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Comparative Study of Etomidate versus Propofol as Induction Agent on Hemodynamic Parameters during Endotracheal Intubation Using Entropy Guided Hypnosis Levels in General Anaesthesia

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Abstract
Background and Aims: *This study aimed at the comparative study of etomidate versus propofol as induction agent on haemodynamic parameters during endotracheal intubation using entropy guided hypnosis levels in general anaesthesia.*
Material and Methods: *60 patients in the age group 18-50 years with ASA I & II, undergoing endotracheal intubation during general anaesthesia were randomly distributed in 2 groups based on induction agent Etomidate/Propofol. Tab. Alprazolam (0.25 mg) & Ranitidine (150mg) on the night before surgery. Ranitidine (50mg i.v), inj. Glycopyrrolate (0.25mg i.v) and inj. Metoclopramide (10mg i.v), are given as premedication. After induction with desired agent titrated to entropy 40, vecuronium 0.1 mg/kg was administered for neuromuscular blockade. HR, SBP, DBP and MAP, response entropy [RE] and state entropy [SE] were recorded at baseline, induction and upto 3 mins post intubation. Data was subject to statistical analysis SPSS the paired and the unpaired Student's T-tests for equality of means.*
Results: *Etomidate provided more hemodynamic stability without the requirement of any rescue drugs whereas rescue drug mephentermine was required in patients with propofol group.*
Conclusion: *Etomidate is more hemodynamically stable than propofol during induction and intubation during general anaesthesia. Reduced induction doses of etomidate and propofol titrated to entropy translated into increased hemodynamic stability for both drugs and sufficed to give an adequate anaesthetic depth.*
Keywords: *Entropy, etomidate, hemodynamic changes, propofol.*

Introduction

In general anaesthesia (GA), airway management and patient safety is the most important aspect of patient management. Noxious stimuli such as laryngoscopy, endotracheal intubation & placement of nasopharyngeal or oropharyngeal airways may produces changes in cardiovascular physiology.

GA induction agents may decrease arterial blood pressure via myocardial depression, vasodilation and attenuation of autonomic nervous activity. On the other hand, unwanted cardiovascular response

like hypertension, tachycardia and dysrhythmia are elicited by laryngoscopy & endotracheal intubation. The exact induction dose for maintaining hemodynamic stability has not been zeroed upon. Intravenous drugs such as Etomidate and Propofol are the most common agents for induction of general anaesthesia.[1]

Etomidate is an imidazole derivative intravenous anaesthetic induction agent remarkable for its minimal haemodynamic effects, rapid onset of action and short elimination t1/2 life[2]. Cardiovascular stability, i.e. small increase in heart rate and little or no decrease in blood pressure or cardiac output with no release of histamine, after induction is a major advantage of etomidate[3]. Despite these, its side effects are primarily injection pain, myoclonus, nausea and vomiting[4].

Propofol is one of the most commonly used parenteral drugs for induction of general anaesthesia. Because of its reasonably short half-life, rapid elimination from the blood circulation, mild sedation, anti-emetic and early recovery property, it's often used for induction of anaesthesia[5]. The most important side effects of this drug are hemodynamic instability and cardiovascular complications, such as hypotension and bradycardia.[6]

The Entropy module measures irregularity in spontaneous brain & facial muscular activity, thus aids in the management of GA. It processes electroencephalography (ECG) & frontal electromyography (FEMG) data by using proprietary algorithm to produces two values that measures depth of anaesthesia. The first value, response entropy (RE), is a fast-reacting parameter based on both EEG and FEMG signals, and is sensitive to facial muscle activation (2 second reaction time). It may indicate patient's responses to external stimuli and signal early awakening. The second value, state entropy (SE), is based on EEG and is a stable parameter to assess the hypnotic effect of iv anaesthetic agents on brain.

Therefore, we utilized the entropy monitor to give us a tailor- made induction dose for each patient. It also made the doses of the two induction agents under evaluation comparable.

Considering the common use of Etomidate and Propofol for induction of anaesthesia, the objective of this study is to compare cardiovascular response to endotracheal intubation using propofol and etomidate induction in surgeries under general anaesthesia using entropy guided hypnosis levels. Because in our study induction doses of both the drugs are not based on body weight per kg to minimize side effects e.g. hypotension, myoclonus, bradycardia etc. but on entropy guided induction and intubation to estimate the induction dose of each agent and to find out which agent is more haemodynamically stable or not when used in equipotent dosages.

