A Comparison of the Efficacy of Cisatracurium and Atracurium in Kidney Transplantation Operation

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Abstract

Cisatracurium is a new intermediate-acting benzylisoquinolinium neuromuscular blocking agent that is one of the ten stereoisomers contained in atracurium besylate. Atracurium is known to be the muscle relaxant of choice in end stage renal disease patients. This study aimed to compare the efficacy of cisatracurium and atracurium in the aspect of intubation and maintenance dosages, hemodynamic response after intubation and cost effectiveness between the two agents in kidney transplant patients.

Material and Method : From August 2001 to July 2002, 46 end stage renal disease patients obtained kidney transplantation operation under general anesthesia with 50 : 50 N_2O : O_2, fentanyl, isoflurane anesthesia. Tracheal intubation and maintenance of muscle relaxant with each drug were administered in 23 of each group- atracurium as control (C) while cisatracurium was the study (S) group.

Results : There was no difference in the demographic data of the 2 groups - 13 males/10 females in the S group and 11 males/12 females in the C group. Eighty-seven per cent in the S group underwent living-related kidney transplantation operation, with 55.56 per cent in the C group. Most of the donors were siblings, i.e. 42.11 per cent in the S group and 46.67 per cent in the C group.

The mean dosage for intubation in the S group was 0.17 ± 0.02 mg/kg and 1.25 ± 0.49 μg/kg/min for maintenance. The mean dosage for intubation in the C group was 0.64 ± 0.07 mg/kg and the mean maintenance dose was 5.38 ± 0.83 μg/kg/min. In both groups there was no statistical difference in hemodynamic changes. One patient in the S group received calcium channel blocker to reduce blood pressure before induction of anesthesia, while 2 patients in the C group were given nifedipine 5 mg before induction. Although the cisatracurium cost was higher than atracurium, from the cost-minimization analysis, it turned out to be lower per case.

Conclusion : This study demonstrated the efficacy of cisatracurium in hemodynamic stability and safety in kidney transplantation operations. In spite of the more costly price, cisatracurium is beneficial in some end stage renal disease (ESRD) patients with coronary artery disease who need very stable hemodynamics.

Key word : Cisatracurium, Atracurium, Kidney Transplantation

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More than half a century since Griffith and Johnson first used the muscle relaxant[1], new developments have been made to synthesize an ideal agent with rapid onset, stable hemodynamic effect, no residual curarization, minimal side-effects and low cost. In terms of pharmacokinetic profile, atracurium is the most striking because of Hofmann or organ-independent elimination[2]. But atracurium is a mixture of various isomers and Hofmann just plays 1/3 of a role [2,3]. Cisatracurium is one of the ten isomers of atracurium and shares only 15 per cent of its property[1,4]. The two-compartment study revealed that the drug is mainly eliminated by Hofmann while the rest (23%) by the organ-dependent process[3]. Cisatracurium is three times more potent than atracurium but causes less histamine release[5]. Therefore, theoretically cisatracurium is better than atracurium especially in patients with poor renal function[6]. End-stage renal disease patients who come for a kidney transplantation operation almost always are hypertensive and pose a grave problem during induction and intubation. The purpose of this study was to compare hemodynamic fluctuations between atracurium and cisatracurium during the intubation period and finally discussed pharmacoeconomics of this new muscle relaxant.

MATERIAL AND METHOD

After patient informed consent and approval of the Hospital Ethics Committee were received, 46 patients for kidney transplantation operation were enrolled of which half were administered each drug. Assuming the mean difference of 10 mmHg blood pressure to have clinical minimum difference accepted and the overall standard deviation of blood pressure in each group was 10, d = 10/10, the sample size was calculated by PS (Power and Sample Size Calculation) version 2.1.30 software with α 0.05, power 80 per cent and d 1 to obtain at least 17 patients for each group[7]. Demographic data were recorded including coexisting diseases. Exclusion criteria were patients with diabetic autonomic neuropathy as evidenced by pre-operative lack of heart rate variability test, patients with neuromuscular disease and patients in whom intubation failed at the first attempt. Balanced anesthetic technique was used : thiopental 3-5 mg/kg, fentanyl 1 μg/kg, atracurium 0.5 mg/kg or cisatracurium 0.15 mg/kg, N_2O,O_2, isoflurane and maintenance of each muscle relaxant infusion were titrated to clinical signs till the end of the operation. Hemodynamic changes monitored by NIBP (Datascope®) were recorded 1 minute prior to and post intubation by an observer blinded to the study together with antihypertensive medications and adverse drug effects. Intubation was performed 2 minutes after drug administration.

Statistics

Parametric data of age, body weight, anesthetic time and drug dosages were analyzed by unpaired student *t*-test. Sex, physical status, type of

donated kidney, coexisting diseases were counted and compared by Chi-square test. Using Microsoft Excel 97 software and set $p < 0.05$ as statistical significance.

