IN VITRO AND IN VIVO EVALUATION OF THE METABOLISM AND PHARMACOKINETICS OF SEBACOYL DINALBUPHINE

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ABSTRACT:

A diester prodrug of nalbuphine, sebacoyl dinalbuphine (SDN), and its long-acting formulation are currently being developed to prolong the duration of nalbuphine. A comparative in vitro hydrolysis study was conducted for SDN in rat, rabbit, dog, and human blood. Both SDN and nalbuphine in blood or plasma were measured by high-performance liquid chromatography. The hydrolysis rates of SDN in blood were ranked as follows: rat > rabbit > human > dog. The rapid formation of nalbuphine in the blood accounted for almost 100% of the prodrug, which supported the contention that nalbuphine is the major metabolite after SDN hydrolysis. The hydrolysis profiles of SDN were similar both in plasma and in red blood cells when compared in the blood. In vitro release results of SDN long-acting formulation showed that the rate-limited step of SDN hydrolysis to nalbuphine in blood is the penetration of SDN from oil into the blood. After intravenous administration of SDN in sesame oil into rats, nalbuphine quickly appeared in plasma and, thereafter, exhibited monoexponential decay. Pharmaceutical dosage forms affecting the drug disposition kinetics were demonstrated after intravenous administration. The AUC of nalbuphine was significantly higher and clearance was significantly lower, without changes in the t_{1/2} of nalbuphine after intravenous dosing of SDN in sesame oil when compared with that of intravenous dosing with nalbuphine HCl in rats. Overall, these results suggest that SDN fulfilled the original pro-soft drug design in which the prodrug can rapidly metabolize to nalbuphine, and no other unexpected compounds were apparent in the blood.

Esters have been the most common approach for prodrug development, because ester linkage of prodrugs tends to be converted efficiently to the active species through wide variability of esterase in the organs and tissues (Williams, 1985; Leinweber, 1987). The ester prodrugs apparently show that the safety and pharmacological actions of prodrugs seem to be the same as those for the parent compound (He et al., 1999; Ishikawa, 1999; Noble and Goa, 1999; Doucette and Aoki, 2001; Beaumont et al., 2003; Fischer et al., 2003). Nalbuphine is a potent μ-receptor agonist, μ-receptor antagonist analgesic with relatively low side effects (Jasinski and Mansky, 1972; Beaver and Feise, 1978). However, its short elimination half-life results in frequent injections for control of moderate to severe pain in clinical cases (Lo et al., 1987). SDN is a novel synthetic diester prodrug of nalbuphine designed to have high lipophilicity that consequently prolongs the duration of nalbuphine after intramuscular injection (Fig. 1).

A successfully designed prodrug should not only be well absorbed, but should also metabolize primarily and readily to its active moiety. The prodrug should fulfill several criteria as proposed by Bodor (1984). Basically, no unexpected compound should be formed in vivo. Red blood cells and plasma are known to contain esterase (Leinweber, 1987; Cossum, 1988). In this study, SDN was examined for its in vitro metabolism in rat, rabbit, dog, and human blood. The release of SDN from an oil vehicle in human blood was also examined. Both blood and plasma concentrations of nalbuphine and its prodrug were measured simultaneously. Subsequent in vivo studies, conducted to investigate the pharmacokinetics of SDN and its conversion to nalbuphine in rats after intravenous administration of nalbuphine HCl and SDN in a sesame oil vehicle, are presented in this report.

Materials and Methods

Materials. SDN was prepared by Yong-Shin Pharmaceutical Ind. Co., Ltd. (Taichung Hsien, Taiwan, R.O.C.) by a method obtained from the Pharmaceutical Research Institute, National Defense Medical Center. The structure of SDN was identified by high-resolution mass spectrophotometry, 13C NMR, and infrared spectrophotometry. Nalbuphine HCl and ethylmorphine (HPLC internal standard) were purchased from the Narcotic Bureau, Department of Health, Executive Yuan, R.O.C. All chemicals and solvents were analytical or HPLC grade. Sodium carbonate was purchased from Riedel-de Haen (Seelze, Germany). Acetonitrile, methanol, n-hexane, and isopropyl alcohol were obtained from Merck (Darmstadt, Germany). Water was prepared using a Milli-Q water purification system (Millipore Corporation, Billerica, MA).