Material and Methods

After approval from institutional ethical committee in 60 adult consented patients of physical status ASA I and II, of either sex, in age group of 18 to 50 years undergoing endotracheal intubation using entropy guided hypnosis levels during general anaesthesia.

The patients were randomly assigned into two groups Group E and Group P including 30 patients in each group using closed envelope method, out of all the cases being operated which fulfilled the inclusion criteria of the study. The null hypothesis was that there is no difference between etomidate and propofol regarding hemodynamic changes during entropy guided induction and intubation while the alternate hypothesis was that there is a statistically significant difference in the hemodynamic changes seen with both the drugs during entropy guided induction and intubation.

A thorough pre-anaesthetic evaluation was done including airway assessment, clinical history, general and systemic examination, routine biochemical investigation, chest X-ray and electrocardiography. Previous anaesthetic exposure and drug sensitivity were enquired. A

written and informed consent was taken in the language patient was able to understand and following investigations were confirmed.

Patients were advised to be nil per orally for 8 hour and were pre-medicated with tab. Alprazolam (0.25 mg) & tab. Ranitidine (150mg) on the previous night before surgery. On the day of surgery, patients were secured with 18G (gauge) intravenous (IV) cannula in non-dominant hand and preloading were done with ringer lactate infusion.

All patients were premedicated with inj. Ranitidine (50mg i.v), inj. Glycopyrrolate (0.25mg i.v) and inj. Metoclopramide (10mg i.v), 30 minutes before shifting the patients to operation room.Inj. Midazolam 0.03 mg/kg IV, 2 min before induction and inj. Butorphanol 1mg IV 1 min before induction were injected.

After shifting the patients to Operation Room, standard anaesthesia monitors including electrocardiogram (ECG), non-invasive blood pressure (NIBP), pulse oximetry and entropy sensor were attached and haemodynamic parameters were recorded. Preoxygenation was done with 100% oxygen for 5 minutes.

Anaesthesia was induced using inj. etomidate titrated to response entropy (RE) of 40 in group-E and inj. propofol was used in group-P with similar titration to an RE of 40.The end point for the induction was an RE value of 40 since RE is more comprehensive than state entropy (SE) and includes uncovered nociception as well.

The volume of medication and speed of injection (every 10 seconds) were equal in both groups (Group E & Group P). After induction of anaesthesia, haemodynamic variables were recorded. Later 60 seconds after loss of consciousness, which was confirmed by RE value of 40. Inj. succinylcholine (1.5 mg/kg iv) was administered and when no responses were obtained, laryngoscopy and orotracheal intubation was performed. Duration of laryngoscopy was kept less than 20 seconds. Trachea was intubated with adequate size endotracheal tube (ET) properly lubricated with xylocaine jelly. Proper placement of endotracheal tube was confirmed by capnography and bilateral auscultation of the chest. Following successful placement of ET tube, patients were ventilated and maintained by isoflurane (1-1.5%) started after 3 min of intubation and equal mixtures of oxygen-nitrous oxide (4 L/min). Bolus dose of vecuronium (0.1 mg/kg iv) initially followed with intermittent bolus dose of vecuronium (0.01mg/kg iv) was administered. The rescue drugs utilized were ~ inj. mephentermine 6mg bolus was given if the mean arterial pressure (MAP) decreased by >20% from baseline. Boluses of 2 mg etomidate or 10 mg propofol at a time were given if at any time SE rose above 60. A bolus was defined as 1 ml (10 mg) of propofol or 1 ml (2 mg) of etomidate, each injected over a period of 10 s. These boluses were presumed to be equipotent as they were in the same ratio (5:1) as standard per kilogram body weight induction doses of propofol and etomidate respectively. Diltiazem 2.5 mg IV was used if MAP increased >20% from baseline and esmolol 20 mg was employed in case the heart rate (HR) rose above 100 beats/min.

No surgical stimulus was given; patients were not be touched or otherwise disturbed for 5 min post intubation to discover the magnitude of RE-SE difference and the presence or absence of electromyography during without surgery. Volatile anaesthetic agents were started 3 minutes post intubation.

