5. Kurata J. A potential role of functional magnetic resonance imaging in the diagnosis of pain. Jpn J Anesthesiol. 2009;58: 1350–9. (in Japanese with English abstract).
6. Seifert F, Jungfer I, Schmelz M, Maihofner C. Representation of UV-B-induced thermal and mechanical hyperalgesia in the human brain: a functional MRI study. Hum Brain Mapp. 2008; 29:1327–42.
7. Borsook D, Moulton EA, Tully S, Schmahmann JD, Becerra L. Human cerebellar responses to brush and heat stimuli in healthy and neuropathic pain subjects. Cerebellum. 2007;22:1–21.
8. Niddam DM, Yeh TC, Wu YT, Lee PL, Ho LT, Arendt-Nielsen L, Chen AC, Hsieh JC. Event-related functional MRI study on central representation of acute muscle pain induced by electrical stimulation. Neuroimage. 2002;17:1437–50.
9. Henderson LA, Bandler R, Gandevia SC, Macefield VG. Distinct forebrain activity patterns during deep versus superficial pain. Pain. 2006;120:286–96.
10. Svensson P, Minoshima S, Beydoun A, Morrow TJ, Casey KL. Cerebral processing of acute skin and muscle pain in humans. J Neurophysiol. 1997;78:450–60.
11. Kobayashi Y, Kurata J, Sekiguchi M, Kokubun M, Akaishizawa T, Chiba Y, Konno S, Kikuchi S. Augmented cerebral activation by lumbar mechanical stimulus in chronic low back pain patients: an FMRI study. Spine. 2009;34:2431–6.
12. Gracely RH, Petzke F, Wolf JM, Clauw DJ. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. Arthritis Rheum. 2002;46:1333–43.
13. Talairach J, Tournoux P. Co-planar stereotactic atlas of the human brain: 3-dimensional proportional system—an approach to cerebral imaging. New York: Thieme; 2002.
14. Nie H, Arendt Nielsen L, Andersen H, Graven Nielsen T. Temporal summation of pain evoked by mechanical stimulation in deep and superficial tissue. J Pain. 2005;6:348–55.
15. Mach DB, Rogers SD, Sabino MC, Luger NM, Schwei MJ, Pomonis JD, Keyser CP, Clohisy DR, Adams DJ, O'Leary P, Mantyh PW. Origins of skeletal pain: sensory and sympathetic innervation of the mouse femur. Neuroscience. 2002;113:155–66.
16. Korotkov A, Radovanovic S, Ljubisavljevic M, Lyskov E, Kataeva G, Roudas M, Pakhomov S, Thunberg J, Medvedev S, Johansson H. Comparison of brain activation after sustained non-fatiguing and fatiguing muscle contraction: a positron emission tomography study. Exp Brain Res. 2005;163:65–74.
17. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. J Neurophysiol. 1999;82:1934–43.
18. Ringler R, Greiner M, Kohlloeffel L, Handwerker HO, Forster C. BOLD effects in different areas of the cerebral cortex during painful mechanical stimulation. Pain. 2003;105:445–53.
19. Bingel U, Glascher J, Weiller C, Buchel C. Somatotopic representation of nociceptive information in the putamen: an event-related fMRI study. Cereb Cortex. 2004;14:1340–5.
20. Doyon J, Bellec P, Amsel R, Penhune V, Monchi O, Carrier J, Lehericy S, Benali H. Contributions of the basal ganglia and functionally related brain structures to motor learning. Behav Brain Res. 2009;199:61–75.
21. Marchand WR. Cortico-basal ganglia circuitry: a review of key research and implications for functional connectivity studies of mood and anxiety disorders. Brain Struct Funct. 2010;215:73–96.
22. Grahn JA, Parkinson JA, Owen AM. The role of the basal ganglia in learning and memory: neuropsychological studies. Behav Brain Res. 2009;199:53–60.
23. Chudler EH, Dong WK. The role of the basal ganglia in nociception and pain. Pain. 1995;60:3–38.

Hindawi Publishing Corporation
Anesthesiology Research and Practice
Volume 2011, Article ID 984281, 3 pages
doi:10.1155/2011/984281

Case Report

Oral Local Anesthesia Successfully Ameliorated Neuropathic Pain in an Upper Limb Suggesting Pain Alleviation through Neural Plasticity within the Central Nervous System: A Case Report

Jun Hozumi,[1] Masahiko Sumitani,[1] Arito Yozu,[2] Toshiya Tomioka,[1] Hiroshi Sekiyama,[1] Satoru Miyauchi,[3] and Yoshitsugu Yamada[1]

[1] *Department of Anesthesiology and Pain Relief Center, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*
[2] *Department of Rehabilitation Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan*
[3] *Kobe Advanced ICT Research Center, National Institute of Information and Communications Technology, Kobe 651-2492, Japan*

Correspondence should be addressed to Masahiko Sumitani, sumitanim-ane@h.u-tokyo.ac.jp

Received 20 December 2010; Revised 3 March 2011; Accepted 25 March 2011

Academic Editor: Kouichiro Minami

Neural blockades are considered an alternative to pharmacotherapy for neuropathic pain although these blockades elicit limited effects. We encountered a patient with postbrachial plexus avulsion injury pain, which was refractory to conventional treatments but disappeared temporarily with the administration of the local anesthetic lidocaine around the left mandibular molar tooth during dental treatments. This analgesic effect on neuropathic pain by oral local anesthesia was reproducible. Under conditions of neuropathic pain, cerebral somatotopic reorganization in the sensorimotor cortices of the brain has been observed. Either expansion or shrinkage of the somatotopic representation of a deafferentated body part correlates with the degree of neuropathic pain. In our case, administration of an oral local anesthetic shrank the somatotopic representation of the mouth, which is next to the upper limb representation and thereby expanded the upper limb representation in a normal manner. Consequently, oral local anesthesia improved the pain in the upper limb. This case suggests that pain alleviation through neural plasticity within the brain is related to neural blockade.

1. Introduction

Neuropathic pain typically appears following peripheral nerve injury due to neuropathies, plexopathies, and trauma to selected sites within the central nervous system (CNS). Recently, evidence-based recommendations of pharmacological treatments for neuropathic pain have been proposed based on both positive and negative results from multiple randomized controlled trials. However, approximately 10–15% of all neuropathic pain patients are refractory to pharmacotherapy. For these cases, more invasive pain-management interventions, such as intrathecal drug delivery, neurostimulation, or neural blockade, may be used. Ideally, blocking neural transmission, either temporarily by using local anesthetics or permanently by surgical nerve ablation, can reduce neuropathic pain; however, no neural blockades have been found to be consistently successful [1]. Here, we report on a case of a patient with postbrachial plexus avulsion injury pain whose neuropathic pain had been refractory to several evidence-based pharmacotherapies and interventions, such as spinal cord stimulation, cervical epidural blockade, and brachial plexus blockade. His pain could be well controlled by oral local anesthesia, suggesting pain alleviation through neural plasticity within the CNS.

2. Case Report

A 49-year-old man, who had a left brachial plexus avulsion injury 10 years before, experienced severe neuropathic pain in his left upper limb immediately after the trauma. The patient complained of continuous burning, pressing, and

tingling pain in the upper limb. From the beginning of the perception of the pain in his upper limb, he felt illusory perceptions of fingers touching his face although he did not perceive pain or any other sensory deficits in the face. He had been treated several times for the pain through left brachial plexus blockades and cervical epidural blockades, with no success. His neuropathic pain decreased slightly when taking pregabalin and with the application of cervical spinal cord stimulation (SCS), but it remained severe. He did not have any pain or trigger areas in the face getting caries of the teeth. He once underwent a dental treatment for his left mandibular molar tooth. When local anesthesia was applied around the left mandibular molar tooth (3 mL, 0.5% lidocaine), he felt the enlargement of that region, which was followed by an immediate disappearance of his neuropathic pain. At that time, the illusory finger sensations in the face disappeared. Approximately 2 hours after the dental treatment, the neuropathic pain returned and gradually increased to predental treatment levels. A nonsteroidal anti-inflammatory drug, loxoprofen, completely ameliorated the dental pain but was not effective against the neuropathic pain. Since then, the patient had 3 dental treatments, and local anesthesia around the left molar tooth consistently ameliorated his neuropathic pain. Analgesic effects consistently lasted for several hours following the administration of the local anesthesia. His neuropathic pain was able to be mildly controlled by a combination of pregabalin, SCS, and local anesthesia around the left molar tooth although the molar tooth had completely improved. The use of oral local anesthesia for breakthrough neuropathic pain had been especially effective.

We obtained the patient's consent to report his progress, in accordance with the Declaration of Helsinki.

3. Discussion

Under conditions of neuropathic pain, particularly for deafferentation pain following massive nerve injury, such as postamputation phantom limb pain, postbrachial plexus injury pain, or postspinal cord injury pain, cerebral somatotopic reorganization in the sensorimotor cortices of the brain is observed. Following deafferentation of an upper limb by nerve injury, the somatotopic region corresponding to the upper limb in the sensorimotor cortices shrinks, and the somatotopic region responding to the facial region, which is located next to the upper limb, expands (Figure 1(a)) [2, 3]. The degree of shrinkage of the upper limb representation correlated linearly with the severity of the neuropathic pain [4]. Further, expansion of the somatotopic representation of the affected body part correlated with pain alleviation through neurorehabilitation techniques [5–7]. Therefore, somatotopic reorganization in the sensorimotor cortices closely relates to pathophysiological mechanisms underlying neuropathic pain and its alleviation.

