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Comparative study of hemodynamic stability and neuromuscular blockade of cisatracurium at a higher dose versus recommended intubating dose of atracurium in patients undergoing elective abdominal surgery

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ABSTRACT

Background: The principal uses of neuromuscular blocking drugs are to provide skeletal muscle relaxation to facilitate tracheal intubation and to improve surgical working conditions during general anesthesia. Present study was aimed to compare of hemodynamic stability and neuromuscular blockade of cisatracurium at a higher dose ($6\times ED_{95}$) versus recommended intubating dose ($2\times ED_{95}$) of atracurium in patients undergoing elective abdominal surgery. **Material and Methods:** Present study was single-center, prospective, comparative study, conducted patients of age 20-65 years, either gender, American Society of Anesthesiologist Grade I & II, posted for abdominal surgeries. **Results:** In present study, 60 patients were randomly divided into two groups of 30 each as Group A included patients receiving Inj. Atracurium, Loading dose: 0.5mg/kg Incremental dose: 0.125mg/kg & group C: Included patients receiving Inj. Cisatracurium, loading dose: 0.3mg/kg Incremental dose: 0.025mg/kg. The mean time taken for maximal depression of twitch was 174.00±13.02 and 122.33±13.82 seconds in group A and C respectively. The difference between the two groups was strongly significant statistically ($p<0.001$), with Cisatracurium having an earlier onset of muscle relaxation compared to Atracurium. Excellent intubating conditions were observed in 46.7% and 83.3% of patients in Group A and C respectively, difference was statistically significant. The mean duration of action of loading dose was 39.50±2.91 and 71.20±3.88 minutes in Group A and C respectively, difference was statistically significant. Only two patients in Atracurium group had signs of histamine release in the form of flushing at the site of injection in the forearm, whereas no patients in Cisatracurium group showed signs of histamine release. The difference was however statistically insignificant. **Conclusion:** Cisatracurium, though more costly, is more effective and a better isomer of Atracurium.

Keywords: Cisatracurium, Atracurium, neuromuscular blockade, intubating conditions.

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INTRODUCTION

The principal uses of neuromuscular blocking drugs are to provide skeletal muscle relaxation to facilitate tracheal intubation and to improve surgical working conditions during general anesthesia. Cisatracurium is a new non-depolarizing, benzylisoquinolinium NMBD with intermediate duration of action.[1] It is a stereoisomer of atracurium with a potency of approximately 3 to 4 times greater than that of atracurium.[1,2]

Despite the higher potency, cisatracurium is associated with more stable hemodynamics than atracurium and does not cause histamine release even at doses of up to

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0.4mg/kg ($8\times ED_{95}$).[3] The recommended intubating dose is 0.15mg/kg ($3\times ED_{95}$) & higher.[4,5] Most of the previous clinical studies have compared equipotent doses of atracurium and cisatracurium and concluded that atracurium is more effective than cisatracurium at same dose ($2\times ED_{95}$).

However, few studies have shown that increasing the dose of cisatracurium to $4\times ED_{95}$ (0.2mg/kg) and $6\times ED_{95}$ (0.3mg/kg) provided more effective neuromuscular blockade and excellent cardiovascular stability with no marked histamine release clinically.[4,6] Present study was aimed to compare of hemodynamic stability and neuromuscular blockade of cisatracurium at a higher dose ($6\times ED_{95}$) versus recommended intubating dose ($2\times ED_{95}$) of atracurium in patients undergoing elective abdominal surgery.

MATERIAL AND METHODS

Present study was single-center, prospective, comparative study, conducted in Department of Anaesthesia, Yenepoya medical College, Mangalore, India. Study duration was of 1 year (August 2012 to July 2013). Study approval was obtained from institutional ethical committee.

Inclusion criteria

- Patients of age 20-65 years, either gender, American Society of Anesthesiologist Grade I & II, posted for abdominal surgeries, willing to participate in present study.

Exclusion criteria

- Patients with disorder of cardiovascular, hepatic, renal or neuromuscular systems.
- Pregnant & lactating women.
- Patients with airway problems suggesting difficult intubation.
- Patients receiving drugs known to interact with neuromuscular blocking agents.