Cases in which orotracheal intubation was performed successfully within 20sec in a single attempt were included in the study.

At the end of the surgery residual neuromuscular block was antagonized with inj. Neostigmine (0.05 mg/kg, iv) and inj. glycopyrrolate (0.01 mg/kg, iv), Extubation was performed when responses were obtained on entropy monitor, adequate respiration and were able to obey verbal commands.

The observation and measurement of Heart rate (HR), systolic blood pressure (SBP), Diastolic blood pressure (DBP), Mean arterial pressure (MAP), Response entropy (RE) and State entropy

(SE) at baseline, (T1-T6) till upto 3min. post intubation was done using entropy module and sensors. The data was plotted on specifically prepared proforma for each patient where:

1. T0 = baseline
2. T1 = induction
3. T2 = 1 min. post induction
4. T3 = 3 min. post induction
5. T4 = laryngoscopy
6. T5 = 1 min. post intubation
7. T6 = 3 min. post intubation (volatile anaesthetics started at this point)
8. Side effects and complications.

The entropy monitor displays two variables. SE is computed over the frequency range from 0.8 to 32 Hz and includes the electroencephalography (EEG) - the dominant part of the spectrum. Hence SE primarily reflects the cortical state of the patient. RE is computed over a frequency range of 0.8-47 Hz and includes both the EEG - dominant and electromyogram dominant parts of the spectrum. On the monitor display, SE values vary between 0 (suppressed EEG activity) and 91 (indicating an awake state). RE values vary between 0 and 100. The recommended range of adequate anaesthesia for both parameters is from 40 to 60. When SE was in the recommended range for adequate anaesthesia but RE discrepancy is 5-10 U or more, it indicates patient responsiveness to surgery and can be interpreted as a sign of uncovered nociception.

Data obtained in the study were expressed as mean ± standard deviation (SD). The mean value for each parameter was calculated by using the formula, mean = $\sum Xi/n$ and SD was calculated by using the formula $\sqrt{1/(n\sum(Xi-X)}$). The unpaired student's t- test for equality of means was employed for inter group comparison after obtaining the mean values and the SD and the two - tailed significance (p) were calculated. The paired t-test was utilized for intra group comparison. A P<0.05 was considered to be statistically significant. whereas a value of <0.01 was taken as moderately statistically significant. P<0.001 was consider to be highly significant statistically. SPSS statistical software was utilized for this purpose.

Observation and Results

The demographic profile in both the groups was comparable [Table 1]. At T1 in both the groups there was a comparable fall in HR due to the anxiolytic action of tab. Alprazolam on previous night of surgery and Inj. Midazolam & inj. Butorphanol as premedication before induction.

In Group-P there was sustained increase in HR throughout induction and intubation. This was significant statistically at T2 and T3 (P < 0.05). In Group-E, there was statistically insignificant increase in HR at T2, T3, T4, T5 and T6.

Table 1-Demographic variables

Demographic variables	Group E (n=30)	Group P (n=30)
Age (years)	36.23±8.973	34.33±9.396
Weight (Kg)	58.70±7.173	60.47±6.296
Sex (male: female)	13:17	14:16
ASA-I	25	24
ASA-II	5	6

There was a fall from Baseline in SBP values at T2 and T3 for both Group-E and Group-P, but the mean fall in SBP at T2 in Group-E (15.9%) was approximately half of that seen in Group-P (29%) at T2. Similarly, at T3 the mean fall in SBP seen with Group-E (14.3%) was much less than that seen in Group-P (31.8%). At T4 (laryngoscopy), there was a 3.4% rise in SBP from baseline with Group-E, but in Group-P, the SBP continued to remain below (11.3%) the baseline even at T4.

At T5 and T6 (1st and 3rd min after intubation), the percentage fall in SBP in Group-E was 3.95% and 11.04%, respectively, compared to baseline, whereas in the corresponding period in Group-P the fall in SBP was 12.4% and 18.2% respectively [Figure 1 and Table 2].

