

## Epidural Clonidine Analgesia for Intractable Cancer Pain: Phase I

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Intrathecaly administered clonidine has been reported to produce analgesia in cancer patients tolerant to intrathecal opiates. To assess the efficacy, safety, and appropriate dose of epidurally administered clonidine for the treatment of cancer pain, clonidine (range, 100–900  $\mu$ g in 100- $\mu$ g increments) was injected in nine patients with severe, intractable cancer pain. Clonidine produced analgesia, as measured by change in verbal pain scores, lasting more than 6 h. Clonidine also decreased blood pressure, although this effect was well tolerated and no patient met criteria for receiving iv ephedrine ( $>30\%$  decrease in mean arterial pressure not responsive to 500 ml iv crystalloid infusion). Clonidine decreased heart rate 10–30% and produced transient sedation. Serum glucose and cortisol and oxyhemoglobin saturation were not altered by clonidine. Clonidine was absorbed in a dose-dependent manner into the systemic circulation, although absorption and elimination kinetics were highly variable. Following study seven patients received epidural clonidine/morphine infusions at home for periods of up to 5 months with sustained analgesia. These results suggest that epidurally administered clonidine may offer effective analgesia in patients with severe, intractable cancer pain. (Key words: Anesthetic techniques: epidural. Pain: cancer. Sympathetic nervous system, alpha-adrenergic agonist: clonidine.)

ALTHOUGH pain commonly accompanies cancer, most cancer patients achieve satisfactory pain relief with orally administered analgesics or intraspinaly administered opioids. In some patients, however, tolerance to opioids develops, leading to loss of effectiveness or therapy-limiting side effects, whereas in others, tumor destruction of nerves leads to neurogenic pain syndromes that are poorly responsive to opioids.<sup>1,2</sup> For these small groups of patients, the only current recourse may be neurolytic therapy, which may be ineffective and leads to considerable morbidity.

In this study we examine a novel approach to pain therapy for these patients: epidural clonidine injection. Preclinical toxicity testing of clonidine is reasonably complete.<sup>3</sup> Animal data suggest that clonidine is safe,<sup>4–6</sup> but that it may, depending on route of administration, produce side effects. These include hypotension and brady-

cardia (intrathecal  $>$  epidural  $>$  iv), hyperglycemia (epidural, iv), decreased serum cortisol (epidural), sedation (all routes), and hypoxemia (iv).<sup>7–9</sup> Previous studies of intraspinaly applied clonidine in cancer patients consist of isolated case reports or small series<sup>10–14</sup> and do not address possible toxicities suggested by animal research. In this study using an open-label, dose-ranging design, we examine the analgesic, neurologic, hemodynamic, respiratory, and hormonal effects of epidural clonidine (100–900  $\mu$ g) in patients with intractable cancer pain.

### Materials and Methods

The Clinical Research Practices Committee approved the protocol, all patients gave written informed consent, and clonidine was supplied under an Investigational New Drug from the FDA. Nine ASA physical status 3 or 4 patients with metastatic cancer accompanied by pain and tolerant to oral or epidural opioids were studied. Patients with diabetes mellitus, neurologic disease, angina, congestive heart failure not stable on current medications, pulmonary disease requiring therapy, or poorly controlled hypertension were excluded. In addition, patients weighing over 250 pounds, older than 70 yr, or taking tricyclic antidepressants or  $\alpha_2$ -adrenergic agonists were excluded.

In patients without a surgically implanted epidural catheter, a lumbar epidural catheter was inserted percutaneously and tested with injection of 1.5% lidocaine with epinephrine. Epidural opioid therapy was discontinued at least 12 h prior to study, and supplemental analgesia was provided throughout the study period by patient-controlled analgesia (PCA) with iv morphine. Patients received three escalating doses of epidural clonidine in 100- $\mu$ g increments on consecutive days. The first three patients received 100–300  $\mu$ g, the next three 400–600  $\mu$ g, and the last three 700–900  $\mu$ g epidural clonidine.

