

Infusion dose requirement of rocuronium in patients on phenytoin therapy - A prospective comparative study

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ABSTRACT

Background and Aims: Patients with intracranial tumour are usually on anticonvulsants. Patients on phenytoin therapy demonstrate rapid metabolism of nondepolarising muscle relaxants secondary to enzyme induction. Infusion dose requirement of rocuronium in such patients has been sparingly studied. We studied the continuous infusion dose requirement of rocuronium bromide in patients on phenytoin therapy and its correlation with serum levels of phenytoin. **Methods:** Seventy-five patients scheduled for supratentorial tumour surgery were included in the study. Patients not on phenytoin were taken as control. The primary outcome variable studied was the infusion dose requirement of rocuronium in patients on phenytoin. Based on pre-operative serum phenytoin levels, study group patients were divided into two groups: sub-therapeutic level group (phenytoin level <10 µg/mL) and therapeutic level group (phenytoin level >10 µg/mL). Following anaesthesia induction, rocuronium bromide 0.6 mg/kg was administered to achieve tracheal intubation. Rocuronium infusion was titrated to maintain zero response on the train-of-four response. **Results:** Demographic data were comparable. Patients receiving phenytoin required higher infusion dose compared to the control group (0.429 ± 0.2 mg/kg/h vs. 0.265 ± 0.15 mg/kg/h, $P < 0.001$). The serum phenytoin level had no correlation to infusion dose requirement of rocuronium (0.429 ± 0.205 mg/kg/h vs. 0.429 ± 0.265 mg/kg/h ($P = 0.815$)). The recovery was faster in the phenytoin group compared to the control group. However, it was not clinically significant. **Conclusion:** The infusion dose requirement of rocuronium bromide in patients on phenytoin is higher and the serum levels of phenytoin does not influence the dose required.

Key words: Infusion, phenytoin, rocuronium

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INTRODUCTION

Rocuronium is a nondepolarising neuromuscular blocking agent with an intermediate duration of action and suitable for continuous infusion.^[1] Patients receiving chronic anticonvulsant therapy demonstrate resistance to nondepolarising muscle relaxants.^[2] Resistance to rocuronium and shorter recovery index in patients on chronic phenytoin therapy have been observed. There is also racial variation in the dose requirement of rocuronium.^[3] Most of the studies have observed earlier recovery times following bolus dose.^[2,4] The infusion dose for maintenance varies based on the background anaesthetic.^[5-7] There are no studies that

have looked into infusion dose requirement in patients on chronic phenytoin therapy and correlated with levels of phenytoin. We hypothesised that infusion dose requirements of rocuronium would be higher in patients on chronic phenytoin therapy. The primary

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aim was to determine the infusion dose requirements of rocuronium in patients on phenytoin therapy in comparison with control group. The secondary aim was to look for any correlation between serum levels of phenytoin and infusion dose requirement.

METHODS

After obtaining Institutional Ethics Committee approval and patients consent, 75 patients scheduled for supratentorial tumour surgery between 2011 and 2012 were included for analysis in this prospective comparative study. The primary outcome studied was the infusion dose requirement of rocuronium in patients on phenytoin, and the secondary outcome was to look for any correlation between serum levels of phenytoin and infusion dose requirement. Pre-operative estimation of phenytoin levels was done for all the patients receiving phenytoin. Twenty-one patients not on phenytoin were taken as control. Based on pre-operative serum phenytoin levels, study group patients were divided into two groups: sub-therapeutic level group (phenytoin level $<10\mu\text{g/mL}$) and therapeutic level group (phenytoin level $>10\mu\text{g/mL}$). Patients on multiple anticonvulsants, renal or hepatic disease, pregnant women, history of psychiatric illness or on any medications known to affect the neuromuscular junction, and neuromuscular disorders were excluded from the study. All patients were pre-medicated with fentanyl $2\mu\text{g/kg}$ in the operating room. Anaesthesia induction was accomplished with thiopentone $5\text{--}7\text{ mg/kg}$. Neuromuscular junction was monitored using train-of-four (TOF). Following measurement of baseline train-of-four (TOF) response, 0.6 mg/kg of rocuronium bromide was administered. Trachea was intubated following zero twitch response using the appropriate tube. The maintenance of anaesthesia achieved with $\text{O}_2:\text{N}_2\text{O}$: isoflurane (minimum alveolar concentration of $0.8\text{--}1.0$). The depth of anaesthesia monitoring using entropy was done in all patients and maintained around 40-60. Temperature was maintained between 35°C and 37°C .