Concerning the somatotopic reorganization of the face and hand regions, the overlapping of these regions can sometimes induce the following illusion in patients with a deafferentation of a hand: touching the face creates obvious referred sensation of fingers in the face as if the fingers

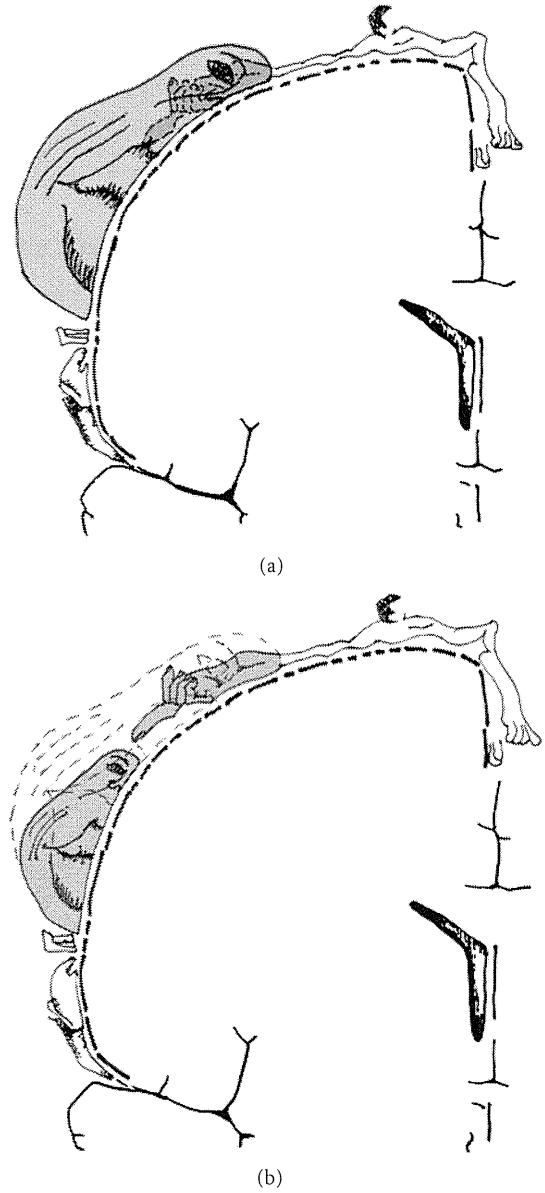


Figure 1: Topographical somatotopic reorganization in the sensorimotor cortices following deafferentation by a brachial plexus avulsion injury (a) and normalization of the reorganization by application of local anesthesia in the mouth (b).

are embedded in the face [8]. We consider one possibility that the analgesic effects of the oral local anesthesia in our case were derived from the neural plasticity in the sensorimotor cortices because our patient perceived a similar illusory sensation of fingers in the face. Deafferentation by local anesthesia, as well as that by nerve injury, shrinks the somatotopic representation of the exposed body part and simultaneously expands the nearby somatotopic representation in the sensorimotor cortices, and these are not associated with subcortical changes [9, 10]. On the basis of this notion, we speculated that, in our case, local anesthesia in the mouth shrank the mouth/face representation and subsequently expanded the somatotopic representation of the hand/upper

limb within the sensorimotor cortices (Figure 1(b)), resulting in amelioration of the neuropathic pain in the upper limb. The disappearance of the illusory finger sensations in the face soon after the oral local anesthesia supported the intimate relationship between analgesic effects of the upper limb pain and cerebral reorganization of hand/upper limb and face/mouth representations.

In general, neural blockades are applied to painful body parts in order to block neural transmission; however, the clinical significance of neural transmission blockades remains unclear for nerve-injured neuropathic pain because of deafferentation. Local anesthesia at an intact limb contralateral to the painful limb has been reported to display clear analgesic effects on postamputation phantom limb pain, suggesting pain alleviation through neural plasticity within the CNS [11]. Thus, several types of local anesthesia or neural blockades on unaffected body parts have distinct clinical significance compared to neural transmission blockades, whereas peripheral nerve blockades shrink the somatotopic area of the exposed body part and seem to have no analgesic effect on neuropathic pain in general. Specific analgesic effects on neuropathic pain from local anesthesia and neural blockade could be derived from CNS plasticity. In the future, functional brain imaging studies examining the relationship between neural blockade application for neuropathic pain and CNS plasticity need to be performed in order to better understand somatotopic reorganization in the sensorimotor cortices induced by neural blockades.

4. Conclusion

For neural blockades, oral local anesthesia is a novel candidate for treating neuropathic pain in the upper limb, and the analgesic effect might be derived from its effects on neural plasticity within the CNS.

Acknowledgments

This paper was partially funded by the New Energy and Industrial Technology Development Organization (no. 08C46216) and the Ministry of Education, Science, Sports, and Culture (Young (B) no. 22791420). The authors declare no conflict of interests.

References

[1] M. S. Chong and Z. H. Bajwa, "Diagnosis and treatment of neuropathic pain," *Journal of Pain and Symptom Management*, vol. 25, no. 5, pp. S4–S11, 2003.

[2] H. Flor, L. Nikolajsen, and T. S. Jensen, "Phantom limb pain: a case of maladaptive CNS plasticity?" *Nature Reviews Neuroscience*, vol. 7, no. 11, pp. 873–881, 2006.

[3] M. Sumitani, S. Miyauchi, A. Yozu, Y. Otake, Y. Saitoh, and Y. Yamada, "Phantom limb pain in the primary motor cortex: topical review," *Journal of Anesthesia*, vol. 24, no. 2, pp. 337–341, 2010.

[4] H. Flor, T. Elbert, S. Knecht et al., "Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation," *Nature*, vol. 375, no. 6531, pp. 482–484, 1995.

[5] H. Flor, C. Denke, M. Schaefer, and S. Grüsser, "Effect of sensory discrimination training on cortical reorganisation and phantom limb pain," *The Lancet*, vol. 357, no. 9270, pp. 1763–1764, 2001.

[6] M. Sumitani, S. Miyauchi, C. S. Mccabe et al., "Mirror visual feedback alleviates deafferentation pain, depending on qualitative aspects of the pain: a preliminary report," *Rheumatology*, vol. 47, no. 7, pp. 1038–1043, 2008.

[7] K. MacIver, D. M. Lloyd, S. Kelly, N. Roberts, and T. Nurmikko, "Phantom limb pain, cortical reorganization and the therapeutic effect of mental imagery," *Brain*, vol. 131, no. 8, pp. 2181–2191, 2008.

[8] V. S. Ramachandran, "Behavioral and magnetoencephalographic correlates of plasticity in the adult human brain," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 90, no. 22, pp. 10413–10420, 1993.

[9] P. M. Rossini, G. Martino, L. Narici et al., "Short-term brain 'plasticity' in humans: transient finger representation changes in sensory cortex somatotopy following ischemic anesthesia," *Brain Research*, vol. 642, no. 1-2, pp. 169–177, 1994.

[10] M. Tinazzi, G. Zanette, A. Polo et al., "Transient deafferentation in humans induces rapid modulation of primary sensory cortex not associated with subcortical changes: a somatosensory evoked potential study," *Neuroscience Letters*, vol. 223, no. 1, pp. 21–24, 1997.

[11] D. Gross, "Contralateral local anesthesia in stump, phantom and post-traumatic pain," *Anaesthesist*, vol. 7, no. 2, pp. 65–73, 1984.

[12] D. B. Bayer and T. G. Stenger, "Trigeminal neuralgia: an overview," *Oral Surgery Oral Medicine and Oral Pathology*, vol. 48, no. 5, pp. 393–399, 1979.

J Anesth
DOI 10.1007/s00540-011-1221-5

ORIGINAL ARTICLE

Impact of remifentanil introduction on practice patterns in general anesthesia

Kanji Uchida · Hideo Yasunaga · Hiroaki Miyata · Masahiko Sumitani · Hiromasa Horiguchi · Ken Kuwajima · Shinya Matsuda · Yoshitsugu Yamada

Received: 16 June 2011 / Accepted: 18 August 2011

Abstract
Purpose The introduction of new medicine can change clinical practice patterns and may affect patient outcomes. In the present study, we investigated whether introduction of remifentanil in Japan affected the practice patterns of anesthesia.
Methods Using the Japanese Diagnosis Procedure Combination database, we extracted records of 423,491 patients who underwent surgery with general anesthesia in 243 hospitals before (2006) and after (2007) the introduction of remifentanil, and identified anesthetic agents used for each patient. A hierarchical mixed-effects logistic regression analysis was performed to analyze the factors that affected selection of remifentanil. Further, we compared postoperative length of stay (LOS), in-hospital mortality, and total costs between 2006 and 2007.
Results In 2007, remifentanil was used for up to 41.4% of all general anesthesia, accompanied by a reduction in nitrous oxide use and an increase in total intravenous anesthesia. Female gender, increasing age, and preoperative comorbidities including diabetes mellitus, hypertension, liver cirrhosis, and chronic renal failure were positively associated with the use of remifentanil, whereas accompanying cardiac disease and co-application of epidural anesthesia were negatively associated. In 2007, a similar in-hospital death rate, similar or decreased total costs, slightly reduced duration of anesthesia, and substantially reduced postoperative LOS were seen compared to those in 2006.
Conclusions Our data revealed rapid changes in practice patterns in anesthesia after the introduction of remifentanil in Japan. Remifentanil was used more often in patients with comorbidities and without epidural anesthesia, and its introduction did not affect increase in total medical costs.