RESULTS

Demographic data are presented in Table 1.

There were significantly more living-related donors in the cisatracurium group than in the atracurium group.

From the present study, there was one patient in the S group and 2 patients in the C group who had very high blood pressure during the induction period and nifedipine 5 mg was given sublingually. Also in the C group, one patient had a second dose of nifedipine to decrease the blood pressure after the intubation period. One patient in the C group developed skin flush after atracurium administration.

DISCUSSION

Kidney transplant patients have their own unique problems from chronic pathophysiologic effects on every organ in the body such as uremic encephalopathy, severe hypertension, pleurisy, ileus, electrolyte disturbances, anemia, hypoalbuminemia, platelet dysfunction and so on, not to mention coexisting diseases that usually accompany end stage renal disease (ESRD) and complications from renal replacement therapy. Renal insufficiency can markedly alter one or more of the pharmacokinetic parameters of a drug including oral bioavailability, volume of distribution, drug binding to plasma proteins, and most importantly the rates of metabolism and excretion, i.e., drug clearance[8]. Intubation is the most stressful to the hemodynamic of these patients and since there is a vast pharmacokinetic aberration in chronic renal failure patients,

Table 1. Demographic data (mean ± SD).

	Cisatracurium (n = 23)	Atracurium (n = 23)	P
Age (years)	41.52 ± 11.70	44.69 ± 11.16	0.35
Weight (kg)	55.11 ± 11.47	59.72 ± 12.31	0.45
Sex M/F	13/10	11/12	0.55
ASA physical status II/III	9/14	12/11	0.37
Type of donated kidney living/cadaveric	21/2	14/9	0.01
Anesthetic time (min)	191.95 ± 58.22	173.13 ± 37.22	0.19
Thiopental (mg)	226.08 ± 29.65	231.52 ± 33.89	0.56
Fentanyl (μg)	57.60 ± 15.87	61.30 ± 12.26	0.38
Dosage (mg)			
Intubation (mg)	10.17 ± 2.50	36.52 ± 3.51	
mg/kg	0.17 ± 0.02	0.64 ± 0.07	
Maintenance (mg)	13.95 ± 10.50	53.21 ± 16.29	
μg/kg/min	1.25 ± 0.49	5.38 ± 0.83	

Table 2. Coexisting diseases in ASA physical status III.

	Cisatracurium (n = 14)	Atracurium (n = 12)
Cardiomegaly, pulmonary congestion	4	2
Cardiomegaly, pericardial effusion	-	2
Cardiomegaly, premature ventricular contraction	3	-
Severe hypertension (> 230/120 mmHg)	-	4
Renal cell carcinoma	2	-
Left ventricular hypertrophy, ischemic heart disease	1	-
Takayasu aortitis	1	-
Ischemic heart disease, hypoalbuminemia	1	-
Left ventricular hypertrophy, ascites	1	-
Prolonged prothrombin time	1	-
Systemic lupus erythematosus	-	2
Heavy smoker	-	2

Table 3. Hemodynamic changes pre- and post-intubation (mean ± SD).

	Cisatracurium	Atracurium	p
Preintubation			
Systolic BP (mmHg)	159.34 ± 31.09	175 ± 26.89	0.06
Diastolic BP (mmHg)	92.52 ± 14.29	102.73 ± 13.46	0.01*
HR (bpm)	82.56 ± 13.16	81.60 ± 13.97	0.81
Postintubation			
Systolic BP (mmHg)	162.43 ± 26.82	173.73 ± 22.08	0.12
diastolic BP (mmHg)	98.82 ± 18.82	101.73 ± 16.96	0.58
HR (bpm)	91.95 ± 17.09	91.39 ± 14.40	0.90

* Differences in baseline diastolic blood pressure prior to intubation were statistically significance.

Table 4. The adverse effects in the common drug dosage[12].

	Cisatracurium (%)	Atracurium (%)
Skin flush	0.2	29.2
Wheezing	0.2	0-0.3
Rash	0.1	0-0.5

selection of anesthetic agents to smooth intubation must be considered. Cisatracurium is the new non-depolarizing muscle relaxant derived from atracurium which is well known for Hofmann elimination or organ-independent degradation. To scrutinize details of Hofmann elimination, atracurium is mainly metabolized by ester hydrolysis in about 60 per cent, then self-degradation[3]. This is in a real contrast to cisatracurium which has been firmly studied to have Hofmann as the major part (77%) and it accounts for a very low level of its cerebrotoxic metabolite, laudanosine[9]. Self-degradation at physiologic pH and temperature of cisatracurium has opened up a non-traditional pharmacokinetic model; the two-compartment model clearance, central and effect compartments, well described the fate of this drug after a bolus. Simultaneous Hofmann elimination in the effect compartment helps explain why the onset of cisatracurium is slightly slower than atracurium, even blood levels of the two drugs peak after 1 minute[3]. A diagram of the two-compartment model and Hofmann elimination of cisatracurium occurrence in the effect compartment is shown in Fig. 1.

