Comparative Study Between Three Intravenous Drugs
Thiopentone Sodium, Propofol and Midazolam:
Study of 100 Cases and Critical Review

S K Mondol¹, M A Rahim²

Abstract

Intravenous anesthesia became possible with drugs available since 1930 and the concept rapidly became popular with patients and anaesthetists. From the patient’s point of view it had the advantage of producing rapid loss of consciousness without excitement, distress, or the sensation of smothering often produced by a tightly pressed facemask. For the anesthetist, there was the predictable anaesthesia which was ideally rapid in onset and without coughing or movements. Thiopentone sodium, propofol and midazolam have been used in our comparative clinical study (About 100 cases) as an intravenous anaesthetic agent. Our clinical study was into three aged groups such as neonates & children (40 cases), middle aged (40 cases) and elderly (20 cases). 100 cases were divided into paediatric cases, in outpatient procedures, in neurosurgical cases, in geriatric anaesthesia, in obstetric cases. In our comparative study, we have seen when propofol used for induction of anaesthesia in briefer procedures, results in a significantly quicker recovery and an earlier return of psychomotor function as compared with thiopentone and midazolam irrespective of the agent used for maintenance of anaesthesia.

Introduction

Intravenous anesthesia became possible with drugs available since 1930 and the concept rapidly became popular with patients and anaesthetists. Intravenous anaesthetic agents are commonly used to induce anaesthesia, for maintenance, may be administered as repeated bolus doses and also used for sedation in the intensive therapy unit (ITU) and treatment of status epilepticus.

Among the current available intravenous anaesthetic agents we have chosen three such as thiopentone, propofol and midazolam for our comprehensive comparative study between them clinically. For that purpose 100 cases were assessed using ASA grading. We have had no anaesthetic deaths. We have found propofol to be a most valuable induction and maintenance agent for a great variety of cases.

Patients and Methods

Our comparative clinical studies were performed on 100 patients (Neonates & children 40 patients) middle aged (male & female – 40 patients) and elderly (20 patients) who had given their informed consent and were undergoing various out patients, paediatric cases, neurosurgical procedures, obstetric cases & geriatric cases etc. at the Rajshahi

¹ Assistant Professor, Department of Anaesthesiology, Rajshahi Medical College, Rajshahi.
² Honorary Medical Officer, Department of Anaesthesiology, Rajshahi Medical College Hospital, Rajshahi.
Medical College Hospital, Rajshahi from June 2005 to July 2006. The trial was conducted with the whole supervision of Associate Professor Md. Latifur Rahman of Rajshahi Medical College Hospital, Rajshahi.

Results

The age of patients under study ranged from 2 yrs to 70 yrs. Out of 100 cases 40% children, 20% male (18-40 yrs), 20% female (18-40 yrs) and 20% elderly patients.

<p>| Table -I : Age distribution of the patients |</p>
<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Number of patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-12 yrs</td>
<td>40</td>
<td>40</td>
</tr>
<tr>
<td>18-40 yrs (Male)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>18-40 yrs (Female)</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>51-60 yrs</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>61-70 yrs</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

| Table- II: Physico-chemical properties |

<table>
<thead>
<tr>
<th>Thiopentone sodium</th>
<th>Propofol</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>This is sodium ethyl (1- methyl butyl) thiobarbiturate. It is soluble in water. Propofol solution contains 1 or the sulphur analogue of pentobarbitone, introduced commercially as pentothal sodium in 1935. It is a yellow amorphous powder, soluble in water (and alcohol) diluted to 2.5% solution with PH 10.8-11. To prevent formation of free acid by CO2 from the atmosphere, 6% anhydrous sodium carbonate is added to the powder which is prepared in an atmosphere of nitrogen. It is largely non ionized at body P^H, a fact which facilitates its diffusion through membranes.</td>
<td>emulsion should not normally be mixed with other drugs or infusion fluids.</td>
<td>midazolam accounts for its stability in solution &amp; rapid metabolism. The high lipophilicity accounts for the rapid central nervous system (CNS) effect as well as for their relatively large volumes of distribution.</td>
</tr>
</tbody>
</table>