Neuromuscular transmission (NMT) monitoring was done by kinemyography technique using the Datex S5 (Helsinki, Finland) NMT module. The TOF mode of stimulation was used to assess the depth of neuromuscular blockade and recovery status. Following induction, the supramaximal stimulus was established and baseline recorded. Neuromuscular block was maintained at $>90\%$ throughout the surgical period. TOF was measured every minute.

Intraoperative maintenance with rocuronium infusion was started 30 min following the initial bolus dose. The infusion was started at 0.15 mg/kg/h and was escalated by 0.05 mg/kg/h , to achieve $>90\%$ blockade. An intermittent bolus of 0.15 mg/kg was given with the appearance of first twitch and the escalation was determined by the requirement of more than two boluses within 30 min. The infusion was stopped 30 min before the end of the surgery. Time to recovery of TOF to 70% and 90% after stoppage of infusion was noted. Number of repeated boluses required in all groups was also noted.

Parameters analysed were serum phenytoin levels ($\mu\text{g/mL}$), infusion dose of rocuronium mg/kg/h and recovery time to 70% and 90% of TOF ratio.

All data are reported as mean \pm standard deviation. Demographic data among the groups were compared using the paired Student's *t*-test. Comparison of neuromuscular response, recovery time and dose requirement were made between the groups using analysis of variance with *post hoc* Tukey test. $P < 0.05$ was considered as statistically significant.

The outcome parameter compared between the groups was the difference in infusion dose requirement to maintain adequate neuromuscular blockade between the groups. Based on the previous studies and assuming to achieve 90% power and Type I error of 0.05, a sample size of twenty-one patients in each group were needed. We allocated twenty-five patients in each group. Two excess patients were incidentally included in each of the phenytoin group during the study, and we retained the data for analysis. The Statistical software SPSS 23.0 (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY:IBM Corp.) was used for the analysis of the data.

RESULTS

A total of 79 patients' data were collected, 25 in control group and 27 in each study group. Four patients in the control group were excluded from the study as infusion dose protocol was not followed [Figure 1]. Thus, a total of 75 patients were available for data analysis. Demographic data between the groups were similar [Table 1]. The duration of infusion ranged from 162 to 274 min. The plasma concentration of phenytoin in sub-therapeutic group and therapeutic level group was 4.32 ± 2.23 (range $2\text{--}9.5$) $\mu\text{g/mL}$ and

18 ± 7.53 (range 10.1–23.9) µg/mL, respectively. The duration of therapy ranged between 3 days to 10 years and 3 days to 7 years in sub-therapeutic group and therapeutic level group, respectively. The infusion dose to maintain >90% neuromuscular blockade in patients receiving phenytoin was significantly higher compared with control (0.429 mg/kg/h vs. 0.265 mg/kg/h, *P* < 0.001) [Table 2]. The level of serum phenytoin had no correlation to infusion dose requirement of rocuronium: 0.429 ± 0.205 mg/kg/h vs. 0.429 ± 0.265 mg/kg/h (*P* = 0.815) [Figure 2]. The average recovery time to 70% was shorter in patients on phenytoin but not statistically significant (control: 44.7 ± 18.5 min, sub-therapeutic group: 39.07 ± 13.2 min, therapeutic group: 40.8 ± 19.7 min). The average recovery time to 90% was found to be shorter in patients on phenytoin compared to

control group (50.2 ± 21.4 min, 47.8 ± 15 min and 45.1 ± 22.3 min in control, sub-therapeutic group and therapeutic level group, respectively), but not statistically significant [Table 2].