In Vitro Metabolism Study. Fresh heparinized blood obtained from male Sprague-Dawley rats, New Zealand rabbits, male beagle dogs, and healthy humans were used for SDN hydrolysis studies. SDN (700 mg) was dissolved in 1 ml of acetoniaflite. Prodrug hydrolysis (n = 3) was performed in 70 ml of fresh whole-blood aliquots containing 1.4 mg of SDN in a 100-ml flask thermostat at 37°C in a shaking water bath. At time 0, the prodrug was added, and after various times of incubation, the blood samples were collected at 3, 6, 10, 15, 30, 60, 90, 120, 180, 240, 300, 360, and 675 min. Plasma samples were

ABBREVIATIONS: SDN, sebacoyl dinalbuphine; HPLC, high-performance liquid chromatography; AUC, area under the curve; C_{p}/C_{Ht}, ratio of the drug concentration in red blood cells versus that in plasma; Hct, hematocrit of whole blood.
obtained from collected blood samples by centrifugation at 0°C to quench the enzymatic hydrolysis of the prodrug. The hydrolysis of the prodrug was stopped completely by the addition of the extraction solvent under 0°C as soon as samples were obtained. Both SDN and nalbuphine in plasma and blood were determined by the same HPLC method reported by Pao et al. (2000). To evaluate the drug concentration in the red blood cells, the hematocrit of blood samples was measured immediately after the blood samples were collected. The drug concentration in red blood cells can be derived from the following equation (Shand et al., 1976):

\[
C_r/\text{Hct} = \left( \frac{C_b}{\text{Hct}} - \frac{C_p}{\text{Hct}} \right) \times 100\%
\]

where \( C_b, C_p, \) and \( C_r \) are the drug concentration in blood, plasma, and red blood cells, respectively. Hct is the hematocrit of the whole blood.

For blood, plasma, and red blood cells, the percentage of SDN remaining to be hydrolyzed to nalbuphine was calculated using the following equation:

\[
\text{% Remaining} = \frac{[\text{SDN}]_t - [\text{SDN}]_0}{[\text{SDN}]_0} \times 100\%
\]

where \([\text{SDN}]_t = 0\) (SDN concentration at time 0) represents the initial prodrug concentration.

The kinetic degradation rate constant \( k_d \) of the prodrug was determined as the reciprocal times the slope, whereas the slope was determined by linear regression of the linear portion of the ln [percentage of remaining prodrug concentration] versus time in whole blood, plasma, and red blood cells. The half-life degradation values were determined by \( \ln 2 \) divided by \( k_d \).

**In Vitro Drug Release from an Oil Vehicle in Human Whole Blood.** SDN is designated as a long-acting intramuscular injection preparation in an oil vehicle. In the present study, SDN was dissolved in sesame oil to give a concentration of 50 mg/ml. A total of 100 \( \mu \)l of drug containing oil was added to 20 ml of fresh human whole blood. In vitro release of SDN from an oil vehicle in human whole blood was carried out in triplicate at 37 ± 0.5°C in a shaking water bath. The oil drop was set at the top of the blood. At appropriate time intervals, blood samples were carefully withdrawn to avoid oil drop contamination. The amount of SDN remaining in the oil vehicle in the blood was calculated according to eq 2.

**In Vivo Metabolism and Pharmacokinetic Study.** Following the guidelines of the American Association for the Accreditation of Laboratory Animal Care, six male Sprague-Dawley rats weighing 300 to 400 g were fasted for 16 to 22 h with free access to water. A cannula was implanted into the right jugular vein for dosing drug solution and a second cannula was implanted into the left jugular artery for blood sampling. The rats were under pentobarbital anesthesia for the entire duration of the surgery. After recovery from the surgery, nalbuphine HCl was administered intravenously as a solution in normal saline at a dose of 22.35 mg/kg. The prodrug was formulated as a solution in sesame oil and other excipients because of its high lipophilicity. SDN was administered intravenously at a dose of 25 mg/kg (22.35 mg Eq/kg nalbuphine HCl). Blood was drawn at predose and at appropriate time intervals until 180 min after drug administration. Plasma samples were immediately

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Fig. 1. Chemical structure of SDN and nalbuphine.
separated from red blood cells by centrifugation under 0°C and kept frozen at −80°C until assayed for SDN and nalbuphine.

