Cardiorespiratory Effects and Kinetics of Intrathecally Injected D-Ala^2-D-Leu^5-Enkephalin and Morphine in Unanesthetized Dogs

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In unanesthetized dogs prepared with chronic tracheostomies and chronically implanted intrathecal (IT) catheters having openings in the cisterna magna and lumbar region, lumbar IT injection of D-Ala^2-D-Leu^5-enkephalin (DADL, 1–10 mg) and morphine (3–30 mg) produced a dose-dependent depression of the slope of the CO_2 response function (minute expired volume [$\dot{V}_E$] vs. end-tidal [ET] CO_2) as investigated by a modified Read rebreathing technique. The maximum depression occurred less than 3 h after IT injection of either agent and lasted as long as 12 h. The depression was totally reversed by naloxone (0.4 mg/kg, iv). Naloxone alone had no effect on ventilatory function. After 10 mg DADL, there was no significant change in heart rate (HR), mean arterial pressure (MAP), mean pulmonary artery pressure (MPAP), cardiac output (CO), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), or Pa_{O_2} during the 3 h postinjection. In contrast, Pa_{CO_2} was significantly elevated and pH significantly decreased ($P < 0.05$). Naloxone administration after high-dose IT DADL resulted in a doubling of MABP, MPBP, CO, and SVR that lasted approximately 20 min. In concurrently measured cisternal cerebrospinal fluid (CSF) levels, both morphine and DADL displayed peak levels by 30–60 min. The lumbar CSF clearance curves for both agents were fitted with a two-compartment intravenous bolus model. The $t_{1/2}\alpha$ was 13.8 ± 3.6 min for DADL and 9.4 ± 1.6 min for morphine (mean ± SE). The $t_{1/2}\beta$ was 101.3 ± 17.7 min for DADL and 116.7 ± 27.9 min for morphine. The volume of distribution at steady state (Vd$_{ss}$) was 1.6 ± 0.88 ml/m^2 for DADL and 3.4 ± 2.1 ml/m^2 for morphine. The clearance was 29.6 ± 1.7 μl · min^{-1} · m^{-2} for DADL and 41.6 ± 12.7 μl · min^{-1} · m^{-2} for morphine. DADL may represent an alternative to morphine for IT administration, especially in morphine-tolerant patients. (Key words: Analgesics, narcotic: morphine. Analgesics, peptides: d-ala^2-d-leu^5-enkephalin. Anesthetic technique: intrathecal injection. Respiratory depression. Opiate receptor.)

SPINALLY ADMINISTERED OPIATES will produce a powerful receptor-mediated analgesia in a variety of animal models and in humans.[1,2] Several lines of evidence developed from *in vitro* bioassay and binding studies have emphasized the likelihood that there are several discrete populations of opioid receptors and that at least two subclasses of opioid receptors, notably the μ and δ, are relevant to the modulation of spinal pain processing in the spinal cord.[3,4] The μ receptor likely represents the receptor through which conventional opiate alkaloids such as morphine act. Some natural enkephalins and some synthetic opioid peptides such as D-Ala^2-D-Leu^5-enkephalin (DADL) are thought to show a relative affinity for the δ receptor.[5] Both μ and δ agonists produce profound analgesia when administered intrathecally (IT) in a variety of animal models.[6,7] Preliminary studies have also indicated that DADL will produce analgesia after IT injection in humans.[8,9] Systematic studies on the pharmacology of δ receptor ligands have indicated that there is a lack of cross-tolerance in morphine-tolerant animals.[10,12] DADL therefore may prove to be a suitable alternative in cancer patients rendered tolerant to high doses of IT morphine. Prior to extensive clinical trials in humans, however, it is necessary to examine systematically the respiratory and cardiovascular effects produced by intrathecally administered DADL and determine reversibility of these effects by naloxone.

Methods

TRACHEOSTOMY AND REBREATHING TECHNIQUE

To assess the respiratory effects of spinally administered drugs, five adult male dogs (19–23.5 kg) were prepared with chronic tracheostomies.[13] The dogs were adapted to stand in a passive restraint and tolerate insertion of a size 7 cuffed endotracheal tube into the tracheostomy site. In this manner, the dogs were trained to undergo CO_2 response determinations by the Read rebreathing technique.[14] The rebreathing circuit consisted of a 5-l bag-in-box connected to a 6-l Collin's spirometer. End-tidal (ET) CO_2 was monitored by a Beckman LB-1® infrared gas analyzer, which was calibrated daily with known gas standards. Respiratory rate (RR) and minute expired volume ($\dot{V}_E$) were determined from the calibrated polygraph tracings. On an experimental day, baseline CO_2 response, ET_{CO_2}, and RR were established. After injection, CO_2 responses were performed at 15, 30, 60, 180, and, in some cases, 360 and 720 min. ET_{CO_2} and RR were continuously recorded. At the end of the experiment, naloxone 0.4 mg/kg was administered intravenously. Fifteen minutes later, the last CO_2 response was done.