The study comparing cisatracurium pharmacokinetic profiles between young and old patients[10] did not reveal any difference, nor the study between normal and renal failure patients[11]. The result of the present study on pharmacodynamic effects during induction-intubation period did not show any difference in hemodynamic changes, even though all of the patients had baseline hypertension. The average intubating dose of cisatracurium was 0.17 mg/kg while that of atracurium was 0.64 mg/kg. Atracurium in this approximate dosage reportedly decreased the mean arterial pressure by 14.3 per cent and increased the heart rate by 4.8 per cent[12], probably from histamine release and baroreceptor reflex. Cisatracurium had such cardiovascular effects less than 1 per cent[12]. The recommended dosage of cisatracurium in adults is 0.15 mg/kg (3 x ED95) for intubation in 2 minutes and 0.2 mg/kg (4 x ED95) in 1.5 minutes with a good or excellent condition under thiopental or propofol induction. The maintenance dosage for intermittent top-up is 0.03 mg/kg every 20 minutes and for initial infusion it is 3 μg/kg/min then 1-2 μg/kg/min or to decrease 30-40 per cent with isoflurane inhalation [12]. Histamine release of atracurium is commonly known as a property of this kind of benzylisoquinolinium muscle relaxant[2] and results in hypotension, although its effect is less than d-tubocurarine and metocurine. The nonimmunologic mechanism is activation of mast cell *via* calcium-involved phospholipases [13]. Cisatracurium is only one isomer that minimally has this effect up to 80 x ED_{95}[14] and thus confers a great advantage for patients with uremic cardiomyopathy[15] and pulmonary hypertension[14]. However, there have been at least 6 reported cases of cisatracurium anaphylactoid reaction with estimated incidence of 1 : 10,000 and a warning that the severity might not be proportional to its low occurrence[16]. In the present study, only one case in atracurium group manifested skin flush, and one patient had occasional

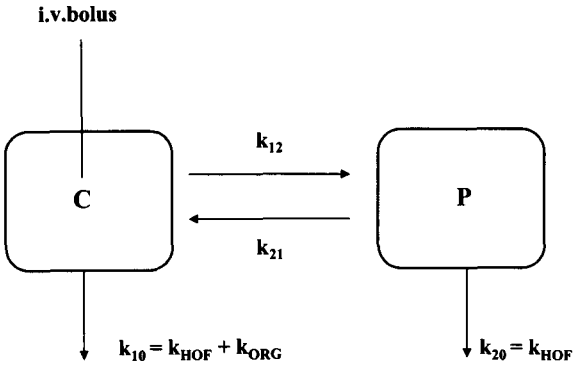

Fig. 1. After an IV bolus of cisatracurium into the central compartment (C), the drug distributes to the effect or peripheral compartment (P) and then undergoes Hofmann elimination in both represented by k_{HOF} [3].

Table 5. Cost of muscle relaxants in the present study.

Cost of total muscle relaxants	Cisatracurium (baht)	Atracurium (baht)
Intubation	123	115.44
Maintenance	182	165.36

Based on cisatracurium 13 baht/mg and atracurium 3 baht/mg.

premature ventricular contraction (PVC) intra-operatively but did not need any treatment, this patient had a potassium level of 4.0 mEq/L pre-operatively.

Adverse drug effects found atracurium in dosage of 0.6 mg/kg were skin flush 29.2 per cent, but was only 0.2 per cent in cisatracurium.

Since the present study showed that cisatracurium was at least as efficacious as atracurium in kidney transplantation operation, the authors compared the cost of both drugs, means of administration and management of adverse drug effects using cost-minimization analysis[17]. The cost from the Ramathibodi Pharmaceutical Reference 2003 in Thai baht was calculated according to obtained average dosages as shown in Table 5 and according to the anesthetic practice in the hospital on the assumption of recommended dosages for 2-hour transabdominal hysterectomy (TAH).

Per kidney transplant patient, the cost of the drugs was 305 baht for cisatracurium and 280.80 baht for atracurium while the cost in TAH was 150 and 200 baht respectively. Cisatracurium is cost saving which may be due to its sharable vials, volume of patients and longer duration of action. From the pharmacoeconomics point of view, in consideration of adverse effects and using a cost-minimization analysis, cisatracurium was an efficient muscle relaxant. Its activity is better than atracurium, with a cost saving of at least 50 baht per TAH patient.