**HPLC Assay.** Both SDN and nalbuphine in plasma and whole blood were analyzed by high-performance liquid chromatography (Pao et al., 2000). Ultraviolet and fluorescence detectors were connected in series for determining SDN and nalbuphine, respectively. The two analytes and an internal standard were extracted from blood or plasma by one-step alkaline liquid-liquid extraction. Briefly, to 0.5 ml of whole blood or plasma, ice-cold extraction solution...
Fig. 3. Formation profiles of nalbuphine from SDN hydrolysis in blood (A), plasma (B), and red blood cells (C) from human (▼), dog (■), rabbit (●), or rat (▲).
was added as soon as possible after collection to inhibit enzymatic hydrolysis of the prodrug. Extraction solution consisted of 20 μl of internal standard, 1 ml of 0.5 M sodium bicarbonate, and 3 ml of a mixture of n-hexane-isooamyl alcohol (9:1, v/v). Analytes were extracted on a rotatory shaker for 30 min at 100 rpm. After centrifugation for 10 min at 3000 rpm (1080g), the aqueous layer was frozen by placing extracted samples in a freezer at −80°C for 20 min. The organic layer was then transferred into clean tubes and evaporated to dryness under vacuum. The sample was reconstituted in 300 μl of acetonitrile, and aliquots of 200 μl were injected onto the column.

Pharmacokinetic Analysis. T_{\text{max}} and C_{\text{max}} were determined directly from the plasma concentration-time curve. Pharmacokinetic parameters such as half-life, clearance, apparent volume of distribution, and area under the plasma concentration-time curve were determined by a noncompartmental method using WinNonlin (Pharsight, Mountain View, CA), calculated for each rat by standard methods (Gibaldi and Perrier, 1982). The apparent conversion of the active moiety, nalbuphine, after intravenous administration of SDN, F_{\text{mex}} was estimated by dividing AUC_{\text{obs}} obtained after intravenous administration of the SDN by AUC_{\text{exp}} following intravenous administration of nalbuphine HCl solution. All results are expressed as mean ± S.D. and were analyzed by analysis of variance using SPSS software (version 10; SPSS Inc., Chicago, IL). Statistical significance was assumed for p < 0.05.

Results

Hydrolysis Profiles of SDN in Blood. The conversion of SDN to nalbuphine in rat, rabbit, dog, or human blood was expressed by plotting the percentage of SDN remaining (Fig. 2) and the percentage of nalbuphine increasing versus time (Fig. 3) after incubation of the prodrug in blood. The hydrolysis of SDN in blood of rats, rabbits, and humans was rapid and complete after 60 min, except in the dogs’ blood (Fig. 2A). The hydrolysis rate of SDN in blood was fastest in rats and slowest in dogs. In all species, the hydrolysis rate of SDN from the blood exhibited apparent first-order decay kinetics. The mean metabolic half-lives of SDN in blood from humans, dogs, rabbits, and rats were 5.3, 34.3, 7.2, and 1.6 min, respectively (Table 1). Nalbuphine was the only measurable metabolic product of SDN in the blood, as judged by the almost complete recovery of nalbuphine (Fig. 3A) and the absence of unidentified products in the HPLC chromatograms (Pao et al., 2000). Nalbuphine concentrations in blood increased proportionally with decreases in the levels of SDN and then reached a plateau within 1 h in all species, except in dogs (Fig. 3A). The results revealed that the hydrolysis of SDN in blood was species-dependent.

