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Clinical Study

Pharmacoeconomics and Pharmacodynamic Interactions of Rocuronium and Pancuronium

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Background. We evaluated the pharmacodynamic interaction of the combination of pancuronium and Rocuronium by analyzing time-response relationship, quality of intubating conditions, changes in the hemodynamics, and cost effectiveness as compared to individual drugs. *Methods*. Sixty patients in the ASA-I category received either 10 ml of 0.9 mg/kg rocuronium (R) plus 10 ml of saline or 10 ml of 0.1 mg/kg pancuronium (P) plus 10 ml of saline or a combination (C) of 10 ml of 0.45 mg/kg R plus 10 ml of 0.05 mg/kg P according to randomization list. Neuromuscular function was measured up to maximal suppression of twitch height. *Results*. The mean times (sec) taken for twitch height to decrease to 50% of baseline in R, P, and C were 36.84 ± 2.54, 74.60 ± 4.94, and 40.81 ± 2.34, respectively. The mean cost of intubation per patient was 316.71 ± 83.61 INR in group R, 52.30 ± 14.94 INR in group P, and 93.33 ± 20.65 INR in group C. *Conclusions*. The combination of P and R provides rapid and smooth intubation with minimal hemodynamic changes at a reasonably priced cost.

1. Introduction

Over the last few decades the focus of research has been on the development of muscle relaxants with a short onset of action that can be used for rapid sequence intubation. It has been shown that speed of onset is inversely related to molar potency [1, 2]. The major disadvantage of use of less potent drugs is pharmacoeconomics burden of intubation [3, 4]. So far, it has been very difficult to find the optimal compromise between potency and rapid onset of action. The pharmacokinetic options to achieve rapid onset of action are use of supramaximal doses, priming, and cocktails of relaxants. Many experimental combinations of amino steroid relaxants and benzo-isoquinolinium relaxants failed to demonstrate either synergism or pharmacoeconomics advantage [5].

Pancuronium is one of the most potent and least expensive nondepolarizing neuromuscular blocking drugs available. However, its onset of action is slow. Pancuronium has predominant postsynaptic mechanism of action, whereas rocuronium, a monoquaternary analogue of Pancuronium has a predominant presynaptic action [6]. It has been hypothesized that combination of these drugs with different pharmacodynamic characteristics might confer advantage of synergism resulting in rapid onset of action at a lesser cost. To this purpose we evaluated the pharmacodynamic interaction by analyzing time-response relationship, quality

Table 1: Comparison of demographic data between groups.

Demography	Group P (0.1 mg/kg) ($n = 20$)	Group R (0.9 mg/kg) ($n = 20$)	Group C (0.45 mg/kg R + 0.05 g/kg P) ($n = 20$)	P value
Age (yrs)	32.71 ± 12.5	25.63 ± 8.99	26.76 ± 8.09	0.06
Weight (kg)	52.30 ± 3.49	54.37 ± 4.26	58.33 ± 2.93	0.43
Male/female	13/7	13/6	17/4	0.49
Dose (mg)	5.23 ± 0.35	48.93 ± 3.83	P = 2.92 ± 0.15 R = 26.24 ± 1.31	—
Cost INR	316.71 ± 83.61	52.30 ± 14.94	93.33 ± 20.65	R versus P = $P < 0.001$ R versus C = $P < 0.001$ P versus C = $P < 0.05$
Onset time for intubation (sec)	68.16 ± 3.84	132.70 ± 6.17	75.67 ± 6.21	R versus P = $P < 0.001$ R versus C = $P < 0.001$ P versus C = $P < 0.001$

of intubating conditions, changes in the hemodynamics, and cost effectiveness of the combination of rocuronium and pancuronium as compared to individual drugs when given alone.

2. Methods

According to randomization list, patients received either 0.9 mg/kg rocuronium (R) (3 X ED 95) or 0.1 mg/kg pancuronium (R) (2 X ED 95) or a combination (C) of 0.45 mg/kg R (1.5 ED 95) plus 0.05 mg/kg P (1 X ED 95). All the study drugs were reconstituted to 10 mL using normal saline. Since the combination group had two syringes, a syringe containing 10 mL of normal saline was included in the other two groups to maintain blinding. All the study medications were administered simultaneously through two different intravenous cannulae placed on the same arm.