As illustrated by Figure 2 and Table 2, both Group-E and Group-P showed a fall in DBP at T2 and T3. The fall in DBP was much sharper in Group-P (25.9% and 28.9%) as compared to Group-E (15.5% and 13.6% respectively at T2 and T3). There was a 5.5% rise in DBP at T4 in case of Group-E. In spite of the stimulus provided by

intubation, the DBP remained 5.08% lower than baseline in Group-P. At the 1st and 3rd min post intubation, the fall in DBP from baseline in Group-P was still 8.05% and 16.1%. In contrast the DBP in the Group-E returned to exactly the same as the baseline DBP and at T5 and at T6, it was only 7.5% below the base line.

At 1st and 3rd min after induction, there was a fall in MAP in case of both Group-E and Group-P. The fall in MAP is much sharper for Group-P (27.3% and 30.2%) as compared with Group-E (15.65% and 13.9%). The stimulus of laryngoscopy and intubation failed to bring the MAP above baseline levels of Group-P (7.8% below baseline) while in case of Group-E there is a 4.58% rise in MAP above baselineat T4 (laryngoscopy). The values for MAP at 1st and 3rd min after intubation for Group-P were 9.96% and 17.06% below the baseline while, for Group-E, MAP values were 1.78% and 9.07% below the baseline values [Figure 2 and Table 2]. No side effects and complications are seen in both groups (group E (etomidate) and group P (propofol).

Etomidate provided hemodynamic stability without the requirement of any rescue drug in any patients whereas rescue drug mephentermine played a role in maintaining hemodynamic stability in 14/30 of patients employing propofol for induction [Table 3]. In the etomidate group 12 patients required a single top-up bolus whereas four patients required two top-up boluses of etomidate each. In the propofol group 10 patients required a single top-up bolus whereas two patients required two top-up boluses of propofol each. The induction doses calculated are inclusive of the amount of drug utilized for top-ups.

Reduced induction doses 0.172 mg/kg for etomidate and 1.16 mg/kg for propofol respectively, sufficed to give an adequate depth of anaesthesia.

Table 2 Hemodynamic Parameters During Entropy Guided Induction And Intubation With Etomidate & Propofol

Hemodynamic Parameters	T0	T1	T2	T3	T4	T5	T6
HR(E)	79.53±6.78	74.73±6.7	82.73±7.66	82.87±7.7	81.93±7.7	81.13±7.8	83.0±8.013
HR(P)	81.87±9.29	77.80±8.9	86.80±7.08	87.93±6.8	85.33±6.9	86.07±7.08	86.67±7.189
SBP(E)	123.13±8.39	114.13±7.4	103.53±7.4	105.53±7.4	127.27±8.3	118.27±7.6	109.53±6.6
SBP(P)	122.33±10.65	107.20±10.21	86.80±6.9	83.33±7.4	108.50±9.5	107.13±9.7	99.97±8.4
DBP(E)	78.73±4.35	72.93±4.2	66.53±4.42	68±4.4	83.07±2.7	78.67±2.54	72.80±3.5
DBP(P)	78.60±7.62	69.13±6.7	58.20±5.18	55.87±5.3	74.60±7.2	72.27±6.9	65.93±6.2
MAP(E)	93.533±5.5	86.67±4.9	78.89±4.98	80.51±4.9	97.82±4.6	91.86±3.9	85.04±4.3
MAP(P)	93.17±8.06	81.82±7.5	67.732±5.3	65.0223±5.6	85.899±7.5	83.89±7.2	77.28±6.4

Figure 1 HR and Systolic Blood Pressure Variation over Time

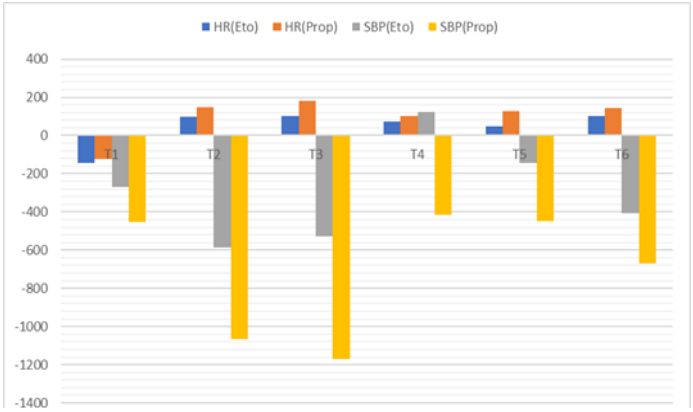
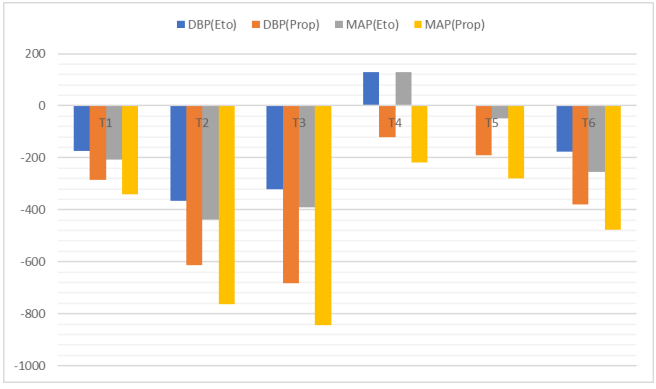