Keywords Remifentanil · Anesthetic practice · Postoperative outcome · In-patient medical cost

Electronic supplementary material The online version of this article (doi:10.1007/s00540-011-1221-5) contains supplementary material, which is available to authorized users.

K. Uchida (✉) · M. Sumitani · K. Kuwajima · Y. Yamada
Department of Anesthesiology, Tokyo University Graduate School of Medicine, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: UCHIDAK-ANE@h.u-tokyo.ac.jp

H. Yasunaga · H. Horiguchi
Department of Health Management and Policy, Tokyo University Graduate School of Medicine, Tokyo, Japan

H. Miyata
Department of Health Quality Assessment, Tokyo University Graduate School of Medicine, Tokyo, Japan

S. Matsuda
Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, Kitakyushu, Japan

Introduction

The introduction of new medical devices such as the drug-eluting stent for angina pectoris [1] or new drugs such as anti-tumor necrosis factor-α antibody for rheumatoid arthritis [2] had a major impact on medical practice patterns over a short time period, affecting not only patient outcomes but also total medical costs, although published reports gave variable results [3].

In anesthesiology, only a limited number of reports show changes in practice patterns in anesthesia [4]. It is

Published online: 09 September 2011

also not clear to what extent such changes affect medical costs and patient outcome [5].

Remifentanil, a mu-opioid receptor agonist, has a unique pharmacokinetic profile, characterized by rapid equilibration with the central compartment, and a short half-life, independent of infusion duration [6, 7]. Although its use is common in Western countries [8], it was finally approved in Japan in December 2006, and its use in clinical practice commenced in January 2007. The unique pharmacological properties of this novel drug facilitated its rapid assimilation into Japanese clinical procedures, making a considerable impact on anesthetic practice. However, accurate data have not been reported on the expansion of remifentanil use and the subsequent changes in practice patterns in general anesthesia. In addition, the effects of remifentanil introduction on patient outcomes remain unclear.

In the present study, we investigated the proportion of remifentanil use in the first year of its introduction and changes in the patterns of anesthetic drug use. Then, we analyzed factors affecting selection of remifentanil. We also compared duration of anesthesia and total costs as well as postoperative length of stay (LOS) and in-hospital mortality before and after introduction of remifentanil, using the nationwide Japanese administrative claims database, the Diagnosis Procedure Combination (DPC) database.

Materials and methods

DPC database and participants

The DPC is a mixed-case system, similar to the diagnosis-related groups (DRG) in the U.S. Medicare program. It was launched in 2002 by the Ministry of Health, Labor and Welfare of Japan and is 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 [9, 10]. All 82 university teaching hospitals must adopt the DPC system, and community hospitals can voluntarily adopt this system. Data are mainly used for profiling practice patterns, refining case-mix classification, and planning health policies such as resource allocation.

The DPC database comprises discharge abstracts and administrative claims, with data compiled between July 1 and December 31 each year by the DPC Research Group [10–13]. The database initially included 82 hospitals in 2003. The numbers of inpatients and participant hospitals are increasing each year, with around 3 million patients from 926 hospitals in 2007, which represented approximately 45% of all acute care inpatient hospitalizations in Japan [11]. The database includes the following data: unique identification number of each hospital; patient age and sex; diagnoses recorded in the Japanese language together with the *International Classification of Diseases, 10th Revision*; surgical procedures coded with original Japanese codes; drugs and devices used; LOS; in-hospital mortality; and total costs (including costs for hospitalization, surgery, anesthesia, drugs and devices used).

The DPC database corresponds to the Nationwide Inpatient Sample in the United States [14] to some extent but has several advantages [10]. To optimize the validity of the recorded diagnoses, physicians in charge record the diagnoses in reference to the medical charts. Detailed data are available for the treatments administered on a daily basis (e.g., types of drugs administered, duration of anesthesia, volume of blood transfusion). Medical clerks and licensed medical information managers accurately record the dates of each surgery and other procedures and the dates of use of each drug and device. Physicians and hospitals consistently comply with data submission because it is mandatory to obtain DPC-based reimbursement of medical fees.

All patient identifiers have been removed from this database. Because of the anonymous nature of the data, obtaining informed consent from patients was unnecessary. The Institutional Review Board of the University of Occupational and Environmental Health approved this study design.

Data extraction

To compare the pre-remifentanil period (July–December 2006) with the remifentanil treatment period (July–December 2007), we included data from all 243 hospitals that participated in the DPC survey in both years. We extracted data on all surgical patients who underwent general anesthesia in these hospitals, including type of hospital, type of admission, patient age, sex, surgical procedures, duration of anesthesia (min), volume of blood transfusion, postoperative LOS (days), in-hospital mortality, and total costs. General anesthesia was defined as anesthesia for surgery for at least 20 min with volatile anesthetics and/or intravenous anesthetics supplemented with oxygen via a mask including laryngeal mask or endotracheal tube.

We also extracted data regarding medications used for general anesthesia, including barbiturates, nitrous oxide, volatile anesthetic agents, muscle relaxants, hypnotics, and narcotics.

Patients who underwent the following eight classes of surgery in 2007 were subdivided to evaluate differences in distribution of remifentanil among surgical subcategories: cardiac surgery, neurosurgery, thoracic surgery, vascular surgery, general surgery, gynecology, orthopedic surgery, and otolaryngology. When a patient underwent two or more surgeries during the hospitalization, the patient was

classified into one group according to the most recent surgery. If a patient underwent multiple surgeries at the same time, we selected the one surgery that required the most medical resources. Postoperative LOS was determined as the days between the day of the surgery and that of discharge.

Descriptive statistics

The proportions of patients who received each drug were compared between 2006 and 2007. Combinations of remifentanil and fentanyl, and of nitrous oxide and volatile agents, were also compared between the 2 years. Further, postoperative in-hospital mortality, duration of anesthesia, postoperative LOS, and total costs were compared between the 2 years for all populations and eight surgical subcategories.

Logistic regression to determine factors for selecting remifentanil

To determine possible contributing factors for selection of remifentanil, we extracted the data of patients who had general anesthesia with either fentanyl alone or remifentanil and fentanyl in 2007. In the logistic regression model, the dependent variable was set as "remifentanil use" (fentanyl alone = 0; both remifentanil and fentanyl = 1). A hierarchical mixed-effects logistic regression analysis was performed in which age, sex, intraoperative use of epidural anesthesia, comorbidities, and surgical subcategories were set as fixed effects, and sites (described by unique identifiers for all 243 hospitals) were used as random intercepts.

Statistical analysis

We performed univariate comparisons of variables for the two groups, using the Mann–Whitney *U* test for nonparametric data and the chi-square test for categorical data as appropriate. All statistical analyses were conducted using the SAS 9.1 (SAS Institute, Cary, NC, USA), and *P* values <0.05 were considered to be significant. The exchange rate was assumed to be 100 yen to 1 U.S. dollar (USD).

Results

Patient demographics

All 243 acute care hospitals that participated in DPC in both 2006 and 2007 were enrolled in this study. A total of 423,491 patients (206,102 in 2006 and 217,389 in 2007) were identified. Overall, 59.6% of patients were admitted to 53 teaching hospitals, while the remaining 40.4% were treated at 190 non-teaching hospitals (Supplemental Tables 1, 2).

Anesthetic drug used

Table 1 shows the use of each anesthetic drug in 2006 and 2007. Remifentanil accounted for 41.4% of all general anesthesia usage in 2007. The proportion of cases in which either fentanyl or remifentanil was used increased from 76.5% in 2006 to 83.3% in 2007. The proportion including remifentanil in 2007 was higher in teaching hospitals than

Table 1 Anesthetic drugs used

Drug	2006 (n = 206,102) (%)	2007 (n = 217,389) (%)	P*
Narcotics			
Remifentanil	0.0	41.4	<0.001
Fentanyl	76.5	71.2	<0.001
Morphine	13.7	13.4	<0.001
Hypnotics			
Barbiturates	18.4	14.9	<0.001
Propofol	72.8	76.9	<0.001
Midazolam	9.4	12.6	<0.001
Nitrous oxide	25.8	14.0	<0.001
Volatile anesthetic agents			
Sevoflurane	79.5	74.2	<0.001
Isoflurane	4.6	3.3	<0.001
Halothane	0.1	0.1	0.732
Muscle relaxants			
Suxamethonium	0.5	1.3	<0.001
Vecuronium	84.2	81.9	<0.001
Rocuronium	0.0	2.6	<0.001
Pancuronium	1.0	0.9	0.158
Others			
Droperidol	12.2	13.9	<0.001
Ketamine	5.1	3.8	<0.001
Diazepam	1.3	1.2	0.023
Combination of fentanyl and remifentanil			
Neither	23.5	16.7	<0.001
Fentanyl alone	76.5	41.9	<0.001
Remifentanil alone	0.0	12.1	<0.001
Both	0.0	29.3	<0.001
Combination of nitrous oxide and volatile agents			
Neither	14.0	21.0	<0.001
Nitrous oxide alone	2.1	1.6	<0.001
Volatile agents alone	60.1	65.0	<0.001
Both	23.8	12.4	<0.001