INTRATHECAL CATHETERIZATION

After adaptation and training over a 2-month period, each dog had chronic lumbar IT and cisternal catheters

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surgically implanted. The animals were anesthetized with
sodium pentobarbital and placed with the head rotated
forward in a stereotaxic head holder. After preparation,
the posterior muscles of the neck were split longitudinally
by blunt dissection on midline and the dural membrane
between the occiput and the first cervical vertebra (C-1)
was exposed. A 1-mm incision was made in the dura on
midline. The dura and the underlying arachnoid were
retracted with a small hook and a PE-50 polyethylene
tubing (diameters: inside 0.58 mm; outside 0.965 mm)
was passed to the level of the (L2–4) (approximate length
40–50 cm). Catheter position was confirmed radiologi-
cally. The external portion of the catheter was then
sheathed with silicone tubing and secured by means of a
stainless steel suture attached to two stainless steel bone
screws placed in the occipital bone. The catheter was then
passed subcutaneously to exit at the back of the neck. The
same procedure was followed with the cisternal catheter
that was placed 1–2 cm inside the cisternal membrane.
The catheters were flushed three times a week with nor-
mal saline (1 ml).

DRUGS AND THEIR INJECTION

Each dog received lumbar intrathecal injections of the
following drugs and doses: normal saline, morphine sul-
fate (Merck West Point, PA) 3 mg and 10 mg (9 and 30
μmoles), or DADL (Burroughs Wellcome Research Tri-
angle Park, NC) 1 mg, 3 mg, and 10 mg (1.75, 5.25, and
17.5 μmol). Two dogs received 30 mg (90 μmol) of mor-
phone. These doses were chosen because DADL is three
to four times as potent as morphine on a microgram basis
in producing analgesia in rodent and primate models.[10–
12] All drugs were dissolved in normal saline and admin-
istered in a 1-ml volume. Solutions were hyperbaric with
specific gravities ranging from 1.009 to 1.017 g/ml at
22° C. Drugs were injected if cerebrospinal fluid (CSF)
could be sampled and no resistance felt during injection.
Each dog received no more than one injection per week
of any of the drugs. Sequence of injection was randomized
for each dog in an effort to eliminate any bias produced
by chronic catheterization. The time from catheter im-
plantation to the last injection was 7 weeks.

In some experiments, tracer amounts of ³H-DADL
(25–55 μCi/nmol) or ³H-morphine (20–30 μCi/nmol)
(Amersham) were added to the injectates. In these studies,
0.2 ml samples of CSF were withdrawn from both the
lumbar and cervical IT catheters immediately prior to
CO_2 response determinations (15, 30, 60, and 180 min
after injection). The catheters were flushed slowly with
0.2 ml of sterile saline after sampling. Aliquots of each
CSF sample were then added to scintillation phosphor
and activity in DPM (disintegrations per minute, back-
ground subtracted) ascertained with a Beckman® scintil-

lation counter. All data points were normalized to 10^6
DPM of injectate. Radioactivity values were converted to
ng/ml.

PULMONARY ARTERY CATHETERIZATION

Additional preparation to ascertain cardiovascular
function was done the day the dog received the 10-mg
dose of DADL. The animal was anesthetized under light
nitrous oxide–halothane anesthesia administered *via* the
tracheostomy. A pulmonary artery catheter (7.5 French)
was then placed percutaneously through the right external
jugular vein using the Seldinger technique. Position was
deemed correct when central venous and pulmonary ar-
terial waves were noted on the proximal and distal ports,
respectively, and a wedged tracing could be obtained by
adding 1–2 ml of air to the catheter balloon. Arterial
pressure and blood samples were obtained by a percuta-
neous femoral artery catheter. To minimize discomfort
at sites of tissue penetration, bupivacaine 0.75% (4 ml)
was administered subcutaneously. Dogs were allowed to
recover from the anesthesia for at least 1 h. The usual
protocol was then followed with, in addition, continuous
monitoring of systemic arterial blood pressure, heart rate,
and pulmonary artery pressures. Central venous temper-
ature, arterial blood gases, and cardiac output (CO) were
measured periodically. All information was recorded on
a Grass Instruments polygraph. Cardiac output was as-
sessed using an Edward's model 9520A cardiac output
computer. Pulmonary artery wedge pressure (PAWP) was
maintained within 3 mmHg of control throughout the
experiment by infusing Lactated Ringer's solution (300–
1,100 ml).