| Table-III: Pharmacokinetics of Thiopentone, Propofol & Midazolam |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Vc (L/kg)</th>
<th>Vdss (L/kg)</th>
<th>Cl e (ml/mi n/kg)</th>
<th>T 1/2 β (h)</th>
<th>Estimated hepatic extraction ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone</td>
<td>0.38 ± 0.10</td>
<td>2.5 ± 1.0</td>
<td>3.4 ± 0.5</td>
<td>11.6 ± 6</td>
<td>0.15</td>
</tr>
<tr>
<td>Propofol</td>
<td>0.8L/kg ± 0.5</td>
<td>2-10</td>
<td>20-30</td>
<td>4-7</td>
<td>-</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.40 ± 0.10</td>
<td>1.1-1.7</td>
<td>6.4-11</td>
<td>1.7-2.6</td>
<td>-</td>
</tr>
</tbody>
</table>

Vc-Central volume of distribution, Vdss- Volume of distribution at steady state, Cl- Elimination clearance, T 1/2 β - Elimination half-life.

| Table-IV: Important clinical properties of the thiopentone, propofol & midazolam |

<table>
<thead>
<tr>
<th>Drug</th>
<th>Predictability of Induction</th>
<th>Induction Pain &amp; Excitement</th>
<th>Cerebral effects</th>
<th>Respiratory effects</th>
<th>Cardiovascular effects</th>
<th>Recovery Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopentone</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Propofol</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

++ To - - a five point qualitative scale describing the relative positive (+,+),neutral (0) or negative (-, --) effect of each agent in each category.
Table-V: Pharmacodynamics.

<table>
<thead>
<tr>
<th>Agent</th>
<th>Cardiovascular</th>
<th>Respiratory</th>
<th>Cerebral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>MBP</td>
<td>SVR</td>
</tr>
<tr>
<td>Thiopentone</td>
<td>↑</td>
<td>↓</td>
<td>0</td>
</tr>
<tr>
<td>Propofol</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Midazolam</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

HR- heart rate; MBP- mean blood pressure; SVR- systemic vascular resistance; LVSWI - Left Ventricular stroke work index; PVR- Pulmonary vascular resistance; PAO - Pulmonary artery occluded pressure; VENT - ventilatory drive; B’dil - bronchodilation; CBF- cerebral blood flow; CMRO2 – cerebral oxygen consumption, ICP – Intracranial pressure.

0 = No effect
↑ = increase (mild, moderate, marked)
↓ = decrease (mild, moderate, marked)

Table-VI: Uses and Doses of Thiopentone, Propofol and midazolam.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Thiopentone</th>
<th>Propofol</th>
<th>Midazolam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>4.5 mg/kg I.V</td>
<td>1.5-2.5 mg/kg I.V</td>
<td>0.05-0.15 µg/kg/min</td>
</tr>
<tr>
<td>Maintenance</td>
<td>50-150 µg/kg/min I.V combined with N2O or an opiate</td>
<td>0.05 mg/kg pm</td>
<td>1 µg/kg/min</td>
</tr>
<tr>
<td>Sedation</td>
<td>An initial loading dose of 2 to 4 mg/kg is followed by an infusion of 30 to 80 µg/kg/min</td>
<td>25-75 µg/kg/min I.V</td>
<td>0.5-1 mg repeated 0.07 mg/kg IM</td>
</tr>
<tr>
<td>Infusion rate</td>
<td>An initial loading dose of 2 to 4 mg/kg is followed by an infusion</td>
<td>To obtain a plasma level of 3 to 4 µg/ml a four stage infusion</td>
<td>The infusion rate during surgical anaesthesia is titrated between 0.25 to 1 µg/kg/min with fentanyl 0.03 to 0.06 µg/kg/min or alfentanil 0.5 to 1.5 µg/kg/min.</td>
</tr>
</tbody>
</table>

Administration of thiopentone, propofol & midazolam by infusions.

