TAJ June 2007; Volume 20 Number 1

ISSN 1019-8555
The Journal of
Teachers Association
RMC, Rajshahi

Original Article

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

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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.

TAJ 2007; 20(1): 28-35

Introduction

Intravenous anaesthesia became possible with drugs available in 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 uring 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

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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

Table -I : Age distribution of the patients

Age group (years)	Number of patients	Percentage
2-12 yrs	40	40
18-40 yrs (Male)	20	20
18-40 yrs (Female)	20	20
51-60 yrs	10	10
61-70 yrs	10	10

Table- II: Physico-chemical properties

Thiopentone sodium	Propofol	Midazolam
This is sodium ethyl (1- methyl butyl) thiobarbiturate. It is 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 co_2 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.	Propofol is an alkylphenol & is virtually insoluble in water. Propofol is normally a 1% formulation in an oil and water emulsion containing 10% soybean oil, 1.2% egg phosphatide and 2.25% glycerol. The P^H is 6-8.5. The preparation has a similar viscosity to that of water. Ampoules must not be frozen & should be shaken before use. The emulsion should not normally be mixed with other drugs or infusion fluids.	Midazolam belongs to the benzodiazepine group. Midazolam solution contains 1 or 5mg/ ml of midazolam with 0.8% sodiumchloride and 0.01% disodium edetate with 1% benzyl alcohol as a preservative. The P^H is adjusted to 3 with HCL & NaOH. It is the most lipid soluble but because of its P^H dependent solubility is water soluble as formulated in a buffered acidic medium (P^H 3.5) The imidazole ring of midazolam accounts for its stability in solution & rapid metabolism. The high lipophilicity accounts for the rapid central nervous system (CNS) effect as well as for their relatively large volumes of distribution.

Table-III: Pharmacokinetics of Thiopentone, Propofol & Midazolam

Drug	Vc (L/kg)	Vdss (L/kg)	Cl e (ml/min/kg)	$T\frac{1}{2}\beta$ (h)	Estimated hepatic extraction ratio
Thiopentone	0.38 ± 0.10	2.5 ± 1.0	3.4 ± 0.5	11.6 ± 6	0.15
Propofol	0.8L/kg ± 0.5	2-10	20-30	4-7	-
Midazolam	0.40 ± 0.10	1.1-1.7	6.4-11	1.7-2.6	-

Vc-Central volume of distribution, Vdss- Volume of distribution at steady state, Cle- Elimination clearance, $T\frac{1}{2}\beta$ - Elimination half-life.

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

Drug	Predictability of Induction	Induction Pain & Excitement	Cerebral effects	Respiratory effects	Cardiovascular effects	Recovery Characteristics
Thiopentone	+	0	+	-	-	+
Propofol	+	-	+	-	-	++
Midazolam	0	0	+	0	0	+

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

Table-V: Pharmacodynamics.

Agent	Cardiovascular				Respiratory				Cerebral		
	HR	MBP	SVR	LVSWI	PVR	PAO	VENT	B'dil'	CBF	$CMRO_2$	ICP
Thiopentone	↑ ↑	↓ ↓	**0**	↓	↓	↓	↓ ↓ ↓	↓	↓ ↓ ↓	↓ ↓ ↓	↓ ↓ ↓
Propofol	**0**	↓ ↓ ↓	↓	↓	↓	**0**	↓ ↓ ↓	**0**	↓ ↓ ↓	↓ ↓ ↓	↓ ↓ ↓
Midazolam	↑	↓ ↓ ↓	↓	↓	**0**	↓	↓ ↓ ↓	**0**	↓ ↓ ↓	↓ ↓ ↓	↓ ↓ ↓

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; $CMRO_2$ – 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.

Drug	Thiopentone	Propofol	Midazolam
Induction	4-5 mg/ kg I.V	1.5-2.5 mg/ kg IV dose reduced with increasing age.	0.05-0.15 mg/kg I.V
Maintenance		50-150 μ g/kg / min I.V combined with N_2O or an opiate	0.05 mg/kg prn 1 μ g/ kg/ min
Sedation	An initial loading dose of 2 to 4 mg/kg is followed by an infusion of 30 to 80 μ g/kg /min	25-75 μ g/kg/min IV	0.5-1 mg repeated 0.07 mg/ kg IM
Infusion rate	An initial loading dose of 2 to 4 mg/kg is followed by an infusion of 200- 300 μ g/kg/min for the first 20 mins & 30 to 70 μ g/kg/min there after.	To obtain a plasma level of 3 to 4 μ g/ml a four stage infusion scheme can be utilized This consists of a loading dose of 1mg/kg over 20 seconds followed by 170 μ g/kg/min (10mg/kg/hr for 10 mins, then 130 μ g/kg /min (8mg/kg/hr) for 10 mins and 100 μ g/kg/ min (6mg/kg/hr) there after.	The infusion rate during surgical anaesthesia is titrated between 0.25 to 1 μ g /kg/min with fentanyl 0.03 to 0.06 μ g/kg/min or alfentanyl 0.5 to 1.5 μ g/ kg/min.

