HIERARCHICAL RULE-BASED MONITORING AND FUZZY LOGIC CONTROL FOR NEUROMUSCULAR BLOCK

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ABSTRACT. Objective. The important task for anaesthetists is to provide an adequate degree of neuromuscular block during surgical operations, so that it should not be difficult to antagonize at the end of surgery. Therefore, this study examined the application of a simple technique (i.e., fuzzy logic) to an almost ideal muscle relaxant (i.e., rocuronium) at general anaesthesia in order to control the system more easily, efficiently, intelligently and safely during an operation. **Methods.** The characteristics of neuromuscular blockade induced by rocuronium were studied in 10 ASA I or II adult patients anaesthetized with inhalational (i.e., isoflurane) anaesthesia. A Datex Relaxograph was used to monitor neuromuscular block. And, ulnar nerve was stimulated supramaximally with repeated train-of-four via surface electrodes at the wrist. Initially a notebook personal computer was linked to a Datex Relaxograph to monitor electromyogram (EMG) signals which had been pruned by a three-level hierarchical structure of filters in order to design a controller for administering muscle relaxants. Furthermore, a four-level hierarchical fuzzy logic controller using the fuzzy logic and rule of thumb concept has been incorporated into the system. The Student's *t* test was used to compare the variance between the groups. $p < 0.05$ was considered significant. **Results.** The system achieved stable control of muscle relaxation with a mean T1% error of −0.19 (SD 0.66) % accommodating a range in mean infusion rate (MIR) of 0.21–0.49 $\mathrm{mg \cdot kg^{-1} \cdot h^{-1}}$. When these results were compared with our previous ones using the same hierarchical structure applied to mivacurium, less variation in the T1% error ($p < 0.05$) but the same variation in infusion rate were observed. The controller activity of these two drugs showed no significant difference ($p > 0.5$). However, the consistent medium coefficient variance (CV) of the MIR of both rocuronium (i.e., 36.13 (SD 9.35) %) and mivacurium (i.e., 34.03 (SD 10.76) %) indicated a good controller activity. **Conclusions.** The results showed that a hierarchical rule-based monitoring and fuzzy logic control architecture can provide stable control of neuromuscular block despite the considerable individual variation in neuromuscular block required among patients. Also, there was less variation in T1% error compared with that of previous study on mivacurium. Meanwhile, the consistent medium CV of the MIR of both rocuronium and mivacurium indicated a good controller activity which is able to withstand noise, diathermy effect, artifacts and surgical disturbances.

KEY WORDS. Fuzzy logic control, electromyography, hierarchical structure, neuromuscular monitoring.

INTRODUCTION

The advent of newer muscle relaxants approaching to an almost ideal neuromuscular blocking agent has grown rapidly in recent years. Rocuronium [1, 2] is a non-depolarizing neuromuscular blocking drug having

Table 1. Comparison of published human clinical results obtained with different atracurium control strategies using an EMG monitoring technique

		Performance measures (mean SD), %)		
Atracurium controller	Type	Mean error	SD	RMSD
Webster and Cohen, 1987 [10]	PD	–1.1 (0.47)	–	–
Wait et al., 1987 [9]	On/off	–	–	–
MacLeod et al., 1989 [13]	PI	–1.3 (1.3)	1.47 (0.69)	2.21 (1.01)
Denai et al., 1990 [14]	Adaptive PD	0.98 (4.3)	3.9 (2.3)	–
O'Hara et al., 1991 [15]	PID	–	–	–
Schwilden and Olkkola, 1991 [16]	Model-based	0.04 (0.46)	–	1.9 (0.6)
Mahfouf et al., 1992 [17]	Model-based	–0.16 (0.37)	3.12 (1.68)	3.41 (1.69)
Mason et al., 1996 [18]				
10% (phase I)	Fuzzy PD+I	1.1 (1.4)	2.4 (0.68)	3.0 (0.62)
20% (phase II)		–0.43 (1.2)	1.5 (0.29)	1.9 (0.36)
10% (phase III)		0.28 (0.94)	3.4 (0.88)	3.5 (0.85)
Shieh et al., 1996 [24]	Fuzzy PD+I	0.62 (1.08)	1.75 (0.86)	2.12 (0.86)
Ross et al., 1997 [19]	Self-learning fuzzy logic control	–0.52 (0.55)	2.30 (0.62)	2.39 (0.66)

an intermediate duration of action similar to that of vecuronium but with much faster onset of effect, thus offering good to excellent intubation conditions like succynlcholine. In addition, extensive clinical trials showed that rocuronium has rapid recovery characteristics coupled with cardiovascular stability and virtually no histamine release or other side effects. These characteristics make rocuronium an ideal neuromuscular blocking drug. However, the duration and recovery of this drug are found to be longer than those of mivacurium [3, 4]. Therefore, it is not suitable for use in short operation.