Patient demographic data were recorded and blood obtained for clonidine, cortisol, and glucose analysis before and 1 h after injection. Cortisol concentrations were determined by a specific radioimmunoassay<sup>15</sup> and glucose concentrations were determined using a Beckman<sup>TM</sup> glucose analysis system. In addition, plasma samples were obtained at specified intervals for 6 h following each clonidine injection for estimation of pharmacokinetic parameters. Clonidine concentrations were determined by radioimmunoassay with minimal detectable concentration of 0.05 ng/ml and intraassay and interassay variations of 7% and 11%, respectively.<sup>16</sup> Morphine use, sedation (5–

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point scale: 1 = wide awake, 2 = drowsy, 3 = dozing intermittently, 4 = mostly sleeping, 5 = awakens only when aroused),<sup>17</sup> pain (10 cm visual analog pain intensity scale), neurologic function (mental status, sensation, deep tendon reflexes), presence of pruritus and nausea, blood pressure, and heart rate were monitored at specified intervals for 6 h following injection. A decrease in mean arterial blood pressure > 30% not responsive to 500 ml iv crystalloid fluid administration was to be treated with ephedrine, 5 mg iv. Oxyhemoglobin saturation was continuously monitored by pulse oximetry. Following completion of the protocol, two patients died within days from complications of their cancer. The remaining seven patients received clonidine under a compassionate use basis until their death. Clonidine was combined with morphine and provided by continuous infusion plus demand bolus *via* an external pump connected to the epidural catheter *via* an external or sc port. During this period only drug usage and adverse reactions were recorded. Analgesia was not systematically examined.

Because the purpose of this study was to provide initial data addressing several safety and efficacy issues, statistical methods used were primarily descriptive. For clarity, data following injection of small (100–300  $\mu$ g), intermediate (400–600  $\mu$ g), and large (700–900  $\mu$ g) doses of clonidine were combined, and group comparisons were performed. Note that there were three patients in each dose range, each of whom received three separate injections, yielding nine data points per dose range. Data are presented as mean  $\pm$  SEM. Pain, hemodynamic, and morphine use data were compared among groups using one-way analysis of variance (ANOVA) and within groups using two-way ANOVA. Serum clonidine pharmacokinetic parameters were determined using PCNONLIN (Statistical Consultants, Inc., Lexington, Kentucky). Time *versus* clonidine concentrations were fit to a one-compartment model, with first order absorption and elimination. Pharmacokinetic

parameters [elimination ( $t_{1/2el}$ ) absorption ( $t_{1/2ab}$ ) half-times and time to maximal concentration ( $T_{max}$ )] were determined according to standard equations. Noncontinuous variables were compared using either Fisher's exact test or chi-square test.  $P < 0.05$  was considered significant.

## Results

Five of the patients were female and four were male. All patients had extensive metastases, and all had experienced increasing pain despite escalation of systemic or epidural opioid dose (table 1). Their age was  $54 \pm 5$  yr, height  $170 \pm 3$  cm, and weight  $62 \pm 4.6$  kg. Pain character was primarily somatic in six patients (chest wall or lower back), neurogenic in two patients (brachial plexus), and visceral in one patient (hepatic). Three patients had a history of hypertension, and two of these were receiving antihypertensive therapy.

Epidurally administered clonidine produced analgesia, as measured by pain scores, and there was a clear, dose-dependent reduction by clonidine in the average pain score during the 6-h study (table 1; fig. 1). Morphine use by PCA was variable and did not correlate with either clonidine dose or pain score (table 1). Onset of analgesia was within 20 min of injection, and duration (defined as time of reduced pain score) was greater than 6 h in each group. Clonidine produced effective analgesia in both patients with neurogenic pain (table 1). Sedation was marked and long-lasting following large clonidine doses (fig. 2).

