The Pharmacokinetics of Droperidol in Anesthetized Patients

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A pharmacokinetic study of droperidol was performed in ten anesthetized patients receiving an intravenous bolus dose of 150 µg/kg of droperidol. Plasma concentrations were measured using a specific radioimmunoassay method. The pharmacokinetics of droperidol can be described according to a three-compartment open model. The mean (±SD) half-life for the rapid (t1/2a) and slow distribution (t1/2b) phases was 1.4 ± 0.5 min and 14.3 ± 6.5 min, respectively. The mean elimination half-life, t1/2β was 105.8 ± 20.2 min. The mean ±SD total body clearance was 14.1 ± 4.4 ml·min⁻¹·kg⁻¹, and the total apparent volume of distribution (Vdβ) was 2.04 ± 0.50 l/kg. The short terminal half-life of droperidol does not correlate with the well-known, relatively prolonged duration of its pharmacologic action. (Key words: Anesthetics, intravenous droperidol. Pharmacokinetics: droperidol.)

DROPERIDOL IS A POTENT neuroleptic drug widely used in various combinations with narcotic analgesics in general anesthesia and in neuroleptanalgesia.

The hemodynamic1-4 and respiratory1,2,5,6 effects of droperidol, either used alone or in combination with other agents, have been extensively studied. But there are few available data on the pharmacokinetics of the drug. Cressman et al.7 studied the absorption, metabolism, and excretion of droperidol in healthy, nonanesthetized subjects following intramuscular or intravenous administration of 3H droperidol and reported that half-life elimination was 134 ± 13 min. Bevilacqua et al.8 evaluated the binding of droperidol on human and bovine serum albumen, comparing it with other psychoactive butyrophenones. We have studied the pharmacokinetics of droperidol in anesthetized patients, using a sensitive radioimmunoassay method.

Methods

Ten patients, ASA Class I and II, undergoing nonhemorrhagic major abdominal, orthopedic, or gynecologic surgery were studied. Informed consent was obtained from each patient. Details of the patients and the operative procedures are summarized in table 1. None of the patients showed clinical or biochemical evidence of cardiac, hepatic, or renal disease. Serum electrolytes and hemoglobin values were within normal values.

All patients were premedicated with diazepam (10 mg) and atropine (0.5 mg) im 1 h before surgery. Anesthesia was induced with thiopental (4–6 mg/kg); suxamethonium (1 mg/kg) was used to facilitate tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen, fentanyl (5 µg/kg), and pancuronium bromide (0.1 mg/kg) to provide muscular relaxation. Controlled ventilation was used throughout the surgical procedure. Supplementary doses of fentanyl (100 µg) and pancuronium (1 mg) were administered when necessary.

After anesthesia induction, 150 µg/kg of droperidol was injected as a bolus dose to a forearm vein. Heparinized blood venous samples were withdrawn from a contralateral forearm vein, before injection and at 2, 4, 6, 10, 20, 40, 60, 80, 120, 180, 240, 300, and 360 min following injection. Plasma was separated by immediate centrifugation and stored at −30°C pending subsequent analysis.

Plasma droperidol concentrations were determined by radioimmunoassay using benperidol antibodies. Droperidol antibodies cannot be used because radioactive-labeled droperidol is unstable in very dilute solutions (appearance of radiolysis products). Consequently, a sensitive radioimmunoassay method has been developed9 (see Appendix) exploiting the high degree of crossreactivity between droperidol and benperidol (butyrophenone piperidinyl derivative of droperidol) antibodies. This method does not interfere with the known metabolites of droperidol.

9H benperidol and rabbit antibodies were supplied by Janssen Pharmaceutica (Beersel, Belgium).

Droperidol concentration as low as 0.2 ng/ml of plasma can be assayed; the coefficient of variation was 5 ± 3.7% in the scale of the standard curves (0.1 to 10 ng for 0.5 ml of plasma). The accuracy of the assay was 100 ± 2.5%.

Initial estimates of the kinetic parameters were obtained by the method of residuals.9 Final estimates were calculated by the nonlinear least-square regression program of SAS with the Marquardt algorithm, and weighting was by the inverse square of the predicted plasma level.** Other kinetic parameters were calculated by standard methods.9 This analysis led to the determination of a

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Received from the Département d’Anesthésie, CMC Foch, 40 rue Worth, 92151 Suresnes, France. Accepted for publication November 26, 1985.

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three-compartment open model to describe droperidol pharmacokinetics. Results are expressed as mean ± SD.

Results

The plasma concentration of droperidol decreased rapidly following injection, about 90% of the administered dose leaving the plasma within 1 h (Fig. 1). The decline in droperidol plasma concentration over a period of time can be expressed as a triexponential equation of the form

\[ C_p(t) = P e^{-\alpha t} + A e^{-\beta t} + B e^{-\gamma t} \]

where \( C_p \) is the plasma concentration of droperidol at time \( t \) and \( P, A, B, \alpha, \beta, \gamma \) are hybrid constants.