DISCUSSION

In this study, patients on phenytoin therapy required higher infusion dose of rocuronium compared to control to maintain >90% neuromuscular blockade. Studies have shown increased dose requirement of rocuronium and accelerated recovery in patients on chronic phenytoin therapy.^[2,4,8,9] All these studies used repeated intravenous bolus doses. Hepatic enzyme induction,^[10] increased binding to α₁ – acid glycoprotein,^[11] upregulation of acetylcholine receptors^[12] or combination of factors have been attributed to the cause.

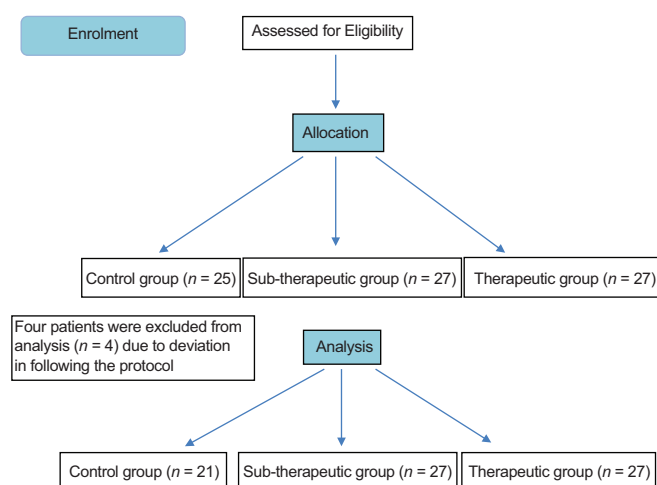


Figure 1: Consort flow diagram

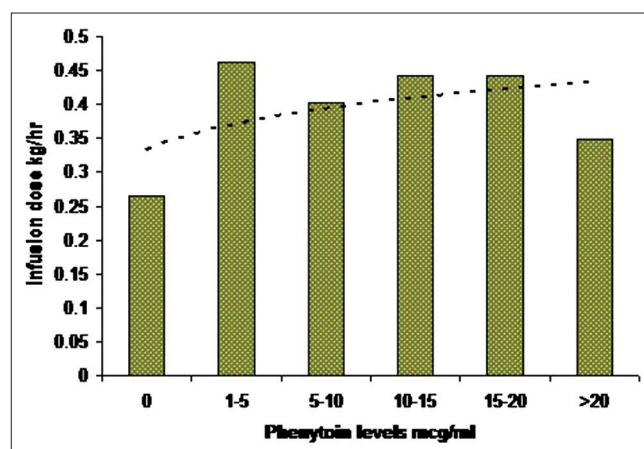


Figure 2: Mean infusion dose mg/kg/h is significantly more with any levels of phenytoin levels when compared to control patients with *P* = 0.011

Table 1: Demographic data

Characteristics	Control group (n=21)	Sub-therapeutic group (n=27) (phenytoin <10 µg/ml)	Therapeutic level group (n=27) (phenytoin >10 µg/ml)
Age (years)	46	46	48
Sex (male:female)	13:8	14:13	12:15
Weight (kg)	70	67	62
Type of intracranial tumours, n (%)			
Glioma	0	16 (60)	14 (52)
Meningioma	1 (5)	7 (26)	6 (22)
Other supratentorial tumour	20 (95)	4 (14)	7 (26)

Table 2: Comparison of study variables in three groups of patients

Parameters	Control (n=21)	Sub-therapeutic level group (phenytoin <10 µg/ml) (n=27)	Therapeutic level group (phenytoin >10 µg/ml) (n=27)	<i>P</i>
Infusion dose mg/kg/h (µg/kg/min)	0.265±0.147 (4.4±2.4)	0.429±0.205 (7.15±3.4)	0.429±0.176 (7.15±2.9)	0.001**
Infusion duration (min)	175±61	209±90	232±42	0.004**
70% neuromuscular block recovery (min)	44.70±18.54	39.07±13.23	40.86±19.79	0.476
90% neuromuscular block recovery (min)	50.2±21.4	47.8±15	45.1±22.3	0.53