Closed-loop drug therapy offers considerable benefits to patient care. It provides the ability to maintain stable neuromuscular block while allowing for variation in individual response to the drug. Also, this benefits the patient because the minimum quantity of drug is administered and clinical workload is reduced, allowing more time for direct patient care. The reliability of neuromuscular block monitored by electromyography enables a closed-loop control strategy to be implemented. However, one problem with feedback control in biomedicine is that there are enormous patient-to-patient variations in dynamic model parameters. This is compounded by large time-varying parameters for an individual patient during the course of an operation, making it difficult to design a fixed-parameter PID controller which will be suitable in all cases. This arose the need to investigate self-adaptive control strategies, and later self-organizing controllers. Although the self-tuning trials have been successful, they involve considerable work in selecting the design parameters and mathematical models of the patient. Hence, various controllers developed from the classical control theory have been proposed in the past ten years, from simple on-off type to complex model-based controllers [5–17]. Intelligent control (e.g., fuzzy logic) has recently been implemented into this system via computer simulation and clinical use with atracurium [18–21]. Table 1 shows the comparison of published human clinical results obtained by different atracurium control strategies with EMG monitor. Fuzzy logic control, therefore, is still a simple and effective technique for controlling non-linear and uncertain processes [22, 23]. The effect of neuromuscular blockers is non-linear, and fuzzy logic provides a simple way to create a non-linear controller. Fuzzy logic not only accommodates uncertainty by dealing with imprecise, qualitative terms such as low, medium and high, but also provides control rules which are easy to understand and modify when discussing with experts. In recent years, there has been a move away from sporadic interest in artificial intelligence concepts by a small number of systems engineers to a worldwide passion for intelligent control, utilizing all the tools that have been developed in the field of artificial intelligence. Fuzzy logic is one of the many methodologies of intelligent control, which has been widely studied, both in industry and academia. Intelligence means the ability to understand or reason (logically) and to learn or adapt. The derivation of fuzzy rules is a common bottleneck in the application of fuzzy logic controllers. Conventionally, these fuzzy rules are derived from emulating the control actions of an expert (i.e., anaesthetist). There is a recent report on the clinical application of fuzzy logic control to muscle relaxation regulation using atracurium [18, 24]. However, with new neuromuscular blocks, no such experience is readily available to draw on for derivation of the fuzzy rule-base. This situation was the main driving force behind the introduction of self-organizing or self-learning fuzzy logic controllers [19, 20].

Almost all of these previous studies were made using atracurium and none of them employed newer agents such as mivacurium and rocuronium. However, we have successfully applied the hierarchical monitoring and fuzzy logic control of neuromuscular block with atracurium and mivacurium via clinical trials [24, 25]. This result has encouraged us to apply this technology using rocuronium. Therefore, this study aimed to investigate the hierarchical rule-based monitoring and fuzzy logic control for neuromuscular block with this almost ideal muscle relaxant (i.e., rocuronium). Also, the filter and control performances of this drug have been investigated in this paper via a comparison with previous clinical trials employing mivacurium [25].

METHODS

Patients

This study was approved by the Ethics Committee of the National Taiwan University Hospital. Ten ASA I or II patients, aged 18–70 yr and weighed 51–90 kg, undergoing surgery anticipated to last at least 30 min were enrolled as subjects and gave written informed consent. Patients with hepatic, renal or neuromuscular disease or those taking medications known or suspected to interfere with neuromuscular transmission were excluded. On arrival in the operating room, blood pressure was measured either noninvasively with a cuff attached to the arm or invasively with an arterial line injected into the artery not involved in neuromuscular monitoring. Pulse oximetry and electrocardiography were monitored continuously.

Anaesthesia

Preoperative anaesthetic visit and evaluation were performed in all patients the previous day with patients' consent. Anaesthetic agents were given by staff members, residents or nurse anaesthetist with at least one year of experience in anaesthesia. An attending anaesthetist involved in the study was always present and responsible for monitoring of the patient. Also, the investigator who designed this monitoring system was always present and responsible for handling any device or computer dysfunction. After the standard monitors were set up (i.e., ECG, blood pressure, pulse oximeter, and capnography monitor), all patients received a standardized anaesthetic regime. After premedication with atropine, anaesthesia was given with pentothal and fentanyl during the induction stage. An inhalational gas of isoflurane was given after induction and controlled by the anaesthetist or the nurse anaesthetist responsible for anaesthesia. The patient's lungs were then ventilated manually with nitrous oxide in oxygen. The loading dose of rocuronium was $0.6\ \mathrm{mg} \cdot \mathrm{kg}^{-1}$ during induction for intubation. After intubation, neuromuscular block was controlled by the closed-loop using a hierarchical rule-based and fuzzy controller of rocuronium throughout the operation.