Administration of these drugs can be explained by looking at the context sensitive halftime (i.e. the time it takes for the plasma concentration in the central compartment to decrease by 50 percent) for thiopental relative to midazolam & propofol. In this study it is believed that recovery after reasonably long thiopental infusions is slow relative to that after propofol. Fig- I. shows this difference.
Fig: Context-sensitive half times as a function of infusion duration for each of the pharmacokinetics models simulated. Note the longer context sensitive halftime for thiopental as compared with propofol and midazolam as the infusion duration increases.

**Discussion**

In our clinical comparative study we selected patients in paediatric cases, outpatient procedures, neurosurgical cases, obstetric cases and elderly patients (61-70yr) in various cases. Here discussion should be based on case basis which as follows:

**In paediatric cases**

Intravenous anaesthetics:

**Thiopentone**

Thiopentone remains the standard intravenous induction agent (2.5% sol 5 to 6 mg/kg) for children. Intravenous injection is painless and produces smooth induction of anaesthesia in one arm brain circulation time. Recovery occurs in 5-10 mins by redistribution of the drug. There are no significant differences in distribution kinetics or apparent recovery times between children and adults.

The dose of thiopentone varies with age. In neonates the ED$_{50}$ sleep dose is only 3.5mg/kg but increases rapidly to around 7mg/kg in infants aged 1-6 months, thereafter declining gradually throughout infancy and childhood. Thus it appears that neonates require 4-5mg/kg, infants 7-8mg/kg and children 5-6mg/kg of thiopentone for fast reliable induction of anaesthesia. These doses may be reduced by up to 50 percent with sedative medication. The reduced requirements in neonates compared with older infants can be explained by a decrease in plasma protein binding. The increased requirements in infants and children compared with adults (usual adult doze 4mg/kg) may be due to their increased cardiac out-put as this would be expected to reduce the first parts concentration of thiopentone arriving at the brain.

**Propofol**

Propofol is highly lipophilic and rapidly distributes into & out of the vessel rich organs, its rapid redistribution, hepatic glucoronidation and high renal clearance account for the rapid termination of its effects. As with thiopentone, the induction dose is higher in younger patients (2.9mg/kg) for infants (2yr) than in older patients (2.2 mg/kg) for patients 6-12yr. This may be related in part to a longer central, volume and greater clearance in the younger patients.

**Midazolam**

Midazolam is water soluble and therefore is not painful on intravenous administration.

Midazolam is the only benzodiazepine approved by the food and drug administration for use in neonates. It should be noted that because of its water solubility, midazolam takes three times as long to reach a peak electroencephalograph effect. The clinical importance of this finding is that one should wait at least 3 minutes between intravenous doses in order to avoid a 'stacking' of effect. The short elimination half-life (2h) offers an advantage for use as a premedication in children. Our study has shown it is rapidly absorbed after 1.m (0.1-0.15mg/ kg), oral 0.5 -0.75mg/kg, rectal (0.75-1mg/kg) administration.

**Out Patients Surgery**

**Patient selection**

The selection of patients must take account of two separate aspects: firstly the patients state of health
and secondly his social circumstances. Patients should normally be ASA I or II i.e. normal healthy people or those with minor systemic disease not interfering with normal activities the latter including medical conditions that are well controlled with therapy e.g. hypertension. An upper age limit of 65-70 years should be judged on biological rather than chronological age. In our study age is not contraindication of out patient surgery with the following exceptions.

- Premature infants
- Infants with a history of bronchopulmonary dysplasia or apnoeic episodes who have been symptomatic within the last 6 months.
- Siblings of infants who have died of sudden infant death syndrome.