* P value for the comparison between 2006 and 2007 evaluated with the chi-square test

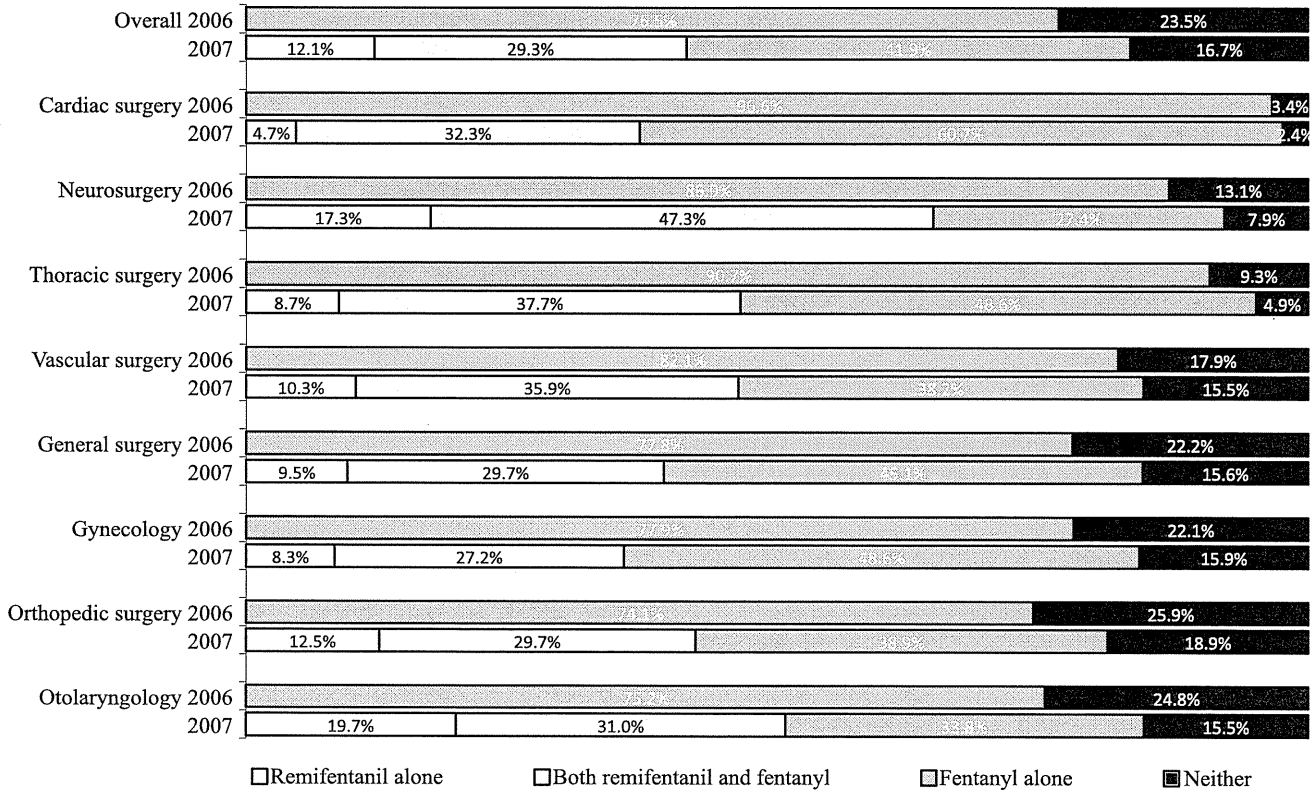


Fig. 1 Combination of remifentanil and fentanyl in each surgical field: percentage of surgeries using fentanyl and/or remifentanil in 2006 and 2007. *Open bars* cases in which remifentanil alone was used; *light gray bars* both remifentanil and fentanyl; *dark gray bars* fentanyl alone; *closed bars* neither remifentanil nor fentanyl

in non-teaching hospitals (48.1% vs. 36.9%, $P < 0.01$). The use of remifentanil in 2007 was exceptionally high in neurosurgery (64.6%) and otolaryngology (50.7%) (Fig. 1). The use of nitrous oxide decreased from 25.9% in 2006 to 14.0% in 2007. The proportion of patients who received neither nitrous oxide nor volatile agents, i.e., those undergoing total intravenous anesthesia (TIVA), increased from 14.0% in 2006 to 21.0% in 2007.

Barbiturate use was lower in 2007 (14.9%) than in 2006 (18.4%), whereas use of propofol was higher in 2007 (76.9%) than in 2006 (72.8%). Vecuronium was used in more than 80% of general anesthesias in both years, whereas rocuronium, which was introduced in September 2007, was utilized in 2.6% of surgeries in that year.

Factors associated with selection of remifentanil

Among 217,389 patients in 2007, 91,097 received fentanyl alone, and 63,739 received both remifentanil and fentanyl. Both patient factors and surgical factors affecting use of remifentanil were analyzed with adjustment for site effects by incorporating hospital identification numbers into the hierarchical mixed-effects logistic regression model. Female sex, increasing age, and comorbidities including diabetes mellitus, hypertension, liver cirrhosis, and chronic renal failure were positively associated with selection of remifentanil. In contrast, cardiac diseases and intraoperative epidural anesthesia were negatively associated with selection of remifentanil. Neurosurgical patients were more than fivefold more likely to receive remifentanil compared with cardiac surgery patients (Table 2).

Postoperative outcomes

Table 3 shows in-hospital mortality, mean duration of anesthesia, mean postoperative LOS, and mean total cost in each surgical field. All outcomes were compared between 2006 and 2007. No significant difference in in-hospital mortality was seen in any surgical subcategory showed between the 2 years. The mean duration of anesthesia was slightly shorter in 2007 than in 2006, and the differences were statistically significant in general surgery, gynecology, and orthopedic surgery. Mean postoperative LOS was shorter in 2007 in all surgical subcategories, and most of these findings were statistically significant, except for otolaryngology cases. Total cost was comparable between the 2 years, except for general surgery and gynecology, which were significantly less in 2007 compared with 2006.

Table 2 A hierarchical mixed-effects logistic regression analysis for selecting remifentanil (fentanyl alone = 0; both remifentanil and fentanyl = 1)

	Odds ratio	95% confidence interval	*P* value
Sex (female)	1.09	1.06–1.12	<0.001
Age	1.02	1.02–1.02	<0.001
Epidural anesthesia	0.36	0.35–0.37	<0.001
Diabetes mellitus	1.07	1.02–1.11	0.006
Hypertension	1.08	1.04–1.13	<0.001
Cardiac diseases	0.91	0.86–0.95	<0.001
Cerebrovascular diseases	1.07	1.00–1.15	0.068
Chronic lung diseases	1.01	0.93–1.08	0.888
Liver cirrhosis	1.19	1.00–1.41	0.049
Chronic renal failure	1.17	1.08–1.27	<0.001
Surgical category			
Cardiac surgery	Reference		<0.001
Neurosurgery	5.49	5.05–5.98	
Thoracic surgery	3.20	2.94–3.47	
Vascular surgery	2.36	2.17–2.58	
General surgery	2.00	1.87–2.13	
Gynecology	2.01	1.86–2.17	
Orthopedic surgery	1.89	1.76–2.02	
Otolaryngology	2.48	2.31–2.76	

Discussion

Population representation

According to the Survey of Medical Institutions 2008 in Japan, the average number of surgeries under general anesthesia throughout the country was 187,097 per month. [Survey of Medical Institutions 2008 (in Japanese). Vital and Health Statistics Division, Ministry of Health, Labour and Welfare, Japan. Available at: http://www.mhlw.go.jp/toukei/saikin/hw/iryosd/08/index.html. Accessed June 14, 2011.] Our data included 423,491 cases in 12 months, representing about 19% of all patients who underwent general anesthesia during the data extraction period in Japan. The age distribution was similar to that in another large database of anesthesia maintained by the Japanese Society of Anesthesiologists [15, 16].

Spread of remifentanil use and factors associated with its selection

Remifentanil was administered in more than 40% of all general anesthesias in the first year of its introduction, an extremely rapid increase in the proportion of its use [17].

Remifentanil was more frequently selected for patients with comorbidities, including hypertension, diabetes mellitus, and liver and kidney disease, presumably because it has advantages over other opioids such as a controllable, strong antinociceptive effect and rapid extrahepatic metabolism and elimination.