Neuromuscular monitoring

Stimulating electrodes for a Datex Relaxograph were placed over the ulnar nerve of the non-infused hand, while the sensing electrodes were placed over the hypothenar area. The ulnar nerve was stimulated supramaximally with repeated train-of-four (TOF) via surface electrodes at intervals of 0.5 sec (2 Hz). The TOF stimulus was repeated every 10 sec that produced the expected degree of neuromuscular block more than every 20 sec [26]. The system comprised an IBM compatible notebook interfaced with a Datex Relaxograph for monitoring neuromuscular block and an Ohmeda 9000 medical infusion pump for administration of rocuronium. The notebook computer was programmed in the language "Borland C++" for using the developed hierarchical rule-based monitoring, the fuzzy logic control structure and co-ordinate communication with the two devices via serial links. The initial default value of EMG (i.e., T1% value) set points was 10% of the baseline, and $10\ \mathrm{mg} \cdot \mathrm{ml}^{-1}$ concentration of rocuronium was allowed to enter so that the computer could convert the controller output from mass rate ($\mathrm{mg} \cdot \mathrm{h}^{-1}$) to volume flow rate ($\mathrm{ml} \cdot \mathrm{h}^{-1}$). In addition, the patient's weight was entered for calculation of the loading dose of muscle relaxants.

A four-level hierarchical fuzzy logic controller

According to anaesthetists, there are many levels for controlling a patient's muscle relaxation from EMG output. To take this problem manageable, the concept of hierarchical structure is employed. The most important level is administered first. If this level does not work, the second more important level will be used and so on. Therefore, a four-level hierarchical fuzzy logic controller (Appendix) using the fuzzy logic and rule of thumb concept has been incorporated into the system in order to control the system more easily, efficiently, intelligently and safely during an operation. The first level uses the fuzzy set theory to build a look-up table to control the EMG signals around the set point. However, if this level is not suitable for controlling the patient, the self-tuning system in the second level is fired to fine-tuning this look-up table. Also, if the T1% error (which means the set point minus the T1% value) and T1% error changed caused by some surgical disturbances are beyond the range in the look-up table in the first level, a coarse table in the third level derived from the anaesthetist is applied in order to control the EMG signals returning quickly to set point. Finally, if some unexpected conditions happen and EMG signals are beyond the range of the safety of the clinical operation, an emergency table in the fourth level derived from the anaesthetist needs to be applied in order to bring the patient under control.

The initial T1% set point was entered as 10% of the baseline. However, if the surgeons complain of insufficient muscle relaxation, the set point can be changed to 5% of the baseline. During all operations, the infusion rate was set at an upper limit of 0.4 mg $\cdot$ h^{-1} and a lower limit of 0.2 mg $\cdot$ kg$^{-1}\cdot$ h^{-1} for the look-up table in the first level. The self-tuning system in the second level was active since the mean infusion rate (MIR) was above the upper limit or below the lower limit. Also, the coarse table in the third level was active since the T1% value was larger than 3% or less than 3% of the T1% set point. In addition, if the T1% was above the 10% of the T1% set point when neuromuscular block started to recover, the computer was programmed to give an additional 0.05 mg $\cdot$ kg^{-1} bolus over 1 min, repeating necessary until the T1% was less than 10% of the T1% set point level. The infusion rate was temporarily stopped if the T1% value is more than 3% below the T1% set point.

A three-level hierarchical filter

There are two types of noises for the Relaxograph to be recognized during the operation. First, when the surgeon uses a high frequency instrument to stop bleeding in the patient (which is called a diathermy effect), the EMG output signal will be disturbed and often the signals reduce to zero in that situation. Second, a noise may occur due to the movement of the patient that causes sudden change in the EMG output. Hence, a three-level hierarchical filter (Appendix), which includes a built-in hardware filter inside the instrument, a pharmacological filter, and a digital median filter, was designed for efficient pruning of the EMG signals. The EMG signals measured from a Datex Relaxograph were first passed through an inside built-in hardware filter, followed by a pharmacological filter according to the fade pattern in the evoked response to train-of-four nerve stimulation after injection of a non-depolarizing or depolarizing neuromuscular blocking agent acting as a second stage filter. If the signals were not matched to the fade pattern, these signals were identified as either noises or diathermy disturbances, and were ignored when entering the next stage filter. Finally, the signals were passed through the median filters that have proved to be suitable for medical signal processing [27]. The length of the filtering window for this system was three samples, corresponding to 30 sec in real time, and producing a real time average delay of 15 sec.