Study was explained to patients in local language & written consent was taken for participation & study. A detailed pre-anaesthetic evaluation including history of previous medical illness, previous surgeries, general examination and appropriate baseline investigations were carried out on the day prior to surgery and recorded.

In the pre-op room, intravenous line was secured and patients were premedicated with Inj. glycopyrrolate 0.005mg/kg body weight IV and Inj. midazolam 0.03mg/kg body weight IV 10 min preoperatively. Pulse oximeter probe was attached and SpO2/HR was monitored continuously. On the operation table, patients were connected to non invasive monitoring with 3-lead electrocardiograph (ECG), pulse oximetry and non-invasive sphygmomanometer. BP cuff was applied to a different arm opposite to the site of neuromuscular monitoring Details of the group and the drug to be given were sealed within envelopes, which was randomly picked and administered by one anesthesiologist unrelated to study.

- Group A (30 patients) received Atracurium 0.5mg/kg IV
- Group C (30 patients) received Cisatracurium 0.3mg/kg IV.

Neuromuscular Monitoring - One forearm was immobilized in splint and ulnar nerve at wrist (1 cm proximal to proximal wrist crease) was selected for neuromuscular monitoring using Fisher &Paykel Innervator 272 neuromuscular monitor (NM). Two disposable pregelled AgCl skin surface electrodes were applied after cleaning and rubbing the skin and were connected to neuromuscular monitor. The ulnar nerve was stimulated supramaximally with square wave pulses (50-70 mA) 0.2 ms duration. The force of contraction of adductor pollicis muscle was noted by visual and tactile means in form of finger flexion and thumb adduction. After ensuring supramaximal stimulation, baseline values for TOF and twitch height were noted after induction of anaesthesia and before administration of muscle relaxant. TOF impulses at 2 hz were applied at 12 seconds interval with a minimum gap of 12 seconds between two stimulation pattern.

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Preoperative hemodynamic parameters (blood pressure, heart rate, SpO_2) recorded on table. Patients were preoxygenated with 100% oxygen for 3min. General anesthesia was induced in all patients with Inj. fentanyl (1.5mcg/kg), Inj. propofol (2mg/kg) IV. Anaesthesia maintained with a mixture of 50% N_2O in O_2, isoflurane (0.5% - 1.5% vol%). Baseline values for TOF and twitch height were noted. After a stable baseline period, the patients randomly received intubating dose of either Inj. Atracurium 0.5mg/kg IV or Inj. Cisatracurium 0.3mg/kg IV injected within 5-10 sec by an anaesthesiologist who was aware of the drug given. The responses (to stimuli delivered by NM monitor) were noted (palpated) every 15 seconds by the anaesthesiologist who injected the drug and was required to inform anaesthesiologist involved with the study who was to perform the tracheal intubation.

Endotracheal intubation was done when train-of-four count (TOFC) became 0 and twitch totally disappeared, using proper size endotracheal tube and the condition of intubation was assessed and recorded as excellent, good, poor, or impossible based on the degree of jaw relaxation, vocal cords position and intubating response. Anaesthesia maintained with a mixture of 50% N_2O in O_2, isoflurane (0.8-1MAC) and intermittent boluses of muscle relaxant. Intraoperatively, the response to TOF was recorded every 5 minutes and incremental dose of muscle relaxant was administered at TOFC of 1 as follows:
Group A: Atracurium 0.125mg/kg IV , Group C: Cisatracurium 025mg/kg IV

Patients were monitored for any signs of histamine release clinically through skin changes gaded as flush (if redness lasted> 120 s), erythema, or wheals and presence of any hemodynamic changes or bronchospasm. Reversal was achieved at the end of surgery by administration of Inj. neostigmine 0.05mg/kg IV and Inj. glycopyrrolate 0.01mg/kg IV when the TOFC <3.

Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Frequency, percentage, means and standard deviations (SD) was calculated for the continuous variables, while ratios and proportions were calculated for the categorical variables. Difference of proportions between qualitative variables were tested using chi-square test or Fisher exact test as applicable. P value less than 0.05 was considered as statistically significant.