Mean arterial blood pressure prior to clonidine injection was similar in all groups:  $101 \pm 4$  mmHg (100–300  $\mu$ g),  $99 \pm 4$  mmHg (400–600  $\mu$ g), and  $94 \pm 5$  mmHg (700–900  $\mu$ g). Blood pressure prior to injection was not different on each of the 3 days for any of the groups (for all groups blood pressure was  $96 \pm 4$  mmHg on day 1,  $103 \pm 3$  mmHg on day 2, and  $95 \pm 5$  mmHg on day 3). All doses of clonidine decreased blood pressure, although

TABLE 1. Patient Characteristics and Analgesic Response to Clonidine

Clonidine Dose ( $\mu$ g)	Patient No.	Cancer Location	Daily Morphine Dose (mg)	Route	Visual Analog Pain†		PCA iv Morphine Use during Study‡ (mg)
					Before	After	
100–300	1	Lung	120	Epidural	4.0	1.3	4.7
	2	Breast*	120	Oral	6.3	1.3	15.6
	3	Cervix	96	Oral	3.3	1.7	4.3
400–600	4	Breast	180	Oral	7.0	1.0	3.0
	5	Breast	360	Oral	3.7	0	15.3
	6	Breast*	72	Epidural	4.3	0	25.3
700–900	7	Thymoma	120	iv	1.7	0	0.0
	8	Lung	48	iv	5.3	0	4.7
	9	Melanoma	120	sc	3.3	0	26.0

\* Patients with neurogenic pain.

† Visual analog scores represent the mean of three injections per patient before clonidine injection and at the time of peak effects fol-

lowing clonidine injection.

‡ PCA morphine use for the 6-h study represents the mean of three injections per patient.

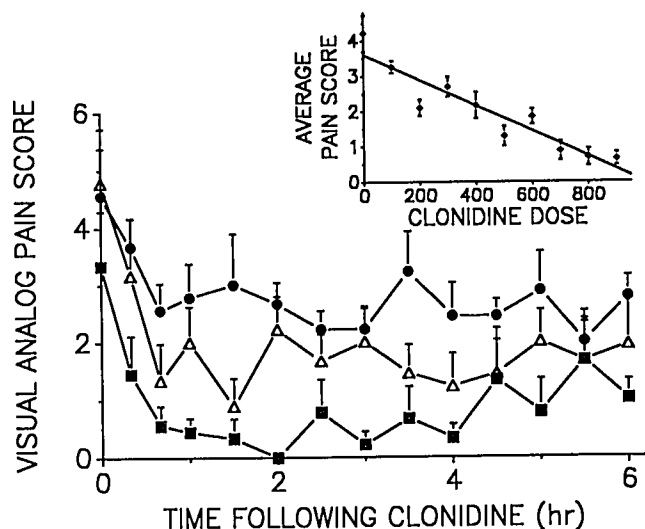


FIG. 1. Pain scores following epidural injection of clonidine, 100–300  $\mu\text{g}$  (●), 400–600  $\mu\text{g}$  (Δ), and 700–900  $\mu\text{g}$  (■). Each point represents the mean  $\pm$  SEM of nine determinations (three patients at each of the three dose levels within each range). A time-dependent effect is present in all groups ( $P < 0.05$ , one-way ANOVA). (Inset) Average pain score over the 6-h study period following clonidine injection. Each point represents the mean  $\pm$  SEM of 39 determinations. Solid line is first order linear regression ( $r = 0.93$ ). The slope is different from zero ( $P < 0.001$ ).

this effect was attenuated following large doses (fig. 3; table 2). The magnitude of blood pressure decrease was numerically greater in patients with hypertension than in those without (fig. 3, inset), although this difference was not significant.