Droperidol pharmacokinetics and calculated kinetic variables are summarized in tables 2 and 3. The average half-life for the \( \alpha \) and \( \beta \) phases was 1.4 ± 0.5 min, 14.3 ± 6.5 min, and 103.8 ± 20.2 min. The calculated apparent volume of the central compartment \( (V_c) \) was 0.172 ± 0.096 l/kg, the total volume of distribution at steady state \( (V_{df}) \) was 1.399 ± 0.323 l/kg, and the total apparent volume of distribution \( (V_{df}) \) was 2.042 ± 0.502 l/kg. The rate constant \( K_31 \) (from the deep compartment to the central compartment) was five times lower than \( K_10 \) (elimination rate constant). Average total body clearance (CI) was 14.1 ± 4.4 ml·min⁻¹·kg⁻¹.

Discussion

Despite the wide use of droperidol, few pharmacokinetic data have been reported in humans. Our study differs from that of Cressman et al. in two respects: 1) the method of assay (isotopic or radioimmunoassay), and 2) the nature of the experimental material (healthy volunteers or surgical patients under anesthesia). Cressman et al., who did not use a mathematical analysis of their results, found that the plasma level profile was consistent with a two-compartment open model. Our method of mathematical analysis tends to show that the pharmacokinetics of droperidol are better described by a three-compartment model.
Table 3. Calculated Kinetic Variables after Bolus Injection of Droperidol

<table>
<thead>
<tr>
<th>Patient Number</th>
<th>$V_c$ (I/kg)</th>
<th>$V_{ss}$ (I/kg)</th>
<th>$V_{re}$ (I/kg)</th>
<th>Cl (ml·min⁻¹·kg⁻¹)</th>
<th>$k_{re}$ (min⁻¹)</th>
<th>$k_{re}$ (min⁻¹)</th>
<th>$k_{re}$ (min⁻¹)</th>
<th>$k_{re}$ (min⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.1993</td>
<td>1.656</td>
<td>2.360</td>
<td>19.4</td>
<td>0.097</td>
<td>0.157</td>
<td>0.144</td>
<td>0.153</td>
</tr>
<tr>
<td>2</td>
<td>0.1817</td>
<td>1.473</td>
<td>1.980</td>
<td>14.5</td>
<td>0.046</td>
<td>0.457</td>
<td>0.111</td>
<td>0.209</td>
</tr>
<tr>
<td>3</td>
<td>0.0689</td>
<td>1.339</td>
<td>2.076</td>
<td>13.9</td>
<td>0.025</td>
<td>0.722</td>
<td>0.222</td>
<td>0.168</td>
</tr>
<tr>
<td>4</td>
<td>0.1500</td>
<td>0.992</td>
<td>1.502</td>
<td>9.7</td>
<td>0.092</td>
<td>0.246</td>
<td>0.079</td>
<td>0.108</td>
</tr>
<tr>
<td>5</td>
<td>0.1400</td>
<td>1.390</td>
<td>1.977</td>
<td>11.9</td>
<td>0.085</td>
<td>0.103</td>
<td>0.150</td>
<td>0.177</td>
</tr>
<tr>
<td>6</td>
<td>0.1159</td>
<td>1.130</td>
<td>1.402</td>
<td>9.7</td>
<td>0.085</td>
<td>0.291</td>
<td>0.202</td>
<td>0.164</td>
</tr>
<tr>
<td>7</td>
<td>0.1746</td>
<td>1.740</td>
<td>2.736</td>
<td>12.9</td>
<td>0.074</td>
<td>0.245</td>
<td>0.076</td>
<td>0.135</td>
</tr>
<tr>
<td>8</td>
<td>0.1124</td>
<td>0.987</td>
<td>1.555</td>
<td>9.4</td>
<td>0.083</td>
<td>0.533</td>
<td>0.555</td>
<td>0.104</td>
</tr>
<tr>
<td>9</td>
<td>0.2081</td>
<td>1.312</td>
<td>1.893</td>
<td>17.2</td>
<td>0.083</td>
<td>0.156</td>
<td>0.059</td>
<td>0.067</td>
</tr>
<tr>
<td>10</td>
<td>0.4121</td>
<td>1.975</td>
<td>2.925</td>
<td>22.2</td>
<td>0.054</td>
<td>0.160</td>
<td>0.029</td>
<td>0.081</td>
</tr>
</tbody>
</table>

Mean ± SD: 0.1716 ± 0.323, 1.399 ± 0.502, 2.042 ± 4.4, 0.093 ± 0.287, 0.112 ± 0.196 ± 0.018

$V_c$ = apparent volume of the central compartment; $V_{ss}$ = total volume of distribution at steady-state; $V_{re}$ = total apparent volume of distribution; Cl = total body clearance; $k_{re}$ = elimination rate constant; $k_{12}$ to $k_{13}$ = transfer rate constants between compartments.