When the hydrolysis profiles of SDN were determined in plasma and red blood cells, similar results were obtained as compared with those in the blood after SDN was spiked into blood (Fig. 2, B and C). The hydrolysis of prodrug in plasma and red blood cells was slower in dogs than in other species. These results were consistent with the appearance of nalbuphine in both plasma and red blood cells (Fig. 3, B and C). The formation of nalbuphine from SDN in dogs was the slowest one among tested species. Similar metabolic half-lives were obtained in blood, plasma, and red blood cells from rats, rabbits, and humans (Table 1). These results also indicated that both plasma and red blood cells were equally weighted in the hydrolysis metabolism of SDN in humans, rabbits, and rats. In dogs, a shorter metabolic half-life was observed in red blood cells than in plasma and whole blood (P < 0.05). The distribution of nalbuphine and SDN in blood is expressed as the ratio of the drug concentration in red blood cells versus the drug concentration in plasma (C/\text{Cp}). The C/\text{Cp} ratios were greater than one for both SDN and nalbuphine in all four species (Table 2). These results indicated that SDN and nalbuphine were more concentrated in red blood cells than in plasma after entering the bloodstream.

In Vitro Drug Release from an Oil Vehicle in Human Whole Blood. The release profiles of the SDN from sesame oil and the formation of nalbuphine in human whole blood are shown in Fig. 4. The release of SDN from sesame oil was considerably slower; more than 90% of SDN remained entrapped in the oil vehicle after 6 h of incubation in human whole blood. The formation of nalbuphine from SDN that was released from the sesame oil into the blood was steadily increased up to 11 h. Based on the results of the hydrolysis study described above, once SDN was released from oil vehicle into the blood, the hydrolysis of SDN occurred rapidly in human blood. These results suggest that the rate-limited step of the metabolism of SDN in sesame oil is the penetration of SDN from oil into the blood.

In Vivo Pharmacokinetics and Metabolism. The mean plasma concentrations after intravenous administration of nalbuphine HCl and SDN in rats are shown in Fig. 5. The high esterase activity of rat blood precludes the measurement of SDN in plasma 20 min after intravenous administration of SDN oil solution in rats, with a terminal half-life of 9.74 ± 3.44 min. The concentration of nalbuphine in plasma appeared quickly, reaching C_{\text{max}} within 20 min of intravenous dosing with SDN and, thereafter, exhibited a monoeponential decay with a terminal half-life of 95.6 ± 34.8 min. The pharmacokinetics of nalbuphine also were studied in rats dosed intravenously with nalbuphine HCl. As shown in Fig. 5, a multieponential decay of nalbuphine was observed after the dose. It had a terminal half-life of 107.0 ± 32.8 min and a clearance of 117.1 ± 20.8 ml/min/kg. The pharmacokinetic parameters of both SDN and nalbuphine in rats after administration of SDN and of nalbuphine after administration of nalbuphine HCl are shown in Table 3. SDN oil formulation did not change the elimination half-life of nalbuphine, which is generally considered an inherent quality of a drug. The AUC of nalbuphine from SDN hydrolysis after intravenous dosing of SDN oil solution was shown to be significantly higher than that after an equimolar nalbuphine administration. The extent of conversion (F_{\text{mex}}) of the active nalbuphine after intravenous administration of SDN was calculated to be 163.8 ± 38.8%. The systemic clearance and the apparent volume of distribution of nalbuphine formed from SDN following intravenous dosing of SDN oil solution were about 50% less than that of nalbuphine HCl dosing.

Discussion

In the present study, species differences in the in vitro conversion of nalbuphine ester prodrug SDN were demonstrated. Prodrug is

### TABLE 1

The metabolic half-life of SDN in blood, plasma, and red blood cells from humans, dogs, rabbits, and rats

<table>
<thead>
<tr>
<th>Species</th>
<th>Whole Blood</th>
<th>Plasma</th>
<th>Red Blood Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>5.3 ± 0.4</td>
<td>5.4 ± 0.4</td>
<td>5.3 ± 0.5</td>
</tr>
<tr>
<td>Dog</td>
<td>34.3 ± 3.8</td>
<td>30.7 ± 2.1</td>
<td>43.6 ± 2.2*</td>
</tr>
<tr>
<td>Rabbit</td>
<td>7.2 ± 1.0</td>
<td>7.7 ± 1.9</td>
<td>6.1 ± 1.8</td>
</tr>
<tr>
<td>Rat</td>
<td>1.6 ± 0.2</td>
<td>2.5 ± 1.8</td>
<td>1.5 ± 0.1</td>
</tr>
</tbody>
</table>

* P < 0.05, as compared with SDN metabolic half-life in whole blood and plasma.