RESULTS

In present study, 60 patients were randomly divided into two groups of 30 each as Group A included patients receiving Inj. Atracurium, Loading dose: 0.5mg/kg Incremental dose: 0.125mg/kg & group C: Included patients receiving Inj. Cisatracurium, loading dose: 0.3mg/kg Incremental dose: 0.025mg/kg.

In present study, the mean age was 37.13±11.27 and 38.73±10.40 years in groups A and C respectively. Difference between the two age groups was statistically insignificant. There were 46.7% and 60% males in group A and C respectively, whereas females were 53.3 and 40% respectively, which was statistically insignificant. Among the diagnoses, cholelithiasis was the most common in both the groups and cholecystectomy (open & laparoscopic) was the commonest surgery performed.

Table 1- General characteristics

Characteristics	**Group A (No. of patients)**	**Group C (No. of patients)**	**p value**
Age groups (in years)			
20-30	11 (36.7 %)	10 (33.3 %)	
31-40	6 (20 %)	8 (26.7 %)	
41-50	10 (33.3 %)	7 (23.3 %)	

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51-60	2 (6.7 %)	5 (16.7 %)	
>60	1 (3.3 %)	0	
Mean age (mean ± SD)	37.13±11.27	38.73±10.40	0.57
Gender			0.301
Male	14 (46.7 %)	18 (60 %)	
Female	16 (53.3 %)	12 (40 %)	
ASA Grade			0.278
Grade I	27 (90 %)	24 (80 %)	
Grade II	3 (10 %)	6 (20 %)	

The mean time taken for maximal depression of twitch was 174.00±13.02 and 122.33±13.82 seconds in group A and C respectively. The difference between the two groups was strongly significant statistically ($p<0.001$), with Cisatracurium having an earlier onset of muscle relaxation compared to Atracurium. Excellent intubating conditions were observed in 46.7% and 83.3% of patients in Group A and C respectively, difference was statistically significant. The mean duration of action of loading dose was 39.50±2.91 and 71.20±3.88 minutes in Group A and C respectively, difference was statistically significant

Table 2- Anesthesia characteristics

Characteristics	**Group A (No. of patients)**	**Group C (No. of patients)**	**p value**
Onset time (sec)			
110-150	2 (6.7 %)	30 (100 %)	
160-200	28 (93.3 %)	0	
Mean ±SD	174.00±13.02	122.33±13.82	< 0.001
Intubating Condition			0.006
Poor	1 (3.3 %)	0	
Good	15 (50 %)	5 (16.7 %)	
Excellent	14 (46.7 %)	25 (83.3 %)	
Duration of action (min)		18 (60 %)	
35-40	21 (70 %)	0	
41-50	9 (30 %)	0	
51-60	0	30 (100 %)	
Mean ± SD (min)	39.50±2.91	71.20±3.88	< 0.001

The mean basal preoperative heart rate was 81.40±10.28 and 80.67±12.52 bpm in Group A and C respectively which were comparable and statistically insignificant. Changes in heart rate after injection of muscle relaxant were indicated as a % change from the basal value. The changes were <10% from the basal value and clinically insignificant. Also the difference in heart rate at 1, 2, and 5 min from the basal value was comparable in both the groups.

Table 3: Comparison of Heart Rate

Heart Rate (bpm)	**Group A (mean ± SD)**	**Group C (mean ± SD)**	**p value**
Before premedication	81.73 ± 9.93	80.33 ± 12.93	0.640
Before induction (basal pre-op)	81.40 ± 10.28	80.67 ± 12.52	0.805
1 min after relaxant	83.93 ± 9.59	82.13 ± 12.27	0.529
2 min after relaxant	86.40 ± 9.97	84.60 ± 12.52	0.540
5 min after relaxant	87.87 ± 9.55	86.80 ± 11.45	0.697
(Difference) from Before Induction			

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• 1 min after relaxant	2.53	1.46	-
• 2 min after relaxant	5.00	3.93	-
• 5 min after relaxant	6.47	6.13	-
% change from Before Induction			
• 1 min after relaxant	+3.1%	+1.8%	-
• 2 min after relaxant	+6.1%	+4.9%	-
• 5 min after relaxant	+7.9%	+7.6%	-

The mean basal preoperative MAP was 80.17±8.85 and 75.13±9.15 mmHg in Group A and C respectively which even though statistically significant were comparable and within limits. Changes in MAP after injection of muscle relaxant were indicated as a % change from the basal value. The changes were <10% from the basal value and clinically insignificant.

