Effects of perzinfotel on the minimum alveolar concentration of isoflurane in dogs when administered as a preanesthetic via various routes or in combination with butorphanol

Raphael J. Zwijnenberg, DVM, MVPHMgt; Carlos L. del Rio, DVM, PhD; Robert A. Pollet, PhD; William W. Muir, DVM, PhD

Objective—To determine the anesthetic-sparing effects of perzinfotel when administered as a preanesthetic via IV, IM, or SC routes or IM in combination with butorphanol.

Animals—6 healthy sexually intact Beagles (4 males and 2 females; age, 18.5 to 31 months; body weight, 9.8 to 12.4 kg).

Procedures—After administration of a placebo, perzinfotel (10 to 30 mg/kg), or a perzinfotel-butorphanol combination, anesthesia was induced in dogs with propofol and maintained with isoflurane in oxygen. The following variables were continuously monitored: bispectral index; heart rate; systolic, diastolic, and mean arterial blood pressures; end-tidal concentration of isoflurane; end-tidal partial pressure of CO₂; oxygen saturation as measured by pulse oximetry; rectal temperature; and inspiration and expiration concentrations of isoflurane. A noxious stimulation protocol was used, and the minimum alveolar concentration (MAC) was determined twice during anesthesia.

Results—IV, IM, and SC administration of perzinfotel alone decreased the mean isoflurane MAC values by 32% to 44% and significantly increased bispectral index values. A dose of 30 mg of perzinfotel/kg IM resulted in significant increases in heart rate and diastolic arterial blood pressure. The greatest MAC reduction (59%) was obtained with a combination of 20 mg of perzinfotel/kg IM and 0.2 mg of butorphanol/kg IM, whereas administration of butorphanol alone yielded a 15% reduction in the isoflurane MAC.


N-methyl-D-aspartate receptors are a class of glutamate-gated ion channels that regulate transmembrane flux of sodium and calcium. They have received particular attention from scientists and clinicians because of their crucial roles in excitatory synaptic transmission, plasticity, and prevention of neurodegeneration in the CNS.1,2 N-methyl-D-aspartate receptors contain various sites at which endogenous ligands and subunit-selective drugs modulate receptor activity. Subunits include NR1 (8 splice variants) and NR2 (A, B, C, and D subtypes), with additional variation possibly provided by the recently discovered NR3 (A and B) subunits. These subunits represent a class of structurally different binding sites with different affinities for receptor agonists and antagonists. Recent evidence suggests that activation of NR2B and NR3A subtypes plays an important role in perception of pain and neuronal injury, respectively. Considerable evidence exists to suggest that pain associated with peripheral tissue or nerve injury involves NMDA receptor activation.3 The receptors have been identified on myelinated and unmyelinated axons in peripheral somatic tissues.4,5 In rats, local injections of glutamate or NMDA result in nociceptive behaviors that can be attenuated by the peripheral administration...
of NMDA receptor antagonists. Administration of NMDA receptor antagonists effectively alleviates pain in animals in experimental and clinical situations. Although the effect of NMDA receptor antagonists has been well documented, use of such drugs as analgesics may be limited by adverse effects such as memory impairment, psychotomimetic effects, ataxia, and motor incoordination. Antinociceptive selective antagonists of NR2B-containing NMDA receptors (eg, ifenprof) have many fewer adverse effects than some other NMDA receptor antagonists.

Perzinfotel (EAA-090) is a potent NMDA receptor antagonist. In rats, a single bolus dose of perzinfotel administered IV after permanent occlusion of the middle cerebral artery results in a reduction in infarct size by 57%, compared with no perzinfotel administration. In vivo characterization revealed that perzinfotel was 10 times as potent at blocking NR2A- versus NR2B- or NR2C-containing NMDA receptors. It also protected chick embryo retina slices and cultured rat hippocampal and cortical neurons from glutamate- and NMDA-induced neurotoxic effects. When compared with uncompetitive channel blockers (eg, memantine, dizocilpine, and ketamine), an NR2B selective antagonist (eg, ifenprof), and other glutamate antagonists (eg, sellotet, CCP, and CGP-39653), perzinfotel has superior therapeutic ratios for effectiveness in treating pain versus adverse behavioral effects. In addition to yielding analgesic effects, NMDA receptor antagonists may reduce the amount of inhaled anesthetic needed to maintain anesthesia (anesthetic sparing). The MAC of an inhalant anesthetic is defined as the amount required to prevent gross purposeful movement in response to a noxious stimulus in 50% of subjects. Apart from an analgesic effect, available NMDA antagonists such as ketamine reduce the MAC of isoflurane needed to maintain anesthesia in dogs by up to 25%. Recently, perzinfotel was found to have anesthetic-sparing effects similar to or greater than ketamine in dogs.

