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Effect of peak action of fentanyl overdose requirement of propofol given intravenously for induction of anaesthesia - A comparative study

[1]Dr. Sunil Kumar K, Junior Resident, Department of Anaesthesiology, A.J. Institute of Medical Sciences, Mangalore.

[2]Dr. Kashinath, Junior resident, Department of Anaesthesiology, A.J. Institute of Medical Sciences, Mangalore.

[3]Dr. Ashith Acharya, Junior Resident, Department of Anaesthesiology, A. J. Institute of Medical Sciences, Mangalore.

[4]Dr. Gurudutt S Rao, Professor, Department of Anaesthesiology, A.J. Institute of medical Sciences, Mangalore.

Corresponding Author: Dr. Sunil Kumar K, Junior Resident, Department of Anaesthesiology, A.J. Institute of Medical Sciences, Mangalore.

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Abstract

Background and objectives: Propofol are the most commonly used intravenous induction agent for General Anaesthesia nowadays. Propofol is ideal Anaesthetic agent as it exhibits rapid onset of action and smooth recovery from anaesthesia. The main disadvantages of propofol in the induction of General Anaesthesia as a sole induction agent is a significant reduction in cardiac output and systemic vascular resistance and hypotension. The adverse effect of propofol, especially hypotension, decreases by reduction of induction dosage. Fentanyl potentiate the action of propofol during induction of anaesthesia reduces its drug dosage for induction. This study has been done on same principle.

The aim is to estimate the effect of fentanyl on reduction of drug dosage of propofol on induction of anaesthesia. The objective of the study is to evaluate and compare the dose requirement of propofol in the induction of general anaesthesia at one minute and seven minutes after administering fentanyl as premedication. And to evaluate and compare the incidence of intra-operative hypo tension due to induction by propofol and incidence of techy cardia, brady cardia, hypertension, and movements as lighter plain of anaesthesia after induction of general anaesthesia using propofol as intra venousness thetic agent.

Methodology: Institutional ethics committee approval was obtained. A comparative, 2 group clinical study was conducted in the Department of Anaesthesiology, A.J. Institute of medical sciences, Mangalore. A total number of twenty-eight ASA grade 1 and 2 patients, 14 in each group, of either sex aged from 20 to 50 years scheduled for various elective surgeries under General anaesthesia. Surgery was done under standard anaesthesia technique. All patients were premedicated with fentanyl 2mcg/kg body weight.

Group A: Propofol was given 1min after Fentanyl administration.

Group B: Propofol was given 7 min after Fentanyl administration.

The titrating dose of propofol was given to the patients until loss of consciousness.

Results: Propofol administration after fentanyl as premedication for induction of general anaesthesia, required in significant less mean dosage in group B compared to group A (95% confidence interval [CI], −16.114 to -0.0452; P = 0.0488,) decrease in mean drug dosage per kg body weight between the two groups, mean ± SD of group A (1.536±0.068) and group B (1.231 ± 0.078) with a P value of 0.0001.

Conclusion: Administration of fentanyl as pre Medi cation before surgery reduces the dose requirement of propofol for induction and risk of hypotension during peak time of action.

Keywords: Anaesthesia, Propofol, Fentanyl.

Introduction

Propofol is the most commonly used intra venous in duction agent for General Anaesthesia nowadays. The reason behind its popularity is that propofol exhibit many of the properties of the exclusive ideal anesthetic agent like the rapid onset of hypnosis and rapid awakening together with minimal excitation [(1)]. Propofol has other advantages like fast induction, short duration of action, fast and clear-headed recovery, inactive metabolites, and no postoperative nausea, and vomiting.

The main disadvantages of propofol in the induction of general Anaesthesia which makes the drug less than ideal for use as a sole induction agent is the significant reduction in cardiac output and systemic vascular resistance with concomitant decrease in systolic blood pressure, brady cardia, and anaphylactic reactions.

Fentanyl a synthetic opioid agonist derived from phenyl piperidine has more rapid onset and peak central action delayed compared to peak plasma concentration due to the effect-site equilibrium time for fentanyl between brain and plasma is 6.4 minutes [(2)].

Therefore, this study is to examine the effect of fentanyl action over central nervous system on dose requirement of propofol to achieve the loss of consciousness during induction of general anaesthesia.

Aims and Objectives of the study:

The aim is to estimate the effect of fentanyl on reduction of drug dosage of propofol on induction of anaesthesia.

The objective of the study is to evaluate and compare the dose requirement of propofol in the induction of general anaesthesia at one minute and seven minutes after administering fentanyl as premedication.

And to evaluate and compare the incidence of intra-operative hypo tension due to induction by propofol and incidence of tachycardia, brady cardia, hypertension, and movements due to lighter plain of anaesthesia after induction of general anaesthesia using propofol as intravenous an aesthetic agent.

Methodology of Study

Study design: A comparative study. Place / site / college-Hospital: Department of Anaesthesiology at A. J. Institute of medical college, Man galore.