**Table-1:** A selection of surgical procedures commonly under taken as day cases.

a) Gynaecology - Dilatation & curettage, laparoscopy, vaginal termination of pregnancy, colposcopy.


c) Ophthalmology: Strabismus correction, lacrimal duct probing, examination under anaesthesia.

d) ENT: Myringotomy, removal of foreign bodies, polyp removal.

e) Urology: Cystoscopy, circumcision, vasectomy.

f) Orthopaedics: Arthroscopy, Carpal tunnel release, ganglion removal.

g) General Surgery: Breast lumps, hernia, varicose veins, and endoscopy.

h) Circumcision, orchidopexy, dental extractions.

The selection of patients for day case surgery is made at the time of out patient consultation where routine measurement of pulse, B.P. and urine analysis and other relevant investigations (e.g. Sickles cell testing) are performed. Studies have demonstrated that a simple preparation questionnaire can be very effective in screening patients to detect common medical problems which are shown in Table - (2).

- Have you had anything to eat or drink in the last 4 hrs?
- Have you had any previous operations?
- Will you go home alone?
- Do you have a cough or a cold?
- Do you suffer with heart disease or high blood pressure?
- Do you get breathless or have chest pain on exercise or at night?
- Do you have asthma or bronchitis?
- Do you smoke?
- Do you have diabetes?
- Do you suffer form anemia, bruise easily or bleed excessively?
- Are you pregnant? (In case of female)

When considering children for day case procedures they should be healthy normally falling into ASA I or II groups. Premature babies who have not reached 34 wks conceptual age should not be considered for day case surgery & special consideration should be given to bodies that have been on ventilatory support.

Our purpose of study of these three drugs is to delivery of safe and effective general anaesthesia with nominal side effects and a rapid recovery in outpatient, surgical procedures. Thiopentone (3-6mg/kg) is usually associated with a rapid induction of anaesthesia without psychomotor recovery and subjective feelings of tiredness and drowsiness limit its usefulness in day case patients. Midazolam (0.2-0.4mg/kg) alone is also an adequate intravenous induction agent. However its onset of action is slower and recovery is prolonged compared with the thiopentone and propofol. Flumazenil a specific benzodiazepine antagonist, given at the end of surgery, speeds recovery following midazolam induction but its duration of reversal is limited in 60 minutes. However, compared with propofol recovery after flumazenil antagonism of midazolam anaesthesia
was still significantly slower. On the other hand
the authors consider propofol (1.5-2.5mg/kg) to be
the best intravenous induction agent of choice for
outpatient anaesthesia. Although induction of
anaesthesia with propofol is associated with a
greater decrease in blood pressure and heart rate
that with thiopentone or midazolam but this is
offset by a more rapid recovery and fewer
postoperative side effects. Propofol may be used in
the elderly out patient but the dose should be
reduced by 25 percent. Pain on injection may be
reduced by the addition of lignocaine or cooling
the propofol to 4°C. The direct anti-emetic action
of propofol may offer a further advantage. The
following figure shows the comparison of mean
changes in choice reaction time in patients -

**Thiopentone**

Thiopentone has played a valuable part in neuro-
anaesthesia. It lowers the CMRO₂ and the CBF
falls in parallel. The effects are dose dependent,
when enough thiopentone has been given to
produce an iso-electric electroencephalogram, the
CMRO₂ is about 50 percent of awake values. No
further fall in CMRO₂ occurs if more thiopentone
in given. The decrease in CBF is associated with a
lowering of ICP and the use of thiopentone during
induction of anaesthesia in patients with
intracranial space occupation is particularly
valuable as it may prevent increases in ICP
remitting from laryngoscopy & tracheal intubation.

**Propofol**

The effects of propofol on CMRO₂ and CBF are
similar to those produced by thiopentone: Propofol
1.5mg/kg produced a 32 percent fall in CSF
Pressure 2 minutes after induction of anaesthesia.
The reduction in MAP may be greater with
propofol and there is evidence that propofol
protects more effectively against the pressor
response to intubation.