Heart rate prior to clonidine injection in the groups was  $86 \pm 6$  (100–300  $\mu\text{g}$ ),  $98 \pm 8$  (400–600  $\mu\text{g}$ ), and  $95 \pm 5$  (700–900  $\mu\text{g}$ ). Heart rate was not different on each

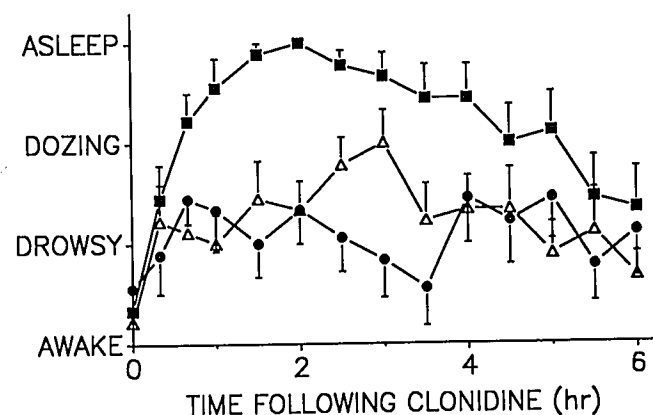


FIG. 2. Sedation following epidural injection of clonidine, 100–300  $\mu\text{g}$  (●), 400–600  $\mu\text{g}$  (Δ), and 700–900  $\mu\text{g}$  (■). Terms on Y-axis refer to sedation scores of 1, 2, 3, and 4. Each point represents the mean  $\pm$  SEM of nine determinations. A time-dependent effect is present in all groups ( $P < 0.05$ , one-way ANOVA).

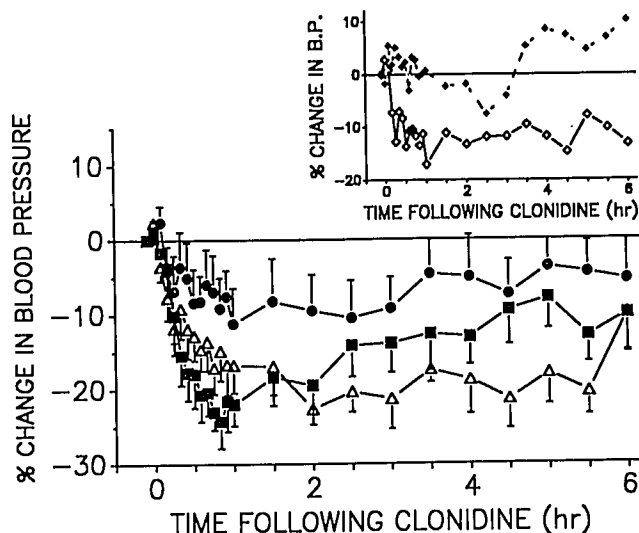


FIG. 3. Change in mean arterial pressure following epidural injection of clonidine, 100–300  $\mu\text{g}$  (●), 400–600  $\mu\text{g}$  (Δ), and 700–900  $\mu\text{g}$  (■). Each point represents the mean  $\pm$  SEM of nine determinations. A time-dependent effect is present in all groups ( $P < 0.05$ , one-way ANOVA). (Inset) Change in mean arterial pressure following epidural injection of clonidine, 100–300  $\mu\text{g}$ , in two patients with hypertension (◇) and in one without (♦). Each point represents the mean of 3–6 determinations.

of the 3 days for any of the groups (for all groups heart rate was  $96 \pm 4$  on day 1,  $89 \pm 4$  on day 2, and  $94 \pm 3$  on day 3). All doses of clonidine decreased heart rate (fig. 4). Maximal change in heart rate occurred later than maximal change in blood pressure, and was more variable in timing (table 2). This effect did not require treatment.