Sampling method

Random number allocation by computer-based applications. Institutional ethics committee approval was obtained.

A total number of twenty-eight ASA grade 1 and 2 patients of either sex aged from20 to 50 years scheduled for various elective surgeries under General anaesthesia was included in the study. Informed consent from patients was obtained after the patient was explained the purposes of study and a pre-structured proforma was used to record the relevant information from the individual subjects selected for the study.

Prior to the day of surgery, we performed a detailed pre-anaesthetic assessment and noted the demo graphic details, base line vitals, and laboratory investigations. We randomly assigned the subjects into two groups based on the random number allocation generated by computer applications. (Figure 1)

All our patients were pre-medicated with the tablet Ranitidine, 150mg, orally, on the night prior to surgery. We advised our patients to remain nil per oral for solids for at least 8 hours, semi-solids for a duration of 4 hours, and clear liquids for a period of 2hours.No sedatives or opioids were used for the purpose of premedication.

On the day of surgery, patient was shifted to the operation theatre, and made to lie supine on the OT table. A standard general anaesthesia technique and monitoring was followed. According to the departmental protocol the basic monitors such as 5 lead ECG, NIBP, and pulse oximetry were connected.

Baseline vitals were recorded and the IV line was secured with a 20GIV cannula, IV fluid Ringer lactate was started at 10ml/kg/hr. 8 litre of O2/min oxygen by non-rebreathing facemask was attached. All patients were premedicated with Glycopyrrolate 0.2 mg and IV Fentanyl l 2 mcg/ kg was administered.

Group A: Propofol was given 1min after fentanyl administration.

Group B: Propofol was given 7 min after fentanyl administration.

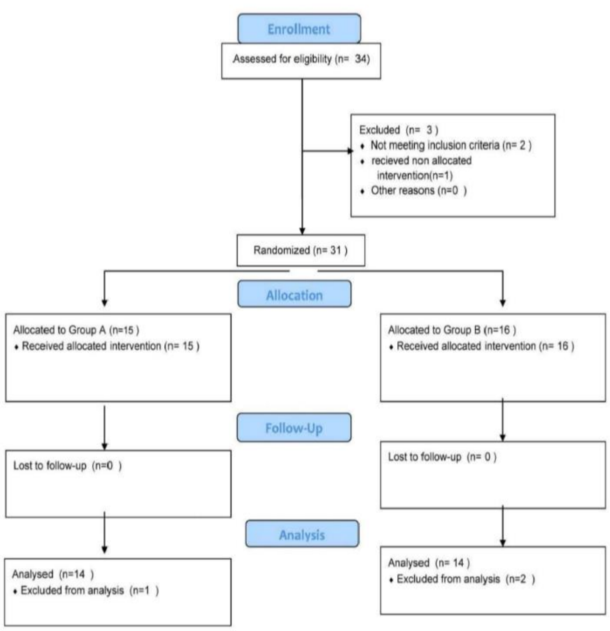
An independent anesthesiologist who was unaware of the time of fentanyl injection was asked to give propofol intravenously to induce the patient.

The titrating dose of propofol was given at the rate of 1ml/ 3sec intravenously while communicating verbally with the patient, who was asked to count backward from 100, induction of anaesthesia was considered complete once counting stopped and eyelashes reflexes were lost and propofol intravenous injection was stopped at that moment and dose of propofol administered were recorded.

After paralyzing with injection of Succinyl Choline 1-2mg/kg, manual ventilation is confirmed with bag and mask ventilation. The airway of the patient was intubated with polyvinyl chloride endotracheal tube of internal diameter 7.0 mm for females and 8.0 mm for males using size 3 or 4, Macintosh blade for laryngoscopy. The endo tracheal tube was secured after confirmation of position by end-tidal CO_2 tracing. We checked for bilateral equal air entry by the 5-point auscultation technique and confirmed the position of the endotracheal tube. Bolus effective dose (2 x ED 95) of vecuronium was given. Oxygen and nitrous oxide mixture was maintained at 33% and67% respectively with target concentration of propofol at 3μg/ml in both the groups to maintain adequate depth of anaesthesia. Muscle paralysis was maintained with Inj. vecuronium, one fourth of the intubating dose, whenever it was necessary, to obtain train-of-four counts of 1-2. We switched to circle absorber and maintained on low-flow anaesthesia with oxygen and nitrous oxide ratio of 1:2 and sevoflurane was used as inhalational agent. We carried out controlled mechanical ventilation throughout the procedure. Systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial blood pressure (MABP) and Heart rate (HR) were monitored every 3rd minute during the entire procedure.

At the end of the surgical procedure the inhalational agent and nitrous oxide was discontinued and the lungs were ventilated with100% oxygen. The neuromuscular blockade was pharmacologically antagonized using the combination of Inj. Neostigmine 0.05mg/kg and Inj. Glycopyrrolate 0.01mg/kg. Once the patient resumed regular spontaneous breathing patterns and opened them yes to command, the patient was extubated after deflating the endotracheal tube and the patient was shifted to post-operative care unit.

