clonidine group achieved a higher plasma clonidine concentration than that seen in the low-dose clonidine group, no additional advantages were obtained with respect to the variables measured. Clonidine-treated patients were more sedated on arrival into the operating room (table 3) , required less isoflurane to maintain the arterial blood pressure at desired levels (table 3) , exhibited more hemodynamic stability (fig. 3) , and required less postoperative analgesic therapy. When considered separately, the wake-up times of patients in each of the clonidine treatment groups were no different from those of the placebo group. However, the combined clonidine-treated groups had shorter wake-up times than did the placebo group, a difference that reflects the lower volatile anesthetic requirement. While variations in heart rate were less likely to occur in clonidine-treated patients, blood pressure variations in these groups did not differ significantly from those in the placebo group.

The higher concentrations of plasma alfentanil in the clonidine-treatment groups was unexpected. Possible explanations for this finding include a clonidine-induced decrease in liver blood flow, resulting in a decreased clearance of drugs (such as alfentanil) with a high extraction ratio.[18] Alternatively, the imidazole compound may interfere with P450 drug enzyme biotransformation[19] and thereby impair metabolism of alfentanil. From this study, it was not possible to distinguish the mechanism for the elevated plasma alfentanil concentrations in the clonidine-treated patients. We did not obtain plasma concentrations for morphine and thus were unable to determine whether the reduction in PCA analgesic requirements was due to a pharmacokinetic or to a pharmacodynamic interaction with clonidine. However, morphine has a low extraction ratio, and therefore, changes in hepatic blood flow are not likely to influence its biodisposition. Similarly, since midazolam blood concentrations were not obtained we cannot exclude the possibility that the clonidine-treated patients had higher midazolam plasma levels, which would contribute to the increased sedation reported during the preoperative period. Clonidine treatment decreased the volatile anesthetic requirements probably through a pharmacodynamic mechanism, given the unique pharmacokinetics of the inhaled anesthetics; however, the higher alfentanil concentrations in the clonidine-treated patients would be expected to decrease the requirement for isoflurane also.

Our findings are in agreement with those of Flacke *et al.*[5] and Ghignone *et al.*,[6,7] who demonstrated lower opioid analgesic and volatile anesthetic requirements in patients receiving preanesthetic medication with clonidine. Our data also confirm a recent demonstration of the analgesic-sparing effects of clonidine when administered to surgical patients postoperatively.[9] Our study, conducted in a double-blind fashion, found no additional benefit of the high

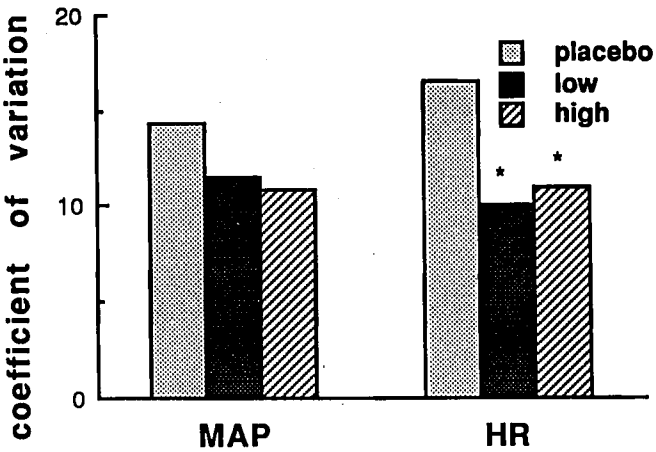

FIG. 3. Intraoperative variation in heart rate (HR) and mean arterial blood pressure (MAP). Heart rate and blood pressure were recorded every 5 min throughout the intraoperative period. The group variance (SD) was divided by the group mean to yield a coefficient of variation (expressed as a percentage) for low- and high-dose clonidine-treated and for placebo-treated patients. Data are analyzed by the unpaired *t* test with Bonferroni correction. *Significantly different from placebo.

dose over the low dose of clonidine; this finding suggests that the lower dose may be preferred since it is less likely to produce hypotension in the postoperative period (fig. 1).

The clonidine transdermal therapeutic system is a cutaneous delivery device that provides effective doses of clonidine at a constant rate over seven days.[17] After plasma concentrations have stabilized, transdermal clonidine has been found to be as effective as oral clonidine at providing blood pressure control.[20] Because clonidine may be clinically desirable for several perioperative days, the transdermal preparation provides a convenient method of achieving a stable long-lasting effect with this drug. Since it takes 48 h to achieve therapeutic concentrations when the patch is used by itself, an oral loading dose is necessary for most patients.

From a computer simulation[21] that plots time *versus* plasma concentration of clonidine after administration of oral doses in either the low- or high-dose regimens (fig. 4), one may appreciate that the higher levels observed are due to the addition of the transdermal preparation. Thus, it is likely that the initial effects (*e.g.*, preanesthetic sedation and intraoperative change in isoflurane supplementation) were due principally to the oral preparation, and that the later effects (*e.g.*, postoperative analgesia were due to the transdermal preparation (table 3). The intermediate effects (*e.g.*, perioperative hemodynamic stability [figs. 1–3]) were due probably to a combination of the two drugs.