Clonidine did not alter serum glucose or cortisol (table 3), and no patient experienced pruritus or nausea following clonidine injection. Pharmacokinetic parameters in plasma were variable (fig. 5). Despite accumulation of clonidine in serum in some patients, this accumulation did not alter baseline hemodynamic parameters. Seven of the

TABLE 2. Maximal Hemodynamic Changes Following Epidural Clonidine Injection

Parameter	Dose ( $\mu\text{g}$ )	Maximal Change (%)	Time of Maximal Change (min)
Blood pressure	100–300	$-18 \pm 4.2$	$83 \pm 14$ (range 0–240)
	400–600	$-31 \pm 2.6^*$	
	700–900	$-28 \pm 3.1^*$	
Heart rate	100–300	$-15 \pm 2.0$	$131 \pm 17$ (range 15–360)
	400–600	$-25 \pm 2.5^*$	
	700–900	$-24 \pm 2.0^*$	

All groups differ from baseline.  
\*  $P < 0.05$  versus 100–300  $\mu\text{g}$ .

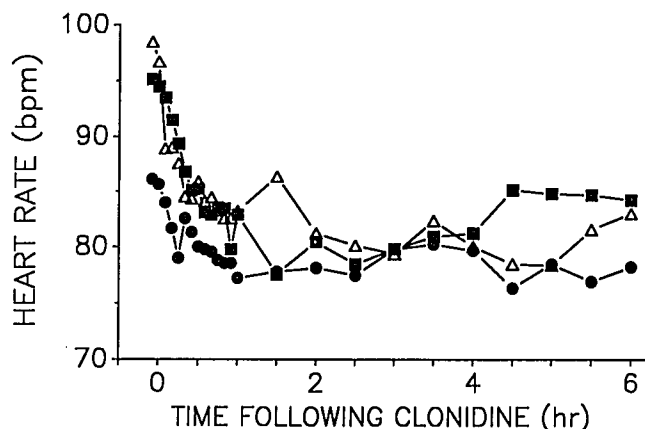


FIG. 4. Heart rate following epidural injection of clonidine, 100–300  $\mu\text{g}$  (●), 400–600  $\mu\text{g}$  (Δ), and 700–900  $\mu\text{g}$  (■). Each point represents the mean of nine determinations. A time-dependent effect is present in all groups ( $P < 0.05$ , one-way ANOVA).

patients were discharged from the hospital following study and received epidural clonidine/morphine infusions at home, for periods up to 5 months, until their death. Several patients reported improved pain relief with less nausea and sedation during this period compared with the time prior to clonidine use. Patients also reported good analgesia during this time with no or minimal escalation of clonidine or morphine dose, except in one patient who reported severe pain for 2 days prior to her death (fig. 6).

### Discussion

Phase I trials in the FDA process of drug development are generally open-label, dose-ranging in nature, with emphasis on defining safety of the new agent or route of administration.<sup>18</sup> This study, although performed in a small number of patients and descriptive in nature, represents the first systematic examination of analgesic efficacy of epidurally administered clonidine in cancer patients with chronic pain. Other reports have consisted of single dose studies, isolated case reports, or have been extremely limited in scope.<sup>10–14</sup> In contrast, the current

TABLE 3. Serum Analyses Following Epidural Clonidine Injection

	Dose ( $\mu\text{g}$ )		
	100–300	400–600	700–900
Glucose (mg/dl)			
Before	159 $\pm$ 9	101 $\pm$ 6	111 $\pm$ 39
After	143 $\pm$ 8	101 $\pm$ 5	137 $\pm$ 49
Cortisol ( $\mu\text{g/dl}$ )			
Before	17.2 $\pm$ 2.5	16.6 $\pm$ 1.8	20.1 $\pm$ 7.1
After	14.3 $\pm$ 2.3	14.3 $\pm$ 2.3	18.9 $\pm$ 5.8

There are no significant differences following injection.

