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Drug-induced Skin Reactions

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Conventionally, the development of new drugs has depended on the use of active ingredients of natural products or the chemical synthesis of artificial compounds. This process has mainly relied on fortuitous discoveries and the empirical experience in past drug development. Our pharmaceutical arsenal is based on the historic legacy of human wisdom over thousands of years.

On the other hand, the rapid progress of genomic study has recently been causing drastic changes in the process of drug discovery. The achievements in genome decoding have elucidated the involvement of genes in various diseases, such as cancer, diabetes, and hypertension. A new strategy called genomic drug discovery, which attempts to use genomic information for the logical and efficient development of new drugs, has been promoted under national projects with university-industry cooperation. The achievements in this direction are expected to provide drugs with better efficacy and less adverse effects, as well as to shorten the time required for the development of new drugs.

Whichever of the various strategies may be used, more and more new drugs will continue to be developed and introduced to the healthcare market. What we need to recognize is the fact that no drugs are free from adverse events. In an aging society, it is now common that aged patients are taking multiple drugs. Frequent coexistence of multiple diseases inevitably leads to the use of multiple drugs. Although this may be an unavoidable choice in some cases, it is well known that the combined use of multiple drugs increases the occurrence of adverse events. Serious adverse drug reactions known to occur in such situations include fulminant hepatitis and agranulocytosis, as well as skin reactions in the form of severe drug eruptions such as Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN). Physicians are notified of the occurrence of serious adverse drug reactions through the issuance of important safety information (Dear Doctor letters). While the system for the feedback of such information to clinical practice has been established, a problem remains regarding the insufficient awareness on the side of physicians receiving it.

Skin reactions, or drug eruptions, represent an important class of adverse drug reactions, because they are easily recognized. Drug eruptions are eruptions caused by the systemic administration (injection, oral use, etc.) of drugs. The reactions occurring in a small minority of treated patients through allergic mechanisms are important. The term drug eruption usually refers to this allergic condition, which develops only in the individuals possessing the cells or antibodies that react to the relevant drug (sensitized to the drug). Because it usually takes 1 or 2 weeks before an immunological condition reacting to the drug is established after the beginning of drug use, symptoms are generally considered to develop after this period. However, some drugs may cause symptoms after a long period of use. When we observe skin reactions, we therefore should not rule out the possibility of drug reactions solely based on the length of drug use or the type of drug administered.

A recent topic attracting much attention is the discovery of a condition called drug-induced hypersensitivity syndrome (DIHS), which is a type of severe drug eruption considered to have close association with a viral activity. Because severe eruptions of this type do not improve after the interruption of the causative drug and may aggravate quickly, prompt initiation of appropriate treatment is essential. Finally, we need to reemphasize the fact that all drugs bear the possibility of causing drug eruptions. Recognizing this fact is important from the standpoint of risk management.

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Skin Reactions to 3-month Depot Type of Luteinizing Hormone-Releasing Hormone Agonist Therapy

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Abstract

Objective Recently, skin reactions to luteinizing hormone-releasing hormone (LH-RH) agonist therapy were reported after the 3-month depot type was released. We evaluate skin reactions to the 3-month depot type of LH-RH agonist by questionnaires obtained from patients with prostate cancer who had been given a subcutaneous injection of LH-RH agonist.

Materials and Methods A questionnaire regarding skin reactions to the subcutaneous injection of LH-RH agonist was given to 64 outpatients with prostate cancer from 6th October 2004 to 31st March 2005, including 31 with goserelin acetate (Zoladex® LA 10.8 mg depot: Group ZLA) and 33 leupropreline acetate 11.25 mg (Leuplin® SR 11.25 mg depot: Group LSR), and the results were analyzed. The content of the questionnaire was as follows: with or without skin reactions; pain, nodule, subcutaneous bleeding and other reactions; anxiety or not; how long the reactions continued.

Results Five in Group ZLA (16.1%) and 8 in Group LSR (24.2%) had skin reactions. In Group ZLA, one patient had nodule, two patients complained of pain, and subcutaneous bleeding occurred in two patients. The nodule resolved in a week. In Group LSR, six patients had nodule and two patients complained of pain, but there were no patients with subcutaneous bleeding. Four of six nodules disappeared in a week, but other patients had nodule over 3 months.

Conclusions There were few cases of severe skin reaction to LH-RH agonist. However, we need to be concerned about skin reaction after the subcutaneous injection of LH-RH agonists based on this data.

Key words Skin reactions, LH-RH agonist, Prostate cancer

Introduction

Hormone therapy for prostate cancer using luteinizing hormone-releasing hormone (LH-RH) agonists has conventionally been conducted selecting 1-month (4-week) depot preparations of goserelin acetate (Zoladex®) or leuprorelin acetate (Leuplin®) in the majority of cases. Both of these agents have adverse effects on the circulatory system, the endocrine system, the liver, the kidneys, and blood. Skin reaction at the site of injection (rash, reddening, nodule, pain, subcutaneous hemorrhage) is caused by these agents in a comparable frequency ranging from 0.16 to 3.41% and from 0.16 to 5.06%, respectively.

The 3-month depot formulations that have recently appeared have reduced the physical and economic burden on the patient. On the other hand, skin reaction to these drugs has occasionally been reported, reflecting increased use in

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Japan. Although we have not encountered severe cases of skin reaction requiring surgical treatment or switching to different regimens in our clinic, there have been few studies comparing the 3-month depot formulations in terms of skin reaction, and we considered it necessary to examine the occurrence of skin lesions among patients treated with 3-month formulations. We conducted a questionnaire survey for this purpose and analyzed the results as reported here.

Subjects and Methods

The subjects were 69 patients who received 3-month depot LH-RH agonists for the treatment of prostate cancer at the outpatient clinic of the Department of Urology, Osaka University Hospital, from October 3, 2004 to March 31, 2005. The 69 patients included 31 receiving Zoladex LA® (ZLA group), 33 receiving Leuplin® (LSR group), and 5 receiving unknown drugs. The questionnaire contained questions about number of doses, the presence or absence of skin reaction at the site of administration, and skin symptoms of lumps, pain, internal bleeding, and other. The patients were asked how concerned they were about how long each of these symptoms persisted. To save patients' time and trouble, the questions were printed on a sheet of A4-size paper so that they could be answered by circling the appropriate choices except for the description of "other" (Table 1).

Results

The analysis covered the 64 patients excluding the 5 receiving unknown drugs (Table 2). The number of doses received by the time of the questionnaire was 1 in 2 cases, 2 in 3 cases, and 3 or more in 26 cases in the ZLA group, and 1 in 0 cases, 2 in 4 cases, and 3 or more in 29 cases in the LSR group. Of these patients, 5 in the ZLA group and 8 in the LSR group answered that they had skin reaction, and all of these patients had received 3 or more doses. As for the breakdown of skin reactions, lumps were reported by 1 patient in the ZLA group (3.2%) and 6 in the LSR group (18.2%). While this symptom occurred more frequently in the LSR group, the difference was not significant ($P = 0.0554$). The 1 patient in the ZLA group described this symptom as "hardly worrying," and it persisted for about a week. Among the patients in the LSR group, 1 answered "hardly worrying," 2 "occasionally worrying," and 1 "always worrying," and 2 omitted this question. In this group, this symptom persisted for "2 or 3 days or less" in 1 case, "about a week" in 3 cases, and "3 months or more" in 2 cases.

Pain in the injected site was experienced by 2 patients in each group. The severity of this symptom was described as "occasionally worrying" by 2 patients receiving ZLA and "hardly worrying" by 1 patient receiving LSR, and 1 patient did not answer.

Answers concerning internal bleeding at the site of injection were "rarely concerned" and "occasionally concerned" in 1 each of the patients in the ZLA group, while none in the LSR group reported this symptom.

No patients provided answers concerning other symptoms.

Discussion

Only 3 cases of severe skin reaction related to the use of depot-type LH-RH agonists in the patients with prostate cancer were reported in Japan in the period up to 2003. However, 12 cases were reported in 2004 and 2005,[1–9] and all of these cases were associated with 3-month depot (Table 3). Nine of these cases developed shortly after switching from 1-month depot to 3-month depot, a case developed after switching from 1-month depot of a different agent, and the remaining 2 cases developed in patients who received 3-month depot from the beginning. All of these reports were associated with the use of leuprorelin acetate. The only report of skin reaction to goserelin acetate is an article of Oida et al.[9] describing experience of a similar skin reaction to the 3-depot form of goserelin acetate. In fact, the post-marketing studies conducted by the manufacturers of these agents showed that skin reaction involving nodules occurred in 3.8% of patients receiving leuprorelin acetate, while goserelin acetate caused skin reaction involving nodules, pain, reddening, hematoma, or blood spots in only 0.31%.

The possible causes of skin reaction suggested so far include a local reaction to base materials and additives, infection at the site of injection, and mechanical stimulation at the site of injection. Previous reports tend to consider that the adverse reactions are attributable to the reaction to the

Table 1 Questions Concerning Injection

Please circle the drug you are receiving

→ LA (10.8 mg) • SR (11.25 mg)

How many times have you received this injection, including this time?	Once	Twice	3 times or more

Please circle the number that best applies to you.

(I) Have you felt pain or discomfort at the injected site after injection?

① Yes ② No ⇨ No more questions. Thank you for your cooperation.

⇩

Please answer the following if your answer to Question (I) was ① "Yes":

(II) What symptoms have you had? (Please circle all applicable items.)

① Lump (swelling) at the injected site
② Pain at the injected site
③ Bleeding (including internal bleeding) at the injected site
④ Other ( )

Please answer the following if your answer to Question (II) was ① "Lump (swelling) at the injected site":

How severe is the symptom? (Please circle the most appropriate number.)

0	1	2	3	4	5
None	Hardly worrying	Occasionally worrying	Always worrying	Very hard to bear	Affecting daily living

How long does the symptom persist?

① 2 to 3 days or less ② About a week ③ About 2 to 3 weeks ④ About a month
⑤ About 2 months ⑥ 3 months or more ⑦ Other ( )

Please answer the following if your answer to Question (II) was ② "Pain at the injected site":

How severe is the symptom? (Please circle the most appropriate number.)

0	1	2	3	4	5
None	Hardly worrying	Occasionally worrying	Always worrying	Very hard to bear	Affecting daily living

How long does the symptom persist?

① 2 to 3 days or less ② About a week ③ About 2 to 3 weeks ④ About a month
⑤ About 2 months ⑥ 3 months or more ⑦ Other ( )

Please answer the following if your answer to Question (II) was ③ "Bleeding (including internal bleeding) at the injected site":

How severe is the symptom? (Please circle the most appropriate number.)

0	1	2	3	4	5
None	Hardly worrying	Occasionally worrying	Always worrying	Very hard to bear	Affecting daily living

How long does the symptom persist?

① 2 to 3 days or less ② About a week ③ About 2 to 3 weeks ④ About a month
⑤ About 2 months ⑥ 3 months or more ⑦ Other ( )

Thank you for your cooperation.

Table 2 Reported cases of skin reaction to LH-RH agonists in patients with prostate cancer in Japan

Drug	Dose at obset (Previous→ New drug)	Number of doses before onset	Skin symptoms*	Treatment	History of allergy	Reported by	Year of report	Journal
Leuprorelin acetate	3.75	3	Subcutaneous indulation	Observation	None	Muya et al.	1999	Japanese Journal of Clinical Dermatology
Leuprorelin acetate	3.75	12	Subcutaneous indulation	Observation	None			
Leuprorelin acetate	3.75	62	Erythema and indulation with ulcer	Observation	None	Hirashima et al.	2001	The Nishinihon Journal of Dermatology
Leuprorelin acetate	3.75→11.25	1	Erythema and indulation with ulcer	Oral antibiotic, local injection of steroid	None	Mizoguchi et al.	2004	Japanese Journal of Dermatology
Leuprorelin acetate	3.75→11.25	2	Indulation with heat sensation and ulcer	Debridement, topical steroid	Only to kumquat	Tachibana et al.	2004	Hinyoukika Kiyo
Leuprorelin acetate	3.75→11.25	1	Subcutaneous nodule	Natural remission	None			
Leuprorelin acetate	3.75→11.25	2	Subcutaneous nodule	Surgical removal	None	Yasukawa	2005	BJD
Leuprorelin acetate	11.25	4	Subcutaneous nodule	Observation	None			
Leuprorelin acetate	Zoladex 3.6→11.25	3	Indulation with pus and ulcer	Surgical removal	None	Takahashi. et al.	2005	Rinsho Derma
Leuprorelin acetate	11.25	3	Subcutaneous nodule with ulcer	Oral and topical steroid	None	Nagata et al.	2005	Rinsho Derma
Leuprorelin acetate	3.75→11.25	1	Indulation with reddening and ulcer	Oral and topical steroid	None			
Leuprorelin acetate	3.75→11.25	3	Subcutaneous nodule	Observation	None			
Leuprorelin acetate	3.75→11.25	3	Subcutaneous nodule with pus	Course unknown	None	Tanaka et al.	2005	Rinsho Derma
Leuprorelin acetate	3.75→11.25	4	Subcutaneous nodule with reddening	Observation	None			
Leuprorelin acetate	3.75→11.25	1–3	Indulation, reddening, and spontaneous pain	Surgical removal	None	Taneda et al.	2005	Hinyoukika Kiyo

* Histopathology was granuloma in all cases.

Table 3 Results of Questionnaire

	<Pts on Zoladex LA>		<Pts on Leuplin>		<Pts on unknown drug>	
	Number	Skin reaction	Number	Skin reaction	Number	Skin reaction
Dosed once	2 pts	0	0 pts	0	0 pts	0
Dosed twice	3 pts	0	4 pts	0	0 pts	0
3 times or more	26 pts	5	29 pts	8	5 pts	1
Total	31 pts	5	33 pts	8	5 pts	1

<ZLA group>

31 pts answered	Number	Frequency	Degree					
			Hardly worrying	Occasionally worriying	Always worrying	Very hard to bear	Affecting daily living	Omitted
Lump	1	3.2%	1					
Pain at injected site	2	6.5%		2				
Bleeding at injected site (incl. internal bleeding)	2	6.5%	1	1				
Other	0	0%						
Total	5	16.1%	2	3	0	0	0	0

	Number	Duration						
		≤2 to 3 days	About a week	About 2–3 wk	About a month	About 2 months	≥3 months	Omitted
Lump	1		1					
Pain at injected site	2		2					
Bleeding at injected site (incl. internal bleeding)	2	1		1				
Other	0							
Total	5	1	3	1	0	0	0	0

<LSR group>

33 pts answered	Number	Frequency	Degree					
			Hardly worrying	Occasionally worriying	Always worrying	Very hard to bear	Affecting daily living	Omitted
Lump	6	18.2%	1	2	1			2
Pain at injected site	2	6.1%	1					1
Bleeding at injected site (incl. internal bleeding)	0	0%						
Other	0	0%						
Total	8	24.2%	2	2	1	0	0	3

	Number	Duration						
		≤2 to 3 days	About a week	About 2–3 wk	About a month	About 2 months	≥3 months	Omitted
Lump	6	1	3				2	
Pain at injected site	2	1	1					
Bleeding at injected site (incl. internal bleeding)	0							
Other	0							
Total	8	2	4	0	0	0	2	0

microcapsules used for achieving the stable controlled release of leuprorelin acetate. The 1-month depot and 3-month depot forms of leuprorelin acetate contain different base materials: The former uses poly-lactic-co-glycolic acid (PLGA), and the latter uses poly-lactic acid (PLA) lacking the glycolic acid component. Because PLGA is used as an additive to all forms of goserelin acetate, skin reaction to microcapsules using PLA as the base material is considered the most probable cause of adverse reaction. In addition, Mizoguchi et al.[3] suggested the possibility of allergic reaction to the active agent itself based on the results of intradermal tests, in which 3-month depot leuprorelin acetate caused strong reaction resulting in ulceration in 7 days in certain patients who showed no histological abnormality after the administration of the base material of 3-month depot leuprorelin. However, because many reported cases developed after switching from 1-month depot to 3-month depot, we cannot rule out the possibility of a complex allergic reaction involving both the base material of the 3-month depot formulation and the active agent. Further investigation is needed in this respect.