Epidural anesthesia was negatively associated with selection of remifentanil. Multiple publications suggest better patient intra- and postoperative condition with epidural anesthesia [18, 19]. It is anticipated that anesthesiologists did not believe it necessary to use remifentanil when they applied epidural anesthesia intraoperatively. The proportion of remifentanil use was higher in the nonepidural group than in the epidural group (45.2% vs. 30.6%). It was also higher in neurosurgery (64.6%) and otolaryngology (50.7%) cases. These results suggest that the pharmacological properties of remifentanil are highly

Table 3 Comparison of in-hospital mortality, average duration of anesthesia, postoperative length of stay, and total cost between 2006 and 2007 in each surgical subcategory

	In-hospital mortality (%)			Duration of anesthesia (min)			Postoperative length of stay (days)			Total costs (USD)		
	2006	2007	*P**	2006	2007	*P*†	2006	2007	*P*†	2006	2007	*P*†
Overall	1.41	1.36	0.242	211	208	<0.001	16.4	15.7	<0.001	12,733	12,648	0.051
Cardiac surgery	4.78	4.53	0.403	407	403	0.111	24.7	24.1	0.039	43,797	43,427	0.327
Neurosurgery	5.46	5.47	0.985	316	314	0.352	28.7	27.6	0.004	23,255	23,193	0.784
Thoracic surgery	1.73	1.69	0.862	259	255	0.296	14.5	14.0	0.046	15,926	15,820	0.669
Vascular surgery	3.59	3.50	0.761	267	262	0.074	24.0	22.6	0.002	18,489	18,458	0.927
General surgery	2.02	2.02	0.952	220	216	<0.001	16.9	16.1	<0.001	12,096	11,935	0.019
Gynecology	0.15	0.12	0.381	163	161	0.043	10.1	9.2	<0.001	7,046	6,951	0.042
Orthopedic surgery	0.66	0.56	0.092	191	188	<0.001	23.0	22.3	<0.001	14,108	14,112	0.957
Otolaryngology	1.33	1.43	0.314	177	174	0.429	12.3	12.1	0.222	8,448	8,555	0.330

LOS length of stay

* *P* value for the comparison between 2006 and 2007 evaluated with the chi-square test. Continuous variables, indicated with †, were evaluated using the Mann–Whitney *U* test

appreciated in those surgeries in which a neuraxial blockade cannot be applied.

Cardiac surgery had the smallest impact on the choice of remifentanil, presumably because of the greater surgical insult to patients, who frequently require postoperative mechanical ventilation; therefore, anesthetists can apply a large dose of fentanyl intraoperatively without considering early postoperative emergence and extubation in the operating theater. Coexisting cardiac disease was negatively associated with selection of remifentanil (Table 2). The well-known circulatory suppressive effect of remifentanil [20] may be another reason for the anesthetists to refrain from applying it in cardiac surgery.

Bramhall pointed out three prerequisites for an anesthetic drug to obtain a major share in the market. (Bramhall J. Remifentanil: Clinical use of an evanescent opioid. Available at: http://faculty.washington.edu/bramhall/lectures/opioids/remife~1.htm. Accessed June 14, 2011.) First, the drug must fit a "niche," allowing techniques to be used that were previously impractical; second, the drug must be cost effective; and third, it must have a safer profile than currently available agents. The safety of novel agents is generally extensively evaluated before clinical application, but it is usually difficult to show that the drug is "safer" than other drugs before substantial use. Similarly, the cost-effectiveness of anesthetic drugs cannot be clearly determined before substantial use, because various parameters can affect postoperative medical costs [21]. In contrast, intraoperative clinical advantages of remifentanil are evident even before substantial use. Its unique property as an ultra-short-acting opioid allowed application of new techniques that were previously impractical. For example, it enabled extensive opioid use as primary treatment for intraoperative pain that did not affect early postoperative emergence [22]. Bramhall also stated that the superiority of a drug over others should be assessed quite accurately, even if subjectively, by individual anesthetists in their daily practice. Because other short-acting opioids, i.e., sufentanil and alfentanil, had not been introduced into clinical use in Japan, the effect of remifentanil was likely to have a greater impression on Japanese anesthesiologists, and this may have boosted its penetration into the market.

The Japanese health insurance system does not offer economic incentives to anesthesiologists, and the reimbursement of costs for surgery and anesthesia is based on a fee-for-service system [23]. Therefore, anesthesiologists in Japan choose drugs according to their clinical applicability and convenience, with little economic consideration. Indeed, the present study revealed that sevoflurane was used in an exceptionally large population of general anesthesia cases despite its relatively high costs compared with other volatile agents (Table 1) [24]. Because there was more than a 10-year delay in the clinical application of remifentanil in Japan from Western countries, anesthesiologists should already have been familiar with its pharmacological properties and practical clinical application, thus making it easy for them to bring it into their clinical practice.

Change in patterns of drugs used for general anesthesia

Along with the rapid escalation of remifentanil use, an increase in TIVA and a reciprocal decrease in nitrous oxide use were obvious. Increase in propofol users by 4.1% in contrast to the reduction in barbiturates users by 3.5% may be the consequence of the increase in TIVA population, because propofol, which is the most popular hypnotic for maintenance of TIVA, can also substitute for barbiturates as an induction agent. Remifentanil may be superior to nitrous oxide for pain control with less environmental effect (i.e., contamination of the atmosphere in the operating room) and fewer adverse effects on patients, such as postoperative nausea and vomiting [25]. Other volatile anesthetic agents, specifically sevoflurane and isoflurane, were significantly reduced in use in 2007, but the magnitudes are less than that of nitrous oxide (Table 1). These observations may possibly be the result of their known organ-protective effects [26], recognized by most of the anesthesiologists in Japan, as well as their easy and titratable properties in regular clinical practice.

Impact on patient postoperative outcome and cost

Postoperative LOS was significantly reduced in all the surgeries except for otolaryngology, although the magnitude of surgical insult indicated by duration of anesthesia were relatively similar in both years. However, whether application of remifentanil led to better postoperative recovery is not clear. Currently few publications have reported association between use of remifentanil and better postoperative recovery [27]. Other factors, such as less-invasive surgical techniques and improved perioperative care, which affects enhanced recovery after surgery [28], may have contributed to the reduction in postoperative LOS in surgical patients.

Remifentanil is relatively expensive, a 2-mg vial costing 25.34 USD, about 10 times that of fentanyl (0.1 mg ampule for 2.45 USD) in Japan. Rapid increase in the proportion of remifentanil use was anticipated to cause increase in total costs. However, all surgical subcategories showed similar or less total cost in 2007 compared with 2006. Although multiple factors affect patient postoperative outcome and total costs, we can at least say from the present results that application of remifentanil did not affect increase in total costs. To disclose the possible contribution of remifentanil to better postoperative recovery, further evaluation using a wider dataset or a randomized controlled trial is necessary.

Limitations

Several limitations to this study should be acknowledged. The first is 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, maximize the accuracy and consistency of reporting. Second, the database does not include actual doses of each anesthetic that might affect patient outcome. Detailed information about patients' signs and symptoms or laboratory data are also missing; thus, it is impractical with the present data to determine whether introduction of remifentanil affected postoperative LOS and in-hospital mortality.

In conclusion, our data revealed a rapid increase in the proportion of surgeries using remifentanil following its introduction in 2007. Comorbidities including diabetes mellitus, hypertension, liver cirrhosis, and chronic renal failure were positively associated and epidural anesthesia and coexisting cardiac diseases were negatively associated with the use of remifentanil. Postoperative LOS was reduced in 2007, and total cost was comparable in the 2 years, indicating higher drug acquisition costs for remifentanil could be offset by reduced postoperative hospital LOS.

Acknowledgments This study was funded by Grants-in-Aid for Research on Policy Planning and Evaluation (grant number: H19-Policy-001) from the Ministry of Health, Labour and Welfare, Japan.