Table 4: Comparison of MAP (mmHg)

MAP (mmHg)	**Group A (mean ± SD)**	**Group C (mean ± SD)**	**p value**
Before premedication	81.47±8.22	75.60±8.97	0.011*
Before induction (basal pre-op)	80.17±8.85	75.13±9.15	0.035*
1 min after relaxant	78.53±9.09	74.20±9.01	0.069+
2 min after relaxant	77.13±9.64	73.80±9.04	0.172
5 min after relaxant	72.90±10.55	75.70±8.96	0.273
□ (Difference) from Before Induction			
• 1 min after relaxant	1.64	0.93	-
• 2 min after relaxant	3.04	1.33	-
• 5 min after relaxant	7.27	0.57	-
% change from Before Induction			
• 1 min after relaxant	-2%	-1.2%	-
• 2 min after relaxant	-3.8%	-1.8%	-
• 5 min after relaxant	-9%	+0.8%	-

Only two patients in Atracurium group had signs of histamine release in the form of flushing at the site of injection in the forearm, whereas no patients in Cisatracurium group showed signs of histamine release. The difference was however statistically insignificant.

Table 5: Signs of histamine release

	Group A (No. of patients)	**Group C (No. of patients)**	**p value**
Flush	2 (6.7 %)	0	0.492
Erythema	0	0	
Wheals	0	0	

DISCUSSION

Cisatracurium is a new stereoisomer of atracurium with a potency of approximately 3 to 4 times greater than that of atracurium and is associated with stable hemodynamics without histamine release even at doses of up to 0.4mg/kg ($8\times ED_{95}$). The recommended intubating dose is 0.15mg/kg ($3\times ED_{95}$) & higher.

The use of neuromuscular blocking agents is well established in practice of anesthesia, although many factors are involved. The selection of type of non-depolarizing muscle relaxant to be used for surgical anesthesia depends mainly on onset time, cardiovascular effects, duration of action, pharmacokinetic profile and reversal of

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neuromuscular blockade.

In this study, onset time was judged by time taken for maximal depression of single twitch response after administration of muscle relaxant. Onset time was found to be significantly shorter for Cisatracurium as compared to Atracurium, which was highly significant. Our findings are similar to those observed by El-Kasaby AM et al., who found that onset of action of $6\times ED_{95}$ dose of cisatracurium (0.3mg/kg) was shorter as compared to $2\times ED_{95}$ dose of atracurium (0.5mg/kg) which was 2±1.2 min and 3.24±0.55 min respectively.[4]

Matthew R. Belmont et al.,[1] found that onset was 1.9±0.1 min and 3.2±0.3 min after cisatracurium (0.4mg/kg) and atracurium (0.5mg/kg) respectively, which correlates with our study. Bluestein LS et al.,[7] concluded that during nitrous oxide/oxygen/propofol/fentanyl anesthesia, by increasing the initial dose of cisatracurium (from 0.1 to 0.15 and 0.2mg/kg), the mean time of onset decreased (from 4.6 to 3.4 and 2.8 min) respectively, which correlates with our study.

Cisatracurium is one of the ten stereoisomers of atracurium accounting for approximately 15% of atracurium mixture. It is on a molar basis, 3 times more potent than atracurium.[8] The slower onset of action of cisatracurium as compared to atracurium at equipotent doses is probably due to its greater potency, a mechanism that has been proposed for other relaxants. The more potent non-depolarizing neuromuscular blockers have a slower onset.[9] Increased doses of all non-depolarizing muscle relaxants are found to decrease the time to onset of maximum block and prolong time to recovery. Onset of block is decreased at the expense of prolonged duration.[7]

In present study, mean duration of action of loading dose was 39.50±2.91 and 71.20±3.88 min in Group A and C respectively, difference was statistically highly significant.