Figure 1: Consort diagram



Inclusion criteria

Adult patients aged between 20 to 50 years of age belonging to ASA grade1 and ASA grade 2, of either gender undergoing elective surgical procedures under General anaesthesia.

Exclusion criteria

Patients with cardiovascular disease including hypertension, broncho spastic disease, cerebrovascular disease, peripheral vascular disease, hepatic and renal impairment, diabetes mellitus, morbid obesity, and anticipated difficult air way. Those taking any drugs affecting hemodynamic parameters and/or requirement of propofol, history of alcohol or substance use, and emergency surgeries.

Patient included to ASA physical status grade 3 and 4.

Those patients are allergic to egg lecithin.

Patient on narcotics and alcohol.

Patient with previous anaphylaxis reactions.

Statistical Analysis

All the parameters measured as mentioned above were subjected to statistical analysis and interpretation. Statistical analysis was done by using Graph Pad Prism Software 7, for the two groups of 14subjectseach.

We checked the data for its normalcy distribution by Shapiro-Wilk test. The Data collected was either a continuous, numerical or a categorical variable.

Continuous data was analysed using unpaired in dependent sample test or equivalent non-parametric Mann-Whitney U test. Analysis of variance (ANOVA) for para metric data or equivalent Kruskal - Wallis ANOVA test for non-parametric data, repeated measures of ANOVA were used to compare the serial measurements within the groups in case of more than two groups. Tests with P value <0.05(5%) were taken as significant.

Demographic data and study parameters comprising numerical data with mean, standard deviations will be analysed using Unpaired test will be used to test significance difference of mean dos age between two groups.

Observation and results

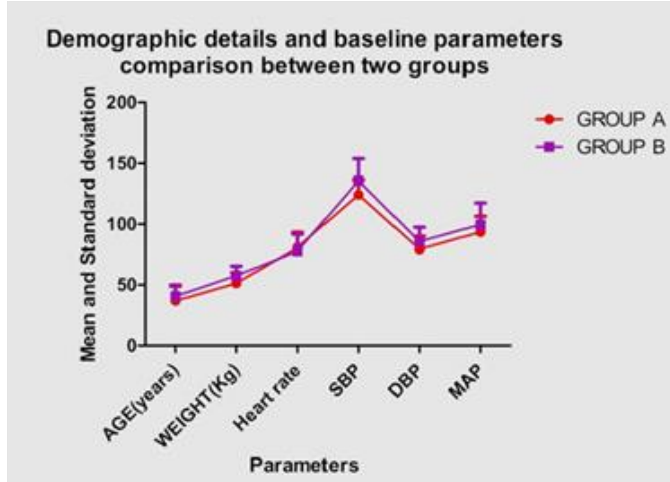
Of 34 patients who underwent elective surgeries, two patients were drop out from inclusion criteria. One patient who had been given not allocated medications before surgery was excluded prior to Randomisation. The remaining 31 were analysed as per protocol (CONSORT flow diagram). The groups did not differ by age, sex, weight, and pre-induction opioid use. Baseline vitals were comparable. Both groups received similar an aesthetic technique with respect to General anaesthesia between the groups. One patient from group A and two patients in group B were excluded after study due to incomplete data collected.

All demographic data and base line vitals were analysed for distribution using Shapiro-Wilk test and found normally distributed. Comparison of age, weight and gender distribution between the two study groups is normally distributed with P values, P=0.3527, P=0.0524, P=0. 2014 respectively. Comparison of base line data parameters between two groups were comparable and non - significant with P value more than 0.05.(Table 1 and Figure 2).

Table 1: Demo graphic details and base line parameters data distribution [mean ± standard deviation or number (percentage)].

	Group A	Group B	P value
AGE (years)	36.79±11.96	40.57±9.37	0.359
WEIGHT(Kg)	51.29±8.462	57.57±7.891	0.052
SEX (male/female%)	3(21.42%)/11(78.57%)	5(28.57%)/9(71.42%)	0.201(0.411)
ASAPS 1/2	9/5	10/4	0.691
Heartrate	80.93±12.29	77.79±13.86	0.531
SBP	124.3±12.05	135.8±18.13	0.121
DBP	79.21±10.89	85.57±11.81	0.150
MAP	93.36±13.02	99.50±17.96	0.309

Figure 2



Propofol administration during the peak action of fentanyl, drug dosage of propofol between groups shown significant difference (95% confidence interval [CI], − 16.114to -0.0452; P = 0.0488 Table 2).

And significance difference in mean drug dosage per kg body weight between two groups, mean ± SD of group A(1.536±0.068) and group B(1.231±0.078) with P value of 0.0001.The dosage of propofol required for induction of anaesthesia in group B is reduced significantly compared to requirement of propofol for induction in group A (Table 3, Figure 3).