**Midazolam**

(0.15mg/kg) has been shown to reduce CMRO₂ by
21-30 percent and CBF by 26 percent in patients
with space occupation. One study showed that
induction of anaesthesia with midazolam (0.32
mg/kg) was associated with no change in ICP.

**In Obstetric Cases**

*Thiopentone* - Thiopentone neither depresses nor
increases the tone of the gravid uterus. Thiopentone is not harmful induction for cesarean
section in doses up to 6mg/kg but 8mg/kg does
depress the foetus. Placental circulatory factors
and re-distribution of thiopentone in the mother
and foetus protect the foetal brain and spinal cord
from high concentrations of thiopentone and
explain why the umbilical cord blood concentration of thiopentone at delivery is one half
that in maternal blood. The neonatal condition is
better after thiopentone induction than after
midazolam induction.

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**Neuro Surgery anaesthesia**

Anaesthetic drugs have major effects on cerebral
function and much work has been done to identify
these effects and to evaluate their clinical
significance. The induction agents (Thiopentone,
propofol and Midazolam) have been given in
patients undergoing neuro surgery which is stated
below:

![Comparison of mean changes in choice reaction time in patients following induction of anaesthesia with thiopentone, midazolam and propofol (P<0.05).](image-url)
**Propofol**

Propofol is suitable for both the induction of and maintenance of anaesthesia and has also been approved for use in neurological, obstetric and cardiac anaesthesia. Because of its pharmacokinetics, Propofol provides a rapid recovery and is thus superior to thiopentone for maintenance of anaesthesia.

**Midazolam**

When Midazolam is used in appropriate doses induction occurs less rapidly than with thiopentone but the anesthesia is more reliable. Numerous factors such as dose, Speed of injection, degree of premedication, age influence the rapidity of action. In obstetric cases the neonatal condition is less good than after thiopentone induction.

**In geriatric Cases**

Anaesthetic problems of the elderly.

**Cardiovascular system**

Ischaemic heart disease, poor cardiac function and perfusion of vital organs, atherosclerosis and hypertension.

**Respiratory System**

Increased closing capacity with airway collapse & hypoxia; poor respiratory response to hypoxia, increased incidence of atelectasis, pulmonary embolus and postoperative chest infection.

**Nervous System**

Cerebrovascular impairment, hearing & sensory impairment, confusion.

**Pharmacology**

Increased sensitivity to CNS depressants and other drugs, impaired drug distribution metabolism and elimination, altered plasma protein and drug finding.

**Metabolism**

Slower metabolic rate; Impaired renal blood flow and function; Impaired fluid balance and malnutrition.

**Other problems**

Physically frail with impaired temperature control increased likelihood of gastro-oesophageal reflux, cervical spondylosis & arthritis with limitation of movement, thin vulnerable skin & diabetes.

Debilitated & sickly older patients are particular prone to preoperative complications but healthy order surgical patients should do well. Whether the age of the patients a satisfactory and uncomplicated anaesthetic course requires (1) an anaesthetic plan compatible with the patients physical status and the type of surgery (2) consistent monitoring and (3) careful attention to detail. In our clinical study the dose as of thiopentone, propofol & midazolam were reduced to 20-40% in elderly patients. No additional or unique major principles need to be observed when caring for the elderly patient.

**Conclusion**

The present study tried to bridge the gap of knowledge of information about the currently available intravenous anaesthetic drugs to the patients as well as for the anaesthetists. It was found in various types of cases that the propofol as compared with thiopentone and midazolam results in a significantly quicker recovery and an earlier return of psychomotor function and very much valuable in maintenance of anaesthesia. Because of its pharmacokinetics profile, propofol provides a rapid recovery and is thus superior to thiopentone and midazolam.

**Acknowledgement**

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**References**


All correspondence to:
Swapon Kumar Mondol
Department of Anaesthesiology
Rajshahi Medical College, Rajshahi.