STATISTICAL ANALYSIS

A least-squares regression analysis was used to calculate
the ED_{50} values, slopes, 95% confidence intervals, and
correlation coefficients.

For cardiovascular parameters, the drug group and
drug plus naloxone group were compared with the control
group using one-way analysis of variance and Newman-
Keuls multiple means analysis.[15]

Pharmacokinetic calculations of lumbar CSF decay
curves were performed using NONLIN least-squares
regression analysis computer program.[16] Areas under the
time–concentration curves (AUC) were measured by the
trapezoidal rule.[17] The areas were expressed in mg/ml
× min.

To compare the relative levels of DADL and morphine
in the cisternal or lumbar IT space as a function of time,
a paired t test was used. For all studies, P values less than
0.05 were considered significant.

Results

CONTROL RESPIRATORY VALUES AND EFFECT OF IT SALINE

Control respiratory values showed a significant increase in $\dot{V}_E$ as ET_{CO_2} rose. RR displayed comparatively small and variable changes. After IT saline injection, the slope of the CO_2 response curves as a function of time was unchanged, and there were no changes from control values for $\dot{V}_E$ and RR.

RESPIRATORY EFFECTS AFTER IT MORPHINE AND DADL

IT administration of DADL and morphine produced significant, time-dependent, dose-dependent, and naloxone-reversible depression of the slope of the $\dot{V}_E$–CO_2 response curves (figs. 1 and 2). Concurrent decreases of resting RR and increases of ET_{CO_2} values were observed. Such changes were maximal 3 h after injection and remained below baseline up to 12 h after injection. Figure 3 shows the log dose–response curves for the maximum depression of RR and $\dot{V}_E$–CO_2 slope values. Table 1 shows the respective ED_{50} and slope values for RR changes and $\dot{V}_E$–CO_2 slope changes as a function of increasing IT doses of DADL or morphine. For both agents, the slopes were less than zero, but not statistically different from each other. In other words, morphine and DADL produced a comparable and significant degree of respiratory depression. DADL was approximately three and seven times more potent than morphine on a molar basis with respect to depression of RR and $\dot{V}_E$–CO_2 slopes, respectively. At low doses, both agents had little effect on RR and $\dot{V}_E$–CO_2 slopes. By contrast, at the highest doses, both agents produced greater than 60% reductions in RR and $\dot{V}_E$–CO_2 slopes. Individual $\dot{V}_E$–ET_{CO_2} plots fitted well to a straight-line model (correlation coefficients: 0.949 ± 0.06; mean $\pm$ SE).

Between periods of CO_2 stimulation, resting ET_{CO_2} did not rise after saline, morphine (3 mg and 10 mg), and DADL (1 mg and 3 mg) injections. By contrast, after DADL 10-mg injections, increased resting ET_{CO_2} values were observed. In the DADL 10-mg group, arterial blood sampled prior to each rebreathing test showed Pa_{O_2} values not different from control throughout the experiment and Pa_{CO_2} values significantly increased after 3 h. For instance, in one animal, 3 h after DADL 10 mg, $ET_{CO_2}\%$ was 6.6%, Pa_{CO_2} 48 mmHg, and RR 4 breaths/min.

ARTERIAL BLOOD GAS AND CARDIOVASCULAR EFFECTS AFTER IT DADL

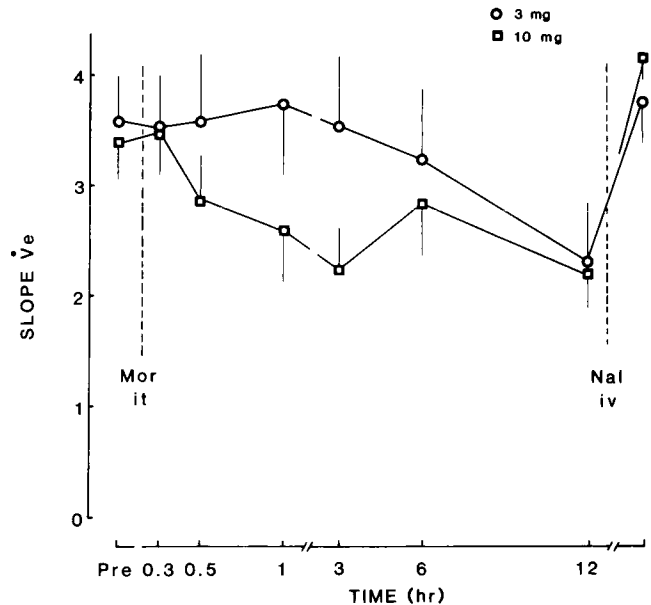IT DADL 10 mg produced no significant changes in CO, HR, SVR, PVR, MABP, or MPBP for 3 h following

