

Special article

Anesthetic practice in Japan: past, present, and future

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Abstract

Significant progress has been made over the past 20 years in the development of anesthetic agents and anesthetic monitors. Due to progress in the development of medical devices and the establishment of an effective medical system, advanced age alone is no longer a contraindication for surgery. However, despite approval of the volatile anesthetic sevoflurane, Japan is lagging behind other developed countries with regard to anesthetic agents. The ultrashort-acting opioid analgesic remifentanyl has finally become available in Japan, and the fast-onset neuromuscular blocking agent rocuronium is expected to be approved soon. Patient recruitment for phase III clinical trials using sugammadex, a selective reversal agent for rocuronium and vecuronium, has been completed in all countries, including Japan. In this article, changes in anesthesia over the past two decades are described and possible future changes in anesthesia in Japan are discussed.

Key words Japan · Sevoflurane · Remifentanyl · Rocuronium · Sugammadex

Introduction

In the 1980s, general anesthesia was mainly conducted using halothane or enflurane with nitrous oxide (laughing gas) [1]. Fentanyl, an opioid analgesic, was also available but was rarely used because it was believed to cause delay in awakening. Epidural anesthesia was used more frequently than it is now. For example, cervical epidural anesthesia was generally used in surgery on upper limbs or for breast cancer. The only intravenous anesthetics available at that time were thiamylal and

ketamine, and ketamine was administered to asthmatic patients despite its known secretion-promoting effect. The depolarizing neuromuscular blocking agent (NMBA) succinylcholine was used for induction of anesthesia and the nondepolarizing NMBA pancuronium was the only NMBA available for maintenance of anesthesia [1]. During the 1980s, there was no awareness of the progression of acute renal failure during emergency surgery, and some patients did not awake from anesthesia for a long time after surgery due to the prolonged effect of pancuronium [2].

Since the 1980s, various anesthetic agents have become available in Japan. The availability of a large range of anesthetic agents together with the development of anesthetic monitors has made anesthesia a much safer and more comfortable procedure for patients. However, Japan (maybe due to its unique medical system) lags behind the US and Europe with regard to the use of anesthetic agents other than sevoflurane. The ultrashort-acting opioid analgesic remifentanyl [3,4] has finally been launched in Japan, and the fast-onset nondepolarizing NMBA rocuronium [5] is expected to become available soon. The selective relaxant binding agent sugammadex [6], that is currently being used in phase III clinical trials throughout the world, is also expected to be approved for clinical use in the near future. In this article, the anesthetic agents and the methods of anesthesia that have been used in Japan are reviewed and probable methods of anesthesia in the near future are discussed.

Inhalation anesthetics

Both sevoflurane and isoflurane were launched in Japan in 1990. Sevoflurane has the unusual history of first being synthesized in the US [7] but being developed for approval in Japan. Inhalation anesthesia with other anesthetics such as halothane or enflurane is not used

Address correspondence to: M. Yamakage
This article was presented in part at the Sugammadex European Reporting Investigators' Meeting, Barcelona, Spain, November 17–18, 2006
Received: January 4, 2007 / Accepted: April 3, 2007

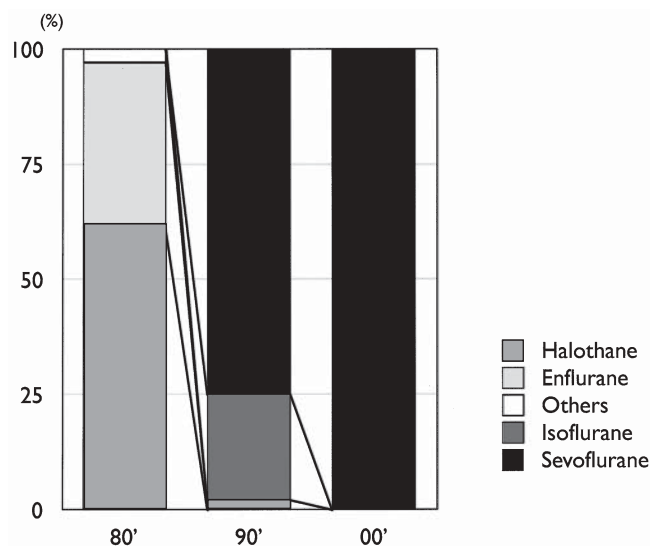


Fig. 1. Changes in the use of volatile anesthetics in our institution. 80', 1880–1889; 90', 1990–1999; 00', 2000–2005. At present, sevoflurane is used in almost all cases in which inhalation anesthetics are used