Although skin reaction to gelatin contained in some leuprorelin preparations was suggested as a possible cause,[10] this is not likely, because gelatin is not contained in the 3-month depot preparation. Infection at the site of injection is not likely to be a cause, because purulent effusion is aseptic in most cases and because abscess was formed even when filter needles preventing bacterial infection were used.[11]

Mechanical stimulation is not a likely cause of reported skin reaction. While leuprorelin acetate is administered to the upper arm in many facilities, goserelin acetate is usually administered to the abdomen, which is prone to receive mechanical stimulation from belts and other objects. The low occurrence of symptoms associated with the latter suggests that a difference in the site of administration does not significantly affect the development of skin reaction. Because local skin reaction occurs even when the site of administration is changed from dose to dose, repeated stimulation at a site is not a likely cause.

Skin reaction that is sufficiently severe to cause induration, if treated at an early stage, may improve after interruption of dosing or a switch to a different drug without requiring further intervention. Even cases involving ulceration may often be treated by the internal or topical use of steroids. However, because the detection of symptoms depended on reporting from patients and observation was usually performed once every 3 months, progression of symptoms to a stage requiring surgical treatment occurred in 4 of the 12 cases associated with 3-month depot.

The occurrence of skin reaction shown by our questionnaire (13 of 64 cases; 20%) was higher than expected. While the reduced frequency of hospital visits is an advantage of the 3-month depot, this results in a situation in which symptoms disappear by the time the patient visits the hospital. Our questionnaire detected skin symptoms in 13 patients including 8 receiving leuprorelin acetate and 5 receiving goserelin acetate, but only 2 of the 13 patients had symptoms that persisted for 3 months or more. In particular, while 7 patients reported "subcutaneous nodule," this symptom that could develop into subcutaneous granuloma had disappeared within about a week in 5 of these patients other than the above-mentioned 2. Allergic reactions in general tend to develop more easily after repeated sensitization by allergens, and repeated administration has been inferred to cause more severe symptoms. While subcutaneous nodules and granuloma formation with aseptic purulent effusion associated with 3-month depot leuprorelin acetate have so far been reported in 12 cases, only 3 of them showed skin reaction after the initial administration, and the remaining cases developed symptoms after 2 to 4 doses. Therefore, irrespective of the type of formulation used, special care should be taken during the first year in outpatient treatment. Patients should be sufficiently informed about side effects including skin reaction at the time of the first administration, and the examination at the time of the second and subsequent administrations should include checking for the persistence, disappearance, and the patient's recognition of skin reaction. In particular, because many patients with prostate cancer are elderly and they are usually seen at 3-month intervals, measures to ensure correct evaluation are considered necessary, such as describing the site of administration on medical records.

There have been no reports that the therapeutic effect against prostate cancer decreases after skin reaction. However, it was reported that the

efficacy in treating central precocious puberty in children decreased after the appearance of local reaction.[12,13] In view of this fact, cases showing local reaction should be closely monitored for changes in PSA, and the need to measure testosterone level and change drugs should be considered. Although extremely rare, subcutaneous nodules that increase in size accompanying increasing levels of PSA can be skin metastasis of prostate cancer in the patients with advanced cancer.[14] Biopsy may be needed in such cases.

Finally, it should be noted that urologists reported 2 of 9 cases of skin reaction in patients with prostate cancer in Japan, while all other cases were reported by dermatologists. The 2 cases reported by the urologists required surgical treatment. All physicians, including urologists, who have the opportunity to prescribe 3-month depot LH-RH agonists should understand the possibility of skin reaction to 3-month depot and consider referral to dermatologists at an early stage after onset.

The 1-month depot preparations of leuprorelin acetate and goserelin acetate are also used for the treatment of breast cancer before menopause, and skin reaction to these 1-month depot drugs has been reported to occur in females.[10] Since 3-month depot leuprorelin acetate was approved for breast cancer before menopause in August 2005, we need to observe the development of skin reaction to the 3-month depot in females.

References

1. Muya M, Takijiri C, Shirahama S. Two cases of granuloma caused by subcutaneous infusion of leuprorelin acetate. Japanese Journal of Clinical Dermatology. 1999;53:801–803. (in Japanese)
2. Hirashima N, Shinogi T, Sakashita N, Narisawa Y. A case of cutaneous injury induced by the subcutaneous injection of leuprolide acetate. The Nishinihon Journal of Dermatology. 2001;63:384–386. (in Japanese)
3. Mizoguchi K, Hamasaki Y, Katayama I, Agawa T. case of drug induced granulomatous reaction by leuprorelin acetate for prostate cancer. Japanese Journal of Dermatology. 2004;114:163–167. (in Japanese)
4. Tachibana M, Yamano Z, Kusuda Y, Hara S, Shimogaki H, Hamami G. Cutaneous epithelioid granulomas caused by subcutaneous infusion of leuprorelin acetate. Acta Urologica Japonica. 2004;50:199–202. (in Japanese)
5. Yasukawa K, Sawamura D, Sugawara H, Kato N. Leuprorelin acetate granulomas: case reports and review of the literature. BJD. 2005;152:1045–1047.
6. Takahashi M, Takeyama Y, Takahashi H, Yamamoto A, Hashimoto Y, Iizuka H. Sakusan ryuupurorerin (sankagetsu jizoku johousei seizai) niyori shoujita nikugeshu no ichirei. Rinsho Derma. 2005;47:782–783. (in Japanese)
7. Nagata K, Indoh M, Hihara S, Shinoda S, Yonehara S. Sakusan ryuupurorerin hikachuusha bui ni shoujita nikugeshu no nirei. Rinsho Derma. 2005;47:784–787. (in Japanese)
8. Tanaka S, Tamura M. Sakusan ryuupurorerin niyori shoujita nikugeshu no sanrei. Rinsho Derma. 2005;47:788–792. (in Japanese)
9. Oida T, Shichiri Y, Takao N, Kanno T, Kanamaru H. Surgical management of inflammatory glanuloma which developed following subcutaneous injection of leuprorelin acetate: A case report. Hinyokika Kiyo. 2005;51:487–489. (in Japanese)
10. Kohno K, Okamoto H, Takahashi S, Iwasaki H, Ishikawa YS. Ryupurin chuuni fukumareru zerachin niyori arerugii hannou wo teishita shourei. Obstetrical and Gynecological Practice. 1998;47:549–553. (in Japanese)
11. Manasco PK, Pescovitz OH, Blizzard RM. Local reactions to depot leuprolide therapy for central precocious puberty. J PEDIATR. 1993;123:334–335.
12. Neely EK, Hintz RL, Parker B, et al. Two-year results of treatment with depot leuprolide acetate for central precocious puberty. J PEDIATR. 1992;121:634–640.
13. Tonini G, Marinoni S, Forleo V, Rustico M. Local reactions to luteinizing hormone-releasing hormone analog therapy. J PEDIATR. 1995;126:159–160.
14. Kuwata Y, Zhang X, Kuroda I, Ishihara M, Takenaka I. Skin metastasis from prostatic cancer: A case report. Nishinihon J Urol. 2000;62:133–135. (in Japanese)

Original Article

Serum Interleukin-18 Concentrations in Burn Patients

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Abstract

Interleukin(IL)-18 is a recently cloned cytokine thought to participate actively in various inflammatory reactions. We investigated relationships between serum IL-18 concentrations and clinical parameters in burn patients, from whom serum samples were collected serially beginning within 24 h after admission. Patients (17 male, 8 female; 22 survivors, 3 nonsurvivors) had a mean age of 49.2 years, a mean total burn surface area (TBSA) of 27.1% (range, 1 to 93%), and a mean burn index (BI) of 19.6 (range, 0.5 to 88). Serum IL-18 concentrations were determined by enzyme-linked immunosorbent assays (ELISA) to examine correlations with TBSA, BI, white blood cell (WBC) count, C-reactive protein (CRP), and oxygenation index (OI; Pao2/Flo2; P/F). On Day 1 serum IL-18 correlated negatively with TBSA ($r = -0.53$, $P<0.05$), BI ($r = -0.48$, $P<0.05$), and WBC ($r = -0.49$, $P<0.05$), while on Day 7 IL-18 correlated positively with TBSA ($r = 0.47$, $P<0.05$), BI ($r = 0.48$, $P<0.05$), WBC ($r = 0.47$, $P<0.05$), and CRP ($r = 0.56$, $P<0.01$). Serum IL-18 had a negative correlation with OI ($r = -0.30$, $P<0.01$), and a positive correlation with the Sequential Organ Failure Assessment (SOFA) score ($r = 0.56$, $P<0.01$). The mean ± SEM for peak IL-18 concentrations in individual survivors was significantly lower than the peak value among nonsurvivors (334 ± 25 vs. 626 ± 215 pg/mL, $P<0.01$).

In conclusion, IL-18 in serum showed significant relationships with TBSA, BI, severity of inflammation, respiratory function, multiple organ dysfunction, and outcome. IL-18 is likely to be involved in the pathophysiology of inflammatory reactions following burn injury.

Key words Interleukin-18 (IL-18), Burn, Inflammatory response, Multiple organ dysfunction syndrome

Introduction

Interleukin(IL)-18 was initially described in 1989 as IGIF (interferon-gamma inducing factor), and was cloned in 1995.[1] IL-18 is considered a proinflammatory cytokine showing marked synergistic action with IL-12 in inducing interferon-gamma (IFN-γ) in T cells. IL-18 also appears to activate natural killer (NK) cells independently of IL-12.[2,3]

While IL-18 is important in the activation of immunity,[4] excessive IL-18 production by activated macrophages may induce dysfunction in multiple organs including disruption of the immune system.[5]

Experimental studies have explored the pathophysiologic and immunologic reactions of IL-18 in various acute or chronic inflammatory diseases including endotoxic shock, hepatitis, cryptococcal infection and mycobacterial infection.[2,6,7] However, in critically ill patients in the intensive care unit (ICU) who undergo life-support procedures to augment the function of various organs, the actions and time-concentration relationships of IL-18 are little known.

We investigated the relationship in burn patients between serum IL-18 concentrations and various clinical parameters, aiming to better understand the effects of IL-18.

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Table 1 Characteristics of patients by burn extent

	TBSA<30%	TBSA≧30%	*P* value
Number	15	10	
Gender (male/female)	10/5	7/3	NS
Age	49±4	49±6	NS
TBSA (%)	11.7±2.0	50.2±6.5	*P*<0.0001
BI	7.0±1.3	39.0±6.5	*P*<0.0001
Inhalation injury (present/absent)	8/7	4/6	NS
Fatal outcome (survival/nonsurvival)	15/0	7/3	NS

TBSA: total burn surface area, BI: burn index, NS: not significant. The data are expressed as the mean±SEM.

Patients and Methods

Patients

Between August 1999 and March 2002, twenty-five consecutive patients (mean age, 49.2 years; range: 22 to 85) admitted to the burn care unit of our hospital were enrolled in this study. The exclusive criteria were a patient age of under 8-years, and incomplete documentation. The mean for the total burn surface area (TBSA) was 27.1% (range, 1 to 93). The mean for the burn index [BI=1/2 of second-degree TBSA(%)+ third-degree TBSA(%)] was 19.6 (range, 0.5 to 88). Inhalation injury was diagnosed by fiberoptic bronchoscopy in 12 cases. Of the 25 patients, 3 died of their burns. Patient characteristics in two groups defined by TBSA are presented in Table 1.

During the acute phase of treatment, all patients were resuscitated according to Parkland's formula with lactated Ringer's solution. Fresh frozen plasma and vasopressors were used additionally if needed. Systemic blood pressure, cardiac output, and pulmonary capillary wedge pressure were monitored. Artificial ventilatory support was performed when indicated. Silver sulfadiazine and vaseline ointment containing polymyxin B powder were applied as topical agents for the care of burn wounds.

After the phase of fluid replacement, total parenteral nutrition with or without enteral nutrition was initiated. Operations necessary for wound debridement and skin grafting were performed as early as possible.

Methods

Blood samples were collected on Day 1 (within 24h after admission), and on Days 3, 5, 7, 10, and 14. After centrifugation at 3000 rpm for 10 min, serum was stored at −80C° until assay. The serum concentrations of IL-18 were measured by an enzyme-linked immunosorbent assay (human IL-18 ELISA kit; Medical & Biological Lab., Nagoya, Japan).

White blood cell (WBC) count in blood, serum concentration of C-reactive protein (CRP), arterial carboxyhemoglobin (CO-Hb) concentration, arterial partial oxygen saturation (Pao2), and the Sequential Organ Failure Assessment (SOFA) score[8] were determined on the same days as serum sampling for IL-18. The SOFA score, considered useful for the prediction of subsequent organ dysfunction, was calculated based on Pao2/FIo2, platelet count, serum bilirubin concentration, degree of hypotension, Glasgow Coma Scale, and serum creatinine concentration.

Statistical correlations were examined between serum IL-18 concentration and TBSA, BI, WBC, CRP, and SOFA score.

To investigate the relationship between IL-18 and respiratory dysfunction, the correlation with blood gas parameters (pH, Paco2, Pao2, and base excess), serum CO-Hb, and the values of the oxygenation index (OI; Pao2 divided by the fraction of O2 in inspired air, or FIo2) was investigated. Differences in serum IL-18 concentrations were also evaluated between patients with and without endobronchial inhalation injury as well as between survivors and nonsurvivors.

Patient numbers (n) for the data sets vary in the figures and tables because of early discharges from the burn care unit.

This study was approved by the local ethics committee of our university.