SUMMARY

The present study of 46 kidney transplantation operations to compare the hemodynamic effects of cisatracurium and atracurium during induction/intubation did not reveal any differences. Histamine-related adverse effect was found in one patient in the atracurium group. Pharmacokinetics of this new muscle relaxant were discussed and cost minimization analysis was presented. Due to a higher potency of cisatracurium, total cost per case is approximately lower. Both cisatracurium and atracurium are muscle relaxants of choice in patients with problems of organ metabolism, especially the former which is recommended in ESRD which needs very stable hemodynamics and a minimal histamine release effect. The present challenge facing the anesthesiologist is to continue delivering the same high-quality of patient care while consuming fewer resources ("value-based anesthesia care")[17].

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การเปรียบเทียบผลของยาคลายกล้ามเนื้อซิสอาทราคูเรียมและอาทราคูเรียมในการระงับความรู้สึกสำหรับการปลูกถ่ายไต

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Cisatracurium เป็นยาคลายกล้ามเนื้อลายตัวใหม่ในกลุ่ม benzylisoquinolinium ที่ออกฤทธิ์ปานกลางและเป็น stereoisomer หนึ่งในสิบของ atracurium besylate ซึ่งเป็นยาคลายกล้ามเนื้อลายที่เหมาะสำหรับผู้ป่วยโรคไตระยะสุดท้าย การศึกษานี้เพื่อเปรียบเทียบประสิทธิผลของยาทั้งสองในเรื่องขนาดยาและการเปลี่ยนแปลง hemodynamic ขณะใส่ท่อหายใจและระหว่างการผ่าตัดปลูกถ่ายไต

วัตถุและวิธีการ : ผู้ป่วยจำนวน 46 รายที่มารับการผ่าตัดปลูกถ่ายไตระหว่างเดือนสิงหาคม พ.ศ. 2544 ถึงเดือนกรกฎาคม พ.ศ. 2545 ด้วยวิธีระงับความรู้สึกแบบทั่วไปคือ N_2O : O_2 50 : 50 fentanyl และ isoflurane ใช้ยาคลายกล้ามเนื้อลาย atracurium เป็นกลุ่มควบคุม (C) จำนวน 23 ราย และ cisatracurium เป็นกลุ่มศึกษา (S) จำนวน 23 ราย

ผลการศึกษา : ลักษณะผู้ป่วยทั้งสองกลุ่มไม่มีความแตกต่างกัน โดยกลุ่มศึกษาประกอบด้วย เพศชาย/หญิง 13/10 และ กลุ่มควบคุม เพศชาย/หญิง 11/12 ร้อยละ 87 ของผู้ป่วยกลุ่มศึกษา และ ร้อยละ 55.56 ของผู้ป่วยกลุ่มควบคุมเป็นการผ่าตัดปลูกถ่ายไตแบบ living-related ซึ่งผู้บริจาคอวัยวะส่วนใหญ่เป็นญาติคือร้อยละ 42.11 และ 46.67 ตามลำดับขนาดยาเฉลี่ยของกลุ่มศึกษาคือ 0.17 ± 0.02 มก/กก และ 1.25 ± 0.49 มคก/กก/นาที สำหรับใส่ท่อหายใจและระหว่างผ่าตัด ส่วนของกลุ่มควบคุมขนาดยาเฉลี่ยคือ 0.64 ± 00.7 มก/กก และ 5.38 ± 0.83 มคก/กก/นาที ไม่มีความแตกต่างทางสถิติ ในเรื่องการเปลี่ยนแปลงของ hemodynamic ผู้ป่วยหนึ่งรายในกลุ่มศึกษาและสองรายในกลุ่มควบคุมได้รับยาลดความดันเลือด nifedipine 5 มก ก่อนใส่ท่อหายใจ แม้ว่า cisatracurium จะมีราคาสูงกว่า atracurium แต่เมื่อวิเคราะห์ cost-minimization แล้วกลับพบว่าราคาต่อรายผู้ป่วยต่ำกว่า เนื่องจากระยะเวลาออกฤทธิ์ที่นานกว่าและรูปแบบบรรจุของยาสามารถแบ่งใช้ได้อย่างประหยัด

สรุป : การศึกษานี้เปรียบเทียบประสิทธิผลของ cisatracurium และ atracurium ที่เทียบเท่ากันในเรื่อง hemodynamic และความปลอดภัยในผู้ป่วยปลูกถ่ายไต พบว่า cisatracurium เหนือกว่าในเรื่องผลข้างเคียงที่น้อยมากเกี่ยวกับการหลั่งสาร histamine จึงเป็นยาคลายกล้ามเนื้อที่ใช้ได้อย่างปลอดภัยในผู้ป่วยที่มีภาวะไตวายระยะสุดท้ายที่ต้องมารับการผ่าตัดปลูกถ่ายไต แม้ว่าราคายา cisatracurium จะมีราคาสูงกว่า atracurium ก็ตาม

คำสำคัญ : ซิสอาทราคูเรียม, อาทราคูเรียม, การปลูกถ่ายไต

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