Prevalence of Malignant Hyperthermia and Relationship with Anesthetics in Japan

Data from the Diagnosis Procedure Combination Database

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ABSTRACT

Background: Malignant hyperthermia (MH) is a rare but life-threatening disease that occurs during general anesthesia. The actual prevalence of MH remains unclear, and the association between MH and various anesthetic drugs remains controversial because of a lack of universal reporting.

Methods: Using the Japanese Diagnosis Procedure Combination database, we collected data of inpatients who had general anesthesia between July and December 2006–2008. Patients’ age, gender, diagnoses, procedures, and the use of drugs during anesthesia, including volatile agents, muscle relaxants, and propofol, were investigated. Univariate comparisons were made to examine the relationship of each anesthetic drug or demographic factor with the occurrence of MH.

Results: Of 1,238,171 surgical patients undergoing general anesthesia, we identified 17 MH patients (odds ratio: 13.7, 95% CI 7.2–20.3 per million). Only one in-hospital death was identified. Men were significantly more likely to contract MH (odds ratio: 3.49; 95% CI 1.14–10.7). No MH patient was found among 19,871 suxamethonium users. The prevalence of MH was relatively high in users of sevoflurane (odds ratio: 15.0; 95% CI 7.1–22.9 per million).

Conclusions: No single drug was significantly associated with the occurrence of MH. Data should be continuously compiled, and further analyses with larger numbers of cases are necessary to identify possible causative agents.

MALIGNANT hyperthermia (MH) is a potentially life-threatening pharmacogenetic disease associated with abnormal intracellular calcium regulation that occurs during general anesthesia. The essential biochemical abnormality of MH is characterized by an increase in the release of calcium ions in skeletal muscle cells caused by genetic mutations mainly in two genes: ryanodine receptor type 1 (RYR1) and CACNA1S. In addition to these genes, more than one MH-susceptible allele has been identified.

In previous Western studies, the estimated prevalence of MH ranged widely from 1:10,000 to 1:220,000. In Japan, the prevalence of MH was presumed to be approximately 1:60,000. In New York State, the prevalence of MH was confirmed to be 9.6 per million surgical discharges using a macroscale database. However, these figures were based on rough estimates or data from limited geographical areas. A national prevalence of MH remains unclear because of a paucity of universal reporting in any country.

Investigations on the drugs that might trigger MH have still not reached any conclusions. A well-known potential risk factor for MH is the use of depolarizing muscle relaxants (suxamethonium) or volatile anesthetic agents (sevoflurane, isoflurane, halothane, and enflurane). However, the association between other anesthetic agents and MH occur-

What We Already Know about This Topic

• In Japan, the prevalence of malignant hyperthermia was estimated to be 1:60,000

What This Article Tells Us That Is New

• Using a national database of more than 1.2 million inpatients, malignant hyperthermia was diagnosed in 17 (rate, 1:73,000), and males were three times more likely to be diagnosed and rocuronium (odds ratio: 24.3; 95% CI 4.9–43.8 per million) compared with nonusers but was not statistically significant.

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rence remains unclear. Nondepolarizing muscle relaxants (vecuronium, pancuronium, and rocuronium) are considered to be safer than suxamethonium, but this still has not been fully evaluated. It is controversial whether propofol can induce MH.11–13

In this report, we verified the prevalence of MH in Japan and analyzed the relationship between the use of several drugs administered during general anesthesia and the occurrence of MH, using a nationally representative inpatient database, the Japanese Diagnosis Procedure Combination (DPC) database.