Figure 2- Diastolic Blood Pressure and Mean Arterial Pressure Variation over Time



Discussion

The magnitude of hypotension is directly proportional to the plasma concentration of the induction agent which in turn depends on many factors such as age, gender, body weight, dose, the infusion rate and cardiac output. There is no agreement regarding the minimum propofol dose and method of administration that minimizes the risk of hypotension. The dose of etomidate utilized by various studies ranges from 0.2 to 0.4 mg/kg. The doses at the higher end of the spectrum (0.4 mg/kg) for etomidate may cause direct myocardial depression.[7] The exact induction dose of etomidate for maintaining hemodynamic stability has not been zeroed upon as yet.

A depth of anaesthesia monitor is said to be the "Holy Grail" of anaesthesia. Of all the depth of anaesthesia monitors, it is the entropy monitor which gives a combined status of inadequate muscle relaxation, inadequate pain suppression and, above all, adequate hypnosis.[8-11]

Therefore, we utilized the entropy monitor to give us a tailor- made induction dose for each patient. It also made the doses of the two induction agents under evaluation comparable.

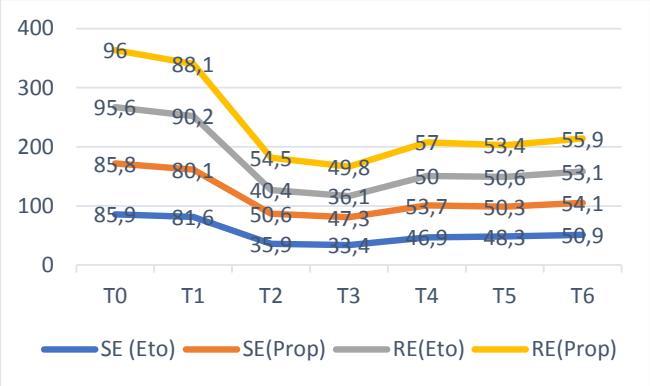
As per our results demonstrated no statistical differences ($p>0.05$) in mean heart rate of patients at various time interval in group E and P during baseline, induction, laryngoscopy and 3min. post intubation. Inter group comparison of mean heart rate between group E and group P showed that there are significant statistical differences ($p<0.05$) at 1min. post induction, 3min. post induction and 1min. post induction. Baseline mean systolic blood pressure, mean diastolic blood pressure and mean arterial pressure were comparable among both groups with no statistically significant differences ($p>0.05$). Significant statistical differences were seen in SBP, DBP and MAP at T1, T2, T3, T4, T5 and T6 with p value <0.05.

Table 3 Requirement of rescue drugs

Rescue drug	Group E (n=30)	Group P (n=30)
Mephentermine	0	14
Diltiazem	0	0
Esmolol	0	1

Saricaoglu et al.[12] after studying the hemodynamic effects of an induction dose of propofol and etomidate found that propofol was associated with significant decreases in SBP and mean blood pressure. They attributed this hypotension to the negative inotropic effect of propofol.

Figure 3 State entropy and response entropy variation over time



Larsen et al.[13] examined the effects of propofol upon myocardial function by measuring changes in left ventricle function using transthoracic tissue-Doppler echocardiography and concluded that a decrease in MAP with propofol is secondary to reduce cardiac filling or a consequence of a direct negative inotropic action of propofol. **Weisenberg et al.**[14] concluded that lower doses of propofol (1.3 mg/kg) reduce hemodynamic instability.

