

## Effect of Epidural Clonidine on Analgesia and Pharmacokinetics of Epidural Fentanyl in Postoperative Patients

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Epidural clonidine produces postoperative analgesia in patients and potentiates opioid analgesia in animals. The aim of the current study was to assess the effect of epidural clonidine on the plasma concentrations and analgesic effect of fentanyl after epidural administration. Twenty ASA physical status 2 or 3 patients recovering from abdominal surgery were allocated randomly to receive either epidural fentanyl (100  $\mu\text{g}$  in 10 ml isotonic saline; EF group) or epidural fentanyl (same dose) plus epidural clonidine (150  $\mu\text{g}$ ; EF+C group) in isotonic saline solution. Analgesia was assessed over a period of 12 h after epidural injection. Venous samples were obtained until 360 min after epidural injection for radioimmunoassay determination of plasma fentanyl concentration. Onset of analgesia was similar in the two groups of patients ( $13 \pm 6$  and  $13 \pm 3$  min, respectively, after injection), but duration was more than doubled in the patients receiving clonidine ( $543 \pm 183$  vs.  $250 \pm 64$  min). Peak plasma fentanyl concentrations ( $F_{\text{max}}$ ) and the time to reach  $C_{\text{max}}$  ( $T_{\text{max}}$ ) were comparable in the two groups ( $0.29 \pm 0.15$  ng  $\cdot$  ml $^{-1}$  at  $16.2 \pm 14.8$  min in the EF group and  $0.27 \pm 0.11$  ng  $\cdot$  ml $^{-1}$  at  $8.3 \pm 5.5$  min in the EF+C group), as were plasma concentrations at each definite time of measurement. Drowsiness and hypotension were noticed in the EF+C group. Thus, epidural clonidine appears to prolong epidural fentanyl analgesia without affecting its plasma concentration. (Key words: Analgesics: opioids; fentanyl. Anesthetic techniques: epidural. Sympathetic nervous system,  $\alpha_2$ -adrenergic agonist: clonidine.)

EPIDURAL CLONIDINE produces effective analgesia in postoperative patients.<sup>1-5</sup> Nevertheless, the duration of action of clonidine is limited, and side effects such as drowsiness and hypotension are common.<sup>1-5</sup> Spinal clonidine enhances opioid-induced analgesia in laboratory animals.<sup>6-8</sup> Therefore, the combination of spinal or epidural opioid with clonidine may be an attractive alternative for postoperative analgesia. It is well documented that the agonist action of clonidine on  $\alpha_2$  adrenergic receptors of the spinal cord is responsible for its analgesic effect.<sup>9,10</sup> In addition,  $\alpha_2$  agonist agents are able to induce vasoconstriction.<sup>11</sup> When administered epidurally, clo-

nidine may enhance the effect of epidural fentanyl by one or both of these two mechanisms. Therefore, the current study was designed to assess the analgesic effect of epidural clonidine combined with epidural fentanyl and to evaluate the consequences of epidural administration of clonidine on plasma fentanyl concentrations.

### Materials and Methods

Informed consent and approval from our institutional Ethics Committee were obtained. Twenty ASA physical status 2 or 3 patients recovering from abdominal aorta surgery were included in the study. Surgery was performed under epidural anesthesia combined with general anesthesia. Epidural catheters were inserted at the T12-L1 or L1-L2 level. The anesthetic agents administered were 0.5% bupivacaine, thiopental, nitrous oxide 50% in oxygen, and isoflurane. Fentanyl 100  $\mu\text{g}$  was injected intravenously before orotracheal intubation; no additional opioid was given thereafter. Postoperatively, patients' vital signs were monitored in an intensive care unit. Before the study was begun, patients had recovered fully from the bupivacaine-induced sensory and motor blockade. We considered recovery complete when no fade in tactile sensation could be discerned and when patients moved their lower limbs freely. Patients were fully conscious and were breathing spontaneously when the study began. In all patients a nasogastric tube and a bladder catheter had been inserted.

