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Effect of Rocuronium bromide in patients of Chronic Renal failure vs Normal patients

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Abstract:
Background: Rocuronium bromide, a mono quaternary amino steroid with a short onset and an intermediate duration of action, is currently one of the most commonly used neuromuscular blocking agent. In common with vecuronium, hepatic uptake & biliary excretion have been suggested to be the main mechanism of rocuronium metabolism with renal elimination accounting for 10-20% of its overall excretion. This study was conducted to investigate the neuromuscular effects of 0.6mg/kg rocuronium under general anaesthesia in patients with and without renal failure.
Methodology: This prospective observational study includes 110 patients (pts.) divided into two groups, Group 'S' (n=55) pts. with renal failure and Group 'C' (n=55) without renal failure. Neuromuscular transmission was monitored, parameters recorded were onset, time to maximal block, time to recovery of first twitch response to 25%, 50%, 75% and 90% of base line, time to recovery of train-of-four (TOF) ratio of 70% and recovery index 25% - 75%.
Results: In both the groups demographic data were similar. Both onset time and maximum block for rocuronium were comparable in group S and group C, found not significant. Time to recovery of first twitch response to 25%, 50%, 75% and 90% of baseline, time for recovery of TOF ratio to 70% and recovery index were significantly prolonged in group S compared to group C.
Conclusion: Rocuronium can be used with caution in patients with renal disease and monitoring of neuromuscular block in this group of patients is essential.

Key words: Neuromuscular relaxants, rocuronium, renal disease, pharmacokinetics

Introduction

Rocuronium bromide is an amino steroidal non depolarising neuromuscular blocking agent. It is widely used during anaesthesia for its short onset time and intermediate duration of action.[1,2]
The pharmacokinetic profiles of rocuronium resembles that of vecuronium.[3,4,5]However in contrast to vecuronium, rocuronium has no metabolites. [6,7] In common with vecuronium, hepatic uptake & biliary excretion have been suggested to be the main mechanism of rocuronium metabolism with renal elimination accounting for only 10-20% of its overall excretion. It is been

reported that 33% of a dose of 1mg/kg rocuronium was recovered from urine within 24 hrs in humans.[8,9,10] In accordance with this finding rocuronium clearance was shown to be decreased & the duration of neuromuscular block of rocuronium 0.6mg/kg was shown to be prolonged during general anaesthesia in patients with end stage renal disease compared with healthy control patients.[11]

Renal failure influences the pharmacologic characteristics of non-depolarizing neuromuscular blockade either by decreased elimination of the drug or its metabolites via the kidney or by decreased activity of butyrylcholinesterase. Consequently duration of action of neuromuscular blockade prolonged in patients with renal failure. Neuromuscular blocking drugs that undergo organ dependent elimination such as pancuronium, vecuronium & rocuronium can have significantly prolonged duration of action in renal failure patients due to altered pharmacokinetics. [12]

Multiple physiological changes that occur in renal failure patients which have an impact on pharmacology of neuromuscular blocking agents. [13]Therefore we choose to investigate the effects of onset time, maximum time to blockade and recovery of rocuronium in renal failure patients comparing with normal patients.

Material and methods:

This prospective observational study was undertaken after approval of Institutional Research and Ethics committee and obtaining patients written informed consent.

Patients were into two groups of 55 each, i.e. Group S - patients with renal failure and Group C – with normal renal function. The study population consists of 50 ASA Grading III or IVpatients with creatinine clearance less than 15 ml/min,aged between 18-70 years of either sex scheduled for elective procedure under general anaesthesia. Patients with anticipated difficult intubation, requiring drugs that are known to interfere with neuromuscular function of rocuronium, burns, trauma, pregnancy, obesity (wt. > 130% of ideal body weight), hepatic and neuromuscular disorder were excluded from the study.

Following detailed examination, Patients who fulfilled the required criteria were taken for the study. 18G IV line was secured. Routine monitors like ECG, NIBP, SpO_2 were connected and baseline vital parameters were noted. Electrodes of Train of Four (TOF) guard were connected, supramaximal stimulus and the basal TOF were noted using neuromuscular monitor.

All patients with renal failure were allowed to continue medications for essential therapy of renal failure. No pre-anaesthetic medication was given in them.

All patients were received i.v. fentanyl 2µg/kg, i.v. midazolam 1mg & i.v. glycopyrrolate 0.2mg 5min before induction. All patients were pre-oxygenated with 100% oxygen for 3 min. Anaesthesia was then induced with propofol 2 mg kg i.v. Neuromuscular monitoring was started immediately after the induction of anaesthesia and before the administration of muscle relaxant. The forearm was immobilized in splint and neuromuscular transmission was monitored using a peripheral nerve stimulator. The ulnar nerve was stimulated supra-maximally at the wrist every 15 second via the cutaneous electrodes using TOF nerve stimulation. After the stabilization of control responses, 0.6mg kg rocuronium iv was administered. Tracheal intubation was performed at the time of maximum depression of the twitch. Anaesthesia was maintained with propofol 100-200microgram/kg/min. iv, 60% nitrous oxide in oxygen, supplemental iv 50µg fentanyl as required and controlled ventilation to maintain end tidal CO_2 between 35-40 mmHg.

The parameters recorded from the end of injection of rocuronium were - onset time, time to maximum block, time to recovery of first twitch response to 25% and first twitch response to 50%, 75% and 90% of baseline, time to recovery of TOF ratio to 70% and recovery index i.e., time from 25% to 75% twitch height recovery.

Statistical analysis

The sample size was calculated based on the onset of blockade obtained by Kim KS et al., [8]with power as 80% and CI as 95%. The sample size obtained was 53. We enrolled 55 pts. in each group.