Statistical analysis

All values are expressed as means±SEM. Comparisons between data sets were performed with unpaired Student's t-test or one-way analysis of variance (ANOVA) followed by F analysis. Post hoc correction was performed by applying Fisher's protected least significant difference (PLSD) to the ANOVA findings. When parametric methods were not appropriate, the nonparametric method used was the Mann-Whitney U

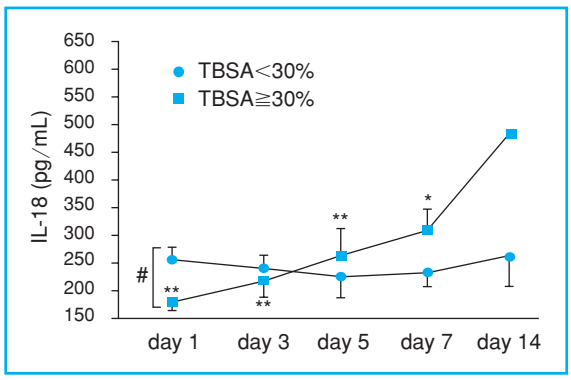

Fig. 1 Changes in serum interleukin(IL)-18 concentrations after burn injury

For TBSA (total burn surface area)≧30% (■), serum IL-18 concentrations on Day 14 were significantly higher than on previous days (Day 1**, Day 3**, Day 5** and Day 7*; *P<0.05, **P<0.01). On Day 1, the initial concentration of IL-18 for TBSA≧30% (182.4±14 pg/mL), was significantly lower than for TBSA<30% (●; 260.5±29 pg/mL, #P<0.05). The data are expressed as the mean±SEM.

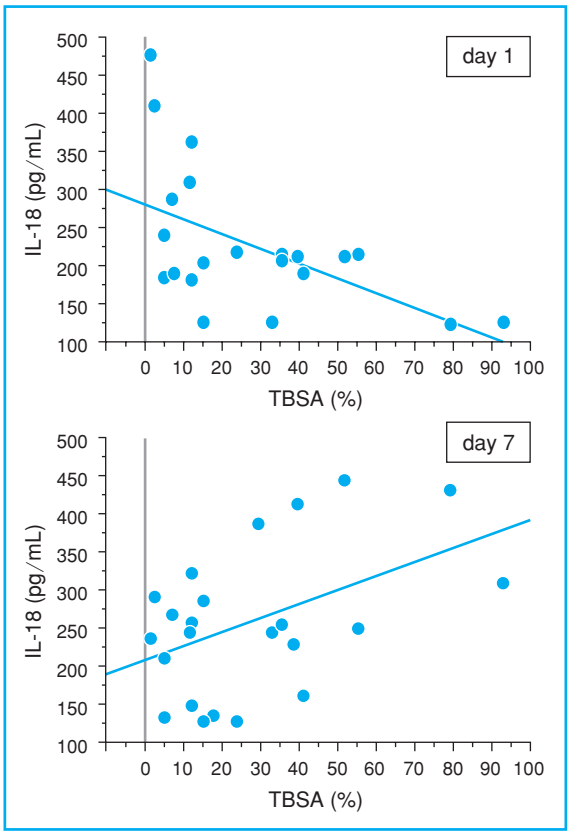

Fig. 2 Correlations between serum interleukin(IL)-18 concentrations and burn extent at two time points

A negative correlation was evident between IL-18 and total burn surface area (TBSA) on Day 1 (upper scattergram); (Y=−1.9X+280, r=−0.53, P<0.05, n=22), while a positive correlation was present on Day 7 (lower scattergram); (Y=2.0X+212, r=0.47, P<0.05, n=23).

test or a chi-squared test. The scattergrams were analyzed by linear regression. A P value of <0.05 indicated significance.

Results

The serum IL-18 concentrations in 46 healthy volunteers were 126±44.5 pg/mL. In the patients, serum IL-18 concentrations over time are presented in Fig. 1. On Day 1, initial IL-18 concentrations in patients with TBSA≧30% were significantly lower than in patients with TBSA<30%. IL-18 in the group with TBSA≧30% then gradually increased to maximal levels on day 14, which were significantly higher than at earlier time points in the same group, but were not statistically different from concentrations on Day 14 in the group with TBSA<30%. These two groups divided by burn size, had no statistical difference in their characteristics, age, sex, complications or outcome (Table 1).

A significant negative correlation between serum IL-18 and TBSA was observed on Day 1, and a significant positive correlation was seen on Day 7 (Fig. 2). However, a significant correlation was not observed on Day 14.

BI showed relationships with IL-18 that were similar to those of TBSA. On Day 1, WBC correlated negatively with IL-18, while both WBC and CRP correlated positively with IL-18 on Day 7. On Day 14, only CRP correlated positively with IL-18 (Table 2).

Table 2 Correlation of serum IL-18 with BI, WBC count, and CRP at three time points

IL-18 vs.	day 1	day 7	day 14
BI	r=−0.48 (P<0.05)	r=0.48 (P<0.05)	NS
WBC	r=−0.49 (P<0.05)	r=0.47 (P<0.05)	NS
CRP	NS	r=0.56 (P<0.01)	r=0.90 (P<0.05)

IL-18: interleukin-18, BI: burn index, WBC: white blood cell, CRP: C-reactive protein, NS: not significant.

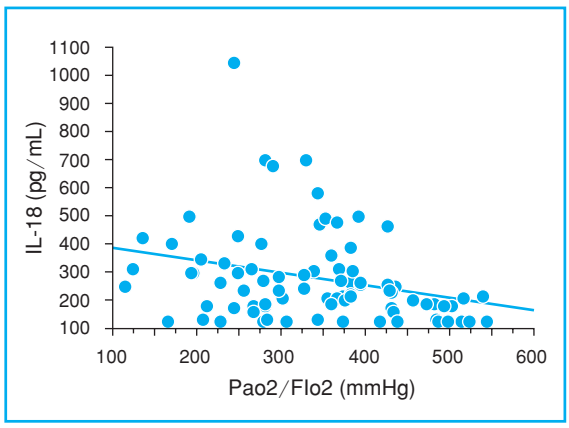

Fig. 3 Correlation between serum interleukin(IL)-18 concentration and oxygenation index

Oxygenation index (Pao2/Flo2; normal, ≧300 mmHg), which indicates respiratory status, showed a negative correlation with IL-18 ($Y = -0.44X + 431$, $r = -0.30$, $P = 0.009$, $n = 85$).

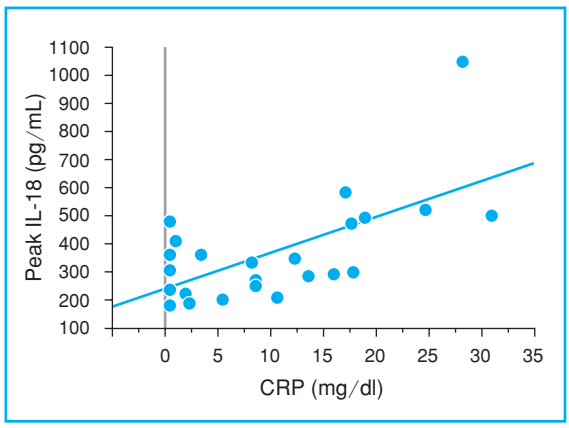

Fig. 5 Correlation between peak serum interleukin(IL)-18 concentration and C-reactive protein (CRP)

The peak IL-18 concentration each patients is shown. The peak values correlated positively with CRP on the day of the IL-18 peak ($Y = 12.6X + 241$, $r = 0.63$, $P = 0.0009$, $n = 24$).

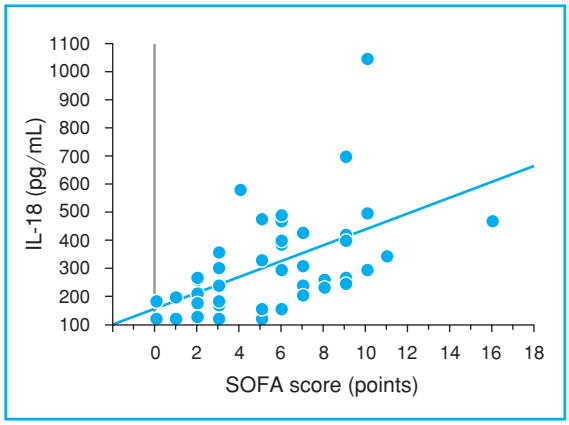

Fig. 4 Correlation between serum interleukin(IL)-18 concentration and Sequential Organ Failure Assessment (SOFA) score

The score, which predicts subsequent multiple organ dysfunction, showed a positive correlation with IL-18 ($Y = 28.3X + 157$, $r = 0.56$, $P < 0.0001$, $n = 48$).

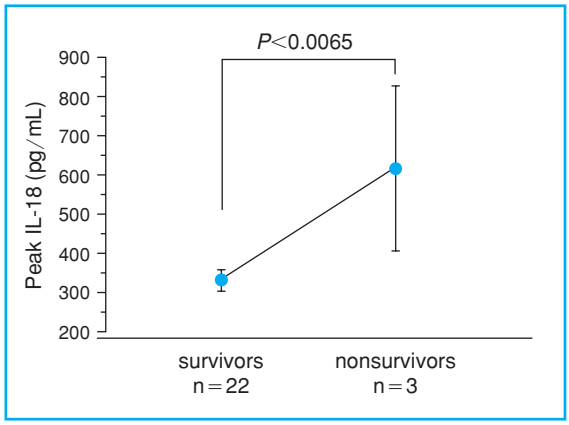

Fig. 6 Peak serum interleukin(IL)-18 concentration according to survival

Peak IL-18 concentrations for non-surviving patients (626 ± 215 pg/mL) were significantly higher than those for survivors (334 ± 25 pg/mL; $P < 0.0065$). The data are expressed as the mean ± SEM.

As shown in Fig. 3, IL-18 correlated negatively with OI, and also correlated positively with the SOFA score determined on the same day (Fig. 4).

To analyze the relationship between the intensity of inflammatory response and serum IL-18 concentration, the peak IL-18 value for each case was considered in terms of various parameters.

Peak IL-18 concentrations in burn patients (369 ± 182.1 pg/mL) were higher than in normal controls ($P < 0.0001$). In addition, the peak IL-18 value correlated positively with CRP on the day of the IL-18 peak (Fig. 5). However, no statistical correlation was observed between the peak concentration of IL-18 and simultaneous WBC count.

As for respiratory status immediately after burn injury, serum IL-18 concentrations were not associated with blood gas parameters or CO-Hb on admission. Although the difference fell short of statistical significance, patients with

endoscopically demonstrable inhalation injury tended to have higher serum concentrations of IL-18 (265 ± 35 pg/mL) than those without (199 ± 18 pg/mL).

Peak concentrations of IL-18 in nonsurvivors, were higher than those in survivors (Fig. 6).

Discussion

IL-18 has been reported to act importantly to maintain and reinforce T helper cell-type 1 (Th1) responses, acting together with IL-12. IL-18 also stimulates NK cell function and can augment antibody production by B cells. If upregulation of this pathway becomes excessive, macrophages activated by IFN-γ will produce excesses of tumor necrosis factor alpha (TNF-α), nitric oxide, and superoxide, causing cell damage and tissue injury. However, IL-18 also stimulates macrophages to produce prostaglandin E2, which results in the upregulation of Th2 responses. The latter include the release of IL-4, IL-10, and IL-13, and tend to inhibit excessively activated Th1 immune responses.[5,9]

Another important action of IL-18 is to act directly on murine NK cells.[10,11] and murine Th1 cells[10,12] to induce the expression of Fas ligand, augmenting their cytotoxicity.

In addition, caspase-1 [IL-1 beta(β)-converting enzyme, or ICE] acts in producing mature bioactive IL-1β from a inactive precursor form.[2] IL-1 is a potent proinflammatory cytokine that regulates the acute-phase gene expression of CRP.[13,14] Since IL-18 also requires proteolytic processing by ICE to acquire activity, IL-1 and IL-18 are regarded as members of the same family.

Recent studies suggest that IL-18 may be activated prior to other cytokines, and has proinflammatory actions involving the direct stimulation of gene expression and the synthesis of TNF-α and the activation of NK cells with the subsequent production of IL-1β and IL-8.[15] These reports also indicate that IL-18 is involved in the regulation of cytokine production during the early phase of bacterial infections.[9]

The pathophysiology of the various mediators following severe burns or trauma is extremely complex. Especially in patients with burn injury, cytokines have a variety of roles in modulating immunologic and inflammatory responses by the up- or downregulation of immune responses.[3,16–23]

Changes in the concentrations of plasma cytokines over time [e.g. IL-1β, IL-1 receptor antagonist (ra), IL-6, TNF-α, and IFN-γ], as well as their relationships to various clinical parameters after burn injury, have been described in previous studies.[24–29] Serum concentrations of IL-6 increase during the early phase after burn injury, and then decline over time.[24,26,27] IL-6 correlates positively with burn size,[24,27] and also shows a relationship with complicating infections.[25] Higher serum concentrations are seen in nonsurvivors than in survivors.[25,26]

In our study, IL-18 showed similar patterns to those of IL-6 in terms of burn size and mortality. Changes in IL-18 were time-dependent, with IL-18 being significantly more abundant on Day 14 in patients with extensive burns.

These results suggest that thermal damage evidence immediately after burn injury, may have little direct effect in inducing IL-18. On the other hand, wound infections that begin to occur on Day 4–5 to 2 weeks are likely to stimulate IL-18, since serum concentrations of IL-18 correlated positively with TBSA, BI, WBC count, and CRP on Day 7, but not Day 1. Few correlations persisted up to Day 14, although a continuing correlation between peak IL-18 levels and CRP presumably reflected the magnitude of the inflammatory response.[30]

This reason is supported by our result that the incidence of the positive rate of pathogens (e.g. *Staphylococcus aureus, Pseudomonas aeruginosa*) isolated from burn wounds, were increased daily after Day 4–5. It is also supported by the report that IL-18 levels are increased in patients with sepsis, and *Staphylococcus aureus* markedly increased the release of IL-18 while endotoxin was ineffective.[31]

On Day 1, the patients with a larger size of burn wound had signinficantly lower IL-18 concentrations (Fig. 1 and Fig. 2). This result suggests that thermal impact plays an immunosuppressive role in IL-18 induction, although this speculation is not be supported by any other recent study.

The relationship between IL-18 and the inflammatory response on Day 7 may involve the need for activation by ICE protease that is common to both IL-18 and proinflammatory cytokine IL-1β. As mentioned earlier, IL-12 and IL-18 induce T cells to produce IFN-γ. This synergistic action is a Th1 response, so that IL-18 is a co-stimulatory factor in the activation of Th1 but not

Th2 cells.[3,10,32]

Once inflammatory reactions are activated in burn patients, Th1-cellular immunity might be augmented by the action of IL-12 and IL-18. Other cytokine responses were not investigated in this study, so this hypothesis will be the subject of a future study.