FIG. 1. The slope of the $\dot{V}_E$ vs. CO_2 response measured by the Read rebreathing procedure, as a function of time (in hours) after the intrathecal administration of morphine sulfate (3 mg or 10 mg). At the time indicated by the right *dotted line*, naloxone (0.4 mg/kg, iv) was administered. Each point represents the mean $\pm$ SE of five dogs.

injection. Arterial CO_2 tension increased significantly by 3 h after injection, and arterial pH showed a concomitant respiratory acidemia (table 2). By contrast, naloxone administration brought about immediate significant increases in CO, MAP, MPAP, and HR (table 2). Pa_{CO_2} and ET_{CO_2} values returned to control. SVR and PVR remained unchanged.

BEHAVIORAL EFFECTS AFTER IT MORPHINE AND DADL

After high doses of morphine (10 and 30 mg) and DADL (10 mg), the dogs were sedated and somnolent, but easily aroused. No sign of muscle weakness or motor dysfunction (*e.g.*, placing, stepping reflexes, hindlimb strength) was noted. There was no evidence of seizures after any IT drug treatment, except for one of the two dogs that received 30 mg of IT morphine. In this animal, within 2–5 min of injection, the dog displayed sustained efforts to bite and nip at its flank as if in response to local irritation. After 15 min, while still breathing, the dog displayed convulsions and died shortly thereafter.

After naloxone injection, all animals became alert, agitated, and excited for 10–20 min. The dogs showed otherwise normal behavior. No evidence of seizure activity or undue irritability was observed after naloxone treatment.

Retching and vomiting were observed in eight of 25 experiments within 5–10 min of injection of morphine (3
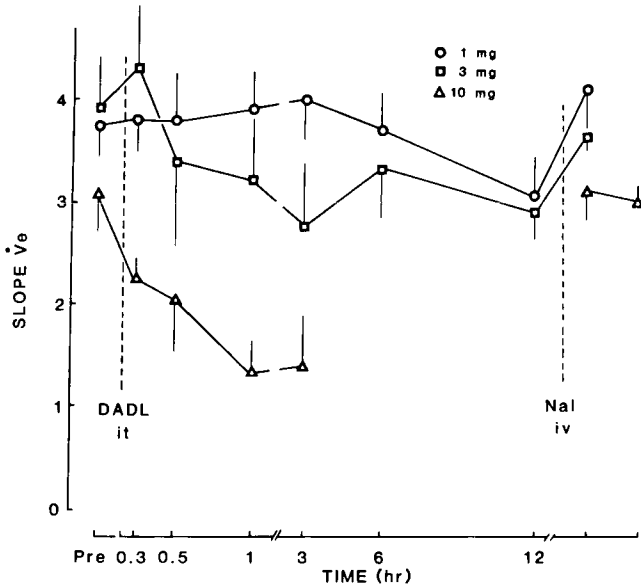
FIG. 2. The slope of the $\dot{V}_E$ vs. CO_2 response measured by the Read rebreathing procedure as a function of time (in hours) after the intrathecal administration of DADL (1, 3, and 10 mg). At the time indicated by the right *dotted line*, naloxone (0.4 mg/kg, iv) was administered. For the animals receiving 10 mg, the postnaloxone response was measured immediately after the 3-h mark, but was displayed for clarity at the post-12-h mark. Each point represents the mean ± SE of five dogs.

mg: two of five dogs; 10 mg: one of five dogs) or DADL (3 mg: two of five dogs; 10 mg: three of five dogs). No retching or vomiting was observed when animals received IT saline or DADL 1 mg.

CISTERNAL REDISTRIBUTION OF MORPHINE AND DADL AFTER LUMBAR IT INJECTION

Both morphine and DADL displayed cephalad spread after lumbar IT injection in some animals (fig. 4), with significant levels of radioactivity for either compound being observed in the cisterna magna within 30 to 60 min of the lumbar injection. Comparison of the relative levels of DADL and morphine as a function of time revealed no statistical differences ($P > 0.10$) between the two agents at the lumbar or cisternal levels. There are wide variations in the cisternal levels of both agents. Therefore, the amount of drug at any given time reaching the cisterna is unpredictable.