The synthetic morphinan derivative butorphanol is a mixed agonist-antagonist opioid analgesic commonly administered alone or in conjunction with other sedatives as a preanesthetic prior to induction of general anesthesia in animals in experimental and clinical situations. Although the effect of NMDA receptor antagonists has been well documented, use of such drugs as analgesics may be limited by adverse effects such as memory impairment, psychotomimetic effects, ataxia, and motor incoordination. Antinociceptive selective antagonists of NR2B-containing NMDA receptors (eg, ifenprof) have many fewer adverse effects than some other NMDA receptor antagonists.

Perzinfotel (EAA-090) is a potent NMDA receptor antagonist. In rats, a single bolus dose of perzinfotel administered IV after permanent occlusion of the middle cerebral artery results in a reduction in infarct size by 57%, compared with no perzinfotel administration. In vivo characterization revealed that perzinfotel was 10 times as potent at blocking NR2A- versus NR2B- or NR2C-containing NMDA receptors. It also protected chick embryo retina slices and cultured rat hippocampal and cortical neurons from glutamate- and NMDA-induced neurotoxic effects. When compared with uncompetitive channel blockers (eg, memantine, dizocilpine, and ketamine), an NR2B selective antagonist (eg, ifenprof), and other glutamate antagonists (eg, sellotet, CCP, and CGP-39653), perzinfotel has superior therapeutic ratios for effectiveness in treating pain versus adverse behavioral effects. In addition to yielding analgesic effects, NMDA receptor antagonists may reduce the amount of inhaled anesthetic needed to maintain anesthesia (anesthetic sparing). The MAC of an inhalant anesthetic is defined as the amount required to prevent gross purposeful movement in response to a noxious stimulus in 50% of subjects. Apart from an analgesic effect, available NMDA antagonists such as ketamine reduce the MAC of isoflurane needed to maintain anesthesia in dogs by up to 25%. Recently, perzinfotel was found to have anesthetic-sparing effects similar to or greater than ketamine in dogs.

The synthetic morphinan derivative butorphanol is a mixed agonist-antagonist opioid analgesic commonly administered alone or in conjunction with other sedatives as a preanesthetic prior to induction of general anesthesia in dogs. It is believed that butorphanol acts as a partial δ-receptor agonist, pure κ-receptor agonist, and δ-receptor antagonist, although species differences have been reported. Studies conducted to investigate the inhalant anesthetic– (MAC-) sparing effects of butorphanol in dogs have revealed variable effects and minimal (8% to 19%) inhalant anesthetic–sparing effects. Results of several of these studies suggest that the anesthetic-sparing effect of butorphanol is enhanced and potentially additive when administered in combination with NSAIDs, although appropriate experiments to test this hypothesis were not performed.

Bispectral index processing is a proprietary method for analyzing the degree of sedation and hypnosis. Bispectral analysis examines the harmonic and phase relation of EEG signals and quantifies the amount of synchronization in the EEG. The BIS is a numeric value derived from the EEG and provides a reasonably accurate index of anesthetic depth and the presence or absence of consciousness. Values < 70 are generally associated with pronounced sedation, and values < 60 indicate unconsciousness from which an animal cannot be aroused. Changes in BIS values are used to indicate a return to consciousness during inhalant anesthesia and to help identify differences between drug-induced analgesic and hypnotic effects. The purpose of the study reported here was to determine the anesthetic-sparing effects of perzinfotel when administered as a preanesthetic via IV, IM, or SC routes or in combination with butorphanol.