In a previous report,[6] combined treatment with IL-18 and IL-12 prolonged survival in mice with experimental *Cryptococcus neoformans* infection. These protective effects were associated with elevated IFN-γ[33] and reduced IL-4 in bronchoalveolar fluid.[6,34] On the other hand, IL-18 also acts alone to increase Th2 cytokine production, serum IgE levels, and eosinophil recruitment, which may result in allergic sensitization and contribute to the pathogenesis of allergic asthma.[35,36]

Since we have found that IL-18 shows a relationship with OI as a respiratory parameter, measurements of this cytokine might play a role in respiratory dysfunction via systemic inflammatory response. Inhalation injury could have some influence on IL-18, although this association did not attain statistical difference.

SOFA score and mortality were both related to IL-18 in our burn patients. These results agree with those of previous reports,[31,37] and the higher the IL-18 values were, the higer the Acute Physiology and Chronic Health Evaluation (APACHE) II score was in the septic burn group.[29]

In conclusion, increased IL-18 in burn patients appears to be a response to wound infection and the magnitude of systemic inflammation, and is also related with mortality.

Further study is needed to delineate the role of IL-18 in the pathophysiology of burn patients in the future.

References

1. Okamura H, Tsutsui H, Komatsu T, et al. Cloning of a new cytokine that induces IFN-γ production by T cells. Nature. 1995; 378:88–90.
2. Kashiwamura S, Okamura H. IL-18 and IL-18 receptor. Nippon Rinsho. 1998;56:1798–1806.
3. Xu D, Chan WL, Leung BP, et al. Selective expression and functions of Interleukin 18 receptor on T helper (Th) type 1 but not Th2 cells. J Exp Med. 1998;188:1485–1492.
4. Hoshino T, Wiltrout RH, Young HA. IL-18 is a potent coinducer of IL-13 in NK and T cells: a new potential role for IL-18 in modulating the immune response. J Immunol. 1999;162:5070–5077.
5. Okamura H, Kashiwamura S, Tsutsui H, et al. Regulation of interferon-gamma production by IL-12 and IL-18. Curr Opin Immunol. 1998;10:259–264.
6. Qureshi MH, Zhang T, Koguchi Y, et al. Combined effects of IL-12 and IL-18 on the clinical course and local cytokine production in murine pulmonary infection with Criptococcus neoformans. Eur J Immunol. 1999;29:643–649.
7. Sugawara I, Yamada H, Kaneko H, et al. Role of interleukin-18 (IL-18) in mycobacterial infection in IL-18-gene-disrupted mice. Infect Immun. 1999;67:2585–2589.
8. Vincent JL, Mendonca AD, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Crit Care Med. 1998;26:1793–1800.
9. Bohn E, Sing A, Zumbihl R, et al. IL-18 (IFN-gamma-inducing factor) regulates early cytokine production in, and promotes resolution of, bacterial infection in mice. J Immunol. 1998;160: 299–307.
10. Okamura H, Tsutsui H, Kashiwamura S, et al. IL-18: A novel cyotokine that augments both innate and acquired immunity. Adv Immunol. 1998;70:281–312.
11. Tsutsui H, Nakanishi K, Matsui K, et al. IFN-gamma-inducing factor up-regulates Fas ligand-mediated cytotoxic activity of murine natural killer cell clones. J Immunol. 1996;157:3967–3973.
12. Tao D, Ohashi K, Kayano T, et al. Interferon-gamma-inducing factor, a novel cytokine, enhances Fasligand-mediated cytotoxicity of murine T helper 1 cells. Cell Immunol. 1996;173: 230–235.
13. Schultz DR, Arnold PI. Properties of four acute phase proteins: C-reactive protein, serum amyloid A protein, alpha 1-acid glycoprotein, and fibrinogen. Semin Arthritis Rheum. 1990;20:129–147.
14. Ganter U, Arcone R, Toniatti C, et al. Dual control of C-reactive protein gene expression by interleukin-1 and interleukin-6. EMBO J. 1989;8:3773–3779.
15. Puren AJ, Fantuzzi G, Gu Y, et al. Interleukin-18 (IFNgamma-inducing factor) induces IL-8 and IL-1beta via TNFalpha production from non-CD14+ human blood mononuclear cells. J Clin Invest. 1998;101:711–721.
16. Suzuki F, Pollard RB. Mechanism for the suppression of gamma-interferon responsiveness in mice after thermal injury. J Immunol. 1982;129:1811–1815.
17. Hultman CS, Napolitano LM, Cairns BA, et al. The relationship between interferon-gamma and keratinocyte alloantigen-expression after burn injury. Ann Surg. 1995;222:384–389; discussion 392–393.
18. Matsuo R, Kobayashi M, Herndon DN, et al. Interferon-12 protects thermally injured mice from herpes simplex virus type 1 infection. J Leukoc Biol. 1996;59:623–630.
19. O'suilleabhain C, O'sullivan ST, Kelly JL, et al. Interleukin-12 treatment restores normal resistance to bacterial challenge after burn injury. Surgery. 1996;120:290–296.
20. Schwacha MG, Somers SD. Thermal injury-induced immunosuppression in mice: the role of macrophage-derived reactive nitrogen intermediates. J Leukoc Biol. 1998;63:51–58.
21. Schwacha MG, Samy TS, Catania RA, et al. Thermal injury alters macrophage responses to prostaglandin E2: contribution to the enhancement of inducible nitric oxide synthase activity. J Leukoc Biol. 1998;64:740–746.
22. Peter FW, Schuschke DA, Barker JH, et al. The effect of severe burn injury on proinflammatory cytokines and leukocyte behavior: its modulation with granulocyte colony-stimulating factor. Burns. 1999;25:477–486.
23. Zedler S, Bone RC, Baue AE, et al. T-cell reactivity and its predictive role in immunosuppression after burn. Crit Care Med. 1999;27:66–72.
24. Ueyama M, Maruyama I, Osame M, et al. Marked increase in

plasma interleukin-6 in burn patients. J Lab Clin Med. 1992;120: 693–698.
25. Drost AC, Burleson DG, Cioffi WG, et al. Plasma cytokines after thermal injury and their relationship to infection. Ann Surg. 1993; 218:74–78.
26. Drost AC, Burleson DG, Cioffi WG, et al. Plasma cytokines following thermal injury and their relationship with patient mortality, burn size, and time postburn. J Trauma. 1993;35:335–339.
27. de Bandt JP, Chollet-Martin S, Hernvann A, et al. Cytokine response to burn injury: relationship with protein metabolism. J Trauma. 1994;36:624–628.
28. Vindenes HA, Ulvestad E, Bjerknes R. Concentrations of cyotokines in plasma of patients with large burns: their relation to time after injury, burn size, inflammatory variables, infection, and outcome. Eur J Surg. 1998;164:647–656.
29. Endo S, Yanada Y, Inada K, et al. Interleukin 18 levels in patients with infectious burns. In: Endo S ed. Burn-Mediators and Pathophysiology. Tokyo: Influx Com Inc; 2001:55–59.
30. Dinarello CA. IL-1beta, IL-18, and the IL-1 beta converting enzyme. Ann NY Acad Sci. 1998;856:1–11.
31. Oberholzer A, Steckholzer U, Kurimoto M, et al. Interleukin-18 plasma levels are increased in patients with sepsis compared to severely injured patients. Shock. 2001;16(6):411–414.
32. Kohno K, Kataoka J, Otsuki T, et al. IFN-gamma-inducing factor is a costimulatory factor on the activation of Th1 but not Th2 cells and exerts its effect independently of IL-12. J Immunol. 1997; 158:1541–1550.
33. Kawakami K, Qureshi MH, Zhang T, et al. Involvement of endogenously synthesized interleukin (IL)-18 in the protective effects of IL-12 against pulmonary infection with cryptococcus neoformans in mice. FEMS Immunol Med Microbiol. 2000;27: 191–200.
34. Hofstra CL, Van Ark I, Hofman G, et al. Prevention of Th2-like cell responses by coadministration of IL-12 and IL-18 is associated with inhibition of antigen-induced airway hyperresponsiveness, eosinophilia, and serum IgE levels. J Immunol. 1998;161: 5054–5060.
35. Kumano K, Nakao A, Nakajima H, et al. Interleukin-18 enhances antigen-induced eosinophil recruitment into the mouse airways. Am J Respir Crit Care Med. 1999;160:873–878.
36. Wild JS, Sigounas A, Sur N, et al. IFN-gamma-inducing factor (IL-18) increases allergic sensitization, serum IgE, Th2 cytokines, and airway eosinophilia in a mouse model of allergic asthma. J Immunol. 2000;164:2701–2710.
37. Emmanuilidis K, Weighardt H, Matevossian E, et al. Differential regulation of systemic IL-18 and IL-12 release during postoperative sepsis: high serum IL-18 as an early prdictive indicator of lethal outcome. Shock. 2002;18(4):301–305.

Recent Trend in Pressure Ulcer Treatment in Japan

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Abstract

Pressure ulcers represent an important class of chronic skin ulcers. The treatment of this condition has been making remarkable progress reflecting advancement in the theory of wound healing, which has led to the introduction of new concepts of wound bed preparation and moist wound healing, as well as the development of new topical medications and dressing materials. Scientific methods for the prevention and management has come to be practiced widely through the establishment of risk assessment tools and evaluation of wound surface condition, and a set of treatment guidelines based on the methodology of EBM has been formulated. A future agenda include the efforts to promote the use of the new wound management methods by all medical professionals and to solve the problem of pressure ulcer development in acute care hospitals.

Key words Wound healing, Pressure ulcer, Risk assessment, Wound bed preparation, Moist wound healing, Guideline

Introduction

While pressure ulcers or bedsores were once regarded as a chronic skin complication that inevitably occurs in bed-ridden aged patients, a major tectonic change is taking place regarding the situation of this disorder. There are several factors in the background of this change: The new policy of the Ministry of Health, Labor and Welfare (MHLW) introducing "reimbursement reduction for not using pressure ulcer prevention" revealed the fact that pressure ulcers develop not only in chronic care hospitals but also in acute care hospitals mainly during the perioperative period; advancement in the theory of wound healing led to the establishment of new concepts of wound bed preparation and moist wound healing, as well as the development of new topical medications and dressing materials; and the development of risk assessment tools and evaluation of wound surface condition anticipating treatment strategies for pressure ulcers enabled the treatment of bedsores and skin ulcers based on scientific methodology. In response to this changing situation, the Japanese Society of Pressure Ulcers published the Guidelines for the Topical Treatment of Pressure Ulcers Based on Scientific Evidence in 2005.[1] These guidelines embody an approach from evidence-based medicine (EBM), as they include an evaluation of the level of evidence based on a literature search and determination of the level of recommendation incorporating expert opinions. This article outlines the newest trends in pressure ulcer treatment in Japan according to these guidelines.

Pressure Ulcer in Acute Care Hospitals[2]

Traditionally, verification of the prevention and management of pressure ulcers has been based on data from aged patients. However, the data related to the implementation of "reimbursement reduction policy for not using pressure ulcer

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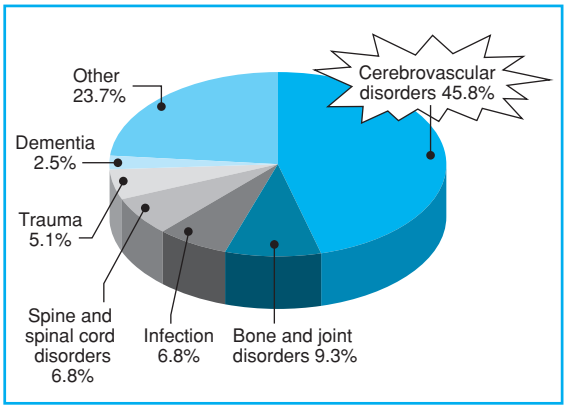
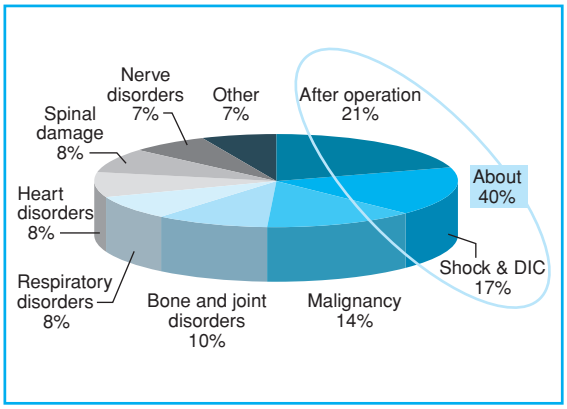


(Quoted from Epidemiological survey of pressure ulcers in hospitals, geriatric health facilities, and domiciliary mursing care stations in Gunma Prefecture[3])

Fig. 1 Underlying diseases in patients with pressure ulcers in acute care hospitals



(Data from the Pressure Ulcer Management Committee of Kyoto University Hospital)

Fig. 2 Underlying diseases in patients with pressure ulcers in acute care hospitals

prevention" revealed that pressure ulcers also occur in acute care hospitals such as university hospitals, and the features of cases there differ remarkably from those in chronic care hospitals. Severe pressure ulcers are now regarded as medical accidents, and much attention is directed to the management of pressure ulcers in acute care hospitals as a major cause of healthcare cost.

Facts about pressure ulcers in acute care hospitals

In the case of pressure ulcers in chronic care hospitals, the most common underlying disease is cerebrovascular disorders (nearly a half of all cases), followed by bone and joint disorders and then by infections (Fig. 1).[3] On the other hand, pressure ulcers in acute care hospitals most frequently develop in patients lying in bed after an operation, followed by those lying in bed due to shock and DIC (Fig. 2). About 40% of pressure ulcers in acute care hospitals develop during the perioperative period.