LUMBAR CSF DECAY CURVE ANALYSIS

As shown in figure 4 and table 3, morphine and DADL lumbar CSF decay curves are fitted to the two-compartment iv bolus model (with $1/y$ weighting factor). The mean (±SE) initial elimination half-life ($t_{1/2}\alpha$) was 13.8 ± 3.6 min for DADL and 9.4 ± 1.6 min for morphine.

The mean (±SE) terminal elimination half-life ($t_{1/2}\beta$) was 101.3 ± 17.7 min for DADL and 116.7 ± 27.9 min for morphine. The mean (±SE) volume of distribution at steady state (Vd$_{SS}$) was 1.6 ± 0.88 ml/m^2 for DADL and 3.4 ± 2.1 ml/m^2 for morphine. The mean (±SE) clearance was 29.6 ± 1.7 $\mu l \cdot min^{-1} \cdot m^{-2}$ for DADL and 41.6 ± 12.7 $\mu l \cdot min^{-1} \cdot m^{-2}$ for morphine. The mean AUC value (0–180 min) was 111 min × mg/ml for DADL 3 mg; 298.2 min × mg/ml for DADL 10 mg, and 94.1 ± 25.7 min × mg/ml (mean ±SE) for morphine 3 mg.

Discussion

This study was aimed chiefly at evaluating the respiratory and cardiovascular effects of intrathecally administered DADL and their antagonism by naloxone. Morphine was also studied because this agent is commonly administered intrathecally and thus provides a benchmark for comparison of respiratory depression.

Because the action of spinal drugs in the canine model relative to humans is not known, a ten-fold range of doses was examined. We thus employed concentrations likely in excess of those which might be employed clinically.
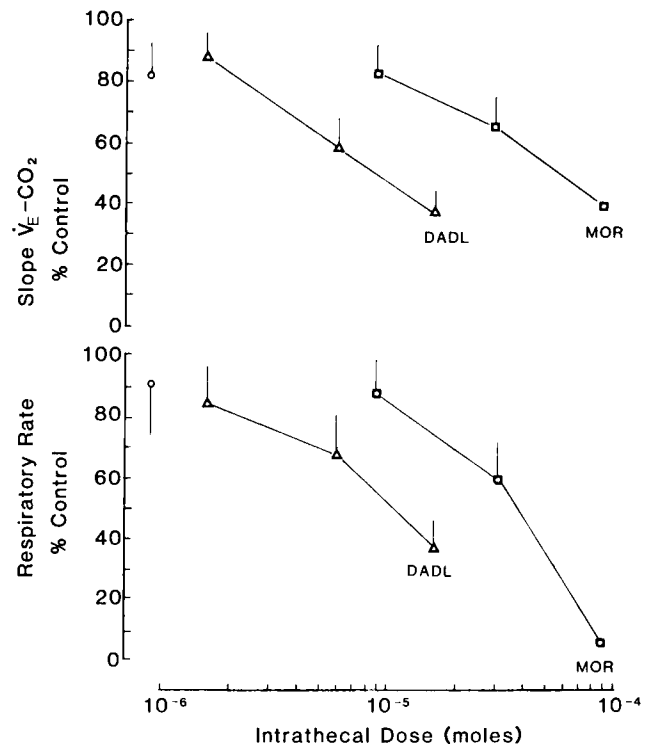

FIG. 3. Log dose–response curves showing the effect of intrathecally administered morphine 9, 30, and 90 μmoles (3, 10, and 30 mg) and DADL 1.75, 5.25, and 17.5 μmoles (1, 3, and 10 mg). *Upper panel.* Effect on $\dot{V}_E$–CO_2 slope values (% control). *Lower panel.* Effect on respiratory rate (% control). The effect of IT saline is shown by the *open circle* in the left upper corner of each panel. Each point represents the mean ± SE of five dogs.

TABLE 1. ED_{50} (μmoles), Slope Log Values, and 95% Confidence Intervals for $\dot{V}_E$-CO_2 Slope Changes and Respiratory Rate Changes as a Function of Increasing Intrathecal Doses of DADL or Morphine

	DADL		Morphine	
	ED_{50}	Slope	ED_{50}	Slope
$\dot{V}_E$-CO_2 slope changes	8.6 (3.8–19.3)	−51.6 (±18.3)	59.2 (22.5–156)	−39.3 (±19.2)
Respiratory rate changes	10.2 (4.1–25.6)	−58.3 (±15.2)	31.3 (12.2–81)	−82.3 (±24.1)

Moreover, the volume for IT injection in this dog model was 1 ml, a volume similar to that injected in humans whose spinal cord and CSF volumes are significantly greater. These aspects were considered to maximize the likelihood of redistribution and to mimic a clinical situation such as might occur with an accidental overdosage.