Manish Jagia et al (2008)[15] after conducted a study on Comparative Evaluation of Spectral Entropy and Bispectral Index during Propofol/ Thiopentone Anaesthesia in Patients with Supratentorial Tumours. They found that BIS and Entropy parameters correlated strongly at different stages of induction. The correlation was significant between BIS and Entropy at baseline, after fentanyl administration, after induction, and after intubation. We also noted that Entropy parameters unlike BIS are not affected by haemodynamic response due to intubation.

In our study, we also found that during induction with etomidate and propofol and after orotracheal intubation entropy parameters were unaffected throughout the process.

A.moller petrun et al (2013)[16] conducted Bispectral index-guided induction of general anaesthesia in patients undergoing major abdominal surgery using propofol or etomidate: a double-blind, randomized, clinical trial. They showed that the use of propofol resulted in less hypertension and tachycardia at and after intubation than etomidate. But even with the reduced doses given with the BIS-guided protocol, it often caused significant hypotension.

In our study the incidence of hypotension in Group P was higher than Group E and there was increase in heart rate in group-P but there were relatively insignificant changes in heart rate in group-E.

Shagun Bhatia Shah et al (2015)[17] after comparing the haemodynamic responses during induction and intubation between propofol and etomidate using entropy guided hypnosis. The magnitude of variations in SBP, DBP and MAP from baseline was greater when propofol was used as an induction agent versus etomidate in comparable doses. Our study has similar finding.

As per our results it is evident that propofol causes sustained increase in HR throughout induction and intubation while etomidate keeps the HR stable for the complete duration of induction and intubation.

The magnitude of variations in SBP, DBP and MAP from baseline was greater when propofol was used as an induction agent versus etomidate in comparable doses. The mechanisms of arterial hypotension following IV anaesthetic induction are multifactorial. The hemodynamic stability seen with etomidate may be due to its unique lack of effect on both the sympathetic nervous system and baroreceptor function[18-19] and capacity to bind and stimulate peripheral α_{2b} adrenergic receptors with a subsequent vasoconstriction.[20] Decrease in SBP after bolus injection of propofol is dependent on both vasodilation with reduced preload and afterload and myocardial depression (negative inotropic action).[12-18]

This study reveals that at RE of 40, the hemodynamic variations with etomidate were less than propofol throughout the period induction and intubation.

As per the results of our study, the mean absolute dose of etomidate required for the complete duration spanning induction and intubation was 10 mg or 0.172 mg/kg body weight. This is much less (just less than 50%) than the conventional 0.2-0.6 mg/kg body weight dose (average: 0.3 mg/kg).[12,18,19,20] The mean absolute dose of propofol also showed a similar reduction (70.2 mg). The propofol dose per kilogram body weight was 1.16 which again is less than the conventional dose of 1-2.5 mg/kg body weight[12-18] (average: 1.75 mg/kg body weight). We attribute this wholesome dose reduction to the anaesthetic - sparing effect of the entropy monitor. butorphanol (2 μ/kg) and midazolam (0.03 mg/kg) may also have played a role in dose reduction of etomidate and propofol.

Riad et al.[21] studied entropy guided propofol induction in 72 elderly patients and found that total dose of propofol and the per kilogram body weight dose were significantly reduced by 37.1% and 31.8%, respectively in the entropy group. They concluded that the use of M-entropy during induction of anaesthesia in elderly patients reduces propofol requirements and maintains cardiovascular stability that is consistent with our findings.

To conclude, our induction technique utilizing midazolam, butorphanol and the entropy monitor can be utilized to give greater hemodynamic stability to both induction agents propofol and etomidate by dose reduction effect. On using the entropy monitor the fall in SBP, DBP, and MAP on induction with propofol and etomidate can be reduced whereas the rise in SBP, DBP and MAP during laryngoscopy and intubation with etomidate is also reduced. Dose reduction also resulted in a reduction in the incidence of myoclonus in case of etomidate. Our results highlight the importance of using the entropy monitor to guide hypnosis levels for induction, as it translates into significant dose reductions both for etomidate and propofol. Entropy guided

reduced induction doses (0.172 mg/kg for etomidate and 1.16 mg/kg for propofol respectively) result in lesser hemodynamic changes than propofol and etomidate induction with standard per kilogram body weight doses.

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