DISPOSITION OF NALBUPHINE IN PATIENTS UNDERGOING GENERAL ANAESTHESIA

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Nalbuphine is an agonist-antagonist opioid, structurally similar to oxymorphone. It is an effective analgesic with a potency comparable to that of morphine 8–10 mg (Beaver and Feise, 1978). Nalbuphine offers several potential advantages if used during balanced anaesthesia: haemodynamic stability, a ceiling effect on ventilatory depression at doses of about 0.5 mg kg\(^{-1}\), rapid recovery of wakefulness, and a low incidence of nausea and vomiting after surgery. Its efficacy in suppressing reflex activity during laryngoscopy, tracheal intubation and intestinal traction is limited (Fahmy, Sunder and Roberts, 1982; Kay Healy and Bolder, 1985).

In the present study we present data on the plasma concentrations and disposition of nalbuphine when 20 mg was administered i.v. during anaesthesia for lower abdominal surgery.

PATIENTS AND METHODS

Ten patients (eight female; ages 24–61 yr, weights 53–81 kg, ASA I or II) were studied after giving informed consent. No patient had clinical evidence of renal, hepatic, cardiac or pulmonary disease. None had received, during the previous 7 days, drugs known to influence hepatic blood flow or hepatic microsomal enzyme activity.

Patients were premedicated with diazepam 10 mg 1.5–2 h before surgery. Anaesthesia was induced with thiopentone 4–5 mg kg\(^{-1}\) and after neuromuscular transmission had been blocked, the trachea was intubated and the lungs ventilated with 67% nitrous oxide in oxygen at a rate of 12 b.p.m. and a tidal volume of 10 ml kg\(^{-1}\). Halothane (10–15%) or enfurane (0.8%) was added to the inspired gas mixture.

Analgesia was provided by nalbuphine 20 mg i.v. Patients received Hartmann's solution 5 ml kg\(^{-1}\) h\(^{-1}\) to replace insensible and blood losses. During the operation, the ECG was recorded continuously, and arterial pressure measured at 5-min intervals by oscillotonometry. Analgesia after surgery was provided by papaveretum 10–15 mg i.m.

Nalbuphine 20 mg (Nubain), was diluted to 10 ml with sodium chloride 0.154 mol litre\(^{-1}\), and given over 20 s via a peripheral infusion. Venous blood samples (6 ml) were collected via a separate cannula, placed in a vein in the contralateral arm, at 0, 1, 2, 5, 10, 15, 30, 45, 60, 90, 120, 180, 300 and 600 min after the administration of the drug. Heparinized plasma was separated by centrifugation, and stored at -20°C until analysed in duplicate.

Drug analysis

Nalbuphine was measured by high pressure liquid chromatography using an electrochemical detector (Keegan and Kay, 1984) with naloxone.

SUMMARY

The pharmacokinetics of nalbuphine 20 mg i.v. were studied in 10 patients undergoing lower abdominal or body surface surgery. Blood sampling was carried out for 600 min after injection and drug concentrations were measured by HPLC using electrochemical detection.Disposition was best described as a triexponential function, with a mean elimination half-life of 135.5 min. Mean residence time, clearance, and volumes of distribution, \(V^{38}\) and \(V^{10}\), were determined by a model independent method, and gave mean values of 149.7 min (MRT), 1095 ml min\(^{-1}\) (Cl\(_p\)), 159.9 litre (\(V^{38}\)) and 207.1 litre (\(V^{10}\)).
hydrochloride as the internal standard. The sensitivity of the assay was 0.1 ng ml\(^{-1}\) and the coefficient of variation 1–3.5% at plasma concentrations between 10 and 100 ng ml\(^{-1}\).

Data analysis

The decreases in plasma nalbuphine concentration after i.v. injection were analysed by non-weighted non-linear regression analysis (NONLIN) to determine the terminal half-life. However, initial estimates showed that the rapid distribution half-life of the triexponential model was less than 30 s for most patients and, because of the chosen sampling regimen, subject to considerable error. Consequently, further kinetic analyses were carried out using a non-compartmental approach, as described by Benet and Galeazzi (1979).