At the first complaint of pain during recovery from blockade, each patient rated his or her pain on a visual analog scale (VAS) graded from 0 (no pain) to 10 (maximum pain).<sup>12</sup> Patients were randomly assigned to receive an epidural injection of 100  $\mu\text{g}$  fentanyl (EF group) in a 10  $\mu\text{g} \cdot$  ml $^{-1}$  isotonic saline solution administered in 2-3 min or 100  $\mu\text{g}$  fentanyl plus 150  $\mu\text{g}$  clonidine in an equivalent volume of isotonic saline (EF+C group). The pain score was assessed by an independent observer and recorded every 5 min for 15 min and every 15 min for 1 h after epidural fentanyl or fentanyl plus clonidine injection and then every 30 min for 11 h.

At the first complaint of pain after injection of fentanyl or fentanyl plus clonidine, patients were given an intravenous injection of 1 g paracetamol. Pain scores after paracetamol were not included in analysis.

To measure the analgesic effects in each patient by the

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Received from the Département d'Anesthésie, Hôpital Henri Mondor, Créteil, France. Accepted for publication May 6, 1991. Presented in part at the Annual Meeting of the American Society of Anesthesiologists, Las Vegas, Nevada, October, 1990.

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percent reduction in pain after epidural fentanyl or fentanyl plus clonidine injection, we used the equation<sup>13</sup>:

Pain reduction (%)

$$= \frac{\text{initial VAS score} - \text{EF or EF+C VAS score}}{\text{initial VAS score}} \times 100$$

where the initial VAS score is the value recorded before injection of fentanyl or fentanyl plus clonidine, and the EF or EF+C VAS score represents the pain score for each patient after administration of fentanyl or fentanyl plus clonidine. We considered the duration of analgesia to be the time elapsed between drug administration and the first paracetamol injection.

Patients received a 5-ml/min Ringer's lactate infusion during the study. We measured arterial blood pressure and heart rate before and every 5 min during the study with an automatic blood cuff (Dinamap,<sup>®</sup> Critikon). Hypotension was treated by intravenous colloid infusion and then by intravenous ephedrine bolus when mean arterial blood pressure decreased by more than 25% of control value or when systolic arterial pressure was lower than 90 mmHg. We also monitored expired carbon dioxide partial pressure and respiratory rate with a capnograph (Capnomac,<sup>®</sup> Datex) connected to a nasopharyngeal cannula and arterial hemoglobin saturation (SpO<sub>2</sub>) with a pulse oximeter (Nellcor 200<sup>®</sup>) for 360 min. If SpO<sub>2</sub> became < 93%, 3 l·min<sup>-1</sup> oxygen was administered via a pharyngeal cannula and the corresponding values of expired carbon dioxide pressure were not included in analysis.

Blood samples for determination of plasma fentanyl concentrations were collected in heparin tubes via a venous catheter immediately before and at 5, 10, 15, 20, 25, 30, 40, 60, 90, 120, 180, 240, and 360 min after epidural fentanyl injection. Blood samples were centrifuged at 4° C and 3,000 rpm and plasma frozen at -30° C before analysis. Fentanyl concentrations were determined by radioimmunoassay technique<sup>14,15</sup> (developed in the Department of Biochemistry and Medical Chemistry, Janssen) with a minimum detected concentration of 0.1 ng/ml. The intra- and interassay coefficients of variance were 3%. We plotted plasma concentration versus time for each sampling interval. Peak plasma fentanyl concentrations were identified as F<sub>max</sub> and the time to reach peak concentrations as T<sub>max</sub>.

TABLE 1. Patient Characteristics

Group	Sex (M/W)	Age (yr)	Weight (kg)	Height (cm)
Epidural fentanyl	9/0	63 ± 11	69 ± 13	167 ± 8
Epidural fentanyl + clonidine	6/3	63 ± 15	67 ± 17	164 ± 5

Data are means ± SEM.

TABLE 2. Features of Epidural Fentanyl Analgesia

Group	Pain Assessment before Clonidine Administration (VAS score)	Maximum Pain Relief (%)	Duration of Action (min)
Epidural fentanyl	6.0 ± 1.0	93 ± 15	250 ± 64*
Epidural fentanyl + clonidine	6.1 ± 1.2	85 ± 22	543 ± 183*

Data are means ± SEM.

\* P < 0.05, intergroup comparison.