**Materials and Methods**

**Animals and instrumentation—**Six healthy sexually intact Beagles (4 male and 2 female) were included in the study. Ages ranged from 18.5 to 31.0 months, and body weight ranged from 9.8 to 12.4 kg. Each dog was equipped with a telemetry device that had been surgically implanted a minimum of 2 weeks before beginning the study. The telemetry device permitted the simultaneous and continuous monitoring of respiration, ECG activity, arterial (femoral artery) blood pressure, and rectal temperature. The study protocol was approved by an institutional animal care and use committee.

**Experimental design—**Each dog underwent 8 treatments with perzinfotel (20 mg/kg, IV; 20 mg/kg, SC; 20 mg/kg, IM; 10 mg/kg, IM; and 30 mg/kg, IM), perzinfotel (20 mg/kg, IM) and butorphanol (0.2 mg/kg, IM), or saline (0.9% NaCl) solution (0.2 mL/kg; control treatment). Except for the first and last treatments (MAC0 and G, respectively), all treatments were administered following a Latin square crossover design. All treatments were separated by a minimum washout period of 7 days.

To determine the baseline MAC and other variables in all dogs, saline solution was first administered. Perzinfotel, butorphanol, or both were subsequently administered 30 minutes before anesthetic induction. The MAC of isoflurane was determined twice during each treatment at approximately 30 minutes after anesthesia onset (MAC1) and 2 hours later (MAC2). During the last treatment (treatment G), the control MAC of isoflurane was redetermined (MAC0) after administration of saline solution in all dogs to evaluate any possible confounding effects (ie, lessening of anesthetic requirements) resulting from habituation to the laboratory environment, the noxious stimulation protocol, or the repeated anesthesia (ie, temporal factors). Following determination of MAC0, the independent anesthetic-sparing effect of butorphanol was determined.

**Experimental procedures—**Food was withheld from dogs for 12 hours and water was withheld for 2 hours prior to administration of experimental premedications. The degree of sedation after administration of perzinfotel was scored. A cephalic vein was catheterized, and propofol administered to effect at a dose of 4 to 6 mg/kg. The dogs were orotracheally intubated and positioned in right lateral recumbency. Isoflurane in oxygen was used to maintain anesthesia through an out-of-circle, agent-specific vaporizer in a semiclosed anesthetic circle rebreathing system. The PETCO2 was maintained between
The BIS value was determined by delivering a noxious supra-maximal electrical stimulus to the buccal mucosa of each dog. Two 24-gauge, 10-mm insulated stimulating electrodes were inserted 1 cm apart into the buccal mucosa at a location dorsal and caudal to the incisors. The opposite ends of the electrodes were connected to an electrical stimulator that delivered a predetermined stimulus of 50 V, 5 Hz, and 10 milliseconds. Stimulation continued for 1 minute unless the dog had gross purposeful movement before the stimulus ended. Lifting of the head and repeated movement of the limbs were considered gross purposeful movement. Slight paw movement, arching of the back, chewing, swallowing, blinking, opening of the eyes, and nystagmus were not considered gross purposeful movement but, rather, a negative response. The ET\textsubscript{ISO} was initially set at 1.3% during each dog's first MAC\textsubscript{ISO} determination and at 1.2% each dog's control MAC value during subsequent days when experimental treatments were administered. If there was a negative response to the stimulus, the ET\textsubscript{ISO} was decreased by 20% and allowed to equilibrate for at least 15 minutes before applying the stimulus. This process was continued until a dog responded with gross purposeful movement. The ET\textsubscript{ISO} was then increased in increments of 10% until a dog failed to have gross purposeful movement. The MAC was considered to be the mean of the lowest ET\textsubscript{ISO} value that did not yield gross purposeful movement and the highest ET\textsubscript{ISO} value that yielded gross purposeful movement.