Generally, the prevalence of pressure ulcers in Japan is reported to be in the range from 4.2 to 7.6%. While this figure is lower than the prevalence in Western countries (7 to 23%), patients in Japan include a higher percentage of severe cases of deeper lesions. This difference is considered to reflect the fact that mild cases are overlooked, and the delay in the provision of appropriate treatment tends to increase the number of severe cases in Japan, compared with Western countries. The prevalence of pressure ulcers in acute care hospitals in Japan is reported to be in the range from 2.2 to 3.3%, but the actual situation is unclear. Both the apparent occurrence rate and the reported percentage of patients with pressure ulcers increased temporarily after the implementation of the "reimbursement reduction policy for not using pressure ulcer prevention", as a result of the improved reporting rate of previously overlooked cases of pressure ulcers, but both figures decreased thereafter. This demonstrated that appropriate management during the perioperative period in acute care hospitals was effective in preventing pressure ulcers. The interim report of the national survey conducted by the Japanese Society of Pressure Ulcers indicated that the new reimbursement policy triggered a significant decrease in the prevalence rate (an estimation showed a decrease of about 10,000 cases nationwide) and improvement in severity profile (Table 1). As shown by this fact, the new policy clearly reduced pressure ulcers resulting from inadequate management both in chronic care hospitals and in acute care hospitals

Risk factors for pressure ulcers: difference from those in chronic care hospitals

The Clinical Protocol for Pressure Ulcer Management lists 6 risk factors including 1) basic motor ability, 2) pathological bone protrusion, 3) joint

Table 1 Changes in the prevalence of pressure ulcers (overall)

Time of survey	Prevalence (per 1,000)	95% confidence range
Before implementation of reimburse reduction policy for not using pressure ulcer prevention	49.1	48.1–50.0
Shortly after implementation	47.1*	46.2–48.0
Half-year after implementation	46.9*	46.0–47.8
One year after implementation	42.8*	42.0–43.6

*$P<0.05$ vs. the data before September 2002 based on 95% CI.
Prevalence of pressure ulcers before and after the implementation of reimbursement reduction policy for not using pressure ulcer prevention (Data published by the Japanese Society of Pressure Ulcers)

contracture, 4) poor nutrition, 5) wet skin (excessive sweating, urinary incontinence, and fecal incontinence), and 6) edema (in body parts other than the affected site). These are intended for pressure ulcers in chronic care hospitals, and cannot be applied directly to pressure ulcers in acute care hospitals. Pathological bone protrusion and joint contracture are not extracted as significant risk factors among patients with pressure ulcers that develop during the perioperative period. These patients usually have albumin levels of higher than 3.0 g/dL, and this parameter is not so likely to be a risk factor as it is for pressure ulcers in chronic care hospitals. Instead, the duration of operation, method of anesthesia (such as hypothermic anesthesia), volume of blood loss during the operation, and duration of the use of extracorporeal circulation have been extracted as risk factors. Because pressure ulcers in acute care hospitals present different features from those in chronic care hospitals, conventional risk assessment methods are less effective in terms of specificity and sensitivity in acute care hospitals. A new method for risk factor evaluation should be developed for use in acute care hospitals.

Although various bedding products improving pressure distribution and other devices for bedsore prevention have been developed and marketed, these are intended for use in chronic care hospitals and in home care rather than for use in ICUs and operating rooms. The development of devices for the management of pressure ulcers in acute care hospitals is urgently required.

Importance of team practice for pressure ulcers

A byproduct of the implementation of reimbursement reduction policy for not using pressure ulcer prevention is the fact that the required response to pressure ulcers prompted acute care hospitals to use team practice consisting of the systematic involvement of multidisciplinary professionals. Conventionally, acute care hospitals such as university hospitals providing advanced medical care tended to have a vertical organization lacking sufficient interaction among different professions. Pressure ulcer teams enabled different professionals to work toward better pressure ulcer management cooperatively, while respecting their specialties. These teams proved their effectiveness, and their functions continued to improve. A system was established in which wound osmosis continence-certified (WOC) nurses took a central role in a team consisting of dietitians, pharmacists, physical therapists, etc., cooperating with physicians in the management of pressure ulcers. This form of collaboration across the boundaries of professions in the treatment of a disorder set a precedent for team practice and facilitated similar activities in other areas in the hospital (such as infection control team, nutrition support team, and the prevention of medical accidents).

New Concepts concerning Pressure Ulcer Treatment

While pressure ulcers are a form of ischemic skin damage caused by persistent local compression,

it involves not only local skin problems (fragile skin due to aging, moisture and contamination due to incontinence, mechanical factors such as pressure, friction, and shearing) but also a combination of systemic factors (underlying disease, malnutrition, emaciation) and social factors (lack of care manpower). Scientific analysis of these factors has resulted in the establishment of risk assessment methods for pressure ulcers and the development of preventive measures such as bedding products improving pressure distribution. On the other hand, the local management of pressure ulcers has also been making progress. New concepts such as wound bed preparation and moist wound healing were introduced, and a tool for evaluating the condition of pressure ulcer called "DESIGN" was developed by the Japanese Society of Pressure Ulcers. There has been a steady shift from standardized local treatment depending on experience and intuition to the selection of optimal local treatment based on the evaluation of the wound surface. The new trends in pressure ulcers are summarized in the following sections.

Risk assessment methods

The thorough removal of the causes of pressure ulcers is an extremely important part of treatment for pressure ulcers. Failure in achieving this makes it impossible to expect any improvement in pressure ulcers even if appropriate local treatment is given. Risk assessment tools serve for this purpose by providing the means for the scientific scoring of the individual patient's risk factors for pressure ulcers without depending on experience or intuition, identifying individuals that are prone to develop pressure ulcers, and supporting the planning of preventive measures. A risk assessment method must have high reliability and predictive validity, ensuring that any physician can obtain consistent results. The Braden scale is used commonly in the world, and the K scale and the OH scale have been developed incorporating the special traits of the Japanese patient population (such as pathological bone protrusion). However, the method that is simplest and most commonly used in Japan is the MHLW Risk Factor Assessment. This method was employed in the Clinical Protocol for Pressure Ulcer Management (Annex Form 5), which was introduced in combination with the reimbursement reduction policy for not using pressure ulcer prevention. It is a list of evaluation items needed for the formulation of treatment plans and the practice of pressure ulcer management for patients with limited independence in daily living activities. This useful list can conveniently evaluate the 6 items of basic motor ability, pathological bone protrusion, joint contracture, poor nutrition, wet skin (excessive sweating, urinary incontinence, and fecal incontinence), and edema (in body parts other than the affected site). The Japanese Society of Pressure Ulcers has also published guidelines for the use of this assessment method.[4] However, a risk assessment tool for pressure ulcers in acute care hospitals has yet to be developed.

New concepts reflecting the advancement in wound healing theory

Supported by the development of study in cell biology, the theory of wound healing has undergone dramatic changes. The method of wound management has also changed accordingly, and old knowledge is no longer useful for appropriate treatment. Here, 2 new concepts are outlined.

1. The concept of wound bed preparation[5]

This refers to the adjustment of the environment and the management of wound beds in chronic wounds to facilitate wound healing. It corresponds to what was traditionally called "making an environment for wound healing." A failure in wound healing indicates the presence of some factors preventing healing. These factors may include excessive exudate, the presence of infection, necrotic tissues and exuberant granulation, and cells that do not respond to growth factors. Debridement represents the main part of wound bed preparation in acute-phase wounds. In chronic-phase wounds, exudate management, infection control, and measures to prevent recurrence have also become important in addition to debridement.

2. The concept of moist wound healing

It was once a norm that wounds should be dried up to facilitate healing. However, it is easily understood that a moist environment is more suitable for wound healing in view of cell growth and the production of extracellular matrix.[6] Like a burn blister with an unbroken roof, the interior of a wound is kept moist, protected from the invasion of bacteria and foreign bodies, and rich in cytokines that are effective in wound healing, which is an ideal environment. Experimental

evidence has been accumulated since the 1960s, and the concept of moist wound healing has now become widely accepted. The application of this theory has resulted in the development of modern dressing materials, such as film dressing materials and hydrocolloid dressing materials. It should be noted that these materials are often unsuitable when there is infection, necrotic tissues, or excessive exudate. Dressing materials that can be used at such stages have been developed recently. As long as new dressing materials are used according to the correct indications, they are expected to make an important contribution to the improvement in the QOL of patients by facilitating home care and outpatient care and allowing patients to take a bath.

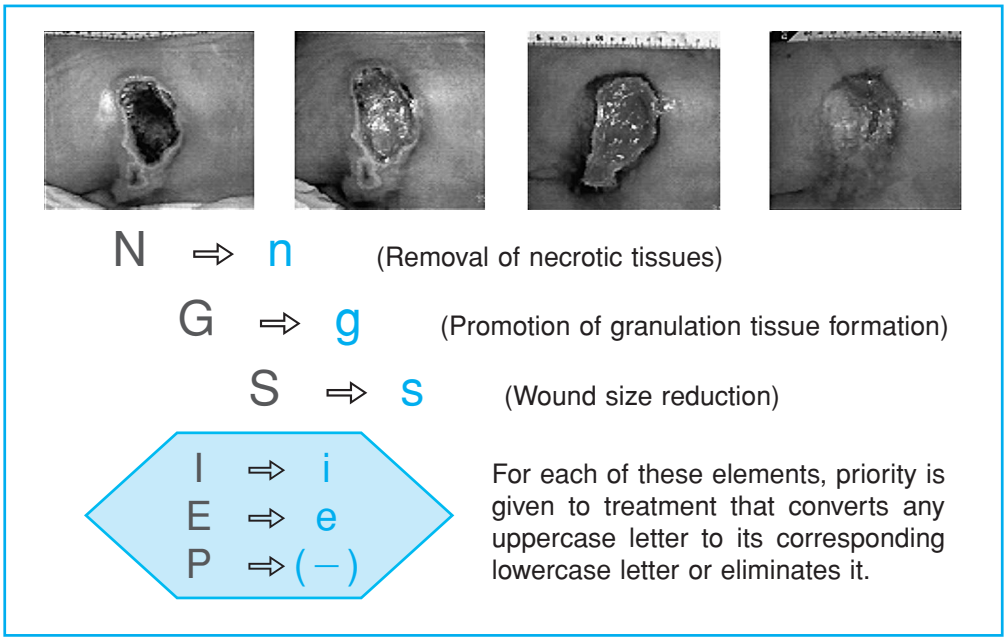
Methods for assessing the condition of pressure ulcers

Because there is no single treatment that is effective in all cases of pressure ulcers, it is important to assess the condition of the wound surface accurately and determine appropriate local treatment. A treatment based on wrong judgment not only delays wound healing but also invites a great loss in the health care economy. What is needed here is a procedure to evaluate the wound surface to understand the phase of the

Fig. 3 DESIGN method for evaluating the condition of pressure ulcers

Depth: Evaluate at the deepest point in the wound. If improvement has resulted in shallowing of the wound bottom, evaluate the corresponding depth.			
d	0 No skin damage or reddening 1 Persistent reddening 2 Damage reaching the dermis	D	3 Damage reaching subcutaneous tissues 4 Damage exceeding subcutaneous tissues 5 Damage reaching articular cavity or body cavity, or damage of unknown depth
Exudate			
e	0 None 1 Little: Daily exchange of dressing is not needed 2 Moderate: Exchange of dressing is needed once daily	E	3 Profuse: Exchange of dressing is needed twice or more daily
Size: Measure the extent of skin defect: Diameter (cm) × Largest width perpendicular to the diameter (cm)			
s	0 No skin damage 1 < 4 2 ≥ 4, < 16 3 ≥ 16, < 36 4 ≥ 36, < 64 5 ≥ 64, < 100	S	6 ≥ 100
Inflammation/Infection			
i	0 No local signs of infection 1 Local signs of infection present (reddening, swelling, heat sensation, pain around the wound)	I	2 Distinct local signs of infection (inflammation signs, pus, foul odor, etc.) 3 Systemic effects (fever, etc.)
Granulation			
g	0 Granulation cannot be evaluated because of healing or shallowness of wound 1 Normal granulation occupies ≥ 90% of wound surface 2 Normal granulation occupies ≥ 50% and < 90% of wound surface	G	3 Normal granulation occupies ≥ 10% and < 50% of wound surface 4 Normal granulation occupies < 10% of wound surface 5 Normal granulation is not present
Necrotic tissue: If different types of necrotic tissues coexist, evaluate based on the predominant type			
n	0 No necrotic tissue	N	1 Soft necrotic tissue is present 2 Hard, thick, tightly bound necrotic tissue is present
Pocket: Always evaluate using the same body position. The overall area encompassing the pocket (including ulcer surface) [Diameter (cm) × Minor axis (cm)] minus the size of the ulcer			
none	No letter is added	– P	1 < 4 2 ≤ 4, < 16 3 ≤ 16, < 36 4 ≤ 36

Method for evaluating the condition of pressure ulcers
(Developed by the Academic Education Committee of the Japanese Society of Pressure Ulcers)



(Quoted from Guideline for Local Treatment of Pressure Ulcers Based on Scientific Evidence[1])

Fig. 4 Treatment scheme for deep pressure ulcers in the chronic phase

pressure ulcer in the process of wound healing and determining the type of care needed in this phase. Traditionally, the severity of a pressure ulcer was judged based on the depth of the skin defect. However, evaluation of the condition of the wound surface is more relevant to the determination of treatment strategies. Clinical practice in the past often involved the indiscriminate use of standardized local treatment partly because of a lack of this evaluation of the wound surface. The Japanese Society of Pressure Ulcers has been proposing the DESIGN classification as a new method of evaluating the condition of pressure ulcers, and this method was incorporated in the reimbursement reduction policy for not using pressure ulcer prevention. In this classification, the wound surface is evaluated quantitatively in terms of depth, exudate, size, inflammation/infection, granulation, and necrotic tissues. The name "DESIGN" consists of the initials (D, E, S, I, G, and N) of these evaluation items (Fig. 3).[7] In the classification system for severity evaluation, a severe condition is denoted by an uppercase letter and a mild condition is denoted by a lowercase letter for each evaluation item. If wound healing is making progress in the right direction, uppercase letters decrease and lowercase letters increase gradually, providing an indication that the treatment strategy is right. In addition, there is another DESIGN classification system for the evaluation of treatment progress. In this system, the progress is evaluated in scores, which may be used as objective data to evaluate therapeutic intervention and clinical trials.

A New Guideline Based on Scientific Evidence

In view of the actual situation of pressure ulcer treatment as described above, the Japanese Society of Pressure Ulcers keenly felt the need for guideline for the local treatment of pressure ulcers based on scientific evidence. After 2 years of efforts, the Society formulated a new guideline complying with EBM. This guideline has been developed according to the methodology based on scientific evidence, in which the guideline development committee of the Society conducted a literature search and validation of evidence level to determine the level of recommendation. For clinicians treating pressure ulcers in daily practice, knowledge of the evidence for topical medications, dressing materials, surgical treatments, and physical therapies has great

importance in making clinical decisions and determining treatment strategies. Every physician should read the guidelines as a part of the system supporting pressure ulcer treatment.

This guideline first presents the basic treatment scheme of wound treatment (Fig. 4), and describes the concepts that should be used in wound treatment. Employing the new concepts of wound bed preparation and moist wound healing, the guideline provides for the use of the DESIGN wound surface evaluation proposed by the Japanese Society of Pressure Ulcers and prescribes clinical questions that are useful in making clinical decisions (Fig. 5).

The methodology of EBM has been embodied perfectly in the formulation of the guideline. The level of evidence was determined based on a literature search. The level of recommendation was then determined based on the level of evidence and the expected benefit and harm, incorporating expert opinions.