Materials and Methods

DPC Database

The DPC is a case-mix system, which is similar to the diagnosis-related groups in Medicare in the United States. This patient classification system was launched in 2002 by the Ministry of Health, Labor, and Welfare of Japan and linked with a lump-sum payment system. Key objectives of the DPC system are to implement a standardized electronic claims system and to provide transparency of hospital performance.14 All 82 university teaching hospitals are obliged to adopt the DPC system, but adoption by community hospitals is voluntary. The survey of the DPC hospitals is conducted between July 1 and December 31 each year by the DPC Research Group, in collaboration with the Ministry of Health, Labor, and Welfare.15–17 Not only administrative claims data, but also detailed patient data, are collected for all inpatients discharged from the participating hospitals between July 1 and December 31. Data are used mainly for profiling practice patterns, refinement of case-mix classification, and health policy planning, such as resource allocation. The survey started in 2003 with 82 teaching hospitals, and the number of participating hospitals steadily has increased: 262 in 2006, 926 in 2007, and 855 in 2008. Today, DPC hospitals are distributed throughout Japan. Data on all the acute-care patient admissions in the participating hospitals were compiled, and the capture rate of patient admissions was 100%. The numbers of patients included were 1.08, 2.99, and 2.86 million in 2006, 2007, and 2008, respectively. The number in 2008 (2.86 million) represented approximately 40% of all inpatient admissions to acute-care hospitals in Japan. All of the data for each patient were recorded at discharge. Hospitals sent all of the anonymous data for each month between July and December to the research group, and data were compiled in the database server in the Department of Health Management and Policy at the University of Tokyo.

The database includes the following data: location of hospitals; patients’ age and gender; diagnoses and comorbidities at admission and complications after admission recorded with text data in the Japanese language and the International Classification of Diseases, 10th Revision codes; procedures coded with Japanese original codes; drugs and devices used; lengths of stay; and discharge status.

The DPC database partially corresponds to the Nationwide Inpatient Sample in the United States18 but has several unique advantages. In the DPC database, complications that occurred after admission are clearly differentiated from comorbidities that were already present at admission. To optimize the accuracy of the recorded diagnoses, physicians in charge are obliged to record the diagnoses with reference to medical charts. At discharge, the diagnoses and comorbidities were registered to the DPC database once per admission. Medical clerks and licensed medical information managers accurately record the dates of all major and minor procedures and of drug administration and device use. Physicians and hospitals have a strong incentive for data compliance because it is mandatory to obtain the DPC-based reimbursement of medical fees.

Data Extraction

From the DPC database, we identified records of all patients who underwent surgical procedures with general anesthesia in 2006–2008. We extracted information on patients’ age and gender and the use of several potentially causative drugs, including volatile anesthetic agents (sevoflurane, isoflurane, enflurane, and halothane), muscle relaxants (suxamethonium, vecuronium, pancuronium, and rocuronium), and propofol.

For the identification of MH patients from the database, we performed a free text search with the term malignant hyperthermia (akusei-konetsu in Japanese), using Microsoft SQL Server 2008 software (Microsoft Corp., Redmond, WA). With regard to identification of MH patients, a simple search using the specific International Classification of Diseases code for MH (T883) was considered unreliable. Because T883 was rarely used and physicians and medical information managers in Japan were unfamiliar with the choice of T883 code, miscoding, such as a coding of R509 (fever, unspecified), could occur. For this reason, we performed a text-based search to accurately capture all of the patients with a diagnosis of MH. To ensure the reliability of the search results, two authors (Yasunaga and Horiguchi) independently performed these procedures.

Detailed profiles of the MH patients were collected, including age, gender, comorbid diagnoses, surgical procedures, use of causative agents, and use of dantrolene.

This study was based on a secondary analysis of the administrative claims data. Given the anonymous nature of the data, the requirement for informed consent was waived. Study approval was obtained from the Institutional Review Board in University of Occupational and Environmental Health (Kitakyushu, Fukuoka, Japan).

Statistics

Univariate logistic regression analyses were performed to examine the relationship of each anesthetic drug or demographic factor with the occurrence of MH. The threshold for
significance was set at $P < 0.05$. All statistical analyses were conducted using the software Statistical Package for Social Sciences version 17.0 (Statistical Package for Social Sciences Inc., Chicago, IL).