Analysis of data

As we were mainly interested in studying the behaviour of the system during the period of steady neuromuscular block, we needed an operational definition of the "stable period." The start of this period can be defined in two ways, depending on whether or not there is an overshoot above the target after starting automatic control. If there is, the beginning of the stable period is the time at which T1% returns to 10% after the overshoot. If there is no overshoot, the stable period begins when T1% first starts to decline after the controller has been started. The stable period ends when muscle relaxants stops and surgery is completed. Also, the beginning of the "controller in operation" is defined by the time at which the maintenance starts after finishing the intubation. The controller in operation ends the same as the stable period. To assess the performance of the filters for each group, the following parameters were measured: the mean T1% value, the standard deviation (SD) of T1% value and the coefficient variance (CV) of each patient. To compare the performance of the controller, the following parameters were measured: the mean of T1% error and the SD of T1% error. To compare the controller activity, the following parameters were also measured: the mean infusion rate (MIR), the SD of MIR, and the CV of MIR. The results obtained from this study and a previous study on mivacurium [25] were compared using the Student's *t* test.

Table 2. Controller performance analysis for rocuronium in 10 patients

Parameter	Mean error (%)	SD (%)	Range (%)
Mean of T1% error	−0.18	0.64	−1.12–0.66
SD of T1% error	1.82	0.64	0.99–3.03
Mean of T1% (F) error	−0.19	0.66	−1.24–0.63
SD of T1% (F) error	1.47	0.35	0.96–1.93

T1% error: set point – relaxograph reading of T1%; T1% (F) error: set point – relaxograph reading of T1% with filters; SD: the standard deviation of T1% error value.

Table 3. The controller activity analysis for rocuronium in 10 patients

Parameter	MIR (mgkg^{-1}h^{-1})	SD (mgkg^{-1}h^{-1})	Range (mgkg^{-1}h^{-1})
Mean of MIR	0.32	0.09	0.21–0.49
SD of MIR	0.11	0.04	0.066–0.191
CV of MIR	36.13	9.35	25.40–53.30

MIR: the mean infusion rate (mgkg^{-1}h^{-1}); SD: the standard deviation of the MIR; CV: the coefficient of the variance of the MIR.

RESULTS

We studied 10 patients, mean age 48 (range 18–69) yr and mean weight 63 (51–90) kg. The mean total stable period of control was 118 (28–270) min. Satisfactory muscle relaxation was maintained throughout the surgical procedure in all cases. Table 2 shows the controller performance analysis of 10 patients. The mean T1% error from set point was −0.18% (SD 0.64%; range −1.12 to +0.66%) without filter, and −0.19% (SD 0.66%; range −1.24 to +0.63%) with filter. Mean SD values were 1.82% (SD 0.64%; range 0.99 to 3.03%) without filter, and 1.47% (SD 0.35%; range 0.96 to 1.93%) with filter, confirming that the mean error was close to zero. Table 3 shows the controller activity analysis of 10 patients. The mean infusion rate of rocuronium was 0.32 (SD 0.09; range 0.21 to 0.49 mg · kg^{-1}· h^{-1}) for the total stable period of control. Also, the mean SD rocuronium infusion rate was 0.11 (SD 0.04; range 0.066 to 0.191 mg · kg^{-1}· h^{-1}). As we know, the SD of the infusion rates of rocuronium delivered over the period of control indicates the variation in infusion rate for that period in each patient. Also, it is noted that coefficient variance (CV) is the ratio of standard deviation to the sample mean and is often expressed as a percentage. And, it is valuable in describing the variability of the sample. Therefore, using CV to interpret the controller activity for rocuronium is thought to be suitable. The high CV of the mean infusion rate (MIR) indicates high controller activity. On the other hand, fluctuating infusion rates show the impact of noise, diathermy effect, artifacts and surgical disturbances. Also, the low CV of the MIR means that the controller is not sensitive enough to cope with the disturbances. In this study, the CV of MIR was 36.13 (SD 9.35) % in rocuronium as shown in Table 3. Figure 1 shows sample clinical records from one patient to demonstrate the controller performance: (a) representative EMG signals with filters and set points, (b) representative MIR and the variation of the self-tuning parameter, and (c) representative controller output of infusion rate during an operation.