in our institution; sevoflurane and isoflurane are preferred because of their rapid onset and offset effects and low metabolism [8] and also to avoid the occurrence of hepatitis and convulsive brain waves, which have been a problem with halothane and enflurane.

In our institution, we use only sevoflurane (Fig. 1) [1] because isoflurane has a stimulatory action on the airway and because anesthesia is induced in some patients using inhalation anesthetics [9,10]. For reasons given later, we have avoided using nitrous oxide and have used the opioid analgesic fentanyl in an increasing number of patients. Low-flow anesthesia with a reduced fresh gas flow is also being used in an increasing number of patients, mainly due to environmental considerations [9]. Because of the increasing use of low-flow anesthesia, it might be thought that the amount of sevoflurane used in Japan is decreasing, but this is not the case (data not shown due to prohibition). Reasons for this are that the number of surgery cases is rising and that sevoflurane is still being increasingly used instead of isoflurane in some institutions (Fig. 2). With the availability of remifentanyl and with rocuronium likely to be approved soon in Japan, it is expected that more balanced methods of anesthesia will be selected. However, at the present time, the selection of a hypnotic agent, i.e., sevoflurane or propofol, when most institutions have anesthetic machines equipped with a vaporizer, seems to depend on the preference of the anesthesiologist. For example, we conducted trials with remifentanyl in our institution and obtained good results even for general anesthesia management with sevoflurane, which has little suppressive effect on the cardiovascular system [11].

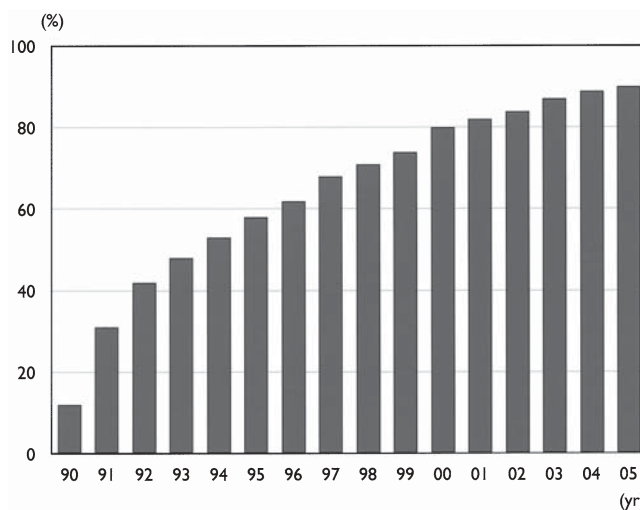


Fig. 2. Changes in the ratio of sevoflurane used in Japan (quantity basis) compared to all other volatile anesthetics. Data are provided by Maruishi Pharmaceutical Co. (Osaka, Japan). In 2005, the ratio of sevoflurane for inhalation anesthesia was almost 90% in Japan

Sevoflurane was approved in 1994 in South American countries, including Peru, Argentina, and Mexico, and was approved the following year in the US, Finland, France, the UK, The Netherlands, Sweden, Canada, and Germany. This inhalation anesthetic is now being administered clinically in more than 100 countries and is estimated to have been used in more than one hundred million patients.

There are conflicting views regarding the use of nitrous oxide [12]. There seems to be a trend in Japan, mainly in younger anesthesiologists, to avoid its use. Fentanyl is currently being used as an alternative adjuvant analgesic, and it is expected that the use of nitrous oxide will further decrease because the ultrashort-acting opioid analgesic remifentanyl has been approved in Japan [13].