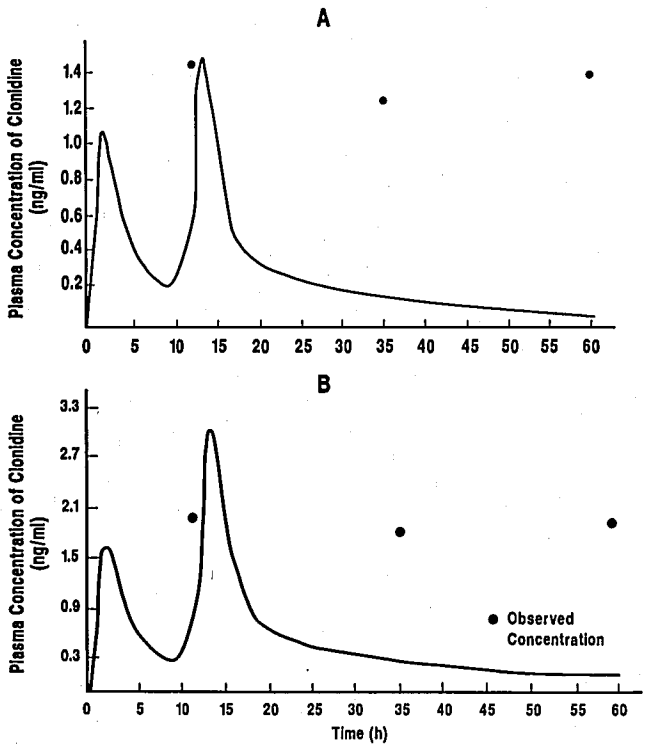

FIG. 4. Time *versus* plasma clonidine concentration. For the average patient in either the low- or high-dose regimen (*A* or *B*, respectively), computer-simulated plasma concentrations are plotted for the contribution from the oral clonidine preparation.[21] The mean plasma concentrations, which were observed at the different sampling times, are included for comparison.

It is noteworthy that no clinically significant sides effects (*e.g.*, postoperative hypotension, rebound hypertension) were seen. However, there are limited reports that rebound hypertension can occur in hypertensive patients after discontinuation of chronic transdermal clonidine.[22] Other side effects of transdermally delivered clonidine include contact dermatitis, which is present in approximately 19% of chronically treated patients.[20] In our study, no patients in the clonidine-treated groups developed dermatitis after the 3-day application.

Patients in the clonidine treatment group had significantly lower heart rates on arrival in the operating room. Although a low heart rate by itself is not cause for concern, in association with a significant decrease in blood pressure and/or cardiac output, it could prove to be a serious problem. Also, the advent of bradycardia in patients with a fixed stroke volume (*e.g.*, aortic stenosis) may be tolerated poorly. Clonidine is known to potentiate disturbances of atrioventricular conduction and of the sinus node; therefore, clonidine probably should not be used in patients with these conditions. Also, it is not known how transdermal drug delivery is affected in circumstances in which intravascular volume changes rapidly. One of the most consistent clinical effects of clonidine administration is the decrease in sympathetic nervous system activity.[23] Although in the surgical patient this may be considered a beneficial action, it may be detrimental in patients with hypovolemia or congestive cardiac failure, in whom the high circulating catecholamines compensate for the cardiovascular instability.

From the clinical anesthesiologist's point of view, there may be several desirable features of α_2-adrenergic agonist drugs. Clonidine has been found to diminish shivering in postoperative surgical patients.[24] Also, opioid-induced rigidity in rats is prevented by pretreating with potent α_2-adrenergic agonists[25]; this finding, however, has not yet been corroborated in clinical studies. Ghignone and colleagues examined the clinical effect of oral premedication with clonidine (*versus* diazepam) in an elderly ophthalmologic surgical population.[26] The rise in intraocular pressure seen with endotracheal intubation was attenuated in the clonidine-treated patients.[26] A decrease in intraocular pressure is not useful except in patients with glaucoma; however, changes in intraocular pressure may reflect changes in intracranial pressure.[27] Xerostomia (dry mouth), a troubling side effect of α_2-adrenergic agonists chronically prescribed for the management of hypertension, may be desirable in the preoperative surgical patient.

Also, it appears that clonidine and other α_2-adrenergic agonists may enhance renal blood flow, inhibit antidiuretic hormone (ADH) release, and block the effect of ADH on tubular function, and thereby promote a diuresis.[28]

The clinical utility of α_2-adrenergic agonists in veterinary anesthetic practice has been enhanced by the availability of more selective agonists[29] and antagonists.[30] The greater selectivity of the agonists has facilitated even greater reductions in anesthetic requirements, while the more selective antagonists can be used to specifically reverse the anesthetic action of the α_2-adrenergic agonist.[31] If these applications can be successfully implemented in humans, this class of compounds may represent a significant addition to the anesthesiologist's's pharmacopoeia.

In summary, the perioperative use of two clonidine regimens containing both an oral loading dose and a transdermal maintenance dose may significantly benefit ASA physical status 1 and 2 surgical patients undergoing intraabdominal operations.

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