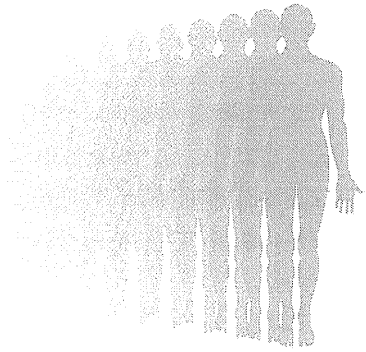
References

1. Horiguchi H, Yasunaga H, Hashimoto H, Matsuda S. Impact of drug-eluting stents on treatment option mix for coronary artery disease in Japan. Circ J. 2010;74:1635–43.
2. van Vollenhoven RF. Treatment of rheumatoid arthritis: state of the art 2009. Nat Rev Rheumatol. 2009;5:531–41.
3. Ligthart S, Vlemmix F, Dendukuri N, Brophy JM. The cost-effectiveness of drug-eluting stents: a systematic review. CMAJ. 2007;176:199–205.
4. Clergue F, Auroy Y, Péquignot F, Jougla E, Lienhart A, Laxenaire MC. French survey of anesthesia in 1996. Anesthesiology. 1999;91:1509–20.
5. Cohen MM, Rose DK, Yee DA. Changing anesthesiologists' practice patterns. Can it be done? Anesthesiology. 1996;85:260–9.
6. Egan TD. Remifentanil pharmacokinetics and pharmacodynamics. A preliminary appraisal. Clin Pharmacokinet. 1995;29:80–94.
7. Kapila A, Glass PS, Jacobs JR, Muir KT, Hermann DJ, Shiraishi M, Howell S, Smith RL. Measured context-sensitive half-times of remifentanil and alfentanil. Anesthesiology. 1995;83:968–75.
8. Komatsu R, Turan AM, Orhan-Sungur M, McGuire J, Radke OC, Apfel CC. Remifentanil for general anaesthesia: a systematic review. Anaesthesia. 2007;62:1266–80.
9. Matsuda S, Ishikawa KB, Kuwabara K, Fujimori K, Fushimi K, Hashimoto H. Development and use of the Japanese case-mix system. Eurohealth. 2008;14:25–30.
10. Sumitani M, Uchida K, Yasunaga H, Horiguchi H, Kusakabe Y, Matsuda S, Yamada Y. Prevalence of malignant hyperthermia and relationship with anesthetics in Japan. Data from the diagnosis procedure combination database. Anesthesiology. 2011;114:84–90.
11. Kuwabara K, Matsuda S, Imanaka Y, Fushimi K, Hashimoto H, Ishikawa KB, Horiguchi H, Hayashida K, Fujimori K, Ikeda S, Yasunaga H. Injury severity score, resource use, and outcome for trauma patients within a Japanese administrative database. J Trauma. 2010;68:463–70.
12. Yasunaga H, Yanaihara H, Fuji K, Horiguchi H, Hashimoto H, Matsuda S. Impact of hospital volume on postoperative complications and in-hospital mortality following renal surgery: data from the Japanese Diagnosis Procedure Combination Database. Urology. 2010;76:548–52.
13. Matsui H, Hashimoto H, Horiguchi H, Yasunaga H, Matsuda S. An exploration of the association between very early rehabilitation and outcome for the patients with acute ischaemic stroke in Japan: a nationwide retrospective cohort survey. BMC Health Serv Res. 2010;10:213.
14. Park B, Messina L, Dargon P, Huang W, Ciocca R, Anderson FA. Recent trends in clinical outcomes and resource utilization for pulmonary embolism in the United States: findings from the Nationwide Inpatient Sample. Chest. 2009;136:983–90.
15. Morita K, Kawashima Y, Irita K, Iwao Y, Seo N, Tsuzaki K. Perioperative mortality and morbidity in the year 2000 in 520 certified training hospitals of Japanese Society of Anesthesiologists with a special reference to age: report of Japanese Society of Anesthesiologists Committee on Operating Room Safety. Masui (Jpn J Anesthesiol). 2002;51:1285–1296 (in Japanese with English abstract).
16. Iwao Y, Kawashima Y, Seo N, Kobayashi T, Goto Y, Morita K, Irita K, Tsuzaki K, Dohi S, Tanaka Y, Shiraishi Y, Tozaki Y, Nakao Y, Japan Society of Anesthesiologist Committee on Operating Room Safety. Perioperative mortality and morbidity for the year 2000 in 532 Japanese Society of Anesthesiologists certified training hospitals with a special reference to surgical sites: report of the Japan Society of Anesthesiologists Committee on Operating Room Safety. Masui (Jpn J Anesthesiol). 2002;51:791–800 (in Japanese with English abstract).
17. McGavock H, Webb CH, Johnston GD, Milligan E. Market penetration of new drugs in one United Kingdom region: implications for general practitioners and administrators. Br Med J. 1993;307:1118–20.
18. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA. 2003;290:2455–63.
19. Liu S, Carpenter RL, Neal JM. Epidural anesthesia and analgesia. Their role in postoperative outcome. Anesthesiology. 1995;82:1474–506.
20. Elliott P, O'Hare R, Bill KM, Phillips AS, Gibson FM, Mirakhur RK. Severe cardiovascular depression with remifentanil. Anesth Analg. 2000;91:58–61.
21. Pedersen T. Evidence-based anaesthesia and health economics. Best Pract Res Clin Anaesthesiol. 2006;20:347–60.
22. Scott LJ, Perry CM. Spotlight on remifentanil for general anaesthesia. CNS Drugs. 2005;19:1069–74.
23. Nomura H, Nakayama T. The Japanese healthcare system: the issue is to solve the "tragedy of the commons" without making another. Br Med J. 2005;331:648–9.

24. Stachnik J. Inhaled anesthetic agents. Am J Health Syst Pharm. 2006;63:623–34.
25. Apfel CC, Korttila K, Abdalla M, Kerger H, Turan A, Vedder I, Zernak C, Danner K, Jokela R, Pocock SJ, Trenkler S, Kredel M, Biedler A, Sessler DI, Roewer N, IMPACT Investigators. A factorial trial of six interventions for the prevention of postoperative nausea and vomiting. N Engl J Med. 2004;350:2441–51.
26. De Hert SG, Turani F, Mathur S, Stowe DF. Cardioprotection with volatile anesthetics: mechanisms and clinical implications. Anesth Analg. 2005;100:1584–93.
27. von Dossow V, Luetz A, Haas A, Sawitzki B, Wernecke KD, Volk HD, Spies CD. Effects of remifentanil and fentanyl on the cell-mediated immune response in patients undergoing elective coronary artery bypass graft surgery. J Int Med Res. 2008;36:1235–47.
28. Fearon KC, Ljungqvist O, Von Meyenfeldt M, Revhaug A, Dejong CH, Lassen K, Nygren J, Hausel J, Soop M, Andersen J, Kehlet H. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. Clin Nutr. 2005;24:466–7.

【テーマ①】

痛みの質的評価



1：東京大学医学部附属病院麻酔科・痛みセンター，2：東京大学医学部附属病院整形外科・脊椎外科
住谷昌彦[1)]，竹下克志[2)]，原　慶宏[2)]，山田芳嗣[1)]

はじめに

「痛み」(Pain)は“組織の実質的ないし潜在的な傷害と関連した，あるいはこのような傷害と関連して述べられる不快な感覚的かつ情動的体験”と国際疼痛学会(International Association for the Study of Pain；IASP)によって定義されているとおり，主観的な身体経験である．このような主観的な経験を臨床的に，なおかつ科学的に正しく扱うことを目的として，疼痛の量的評価とともに質的評価も行われてきた．

疼痛の量的評価としては，疼痛強度を数値化するvisual analogue scale(VAS)やnumerical rating scale(NRS)が主に用いられている．このような量的評価尺度は重症度評価や治療効果の判定を簡便に行えるが，痛みという主観的身体経験を表すためには不十分である．われわれが日常的に経験する痛みを例に挙げると，皮膚を鋏で切ったときの痛みと筋肉が攣ったときの痛みが同じ強さであったとしても疼痛の性質は大きく異なり，さらに，これらの疼痛に対する生体反応は皮膚に対する疼痛刺激では交感神経系が興奮(血圧や脈拍が上昇)する一方で，筋骨格系に対する疼痛刺激では交感神経系がむしろ抑制される傾向にあることが知られ[1)]，疼痛の量的評価(強度)だけでなく疼痛の質的評価も重要である．

疼痛の質的評価方法では，マギル疼痛質問票(McGill pain questionnaire)が最も有名で国際的にも非常に広く用いられている[2)]．マギル疼痛質問票には78個の痛みの性質を表す単語(例：ズキズキ，切り裂かれるような，灼かれるような，圧迫されるような，など)が列挙されており，それぞれの単語が20の特徴(例：空間的，時間的，温度的，など)に分類され，さらにそれぞれの特徴を4つの要因(感覚的，情動的，評価的，その他)に大別することができる．疼痛は不快な感覚的かつ情動的身体経験であるため，感覚面のみならず情動面についても質的に評価できるマギル疼痛質問票はその臨床的有用性が非常に高く，さらに，78単語から選択された単語の合計数や単語に付与された点数の合計得点から，疼痛の質的評価だけでなく量的評価も網羅的に行うことができる．

痛みの性質を利用した疼痛疾患の診断

がんが内臓に浸潤したがん疼痛患者の多くは“重苦しい”や“ズキズキした”痛みの性質を訴える一方，肺がんによる腕神経叢浸潤の患者は“電気が走るような”や“ビリビリした”痛みの性質を訴えることが多い．このように疼痛の発症機序に応じて痛みの性質が異なることが示唆されており，マギル疼痛質問票を用

いて疼痛疾患の病態解明(分類)が行われている[3]．がん疼痛以外にも，虚血性疼痛の病態解明や侵害情報を伝達する神経線維(Aδ線維，C線維)ごとの障害をマギル疼痛質問票で明らかにする試み[4]などが報告されている．

このような，痛みの性質から疼痛疾患の病態を推測する方法論の可能性から，われわれは疼痛発症機序がいまだ不明瞭なcomplex regional pain syndrome (CRPS) type I患者の疼痛が，炎症性疼痛であるか神経障害性疼痛であるかを判別することを試みたが，疼痛の性質からは明確な結果を得ることはできなかった．このことから，CRPS患者の発症機序が炎症性疼痛と神経障害性疼痛の両機序を併せもつ混合性疼痛機序に起因することが考えられる．