Intravenous anesthetics

Changes in the use of intravenous anesthetics for induction of anesthesia in our institution are shown in Fig. 3. Most commonly, thiamylal was used in the 1980s, but propofol was introduced in the 1990s and its use has increased ever since. Similar trends have been seen in other Japanese institutions (data not shown due to prohibition). The merits of propofol outweigh those of thiamylal/thiopental despite its high cost and the associated injection pain. Infusion of propofol is smoother than that of barbiturates when a laryngeal mask is used, which is increasingly common, and good recovery from anesthesia can be obtained even with subsequent infu-

sion of propofol [14,15]. It is expected that propofol, including generic anesthetic versions, will continue to be used widely as an intravenous anesthetic in the future despite “propofol infusion syndrome,” currently the focus of a controversial debate [16,17].

The ultrashort-acting opioid analgesic remifentanyl has been used in the US and Europe since 1996. Remifentanyl has obvious merits compared with other opioid analgesics [13], although it is not currently being used widely in the US or Europe (data not shown due to prohibition). Reasons for this, in addition to the availability of alternative drugs to fentanyl and remifentanyl (e.g., alfentanil and sufentanil), include the high cost of remifentanyl and the fact that it is not covered by insurance in some countries and/or regions. This is also reflected in changes in the ratios of use of the various drugs on a cost basis (data not shown due to prohibition). Use of remifentanyl is expected to increase in Japan since there is no insurance billing problem and since alfentanil and sufentanil cannot be used (Fig. 4);

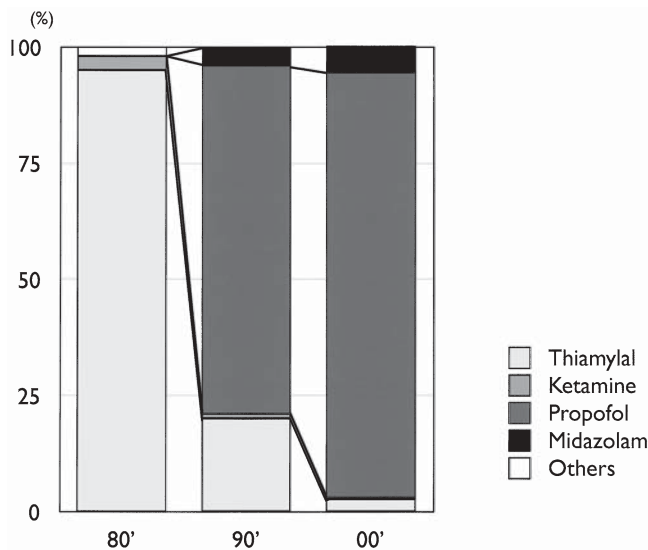


Fig. 3. Changes in the use of intravenous anesthetics at the time of induction of anesthesia in our institution. At present, propofol is being used almost exclusively. Midazolam is used only in cases of severe cardiac dysfunction

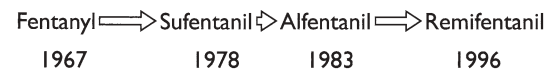
another reason is that the amount of sedatives (e.g., propofol and sevoflurane) used can be reduced by sufficient use of remifentanyl [11].

Neuromuscular blocking agents (NMBAs)

Table 1 shows the history of the development of NMBAs in developed countries. Japan is also lagging behind other countries in the use of NMBAs. Cisatracurium and atracurium, which are available in the US and Europe, and even rocuronium are not currently approved for clinical use in Japan. As shown in Fig. 5 [18], various NMBAs are being used depending on the situation in each country. In Japan, vecuronium is the main agent used for both induction and maintenance of anesthesia, but the precise reason for this is not known, except for the limited choice of NMBAs. Although it is not known yet whether rocuronium will be costly, it is expected that this drug will replace vecuronium when it becomes available in Japan because of the fast onset of its effect [19]. It is unlikely that there will be any objection to this expected trend, considering the limited availability of NMBAs, as well as opioids, in Japan.