All data were analyzed with SPSS version 21.0 software (IBM Corp. released 2015. IBM SPSS Statistics for Windows, Version 23.0; Armonk, NY). Continuous variables were presented as mean, for parametric data and median if data is non parametric or skewed. Student 't' test or Mann Whitney test were applied for calculation of statistical significance when the data followed normative or non-normative distribution respectively. Nominal categorical data between the groups was compared using Chi-square test or Fisher's exact test as appropriate. P value of less than 0.05 was considered significant.

Results

There were no differences in demographic data between two groups (table 1). No statistical significance for onset of time in Group S (120.2 ±14.32 sec.) and Group C (117.2 ± 22.92 sec.).The time taken for maximum block was similar in both Group S and Group C, found not significant statistically. Time to recovery of first twitch response to 25%, 50%, 75% and 90% of baseline, time for recovery of TOF ratio to 70% were prolonged in group S compared to group C and significant.Recovery index is statistically significant and prolonged in group S (25.8 ±5.21 min.) when compared to group C (13.0 ±3.4 min.) (table 2)

Table 1: Demographic data in both the groups.

	Group S Mean ± SD	**Group C Mean ± SD**	**P value**
Age (years)	46.80±15.34	45.26±12.06	0.558
Weight (kg)	59.80± 9.54	60.71±11.16	0.645
Height (cm)	160.14±9.85	162.42±10.4	0.475
Gender (M/F)	42/13	39/16	0.516

Table 2: Characteristics of neuromuscular block

Parameters	**Group S Mean ±SD (median)**	**Group C Mean ±SD (median)**	**P value**
Onset time (sec.)	120.2 ±14.32 (120.0)	117.2 ± 22.92(120.0)	0.838
Max block (sec.)	235.0±17.56 (230.0)	220.36±34.97(225.0)	0.068
T 25 (min.)	51.16 ±9.27 (51)	20.12 ±4.20 (19)	0.00

T 50 (min.)	65.28 ±10.06 (66)	26.92 ±5.76 (27)	0.00
T 75 (min.)	76.96 ±11.34 (79)	33.12 ±6.92 (32)	0.00
T 90 (min.)	88.68 ±13.26 (88)	40.48 ±9.39 (41)	0.00
TOF 0.7 (70%) (min.)	74.0 ±10.72 (76)	31.32 ±6.81 (31)	0.00
Recovery index (min.)	25.8 ±5.21 (25)	13.0 ±3.4 (14)	0.00

Discussion

Rocuronium was a rapidly acting agent with an onset time just greater than 1 min after a bolus of 0.6 mg/kg in patients with or without trenal failure.Multiple physiological changes that occur in patients with renal failure, which can have significant effects on the pharmacology of neuromuscular blocking drugs. Appropriate changes must be made to drug dosage and dose intervals. Thus, the aim of our study was to investigate the time course of neuromuscular effects of 0.6 mg / kg rocuronium under propofol anaesthesia in patients with or without renal failure undergoing elective surgical procedures.

In our study, onset time of rocuronium action in group S and group C was found not much difference and statistically insignificant. Also time taken for maximum block in group S was 235.0 ±17.56 sec. and in group C 220.36±34.97 sec., which is not significant. Our results coincide with the study by Cooper RA et al.,[14]they found that there was no significant difference in the onset of action and duration of blockade of rocuronium in renal failure patients. Kim KS et al.,[8]studied effects of rocuronium during desflurane anesthesia in patients with or without renal failure and found similar results. The Onset time for relaxants was not different among varying age groups with impaired renal functions. This is most likely a reflection of multiple factors. The initial volume of distribution is the same for renal failure and normal patients. Thus in both groups the acetylcholine receptors at neuromuscular junction are presented initially with the same concentration. The age related changes occur in the neuromuscular junction, but the sensitivity of acetylcholine receptor to neuromuscular blocking agents is not much affected. [15, 16]

We found all the recovery indices, i.e., time to recovery of first twitch response to 25%, 50%, 75% and 90% of baseline, time for recovery of TOF ratio to 70% and recover index were significantly increased in group S compared to group C in our study. similar results were found in the study by Kocabas S et al.,.[17] They studied the neuromuscular effects of 0.6mg/kg rocuronium in patients with or without renal failure under propofol anaesthesia. The time to recovery of the first twitch to 25%, 50%, 75%, 90%, the train of four ratio to 70% and recovery index were found significantly prolonged in renal failure patients. Furuya T et al.,[18] studied the

effects of age on maintenance of intense neuromuscular block with rocuronium. They observed that the times from rocuronium injection to reappearance of the first response to PTC stimulation were approximately two fold longer and more variable in older than younger patients. They suggested that the dosing interval of rocuronium should be adjusted using neuromuscular monitoring when maintaining intense neuromuscular block, especially in older patients. The physiological changes associated with ageing such as, decreased total body water, decreased lean body mass & changes in serum albumin levels may reduce the volume of distribution at steady state. The accompanying changes in the cardio vascular system, decreased splanchnic & renal blood flow, low GFR & smaller liver mass may decrease the rate of elimination of neuro muscular blocking agents. Thus, the differences in distribution & elimination have been suggested to be likely explanations for prolonged duration of action of neuromuscular blocking agents in renal failure patients.

Conclusion

The neuromuscular effects of 0.6mg/kg rocuronium under propofol anaesthesia were markedly prolonged in patients with impaired renal function compared to patients with normal renal function. Although the duration of action of rocuronium is increased in patients with reduced renal function, rocuronium bromide can be used as an acceptable neuromuscular blocking agent with supportive peripheral neuromuscular monitoring.

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