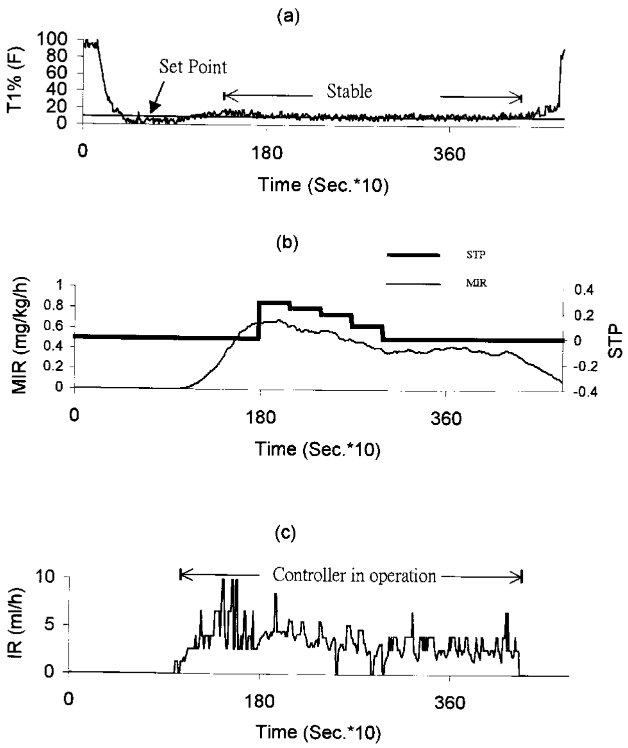

*Fig. 1. The results of a clinical record from a patient to demonstrate the controller performance: (a) representative EMG (T1%) with filters and 10% set point, (b) representative MIR and the variation of the STP, and (c) representative a controller output of infusion rate. Notation in the horizontal axis of figures: Sec.*10: 10 seconds for one unit of time scale. In the vertical axes of figures: T1% (F), EMG reading with filters (%); MIR: mean infusion rate (-mgkg^{-1}h^{-1}; STP: self-tuning parameter (mgkg^{-1}h^{-1}); IR: infusion rate (ml · h^{-1}).*

Table 4 shows the filter performance analysis of each patient. It can be noted that after passing through the filters, some CV values were reduced largely but some

Table 4. Filter performance for rocuronium in individual patient

Patient no.	T1%	SD	CV	T1%	SD (F)	CV (F)
1	9.45	1.66	17.6	9.44	1.65	17.5
2	9.83	0.99	10.1	9.86	0.96	9.74
3	10.64	1.76	16.5	10.73	1.38	12.9
4	10.96	2.26	20.6	10.94	1.74	15.9
5	10.55	3.03	28.7	10.47	1.28	12.2
6	10.39	1.16	11.2	10.38	1.13	10.9
7	9.59	1.90	19.8	9.58	1.82	19.0
8	9.34	1.88	20.1	9.37	1.74	18.6
9	11.12	2.44	21.9	11.24	1.93	17.2
10	9.91	1.09	11.0	9.9	1.03	10.4

T1%: relaxograph reading of T1%; T1% (F): ralaxograph reading of T1% with filters; SD: the standard deviation of the T1% value; CV: the coefficient of the variance of the T1% value.

Table 5. The overall filter performance analysis for rocuronium in 10 patients

Parameter	Mean error (%)	SD (%)	Range
Mean of T1%	10.18	0.64	9.34–11.12
SD of T1%	1.82	0.64	0.99–3.03
CV of T1%	17.75	5.81	11.0–28.7
Mean of T1% (F)	10.19	0.66	9.37–11.24
SD of T1% (F)	1.47	0.35	0.96–1.93
CV of T1% (F)	14.43	3.58	9.74–19.0

T1%: relaxograph reading of T1%; T1% (F): relaxograph reading of T1% with filters; SD: the standard deviation of the T1% value; CV: the coefficient of the variance of the T1% value.

were not. It strongly depends on the type of the surgery because of diathermy effect. However, the overall filter performance of the CV of the T1% value as shown in Table 5 was 17.75 (SD 5.81) % without filter and 14.43 (SD 3.58) % with filter ($p > 0.05$). Although there is no significant difference after filtering, the SD of the EMG signals was slightly reduced after passing through the filters. It means that the EMG signals become smooth and can be used to design a controller. Figure 2 shows clinical records from another patient to demonstrate the filter performance: (a) representative raw EMG signals without filters and 10% set point, and (b) representative EMG signals with filters and 10% set point.

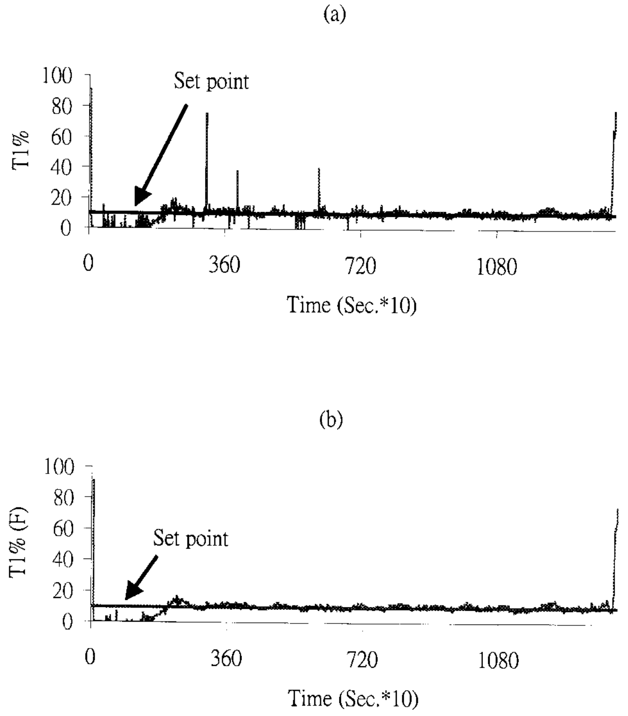

*Fig. 2. The results of a clinical record from a patient to demonstrate the filter performance: (a) representative raw EMG (T1%) signals without filters and 10% set point, (b) representative EMG signals with filters and 10% set point. Notation in the horizontal axis of figures: Sec.*10, 10 seconds for one unit of time scale.*