The general notation used in this paper is that defined by Hull (1979).

Data are presented as mean (±SD) except where otherwise indicated. The relationship between the age or the weight of the patient and the derived kinetic variables was investigated by linear correlation analysis.

RESULTS

Anaesthesia was uneventful in nine of the 10 patients; the remaining patient, a 41-year-old female, developed a sinus bradycardia (38 beat min\(^{-1}\)) and associated hypotension following the administration of the nalbuphine. These effects were readily corrected with atropine 0.3 mg i.v.

The mean nalbuphine plasma concentration–time curve is shown in figure 1. The mean elimination half-life was 135.5 min. The derived kinetic parameters (clearance, volume of distribution at steady state \(V^{\text{ss}}\), apparent volume of distribution during the elimination phase \(V^b\) and mean residence time) are shown in table I.

Correlation analysis showed no relationship between body weight or age and systemic drug clearance and \(V^{\text{ss}}\). The initial volume of distribution \(\left(V_i^b\right)\) varied between 0.73 and 13.55 litre (mean 5.84 litre).

![Fig. 1. Plasma nalbuphine concentrations (mean ± SD) following administration of 20 mg i.v. to 10 anaesthetized patients. For clarity, the SD bars have been omitted from the mean points at 1, 2, 5 and 10 min after injection.](image)

**Table I.** Derived pharmacokinetic parameters (mean ± SD) following i.v. injection of nalbuphine 20 mg in anaesthetized patients. Notation according to Hull (1979). MRT = Mean residence time

<table>
<thead>
<tr>
<th>Patient</th>
<th>(T^b_i) (min)</th>
<th>MRT (min)</th>
<th>(V^{\text{ss}}) (litre)</th>
<th>(V^b) (litre)</th>
<th>(Cl_p) (ml min(^{-1}))</th>
<th>(V^{\text{ss}}/V^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>131.0</td>
<td>140.8</td>
<td>191.97</td>
<td>257.81</td>
<td>1363.4</td>
<td>0.745</td>
</tr>
<tr>
<td>2</td>
<td>77.0</td>
<td>88.5</td>
<td>66.73</td>
<td>83.31</td>
<td>751.1</td>
<td>0.801</td>
</tr>
<tr>
<td>3</td>
<td>262.7</td>
<td>186.3</td>
<td>171.04</td>
<td>348.01</td>
<td>918.2</td>
<td>0.491</td>
</tr>
<tr>
<td>4</td>
<td>122.5</td>
<td>168.4</td>
<td>182.45</td>
<td>191.46</td>
<td>1083.3</td>
<td>0.953</td>
</tr>
<tr>
<td>5</td>
<td>173.8</td>
<td>196.9</td>
<td>187.85</td>
<td>239.26</td>
<td>954.2</td>
<td>0.785</td>
</tr>
<tr>
<td>6</td>
<td>115.6</td>
<td>150.4</td>
<td>154.94</td>
<td>171.77</td>
<td>1030.2</td>
<td>0.902</td>
</tr>
<tr>
<td>7</td>
<td>159.4</td>
<td>190.1</td>
<td>202.40</td>
<td>244.83</td>
<td>1064.5</td>
<td>0.827</td>
</tr>
<tr>
<td>8</td>
<td>139.7</td>
<td>165.0</td>
<td>167.51</td>
<td>205.48</td>
<td>1015.3</td>
<td>0.815</td>
</tr>
<tr>
<td>9</td>
<td>103.6</td>
<td>128.4</td>
<td>130.89</td>
<td>152.45</td>
<td>1019.5</td>
<td>0.859</td>
</tr>
<tr>
<td>10</td>
<td>69.8</td>
<td>81.9</td>
<td>143.37</td>
<td>176.26</td>
<td>1750.7</td>
<td>0.813</td>
</tr>
<tr>
<td>Mean</td>
<td>135.5</td>
<td>149.7</td>
<td>159.92</td>
<td>207.06</td>
<td>1095.0</td>
<td>0.799</td>
</tr>
<tr>
<td>SD</td>
<td>55.4</td>
<td>40.4</td>
<td>39.62</td>
<td>71.21</td>
<td>276.6</td>
<td>0.123</td>
</tr>
</tbody>
</table>
Plasma drug concentrations at extubation of the trachea varied between 30 and 62 ng ml$^{-1}$. In no patient was extubation delayed because of ventilatory depression.