2.1. Statistical Analysis. Statistical analysis was performed using SPSS (version 13) and Graph pad prism (version 4). The categorical data are expressed as frequencies and percentages and continuous variables are expressed as mean and standard deviation. The categorical variables between the groups were compared using chi-square test and Fischer's exact test. The continuous data between the groups were compared by ANOVA and Bonferroni post hoc test for normally distributed. The mean time-response (twitch height) curve was plotted for the three groups. A nonlinear sigmoid regression analysis was performed and the slopes of the curves were compared. A hypothetical line that would correspond to the predicted additive response of the two drugs was drawn at the mid-points of the rocuronium and pancuronium curves. The combination of the drugs would be considered to be additive if the actual response curves lies on the predicted additive-response curve, synergistic if it lies below the predicted curve. P value < 0.05 was considered significant.

3. Results

There was no statistically significant difference in the demographic characteristics among the three groups (Table 1). The baseline line hemodynamic parameters were comparable in the three groups. As expected there was a statistically significant increase in heart rate at 1 min and a significant reduction in the systolic, diastolic, and mean blood pressures at 1 and 5 minutes after induction in all the three groups which returned to baseline after intubation. However, there were no significant differences in the hemodynamic changes between the groups (Table 2). The mean times taken for twitch height to reduce to 50% of baseline twitch height in R, P, and C were 36.84 ± 2.54, 74.60 ± 4.94 and 40.81 ± 2.34, respectively. There was statistical difference in the onset time for intubation between R and P (<0.001), C and P (<0.001), and R and C (<0.01) (Table 3). Time to fading of twitch response was 92.0 ± 4.20, 170 ± 6.10, and 108 ± 3.92 in R, P, and C, respectively. This was statistically significant between R and P (<0.001) and C and P (<0.001) and R and C (<0.001). However the rate of decline of twitch response was similar among all the three groups. The time-response curve for the group C was below the hypothetical additive response curve indicating synergism between the two drugs (Figure 1). The onset times for intubation in R, P, and C were 68.2 ± 15.9, 132.70 ± 6.17, and 75.67 ± 6.21 sec, respectively. This was statistically significant between R and P (<0.001) and C and P (<0.001) and R and C (<0.001).The intubation conditions were excellent in 13 (68%) of R, 10 (50%) P, and 17 (81%) C, whereas it was good in 6 (32%) of R, 8 (40%) P, and 4 (19%) C. Only 2 (10%) patients in P had poor intubation conditions. However, there was no statistically significant difference in the intubation conditions between the groups. The mean cost of intubation per patient was 316.71 ± 83.61 Rs. in group R, 52.30 ± 14.94 Rs. in group P, and 93.33 ± 20.65 Rs. in group C. This was statistically significant between P versus R ($P < 0.001$), P versus C ($P < 0.001$), and R versus C

Table 2: Comparison of hemodynamic changes following administration of muscle relaxant.

Hemodynamic parameters	Group R ($n = 20$)	Group P ($n = 20$)	Group C ($n = 20$)	Between group comparison P value
Heart rate (beats/min)				
Baseline	86.42 ± 4.11	90.05 ± 4.45	89.86 ± 3.87	0.77
1 min PIT	98.32 ± 3.3*	103.85 ± 3.6*	98.48 ± 3.4*	0.42
5 min PIT	89.05 ± 3.7	94.15 ± 4.5	88.30 ± 3.8	0.48
*P value	0.000	0.005	0.004	
SBP (mm Hg)				
Baseline	127.47 ± 2.5	127.00 ± 4.9	130.19 ± 2.7	0.73
1 min PI	108.63 ± 3.5*	105.65 ± 3.0*	108.38 ± 4.1*	0.77
1 min PIT	125.68 ± 4.5	125.55 ± 3.8	123.29 ± 3.2	0.86
5 min PIT	109.05 ± 2.7*	109.30 ± 3.6*	111.80 ± 2.9*	0.75
*P value	0.000	0.000	0.000	
DBP (mm Hg)				
Baseline	79.37 ± 1.7	78.25 ± 3.2	81.43 ± 1.5	0.54
1 min PI	65.63 ± 3.7*	63.25 ± 3.9*	67.81 ± 3.3*	0.59
1 min PIT	79.79 ± 3.7	78.40 ± 3.6	79.19 ± 2.5	0.94
5 min PIT	68.63 ± 3.1*	69.30 ± 3.2*	70.85 ± 2.5*	0.82
*P value	0.000	0.001	0.000	

*Comparison to baseline.