DISCUSSION

Several different computer systems for feedback control of neuromuscular blocking agents have been reported [5–21]. However, no previous study has applied computer systems to feedback control of rocuronium infusions. In this paper, the hierarchical rule-based monitoring and fuzzy logic control architecture have been successfully employed to control rocuronium infusions. We have used a fuzzy logic controller in the first level to provide a simple and efficient way to communicate with the anaesthetist in order to control the muscle relaxation more easily and efficiently during operation. The second level of this hierarchical structure is a self-tuning fuzzy logic algorithm that can control the muscle relaxation more intelligently. A coarse table in the third level and an emergency table in the fourth level derived from the anaesthetist ensure that the muscle relaxation can be controlled more safely. Hence, we develop a hierarchical structure of a portable closed-loop control system for rocuronium-induced muscle relaxation in order to control the system more easily, efficiently, inteligently and safely during operation.

As shown in Table 1, the control performance of mean T1% error with rocuronium in this study has become better than that of previous studies with atracurium. Meanwhile, it has also achieved better control performance in comparison with that of our previous study with mivacurium using the similar architecture. The mean of T1% error with filters of −0.19 (SD 0.66) % in rocuronium is significantly less than 1.67 (SD 0.97) % in mivacurium ($p < 0.05$). It means that the controller performance in the intermediate duration of action in neuromuscular blocking agents is better than in the short duration of action under this hierarchical structure. Regarding the controller activity of rocuronium and mivacurium in 10 patients, the CV of the mean infusion rate was 36.13 (SD 9.35) % in rocuronium as compared to 34.03 (SD 10.76) % in mivacurium ($p > 0.5$). The consistent medium CV of the MIR either in rocuronium or mivacurium indicates a good controller activity. Also, we have used a three-level hierarchical filter which includes a built-in hardware filter, a pharmacological filter and a median digital filter, in contrast with Mahfouf [28] who used the three-point non-recursive averaging filter, and with Mason et al. [18] who employed a three-term median filter, and our recent work [25] which adopted a similar filter structure in mivacurium. However, in mivacurium, the CV of the T1% value was 33.15 (SD 10.10) % without filter and 24.03 (SD 5.14) % with filter ($p < 0.05$). But, in rocuronium, the CV of the T1% value was 17.75 (SD 5.81) % without filter and 14.46 (SD 3.56) % with filter ($p > 0.05$). Hence, the SD of the EMG signals are either significantly reduced in mivacurium or slightly reduced in rocuronium. It means that the EMG signals become smooth and can be used to design a controller, after passing through the filters. However, a three-level hierarchical filter in this study may be not a significant improvement over previous research using an instrument and median filter [18, 25] because no comparison was made in this paper. However, we did know that it is more logical to prune a clinical vital sign via a pharmacological filter that has been proved by pharmacokinetics and pharmacodynamics. From the viewpoint of electrical engineering, the sensitivity of instrument detection may not be enough. Another independent pharmacological filter can provide a double check on the signals.

The reduction in CV values after passing through the filters depends strongly on the type of the surgery. For example, the patient in Figure 2 (i.e., patient no. 5 in Table 4) had a colon cancer operation which used the electrosurgical units (ESU) a lot of times. The heating effect of the cutting currents and sparks in the ESU electrode has a cauterizing effect on the tissue that inhibits bleeding. Therefore, the ESU can reduce blood loss and minimize the surgery time. However, the basic ESU consists of a radio-frequency oscillator operating between 300 kHz and 3 MHz. It has been reported as a big disturbance to many instruments causing diathermy effect. Fortunately, a three-level hierarchical filter designed in this study had been proved to be able to eliminate the diathermy effect even when the surgical operation uses the ESU very often.

Both mivacurium and rocuronium are non-depolarizing neuromuscular blocking drugs. While mivacurium has a short duration of action, rocuronium has an intermediate duration of action. Both have potential influence on isoflurane or desflurane anaesthesia. Mivacurium is more difficult to control than rocuronium if steady-state anaesthesia with isoflurane or desflurane has not been established. In our previous and current studies, the mean of the T1% error in 10 patients for mivacurium was 1.67 (SD 0.96) % with filters. And, the mean of the T1% error in 10 patients for rocuronium was −0.19 (SD 0.66) % with filters. Hence, the neuromuscular agent with an intermediate duration of action is easier to control than that with a short duration of action.