Nevertheless, the results of half-life of elimination are not very different: 134 ± 13 min⁻¹ and 103.8 ± 20.2 min in our study. This discrepancy cannot simply be explained by the difference of the periods during which droperidol concentrations were measured because our 6h period represents more than three half-lives of elimination.

The observed variation in P, A, and B intercepts, and, consequently, in the calculated kinetic parameters, is common in pharmacokinetic studies. Numerous suggested causes include different age groups of the patients, modification of hydration in the perioperioperioperiod, blood loss, alteration in the degree of protein binding, and so forth. For some of these reasons, we therefore chose short, nonhemorrhagic surgical procedures in patients within 32–63-yr age group, because droperidol is commonly used in such patients. No relation was established between any of the clinical data (age, sex, weight, or body area) and the pharmacokinetic parameters in our group of patients.

The total apparent volume of distribution ($V_{re}$ = 2.04 ± 0.502 I/kg) was twice the body weight, indicating an extensive uptake of droperidol in the tissues, probably due to a high liposolubility (Log P = 3.75). The deep compartment, compartment-3, represents the major constituent of the total volume of distribution and acts as a tissue reservoir. The $K_{13}/K_{12}$ ratio is 6.2, and the $K_{23}/K_{12}$ ratio is 0.2. This implies that elimination of droperidol is dominated by the deep compartment.

Cressman et al.⁷ have demonstrated the importance of the hepatic metabolism of droperidol; the mean value of the total body clearance of droperidol in the present study (14.1 ± 4.4 ml·min⁻¹·kg⁻¹) appears the same as the hepatic plasma flow (900 ml·min⁻¹).†† Droperidol may be considered to have a high hepatic extraction ratio. Potential accumulation of droperidol would occur when the elimination-rate constant from the central compartment is altered, i.e., decrease of the hepatic blood flow rather than alteration of the biotransformation capacity. However, this phenomenon is probably masked by the fact that elimination is largely controlled by transfer from the deep compartment to the central one.


Fig. 1. Plasma concentration of droperidol following intravenous injection of 150 μg/kg (mean ± SD) and the fitted curve.
Droperidol is frequently administered in combination with fentanyl (Innovar®). These drugs are very different pharmacokinetically, in that droperidol has a short elimination half-life (103.8 ± 20.2 min), and fentanyl has a longer one (ranging from 219 min\(^{10}\) to 522 min\(^{11}\)). Alfentanil half-life elimination (94 ± 6)\(^{12}\) is similar to that of droperidol; additional studies are required to show the possible clinical advantages of the combination of alfentanil and droperidol.

In conclusion, we found that the pharmacokinetics of droperidol can be described as a three-compartment open model. The half-life of elimination is short; the well-known, prolonged central action of that drug and possible delayed neurologic side effects\(^{13}\) cannot be explained by this pharmacokinetic finding. We offer tentative explanations such as a slow dissociation of droperidol from its receptor or a retention of droperidol in the brain. Finally, the dose–response relationship for the neuroleptic action may be shallow. However, it is difficult to establish such a curve when droperidol is used in the context of general anesthesia.

The authors thank Mr. R. Gasparini (Janssen Pharmaceutica, Beerse, Belgium) for performing the mathematical analysis.

References


Appendix

ABSTRACT OF THE JANSSEN PRECLINICAL RESEARCH REPORT

Preparation of the immunogen. Benperidol, 1-(1-(4-(4-fluorophenyl)-4-oxobutyl)-4-piperidinyl)-1,3-dihydro-2H-benzimidazol-2-one was converted to 3-(1-((4-(4-fluorophenyl)-4-oxobutyl)-4-piperidinyl)-2,3-dihydro-2-oxo-1H-benzimidazole-1-acetic acid, in order to obtain a hapten, suitable for coupling chemically to a protein carrier. This hapten was linked to bovine serum albumin with the aid of a carbodiimide derivative.

Immunization. The protein conjugate was dissolved in phosphate-buffered saline, pH 7.4, at a concentration of 1 mg/ml and emulsified with an equal volume of complete Freund's adjuvant. Two female New Zealand albino rabbits received 1.0 ml of the emulsion in multiple intradermal injections along both sides of their back. Beginning about 1 month after the initial dose, four booster injections were given subcutaneously with intervals of about 3 weeks. Blood was collected from the central ear artery 7 to 10 days after each booster injection, and serum was tested for antibodies to benperidol. The rabbits were killed 8 days after the last booster, and the collected serum was pooled and stored at −20°C.

Radioimmunoassay. Antibody titers were determined by adding 0.2 ml of various antisera dilutions to 0.5 ml of phosphate buffer (pH 7.4, 0.1 m) and 0.5 ng of tritium-labeled benperidol (R 4584) (spec. act. 9 Ci/mmol, corresponding to about 27,000 dpm) in 0.05 ml of 30% methanol-water. Incubation and separation of bound-free antigen were effected as described by Michels et al. (Radioimmunoassay of the new opiate analgesics alfentanil and sufentanil. Preliminary pharmacokinetic profile in man. J Pharm Pharmacol 35:86–93, 1983).