Atracurium Infusion Assessment

S Sunatrio

Abstrak

Tidak seperti pelumpuh otot kompetitif konvensional, atracurium cocok diberikan dalam bentuk infusi karena pemecahannya terjadi secara spontan melewati eliminasi Hoffman yang tidak bergantung pada fungsi ginjal atau hati. Lagi pula Atracurium tidak berakumulasi walaupun setelah diberikan beberapa penambahan dosis infusi yang berlangsung beberapa jam atau bahkan berhari-hari. Tujuan utama penelitian ini adalah untuk menentukan apakah atracurium cocok diberikan dalam bentuk infusi pada operasi yang diperkirakan berlangsung lebih dari 3/4 jam, pada berbagai macam pasien dan untuk segala umur. Termasuk dalam studi ini sebanyak 59 pasien dibagi dalam 3 kelompok. Kelompok I (n=20) dinilai dengan memakai alat stimulator saraf dan kelompok II (n=22) tanpa memakai alat tersebut. Pasien-pasien dengan gangguan ginjal atau hati dimasukkan dalam kelompok III (n=17) dan dinilai dengan menggunakan alat stimulator saraf. Anestesia dimulai dengan tiopenton serta dipelihara dengan petidin dan diazepam dengan 33% O_2 dalam N_2O. Setelah induksi, pada pasien diberikan suntikan bolus atracurium 0,6 mg/kg, dan kemudian dilakukan intubasi, seterusnya ventilasi. 20 menit kemudian penambahan atracurium 0,3-0,6 mg/kg/jam, dengan dilakukan penyesuaian seperlunya untuk mendapatkan kelumpuhan otot 90-100%. Infusi dihentikan 15-20 menit sebelum akhir operasi. Laju infusi rata-rata pada semua pasien adalah 0,41 ± 0,11 mg/kg/jam. Secara statistik tidak ada perbedaan antara kelompok I (normal) dan kelompok III (dengan gangguan ginjal dan hati). Kualitas relaksasi sangat baik pada semua pasien. Penilaian menyeluruh yang berdasarkan kemudahan pemakaian, kemanjuran dan penawarannya (antagonisasinya) dianggap sangat baik pada setiap pasien. Teknik infusi atracurium secara khusus dianjurkan karena variasi kebutuhan atracurium berkurang baik pada subyek normal maupun yang dengan gangguan berat fungsi ginjal dan atau fungsi hati. Teknik ini dapat dipakai dengan atau tanpa pemantauan alat stimulator saraf (perangsang train of four). Didapat kesan dari penelitian ini bahwa laju infusi dapat distandardisasikan/dibakukan pada atau sekitar 0.5 mg/kg/jam.

Abstract

Unlike conventional competitive neuromuscular blocking agents atracurium particularly commends itself for use by infusion since it utilises a unique spontaneous degradation pathway, the Hoffman elimination, which is independent of renal or hepatic function. Moreover it doesn't accumulate even after several supplementary doses of infusions lasting several hours or indeed days. The primary aim of this assessment is to establish the suitability of atracurium by infusion in operations expected to last longer than 3/4 hour, in a variety of patient types and ages. Included in this study were 59 patients who were divided into 3 groups. Group I (n=20) was assessed by using a nerve stimulator and group II (n=22) without a nerve stimulator. Patients with renal or hepatic dysfunction were included in group III (n=17) and assessed by using a nerve stimulator. Anaesthesia was induced with thiopentone and maintained with pethidine and diazepam in 33% O_2 in N_2O. Following induction, a bolus of atracurium 0,6 mg/kg was given and the patient was intubated and the ventilation was controlled afterwards. Twenty minutes later an infusion of atracurium 0,3-0,6 mg/kg/hour was commenced, with adjusment as necessary to provide 90-100% neuromuscular blockade. The infusion was stopped 15-20 minutes before the end of surgery. Mean infusion rate of all patients was 0,41 ± 0,11 mg/kg/hour. Statistically there are no differences between group I (normal) and group III (with renal or hepatic dysfunction). In all patients the quality of relaxation was excellent. Overall assessment based on ease of use, efficacy and reversal was considered excellent in every patient. The infusion technique of atracurium is particularly advisable because of the reduced inter-patient variations in requirement for blocking agent in normal subjects and also in cases of severe renal or hepatic dysfunction or both. This technique can be employed with or without monitoring by TOF stimuli. It seems that the infusion rate could be standardised at or around 0,5 mg/kg/hour.