### TABLE 2

Ratio of red blood cells and plasma concentration of SDN and nalbuphine after SDN was added to blood of humans, dogs, rabbits, and rats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Human</th>
<th>Dog</th>
<th>Rabbit</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDN</td>
<td>1.7 ± 0.2</td>
<td>1.4 ± 0.2</td>
<td>1.5 ± 0.2</td>
<td>7.5 ± 0.3</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>2.2 ± 0.4</td>
<td>5.6 ± 1.2</td>
<td>1.7 ± 0.4</td>
<td>2.6 ± 0.2</td>
</tr>
</tbody>
</table>
readily converted to the clinically useful active drug. The study initially focused on the rate and extent to which prodrug was converted to the active compound in blood from four different species. The time course of the hydrolysis of SDN differed significantly among rats, rabbits, dogs, and humans, although they all followed the apparent first-order kinetic decay in blood. The conversion of SDN to nalbuphine was rapid in rat blood. The rank order of the hydrolysis rates of SDN in blood among the species was rat > human > rabbit > dog. This is consistent with relatively low esterase activities reported in dogs (Ecobichon, 1972). Furthermore, the overall recovery of nalbuphine from SDN in blood was around 100% (Fig. 3A). The hydrolysis of nalbuphine prodrug SDN in whole blood from rats, rabbits, dogs, and humans was 100% over a 5-, 60-, 120-, and 60-min incubation, respectively (Fig. 3). The metabolism half-life of SDN in human whole blood is very short (5.3 min). It may complete hydrolysis to nalbuphine within 30 min upon entering the bloodstream.

The ratios of $C_r/C_p$ were greater than unity for both SDN and nalbuphine in all four species. This is in agreement with the high lipophilicity of both compounds. The higher concentrations of SDN in red blood cells as compared with those in plasma revealed that the penetration of SDN into red blood cells was much faster than the metabolic hydrolysis of the drug, especially in rats. The $C_r/C_p$ ratios of nalbuphine from the conversion of SDN in blood were much higher in dogs than in the other species. Despite the species differences in drug distribution in blood, the hydrolysis rates and patterns in blood, plasma, and red blood cells were consistent for each species except dogs (Fig. 2). For example, the hydrolysis half-life of SDN in human was 5.3, 5.4, and 5.3 min in blood, plasma, and red blood cells, respectively (Table 1). The results suggested that both red blood cells and plasma would be likely to play a significant role in the metabolism of SDN ester prodrug in rats, rabbits, dogs, or humans.
The conversion efficiency obtained from an in vitro study was demonstrated, and nalbuphine was the major and only measurable metabolic product of SDN in the blood of all the species. For the purpose of validation of these in vitro results, it is necessary to demonstrate that SDN is converted to nalbuphine in vivo as efficiently as it is in vitro. In the present study, this goal was achieved by monitoring the formation of nalbuphine after intravenous administration of SDN, as well as determining the plasma concentrations of the nalbuphine after administration of nalbuphine HCl in rats. As expected, the $C_{\text{max}}$ of nalbuphine after intravenous administration of SDN oil solution was reached at 20 min, which was consistent with the rapid disappearance of SDN in the same time frame. The high lipophilic property of SDN was reflected in 95-fold and 10-fold increases in systemic clearance and apparent volume of distribution of SDN as compared with nalbuphine, respectively, following intravenous dosing of the SDN oil solution in rats (Table 3).

Lipid or oily formulations have been used for parenteral administration of lipophilic drugs as potential drug delivery systems. These formulations have been shown to have the ability to change drug pharmacokinetics profiles such as slowing the rate of systemic clearance, enhancing tissue distribution, and resulting in a prolonged plasma-time course for the drug (Kim et al., 1995; Jia et al., 2002). SDN is a novel synthetic diester prodrug of nalbuphine that prolongs the duration of nalbuphine after intravenous administration. The ester prodrug also possesses high lipophilicity. Consequently, ester prodrug can easily be formulated into an oily long-acting dosage form to overcome the frequent dosing of nalbuphine HCl injection. After intramuscular injection of an oily formulation, the release rate of the prodrug from the injection site is restrictively limited by its high lipophilicity and has the effect of a long duration of action. The ester linkage of a prodrug can be hydrolyzed by esterase that appears extensively in organs and tissues such as the blood, brain, liver, lung, heart, and etc. (Mistry and Houston, 1987; Nambu et al., 1987; Hussain et al., 1987). SDN was formulated in an oil solution because of its high lipophilicity and fulfilled the original design aim of a long-acting intramuscular preparation. In the present study, we demonstrated that the apparent conversion of SDN to nalbuphine after intravenous dosing of SDN in sesame oil to rats was 163.8% that of intravenous dosing with nalbuphine HCl. The higher AUC of nalbuphine in the SDN oil formulation could be attributed to the lower clearance rate of nalbuphine. The clearance of nalbuphine after intravenous dosing of SDN in an oil solution and of nalbuphine HCl to rats (n = 6; mean ± S.D.)