While wound treatment represents a very

Fig. 5 Clinical questions in the Guidelines for the Local Treatment of Pressure Ulcers Based on Scientific Evidence[1]

Clinical Questions (CQs)	
In the case of a shallow pressure ulcer (d)	
Clinical Question 1	
①	What topical medication should be used for reddening (d1)?
②	What dressing material should be used for reddening (d2)?
③	What topical medication should be used for blisters?
④	What dressing material should be used for blisters?
⑤	What topical medication should be used for erosion and shallow ulcers (d2)?
⑥	What dressing material should be used for erosion and shallow ulcers (d2)?
In the case of a deep pressure ulcer (D)	
Clinical Question 2	To convert N to n
①	How should surgical debridement be performed?
②	What topical medication should be used?
③	What dressing material should be used?
④	How should cleansing be performed?
⑤	What physical therapies are available?
Clinical Question 3	To convert G to g
①	What topical medication should be used?
②	What dressing material should be used?
Clinical Question 4	To convert S to s
①	What topical medication should be used?
②	What dressing material should be used?
③	In what cases should surgical treatment be performed?
④	What physical therapies are available?
Clinical Question 5	To convert I to i
①	What topical medication should be used?
②	What dressing material should be used?
③	Is disinfection necessary?
④	How should cleansing be performed?
⑤	In what cases should surgical treatment be performed?
⑥	What physical therapies are available?
Clinical Question 6	To convert E to e
①	What topical medication should be used?
②	What dressing material should be used?
Clinical Question 7	To eliminate P
①	What topical medication should be used?
②	What dressing material should be used?
③	In what cases should surgical treatment be performed?
④	What physical therapies are available?

important area of the daily practice of clinicians, advancement in this field is rapidly outdating old theories of wound management. There are many pieces of information that physicians need to facilitate wound healing, such as the appropriateness of disinfection, the maintenance of a moist environment, the use of new dressing materials, the management of local infection, and the unresponsiveness of cells at the woundedge. The new concepts of wound management introduced concisely in the guideline may be applied to the management of lower leg ulcers, diabetic ulcers, and burns, in addition to pressure ulcers. In this sense, all clinicians should read the guideline, master the new wound management theories, and use them in daily practice.

Conclusion

Focusing on pressure ulcers, this article outlined the present state of wound treatment in Japan. The situation of medical practice involving pressure ulcers underwent drastic changes during the past 10 years, exerting considerable influence on medical practice as a whole. Supported by the advancement in theories of wound healing, new therapeutic concepts took root and new medications and dressing materials were developed one after another. The reality of pressure ulcer development in acute care hospitals prompted us to understand the importance of nutrition management and team practice, and this produced a major transformation in our thinking about the prevention and management of pressure ulcers. A remarkable fact is that new trends and innovative concepts were accepted smoothly because wound treatment was an interdisciplinary undertaking and it was relatively new as a field of study. Various efforts in this field culminated in the formulation of guidelines according to EBM. We need to keep our eyes on the further development of wound treatment, which is relevant to all clinical departments.

References

1. Japanese Society of Pressure Ulcers. Guideline for Local Treatment of Pressure Ulcers Based on Scientific Evidence. Tokyo: Shorinsha; 2005.
2. Miyachi Y. Pressure ulcers in acute care hospitals and the roles of pressure ulcer treatment teams. Journal of Clinical and Experimental Medicine. 2005;213(8):2816–2819.
3. Ishikawa O, Okada K, Miyachi Y, et al. Epidemiological survey of pressure ulcers in hospitals, geriatric health facilities, and domiciliary nursing care stations in Gunma Prefecture. Japanese Medical Journal. 1998;3864:25–30.
4. Japanese Society of Pressure Ulcers. Guidelines for Pressure Ulcer Management. Tokyo: Shorinsha; 2002.
5. Schultz GS, Sibbald RG, Falanga V, et al. Wound bed preparation: a systematic approach to wound management. Wound Repair Regen. 2003 Mar;11(Suppl 1):S1–S28.
6. Jones J. Winter's concept of moist wound healing: a review of the evidence and impact on clinical practice. J Wound Care. 2005 Jun;14(6):273–276.
7. Sanada H, Moriguchi T, Miyachi Y, et al. Reliablility and validity of DESIGN, a tool that classifies pressure ulcer severity and monitors healing. J Wound Care. 2004;13:13–18.

Current Status of Electronic Medical Recording in Japan and Issues Involved

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Abstract

For team care to function smoothly, it is necessary for healthcare providers to have unified management and convenient sharing of medical care information and to promptly implement such information in the planning of examinations, diagnosis, and treatment. In addition, to provide patients with appropriate medical care information on the basis of informed consent, healthcare providers need to prepare medical records that are worthy of disclosure. Electronic medical recording systems can serve as a good tool to this end.

In Japan, the storage of medical records in electronic media was permitted in 1999, and 2 years later, the Grand Design toward Computerization in the Medical Field implemented by the Ministry of Health, Labor and Welfare targeted the dissemination of electronic medical records in at least 60% of clinics and at least 60% of hospitals with 400 or more beds throughout the country during the five years prior to 2006. The form of medical records and their method of storage have been left up to each medical institution provided that three criteria, namely, authenticity, visual readability, and storage property, are ensured. However, as of April 2004, electronic medical recording systems had been introduced in only 11.7% of medical institutions with 400 or more beds. The reasons for the delay in the spread of electronic recording are its high introductory costs and unknown cost-effectiveness. A governmental subsidy for the introduction of electronic medical recording that was provided during the initial two years has been abolished owing to financial constraints. Moreover, the introduction of such a recording system may impose an increased burden on doctors and other staff members in terms of data input, and consequently may adversely affect the quality of patient services by, for example, increasing waiting time.

To further disseminate electronic medical recording systems, it is desirable for each medical institution to review its current daily clinical practices and for the Government to provide some form of official support to institutions in which an electronic medical recording system has been adopted.

Key words Electronic medical records, Information sharing, Cost-effectiveness, Task burden, Official support

Introduction

The history of computerization of medical information in Japan began in 1988 with permission from the Ministry of Health and Welfare to prepare medical records by using office automation equipment. In 1994, the storage of image data such as radiographs in electronic media such as magneto-optical disks was permitted under prescribed criteria of safety, reproducibility, and common availability. The subsequent issuance on April 22, 1999, of notification concerning the storage of medical records and other data in electronic media opened the door to an era of electronic medical recording. The introduction of electronic medical recording systems was intended to 1) ensure the quality of medical care, 2) improve patient services, and 3) upgrade management efficiency. From the viewpoint of healthcare providers, the introduction of such systems was advantageous in that they allowed

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for unified management and convenient sharing of medical care information, making it possible, for instance, to view medical records inside the institution without the limitations of time and place. Moreover, prompt circulation of information among healthcare providers is indispensable for decision-making in diagnosis and treatment policies under the current model of team care. Further, it has become easier for patients to receive appropriate medical care information in the form of neat, legible medical records, time series displays, graph illustrations of test results, and printed image data. These enhancements have enhanced patient-oriented medical care, in which patients are fully informed of their situation and have input into decisions regarding the examination and treatment of their disease.

In recent years, computerization in the field of medical care has progressed rapidly in advanced Western countries such as Australia, Canada, the United Kingdom, and the United States. In the US, President Bush announced in 2004 that electronic medical records should be available for every American citizen within 10 years, and efforts have been made to develop and disseminate electronic medical recording systems as part of the project to establish a more electronically based government. In the UK and Canada, computerization projects initiated by the national government were begun in 2002, preceding the US. In the UK, standardization procedures have been promoted through a national project on medical information technology, while in Canada electronic medical recording was facilitated by an organization co-financed by the national government and the private sector, and construction of electronic medical records and enhancement of patient management have been carried out within each province.[1] In these countries, as in Japan, the increased demands of the citizenry for better quality medical care and greater patient safety on the one hand and the need for reduced medical care costs on the other underlie these movements.

In Japan, although the introduction of electronic medical records was encouraged by the Grand Design toward Computerization in the Medical Field issued by the Ministry of Health, Labor and Welfare in 2001, the rate of introduction is still only about 10%. In Japan, it seems that more attention is being focused on improving the quality of medical records, on securing their authenticity and readability, and on storage, whereas the emphasis in other countries is on constructing networks of medical institutions. One might wonder why the introduction of electronic medical records has made such slow progress in Japan. Current problems of medical care computerization in this country are discussed in this paper, including a retrospective examination of the history of computerization.

History of medical computerization in Japan

Historically, much of Japan's knowledge of Western medical science was introduced from Germany prior to World War II, followed by the influence of American medical science after the war. This dual ancestry resulted in some confusion in recording medical records, since for many years German, English, and Japanese medical terms all were in common usage. In addition, cipher-like descriptions or abbreviations understandable only to doctors, but not to patients or third parties, tended to be used frequently in communicating medical information. Unfortunately, conventional medical records sometimes conveyed information that was difficult to understand and largely illegible. Thus, patients developed the impression that medical records were confidential and were the possession of the physician. However, increasing public pressure to disclose medical care information and progress in patient-oriented team care resulted in greater transparency.

After the 1980s, patients' increasing awareness of their rights led to rapid changes in the disclosure of medical care information in Japan, and it currently is widely recognized that patients have the right to access their medical records. Society now demands that information regarding medical care should be provided to the patient, and doctors are required to prepare medical records appropriate for disclosure. Because they offer clear, legible descriptions in Japanese and adopt a standardized method of description based on the principle of problem-oriented medical records (POMR), electronic medical records have become commonly used in Japan as a support for the provision of appropriate medical care information, replacing the conventional paper media.

In the current team care setting, decisions concerning treatment policy are made not only by physicians and nurses but also by various other

healthcare professionals, including pharmacists, radiological technicians, clinical laboratory technicians, physiotherapists, dietitians, and medical social workers who are employed by the medical institution. Professional information and knowledge are incorporated into medical records, which are then shared by the various healthcare providers who are part of the team. In preparing medical records, healthcare professionals should not make mere memos or personal notes, but should provide simple descriptions that are comprehensible to anyone. The introduction of electronic medical recording is expected to promote the unitary management of information and sharing of information among healthcare providers and contribute to the standardization of medical care based on the policies of clinical pathways and evidence-based medicine (EBM).

Major events during the progress of medical computerization in Japan are described below.

—May 6, 1988—

"Methods of description for medical records, etc." (Notification from the Health Policy Bureau, Ministry of Health and Welfare)

The use of office automation equipment, including word processors, instead of handwriting, was permitted for preparing medical records. This ensured that medical records would be clear and legible. However, the storage of records in electronic media was not authorized, and the paper printouts of medical records prepared with word processors, etc., were stored. The printouts required the signature and seal of the doctor or other staff member who prepared the medical record, to define the responsibility of the preparer. Despite the notification, most medical institutions continued to use handwritten paper records because of the slow adoption of office automation equipment and lack of experience in keyboard operation.

—March 29, 1994—

"Storage of radiographic data, etc., in magneto-optical disks and other media" (Notification from the director of the Health Policy Bureau, Ministry of Health and Welfare)

This notification permitted the storage of radiographic data in magneto-optical disks and other electronic media so long as the requirements of safety, reproducibility, and common availability are met. Although this was the first notification to permit electronic storage, it did not disseminate to the extent that the Ministry of Health and Welfare had expected. Insufficient adoption of the notification was attributed to the fact that first priority was given to magneto-optical disks as the storage medium, and cooperation within the Ministry of Health and Welfare was inadequate.

—April 22, 1999—

"Storage of medical records in electronic media" (Notification from the directors of three bureaus of the Ministry of Health and Welfare)

Storage of medical records in electronic media was permitted, provided that the criteria of authenticity, visual readability, and storage property were satisfied. The use of electronic medical records in place of paper medical records was permitted by this notification.

—August 8, 2001—

"Grand Design toward Computerization in the Medical Field" (Healthcare Information System Committee)

A five-year plan for healthcare computerization was developed, and an overall design was formulated to indicate the path and promotional strategies leading to the goal.

Disclosure of medical care information

In Japan, electronic medical recording has been disseminated as an improved means of providing medical care information. In tracing back the history of disclosure of medical care information, it is apparent that movements seeking the disclosure of medical records have been in existence since the 1980s, together with movements of citizens toward wider disclosure of information contained in other formal documents. The background for such initiatives was patients' increased awareness of their rights and their desire to make their own decisions as to examinations, procedures, and treatments after having received full disclosure as to the nature of their situation. In 1986, in a civil action in which patients sought access to their medical records, the Tokyo High Court rejected the appeal, handing down the decision that patients are not guaranteed the right to access their medical records, thereby raising the bar for disclosure of medical records. Eventually, the movements for disclosure of medical records became more strident with the lead of citizens' groups, and the momentum for disclosure increased after the World Medical Association published in 1995 the "Declaration of Lisbon on the Rights of the

Table 1 History of the patients' rights movement to obtain disclosure of medical records in Japan

Apr. 1996	"Citizens' Association to Claim Disclosure of Medical Healthcare Information" was set up.
Jun. 1997	Notification of patients' rights to obtain receipts for medical fees. (Ministry of Health and Welfare)
Jun. 1998	Report calling for legislated disclosure submitted to the Ministry of Health and Welfare. (Study Panel on Utilization of Medical Care Information Including Medical Records)
Jan. 1999	"Guidelines for Provision of Medical Care Information" issued. (Japan Medical Association)
Feb. 1999	"Guidelines for Provision of Medical Care Information in Hospitals Affiliated with National Universities" issued. (Ministry of Health and Welfare)
Apr. 1999	Storage of medical records in electronic media permitted. (Ministry of Health and Welfare)
Apr. 2000	"Guidelines for Provision of Medical Care Information in Tokyo Metropolitan Hospitals" issued. (Tokyo Metropolitan Government Bureau of Public Health) Development of the department for medical record management in medical institutions encouraged. (Ministry of Health and Welfare)
Mar. 2001	Fourth revision of the Medical Service Law issued. The revised Law allowed for medical institutions to notify in their advertisements the status of disclosure of patients' medical records and the result of evaluation of their medical practices as determined by the Japan Council for Quality Health Care.

Patient (revised)", which prescribed that the patient has the right to receive any information about himself/herself recorded in his/her medical records (Table 1).

During the past 10 years, various medical institutions developed their own guidelines for the disclosure of medical care information on the basis of JMA's guidelines, and have been providing medical care information in an active manner to meet the demands of society. To prepare medical records suitable for disclosure, storage of medical records in electronic media (electronic medical records) was permitted, and the management system for medical care information was enhanced through the development of a department for the management of medical care information in each medical institution. Although JMA accedes to the disclosure of medical records, it is against legislating disclosure, because it believes that disclosure should be a matter of the doctor's discretion. JMA takes the view that the disclosure of medical records would be implemented by the doctors themselves, without the need of compulsory regulation.