Keywords : *Neuromuscular blockers, Accumulation, Infusion.*

INTRODUCTION

Atracurium is a competitive intermediate duration neuromuscular blocking agent which was first introduced in the United Kingdom in 1982. Unlike conventional competitive neuromuscular blockers it particularly commends itself for use by infusion since it utilises a unique spontaneous degradation pathway, the

Department of Anaesthesiology, Faculty of Medicine University of Indonesia/Cipto Mangunkusumo Hospital, Jakarta, Indonesia

Hoffman elimination, which is independent of renal or hepatic function. Moreover, it does not accumulate even after several supplementary doses or infusions lasting several hours[1,2,3] or indeed days.[4]

The primary aim of this assessment is to establish the suitability of atracurium by infusion in operations expected to last longer than 3/4 hour, in a variety of patient types and ages.

Optional subsidiary aims concern :

1. The possibility of standardising the atracurium infusion rate at or around 0,5 mg/kg/hour (0,0083 mg/kg/min), and/or;
2. The possibility of using atracurium infusions without sophisticated neuromuscular monitoring equipment (eg. using a peripheral nerve stimulator) or without using any monitoring equipment. One report in the literature suggest this may be possible.[5]

PATIENTS AND METHODS

The study included 59 patients, ASA groups I-II-III undergoing elective surgery at Cipto Mangunkusumo Hospital, Jakarta and was approved by the local ethics committee. The patients' ages ranged from 19 to 75 years and their body weights from 34 to 70 kg. Pregnant women, severely obese patients and patients with neuromuscular disease were excluded from the study. Patients with renal of hepatic dysfunction were included in this study. As monitoring equipment, a capnograph, a Wright spirometer, an EKG monitor and a non-invasive blood pressure monitor were used throughout the procedures. For assessment of neuromuscular blockade train of four (TOF) stimulation using a nerve stimulator (Digstim III) was employed. The patients were divided into 3 groups. Group I (n=20) was assessed by using a nerve stimulator and group II (n=22) without a nerve stimulator. Patients with renal or hepatic dysfunctions were included in group III (n=17) and assessed by using a nerve stimulator.

Premedication was with pethidine 1-2 mg/kg and droperidol 2,5-5 mg given intramuscularly 1/2-1 hour before surgery. Anaesthesia was induced with thiopentone and maintained with pethidine and diazepam in 33% oxygen in nitrous oxide. The patients were kept normocapnic. Following induction, a bolus of atracurium 0,6 mg/kg was given and the patient was intubated and the ventilation was controlled afterwards. Twenty minutes later (which corresponds approximately to the half life of atracurium) an infusion of atracurium 0,3-0,6 mg/kg/hour was commenced, with adjustments as necessary (to provide 90-100 % neuromuscular blockade in patients monitored by the TOF stimuli).

The infusion was stopped by the time of skin closure or an estimated 15-20 minutes before the end of the operation. If necessary, neuromuscular blockade was reversed by neostigmine, preceded by atropine.

Data collection by the anaesthetist were as follows :

1. Quality of relaxation
2. TOF count when infusion was stopped and recovery time to the reappearance of a TOF score of 4.
3. Time to extubation (after spontaneous of induced recovery).
4. Any adverse events
5. Overall assessment based on ease of use, efficacy and reversal.

Data collection by the surgeon were quality of surgical access : excellent/satisfactory/poor.

Table 1. Types and numbers of procedures in patients of group I and Group III

Operation	Group I (n=20)	Group III (n=17)
Relaparotomy	1	
Cholecystectomy	2	3
Extended pyelolithotomy	5	3
Radical mastectomy	1	
Radical mastoidectomy	1	
Open reduction with nail	1	
Nephrectomy	1	
Thyroidectomy	2	
Extirpation of epidermal cyst	1	
Hysterectomy	2	
Ureterolithotomy		5
Splenectomy		1
Colostomy closure	1	
Vesicovaginal fistula repair	1	
Bilateral cystectomy	1	
Nephrostomy		5
Whipple operation	1	
Splenorenal shunt	2	