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.

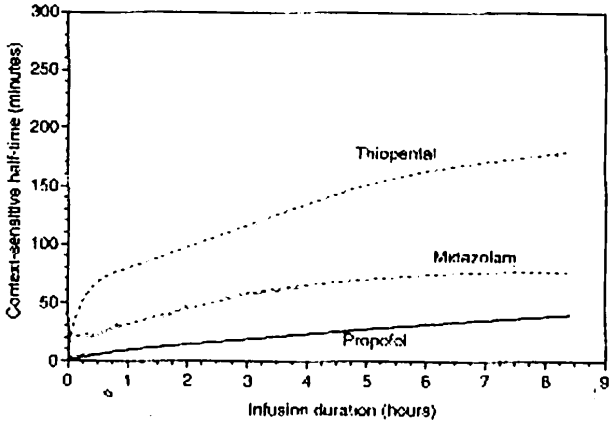


Fig: Context- sensitive half times as a function of infusion duration for each of the pharmacokinetics models simulated. Note the longer context sensitive halftime for thiopental as compared with propofol and midazolam as the infusion duration increases.

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:

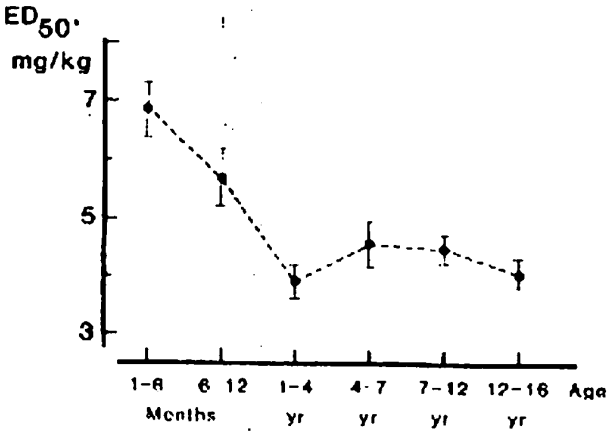
In paediatric cases

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 in5-10 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.
b) Plastic surgery: Dupytren's contracture release, removal of small skin lesions, nerve decompression.
c) Ophthalmology: Strabismus correction, lacrimal duct probing, examination under anaesthesia.
b) 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. Sickle cell tasting) 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 he 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 4^0C. 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 -

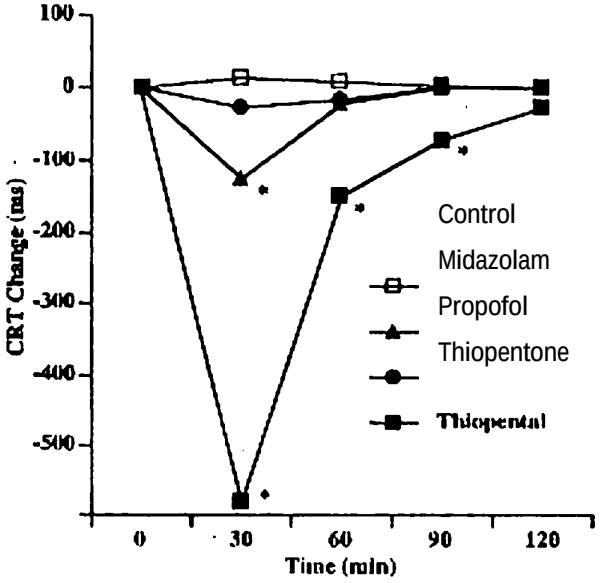


Fig. Comparison of mean changes in choice reaction time (CRT) in patients following induction of anaesthesia with thiopentone, midazolam and propofol ($P<0.05$).

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:

Thiopentone

Thiopentone has played a valuable part in neuro-anaesthesia. It lowers the $CMRO_2$ and the CBF falls in parallel. The effects are dose dependent, when enough thiopentone has been given to produce an iso-electric electroencephalogram, the $CMRO_2$ is about 50 percent of awake values. No further fall in $CMRO_2$ 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 $CMRO_2$ 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 presser response to intubation.

Midazolam

(0.15mg/kg) has been shown to reduce $CMRO_2$ 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 letter after thiopentone induction than after midazolam induction.

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 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

In creased 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

We acknowledge the help rendered by M.A. Rahim (Honourary - Anaesthesiology) and also by Director, Rajshahi Medical College in collecting data. We are very much thankful for their kind co-operation in preparing this study work.

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