Clinically, the controller does not take too much effort (i.e., it changes the drug infusion rate too often) controlling the drug administration manually. However, the closed-loop drug therapy and the advance of modern computer technology have changed this situation dramatically. From the closed-loop control theory, the controller is expected to adjust the drug as quickly as possible. Hence, the train-of-four (TOF) was repeated every 10 sec, that is the fastest interval provided by the Datex Relaxograph. And, the controlling interval was set every 10 sec to control the drug administration automatically. However, over-activity of the controller may be caused by either high system noise or too big scaling factor of the output in fuzzy logic controller. Fortunately, the consistent medium CV of the MIR either in mivacurium (i.e., 34.03 (SD 10.76) %) or in rocuronium (i.e., 36.13 (SD 9.35) %) indicates a good

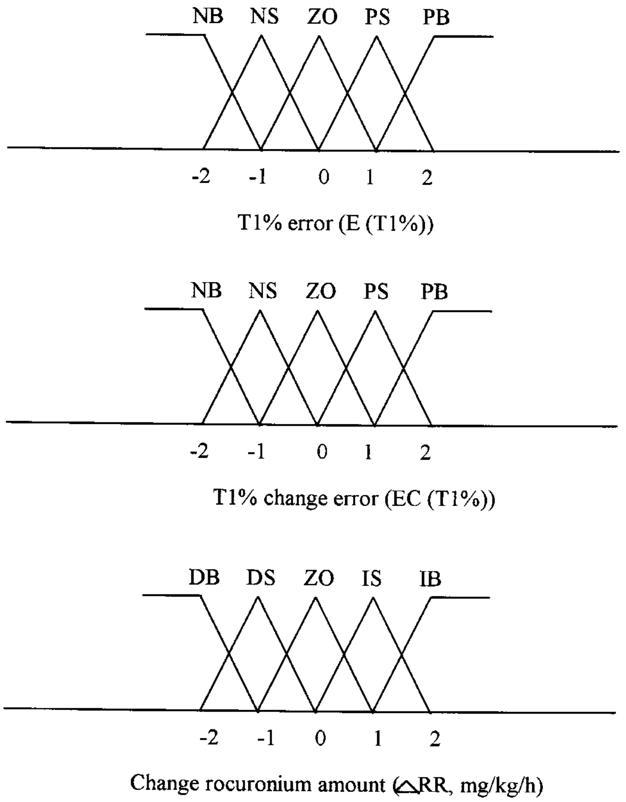

Fig. A.1. The membership function of two inputs and one output. Notation in the figure: NB: negative big; NS: negative small; ZO: zero; PS: positive small; PB: positive big; IB: increasing big; IS: increasing small; DS: decreasing small; DB: decreasing big.

controller activity compared with Mason et al. [18] who obtained consistent high CV values (i.e., 57.50 (SD 12.50) %, 57.89 (SD 12.78) % and 64.70 (SD 20.58) % for phase I, II and III, respectively). In this study, a hierarchical filter has been designed and introduced to reduce the system noise and a self-tuning system in the controller can tune automatically the response of each patient to the muscle relaxant in order to administer the suitable infusion rate.

APPENDIX

A four-level hierarchical fuzzy logic controller

The E (T1%), EC (T1%), ΔRR, IR, MIR, STP and SP used for analysis were defined as follows:

E (T1%): T1% error (i.e. the difference between the set point and the T1% value)

EC (T1%): T1% error change (i.e. the difference between the present error and the previous error)

Table A.1. The anaesthetist's rule-base for controlling a rocuronium neuromuscular blocking agent

	E (T1%)				
EC (T1%)	NB	NS	ZO	PS	PB
NB	IB	IB	IS	IS	ZO
NS	IB	IS	IS	ZO	ZO
ZO	IS	IS	ZO	DS	DB
PS	IS	ZO	DS	DS	DB
PB	ZO	ZO	DB	DB	DB

NB: negative big; NS: negative small; ZO: zero; PS: positive small; PB: positive big; DB: decreasing big; DS: decreasing small; IB: increasing big; IS: increasing small.

ΔRR: control output of change in rocuronium amount

IR: infusion rate ($\mathrm{ml} \cdot \mathrm{h}^{-1}$)

MIR: mean infusion rate ($\mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{h}^{-1}$)

STP: self-tuning parameter ($\mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{h}^{-1}$)

SP: the set point of T1% value

Therefore, a four-level hierarchical fuzzy logic controller was designed as follows:

(i) First level (i.e. a fuzzy logic controller):

There are three steps (membership functions, rules, and defuzzification) which determine fuzzy logic control. The membership functions are shown in Figure A.1 and the rules are listed in Table A.1. Also, the defuzzification procedure uses the center of area and the equation can be written as follows.

$$I = \frac{\sum_{1}^{n} (Mn \times Un)}{\sum_{1}^{n} (Mn)}$$

Where M is the membership function; U is the universe of discourse; n is the number of rules; and I is the control input.