Values are mean±SD, ***P*<0.05. SD – Standard deviation

We observed that the average infusion dose of rocuronium required to achieve >90% block when maintained with isoflurane anaesthesia in patients, not on anticonvulsant was lower compared to another study (0.26 ± 0.14 mg/kg/h vs. 0.4 ± 0.09 mg/kg/h).^[13] In yet another study, rocuronium characteristics with maintenance inhalational or propofol anaesthesia in 84 patients and cumulative infusion dose rate of rocuronium with isoflurane was 0.378 ± 0.09 mg/kg/h.^[7] Similarly, in a randomly assigned open label study of 30 patients, the authors observed rocuronium infusion requirements of 0.36 ± 0.16 mg/kg/h which is higher compared to our study.^[5] This probably is explained by ethnic variation in dose requirement. A group of researchers, in a study of 54 patients from three countries demonstrated a significant difference in the potency and duration of rocuronium.^[3] Ethnic or racial variations in hepatic metabolising enzymes, as well as environmental factors such as pollution, lifestyle, diet and ambient conditions, may be the contributing factor for differences in drug pharmacogenetics in different population.^[14]

There was no difference in infusion dose in relation to serum levels of phenytoin. We observed that even the sub-therapeutic levels of phenytoin had a similar effect on the increased dose requirement. The cause for this effect is hepatic enzyme induction by phenytoin.

There are no studies correlating sub-therapeutic and therapeutic levels of phenytoin and dose requirement.

We observed that there was no difference in recovery time in patients on phenytoin. The recovery time was longer in the control group compared to study group. Most studies in patients on chronic anticonvulsant therapy have used intermittent intravenous boluses of rocuronium rather than continuous infusion.^[2,4] They have demonstrated statistically significant increase in recovery times from rocuronium induced neuromuscular blockade in the control group compared to the phenytoin group. Another report in a patient on chronic phenytoin therapy who underwent cadaveric renal transplant showed early recovery from rocuronium induced neuromuscular blockade with increased plasma clearance of the drug, signifying pharmacokinetic interaction.^[15]

Literature also shows gender- and age-related differences with rocuronium administration. In a study comparing thirty males and thirty female patients to determine differences in their response to rocuronium

administration using cumulative dose response technique, authors found that women are 30% more sensitive to rocuronium than men.^[16] They related this to the differences in body composition, distribution volume and plasma protein concentration.

Spontaneous recovery from rocuronium dose of 0.45 mg/kg to TOF 0.7 was faster in children (28.8 ± 7.8 and 34.6 ± 9.0 min) than in adults (45.7 ± 11.5 and 52.5 ± 15.6 min) as observed by a group of investigators.^[17] In another study, authors have compared the recovery characteristics of rocuronium with bolus or prolonged infusion.^[13] They noted that 75% recovery from neuromuscular blockade was significantly prolonged after infusion (38.1 min) when compared to bolus (28.8 min) dose. This is because infusions will saturate the peripheral compartment and drug concentration will become elimination dependent.

This study was limited to specific group of patients. However, this is the first study of this kind and larger number would further add to the strength of the study. We also postulate that infusion dose requirement in our population is lower, compared to the recommended dose based on western population studies, as observed in our study.

CONCLUSION

Patients on phenytoin therapy irrespective of the serum levels require higher infusion dose of rocuronium bromide and they recover faster.

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Conflicts of interest

There are no conflicts of interest.

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Cut Off Date	Name of Award / Competition	Application to be sent to
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30 June 2017	Late Prof. Dr. A .P. Singhal Life Time Achievement Award	Hon. Secretary, ISA
30 June 2017	Rukmini Pandit Award	Hon. Secretary, ISA
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30 Sept. 2017	ISA Goldcon Quiz	Chairperson, Scientific Committee ISACON 2017
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