RESPIRATORY EFFECTS

Results show that DADL, like morphine, can produce a profound dose-dependent respiratory depression. Response to the stimulatory effects of CO_2 appeared to be the most sensitive respiratory parameter in these experiments. Resting RR was also decreased and ET_{CO_2} elevated, but these measures were relatively less sensitive than the changes in slope of the $\dot{V}_E$-CO_2 response curves. The ventilatory response during rebreathing was already significantly depressed at a time when resting RR and ET_{CO_2} were practically unchanged. This is consistent with reports on human volunteers[18] and postoperative pain patients[19-21] in which RR prior to apnea was relatively unchanged, but the ventilatory response to CO_2 was consistently attenuated.

The depressant effects of spinally administered opiates are thought to be mediated by a redistribution of these
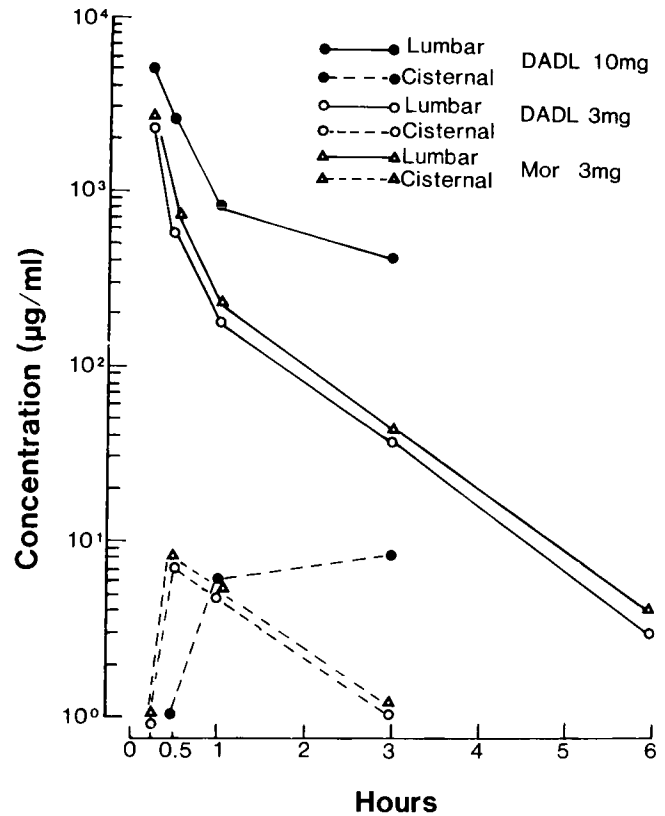

FIG. 4. Levels of DADL and morphine (in μg/ml) measured in cisternal (dashed lines) and lumbar (solid lines) CSF as a function of time (in hours) after lumbar IT administration in a typical dog for each dose. Dog no. 1 (DADL 3 mg) has exactly the same lumbar and cisternal profiles as dog no. 5 (morphine 3 mg). At 15 min, cisternal drug levels were undetectable. In some animals, a small but significant peak was observed in the cisterna 30–60 min after injection.

agents to the brain stem opioid receptors associated with regulation of respiratory rhythmicity and chemosensitivity.[22,23] The observation that DADL did produce a sig-

TABLE 2. Physiologic Effects of IT DADL (10 mg) in Unanesthetized Dogs

	Control	3 h Post-DADL (10 mg)	Post-naloxone (0.4 mg/kg iv)
CO (ml·kg^{-1}·min^{-1})	230 ± 36	184 ± 40	443 ± 58*·†
MAP (mmHg)	102 ± 22	89 ± 11	188 ± 19.4*·†
MPAP (mmHg)	17.3 ± 3.48	18.4 ± 7.31	31.84 ± 6.07*·†
HR (beats/min)	100 ± 7	99 ± 3	139 ± 12.4*·†
SVR (mmHg·kg·min·ml^{-1})	0.474 ± 0.133	0.536 ± 0.060	0.460 ± 0.163
PVR (mmHg·kg·min·ml^{-1})	0.048 ± 0.011	0.055 ± 0.017	0.043 ± 0.011
Pa_{O_2} (mmHg)	90.67 ± 2.80	87.83 ± 1.30	87.67 ± 1.56
Pa_{CO_2} (mmHg)	36 ± 0.45	41 ± 2.08*	34.84 ± 1.14†
pH	7.43 ± 0.01	7.39 ± 0.02*	7.43 ± 0.01†
% ET_{CO_2}	5.04 ± 0.17	5.52 ± 0.67	4.88 ± 0.33†

Number of animals = 5 (mean ± SE).
CO: cardiac output; MAP = mean arterial pressure; MPAP = mean pulmonary artery pressure; HR = heart rate; SVR = systemic vascular resistance; PVR = pulmonary vascular resistance; ET_{CO_2} = end-tidal

CO_2.
* $P < 0.05$ as compared with control.
† $P < 0.05$ as compared with 3-h DADL.