Results

Of 6.9 million inpatients in the DPC database, a total of 1,238,171 surgical patients, who underwent general anesthesia, were identified during the survey period, including 344,224 (27.8%) in teaching hospitals and 893,947 (72.2%) in community hospitals. Table 1 shows the surgical patients’ backgrounds and the use of potentially causative anesthetic agents. Overall, 48% of patients were men, and 18% were at least 29 yr of age. Sevoflurane was applied in approximately 75% of patients, whereas isoflurane, halothane, and enflurane were rarely used. Suxamethonium was infused in only 1.6% (19,871) of patients. Approximately 63% were given vecuronium, 20% were given rocuronium, and pancuronium was rarely used. Propofol was administered to 77% of patients.

We identified 17 patients with a diagnosis of MH during the study period. The two authors who independently per-

<table>
<thead>
<tr>
<th>No.</th>
<th>Gender</th>
<th>Age</th>
<th>Diagnosis</th>
<th>Surgery</th>
<th>Dead or Alive</th>
<th>Iso, Hal, Sev, Enf, Sux, Vec, Pan, Roc, Pro, Dan</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>49</td>
<td>Acute epidural hematomata</td>
<td>Open craniotomy</td>
<td>Dead</td>
<td>+</td>
</tr>
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<td>2</td>
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<td>+</td>
</tr>
<tr>
<td>3</td>
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<td>+</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
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<td>Low anterior resection</td>
<td>Alive</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>60</td>
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<td>+</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
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<tr>
<td>7</td>
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<td>Hemicolecotomy</td>
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<td>+</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
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<td>Low anterior resection</td>
<td>Pancreatocoduodenectomy</td>
<td>Alive</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>61</td>
<td>Pancreatic head carcinoma</td>
<td>Thoracoscopic lobectomy</td>
<td>Alive</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>F</td>
<td>80</td>
<td>Thoracic aortic aneurysm</td>
<td>Aortic arch replacement</td>
<td>Alive</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>1</td>
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<td>+</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>30</td>
<td>Repeated shoulder abartication</td>
<td>Shoulder synovectomy</td>
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<td>+</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>69</td>
<td>Lung carcinoma</td>
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<td>Alive</td>
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<tr>
<td>14</td>
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<td>Descending colon carcinoma</td>
<td>Thoracoscopic lobectomy</td>
<td>Colectomy</td>
<td>Alive</td>
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<tr>
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<td>+</td>
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<td>16</td>
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<td>Alive</td>
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<tr>
<td>17</td>
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<td>2</td>
<td>Severe respiratory depression</td>
<td>Tracheostomy</td>
<td>Alive</td>
<td>+</td>
</tr>
</tbody>
</table>

Dan = dantrolene; Enf = enfurane; Hal = halothane; Iso = isoflurane; Pan = pancuronium; Pro = propofol; Roc = rocuronium; Sev = sevoflurane; Sux = suxamethonium; Vec = vecuronium.
formed the text-based search obtained the same results. The prevalence was calculated to be approximately 13.7 per million patients (or 1.73,000), and the 95% CI was 7.2–20.3 per million. None of the 1,238,171 patients had a preoperative diagnosis of MH. None of the 17 MH patients had a comorbid disease that was likely to constitute a risk factor for MH (e.g., Duchenne muscular dystrophy).

Table 2 shows the details of the 17 patients with MH. Only one in-hospital death was identified (patient no.1), a 49-yr-old man, who underwent open craniotomy for acute epidural hematoma, and was given sevoflurane and vecuronium. Of the 17 MH patients, 14 were given sevoflurane, 6 vecuronium, and 12 propofol, whereas no MH patient was found in patients who received isoflurane, halothane, enflurane, suxamethonium, or pancuronium. All 10 patients who were given vecuronium also received sevoflurane. Of the three patients without sevoflurane (patients no. 15, 16, and 17), all received rocuronium and two received propofol. Dantrolene was administered to 11 of 17 MH patients.