Table 3: Comparison of neuromuscular blockade and intubation conditions.

Twitch Height TH (%)	Group R ($n = 20$)	Group P ($n = 20$)	Group C ($n = 20$)	P value
TH 75%	32.53 ± 2.42	62.00 ± 4.2	33.90 ± 1.94	R versus P = $P < 0.001$ R versus C = $P > 0.05$ P versus C = $P < 0.001$
TH 50%	36.84 ± 2.54	74.60 ± 4.94	40.81 ± 2.34	R versus P = $P < 0.001$ R versus C = $P < 0.01$ P versus C = $P < 0.001$
TH 25%	43.42 ± 2.84	91.85 ± 5.06	50.90 ± 3.16	R versus P = $P < 0.001$ R versus C = $P < 0.001$ P versus C = $P < 0.001$
TH 0%	92.0 ± 4.20	170 ± 6.10	108 ± 3.92	R versus P = $P < 0.001$ R versus C = $P < 0.001$ P versus C = $P < 0.001$

Table 4: Comparison of intubation response.

	Group R ($n = 20$)	Group P ($n = 20$)	Group C ($n = 20$)
Excellent (≤4)	13 (68%)	10 (50%)	17 (81%)
Good (5–7)	6 (32%)	8 (40%)	4 (19%)
Poor (>7)	0	2 (10%)	0

($P < 0.05$). None of the patients required more than one attempt at intubation.

4. Discussion

The results of this study show that the combination of rocuronium and pancuronium was synergistic. The onset of intubation conditions of the combination of the two dugs was comparable to that of rocuronium at a significantly lower cost. The desirable features of an ideal muscle relaxant are early onset and high potency. The onset of time is inversely related to potency and the pharmacoeconomic feature deliberately focuses on for a low-potency drug in the hope of finding something with a fast onset will inevitably result in cost : benefit ratio. In addition to obtaining faster onset time, good intubation conditions are also essential requirements. Excellent endotracheal intubation conditions are associated with less laryngeal morbidity than good or poor intubation conditions [7, 8] (Table 4). The intubation conditions with rocuronium with a dose of 2X ED 95 were inferior to that produced by suxamethonium [9]. Increasing the dose of rocuronium will shorten the onset time of complete neuromuscular block but significantly

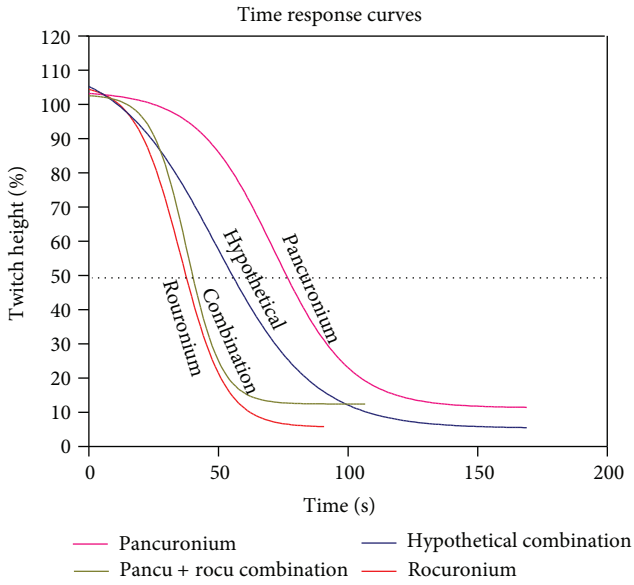

Figure 1: Time response curves (twitch height versus time in sec) of R, P, C, and H.