TABLE 3. CSF Decay Curves of DADL (3 mg and 10 mg) and Morphine (3 mg) at the Site of Intrathecal Injection

	Dog. No.	$t_{1/2}\alpha$ (min)	$T_{1/2}\beta$ (min)	VD_{ss} (ml/ml²)	CSF Clearance ($\mu l \cdot min^{-1} \cdot m^{-2}$)	AUC (0–180 min) ($min \cdot mg \cdot ml^{-1}$)
DADL						
3 mg	1	8.3	105	0.8	32.0	105.7
	2	11.1	69	0.7	26.4	116.4
10 mg	2	24.4	—*	—	—	—
	3	11.5	130	3.4	30.4	298.2
Mean ± SE		13.8 ± 3.6	101.3 ± 17.7	1.6 ± 0.88	29.6 ± 1.7	
Morphine						
3 mg	2	9.5	159	2.1	31.5	108.7
	4	12.2	127	7.5	66.8	44.2
	5	6.5	64	0.7	26.6	129.5
Mean ± SE		9.4 ± 1.6	116.7 ± 27.9	3.4 ± 2.1	41.6 ± 12.7	94.1 ± 25.7

Note: In dogs, 1 m² = 22.9 kg.

$t_{1/2}\alpha$ = initial elimination half-life; $t_{1/2}\beta$ = terminal elimination half-life; VD_{ss} = volume of distribution in the CSF at steady state. AUC = area under the concentration–time curve for the first 180 min following injection.

* Data not available for lack of sufficient points to define the second phase.

nificant respiratory depression is consistent with iontophoretic studies in which δ-receptor ligands inhibited bulbar respiratory neurons.[24] In addition, following intracerebral administration, respiratory changes have been noted in animal models.[25]

CARDIOVASCULAR EFFECTS

Cardiovascular responses to the highest doses of DADL were minimal. These results are comparable with those observed after IT morphine in animals[26,27] and human beings.[2] Such apparent lack of effect is surprising in view of marked hypotension and bradycardia following intracerebral, intraventricular, or intracisternal injections of μ and δ agonists.[25,28–30] However, a significant increase in Pa_{CO_2}, as noted in our experiments, stimulates the sympathetic nervous system. Such stimulation may be enough to compensate and mask cardiovascular depression. The lack of cardiovascular depression may also reflect a species related (canine) physiologic resistance to the hypotensive effects of opioids.

NALOXONE REVERSIBILITY

All of the effects, especially those on respiratory function, were readily reversed by naloxone. Systematic studies were not carried out to determine the minimum effective dose required to produce the antagonism. Our data show that the dose injected produced a total reversal of the agonist effects of the intrathecally administered agents.

One of the discriminating aspects of the pharmacology separating μ versus δ receptor interactions is that naloxone has approximately one-tenth the affinity for the δ as for the μ receptor.[7] This might suggest that the effects from DADL would be relatively resistant to antagonism as compared with a μ (morphine) type agent. Nevertheless, it should be stressed that naloxone and DADL clearly

interact in a competitive fashion; and, the agonist effects, as are those of morphine, are reversed in a dose-dependent fashion by naloxone.[10–12] In humans, the effects of high doses of IT DADL (1 mg IT) leading to profound respiratory depression have also been shown to be readily reversed by systemic naloxone.[8]

The powerful effects of naloxone on blood pressure after prior opiate administration leading to the transient hypertension may reflect the rebound or acute withdrawal phenomenon occurring when opiate antagonists are given in the presence of opiate agonists. The mechanism of rebound is not clear, but has been described as receptor changes or the uncovering of homeostatic mechanisms,[31] such as increased arterial CO_2.