Whenever homogeneous variance between the groups was not verified, a nonparametric analysis (the Mann-Whitney test) was performed for comparing the two groups. Mean arterial blood pressure, heart rate, respiratory rate, expired carbon dioxide concentrations, and SpO<sub>2</sub> data were analyzed using a two-way analysis of variance for repeated measurements and Student's *t* test. VAS scores were analyzed using a Mann-Whitney test. Durations of analgesia in the two groups were compared using the Kaplan-Meier method and a log-rank test. Differences were considered significant when P < 0.05.

### Results

Our study groups were similar in age, weight, height, and sex ratio (table 1). The study was conducted on the first postoperative day. VAS scores before epidural fentanyl administration were high (table 2). Epidural fentanyl administration was performed 645 ± 85 and 690 ± 105 min after the end of surgery in the EF and the EF+C groups, respectively. Onset of analgesia was apparent after 13 ± 6 min in the EF patients and after 13 ± 3 min in the EF+C patients (figs. 1 and 2). The maximum reduc-

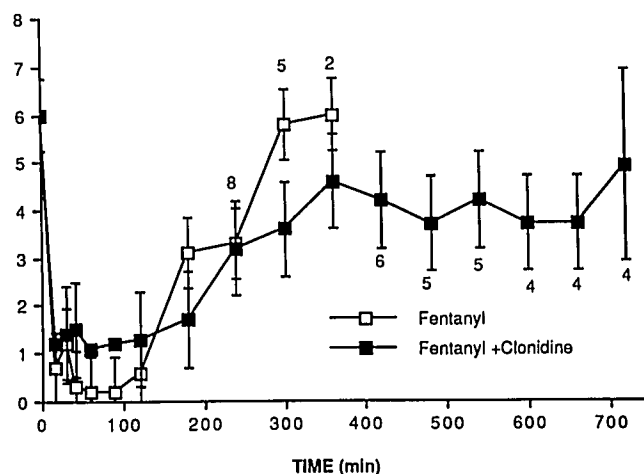


FIG. 1. Changes in VAS score until 700 min after epidural fentanyl or fentanyl plus clonidine. After 360 min, all patients of the epidural fentanyl group had received paracetamol; their scores after 360 min were deleted from analysis.

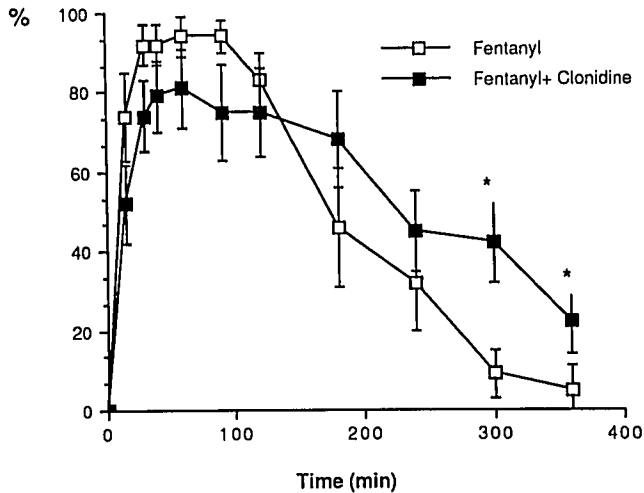


FIG. 2. Percentage reduction in VAS pain score obtained in the two study groups after epidural fentanyl or fentanyl plus clonidine injection.

tion in VAS pain score ranged from 57 to 100% in EF patients and from 40 to 100% in EF+C patients (figs. 1 and 2 and table 2) and occurred  $35 \pm 25$  and  $45 \pm 25$  min after the epidural injection in groups EF and EF+C, respectively ( $P$  not significant). The duration of analgesia was significantly longer in the EF+C group (table 2 and fig. 3). At 360 min all the patients of the EF group but only 1 of the patients of the EF+C group had received paracetamol. The actual time elapsed between fentanyl and the first paracetamol injection was  $261 \pm 59$  min in EF patients and  $576 \pm 184$  min in EF+C patients ( $P < 0.01$ ) (table 2).