Clinical trials using sugammadex, a selective relaxant binding agent for nondepolarizing steroidal NMBAs, have been conducted globally. This drug, which has high affinity for rocuronium and vecuronium and has to date

US



Japan

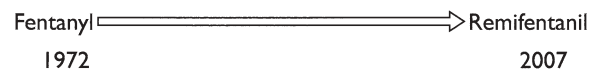


Fig. 4. History of opioid use as intraoperative analgesics in the US and Japan. The ultrashort-acting opioid analgesic remifentanyl has finally been approved for use in Japan

Table 1. History of neuromuscular blocking agents

Generic name	Trade names	Corporation	First launched	US	Japan
Suxamethonium	Succin, Relaxin, Anectin		1951 in Germany	1975	1955
Pancuronium	Mioblock, Pavulon	Organon	1968 in The Netherlands	1974	1973
Vecuronium	Musculax, Norcuron	Organon	1983 in The Netherlands	1984	1988
Pipecuronium	Arduan, Arpilon	Organon	1983 in Hungary	1990	Discontinued
Rocuronium	Esmeron, Zemuron	Organon	1994 in the US	1994	Registration file submitted
Atracurium	Tracrium	GW, Abbott	1982 in the UK	1984	
Mivacurium	Mivacron	GW, Abbott	1992 in the US	1992	
Cisatracurium	Nimbex	GW, Abbott	1996 in the UK	1996	

GW, Glaxo Wellcome

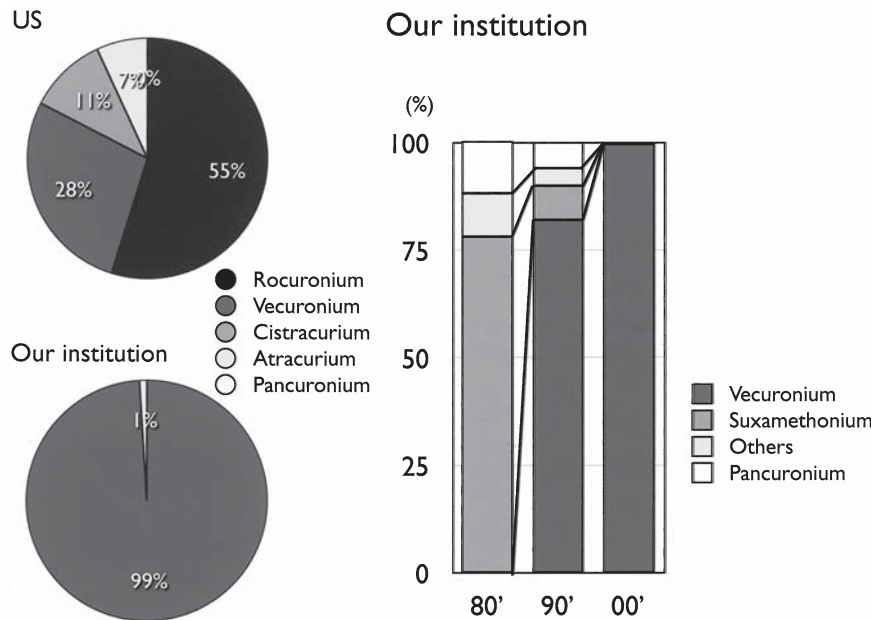


Fig. 5. Break down of neuromuscular blocking agents used in the US [16] and in our institution (quantity basis, 2004). The neuromuscular blocking agents used in the US depend on the time of sales approval and the medical insurance system. Vecuronium is used in almost 100% of cases in our institution as well as in Japan as a whole

not shown any side effects on the autonomous nervous system, is expected to become a valuable addition in the field of anesthesia [20]. Results of clinical trials using sugammadex indicate that this drug will undoubtedly become widely used in the clinical field [6]. The introduction of sugammadex will allow continuous infusion of the nondepolarizing NMBA rocuronium, ensuring immobility during surgery. When patients need reintubation of the trachea after injection of sugammadex and extubation, we should use a sufficient dose of rocuronium/vecuronium under the monitoring of muscle relaxation or suxamethonium instead of nondepolarizing NMBAs.

