Comparison of Propofol Consumption and Recovery Time in Caucasians from Italy, with Chinese, Malays and Indians from Malaysia

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SUMMARY

Differences in sensitivity to anaesthetic drugs may exist among different ethnic groups. Allelic variants for drug metabolizing isoenzymes and pharmacokinetic differences may account for a variable response to some anaesthetic drugs. This study was designed to compare propofol consumption and recovery characteristics in four ethnic groups: Chinese, Malays, and Indians in Malaysia and Caucasians in Italy.

Patients undergoing total intravenous anaesthesia with propofol and fentanyl were evaluated for propofol consumption and recovery time. The Bispectral Index (BIS) was used to maintain the same anaesthesia depth in all patients. The BIS value, the response to verbal stimuli and eye-opening time were used to assess recovery.

After propofol discontinuation the BIS values returned to baseline in 11±4.2 min for Caucasians, in 12.5±5.1 min for Chinese, 15.9±6.3 min for Malays and 22.1±8.1 for Indians. Time to eye-opening was 11.63±4.2 min in Caucasians, 13.23±4.9 min in Chinese, 16.97±5.2 min in Malays and 22.3±6.6 min in Indians. The propofol consumption was significantly lower in Indians compared to the other three groups (P<0.01).

The recovery of Indians was much slower compared to Chinese, Malays and Caucasians. The recovery time of Malays is significantly slower compared to Chinese and Caucasians. Differences in propofol consumption and recovery time were not significant between Chinese and Caucasians, but the ratio recovery time/propofol consumption was significantly lower in Caucasians compared to all the other groups.

Key Words: ANAESTHESIA, ANESTHESIA; INTRAVENOUS: propofol, fentanyl, cytochrome P450, Caucasian, Asian

Variations in patient sensitivity to intravenous anaesthetic drugs are very important when using total intravenous anaesthesia (TIVA), especially if computerized Target Controlled Infusion (TCI) devices, based on population data, are used for propofol administration. Pharmacodynamic and pharmacokinetic differences may result in variable responses to anaesthetic drugs. Genetic polymorphisms may be responsible for drug inefficacy or toxicity. These problems are of great interest when dealing with patients of different ethnic groups.

In a previous study we demonstrated that the recovery time from anaesthesia with propofol and remifentanil is slower in Senegalese black Africans compared to European Caucasians. Senegalese blacks also showed a much higher mean arterial pressure stability than Caucasians during induction and maintenance of anaesthesia.

The present study was designed to extend the investigation to some populations from Asia: Chinese, Indians and Malays. The study was carried out in Malaysia, where all three ethnic groups are present, and Italy. Propofol consumption and recovery time from anaesthesia for Chinese, Malays and Indians from Malaysia and white Caucasians from Italy were compared to investigate whether there was a different response in the different ethnic groups.
MATERIALS AND METHODS

The present study was carried out in two hospitals: “Policlinico Careggi” in Florence (Italy), and the University of Malaya Medical Centre, in Kuala Lumpur (Malaysia).

After obtaining Institutional Ethics Committee approval in Florence and Kuala Lumpur and the patient’s written informed consent, white Caucasian, Chinese, Malay and Indian patients were enrolled. Based on a questionnaire and on the family names a local anaesthesiologist assigned the patients to a particular group. Each patient was informed about the group he was in and gave his consent. Caucasian patients were all Catholics, Chinese patients were Tao Buddhists, Malay patients were Muslims and Indian patients were Hindu. The patients considered were of both sexes, aged between 20 and 55 years, weight between 55 and 75 kg, height between 1.55 and 1.75m, body mass index (BMI) between 20 and 25, American Society of Anesthesiologists Physical Status (ASA) 1. No patient had any associated pathology. These subjects underwent general abdominal surgery lasting 60 to 90 minutes. Patient heart rate, non-invasive blood pressure and arterial haemoglobin oxygen saturation (SpO2) were recorded during anaesthesia. Enrolment continued until 25 subjects in each group completed the trial.

Exclusion criteria were a history of hypertension, liver or renal disease, tobacco, other drug or alcohol use, BMI >25, presence of sickle cell anaemia, haemoglobin SC disease and sickle cell trait. Patients who were not stable when the Bispectral Index (BIS) was at the target 40±5 level during anaesthesia were also excluded.

Patients received Hartmann’s solution 10 ml/kg IV, atropine sulphate 0.5 mg and fentanyl 0.7 µg/kg IMI 30 minutes before induction of anaesthesia. Anaesthesia was induced using a total intravenous technique including the administration of fentanyl 1.5 µg/kg and propofol 1.5 mg/kg (initial bolus). Patients underwent tracheal intubation and artificial ventilation (FiO2=0.4) with fixed parameters: 10 breaths/min, inspiratory ventilation volume 120 ml/kg/min. Propofol and fentanyl were delivered by Alaris IVAC-TIVA 6000 L pumps (Alaris Medical Systems, Basingstoke, U.K.) with a manually controlled technique. If needed, propofol infusion speed was increased to reach the target BIS value of 40.