**Determination of BIS**—The BIS value was derived by continuously monitoring EEG activity. The EEG was obtained from platinum subdermal needle electrodes by use of a 3-lead referential montage, where the reference electrode was positioned on the midline of the head rostral to the medial canthus of the eyes. The ground electrode was positioned on the midline in the atlanto-occipital region. The EEG and BIS values were continuously acquired and displayed by use of a BIS monitor with the high-frequency filter set at 70 Hz and the low-frequency filter set at 2 Hz. The BIS number was automatically calculated and digitally displayed every 5 seconds and represented the EEG activity during the previous 60 seconds. Eight BIS values were recorded during a 2-minute period before and after buccal mucosal stimulation. It has been demonstrated that perzinfotel administration does not change BIS values in isoflurane-anesthetized dogs.

**Interval to sternal recumbency**—Interval to sternal recumbency was defined as the interval between extubation of a dog (laryngeal cough reflex) and its maintenance of sternal recumbency. Time was measured with a digital clock.

**Statistical analysis**—For each dog, mean values for all MAC determinations for a given treatment were calculated. Group data for each treatment are reported as mean ± SD. Responses of dogs when treated with experimental compounds or saline solution were compared. Comparisons of hemodynamic and BIS values were made at MAC level of isoflurane. For all comparisons, ANOVA was used, and the least-square means of each type of treatment were compared with each other with a 2-sided Student t test. A value of P < 0.05 was considered significant.

**Results**

All treatments were administered at a median interval of 7 days (mean ± SD interval, 10 ± 0.8 days). Mean ± SD control MAC (MAC\textsubscript{c}) values for isoflurane were 1.13 ± 0.12% (MAC1) and 1.20 ± 0.10% (MAC2) when determined approximately 30 minutes and 2 hours after the onset of anesthesia, respectively. The mean MAC determined at the end of the experiment was 1.12 ± 0.05%.

Administration of all doses of perzinfotel via all routes (IV, SC, and IM) 30 minutes before induction of isoflurane anesthesia resulted in a significant decrease in isoflurane MAC, heart rate, and BIS in 6 dogs premedicated with perzinfotel, butorphanol, or both and anesthetized with propofol (to effect) and isoflurane in an 8-treatment crossover study.

**Table 1**—Mean ± SD values and percentage changes relative to control values (saline [0.9% NaCl] solution) for isoflurane MAC, heart rate, and BIS in 6 dogs premedicated with perzinfotel, butorphanol, or both and anesthetized with propofol (to effect) and isoflurane in an 8-treatment crossover study.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>MAC Mean ± SD</th>
<th>Change (%)</th>
<th>Heart rate Mean ± SD</th>
<th>Change (%)</th>
<th>BIS Mean ± SD</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline solution*</td>
<td>18</td>
<td>1.14 ± 0.11</td>
<td>—</td>
<td>92.0 ± 20.1^{a,c}</td>
<td>—</td>
<td>73.1 ± 8.6</td>
<td>—</td>
</tr>
<tr>
<td>Perzinfotel (20 mg/kg, IV)</td>
<td>12</td>
<td>0.74 ± 0.10^{a}</td>
<td>−35</td>
<td>91.1 ± 16.0^{b,c}</td>
<td>−1</td>
<td>82.5 ± 0.9</td>
<td>13</td>
</tr>
<tr>
<td>Perzinfotel (20 mg/kg, SC)</td>
<td>12</td>
<td>0.77 ± 0.08^{b}</td>
<td>−32</td>
<td>108.7 ± 14.1^{a,c}</td>
<td>18</td>
<td>84.8 ± 4.8</td>
<td>14</td>
</tr>
<tr>
<td>Perzinfotel (10 mg/kg, IM)</td>
<td>12</td>
<td>0.78 ± 0.11^{a,c}</td>
<td>−32</td>
<td>105.8 ± 26.8^{a,b}</td>
<td>15</td>
<td>80.9 ± 4.9</td>
<td>11</td>
</tr>
<tr>
<td>Perzinfotel (20 mg/kg, IM)</td>
<td>12</td>
<td>0.72 ± 0.13^{a,d}</td>
<td>−37</td>
<td>108.9 ± 18.5^{a,b}</td>
<td>18</td>
<td>79.8 ± 3.4</td>
<td>9</td>
</tr>
<tr>
<td>Perzinfotel (30 mg/kg, IM)</td>
<td>12</td>
<td>0.64 ± 0.16^{a,c}</td>
<td>−44</td>
<td>117.9 ± 17.7^{a}</td>
<td>28</td>
<td>83.6 ± 4.9</td>
<td>14</td>
</tr>
<tr>
<td>Perzinfotel (20 mg/kg, IM)</td>
<td>12</td>
<td>0.47 ± 0.05^{b}</td>
<td>−59</td>
<td>83.5 ± 11.7^{a}</td>
<td>−9</td>
<td>85.6 ± 7.4</td>
<td>17</td>
</tr>
<tr>
<td>and butorphanol (0.2 mg/kg, IM)</td>
<td>6</td>
<td>0.97 ± 0.12</td>
<td>−15</td>
<td>74.7 ± 16.3^{a}</td>
<td>−19</td>
<td>74.8 ± 5.1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Two control measurements were made: 1 at the beginning and 1 at the end of the experiment for each dog.
— = Not applicable, n = Number of measurements.
^{a,b,c,d}Values without the same superscript letter grouping in each column are significantly (P < 0.05) different.
Heart rates and BIS values were measured at the isoflurane MAC level.
increase in mean isoflurane MAC values by 32% to 44% in the healthy dogs evaluated (Table 1). The decrease after administration of perzinfotel at 30 mg/kg, IM, was also significant compared with values for 20 mg/kg, IV, and 10 mg/kg, IM, indicating mild dose dependency. The greatest MAC reduction (59%; significant compared with reductions after all other treatments) was evident when the combination of 20 mg of perzinfotel/kg and 0.2 mg of butorphanol/kg was administered IM, whereas administration of the same dose of butorphanol alone yielded a much smaller reduction in the isoflurane MAC (15%).