痛みの性質を利用した神経障害性疼痛のスクリーニング

さまざまな疼痛疾患のなかでも，神経障害性疼痛の性質は詳細に調査されており，マギル疼痛質問票の78単語のうち，神経障害性疼痛患者がしばしば訴える疼痛の性質(いいかえると，疼痛専門医が神経障害性疼痛と診断した患者からしばしば聴取される疼痛の性質)が明らかにされている．マギル疼痛質問票では78単語についての煩雑な調査を必要とするため，より簡便に神経障害性疼痛に特徴的な5～7単語だけを調査する神経障害性疼痛スクリーニング質問票が各国で開発されており，本邦独自のスクリーニング質問票も存在する[5]．いずれのスクリーニング質問票も内容は類似しており，神経障害性疼痛に特徴的な痛みの性質が列挙されており，それらを点数化して神経障害性疼痛であるか否かをスクリーニングできる．臨床現場では，患者の訴える痛みを神経障害性疼痛か否か(つまり体性感覚系の損傷あるいは疾患が存在するか否か)の二者択一で判断するのは時として困難であるが，スクリーニングツールでは神経障害性疼痛の可能性がきわめて高い，可能性が高い，要素が含まれている，可能性がほとんどないという臨床に即した段階的なスクリーニングを行うことができるため，神経障害性疼痛(体性感覚系の障害)の要素を含む可能性を議論することは比較的容易であり，続く治療方針の決定に対する有用性が期待できる．実際，ドイツのグループが開発したPainDETECT(図1)はこれまで筋骨格系の機械的刺激や炎症がその主病態とされてきた慢性腰痛にも神経障害性疼痛の要素が含まれていることを明確に示し[6]，神経障害性疼痛に対する治療薬の導入が容易に図れるようになった．

痛みの性質に応じた神経障害性疼痛の重症度評価と治療効果判定

これまでわれわれは，四肢切断後の幻肢痛や脊髄損傷後疼痛患者に対して鏡を用いた神経リハビリテーション治療(鏡療法)を行い，“ナイフで刺されているような”，“電気ショックのような”など，皮膚表面で感じているような痛みの性質には鏡療法は無効である一方，“関節を捻られるような”，“筋肉を絞られるような”など，深部組織で感じているような痛みの性質にはきわめて有効であることを明らかにした[7]．痛みの性質の違いはその病態に起因しているため，痛みの性質に応じて治療効果が異なることは妥当であると考えられる．このような観点から，神経障害性疼痛患者に特徴的な痛みの性質10個それぞれについての重症度を点数化し，それらを合計することによって総合的な重症度を評価する神経障害性疼痛に特化した質問票(neuropathic pain symptom inventory：NPSI)も開発されている(図2)[8]．われわれは，自己免疫性脊髄炎による神経障害性疼痛をNPSIで評価すると疼痛の性質によって治療効果が異なることを経験している[9]．このように，NPSIを用いて神経障害性疼痛治療の知見を蓄積することによって，痛みの性質に応じて特異的に有効な治療方法の発見や，神経障害性疼痛の病態解明に繋がる可能性があると考えられる．

painDETECT

痛みの質問票

日付		名前	

いま現在のあなたの痛みは 10 点満点でどの程度ですか？

0 1 2 3 4 5 6 7 8 9 10
なし 最大

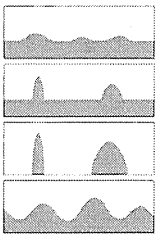
過去 4 年間で最も激しい痛みはどの程度でしたか.

0 1 2 3 4 5 6 7 8 9 10
なし 最大

過去 4 年間の痛みの平均レベルはどの程度ですか.

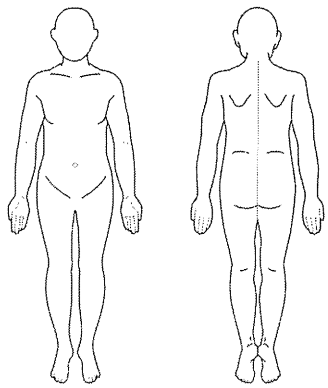
0 1 2 3 4 5 6 7 8 9 10
なし 最大

あなたの痛みの経過を表す図として，どれが最もあてはまりますか？
□印にチェックを付けてください.



- 持続的な痛みで，痛みの程度に若干の変動がある □
- 持続的な痛みで，ときどき痛みの発作がある □
- 痛みがときどき発作的に強まり，それ以外のときは痛みがない □
- 痛みがときどき発作的に強まり，それ以外のときも痛みがある □

痛みのある場所を図に示してください.



痛みはほかの部位にも広がりますか？
□はい □いいえ
はいと答えた方は，その場所と広がり方も書いてください.

痛みのある部位では，焼けるような痛み(例：ヒリヒリするような痛み)がありますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

ピリピリしたり，チクチク刺したりするような感じ(蟻が歩いているような，電気が流れているような感じ)がありますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

痛みがある部位を軽く触れられる(衣服や毛布が触れる)だけでも痛いですか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

電気ショックのような急激な痛みの発作が起きることはありますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

冷たいものや熱いもの(お風呂のお湯など)によって痛みが起きますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

痛みのある場所に，しびれを感じますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

痛みがある部位を，少しの力(指で押す程度)で押しても痛みが起きますか？
一度もない□ ほとんどない□ 少しある□ ある程度ある□ 激しい□ 非常に激しい□

一度もない	ほとんどない	少しある	ある程度ある	激しい	非常に激しい
□×0=0	□×1=□	□×2=□□	□×3=□□	□×4=□□	□×5=□□

総数 □□ (最大 35 点)

図 1 PainDETECT 日本語版

painDETECT

痛みの質問票のスコア

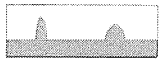
日付		名前	

「痛みの質問票」の総スコアをここに書き写してください．

総計 □□

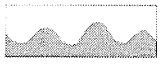
該当する痛みの経過のパターンと痛みの広がりの有無に応じて，以下の数値の合計を出し，それを総計スコアに加算して最終スコアを出してください．

持続的な痛みで，痛みの程度に若干の変動がある　0

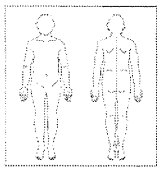


持続的な痛みで，ときどき痛みの発作がある　−1　（これに印をつけた場合）

痛みがときどき発作的に強まり，それ以外のときは痛みがない　+1　（これに印をつけた場合）



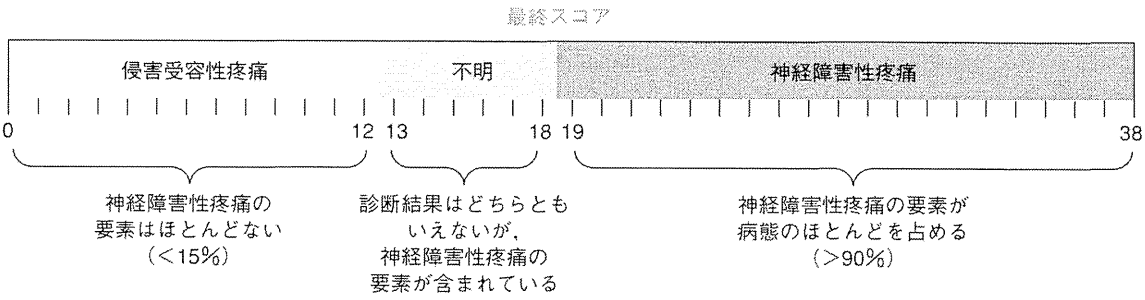
痛みがときどき発作的に強まり，それ以外のときも痛みがある　+1　（これに印をつけた場合）



痛みの広がり　+2　（はいの場合）

最終スコア □□

スクリーニング結果



このシートは医師の診断に代わるものではありません．
神経障害性疼痛の要素についてのスクリーニングに使用してください．

Curr Med Res Opin 2006；22：1911-20 を改変
責任監訳：東京大学医学部附属病院麻酔科痛みセンター　住谷昌彦

PainDETECT は慢性腰痛症のうち神経障害性疼痛（神経根障害による腰痛）をスクリーニングするために開発され，ドイツでその妥当性・有用性が検証されたものである．ここに示した PainDETECT 日本語版は筆者が和訳後，日英２言語使用の一般人が英訳して和訳に不適切な箇所がないかを検証したものである．PainDETECT 日本語版の妥当性・有用性は検証中である．　（文献６から改変して引用した図を文献 10 から許可を得て掲載）

神経障害性疼痛重症度評価ツール(neuropathic pain symptom inventory)日本語版

日　付：
名　前：
性　別：男　　女
年　齢：

あなたが感じている神経系の障害によって引き起こされる疼痛にはいくつかのタイプがあることが知られています．“自発痛”，すなわち疼痛刺激がないにもかかわらず起こる痛みを感じていて，そしてその痛みはずっと続いているか，あるいは発作的に痛みが起こっていると思います．さらに，痛みを感じている場所の皮膚表面をこすられたり押されたり，冷たいもので触られたりすると痛みが生じたり，自発痛が強くなる可能性があります．
この質問票は，あなたが感じているさまざまなタイプの疼痛に対して，あなたの主治医がより的確に評価し，よりよい治療へと繋げることを目的としています．

あなたが感じている**“自発痛”(刺激がなくても感じる痛みのこと)**について教えてください．
以下の質問で，あなたが過去24時間に感じた“自発痛”の平均的な強さを最も的確に表す数字を選んでください(下記の数字のうち，1つだけ○で囲んでください)．
0は，下記の質問にあるような自発痛を感じていなかったことを意味します．

1. 焼けつくような自発痛がありますか？
(ない) 0　1　2　3　4　5　6　7　8　9　10 (想像しうる最も強い焼けつくような痛み)

2. 絞り上げられるような自発痛がありますか？
(ない) 0　1　2　3　4　5　6　7　8　9　10 (想像しうる最も強い絞り上げられるような痛み)