Anaesthesia was performed in Florence and in Kuala Lumpur by the same anaesthetist.

After reaching BIS 40 and about 10 minutes after induction, the infusion of propofol was regulated in order to keep the BIS=40±5 throughout the intervention. Fentanyl was given at a fixed rate of 1 µg/kg/h. Pancuronium 0.08 mg/kg was administered as a muscle relaxant. All patients received 800 ml/h of saline solution IV during surgery. Fentanyl and propofol administration were suspended at the end of surgery and muscle relaxant reversal (neostigmine 2 mg+atropine sulphate 1 mg IV) was given at the same time.

Evaluation of Propofol Consumption and Wake-up Time from Anaesthesia

Mean arterial blood pressure, heart rate, pulse oximetry, clinical criteria and the Bispectral Index were used to monitor anaesthesia. Arterial pressure, heart rate and SpO2 were monitored with a Dynamap (Critikon, Tampa, FL) continuous monitor.

The EEG signal was obtained using 3 XP BIS strip sensor electrodes (Aspect Medical Systems Inc, Newton, MA, U.S.A.) from frontal electroencephalography (At-Fpzt). The EEG bispectral index was calculated using a commercially available EEG monitor (A-2000, Software Rev. 1.06) (Aspect Medical Systems Inc., Newton, MA, U.S.A.). Data were chosen with SQI (that is the percentage of good epochs in the last 120 epochs) >50. Mean BIS values for each patient were calculated from 5 minutes of monitoring data before the induction of anaesthesia (B0) and from 3 minutes of monitoring data starting 6 minutes (B1) and 10 minutes (B2) after propofol and fentanyl discontinuation. Values B1 and B2 were considered as recovery BIS. These were used in order to evaluate wake-up behaviour. Recovery time was assessed by response to verbal stimuli applied every 30 seconds starting from the discontinuation of the propofol and fentanyl infusions. Time to spontaneous eye-opening and movement to verbal command were recorded. Propofol consumption was calculated for each patient from induction up to propofol discontinuation. Data are expressed as value ±1 standard deviation (SD)

Statistics

BIS and wake-up data from Chinese, Malays, Indians and Caucasians were compared.

Endpoint BIS, recovery data and consumption data were tested for normality using the Kolmogorov-Smirnov statistic. As they were normally distributed (P>0.10), one-way analysis of variance (ANOVA) was used to compare BIS data at B0, B1, B2 and wake-up data, in the three groups. The Bonferroni test was applied as post hoc evaluation. A sample size of 25 patients per group was chosen corresponding to
a statistical power of 84% for the consumption of propofol and >95% for the wake-up time.

Statistical analysis was performed by using the GraphPad InStat utility, version 3 for Windows (GraphPad Software Inc, San Diego, CA, U.S.A.) and the Analyse-it Software for Microsoft Excel, version 1.62 (Leeds, U.K.). Statistical significance was defined as a $P$ value <0.05.

RESULTS

Figure 1 describes the trial profile. Demographic data for the 25 patients per group that fulfilled our criteria are summarized in Table 1.

Table 2 describes in detail the number of patients withdrawn from the trial together with the reasons for withdrawal.

The four groups examined in this study showed no statistically significant differences in BIS basal values $B_0$. Intraoperative mean BIS values are detailed in Table 1.

The time from discontinuation of propofol infusion to eye-opening was $22.3 \pm 6.6$ min in Indians ($P<0.001$)
TABLE 1
Demographic data and surgery details of the patients enrolled in the trial (n, or mean±sd)

<table>
<thead>
<tr>
<th></th>
<th>Caucasians</th>
<th>Chinese</th>
<th>Malays</th>
<th>Indians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number</td>
<td>25</td>
<td>25</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Males</td>
<td>13</td>
<td>12</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>37±16</td>
<td>38±18</td>
<td>37±14</td>
<td>39±15</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>67±10</td>
<td>64±12</td>
<td>65±14</td>
<td>68±12</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>80±17</td>
<td>85±18</td>
<td>83±20</td>
<td>79±21</td>
</tr>
<tr>
<td>Intraoperative BIS values</td>
<td>41±8</td>
<td>39±8</td>
<td>41±7</td>
<td>40±7</td>
</tr>
<tr>
<td>Surgery Details</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrectomy</td>
<td>9</td>
<td>8</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Cholecytectomy</td>
<td>7</td>
<td>7</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Colectomy</td>
<td>5</td>
<td>5</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Hysterectomy</td>
<td>4</td>
<td>5</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

TABLE 2
Patients who did not reach the primary endpoint with main reasons for exclusion

<table>
<thead>
<tr>
<th></th>
<th>Caucasians</th>
<th>Chinese</th>
<th>Malays</th>
<th>Indians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure decrease &gt;30%</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Variation in anaesthetic requirements</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Blood transfusion or more fluids</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Variations of ventilation parameters</td>
<td>2</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Unstable BIS</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>11</td>
<td>13</td>
<td>11</td>
</tr>
</tbody>
</table>

when compared to Chinese and Caucasians, \( P<0.01 \) when compared to Malays, 13.23±4.9 in Chinese \((P<0.05 \text{ when compared to Malays, not significant when compared to Caucasians})\), 16.97±5.2 in Malays \((P<0.01 \text{ when compared to Caucasians})\), versus 11.63±4.2 min in Caucasians.