El-Kasaby AM et al., concluded that duration of action of cisatracurium (0.3mg/kg) and atracurium (0.5mg/kg) was 78.4±8.6 and 44.4±4.13 min respectively, which correlates with our study.[4] Bluestein LS et al.,[7] reported that increasing the initial dose of cisatracurium (from 0.1 to 0.15 and 0.2mg/kg) increased the mean time of clinically effective duration (45 to 55 and 61 min) respectively. They also showed that the mean time of clinically effective duration of atracurium (0.5mg/kg) was 45.6 min, which is in consonance with our study results.

Jean-Yves Lepage et al.,[2] concluded that time to 25% recovery of T1% (duration of action) of atracurium (0.5mg/kg) and cisatracurium (0.1, 0.2, 0.25mg/kg) was 42, 33, 55 and 79 min respectively which infers that increasing the dose of cisatracurium prolongs the duration of action, whereas at equipotent doses, cisatracurium has a shorter duration of action compared to atracurium. These findings correlate with our study.

A significant direct relationship has been found between duration of action and potency of the drug after administration of appropriate ED_{95} doses different non- depolarizing neuromuscular blocking drugs. Duration of action of cisatracurium is prolonged as compared to atracurium because of the above relation.[7]

In the present study intubation was done when the response to twitch totally disappeared and TOFC = 0. It was assessed and recorded as excellent, good, poor, or impossible based on the degree of jaw relaxation, vocal cords position and intubating response. Excellent intubating conditions were observed in 46.7% and 83.3% of patients in Group A and C respectively.

Our findings are in consonance with A. M. El-Kasaby et al.,[4] who observed that after cisatracurium (0.3mg/kg), 81.25% and 18.75% of patients had excellent and good intubating conditions respectively as compared to 37.5% and 50% after atracurium (0.5mg/kg). (2 min after administering the drug).

Carrol MT et al.,[9] compared the intubating conditions of atracurium (0.5mg/kg) and

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cisatracurium (0.1 and 0.15mg/kg) 2 minutes after administration of the drug. They found that increasing the dose of cisatracurium from 0.1 to 0.15mg/kg increased the excellent intubations from 17% to 54%. With atracurium, excellent and good intubating conditions were seen in 60% and 40% of patients respectively. These findings correlate with our study results.

Bluestein LS et al.,[7] compared the intubating conditions of cisatracurium 0.1mg/kg ($2\times ED_{95}$), 0.15mg/kg ($3\times ED_{95}$) and 0.2mg/kg ($4\times ED_{95}$) and atracurium 0.5mg/kg ($2\times ED_{95}$) during propofol/fentanyl anaesthesia. Intubation conditions were good to excellent in over 90% of patients in all the groups (2 minutes after $2\times ED_{95}$ doses of cisatracurium or atracurium and 1.5 minutes after 3× and $4\times ED_{95}$ dose of cisatracurium). They concluded that by increasing the dose of cisatracurium from 0.1 to 0.2mg/kg, good to excellent intubation conditions could be achieved earlier (2 min vs 1.5min). These findings are in consonance with our study results.

Because the onset of block occurs faster in the larynx and airway musculature than in adductor pollicis, one can expect that even with some response visible in the adductor pollicis, intubating conditions may be quite good because of complete relaxation of the airway musculature.[10]

In our study, basal preoperative heart rate was comparable between Group A and C (81.40±10.28 and 80.67±12.52 bpm respectively). Basal preoperative mean arterial blood pressure was 80.17±8.85 and 75.13±9.15 mmHg in Group A and C respectively.