Administration of perzinfotel alone yielded little sedative effect during the 30 minutes prior to induction of isoflurane anesthesia. However, the combination of perzinfotel and butorphanol yielded moderate sedation. Administration of perzinfotel resulted in dose-dependent, significant increases in interval to sternal recovery following extubation.

The BIS values significantly increased with all doses of perzinfotel administered (Table 1). In addition, when perzinfotel was administered in combination with butorphanol, BIS values increased significantly, whereas administration of butorphanol alone had no effect on BIS. These BIS values were measured at MAC level.

Heart rate decreased albeit nonsignificantly, compared with the control heart rate, in anesthetized dogs after treatment with the perzinfotel-butorphanol combination and with 0.2 mg of butorphanol/kg (Table 1). It increased (≥ 15%) relative to the control heart rate for all other doses of perzinfotel administered. Only treatment with 30 mg of perzinfotel/kg resulted in a significant increase in heart rate, compared with the control heart rate. These heart rate values were also measured at MAC level.

Treatment with perzinfotel resulted in a significant increase of DAP at a dose of 30 mg/kg (Table 2). Other increases in MAP, SAP, and DAP during isoflurane anesthesia were not significant. The perzinfotel-butorphanol combination had little effect on blood pressure, whereas administration of butorphanol alone resulted in a nonsignificantly lower DAP, SAP, and MAP by a mean of 13% to 21%. These blood pressure values were measured at MAC level.

When saline solution was administered, dogs took a mean of 58 ± 53 seconds to reach a sternal position after anesthesia with propofol and isoflurane; premedication with 20 mg of perzinfotel/kg, IV, increased this interval to 11.60 ± 5.80 minutes, whereas doses of 10, 20, and 30 mg of perzinfotel/kg, IM, resulted in an interval to sternal recency of 3.17 ± 2.65 minutes, 9.05 ± 3.85 minutes, and 16.55 ± 9.43 minutes, respectively. Administration of the perzinfotel-butorphanol combination resulted in an interval to sternal recency of 13.05 ± 11.83 minutes, compared with 3.43 ± 2.40 minutes in dogs that received only butorphanol (0.2 mg/kg, IM). With the exception of recovery intervals after treatment with only 10 mg of perzinfotel/kg, IM, or only 0.2 mg of butorphanol/kg, IM, all other recovery intervals were significantly longer than with the control treatment. No adverse reactions were observed during anesthesia or recovery.