The number of subjects requiring additional dosage of propofol administration, was similar in patients who received the additional propofol (14.28%) in Group A compared with Group B (21.42%), (P = 0.6281 ; CHI square = 0.235, 95% confidence interval [CI] -22. 0163 % to 35.24%).

The fall in the systolic blood pressure after induction with large dosage of propofol ingroup A compared to group B is significant with P value of 0.010(Table 4). Incidence of lighter plain of anaesthesia and movements of patient during instrumentation is non - significant with P value of 0. 628.There was no incidence of hypertension, and bradycardia. There was no significant techy cardia in group B compared to group A with P value of 0.1496.

Table 2: Comparison of mean dosage of propofol between two groups A and B.

Group	N	Mean	SD	SE	95%CI mean	P value
A	14	78.79	12.49	3.338	86.00-71.57	0.0488
B	14	70.71	7.61	2.034	75.11-66.32	

Table 3: Comparison of dos age of Propofol per kg body weight between group A and B

Group	N	Mean	SD	SE	95% CI mean Upper limit-lower limit	P value
A	14	1.536	0.068	0.018	1.575-1.496	0.0001
B	14	1.231	0.078	0.020	1.277-1.186	

High significance level between two groups using unpaired t test with P value of 0.0001, 95% CI. Significant reduction of dos age of Propofol required for induction of anaesthesia per kg body weight in Group B compared to Group A.

Figure 3

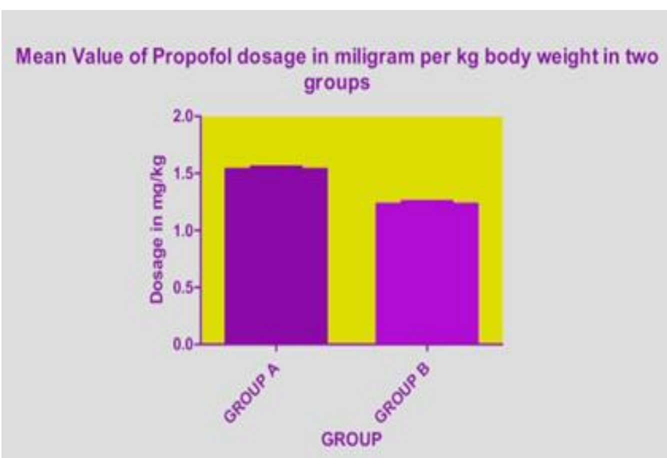


Table 4: Uni variant comparison of mean SBP at different time interval.

	Group a			Group b			P value
	Mean	SD	N	Mean	SD	N	
Baseline	125.6	15.48	14	135.8	18.13	14	0.121
After Fentanyl	121.2	16.09	14	128.5	19.42	14	0.288
After Propofol	110.6	12.56	14	127.8	19.46	14	0.010

Foot note

Significance level of P value in comparing mean of SBP between two groups after Propofol administration (P value=0.010). (Figure 17)

Discussions

Propofol alone as inducing agent requiring large doses of drug has various side effects. Drug dosage are attenuatred by various adjuvents like benzodiazepines, barbiturates and opiods.

Therefore, commonly used opioids as pre- induction medication to study the effect of fentanyl over drug dosage reduction of propofol [3]. Primary results in this study summarizes, propofol using as intravenous inducing agent along with fentanyl as pre-anaesthetic medication, fentanyl act as adjuvant to propofol and decreases the dosage of propofol given to patients at time of peak action of fentanyl.

In this study after administration of fentanyl 2mcg/kg in both the study group, the propofol dosage decreased in the group B of the study, as the fentanyl peak action reached after 2-5min, resulted significance decrease in the dosage. Significant difference in mean drug dosage per kg body weight between two groups, Mean±SD of group A (1.536±0.068) and group B (1.231±0.078) with P value of 0. 0001

The dosage of propofol required for induction of anaesthesia in group B is reduced significantly compared to requirement of propofol for induction in group A. The fall in the systolic blood pressure after induction with large dosage of propofol ingroup A compared to group B is significant with P value of 0.010.

The incidence of hypotension also decreases and stable haemo dynamic parameters as decreased the dosage of propofol required for induction of anaesthesia.

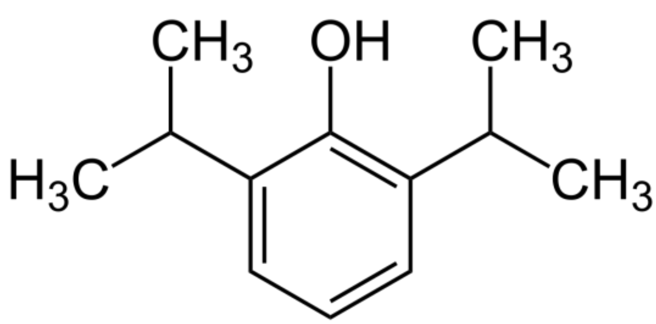
There is no significant difference between lighter plain of Anaesthesia in the two study groups. Movements during mask ventilation and intubation is less in both the patients, comparatively higher in group B, due to the result of decreased dosage of propofol administered for induction of anaesthesia.