Time to respond to verbal commands was 18.9±8 min in Indians \((P<0.01 \text{ when compared to all the other groups})\), 12.9±5.5 in Chinese, 14.8±7.1 in Malays versus 11±5.1 min in Caucasians.

Figure 2 shows the propofol consumption, time to eye-opening and the ratio of time to eye-opening/propofol consumption in the four groups. Comparison of the ratios shows that the Caucasians had a significantly lower ratio compared to all the other groups \((P<0.001)\). The ratio in Chinese patients was significantly lower \((P<0.001)\) than that of both Malays and Indians and the ratio in Indians was significantly higher than all the others \((P<0.001)\).

Mean BIS values at B1 (6-9 min after propofol discontinuation) and B2 (10-13 min after propofol discontinuation) in all the groups are shown in Figure 3. BIS values of Caucasians were significantly higher at B1 when compared to the other groups. BIS values were not significantly different between Chinese, Malays and Indians.

At B2 the BIS values for Caucasians and Chinese
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were significantly higher than the BIS of Malays and Indians. BIS values of Indians were significantly lower when compared to all the other groups.

DISCUSSION

The different pharmacokinetics and pharmacodynamics of some drugs in different populations may be caused by both genetic and acquired factors (including general health, nutrition, enzymatic induction and physical exercise). The recovery time from anaesthesia with propofol and remifentanil is faster in Caucasians than in African blacks from Senegal. Similar results have been confirmed in a comparison of African blacks from Kenya and Caucasians. The similarity in the results of these studies are striking despite substantial dietary and lifestyle differences between the Senegalese and Kenyan populations.

Genetic polymorphisms may account for differences in pharmacokinetics (and pharmacodynamics). One of the most studied polymorphic enzymes involved in drug metabolism is the cytochrome P450 family. Different allelic variants for P450 enzymes may be present in different ethnic groups. More than 70 variant alleles of the CYP2D6 locus have been described. Recent studies have demonstrated that in European Caucasians and their descendants functional alleles of cytochrome P450 are predominant (71%), whereas in Africans and African Americans the frequency of functional alleles is about 50%.

The present study shows a slower recovery time after anaesthesia with propofol and fentanyl in Indians when compared to Caucasians, Chinese and Malays. The recovery time of Malays was faster than that of Indians, but significantly slower than that of Chinese and Caucasians. These apparent differences in sensitivity to propofol are confirmed in the propofol consumption data. Propofol consumption was much lower in Indians when compared to the other groups and lower in Malays when compared to Chinese and Caucasians. Theoretically, variation in BIS reading with ethnicity could influence our results, but we know of no evidence to suggest that this occurs.

Recovery time was higher and propofol consumption lower in Chinese when compared to Caucasians, but the mean differences were not statistically significant. Data become significant when we consider the ratio between the recovery time and the propofol consumption rate.

Even though the main route of propofol metabolism is the glucuronidation by UDP-glucuronosyltransferase 1A, propofol is also widely metabolised in the liver by cytochrome P450 to form 4-hydroxy-propofol. In humans, CYP2B6 is the principal determinant of interindividual differences in propofol metabolism and there is a 20-fold interindividual variation, due to genetic factors.

Fentanyl metabolism is also linked to cytochrome P450. Propofol and fentanyl effects are synergic. A fixed low dose of fentanyl is reported to not influence the BIS. As BIS values are not affected by low dose fentanyl administration, we presume that propofol consumption in this study cannot be ascribed to differences in fentanyl metabolism, but there is a possibility that differences in individual sensitivity to fentanyl could influence the recovery time and wake-up behaviour.

In conclusion, important differences have been found in propofol consumption between Indians, Chinese and Malays in Malaysia and Caucasians in Italy. Recovery was also significantly different among...
the groups. Indians showed the longest recovery time and the lowest propofol consumption rate when compared to all the other groups. These results suggest pharmacokinetic or pharmacodynamic differences do occur among different ethnic groups in relation to propofol (and possibly fentanyl). Caution is also advised in applying our results to apparently similar ethnic groups living elsewhere. A computerized propofol infusion scheme derived in one population should not be assumed to have the same effect if used in a different ethnic group.

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