Table 2. Types and numbers of procedures in patients of group II

Operation	Group II (n=22)
Excision of mandibular tumor	1
Excision of abscess (breast)	1
Ureterolysis	1
Radical hysterectomy	2
Open reduction with K nail	2
Oophorectomy	2
Fistulectomy ec. nephrocutaneous fistula	1
Fistulectomy ec. enterocutaneous fistula	1
Total hip replacement	1
Extended pyelolithotomy	3
Ureterolithotomy	5
Ureteroplasty	1
Release flap	1

Table 3. Age and body weight of the patients and amount of anaesthetics

	Group I (n=20) mean ± SD	Group III (n=17) mean ± SD	p
Body weight (kg)	46,85 ± 4,67	44,35 ± 11,12	0,398
Age (year)	36,15 ± 10,67	44,18 ± 11,24	0,034
Droperidol, premedication (mg)	4,90 ± 0,31	7,53 ± 8,65	0,228
Pethidine, premedication (mg)	49,50 ± 3,94	44,41 ± 5,56	0,004
Thiopentone (mg)	251,25 ± 12,76	222,06 ± 44,97	0,018
Diazepam (mg)	12,10 ± 4,81	12,76 ± 9,25	0,415
Pethidine (mg)	61,58 ± 21,15	63,82 ± 24,59	0,794
Intubation dose of atracurium (mg)	27,80 ± 2,505	26,59 ± 5,550	0,772

The two groups (Group I and Group III) were comparable in respect of body weight and amount of anaesthetics used, except for pethidin premedication, thiopentone and age.

RESULTS

The duration of infusion and doses of atracurium are shown in Tables 4, 5 and 6.

Table 4. Body weight, duration of infusion and doses of atracurium in group I

No.	Body weight (kg)	Duration of infusion (min)	Total Dosage (mg)	Doses/kg/hr (mg/kg/hr)	Mean doses ± SD
1	50	256	104	0,6	
2	50	59	15	0,31	
3	49	32	16	0,6	
4	41	151	36	0,35	
5	41	75	22	0,42	0,41 ± 0,097
6	45	74	20	0,36	
7	42	181	49	0,38	
8	45	71	22	0,41	
9	41	63	15	0,35	
10	46	143	43	0,39	
11	41	70	21	0,44	
12	46	40	14	0,51	
13	50	157	62	0,47	
14	50	35	11	0,38	
15	52	91	23	0,29	
16	50	109	54	0,59	
17	42	25	7	0,40	
18	51	56	14	0,29	
19	47	60	15	0,32	
20	58	53	19	0,37	

The infusion rate of atracurium needed to provide 90-100 % muscular blockade in Group I ranged from 0,29 to 0,6 mg/kg/hour and the mean dose was 0,41 ± 0,097 mg/kg/hour.

Table 5. Body weight, duration of infusion and doses of atracurium in group II

No.	Body weight (kg)	Duration of infusion (min)	Total Dosage (mg)	Doses/kg/hr (mg/kg/hr)	Mean doses ± SD
1	51	40	18	0,59	
2	58	40	15	0,43	
3	47	81	32	0,50	
4	53	154	47	0,35	
5	58	125	45	0,37	0,427 ± 0,096
6	50	38	10	0,32	
7	40	83	13	0,24	
8	54	98	35	0,40	
9	55	180	78	0,47	
10	48	140	30	0,27	
11	47	38	17	0,57	
12	62	177	91	0,49	
13	51	199	77	0,45	
14	65	204	90	0,41	
15	45	23	6	0,35	
16	43	25	9	0,50	
17	59	32	10	0,32	
18	50	85	35	0,49	
19	53	56	19	0,38	
20	72	222	112	0,42	
21	53	65	25	0,44	
22	45	32	15	0,63	

In this Group II, the infusion rate of atracurium needed to provide adequate muscular relaxation by clinical assessment ranged from 0,24 to 0,63 mg/kg/hour with the mean dose of 0,42 ± 0,096 mg/kg/hour.