Then, combining these three steps produces a lookup table as shown in Table A.2.

(ii) Second level (i.e. a self-tuning level):

Rule-base for rocuronium infusion rate in a self-tuning level:

IF (MIR $\geq$ (0.4 + STP)) THEN STP = 1.1 $\times$ (MIR−0.4) $\mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{h}^{-1}$

IF (MIR $\leq$ (0.2 + STP)) THEN STP = 1.1 $\times$ (MIR−0.2) $\mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{h}^{-1}$

Table A.2. A lookup table for E (T1%) and EC (T1%)

	E (T1%)				
EC (T1%)	−2	−1	0	1	2
−2	1.57	1.28	1.0	0.78	0.57
−1	1.2	0.95	0.7	0.35	0
0	0.67	0.35	0	−0.39	−0.78
1	0	−0.35	−0.7	−1.12	−1.55
2	−0.33	−0.71	−1.14	−1.42	−1.7

Where MIR is calculated every 10 min and the STP is updated every 5 min.

(iii) Third level (i.e. a coarse level):

Rule-base for rocuronium infusion rate in a coarse table:

IF E (T1%) $\geq$ (SP+3) % THEN Infusion Rate = $0.6\ \mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{h}^{-1}$
IF E (T1% $\geq$ (SP+5) % THEN Infusion Rate = $1.0\ \mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{h}^{-1}$
IF E (TI% $\geq$ (SP+7) % THEN Infusion Rate = $1.5\ \mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{h}^{-1}$
IF E (TI%) $\leq$ (SP−3) % THEN Infusion Rate = $0.0\ \mathrm{mg} \cdot \mathrm{kg}^{-1} \cdot \mathrm{h}^{-1}$

(iv) Fourth level (i.e. an emergency level):

Rule-base for rocuronium infusion rate in an emergency table:

IF E (T1%) $\geq$ (SP+10) % THEN
Give an additional $0.05\ \mathrm{mg} \cdot \mathrm{kg}^{-1}$ bolus over 1 min and repeat as necessary until E (T1%) < (SP+10) %

A three-level hierarchical filter

The T1, T2, T3 T4, T1% and TR% used for analysis were defined as follows:

T1, T2, T3, T4: first, second, third and fourth twitches of the Datex Relaxograph
T1%: (first twitch/reference response) × 100%
TR%: (fourth twitch/first twitch) × 100%

Hence, a three-level hierarchical filter was designed as follows:

(i) First level (i.e. an instrument filter):

The computer output of the Datex Relaxograph from the RS232 serial I/O connector has some built-in functions for detecting background noises and high frequency disturbances (i.e. diathermia).

Rule-base for filter of T1% value in an instrument filter:

IF (NOISE > 40) THEN Filter out this T1% and use the previous T1% value
IF (High frequency disturbance value = 1) THEN Filter out this T1% and use the previous T1% value

Where NOISE is sent from the instrument and the value is between 0–100; the high frequency disturbance value is also sent from the instrument and the value is either 0 or 1.

(ii) Second level (i.e. a pharmacological filter):

According to the pharmacology of injecting a non-depolarizing neuromuscular blocking agent (e.g. rocuronium), the evoked response to train-of-four nerve stimulation from T1 to T4 is gradually decreased for each stimulus. Therefore, if it is not matched with this trend, these signals are identified as artifacts.

Rule-base for filter of T1% value in a pharmacological filter:

IF (TR% > 110%) THEN Filter out this T1% and use the previous T1% value
IF (T2 > (T1 × 5)) THEN Filter out this T1% and use the previous T1% value
IF (T3 > (T2 × 5)) THEN Filter out this T1% and use the previous T1% value
IF (T4 > (T3 × 5)) THEN Filter out this T1% and use the previous T1% value

(iii) Third level (i.e. a median filter):

The median filter algorithm is a simple operation of choosing the median value of the sample inside a moving average window of fixed length. It incorporates a non-linear filtering technique known for preserving sharp changes in signal and for being particularly effective in removing impulsive noise. Let S_N be a set of N samples $\{x_1, x_2, \ldots, x_N\}$, where $N = 2k + 1$. The median is defined by:

$$\mathrm{Y(N)} = \mathrm{MED}\{\mathrm{x_i} | \mathrm{x_i} \in \mathrm{S_N}\}$$

Where the median Y is both the $(k + 1)$th largest and the $(k + 1)$th smallest element in S_N. In our system, the length of the filtering windows was three samples (i.e. $N = 3$).

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