Bisbenzylquinolinium compounds, in general tend to cause histamine release, which can result in facial flushing and hemodynamic aberrations. The cardiovascular effects normally noted secondary to histamine release are a decrease in mean arterial pressure and a compensatory increase in heart rate. These responses normally are transient and are related to both the size of the dose of the relaxant administered and the time course over which the relaxant is given.[3]

Administration of large doses of these relaxants over 30-60 seconds, rather than over 5 seconds, will attenuate the hemodynamic changes associated with their rapid administration. The circulatory changes are transient, occurring 60-90 seconds after administration of atracurium and disappearing within 5 minutes. Cisatracurium is devoid of histamine-releasing effects, so that cardiovascular changes do not accompany the rapid IV administration of even large doses ($8\times ED_{95}$) of cisatracurium.[11]

Cynthia A. Lien et al., conducted a study to compare and determine the cardiovascular effects and histamine releasing properties of different doses of cisatracurium (2, 4 and 8xED95) and atracurium ($2xED_{95}$ dose). No patient developed a decrease in MAP>=20% or an increase in HR>=20% that was attributable to muscle relaxant administration.[3] These results correlate well with our study.

CONCLUSION

Cisatracurium at a higher dose ($6\times ED_{95}$) as compared to Atracurium ($2\times ED_{95}$) provided more effective, more rapid neuromuscular blockade with excellent intubating conditions, longer duration of action, stable hemodynamic status without clinically significant changes in HR and MAP, and no associated signs of histamine release clinically. Hence Cisatracurium, though more costly, is more effective and a better isomer of Atracurium.

Conflict of Interest: None to declare
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REFERENCES

1. Mathew R. Belmont, Cynthia A. Lien, Steve Quessy, Martha M. Donia, Amy Abalos, Larissa Eppich, John J. Savarese. The clinical neuromuscular pharmacology of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anaesthesia. Anesthesiology 1995;82:1139-1145.
2. Jean-Yves Lepage, Jean-Marc Malinovsky, Myriam Malinge, Thierry Lechevalier, Christine Dupuch, Antoine Cozian, Michel Pinaud, Remy Souron. Pharmacodynamic dose-response and safety study of Cisatracurium (51W89) in adult surgical patients during N2O-O2-opioid anaesthesia. Anesth Analg 1996;83:823-829.
3. Cynthia A. Lien, Mathew R. Belmont, Amy Abalos, Larissa Eppich, Steve Quessy, Martha M. Abou-Donia, John J. Savarese. The cardiovascular effects and histamine releasing properties of 51W89 in patients receiving nitrous oxide/opioid/barbiturate anaesthesia. Anesthesiology 1995;82:1131-1138.
4. El-Kasaby AM, Atef HM, Helmy AM, Abo El-Nazr M. Cisatracurium in different doses versus atracurium during general anaesthesia for abdominal surgery. Saudi J Anesth 2010 Sept-Dec;4 (3):152-157.
5. Kirov K, Motamed C, Decailliot F, Behforouz N, Duvaldestin P. Comparison of the neuromuscular blocking effect of cisatracurium and atracurium on the larynx and the adductor pollicis. Acta Anaesthesiol Scand. 2004 May;48(5):577-81.
6. Jirasiritham S, Tantivitayatan K, Jirasiritham S. A comparison of the efficacy of cisatracurium and atracurium in kidney transplantation operation. J Med Assoc Thai. 2004 Jan;87(1):73-9.
7. Linda S. Bluestein, Lawrence W. Stinson Jr., Robert L. Lennon DO, Stephen N. Quessy, Rebecca M. Wilson. Evaluation of cisatracurium, a new neuromuscular blocking agent, for tracheal intubation. Can J Anaesth 1996; 43(8): 925-31.
8. Bryson HM, Faulds D. Cisatracurium Besylate: A review of its pharmacology and clinical potential in anaesthetic practice. Drugs. 1997 May;53(5):848-66.
9. Carroll MT, Mirakhur RK, Lowry DW, Glover P, Kerr CJ. A comparison of the neuromuscular blocking effects and reversibility of cisatracurium and atracurium. Anaesthesia 1998;53:744-748.
10. Naguib M, Lien CA. Pharmacology of muscle relaxants and their antagonists, Chapter 13 In: Miller's Anesthesia, 6th Ed. Philadelphia: Elsevier-Churchill Livingstone, 2005; 484-515.
11. Stoelting RK & Hillier SC. Neuromuscular-Blocking drugs, Chapter 8 In: Pharmacology and Physiology in Anesthetic Practice, 4th Ed. Philadelphia: Lippincott Williams & Wilkins; 2006; 208-241.