The chemical composition of Propofol is 2,6, di-iso-propyl phenol, available in an emulsified formulation containing1% propofol, 10% soyabean oil,2.25% glycerol, and 1.2% egg phosphatide and with pH of 7-8.5. As a result, people with allergies to soy or eggs should not take propofol.

It is available in 20ml ampoules or vials containing 10mg/ml,50ml vial, and also with 2% concentration for continuous infusion [4]. The injection is due to the intravenous preparation's milk-like look, propofol is also referred to as "milk of amnesia".

Because of its effective induction and quick clearance, propofol is a commonly used intravenous anesthetic. Propofol is invented by “John lain Glen” [5]

Figure 4: Chemical structure



Propofol: 2,6, di-iso-propyl phenol

Mechanism of action

It activates the chloride channel of the GABA (Gamma amino butyric acid) receptor thus enhancing inhibitory synaptic transmission resulting in hypnotic effects. It binds to the β subunit of $GABA_A$ receptors. It also inhibits the N-methyl D-aspartate (NMDA)subtype of glutamate receptors. Propofol acts on $GABA_A$ receptors by positive allosteric modification. Site on the β_1-subunit, β_2-subunit β_3-subunits are the main crucial domains over GABA receptors of hypnotic action of propofol [6]. α-subunit and γ_2-subunit also contribute to modulating the effect of propofol on GABA receptors.

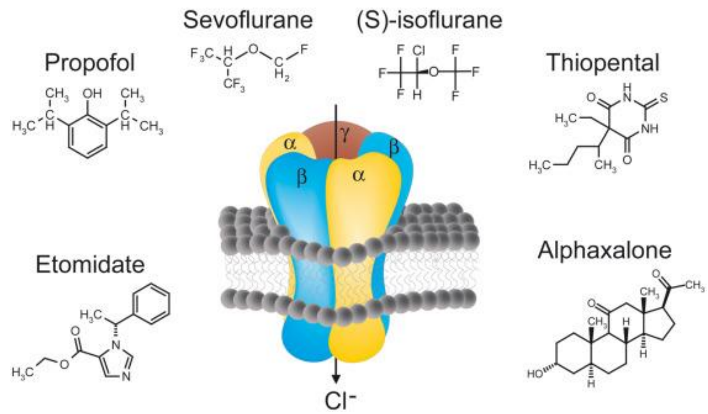


Figure 5: GABA receptor

Dosage and Route of administration

Propofol is always given intravenously for induction of anaesthesia 2-2.5mg/kg in adults and 2.5-3 mg/kg in children with a peak effect starting at 90-100 seconds. The median effective dosage (ED_{50}) of propofol for loss of consciousness is 1 to 1.5 mg/ kg bolus given intra venously. Maintenance of anaesthesia can be done with dosage of 50-150 mcg/ kg/min [7]. Sole total intravenous anaesthesia is given to maintain adequate depth of anaesthesia with the plasma concentration of 2.5-8mcg/ml along with nitrous oxide, opioids which are used as an adjuvant in anesthesia, and can begiven in boluses of 40 mg every 10 seconds, titrated to the beginning of hypnotic action, and a maintenance dose of 6-12 mg/ kg/h for healthy people younger than 55years of age [8,9]. Dosage of propofol decrease with age, largest at age equal to or less than two years.

Onset and duration of action

Onset is usually one arm brain circulation time(15-20sec) with time duration of 3-5minutes when given intra venously. Half-life of 2-5 minutes is the time taken for redistribution of the drug from central compartment to peripheral compartment (10).

Elimination by conjugation to glucuronide and sulphate by the liver. Propofol takes 0.5–1 minute to start working, and its effects last 4–8 minutes. Patient's age, sex, and weight have an impact on the pharmacokinetic parameters of propofol. Lower doses should be administered to elderly people. When administering propofol to less physically fit patients receiving general anaesthesia, such as those falling within the ASA physical status categories ASA 3 or 4, or when using propofol to induce and maintain sedation in critically ill patients in the ICU, this dose should be altered.

Pharmacokinetics

Propofol should only be administered intravenously, bitter in taste and low oral bioavailability brought on by a strong first-pass effect and a high hepatic extraction rate (> 90%), it is not suited for enteral or other routes of administration. Propofol is strongly bound to plasma proteins, primarily albumin, and erythrocytes after intravenous administration. Only 1.2-1.7% of the population is free. As up to 50% of propofol is bound to erythrocytes. The blood-brain barrier is easily crossed by propofol, which produces a rapid loss of consciousness. The rate of induction is influenced by cardiac parameters specific to the patient as well as the rate of infusion (11).