Laryngeal mask and day surgery

General anesthesia with airway management using a laryngeal mask is increasing in Japan due to the promotion of this device [21] and the widespread use of ProSeal (Laryngeal Mask, Jersey, UK), which has high sealability. The use of this method of anesthesia is also increasing in our institution (Fig. 6), which is also a teaching institution, despite the fact that residents or trainees are usually first given instructions on face mask ventilation and tracheal intubation. The indication for this method of anesthesia depends on the anesthesiologist, although it is generally not used for laparotomy, thoracotomy, or for prolonged general anesthesia. If the device has high sealability and can withstand positive pressure ventilation, anesthetic management is sometimes performed under artificial ventilation with the use of NMBAs. The use of the laryngeal mask is expected to increase further.

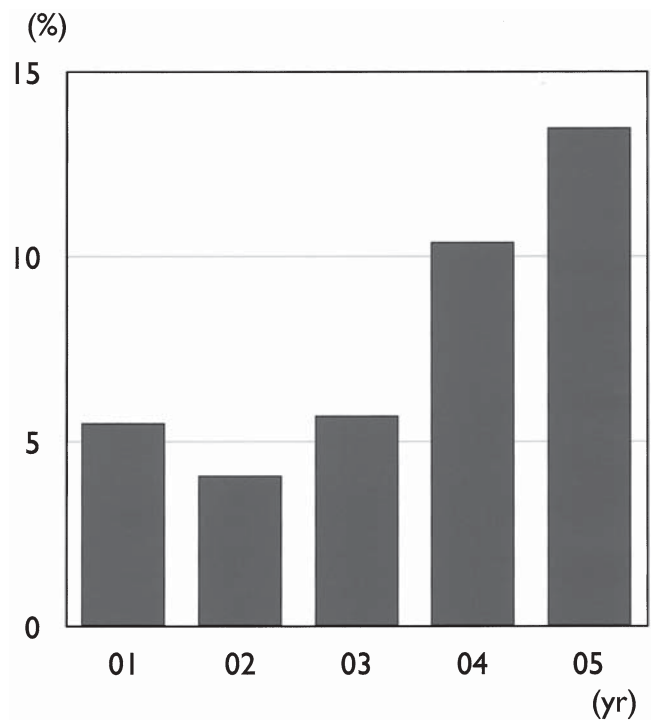


Fig. 6. Changes in the usage of laryngeal mask airways for airway management during general anesthesia in our institution. The usage of the laryngeal mask airway has gradually increased

In the US and Europe, day surgery has become popular due to the high costs of hospitalization [22]. Day surgery is rare in Japan as most patients have national and private medical insurance [23]. However, the duration of hospitalization is expected to become

shorter with the introduction of a comprehensive medical system, though it is impossible to predict at present whether this will have an effect on the methods of anesthesia used.

Postoperative analgesia

Methods used for postoperative analgesia differ greatly between countries, and between institutions in Japan. In the US and Europe, patient-controlled analgesia is popular, and intravenous opioids alone are used in about two-thirds of patients (Fig. 7). The combination of intravenous opioids with epidural analgesia appears to be used only for patients who have undergone upper abdominal surgery or thoracotomy. In Japan, epidural analgesia with or without intravenous opioids is used for postoperative pain control in almost 50% of patients. When delivery of fentanyl by iontophoresis (Ionsys; Ortho-McNeil, Titusville, NJ, USA), which is currently being tested in trials, becomes applicable for clinical use, the methods used for postoperative analgesia might undergo great change.