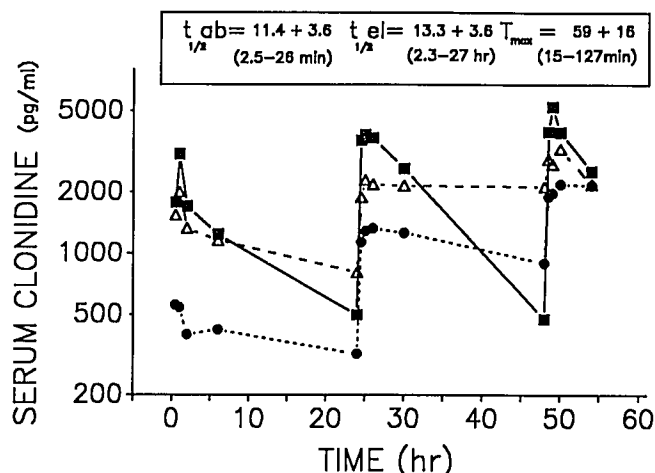


FIG. 5. Serum clonidine concentrations following serial injections at times 0, 24, and 48 hours, of clonidine, 100, 200, and 300  $\mu\text{g}$  (●), 400, 500, and 600  $\mu\text{g}$  (Δ), and 700, 800, and 900  $\mu\text{g}$  (■). Each point represents the mean of three patients. (Inset) Pharmacokinetic parameters of  $t_{1/2ab}$ ,  $t_{1/2el}$ , and  $T_{max}$ . Values are expressed as mean  $\pm$  SEM, with ranges given below.

study describes analgesia and hemodynamic and hormonal side effects following a wide range of clonidine doses. These data provide the basis for subsequent placebo-controlled, double-blind studies.

### ANALGESIA

Assessing efficacy and duration of a new analgesic agent in cancer patients is difficult. Although use of PCA for supplemental analgesia may provide an estimate of the new agent's efficacy and ethically allows dose-ranging, PCA usage may reflect other factors besides level of pain. Highly variable PCA usage in this study following clonidine injection, despite patient reports of minimal or no pain, suggests that other factors, such as prevention of opioid withdrawal symptoms, may have been present.

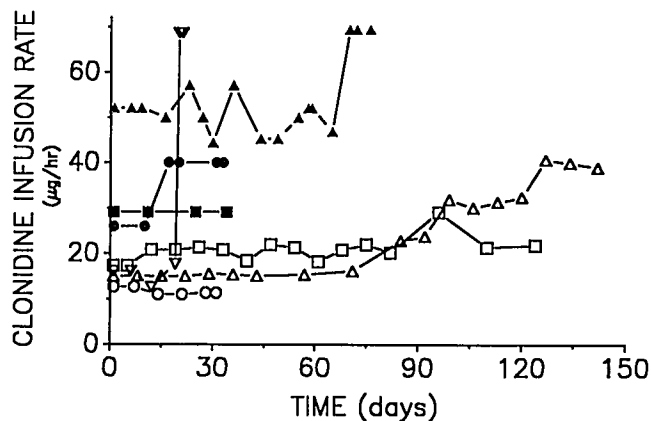


FIG. 6. Hourly clonidine infusion rates in seven patients receiving continuous plus PCA epidural clonidine.

Lack of placebo control and study blinding, although appropriate for Phase I testing, may result in overestimation of the new agent's efficacy. Nonetheless, the consistent reduction in pain scores following clonidine injection and sustained improvement in pain relief following chronic infusion argue strongly for clonidine's analgesic efficacy.