We obtained plasma fentanyl concentration *versus* time curves in nine EF and nine EF+C patients. In none of the patients was the plasma concentration of fentanyl detectable before epidural injection. There was marked

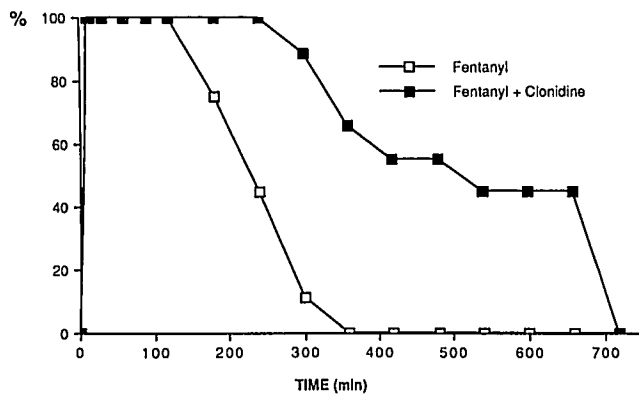


FIG. 3. Percentage of patients not requesting analgesia after epidural fentanyl or fentanyl plus clonidine. At the first request for additional analgesia, study of the individual patient was terminated. A log-rank test indicates that the two curves representing the epidural fentanyl and fentanyl plus clonidine groups are significantly different.

variability among patients of both groups in plasma concentration *versus* time (fig. 4). Values of  $C_{max}$  and  $T_{max}$  were comparable in the two groups:  $C_{max}$  was  $0.29 \pm 0.15$  in the EF group and  $0.27 \pm 0.11$   $ng \cdot l^{-1}$  in the EF+C group, and  $T_{max}$  was  $16.2 \pm 14.8$  min in the EF group and  $8.3 \pm 5.5$  min in the EF+C group.

Arterial blood pressure decreased in both groups (fig. 5). The maximum decrease in systolic pressure was  $15.5 \pm 17.9\%$  in the EF group and  $35.5 \pm 13.3\%$  in the EF+C group ( $P < 0.05$ ), and the maximum decrease in diastolic pressure was  $12.0 \pm 16.3\%$  in the EF group and  $30.4 \pm 10.7\%$  in the EF+C group ( $P < 0.05$ ). Eight patients required an intravenous colloid infusion ( $556 \pm 132$  ml), and of these eight, three in the EF+C group received ephedrine for hypotension (lowest limit 89/57 mmHg). Heart rate also decreased significantly ( $P < 0.05$ ) but transiently (120 min) in both groups; there was no significant difference between groups. We detected bradycardia (heart rate  $< 50$  beats per min) in one EF+C patient.

Respiratory rate decreased slightly but significantly in both groups (from  $20.7 \pm 4.0$  to  $18.3 \pm 4.3$  breaths per min at 60 min in the EF group [ $P < 0.05$ ] and from  $20.8 \pm 5.8$  to  $18.1 \pm 3.6$  breaths per min at 60 min in the EF+C group [ $P < 0.05$ ]), but no difference was found between groups. Expired carbon dioxide partial pressure increased similarly in the two groups (from  $39.4 \pm 3.6$  to  $42.2 \pm 3.9$  mmHg at 120 min in the EF group [ $P < 0.05$ ] and from  $35.6 \pm 5.8$  to  $37.4 \pm 5.1$  mmHg at 90 min in the EF+C group [ $P < 0.05$ ]).  $Sp_{O_2} < 93\%$  was noted at least once in three patients in the EF group and in four in the EF+C group and was treated with oxygen through a nasal cannula; these patients were deleted from carbon dioxide data analysis. All patients after EF+C administration were sedated, *i.e.* asleep most of the time. Sedation lasted  $128 \pm 66$  min (range 30–225 min) in this group. In the EF group patients were occasionally drowsy or were

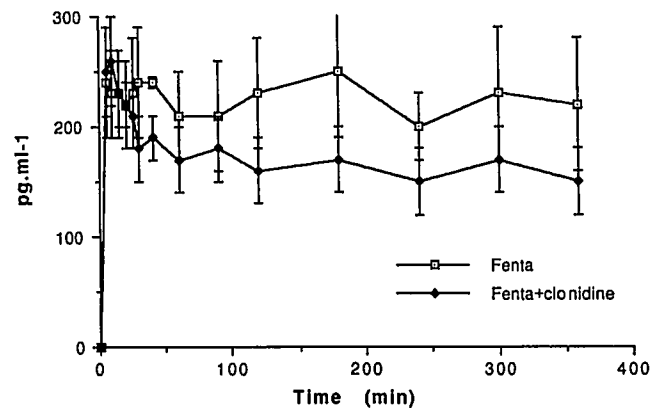


FIG. 4. Measured plasma fentanyl concentrations after epidural administration. Each point represents the mean value  $\pm$  SEM.