KINETICS OF MORPHINE AND DADL IN THE CSF

Although the present experiments were not designed to ascertain precise pharmacokinetic data of intrathecally administered DADL or morphine, peak levels of labeled morphine and DADL could be found at the level of the cisterna magna within 30–60 min after lumbar IT injection in some of the animals. By 2–3 h, radioactivity at the level of the cisterna had fallen to near the level of sensitivity. The relatively rapid rise in cisternal concentrations may be responsible for the retching and vomiting behavior. However, the onset of respiratory depression did not mirror either the periods of peak concentration in the cisterna, nor the time course of the retching and vomiting. Calculation of the approximate concentration in the cisterna suggests that, at the time of peak effect, less than 0.1% of the IT-injected dose made its way into the cisternal fluid. These numbers are in approximate agreement with previous reports in which cisternal levels of agents have been examined after IT administration.[32] Likewise, in studies of cervical CSF in humans after epi-

dural morphine, drug was detectable by 60 min, but peaked at about 180 min. The reason for the discrepancy between the time course of maximal respiratory depression and the peak levels of the opioids in the cisternal fluid is not known. Perhaps the delayed respiratory depression may arise from time needed for the drug to reach supracisternal respiratory centers. However, in this study, cisternal drug levels must be interpreted with caution because the volume of the injectate was relatively large (1 ml) and the cisternal levels may simply reflect physical spread in the CSF.

For both morphine and DADL, clearance by bulk flow may explain the similarities in $t_{1/2}\alpha$, $t_{1/2}\beta$ and Vd_{SS} values. Therefore, distribution and elimination appear to be quite similar for the two agents in dogs. In addition, our values of $t_{1/2}\beta$ and clearance converted in kg are comparable with those obtained in patients after IT injection of morphine (0.5 mg) ($t_{1/2}\beta$: 175 ± 9 min; clearance: 2.81 ± 0.41 $\mu l \cdot min^{-1} \cdot kg^{-1}$).[32] The volume of distribution is four to eight times higher in humans than in dogs. Therefore, the CSF kinetics of intrathecal DADL in the canine mimic closely the events occuring in human beings.

BEHAVIORAL EFFECTS

The somnolence and depression likely reflect a supraspinal action of the drug. Although no systematic measures were carried out, it appeared that the somnolence corresponded with the time course of the respiratory depression.

Of particular significance is that no seizure activity was noted even at the highest doses of DADL. Likewise, in dogs prepared with chronic EEG and hippocampal electrodes, DADL 200 μg injected into the lateral ventricle failed to produce EEG signs of seizures (G. E. Walker and T. L. Yaksh, unpublished observations). In contrast, the intraventricular administration of delta ligands can produce seizure discharges in cortex and hippocampus in the rat.[33] Therefore, the appearance of seizures seems to be species specific.

PHARMACOLOGY OF DADL EFFECTS

Previous studies in a variety of animal models have shown that IT DADL will produce a dose-dependent analgesia with a potency greater than morphine.[7,11,34] The present studies suggest comparable properties for the respiratory effects of DADL. Of principle significance is the fact that animals rendered tolerant to the analgesic effects of morphine show little loss of response to δ ligands such as DADL.[10,11] Unfortunately, an asymmetric tolerance has been reported, e.g., animals rendered tolerant to DADL or other δ ligands (metkephamid) show a loss of response to morphine.[11,35]

CLINICAL USE OF INTRATHECAL DADL

Onofrio and Yaksh observed that 1 mg of DADL given IT in 1 ml produced a quite significant respiratory depression antagonized by naloxone in a terminal cancer patient who was refractory to the analgesic effects of chronically infused IT morphine.[8] During approximately 30 h, the patient was pain free. Moulin and colleagues have recently completed a series of experiments with IT DADL given to terminal cancer patients.[9] In an effort to compare the effects of IT morphine and DADL, a nomogram was established in which the patient received 1 mg of IT morphine for each 40 mg of morphine equivalents/day given po required to produce adequate analgesia. DADL doses were established by giving one-fourth of the mg dose employed for IT morphine, under the assumption that DADL was approximately four times more active than morphine. In those experiments, DADL appeared to produce analgesia of greater intensity and longer duration than morphine.

CONCLUSIONS

Our study demonstrates that lumbar IT injection of DADL causes no apparent cardiovascular depression and a significant, dose-dependent, naloxone-reversible respiratory depression. As shown in other studies, intrathecally injected DADL produces powerful dose-dependent analgesia, even in morphine-tolerant animals and humans. Therefore, we conclude that DADL may represent an alternative to more traditional opiates such as morphine for IT administration, especially in morphine-tolerant patients. The significance of the asymmetric cross-tolerance is not known, but it seems reasonable not to use DADL as a drug of first choice in the chronic pain patient. Finally, respiratory and cardiovascular effects of intrathecally injected enkephalins such as DADL should be further investigated and compared with those of morphine.

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