**DISCUSSION**

Previously available data on the i.v. kinetics of nalbuphine relate to volunteer studies (Dupont: on file) and patients undergoing cardiac surgery (Lake et al., 1982). In the former studies, the quoted clearance values varied between 1.54 and 2.53 litre min$^{-1}$, and the elimination half-lives between 2.16 and 3.35 h. The results determined in the patients undergoing cardiac surgery indicated an elimination half-life of 3–3.5 h. The terminal half-life in patients in the present study (mean 136 min) was shorter than that reported for other synthetic opioids such as fentanyl (McClain and Hug, 1980), and buprenorphine (Bullingham et al., 1980). Recent work by Reilly and colleagues (1985, 1986) has suggested that the use of halothane or enflurane as a supplement to nitrous oxide in oxygen anaesthesia is accompanied by a decrease in liver blood flow and the intrinsic hepatic clearance of flow-dependent, high hepatic extraction ratio drugs such as propranolol. A similar alteration in the disposition of verapamil (decreased clearance and decreased volume of distribution) has been described during volatile-supplemented anaesthesia in the dog (Merin et al., 1985). By extrapolation, it is possible that a similar alteration in disposition has been seen with nalbuphine in the anaesthetized patient, as our patients show a lower clearance and reduced volume of distribution when compared with the results obtained in awake volunteers.

The kinetics in this study were based on plasma total drug concentrations. Data from healthy volunteers indicate that nalbuphine binds to plasma proteins to the extent of 25–40% over the concentrations range 1–100 ng mg$^{-1}$. Hence binding, and therefore disposition, are unlikely to be significantly affected by other drugs or volatile agents given concurrently during anaesthesia, or in the immediate postoperative period (Dale and Nilsen, 1984).

The volumes of distribution of nalbuphine ($V_B$ and $V_{ns}$) are similar to those found for morphine (Murphy and Hug, 1981; Stanski, Greenblatt and Lowenstein, 1978) in the anaesthetized patient, but are less than those for the highly lipophilic opioid, methadone (Gourlay, Wilson and Glynn, 1982).

As a result of the sampling regimen adopted in this study, any estimates for $\pi$ and $\alpha$ half-lives would be liable to considerable error. Hence, the kinetic parameters were determined by a non-compartmental approach involving determination of the area under the concentration–time curve, and its first statistical moment. The estimates for $V_B$ (0.73–13.55 litre) showed a 20-fold variability. This is further evidence of poor characterization of the hybrid constants describing the distribution phases, and probable overestimation of $V_B$ in some patients (Chiou, 1980).

Criticism may be levelled at the use of samples of venous blood. Major and coworkers (1983) have shown considerable differences in propofol concentrations in arterial, peripheral venous and central venous samples for up to about 60 s after the end of administration. Thereafter, no significant differences were observed. Thus, although drug disposition in body tissues is dependent on arterial drug concentrations, the overestimation of $V_{ns}$, when based on venous sampling, will be significant only if extensive tissue drug uptake occurs (Chiou, 1982). However, Chiou (1982) has suggested that the determination of $V_{ns}$ by a physiological or model independent method will limit the magnitude of this overestimation. The value of $V_{ns}/V_B$ was high in our patients (mean 0.773), indicating that the return of drug from peripheral tissues to the plasma will not be the rate limiting factor in drug clearance.

In summary, nalbuphine has a high systemic clearance, and will have an estimated hepatic extraction ratio of 0.5–0.7. On account of this high clearance, and the accompanying short elimination half-life (136 min), it should be possible to administer nalbuphine by continuous i.v. infusion and achieve constant blood concentrations during the operative period.

**ACKNOWLEDGEMENT**

We are grateful to those surgeons who allowed us to study patients under their care.

**REFERENCES**