Definition and dissemination of electronic medical records

In general, ordering systems as well as systems for recording medical care data by doctors, nurses, and co-medical personnel are referred to as electronic medical recording systems. "Practice guidelines for the introduction of electronic medical recording"[2] issued by the Japan Municipal Hospital Association defines the electronic medical recording system, as follows:

The electronic medical recording system is an information technology system for recording all data including those related to doctors' medical care (medical records in a narrow sense). It involves medical care data including the medical care record prescribed in Article 24 of the Medical Practitioners Law, and nursing records, image findings, rehabilitation records, nutritional guidance records, and patient compliance instruction records. This is regardless of the extent of ordering and whether imaging data are processed by IT.

The above is the minimal requirement for an electronic medical recording system. The practice guidelines also cite the following conditions desirable for such a system.

1) It adopts Problem Oriented Medical Record (POMR) as a descriptive form.
2) It allows input, storage, and viewing of information on various specimens, physiological test results, and imaging data.
3) It has a close connection with the doctor's medical care record in terms of clinical pathway.

In addition, a comprehensive discussion is now ongoing, including the development of a definition of electronic medical records by the

Table 2 Grand Design Toward Computerization in the Medical Field

(1)	Introduction of the electronic medical recording system In ≥60% of clinics in the country, and ≥60% of hospitals with ≥400 beds (by 2006)
(2)	Introduction of the electronic processing system for the diagnosis and treatment of patients for medical fee receipts ≥50% of hospital receipts throughout the country (by 2004) ≥70% of hospital receipts throughout the country (by 2006)

(Healthcare Information System Committee, August 8, 2001)

Japan Association of Medical Informatics and grading of electronic medical recording systems by the Japanese Association of Healthcare Information Systems Industry (JAHIS).

In 2001, 2 years after official permission was obtained for electronic medical recording, the "Grand Design toward Computerization in the Medical Field"[3] was issued by the Healthcare Information System Committee in order to facilitate the dissemination of electronic medical records (Table 2).

The Ministry of Health, Labor and Welfare has supported the introduction of the electronic medical recording system through a subsidy system since 2002, as a means of promoting the introduction of such a system. However, after 2 years of implementation, the subsidy was discontinued in 2005 because of the Government's financial situation. Withdrawal of the subsidy inhibited the spread of the electronic medical recording system, with some medical institutions postponing introduction of the system. Thus, there has been little progress in the introduction of the electronic medical recording system in medical institutions. The rate of introduction in medical institutions with 400 beds or more was 11.7% as of April 2004, according to the final report from the Standard Medical Record Promotion Committee, a private advisory panel to the Director of the Health Policy Bureau, Ministry of Health, Labor and Welfare.[4] In addition, the rate of introduction in clinics is also low, less than 10%. On the other hand, receipt computers, which are used in nearly 80% of medical institutions, represent an indispensable tool for them. The cost of introducing the electronic medical recording system remains high. The cost of introducing the system is reported to be 1–1.5 million yen (8,700–13,000 USD) per bed, and the total project cost 5 years after introduction may correspond to 2.5–5% of medical practice income, a heavy burden for a medical institution.

Three criteria for electronic medical record use

When electronic medical records are employed, the form of the medical record and the method of storage are left to the hospital's discretion as long as the three criteria—authenticity, visual readability, and storage property—are met.[5] An extract from the Electronic Medical Record Guidelines is presented below.[6]

1. Securing authenticity

Authenticity of an electronic medical record means that responsibility for preparation of the record is obvious to a third person, and that intentional or negligent input of false data and alteration, deletion, or confusion of data are prevented.

(1) Clarification of where responsibility lies

To define the locus of responsibility, it is necessary to prevent input by persons pretending to be the person responsible and to preclude any confusion of responsibility occurring as a result of subsequent addition, alteration, or deletion of the recorded data. The following measures are necessary to clarify the locus of responsibility for making electronic medical records.

1) Identification and authentication of the person responsible for making the electronic medical record

The person responsible for making the electronic medical record should be identified and authenticated (through ID, password, etc.), to prevent falsification by someone pretending to be the person responsible.

2) Finalization of the procedure

If a clerk, nurse, or other personnel inputs data instead of the person responsible for creating the electronic medical record, the

person responsible (doctor) should ascertain the data that has been input. In addition, the record should pass through a "finalizing" procedure to clarify responsibility for the addition, alteration, or deletion of the finalized record.

3) Recording of identification
When finalizing the record, identification of the person responsible for making the electronic medical record should be recorded.

4) Preservation of updated information
After the medical record has been finalized, any updating should be preserved to permit confirmation of the subsequent addition, alteration, or deletion.

(2) Prevention of false input, alteration, deletion, and confusing items
Incorrect input, alteration, deletion, or confusing items can be caused by negligence that occurs as a result of simple inputting errors, misunderstandings, or mix-up of data. It is useful to prescribe in the operating instructions that the contents be fully confirmed before the finalization procedure. False input, alteration, or deletion by someone pretending to be the responsible person should be prevented by identifying and authenticating the person to whom responsibility has been designated. Intentional false input and falsification are of course against the law.

In Japan, identification and authentication of the operator is generally done through the use of an ID or password, with the latter changed on a regular basis. In addition, biometrics technology with higher security, such as fingerprint verification, has been introduced recently. In general the record is designed to be unalterable after a certain period of time has elapsed, and any history of modification is to be stored with the original record if the original record is modified. It is common for doctors themselves to input orders for prescriptions, tests, and procedures, to avoid mistakes by clerks. However, an increasing number of medical institutions permit clerks to input written data from doctors in order to reduce the burden of data input on doctors. As of now, transcriptionists and real-time reporters are rarely used in medical institutions. In any case, to ensure the authenticity of electronic medical records, the responsible doctor is required to confirm the data input by the clerk. Most electronic medical recording systems currently available in Japan include this function.

2. Securing visual readability

Visual readability means that the data stored in electronic media are easy to read with the naked eye and can be printed on paper if necessary. It often is necessary to respond promptly to claims of disclosure from the patient or orders of submission for audit by the public health center, for lawsuits, and so on. The following measures are necessary to secure visual readability.

(1) Managing the location of information
If data are stored in various types of media, such as electronic and paper media, management of their location should be ensured.

(2) Managing the means to create visually readable data
The equipment, software, and relevant information necessary for visual reading of stored data should be available.

(3) Management of classified information
Information should be classified according to finalization status, extent of use, history of updating, degree of secrecy, etc., and access rights and other rights should be managed according to the class of information.

(4) System operation management
The operating procedure should be defined so as to guarantee safe and appropriate use of the system.

(5) User management
To control the allocation of access to the system, the procedure for user management should be clearly defined.

3. Securing storage property

Storage property refers to the storage of data under conditions such that the data can be restored at any time while maintaining their authenticity and visual readability during a given legally designated period. It is necessary to execute the following measures to secure storage property.

(1) Measures against deterioration of medium
The data should be copied to a new recording medium before the initial medium deteriorates.

(2) Management of software, equipment, and medium
Security measures should be taken to prevent the destruction and falsification of data by improper software, including computer viruses.

(3) Securing continuity
If the system is to be changed, data migration and other measures should be performed to ensure continuous use of the data accumulated by the former system.
(4) Information protection function
An information protection function should be incorporated to prevent intentional or negligent destruction of data. A data restoration function should also be installed in the event that such destruction has occurred.

Securing visual readability and storage are closely correlated, and the system must be able to operate for an extended period. In Japan, medical records are required by law to be kept for five years. Criminal responsibility for malpractice also extends for five years. Therefore, the statute of limitation runs out when the legal storage period has expired. On the other hand, the statute of limitations for liability in civil affairs is 10 years in cases of default of obligation, and, in cases of illegal acts, the statute of limitations is 20 years after the illegal act has occurred. Because of this, a five-year period actually is not adequate for the storage of medical records, and it is generally specified in medical institutions that medical records should be kept for 20 years, until the statute of limitations for civil affairs liability runs out or for an indefinite period. Therefore, although the recording medium of an electronic medical recording system is not designated by law, many medical institutions adopt a high-capacity server.

In addition, as points to keep in mind for system operation, it is recommended that operation and management rules suitable for each medical institution be developed and followed, that data compatibility among different systems be secured to promote efficient, mutual use of data, and that measures to protect privacy be taken.

Packaging and standardization of the system

When an electronic medical recording system is incorporated in a medical institution, the system may be developed from scratch according to the demand specifications of the institution, or packaged system software provided by a vendor may be purchased. In the case of the former, development of the system requires huge expenditures and a prolonged period of time, among other problems. In addition, staff members working in the medical care setting rarely have a clear understanding of system development, and it is difficult to standardize systems if systems addressing various different requirements are developed. The market for electronic medical recording systems is expanding rapidly in Japan, and more than 10 major firms have entered the market. The quality of software applications provided by these vendors is high, and most of them are standardized in regard to basic requirements. When introducing an electronic medical recording system, most medical institutions tend to purchase a software package and customize it if necessary.

The form of medical records and the method of their storage are left to each medical institution under its own responsibility, so long as the three criteria are satisfied: authenticity, visual readability, and storage property. However, if each medical institution were to adopt an arbitrary system, it would be difficult for institutions to share data, and secondary use of the data for constructing a database of medical care information could be difficult. In this connection, a foundation, the Medical Information System Development Center (MEDIS), has developed a nationwide uniform terminology and coding schema under commission from the Ministry of Health, Labor and Welfare, to promote the standardization of electronic medical records. The following items have been standardized up to now.

(1) Terms and examinations/procedures
1) Diagnoses
2) Operations and procedures
3) Clinical laboratory tests
4) Medications
5) Medical materials
The above five items are coded, with diagnoses are specified according to ICD-10 (International Statistical Classification of Diseases and Related Health Problems—10th Revision) and operations and procedures according to ICD-9-CM (International Statistical Classification of Diseases and Related Health Problems—9th-Clinical Modification).
(2) Standardization of information exchange standard
To ensure interchangeability in information exchange, the use of products that have the following specifications as standard features is encouraged.

Table 3 Summy of model hospital

Item	Hospital profile
No. of beds and outpatients	500 beds (capacity operating rate 83%) Average 1,200 outpatients/day Outpatient revenue per capita 8,000 yen (70 USD) Inpatient revenue per capita 40,000 yen (350 USD)
Specialty and department	General hospital (23 specialties, emergency, ICU/CCU) Information technology is introduced in outpatient clinics,ward, and all other departments including PACS.

(Adapted from final report of the Standard Electronic Medical Record Promotion Committee, 2005)[4]

Table 4 Cost of introduction

If the system is introduced on the basis of a 5-year lease with 24-hour support, the total expense is 2,338 million yen (20 million USD). This converts to 467.6 million yen (4 million USD) annually.

Since the revenue from medical practice in the model hospital is estimated to be 8,856 million yen (77 million USD), the introduction and maintenance cost accounts for about 5.2% of the revenue per year. (467,600,000 yen ÷ 2,338,000,000 yen).

1) HL7 Ver. 2.4 or later, and HL7 Ver.3 (XML form)
2) DICOM standard

In addition, standardization (coding) of terms used for recording data from "interviews and findings" is now under consideration.

Cost-effectiveness

One of the reasons for the relative lack of progress in the spread of electronic medical recording systems is their high introductory cost coupled with uncertain economic results. Our hospital, a small hospital with 215 beds, has been working on the systematization of medical information since 1991. The systems so far introduced in our hospital are as follows:

1) Medical practice support system (medical records); 2) Ordering system; 3) Clinical pathway system; 4) Nursing support system; 5) Medical accounting system; 6) Radiation information system (RIS); 7) Image and information management system (PACS); 8) Dispensing support system; 9) Pharmaceutical management and guidance system; 10) Drug information system; 11) TDM system; 12) Clinical examination system; 13) Microbiological examination system; 14) Pathological examination system; 15) Nutritional management system; 16) Thorough health screening system; 17) Referral patient management system; 18) Clinical history management system; 19) Long-term medical care database management system.

Our hospital adopted a system package, and the total project cost was about 320 million yen (2.8 million USD), including the subsidy. The cost of introduction was 1.5 million yen (13,000 USD) per bed. Assuming that the system is used for five years, the per-bed, per-day cost of introduction for each inpatient is:

1,500,000 yen (13,000 USD)
÷ (365 days × 5 years) = 822 yen (7.1 USD).

This means that the hospital incurs a burden of about 800 yen (7 USD) per bed per day (patient service) because of the introduction of the electronic medical recording system. Whether the revenue obtained is worth this cost is an issue. In this regard, the Standard Medical Record Promotion Committee reports that an increase of 600 million yen (5.2 million USD) in annual revenue is expected for a model hospital with 500 beds, 1,200 outpatients per day, outpatient revenue per capita of 8,000 yen (70 USD), and inpatient revenue per capita of 40,000 yen (350 USD) (Table 3).

According to my analysis of the above report, the cost of introducing and maintaining the sys-

Table 5 Increase in revenue from system introduction

1) Prevention of insurance claim omissions: annual revenue increase of 3%
2) Improvement of medical practice functions: annual revenue increase of 1% from change in profit structure
3) Reduced outsourcing of office work: annual revenue increase of 0.7% from reduction of office clerks in the medical processing division and medical practice departments
4) Reduction of office work: annual revenue increase of 2% from reduction of expenses for record forms and covers, etc.
5) Reduction of drug expenses by drug management: annual revenue increase of 0.5% from a 3% reduction in drug expenses
6) Reduction of medical materials by adoption of SPD: annual revenue increase of 0.7% from a 6% reduction in medical material expenses
7) Loss of marginal gain from film use, system maintenance annual revenue decrease of 1.4%

The value obtained by subtracting 7) from the sum of 1)–6) (=6.5%; about 600 million yen (5.2 million USD)) is the revenue increase by adopting the electronic medical recording system.

tem corresponds to 5.2% of the annual revenue derived from medical practice (Table 4). On the other hand, the increase in revenue resulting from system introduction is 6.5% annually (Table 5). The difference results in a net profit of 1.3%. This means that an increase in net profit of 1.3% per year can be expected by introducing the electronic medical recording system. In the above model hospital, the profit is calculated to be about 100 million yen (870,000 USD) per year. However, some of the institutions where the system already has been introduced feel that personnel costs have increased because of complicated input operations and increased overtime work. In addition, although a large reduction of 20 clerks is factored into the above estimate, each medical institution has already been cutting down on the size of its staff under a more severe management environment, and thus further reduction is difficult in actuality. The cost-effectiveness of system introduction remains to be determined by a fact-finding survey of medical institutions using the system.

Changes in workload following introduction of the electronic medical recording system

Our hospital was among the first in this country to proceed with systematization of medical information. A computerized ordering system was adopted in 1991, and Web delivery of radiographic images began in 1997. The electronic medical recording system in our hospital started full-scale operation in May 2004. In December 2004, after 6 months of operation, all staff including doctors (permanent staff members, 189 individuals) were given a questionnaire survey to determine their level of satisfaction with the system. The response rate was 88%. The major items associated with a high degree of satisfaction were as follows:

Viewing medical records is possible anytime inside the hospital (85%); Viewing images (radiography, endoscopy, ultrasonography) on the monitor is possible (85%); Making records legible and easily understandable is possible (81%); Unlike paper records, there is no risk of their becoming scattered or lost, allowing long-term storage (79%); Space required for storage is reduced (73%).