The liver is where propofol is primarily meta bolised. The uridine 5′- diphosphate (UDP) glucuronosyltransferase converts 70% of propofol – to - propofol glucuronide. About 29% of propofol is converted to 2,6-diiso propyl - 1, 4 - quinol by hydroxylation (4 - hydroxy propofol). This process involves a variety of cytochrome P450 (CYP) isoforms. The main catalysts are CYP2B6 and, to a lesser extent, CYP2C9(12,13).

The interindividual variability in propofol hydroxylation in liver micro some can be at least partially explained by environmental and genetic impacts on the CYP2B6. The 4 - (2, 6 - diisopropy l - 1, 4 - quinol) - sulphate, 1 - (2, 6 – diisopropy l - 1, 4 - quinol) - glucuronide, and 4 - (2, 6 – diisopropy l - 1, 4 - quinol) - glucuronide products of the conjugation of propofol metabolites.

Propofol inhibits the CYP3A4 cytochrome P450 enzymes, and leads to reduced metabolism of drugs, which are metabolized by CYP3A4 like midazolam and alfentanil (14).

After metabolism, 88% of propofol is eliminated in the urine within 5 days. The amount of given propofol that is unchanged Ly excreted is less than 0.3%. Rarely (less than 1% of patients) do the phenolic metabolites cause the urine to become green.

Exhalation is another way that propofol is eliminated. Even though the amount of propofol excreted in this way is very little (a few parts per billion or less), the plasma concentrations and the expired con centration are Correlated.

Systemic and Adverse effects

Central nervous system (CNS)

It produces dose-dependent depression of the CNS. Induction of anaesthesia is usually heralded by loss of verbal contact rather than loss of eyelash reflex. It may be used as an anticonvulsant. It reduces the cerebral metabolic rate, reduces cerebral blood flow through autoregulation and thus reduces intracranial pressure and intraocular pressure. However, it may reduce cerebral perfusion pressure by producing greater reduction in mean arterial pressure than intracranial pressure. It may cause some involuntary movements during induction. It binds to the postsynaptic $GABA_A$ receptor's -subunit, where it results in an inward-directed chloride current that causes the postsynaptic membrane to become hyper polarized. Theα_2 adrenergic system plays an indirect role in sedative effects of propofol [15]. Numerous cholinergic and monoaminergic nuclei in the reticular formation of the brainstem that promote sleep and wakefulness also have an impact on higher cortical regions. Inactivating specific wakefulness promoting regions locally, such as the locus coeruleus and dorsal raphe, enhances anaesthesia while activating specific wake fulness promoting regions locally, such as the pontisoralis and Centro medial thalamus, makes it easier to come out of anaesthesia. The ventrolateral preoptic region is one of the sleep promoting nuclei. Propofol also causes analgesia, amnesia and anxiolysis at hypnotic dosage.

Cardiovascular system

It causes hypo tension due to peripheral Vaso dilatation. The change in heart rate is un predictable. Propofol completely obtunds the baroreceptor reflex responses.

Respiratory system

It may cause transientapnoea. It obtunds the airway reflexes well. It does not increase airway secretions. Helps in achieving good intubating conditions even with smaller doses of muscle relaxants.

Gastrointestinal system

It has antiemetic properties as it decreases the serotonin level in the area of postrema at the site of Chemo Trigger Zone [16].

Non hypnotic therapeutic effect of propofol

Decreases cerebral oxygen consumption, reduces intracranial pressure, potent anticonvulsants, potent anti-oxidants, anti – inflammatory and bronc Ho dilator [17].

The propofol has anti-emetic properties and decreases the incidence of post operative nausea and vomiting [18,19].

Adverse effects

Hypo tension, allergic reactions to egg protein. Propofol causes pain on injection and to reduce it, lignocaine (20 mg to be added to 20 ml) is usually added to this solution before injection. Other measures that can help reduce pain on injection of propofol are storing the propofol at 4°C until it is ready for use, choosing a large vein and a small size intravenous cannula, rapid injection, pre-treatment with lidocaine, aspirating blood into propofol syringe prior to injection, use of new propofol 'propofollipuro'. This is an emulsion of both long and medium chain triglycerides in a ratio of 1:1 which helps reduce the proportion of free propofol in the aqueous phase.

Effect of another Anaesthetic related drugs over the effect of Propofol

Some of the Anaesthetic related drugs has shown the effect of decrease in the requirement of propofol dosage for given effect. The plasma concentration depends on the dosage of Propofol given intravenously.

The propofol CP_{50} concentration is plasma concentration needed for 50% of the subjects to not respond to a given defined stimulus.

The CP_{50} of propofol alone administered for loss of response to the verbal command is 2.3 to 3.5mcg/ml. The propofol Cp_{50} to prevent response in terms of movement to skin incision is 16 mcg/ml[20]. This dosage requirement is reduced by increasing the dosage of opioids like fentanyl or alfentanil. The premedication combination of benzodiazepine and 66% nitrous oxide is 2.5mcg/ml. The same concentration was reduced to 1.7mcg/ml when given with morphine.