**Discussion**

Results of the study reported here support and extend those of studies in which the anesthetic-sparing effects of perzinfotel were investigated in dogs. All doses of perzinfotel resulted in a decrease in isoflurane MAC values in healthy dogs, regardless of route of administration (IV, IM, or SC) or combination with butorphanol. Increasing the dose of perzinfotel administered IM resulted in a mild, dose-dependent reduction in isoflurane MAC values, which was augmented when perzinfotel was combined with butorphanol. The 0.2 mg/kg dose of butorphanol yielded a smaller effect when administered IM but also a significant reduction in isoflurane MAC. Collectively, these findings provide evidence that perzinfotel decreases inhalant anesthetic requirements and does not negatively impact the anesthetic-sparing effects of butorphanol in dogs.

The MAC of an inhaled anesthetic is used as a clinical index of drug potency and a guide to selection of the inhalant anesthetic concentration required for general anesthesia. The repeatability and stability over time of the control MAC values reported in the present study indicated that the measured decrease in isoflurane MAC values was scientifically valid. The decrease in MAC values after premedication with perzinfotel was greater than the relatively small decrease in MAC after premedication with butorphanol. The decreases in

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**Table 2—Mean ± SD values and percentage changes relative to control values (saline solution) for DAP, SAP, and MAP in 6 dogs premedicated with perzinfotel, butorphanol, or both and anesthetized with propofol (to effect) and isoflurane in an 8-treatment crossover study.**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>DAP Mean ± SD</th>
<th>Change (%)</th>
<th>SAP Mean ± SD</th>
<th>Change (%)</th>
<th>MAP Mean ± SD</th>
<th>Change (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saline solution*</td>
<td>18</td>
<td>66.5 ± 19.9a</td>
<td>—</td>
<td>115.0 ± 23.9a</td>
<td>—</td>
<td>84.6 ± 21.8a</td>
<td>—</td>
</tr>
<tr>
<td>Perzinfotel (20 mg/kg, IV)</td>
<td>12</td>
<td>79.6 ± 19.6ab</td>
<td>20</td>
<td>134.3 ± 20.3</td>
<td>17</td>
<td>98.0 ± 18.8</td>
<td>16</td>
</tr>
<tr>
<td>Perzinfotel (20 mg/kg, SC)</td>
<td>12</td>
<td>82.8 ± 16.4</td>
<td>25</td>
<td>134.6 ± 23.1</td>
<td>17</td>
<td>101.6 ± 18.3</td>
<td>21</td>
</tr>
<tr>
<td>Perzinfotel (10 mg/kg, IM)</td>
<td>12</td>
<td>78.1 ± 17.5a</td>
<td>19</td>
<td>127.5 ± 22.3</td>
<td>11</td>
<td>98.1 ± 16.7</td>
<td>16</td>
</tr>
<tr>
<td>Perzinfotel (20 mg/kg, IM)</td>
<td>12</td>
<td>81.1 ± 15.9a</td>
<td>22</td>
<td>130.3 ± 19.8</td>
<td>13</td>
<td>99.1 ± 17.4</td>
<td>17</td>
</tr>
<tr>
<td>Perzinfotel (30 mg/kg, IM)</td>
<td>12</td>
<td>85.2 ± 12.9a</td>
<td>28</td>
<td>134.2 ± 16.3</td>
<td>17</td>
<td>101.2 ± 13.2</td>
<td>20</td>
</tr>
<tr>
<td>Perzinfotel (20 mg/kg, IM) and butorphanol (0.2 mg/kg, IM)</td>
<td>12</td>
<td>65.4 ± 12.4a</td>
<td>–2</td>
<td>123.8 ± 11.9a</td>
<td>8</td>
<td>84.3 ± 11.7a</td>
<td>0</td>
</tr>
<tr>
<td>Butorphanol (0.2 mg/kg, IM)</td>
<td>6</td>
<td>52.8 ± 13.2a</td>
<td>–21</td>
<td>100.5 ± 16.1a</td>
<td>–13</td>
<td>69.0 ± 14.0a</td>
<td>–18</td>
</tr>
</tbody>
</table>

See Table 1 for key.
isoflurane MAC values were associated with significant increases in BIS values, suggesting an increase in consciousness. These increases in BIS values suggested a reduction in CNS and anesthetic-associated depression. The lack of change in BIS and hemodynamic values, among all treatments, when isoflurane concentration was held constant at 1.5% suggested that change in the isoflurane concentration was the main factor responsible for the changes observed.