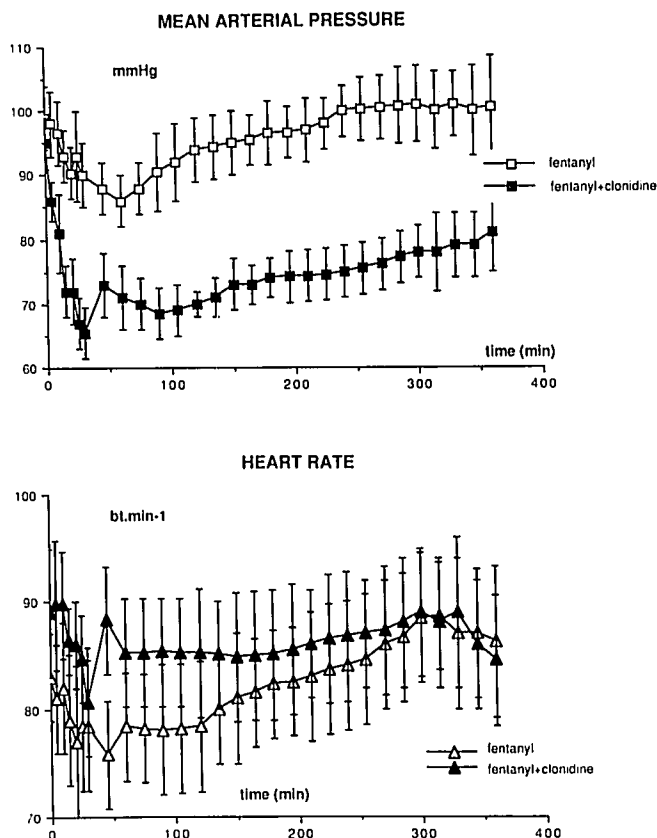


FIG. 5. Changes in mean arterial pressure and heart rate in the two groups of patients. Values are given every 15 min after 60 min. In the fentanyl plus clonidine group, mean arterial pressure was significantly lower than the control value ( $P < 0.05$ ) and than the corresponding value in the fentanyl group ( $P < 0.05$ ) from 5 to 360 min after the epidural injection. In the fentanyl group, mean arterial pressure was significantly lower than the control value at 45 and 60 min. Heart rate did not differ significantly between the two groups but was lower than the control value ( $P < 0.05$ ) at 20, 25, and 30 min in the fentanyl plus clonidine group and at 40 min in the fentanyl group.

sleeping intermittently. No patient complained of pruritus. Since all patients had a bladder catheter, no urinary retention was observed.

### Discussion

This study demonstrates that epidural clonidine markedly prolongs the analgesic effect of epidural fentanyl. The combination of opioid and clonidine has been assessed in humans in previous studies. Eisenach *et al.* documented that epidural clonidine decreased intravenous morphine requirements provided by patient-controlled analgesia in postoperative patients as well as in cancer patients.<sup>4,16</sup> In addition, systemically administered clonidine enhanced postoperative analgesia provided by epidural morphine or alfentanil.<sup>17,18</sup> In one study, spinal clonidine was com-

bined with spinal morphine and decreased the patient-controlled morphine requirements without decreasing significantly pain intensity.<sup>§</sup> In another study, epidural clonidine was combined with epidural sufentanil.<sup>19</sup> In that study,<sup>19</sup> the maximum pain relief was not different between patients who received epidural sufentanil alone and those who received epidural sufentanil plus clonidine. The duration of analgesia was significantly prolonged in those who received epidural clonidine even though they received only half the epidural sufentanil dose of the other group. In the current study, epidural clonidine also significantly prolonged the duration of analgesia induced by epidural fentanyl, and the degree of pain relief and the onset of action were unchanged. The analgesic effect of epidural fentanyl also appears to be prolonged when in combination of epidural clonidine, in comparison to previous studies.<sup>20-22</sup> In addition, analgesia induced by epidural clonidine plus fentanyl appears to last longer than that induced by epidural clonidine as the sole agent, as observed in previous studies in which a 200-210-min duration of action was noted.<sup>2,5</sup>