The higher the opioid concentration in blood, slower the recovery as the opioid potentiates the action of propofol. The adjustments of the propofol drug concentration to optimal level along with administered opioids or benzodiazepines to assure adequate depth of anaesthesia and smooth and early recovery of the patient to consciousness is depicted in the table below.

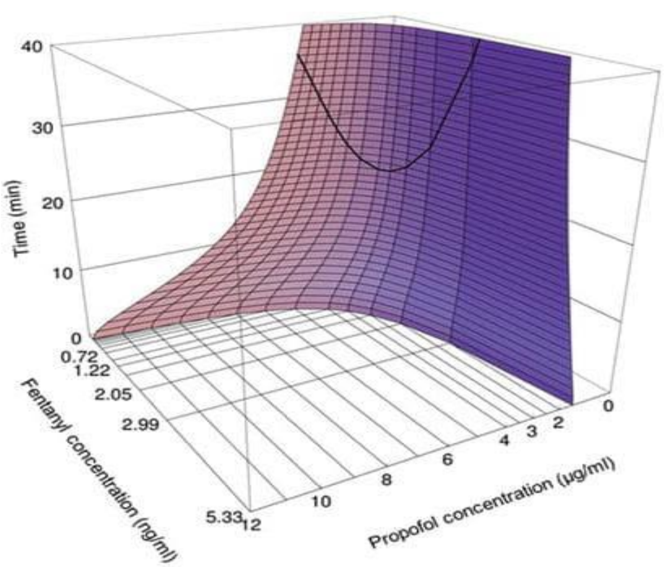
INFUSION SCHEMES* OF PROPOFOL AND THE OPIOIDS COMBINED TO ENSURE ADEQUATE ANESTHESIA AND OPTIMAL RAPID RECOVERY FROM ABDOMINAL SURGERY

Opioid	Alfentanil EC_{50}-EC_{95} (90-130 ng/mL)	Fentanyl EC_{50}-EC_{95} (1.1-1.6 ng/mL)	Sufentanil EC_{50}-EC_{95} (0.14-0.20 ng/mL)	Remifentanil EC_{50}-EC_{95} (4.7-8.0 ng/mL)
Bolus	25-35 µg/kg in 30 sec	3 µg/kg in 30 sec	0.15-0.25 µg/kg in 30 sec	1.5-2 µg/kg in 30 sec
	50-75 µg/kg/hr for 30 min	1.5-2.5 µg/kg/hr for 30 min	0.15-0.22 µg/kg thereafter	13-22 µg/kg/hr for 20 min
Infusion 2	30-42.5 µg/kg/hr thereafter	1.3-2 µg/kg/hr up to 150 min		11.5-19 µg/kg/hr thereafter
Infusion 3		0.7-1.4 µg/kg/hr thereafter		
Propofol	**Propofol EC_{50}-EC_{95} (3.2-4.4 µg/mL)**	**Propofol EC_{50}-EC_{95} (3.4-5.4 µg/mL)**	**Propofol EC_{50}-EC_{95} (3.3-4.5 µg/mL)**	**Propofol EC_{50}-EC_{95} (2.5-2.8 µg/mL)**
Bolus	2.0-2.8 mg/kg in 30 sec	2.0-3.0 mg/kg in 30 sec	2.0-2.8 mg/kg in 30 sec	1.5 mg/kg in 30 sec
Infusion 1	9-12 mg/kg/hr for 40 min	9-15 mg/kg/hr for 40 min	9-12 mg/kg/hr for 40 min	7-8 mg/kg/hr for 40 min
Infusion 2	7-10 mg/kg/hr for 150 min	7-12 mg/kg/hr for 150 min	7-10 mg/kg/hr for 150 min	6-6.5 mg/kg/hr for 150 min
Infusion 3	6.5-8 mg/kg/hr thereafter	6.5-11 mg/kg/hr thereafter	6.5-8 mg/kg/hr thereafter	5-6 mg/kg/hr thereafter

Table 5: courtesy from Miller's Anaesthesia 8th E edition.

Determination of propofol and fentanyl EC50-EC95 concentrations for adequate and rapid recovery from anaesthesia.