Butorphanol administration resulted in comparatively minimal effects on isoflurane MAC and BIS values, although heart rate and arterial blood pressure were lower, albeit nonsignificantly, than control values. Administration of the perzinfotel-butorphanol combination resulted in the greatest decrease in isoflurane MAC (59%). These results support findings of a previous study suggesting that butorphanol has minimal inhalant anesthetic-sparing effects in isoflurane-anesthetized dogs. We did not perform the types of experiments required to determine whether this drug interaction relative to isoflurane MAC reduction was additive or synergistic, but we also did not find evidence of an antagonistic effect.

Administration of the perzinfotel-butorphanol combination led to a 9% decrease in heart rate in anesthetized dogs relative to the control value but a 12% increase in heart rate relative to that achieved via administration of butorphanol alone; however, neither of these differences was significant. The DAP, MAP, and SAP in these anesthetized dogs were higher than control values for all 5 doses of perzinfotel administered; however, this increase was only significant for DAP for the highest dose of perzinfotel (30 mg/kg). Percentage changes in blood pressure values achieved for all doses of perzinfotel alone were significantly higher than those achieved with butorphanol alone. The combination of perzinfotel and butorphanol increased DAP, MAP, and SAP relative to values attained with butorphanol alone. This effect was most likely attributable to the greater decrease in isoflurane concentration with perzinfotel-butorphanol administration, which, however, was not significant (value was similar to the control value).

Given its anesthetic-sparing effect, premedication with perzinfotel appeared to limit the decrease in arterial blood pressure typically associated with isoflurane anesthesia at MAC level. In contrast, premedication with butorphanol alone appeared to result in a further lowering of blood pressure (MAP) by approximately 18% relative to the control value. Neither of these changes was significant. The effects of butorphanol administration on heart rate and blood pressure when administered with perzinfotel or alone suggest that it possesses mild cardiovascular depressant activity in isoflurane-anesthetized dogs. Additional studies are required, however, to determine the dose-dependent cardiovascular effects of perzinfotel when administered alone and in combination with other opioid receptor agonists in isoflurane-anesthetized dogs.

In the present study, recovery from anesthesia was longer when dogs were premedicated with perzinfotel. These data indicated that perzinfotel may produce some immobilizing activity when combined with inhalant anesthetics and supported findings of another study suggesting that NMDA receptor inhibition contributes part of the immobilizing activity of aromatic volatile anesthetics. These longer recovery intervals would be of little or no clinical importance in a clinical setting (eg, 9.05 ± 3.85 minutes at a dose of 20 mg/kg, IM).

The authors are of the opinion that because increases in heart rate, DAP, MAP, and SAP were a general and consistent finding throughout the study and were significant for the highest dose of perzinfotel used (heart rate and DAP), it was of clinical importance to mention and discuss these data, regardless of the lack of statistical significance of many of the reported changes. Results that are statistically significant are not necessarily biologically or clinically important (eg, recovery intervals) and vice versa.

In the study reported here, premedication of healthy Beagles with perzinfotel (IM, IV, and SC) resulted in significant, dose-dependent decreases in isoflurane MAC values that were associated with improvement in BIS and hemodynamic values. The isoflurane MAC reduction was augmented by the concomitant use of butorphanol, and no adverse effects were observed.

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f. DSI Physio Tel D70-PCT transmitter, Data Sciences International, Saint Paul, Minn.
g. Passport 2, Datascope, Montvale, NJ.
h. T/Pump, Gaymar Industries Inc, Orchard Park, NY.
i. Genuine Grass platinum subdermal needle electrodes, Astro-Med Inc, West Warwick, RI.
j. Grass SD9 Stimulator, Grass Medical Instruments, Quincy, Mass.
l. SAS, version 8.2, SAS Institute Inc, Cary, NC.