Table 3 shows the prevalence of MH in each subcategory, and the results of the univariate logistic regression analyses. Men were approximately 3.5 times more likely to have MH (odds ratio: 3.49; 95% CI 1.14–10.7; P = 0.029). The prevalence of MH in patients at least 29 yr of age was relatively high compared with those older than 30 yr (22.5; 95% CI 2.8–42.2 yr. 11.8; 95% CI 5.1–18.5 per million), but the difference was not significant. The rate of MH was relatively high in sevoflurane users (15.0; 95% CI 7.1–22.9 per million) or rocuronium users (24.3; 95% CI 4.9–43.8 per million), but no statistical significance was found for any drug.

### Discussion

#### Diagnosis of MH

There are no validated gold-standard MH diagnostic criteria globally. The diagnosis of MH is based on clinical presentation with or without laboratory testing (e.g., caffeine halothane con-
can MH patients.22 Nevertheless, the prevalence of MH in the Japanese population (13.7 per million) was comparable with that in New York State (9.6 per million).7 Although several genes related to MH have been identified,2,3 there still may be unknown genetic factors both in Japanese and Western populations. The database may be useful not only for determining MH prevalence in Japanese but also for suggesting the existence of other undetected MH mechanisms. Further studies should be conducted to elucidate other etiologies of MH in any population.

Our results also showed that men were three times more likely to contract MH than women. The prevalence of MH was relatively high in patients aged younger than 30 yr compared with those older than 30 yr. These results coincide with recent Japanese and American reports.23,24

In the current study, the patient fatality rate was 5.9% (1 of 17 patients). The patient fatality rate in MH in the 1970s was approximately 70%,8 whereas a recent North American study reported that of 291 events from 1987 to 2006, 8 (2.7%) resulted in cardiac arrest and 4 (1.4%) resulted in death.25 In Japan, the patient fatality rate decreased over time, from 42.3% during 1961–1984 to 15.0% during 1985–2004.23 A possible explanation for the recent decrease in the death rate after MH is the improved system of monitoring and treatment. Widespread use of end-tidal carbon dioxide monitors and continuous body temperature measurement, with improved availability of dantrolene, could have resulted in early detection and improved clinical consequences of MH.1 In the current study, dantrolene was given to only 11 of 17 MH patients. One possible reason is the availability of dantrolene in Japanese facilities. A previous Japanese study reported that 22.5% of hospitals had no stock of dantrolene in their operating rooms and 3.0% of hospitals had no stock on their premises.6 Another reason may be that six patients might have responded to other therapies (e.g., active cooling of the body), resulting in successful improvement without dantrolene use. That there were no in-hospital deaths in the six MH patients treated without dantrolene might support this possibility.

**MH Risk of Anesthetic Agents**

In contrast to the New York database7 and others,18 the unique advantage of the DPC database is that it can provide comprehensive information on all drugs given to all inpatients. We could identify the drugs given during anesthesia not only in MH patients but also in all patients undergoing general anesthesia. Therefore, the database enabled us to make a statistical comparison of the rates of MH between users and nonusers of problematic anesthetic agents.

Suxamethonium is a well-known triggering agent of MH. After exposure to this agent, deterioration of calcium homeostasis in the skeletal muscle cells may lead to muscle contracture, metabolic failure, lactic acidosis, and heat production.1,8 Suxamethonium had commonly been used in anesthetic induction for decades; however, use of this drug has gradually decreased, and use of vecuronium and rocuronium has gradually increased. Our results showed that suxamethonium was used in only 1.6% of all patients who underwent general anesthesia, and the association between suxamethonium and MH could not be assessed because no MH patient was found among suxamethonium users.

As well as suxamethonium, volatile anesthetics also are considered triggering agents of MH. In *vitro* experiments, animal models, and human case series reports showed the potential risk of sevoflurane for MH.9,10 Our data showed that sevoflurane was widely used and other volatile agents were rarely used in Japan. Our epidemiologic study indicated a relatively but not significantly high prevalence of MH in sevoflurane users. There was no MH case with volatile anesthetics other than sevoflurane.