<table>
<thead>
<tr>
<th>Parameters*</th>
<th>SDN (Formed from SDN)</th>
<th>Nalbuphine (Formed from SDN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (µg/ml)</td>
<td>2.47 ± 0.54</td>
<td>2.19 ± 0.74</td>
</tr>
<tr>
<td>$t_{1/2}$ (min)</td>
<td>9.74 ± 3.44</td>
<td>9.56 ± 3.48</td>
</tr>
<tr>
<td>AUC$_{\text{0-t}}$ (µg · min/ml)</td>
<td>5.22 ± 3.82</td>
<td>32.30 ± 7.62</td>
</tr>
<tr>
<td>CL (l/min/kg)</td>
<td>0.066 ± 0.116</td>
<td>0.0116 ± 0.019*</td>
</tr>
<tr>
<td>$V_{p}$ (l/kg)</td>
<td>9.41 ± 5.40</td>
<td>8.52 ± 1.62</td>
</tr>
</tbody>
</table>

Since SDN was trapped in the oil, the release of nalbuphine in the blood was consequently restricted. Therefore, the oil formulation appeared to delay or restrain the contact of SDN with esterase in the blood.

The oil vehicle might also contribute to restraining the distribution of nalbuphine in the blood resulting in decreasing the apparent volume of distribution. The high lipophilicity of nalbuphine might favor distribution into an oil reservoir after hydrolysis from SDN in the blood. The apparent volume of distribution of nalbuphine after intravenous dosing of SDN and nalbuphine HCl was 8.52 ± 1.62 l/kg and 17.43 ± 3.78 l/kg, respectively, assuming that 100% of the SDN was converted into nalbuphine. Since the terminal half-life of nalbuphine after intravenous administration of SDN oil solution did not differ from that of nalbuphine HCl intravenous dosing, the increase in AUC might have resulted from the decrease in the apparent volume of distribution. The oil formulation decreases the apparent volume of distribution of nalbuphine, indicating a prolonged residence of nalbuphine in the central compartment. These results also indicated that the pharmacological dosage form could affect the disposition of the drugs, and consequently would alter the pharmacodynamics of the drugs. The plasma concentrations of nalbuphine converted from SDN after 30 min of intravenous administration of SDN oil solution were much higher than that of intravenous administration of nalbuphine HCl (Fig. 5). However, the half-life of nalbuphine did not change. This would lead to prolonging the analgesic duration of nalbuphine. The peak plasma concentration of nalbuphine following intravenous administration of SDN was much lower than that of intravenous administration of nalbuphine HCl (Fig. 5). This will improve the safety profile of intravenous administration of nalbuphine HCl.

Collectively, the metabolic study of SDN in blood of various animals in vitro and in rats after intravenous administration of SDN oil solution demonstrated that the designed prodrug fulfilled the original pro-soft drug design. It rapidly metabolized to nalbuphine and, apparently, no other unexpected compounds were formed both in vitro and in vivo. It was demonstrated in this study that pharmaceutical dosage forms affected the nalbuphine disposition. The oil formulation of SDN significantly increases the AUC of nalbuphine in rats after intravenous administration as compared with nalbuphine HCl intravenous dosing.

References

TABLE 3
Pharmacokinetic parameters of SDN and nalbuphine after intravenous administration of SDN in sesame oil solution and of nalbuphine after intravenous administration of nalbuphine HCl to rats (n = 6; mean ± S.D.)


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