The future

Finally, changes in the number of cases managed by our Anesthesiology Department and the methods used for anesthesia in our institution are shown in Fig. 8. The number of surgery cases in specialized hospitals, including university hospitals, is expected to continue to rise in Japan. Due to the increasingly advanced age of patients and an increase in incompatibility complica-

tions, the number of cases anesthetically managed by neural block or general anesthesia alone is also growing. In Japan, with the launch of remifentanyl, the anticipated approval of rocuronium, and when sugammadex and the fentanyl iontophoretic transdermal system become available, the methods used for anesthesia will continue to change significantly in the future.

Clinical use in Japan of xenon, an ideal anesthetic [24], and dexmedetomidine, a respiratory-sparing seda-

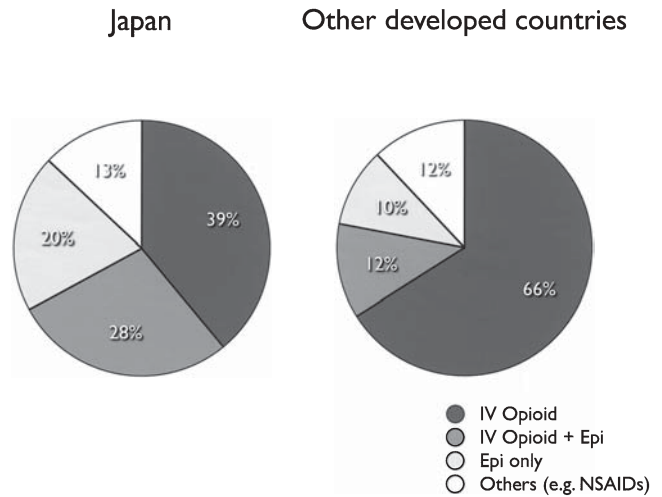


Fig. 7. Techniques used for postoperative analgesia in Japan and other developed countries (US, UK, France, and Germany) in 2004. Data are provided by Janssen Pharmaceutical (Tokyo, Japan). *IV*, intravenous; *Epi*, epidural analgesia; *NSAIDs*, nonsteroidal anti-inflammatory drugs. In the US and Europe, patient-controlled analgesia is popular, although epidural analgesia with or without intravenous opioids is used in almost 50% of patients

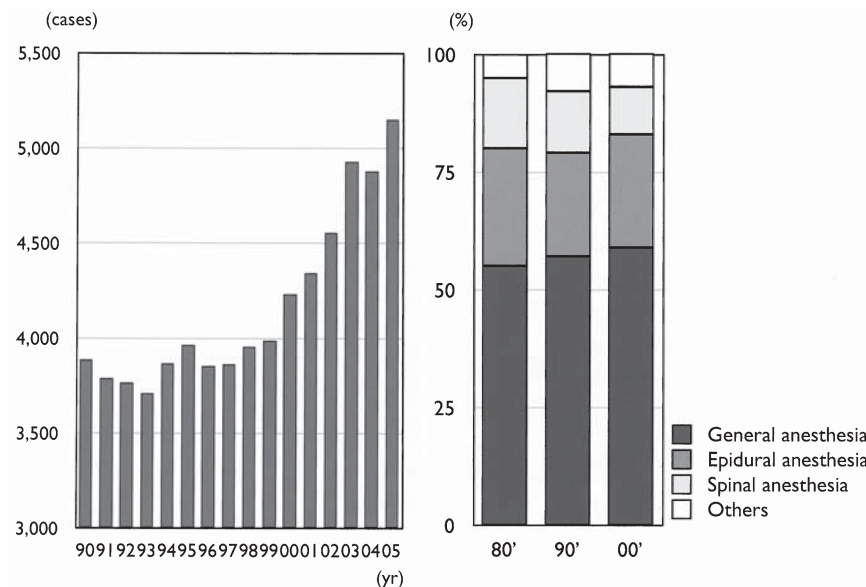


Fig. 8. Changes in the number of cases of anesthesia and the anesthetic techniques used in our institution. The number of cases of anesthesia is increasing in our institution as well as in other university hospitals, and the relative use of epidural anesthesia is gradually decreasing

tive [25], is unknown and controversial due to their high cost and prolonged effect/“off label” use, respectively.

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