Figure 6



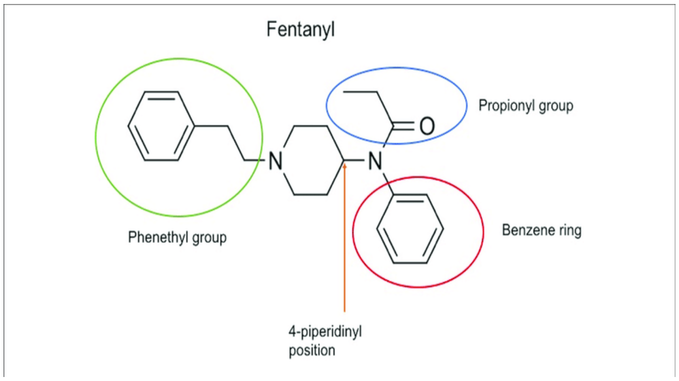
Fentanyl

There are three types of opioid receptors. The three subtypes' designations (mu—morphine, kappa—ketocyclazocine, delta—isolated from mouse vas deferens) were derived from the ligands that were first discovered to bind to them or their tissue of origin. These opioid receptors are a member of the same superfamily as the muscarinic, adrenergic, and soma to statin receptors, which consist of seven trans membrane-segment guanine (G) protein-coupled receptors. The amino acid sequences of the opioid receptors have been determined and they have been cloned. There is only one gene for the -receptor, and there are six different receptors. µ-Opioid receptors are principally responsible for supraspinal and spinal analgesia.

β-Arrestin, a class of proteins that controls the function of G protein-coupled receptors, can have a substantial impact on how agonists react with -opioid receptors. For instance, it has been shown that arrestins both increaseclathrin-mediated endo cytosis and receptor desensitization (or desensitization) [21].

Fentanyl hydrochloride is available as 2 ml and 10 ml ampoules containing 50 µg/ml.

Figure 7: Chemical structure of Fentanyl



Mechanism of action

It stimulates the µ type of opioid receptors and produces analgesia. It also acts on delta and kappa opioid receptors.

Uses, dose and route of administration

It can be given practically by any route: intra venously, intra muscularly, subcutaneously, trans dermally, epidurally, intrathecally, or orally.

Analgesia

Fentanyl is given in a dose of 1 – 2 µg/kg, given intravenously for providing postoperative pain relief. It may be repeated in a dose of 1 – 2 µg/kg intravenously. After the initial bolus is given, the analgesia may also be continued with an infusion at a rate of 1 – 2 µg/kg/h IV.

Onset

More than one arm-brain circulation time (1 – 2 minutes) when given IV,

Duration

One hour when given IV.

Elimination

It is metabolized by liver and excreted by the kidney.

Effects on the body

Central nervous system (CNS)

Initially it causes euphoria and then sedation. It is a good analgesic. Later, it produces dose-dependent depression of the CNS. The pattern of respiratory depression is similar to morphine. It has a cerebral protective effect by reducing cerebral metabolic rate and blood flow.

The periaqueductal grey, locusceruleus, and rostral ventral medulla in the brain and the substantia gelatinosa in the spinal cord are home to opioid receptors, which are implicated in pain perception, integration of pain signals, and reactions to pain [21]. Endorphins may prevent excitatory neurotransmitters from being released from nerve terminals that transport nociceptive signals. Neurons become hyperpolarized as a result, which inhibits spontaneous discharges and evoked reactions. Endorphin release is most likely reflected in analgesia brought on by electrical stimulation of particular brain locations or mechanical stimulation of peripheral areas (acupuncture).

Numerous cortical and subcortical brain areas emit endogenous opioids that interact with -opioid receptors in response to persistent pain and stress. With diverse neuroanatomical involvements, the activation of the opioid receptor system is linked to decreases in the sensory and emotional assessments of the pain experience.

Cardiovascular system

It does not cause histamine release and less cardiovascular effect [22].

Respiratory system

It produces dose-dependent reduction in respiratory rate and in large doses, apnoea. The tidal volume is well-maintained till late. Fentanyl reduces minute ventilation reduces causing hypercarbia and obtunds the airway reflexes as well. It can cause bronchospasm through histamine release. Fentanyl induced cough occurs immediately after IV administration and its mechanism is not known.

Gastrointestinal system

It has emetic properties, delays gastric emptying, and produces constipation.

Musculoskeletal system

Fentanyl causes muscle rigidity. This depends on the dose and speed of administration of fentanyl. If intense, it can be treated with induction or deepening of anaesthesia followed by muscle relaxants.

Adverse effects

Respiratory depression, pruritus, urinary retention, biliary colic, allergic reactions due to histamine release.

Cautions

To be used with caution in patients with respiratory failure. Delayed respiratory depression (about 30-45 min after IV administration) is known to occur with fentanyl.

Contraindication for Fentanyl:

- Administration of fentanyl impedes the hepatic clearance of the medication following surgical operations in the biliary tract obstruction disorders,
- Obstructive airway disorders or respiratory depression (i.e., asthma, COPD, obstructive sleep apnea, obesity hyper ventilation, also know as, Pickwicki an syn drome).
- Fentanyl is contra indicated in chronic liver dis orders and alcohol related disorders.
- With a history of intolerance to codeine, fentanyl, or any of the formulation's other morphine-like medicines.
- Known hypersensitivity (e.g., anaphylaxis) or any widely used excipients for drug delivery (i.e., sodium chloride, sodium hydroxide**).**

Conclusions

Administration of fentanyl in this study as pre-induction medication reduces the dose requirement of propofol for induction of anaesthesia and hypotension due to larger dosage of propofol without fentanyl required for induction of anaesthesia.

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