3. 圧迫されるような自発痛がありますか？
(ない) 0　1　2　3　4　5　6　7　8　9　10 (想像しうる最も強い圧迫されるような痛み)

4. 過去24時間のうち，どれくらいの時間“自発痛”がありましたか？
最も適切なものを下記のうちから1つ選んでください．
・12時間以上，持続的にあった　＿
・8～12時間の間　＿
・4～7時間の間　＿
・1～3時間の間　＿
・1時間以内　＿

ここからの質問は，あなたが感じている**“発作痛(発作的に起こる痛みのこと)”**について教えてください．
以下の質問で，あなたが過去24時間に感じた“発作痛”の平均的な強さを最も的確に表す数字を選んでください(下記の数字のうち，1つだけ○で囲んでください)．
0は，下記の質問にあるような発作痛を感じていなかったことを意味します．

(右頁につづく)

図2　神経障害性疼痛重症度評価ツール(neuropathic pain symptom inventory：NPSI)日本語版

5. 電気ショックのような発作痛がありますか？
（ない）0　1　2　3　4　5　6　7　8　9　10（想像しうる最も強い電気ショックのような痛み）

6. 刃物で刺されるような発作痛がありますか？
（ない）0　1　2　3　4　5　6　7　8　9　10（想像しうる最も強い刺されるような痛み）

7. 過去24時間のうち，どれくらいの回数，“発作痛”がありましたか？最も適切なものを下記のうちから1つ選んでください．
- 20回以上 ＿
- 11～20回 ＿
- 6～10回 ＿
- 1～5回 ＿
- 0回（発作痛はなかった） ＿

ここからは，痛みを感じている皮膚表面をこすられたり押されたり，あるいは冷たいもので触られたりすると痛みが起こったり，自発痛が強くなる**“誘発痛”**について質問します．
以下の質問で，あなたが過去24時間に感じた“誘発痛”の平均的な強さを最も的確に表す数字を選んでください（下記の数字のうち，ひとつだけ○で囲んでください）．
0は，下記の質問にあるような誘発痛を感じていなかったことを意味します．

8. 痛みを感じている場所の皮膚をこすられると疼痛が起こったり，自発痛が強くなりますか？
（ない）0　1　2　3　4　5　6　7　8　9　10（想像しうる最も強い痛みが誘発される）

9. 痛みを感じている場所の皮膚を押されると疼痛が起こったり，自発痛が強くなりますか？
（ない）0　1　2　3　4　5　6　7　8　9　10（想像しうる最も強い痛みが誘発される）

10. 痛みを感じている場所を冷たいもので触れると疼痛が起こったり，自発痛が強くなりますか？
（ない）0　1　2　3　4　5　6　7　8　9　10（想像しうる最も強い痛みが誘発される）

ここからは，痛みを感じている場所に痛み以外の異常な感覚があるかについての質問です．
以下の質問で，あなたが過去24時間に感じた異常感覚の平均的な強さを最も的確に表す数字を選んでください（下記の数字のうち，1つだけ○で囲んでください）．
0は，下記の質問にあるような異常感覚を感じていなかったことを意味します．

11. 針でチクチクとつつかれるような感覚はありますか？
（ない）0　1　2　3　4　5　6　7　8　9　10（想像しうる最も強いチクチクとした感覚）

12. ビリビリとした痺れたような感覚はありますか？
（ない）0　1　2　3　4　5　6　7　8　9　10（想像しうる最も強い痺れ感覚）

（Pain 108：248-257，2004より和訳）

10個の疼痛の性質を自発痛，発作痛，誘発痛，異常感覚の要素に分類し，それぞれについて点数化することによって痛みの性質と要素に応じた重症度評価ができる．NPSI日本語版は筆者が和訳後，日英2言語使用の一般人が英訳して和訳に不適切な箇所がないかを検証したものである．NPSI日本語版の妥当性・有用性は検証中である．
（文献8から改変して引用した図を文献10から許可を得て掲載）

おわりに

痛みは身体の傷害に関連した不快な感覚的経験であると同時に情動的な経験である．患者の訴える疼痛は情動的因子によって大きく影響を受ける．このような情動的因子の存在を無視しては，疼痛に対する治療は成功しない．たとえば，健常者が骨折や捻挫すれば「○○関節の周囲がズキズキと痛み，○○関節を運動したり過重するとズキーンと痛みが増強する」というような表現をすることが一般的である．その一方で，情動的因子の関与が大きい患者の痛みの訴えは「○○関節がなんとなく痛く，過重とか関係なく常に痛む」とか「腰が痛いのだけれども…，とにかく痛い(痛みの性質を答えられない)」というような不確定な表現が用いられていることをしばしば経験する．つまり，痛みの性質の具体性が低い際には，痛みの訴えに身体的な傷害の要素(身体感覚的因子)が少なく情動面の要素が大きいことを示唆し，それに応じて治療戦略を変更することが必要であると考えている．このように痛みを量的だけでなく質的にも評価することは，慢性疼痛患者にとって非常に有益であると考えている．

References

1) Burton AR, Birznieks I, Bolton PS et al：*J Physiol* **587**：183-193, 2009
2) Melzack R：*Pain* **1**：277-299, 1975
3) Wilkie DJ, Huang HY, Reilly N, Cain KC：*J Pain Sympt Manage* **22**：899-910, 2001
4) Beissner F, Brandau A, Henke C et al：*Plos One* **23**：e12944, 2010
5) 小川節郎 編：神経障害性疼痛診療ガイドブック．南山堂，東京，2010，付録
6) Freynhagen R, Baron R, Gockel U et al：*Curr Med Res Opin* **22**：1911-1920, 2006
7) Sumitani M, Miyauchi S, McCabe CS et al：*Rheumatology* **47**：1038-1043, 2008
8) Bouhassira D, Attal N, Fermanian J et al：*Pain* **108**：248-257, 2004
9) 平井絢子，住谷昌彦，富岡俊也ほか：日臨麻会誌(in press)
10) 住谷昌彦，山田芳嗣(エルゼビア・ジャパン社 編)：痛みのマネジメント―痛みの分類と神経障害性疼痛の定義・診断・治療について―．Excerpta Medica, 2010, pp.1-28

慢性疼痛症候群の標準的治療

住谷昌彦[*,**]　山田芳嗣[*]
Masahiko SUMITANI, MD, PhD　Yoshitsugu YAMADA, MD, PhD

1. 痛みは身体面だけの問題ではなく，また心理面だけの問題ではない．痛みは常に身体的情動的問題であることを認識しなければいけない．
2. 慢性疼痛治療の第一歩は，慢性疼痛患者の問題点を生物心理社会的モデルに基づいて多面的に評価することである．
3. 慢性疼痛症候群に対する標準的治療は，複数の異なる専門領域を持つ医療職者が連携して集学的にアプローチすることである．

はじめに

「痛み」は，"An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms such damage（組織の実質的ないしは潜在的な傷害と関連した，あるいはこのような傷害と関連して述べられる不快な感覚的，情動体験）" と定義[1]されている通り，身体のみ，あるいは心理のみの問題ではなく，身体要因と心理要因は常に共存し，身体的な痛みの認知は心理因子によってさまざまに影響を受ける．よって，「痛みは身体だけの問題だから治療も身体に対してのみ行う」あるいは「心理療法は心理的な問題を抱える疼痛患者に対してのみ有効である」などと考えるのは誤りである．さらに，慢性疼痛患者の多くは，痛み以外に睡眠障害や日中の眠気，意欲の低下，不安，抑うつ傾向，食欲不振，日常生活の活動度の低下など非常に多くの activities of daily living（ADL）や quality of life（QOL）上の問題を抱えている[2]．

*東京大学医学部附属病院麻酔科・痛みセンター
（〒113-8655 東京都文京区本郷 7-3-1）
**大阪大学大学院医学系研究科生体統御医学麻酔集中治療医学講座

慢性疼痛疾患の中でも特に重症度が高いことが知られている神経障害性疼痛患者の QOL を，ヨーロッパで標準的に用いられている QOL 尺度の EQ-5D で評価すると，平均的な神経障害性疼痛患者の EQ-5D は 0.4～0.6，重症神経障害性疼痛では 0.2 前後とされる[3]（表）．EQ-5D は 0 を死亡した状態，1 を健康な状態とし 0～1 の間の数字で QOL を評価する尺度で，EQ-5D＝0.4～0.5 はがん終末期患者が日常生活を床上で過ごしている QOL と同程度であり，また，EQ-5D＝0.2 は心筋梗塞患者が絶対安静状態で生活している QOL と同程度である．このように慢性疼痛患者の QOL 障害は著しく，慢性疼痛自体が治療対象としての "疾患" であることが認識されなければならない．

本稿では，疾患として認識される慢性疼痛症候群に対する標準的治療について概説する．

慢性疼痛症候群に対する標準的治療とは？—患者評価の視点から

慢性疼痛症候群に対する治療を実践し成功させるためには，患者の問題点を評価し患者にとって真に必要な治療を厳選することが必須である．アメリカ麻酔科学会が提唱する慢性疼痛治療指針[4]でも患者評価（patient evaluation）として，現病歴とこれまでの治療歴とその反応性，理学所見