Nondepolarizing muscle relaxants are now considered to be much safer than suxamethonium. However, limited evidence suggested a possible MH risk with nondepolarizing muscle relaxants. Several case reports suggested that severe masseter muscle rigidity might have been occasionally induced by administration of a nondepolarizing muscle relaxant.26,27 Severe masseter muscle rigidity was identified as an early sign of generalized muscle rigidity and one of the signs for evaluating the likelihood of MH.28 In practice, 32.7% of Japanese MH patients showed severe masseter muscle rigidity,29 and 50% of Western patients with severe masseter spasms were subsequently confirmed to be MH-susceptible from muscle biopsies and contracture testing.30–32 Based on these limited data, in the current study, we hypothesized a relationship between nondepolarizing muscle relaxants and MH. The prevalence of MH in vecuronium users was relatively low, and no MH patient was found among the pancuronium users. Furthermore, use of rocuronium also was not statistically or significantly associated with MH. Our results thus supported the conventional consideration that nondepolarizing muscle relaxants are safe; however, the current study did not definitely eliminate a possible association of increased MH occurrence with rocuronium because of a relatively increased risk of MH. Our data might be useful in suggesting to anesthesiologists the possibility of MH when using rocuronium. We should continuously follow-up data on the relationship among nondepolarizing muscle relaxants and MH. Furthermore, future studies will be necessary to investigate the direct relationship by means of MH-susceptible muscle biopsy and contracture testing.

Whether propofol can induce MH or not remains controversial.11–13 Our epidemiologic data showed a relatively low prevalence of MH in propofol users and did not support an association between propofol and MH.

We should consider the possible effect of inhalation of residual volatile agents in the anesthetic circuits. Technical recommendations for the management of patients known to be MH-susceptible include: having clean anesthesia equipment and delivery of 10 l/min oxygen flow through the

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We should consider the possible effect of inhalation of residual volatile agents in the anesthetic circuits. Technical recommendations for the management of patients known to be MH-susceptible include: having clean anesthesia equipment and delivery of 10 l/min oxygen flow through the
equipment for more than 5 min preoperatively; removal of volatile agents from the equipment; and having a fresh carbon dioxide absorbent in the canister or nonbreathing sys-
tem. We found three MH patients without exposure to suxamethonium and any volatile anesthetics. It is possible that they might have been accidentally exposed to residual volatile agents in the anesthesia equipment.

Limitations
Several limitations should be acknowledged. The first limitation is related to the use of an administrative claims database. Generally, the recorded diagnoses in such databases are less well validated than those in planned prospective surveys. However, several advantages of the data submission processes in the DPC database, such as physician-dependent diagnosis reporting, requirement of data entry via a strict data format, and mandatory submission linked with reimbursement, maximized the accuracy and consistency of reporting. Second, given the anonymous nature of the database, it is not possible to determine whether the same individual has been noted to have MH more than once during multiple admissions. Third, the database does not include information on patients’ signs and symptoms or laboratory data; thus, we could not evaluate the validity of MH diagnosis and the severity of each individual MH episode. Underreporting or biased reporting (withholding sensitive cases) could lead to underestimation of MH events. Fourth, although the database included 40% of acute-care inpatients in Japan, participation in the DPC system was voluntary for each hospital, and patient selection was not based on a random sampling method. The database only included data between July and December, and such a time restriction will cause inaccurate estimation of the incidence of several diseases that show seasonal variation. However, to our knowledge, the occurrence of MH is unlikely to show seasonal variation, and this time restriction should have little affect. Finally, it was not possible to perform a multivariate analysis to examine the concurrent effect of multiple factors, including patient characteristics and drugs used, because of the extreme rarity of MH occurrence. Data should be continuously compiled, and further analysis with larger numbers of cases is necessary.

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