Table 6. Body weight, duration of infusion and doses of atracurium in group III

No.	Body weight (kg)	Duration of infusion (min)	Total Dosage (mg)	Doses/kg/hr (mg/kg/hr)	Mean doses ± SD
1	48	139	38	0,34	
2	70	120	25	0,18	
3	48	119	29	0,31	0,44 ± 0,137
4	34	56	13	0,41	
5	42	104	44	0,61	
6	37	91	30	0,53	
7	70	120	25	0,18	
8	40	36	8	0,33	
9	33	89	21	0,43	
10	35	35	10	0,49	
11	34	46	13	0,50	
12	40	64	18	0,42	
13	46	503	149	0,39	
14	40	170	83	0,73	
15	42	338	159	0,67	
16	42	193	63	0,46	
17	53	150	44	0,33	

The infusion rate of atracurium for 90-100% neuromuscular blockade in Group III varied between 0,18 and 0,67 mg/kg/hour and the mean dose was 0,44 ± 0,137 mg/kg/hour. The mean dose of all patients (Group I, II, III) was 0,41 ± 0,11 mg/kg/hour. The neuromuscular data are given in Tables 7 and 8.

Table 7. Neuromuscular data in group I

No.	TOF count when infusion stop	Recovery time to the reappearance of a TOF score 4 (min)	Time to extubation after spontaneous or induced recovery (min)
1	0	52	3
2	0	18	13
3	1	15	13
4	0	20	2
5	0	23	12
6	0	13	12
7	0	26	5
8	0	18	0
9	0	19	5
10	1	17	10
11	0	27	4
12	0	14	2
13	0	26	2
14	0	9	7
15	0	27	3
16	0	15	2
17	0	14	18
18	0	24	7
19	0	22	15
20	0	14	9

Reversal with neostigmine was given to patients no. 1 and 2.

Table 8. Neuromuscular data in group III

No.	TOF count when infusion stop	Recovery time to the reappearance of a TOF score 4 (min)	Time to extubation spontaneous or induced recovery (min)
1	0	22	2
2	0	35	2
3	1	20	15
4	0	46	13
5	1	20	4
6	0	54	25
7	0	18	2
8	0	7	6
9	0	31	2
10	0	14	8
11	0	22	3
12	1	11	5
13	0	30	3
14	1	10	20
15	1	31	5
16	0	25	0
17	0	24	2

Reversal with neostigmine was carried out in patients no. 1 and 2.

Table 9. Comparison between group I and group III

	Group I (mean ± SD)	Group III (mean ± SD)	P
Recovery time to the reappearance of a TOF score 4 (min)	20,15 ± 9,03	24,71 ± 12,40	0,219
Time to extubation after spontaneous or induce recovery (min)	7,58 ± 5,07	7,66 ± 7,26	0,969
Atracurium doses (mg/kg/hour)	0,41 ± 0,097	0,44 ± 0,139	0,427

Statistically there are no differences between group I (normal) and group III (with renal or hepatic dysfunction).

In all patients quality of relaxation were considered by the anaesthetists as excellent. Overall assessment based on ease of use, efficacy and reversal

was considered excellent in every patient. There was no adverse event encountered in this study. The quality of surgical access was considered by the surgeon as excellent in all patients.

The mean infusion rate of atracurium of all patients in this study was 0,41 ± 0,11 mg/kg/hour. There was no difficulty in adjusting the infusion rate of atracurium in patients group II even though no TOF stimuli was employed.

DISCUSSION

Until recently, for the majority of anaesthetists, the routine method of administration of nondepolarizing neuromuscular blocking agents consisted of a loading dose, based on the patient's weight, followed by reinjection of one-third to one- fifth of the loading dose.[6,7,8] These injections are given according to clinical signs or impressions observed by the anaesthetist or the surgeon. However, this method may produce unstable and poorly controlled the levels of neuromuscular blockade, and overdosage of blocker at the end of the operation is not an infrequent situation. Moreover, even if this is avoided, clinical judgement alone does not permit precise anticipation of the right moment to reinject the blocking drug. A simple but somewhat quantitative monitoring of the degree of paralysis is therefore mandatory for more precise and objective management. The train of four count appears to be the method of choice.[9] To control and maintain stable neuromuscular blockade during surgery, infusion of the neuromuscular blocking agent is the technique of choice.

With atracurium besylate, as reconfirmed by this study, the infusion technique is particularly advisable because of the reduced inter-patient variations in requirement for blocking agent in normal subjects and also in cases of severe renal or hepatic dysfunction, or both.[10,11,12] This technique can be employed with or without monitoring by TOF stimuli.

Regarding the dose of atracurium used for infusion, it seems that the infusion rate could be standardised at or around 0,5 mg/kg/hour.

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