Several aspects of clonidine's action are relevant to its use in cancer patients with intractable pain. First, because clonidine produces analgesia by a nonopioid mechanism,<sup>4</sup> in theory, it should be effective in individuals tolerant to opioids. Preliminary clinical trials have indeed supported that hypothesis.<sup>10,11,14</sup> Although the degree of cross-tolerance between intraspinally applied opioids and clonidine in animals is controversial,<sup>4,19-21</sup> our results agree with others<sup>10,11,14</sup> that intraspinal clonidine administration produces effective analgesia in patients tolerant to opioids. Second, although intraspinal opioid administration represents a clear advance in chronic pain therapy, it is not effective for all types of pain. Specifically, neurogenic or deafferentation pain syndromes, which may occur in advanced cancer, are poorly responsive to opioids,<sup>1,2</sup> perhaps due to unique neurophysiologic mechanisms in the spinal cord. Our results agree with others<sup>22-24</sup> that intraspinal clonidine administration appears to be effective in patients with neurogenic pain. Third, this and other studies<sup>4,14,22,23</sup> suggest that clonidine is unlikely to produce side effects common to opioids (pruritus, nausea, respiratory depression) and avoids concern by patients of becoming addicted to a controlled substance.

#### SIDE EFFECTS

In humans the main side effect following intraspinal clonidine injection is hypotension,<sup>11,14,22,25-27</sup> and this effect may limit therapy in cancer patients receiving intrathecally administered clonidine.<sup>11</sup> Because clonidine may increase blood pressure by a peripheral action,<sup>28</sup> hypotension can be lessened by increasing plasma concentrations, either by increasing intrathecal dosage<sup>11</sup> or by epidural administration.<sup>8,29</sup> As observed in this study, preexisting hypertension exaggerates the decrease in blood pressure following systemic<sup>30</sup> or epidural<sup>29</sup> clonidine injection. Rebound hypertension may occur with abrupt cessation of clonidine following chronic use, but this was not examined in this or other protocols involving intraspinal clonidine.

Clonidine decreases heart rate by direct cardiac as well as central mechanisms, and may decrease velocity through cardiac conduction systems.<sup>31</sup> The former effect is minor and well tolerated, whereas the latter effect may produce dangerous dysrhythmias in patients with preexisting conduction system disturbances or taking drugs that alter cardiac electrophysiology.<sup>29,32</sup> These factors should be assessed prior to instituting epidural clonidine therapy.

Clonidine may increase serum glucose by inhibiting insulin release,<sup>33</sup> decrease stress-induced adrenocorticotrophic hormone (ACTH) release,<sup>34</sup> and hence cortisol release, and in sheep produce hypoxemia.<sup>7</sup> However, serum glucose, cortisol, and arterial oxyhemoglobin saturation were unaffected by clonidine in our patients, in agreement with other studies of chronic systemic<sup>35</sup> and acute epidural<sup>29</sup> administration.

#### PHARMACOKINETICS

Detailed pharmacokinetic analyses of epidurally administered clonidine have been performed in sheep<sup>8</sup> and pigs,<sup>36</sup> and preliminary results reported in humans.<sup>37,38</sup> In agreement with these reports, epidurally administered clonidine is slowly absorbed into the systemic circulation, perhaps due to slow release from epidural fat, and peak concentrations in plasma may not occur until more than 1 h following injection. Maximal serum clonidine concentrations following large doses (700–900  $\mu$ g) may limit hypotension by producing peripheral vasoconstriction.<sup>39</sup> Clonidine's prolonged plasma elimination half-life observed in this and other studies<sup>37</sup> suggests that accumulation of clonidine in serum may occur with prolonged epidural infusions. In contrast, clonidine's short elimination half-life in cerebrospinal fluid (CSF) (43 min)<sup>37</sup> suggests that accumulation in CSF is unlikely.

In summary, epidural clonidine administration represents a new analgesic approach for cancer patients with intractable pain. This protocol was clearly not designed to examine all possible toxicities of epidural clonidine injection. However, over a dose range of 100–900  $\mu$ g, clonidine-induced side effects were minor, and side effects common to epidural opioids (pruritus, nausea, urinary retention) were not noted in this small sample size. Sedation was transient, and did not limit long-term therapy in cancer patients. Although experience with the seven patients receiving chronic morphine clonidine infusions suggests excellent, sustained analgesia, this result needs to be tested systematically in large multicenter studies.

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