prolong the clinical duration and will become a long acting agent rather than an intermediate acting agent [10]. Also, these doses will cause significant increases in heart rate. Drug combinations have been proposed to decrease the incidence of side effects and cost. However, the results are unequivocal and sometimes even contradictory regarding the interaction among various neuromuscular agents, that is, whether they are additive or synergistic. Structurally dissimilar neuromuscular blocking drugs were shown to result in a potentiating effects as seen with combination of rocuronium and mivacurium [11–17], rocuronium and cis-atracurium [18, 19], and mivacurium and pancuronium [20–22]. It was earlier proposed that combinations of structurally similar neuromuscular blocking drugs produce an additive response in humans. However, Meretoja et al. [23] showed synergistic interaction between atracurium and mivacurium which are structurally benzylisosquinolines. Similarly, England et al. [24] showed that a mixture of rocuronium and vecuronium acts synergistically during early part of their action. The present study examined the combination of pancuronium and rocuronium to evaluate the possibility of synergism between the two. Pancuronium is a potent neuromuscular blocking drug with disadvantages of slow onset of action and ganglion blockade resulting in tachycardia and hypertension. However it is one of the least expensive muscle relaxants available. Rocuronium is a muscle relaxant with rapid onset of action. The inconsistency of lower doses of drug in providing good intubation conditions and the high cost of the drug hamper the routine use of this drug for intubation.

The results of our study revealed that the combination of rocuronium and pancuronium at half the recommended intubation doses of the individual drugs was comparable to that of rocuronium. The dose response curve for the group C falls below the hypothetical curve for the additive effect of combination of 50% doses of the individual drugs suggesting the possibility of synergism between the drugs. The exact mechanism of synergism between rocuronium and pancuronium is speculative. There are no earlier studies using this combination in conditions simulating clinical intubation. Golpariaini and colleagues, on phrenic-nerve-hemi-diaphragm preparations of male Sprague-Dawley rats, constructed isobolograms from the IC50 values and shown that ORG9426 potentiates pancuronium [25, 26]. However, Naguib by the isobolographic analysis observed additive interaction between rocuronium and pancuronium [27]. The hypotheses that have been put forward to explain the synergism between neuromuscular blocking agents include the existence of multiple binding sites at the neuromuscular junction (pre- and postsynaptic receptors) [28–30], non-equivalence of binding sites in the regions of the alpha-chain responsible for ligand recognition, resulting from the asymmetric azimuthal orientation of five subunits in the acetylcholine pentamer which determines different contacts for the alpha-1 and alpha-2 chains [31–33], presence of one molecule of nondepolarizing drug at one of the two alpha subunits of the acetylcholine receptors diminishing the likelihood that a second molecule of a different drug would interact with the second alpha subunit and alteration in the pharmacokinetic behavior of one drug by the other [34]. Standaert [35] suggested that this mechanism could underline the synergism between steroid and bis-isoquinoline antagonist. The possible cause for synergism between pancuronium and rocuronium could be due to the different preferential action of the relaxants at pre-and postsynaptic receptor locations.

The cost of intubation per patient in rocuronium group is Rs.248.55 whereas for pancuronium group is only Rs.10.87. The cost of intubation with the combination of rocuronium and pancuronium can be significantly reduced to an average cost of Rs.146.25 with comparable onset time to intubation and better intubation conditions than rocuronium. The cost saving at the rate of 10,000 intubations per annum would be Rs. 10,23,000 (18945 USD) Pancuronium was shown to produce significant hemodynamic disturbances due to its nonspecific effects on Ach receptors. However the results of this study have not shown significant difference in the hemodynamic changes between the groups. In the clinical situation where administration of muscle relaxant shortly follows induction of anesthesia and intubation succeeds muscle relaxant, the hemodynamic changes specific to the pharmacological effects of the relaxants are likely to be masked. The limitations of the present study are that response surface or isobolographic analysis has to be used for exact determination of synergism or additive nature.

5. Conclusion

The combination of cheap and potent pancuronium with a rapid onset rocuronium results in a near ideal muscle relaxant. The combination provides rapid, smooth intubating conditions with minimal hemodynamic disturbances at an affordable cost.

Disclosure

Reprints will not be available from the author.

Conflict of Interests

None of the authors declared any conflict of interests.

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