Numerous laboratory reports support an  $\alpha_2$ -adrenergic mediation of the analgesic effect of clonidine at the spinal cord level.<sup>7-10</sup> In addition, low doses of intrathecal clonidine and morphine, each unable by itself to suppress the activity of wide-dynamic-range neurons of the spinal dorsal horn, have a significant effect when combined.<sup>7</sup> In other laboratory studies intrathecal clonidine allowed a reduction of the dose of morphine that produces an analgesic effect.<sup>6,23</sup>

Plasma concentrations of fentanyl,  $F_{max}$ , and  $T_{max}$  were comparable in the two groups of patients.

Segal *et al.* reported that plasma alfentanil concentrations were greater in patients who received transdermal clonidine.<sup>17</sup> This result is not at variance with our own, because the routes of administration were different. Indeed, in this previous study,<sup>17</sup> parenteral clonidine might have impaired the elimination of parenteral alfentanil by a decrease in cardiac output and hepatic blood flow.<sup>24</sup> This hypothesis has also been suggested to explain the higher peak plasma concentrations after epidural administration of lidocaine with clonidine as compared to the peak concentration after lidocaine plain solution.<sup>25</sup> Our study cannot demonstrate differences in plasma fentanyl concentrations when epidural clonidine is administered. Nevertheless, one cannot exclude that a decrease in fentanyl vascular uptake related to a vasoconstrictive effect of clonidine on the epidural venous plexus<sup>4</sup> might have counterbalanced its possible effect on fentanyl elimination.

§ Coombs DW, Jensen LB, Murphy C. Microdose intrathecal morphine for postoperative analgesia (abstract). ANESTHESIOLOGY 67: A238, 1987.

Administration of clonidine *via* the epidural or paravertebral route is responsible for the side effects, such as sedation and hypotension, demonstrated in this study as well as in previous studies.<sup>1-5</sup> Sedation is related to a supraspinal effect of clonidine after its vascular absorption.<sup>26,27</sup> Hypotension has been reported to be maximum after a 400-600- $\mu$ g epidural dose of clonidine but was less marked after injection of lower doses<sup>4,17</sup> or of higher doses, because of the vasoconstrictive effect of the drug.<sup>4</sup> In previous studies conducted in ASA physical status 1 patients, hypotension was mild and well tolerated,<sup>2,5</sup> but in the current study, conducted after major abdominal surgery, hypotension required treatment in 8 of 10 patients in the clonidine group, as in two previous reports.<sup>4,¶</sup> The site of the injection also may have been an important factor related to hypotension: Kubo *et al.* demonstrated that spinal injection at the T6-T7 level resulted in more pronounced hypotension than did cervical injection, suggesting that the blockade of the intermediolateral cell column, the main site of origin of the sympathetic preganglionic neurons, is an important mechanism of action of clonidine.<sup>28</sup> Although hypotension responded readily to treatment, it appears to be a limitation in the use of epidural bolus doses of clonidine in postoperative patients.

Respiratory depression is a common feature of epidural opioids.<sup>24,29</sup> Epidural fentanyl has been documented to decrease respiratory rate, to increase arterial carbon dioxide tension,<sup>21</sup> and to depress the slope of the ventilatory response to carbon dioxide.<sup>30</sup> Accuracy of monitoring expired carbon dioxide pressure from a pharyngeal or nasal cannula is controversial but may indicate a trend, if no flow of oxygen is administered.<sup>29</sup> Although this study was not designed to assess ventilatory control after epidural analgesia, respiratory depression was not more marked when patients had received epidural clonidine. Similarly, it has been demonstrated recently that clonidine did not induce respiratory depression in healthy volunteers.<sup>31</sup>

In conclusion, this study demonstrates that epidural clonidine markedly prolongs the analgesic effect of epidural fentanyl in postoperative patients. Epidural bolus administration of clonidine results in side effects such as sedation and hypotension. Whether epidural infusion of small doses of clonidine and opioid produces analgesia with fewer side effects is the now being investigated.

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