Among the staff as a whole, their impression of the workload was reported as "decreased markedly" or "decreased" in 13%, "increased markedly" or "increased" in 40%, and "no change" in the remaining 47%. However, there were large differences of opinion according to occupational category.

In other words, about 30% of nurses and medical technicians felt that the workload had increased, whereas about 90% of doctors felt so, indicating that doctors suffered an increased workload as a result of including input operations. In the overall evaluation, those who were "satisfied" accounted for 60% among doctors and other staff members, with those who reported "no change" or "discontented" accounting for 20% each. The results indicated that doctors

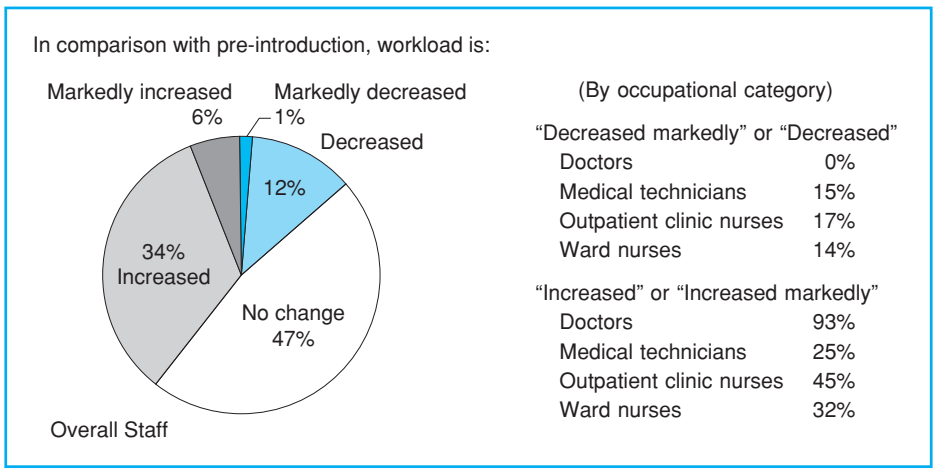

Fig. 1 Changes in workload among the staff

Table 6 Loans to support upgrading of medical institutions (in 2002)

Loan project	No. of sites	Programmed government subsidy (×1,000 yen)
Facility improvement for introducing the electronic medical recording system	108	12,464,271 (108 million USD)
Facility improvement for modernizing the medical institution	20	1,336,926 (11.6 million USD)
Environmental improvement for intern doctors in clinical training hospitals	1	1,961 (17,000 USD)
Environmental improvement for clinical training facilities for dentists	3	78,011 (678,000 USD)
Environmental improvement for education in dental hygienists training schools	1	7,381 (64,000 USD)
Environmental improvement for nursing staff training	19	41,625 (362,000 USD)
Total	152	13,930,175 (121 million USD)

were making an effort to secure the quality of medical care and to improve patient services, although their workload was increased.

Introducing an electronic medical recording system in a hospital often places an increased burden on personnel, and causes stress particularly for those who are unfamiliar with computer operations. Since data input should be carried out at the point of origin, the doctors' workload inevitably is increased to a great extent. One harmful effect is that the increased workload of doctors and other staff members results in longer waiting times for patients. This is not only because doctors are inexperienced and unfamiliar with input operations, but also because the electronic medical recording system has enabled "appropriate medical practice," which takes into account patient safety management and informed consent. Improved quality of medical practice has extended the amount of time for the doctor to see the patient. To address the prolonged waiting time, operational reform, such as more efficient use of time by conducting preliminary examinations in an interview center and the use

of an Internet reservation system, may be helpful. The simple introduction of an electronic medical recording system can cause deterioration in patient services, depending on the type of work.

Governmental support measures

The Ministry of Health, Labor and Welfare gave support to the introduction of electronic medical recording systems by publishing the Grand Design in 2001 and providing grants-in-aid to medical institutions in 2002 and 2003. The grant was set at half the total project cost, and was paid up to an upper limit of 100 million yen (870,000 USD) when the total project cost exceeded 200 million yen (1,740,000 USD). The actual results of implementation in 2002 were Table 6.

Electronic medical recording systems were introduced in 108 medical institutions in 2002, and as many as 90% of the loans to support upgrading medical institutions were used to introduce electronic medical records. The Grand Design set a goal of introducing electronic medical recording systems in at least 60% of hospitals with 400 or more beds, a total of about 500 hospitals, over five years. About 100 hospitals per year were expected to receive the grants-in-aid. However, the subsidy was discontinued in 2004 because of financial difficulties. Therefore, some institutions considering the introduction of the system in expectation of the subsidy postponed it, causing further delay in dissemination of the system. After 2004, support projects limited to promotion of the development of local networks of medical institutions already equipped with electronic medical recording systems have been carried out. Unfortunately, resumption of the discontinued subsidy is unlikely.

Conclusion

There is no doubt that electronic medical records are indispensable for providing appropriate medical information and high-quality medical care that includes patient safety. However, one of the reasons for the delayed dissemination of electronic medical recording systems is the potential increase in workload for doctors and other staff members following introduction of the system. The development of new input devices, such as pen tablets and voice input, which can replace conventional keyboard input, would reduce the burden on doctors. It is also necessary to consider the use of medical secretaries who are engaged in real-time reporting or transcription from voice recorders, instead of direct input by doctors. The simple introduction of an electronic medical recording system can result in deteriorated patient services, such as increases in waiting time, depending on the type of service involved. Thus, successful introduction of the system requires a review of medical care services as a whole.

Medical institutions in Japan commonly adopt packaged systems. Even in such cases, the cost of introduction is 1–1.5 million yen (8,700–13,000 USD) per bed. It is questionable whether these high introduction and maintenance costs should be borne by medical institutions alone. It is desirable that official support from the Government be available to medical institutions where the electronic medical recording system has been introduced.

References

1. Nii M. Current status of the spread of electronic health records (EHR) in overseas countries. Consideration of the Era of Electronic Health Records. Sanyo Electric Co., Ltd.; 2005:10. (in Japanese)
2. The Medical Information System Research Committee of the cooperative aggregate Japan Municipal Hospital Association. Practice Guidelines for Introducing the Electronic Medical Recording System in Municipal Hospitals. 2005. (in Japanese)
3. The Ministry of Health, Labor and Welfare. Grand Design toward Computerization in the Medical Field. 2001. (in Japanese)
4. The Ministry of Health, Labor and Welfare. Final Report of the Standard Medical Record Promotion Committee. 2005. (in Japanese)
5. The Ministry of Health and Welfare. Storage of Medical Records and Other Data in Electronic Media. 1999. (in Japanese)
6. The juridical foundation Medical Information System Development Center (MEDIS-DC). Electronic Medical Record Guidelines. 1999. (in Japanese)

Side Effects of Salbutamol Sulfate Delivered through a Metered-Dose Inhaler in a 14-Year-Old Boy with Bronchial Asthma

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Abstract

A β-adrenergic agent, salbutamol sulfate, is widely used for the treatment of asthmatic attacks. The use of a metered-dose inhaler (MDI) is a clinically preferred doing technique because it achieves effective bronchodilation within a relatively short period of time with fewer side effects. This article reports the side effects of salbutamol sulfate delivered by MDI in a 14-year-old boy. The patient came to our hospital about 1 hour after inhalation of the agent, with the chief complaint of abnormal feelings in chest. Heart rate was 138 beats/min, and QTc on the electrocardiogram was 0.477 second. The serum potassium level was 2.9 mEq/L, blood glucose 156 mg/dL, peripheral white blood cell count 13.600/μL, and neutrophil percentage 79.5%. Correction of potassium levels by fluid therapy led to improvement of his condition in approximately 24 hours. The patient was using salbutamol sulfate by MDI as the only agent. Based on the intervals and frequency of inhalation, this case seems to represent an adverse event of this agent. Our search of the literature revealed no report of side effects of this agent occurring in children. Thus, this case should serve as a warning to be borne in mind when salbutamol sulfate by MDI is used.

Key words Salbutamol sulfate, Metered-dose inhaler, Side effects

Introduction

The relation between asthmatic death and β-adrenergic agents drew attention in the 1960s,[1] when the leading medication was fenoterol hydrobromide MDI. As a result of various controversies since then, it has been suggested that the risk of asthmatic death associated with the use of β-adrenergic agents by MDI is substantial in children, and that there is also increased risk with salbutamol sulfate MDI.[2] A case in which a variety of side effects of salbutamol sulfate MDI occurred in an asthmatic patient is reported herein.

Case Report

The patient was a 14-year-old boy (weight 50 kg) who was diagnosed as having bronchial asthma at the age of 7 years. His disease was of the intermittent type with strong seasonal dependence. His doctor instructed him on how to use salbutamol sulfate MDI when he was 12 years old, and he had been using the medication since then. The patient usually took one puff of 100 μg at bedtime and morning, which achieved good control of asthma. The night before the present episode, he took one puff later than usual, i.e., after 11 o'clock, and fell asleep. About 7 o'clock the

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following morning, he noticed slight respiratory distress, wheezing, and coughing, and took one puff. Because there was no improvement of the symptoms, he took another inhalation, judging by himself that the previous inhalation had been insufficient. Since the symptoms improved, he went to school. At about 8 o'clock in the morning, he began to suffer abnormal feelings in chest and came to the hospital.

Findings on initial physical examination and laboratory tests

The patient had a rather pale complexion and tremor. He exhibited a regular heart rate of 138 beats/min, SpO_2 96%, QTc 0.477 second on electrocardiogram (normal, 0.425 second or less), peripheral white blood cell count 13.600/μL, neutrophil percentage 79.5%, serum potassium 2.9 mEq/L, and blood glucose 156 mg/dL. The patient's condition was considered to be a toxic reaction to overdose of the β-adrenergic agent salbutamol sulfate, and therefore potassium correction with fluid therapy (at a dose of potassium of 0.18 mEq/kg/h) was carried out. About 5 hours after the initiation of treatment, his condition improved, showing a heart rate of 98 beats/min, attenuated tremor, and a serum potassium level of 3.7 mEq/L. After that, a potassium dose of 0.02 mEq/kg/h was continued, and the patient's condition was restored to normal about 22 hours later, with a heart rate of 70 beats/min, eliminated tremor, and a serum potassium level of 4.1 mEq/L.

Discussion

Salbutamol sulfate has hardly any α-adrenergic action and has β_2 selectivity. One puff of 200 μg of this agent by MDI allows a 15% or more increase of forced expiratory volume in one second (EFV_1) to occur in as soon as in 5 or 6 minutes[3] and to last for a median 4.2 hours.[4] Because of these properties, this agent is widely used for relieving the acute symptoms of asthmatic attacks in daily living. In children, one puff of 100 μg may be taken four times a day at intervals of at least 3 hours.[5] Therefore, this agent generally is regarded as an important medication for rescue use during asthmatic attacks, but it is also used as prophylactic maintenance therapy. The current patient was instructed to take one puff twice a day, after rising from bed in the morning and at bedtime. On the morning of the day he came to our hospital, he had had an asthmatic attack that was not relieved by a single puff, and he added another puff, using his own judgment.

A variety of findings obtained upon the patient's physical examination and laboratory tests at the first visit to our hospital suggested side effects of β-adrenergic drug therapy. Tremor, tachycardia, headache, and decreased serum potassium levels as side effects are mentioned in the cautions for use of the product.[6] However, although decreases in serum potassium within the range of reference values have been reported,[7] there has been no report of side effects occurring in children, according to our search of the literature. Our patient also showed a prolonged QT interval, increased peripheral white blood cell count, increased neutrophil percentage, and increased blood glucose.

Reports of asthmatic death in children have been reviewed collectively. Thirteen asthmatic deaths occurred between 1998 and 2001, and two of the 13 cases were attributed to excessive dependence on MDI- or nebulizer-delivered β-stimulant medication.[8] Although it has been pointed out that increased asthmatic deaths due to the use of β-stimulants by MDI are more prominent among children,[8] the causal relationship between side effects and asthmatic death remains a matter of speculation, since the presence/absence of, for example, hypoglycemia and hypokalemia in cases of asthmatic death is not sufficiently clear.

In general, salbutamol sulfate is associated with increasing side effects such as tremor in a dose-dependent manner as the amount of inhalation increases.[9,10] Cardiac symptoms may lead to a fatal situation in the presence of hypoxemia or hypercapnia,[11] or when other drugs are used concomitantly.[12] In addition, inhalation of salbutamol sulfate during asthmatic attacks causes imbalance of the ventilation-perfusion ratio, resulting in a temporary decrease in arterial oxygen tension,[13] and, therefore, closer attention to the development of side effects is necessary. It has been shown that decreased serum potassium has a negative correlation with the cumulative amount of inhalation of this drug and a positive correlation with increased blood glucose.[14] These side effects usually do not cause clinical problems because the patient gains resistance during prolonged use of the usual dose of the drug.[10] In our

patient, however, no resistance to the side effects occurred. Our patient's development of a variety of side effects seems to have resulted from the following causes: 1) the patient inhaled the drug later than usual on the night before the episode, 2) he took two puffs in the morning during an asthmatic attack, and 3) inhalation by MDI is associated with slower renal excretion than oral dosing.[15]

Currently, long-acting β-adrenergic agents are being used more frequently. Since salbutamol sulfate MDI has great value as a medication for rescue use for asthmatic attacks occurring at school,[16] it is important for asthmatics to have a good understanding of the characteristics of this drug and sufficient knowledge of its usage.

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References

1. Inman WHW, Adelstein AM. Rise and fall of asthma mortality in England and Wales in relation to use of pressurised aerosols. Lancet. 1969;2:279–285.
2. Tanihara S, Nakamura Y, Matsui T, et al. A case-control study of asthma death and life-threatening attack: their possible relationship with prescribed drug therapy in Japan. J Epidemiol. 2002; 12:223–228.
3. vanNoord JA, Smeets JJ, Raaijmakers JAM, et al. Salmeterol versus formoterol in patients with moderately severe asthma: onset and duration of action. Eur Respir J. 1996;9:1684–1688.
4. Kemp JP, Bierman CW, Cocchetto DM. Dose-response study of inhaled salmeterol in asthmatic patients with 24-hour spirometry and Holter monitoring. Ann Allergy. 1993;70:316–322.
5. Glaxo Wellcome Company. Interview form of sultanol inhaler. 2000. (in Japanese)
6. Japan Pharmaceutical Information Center, Tokyo, Japan ed. Drug in Japan 27th ed. Tokyo: Jiho; 2004:878–881 (in Japanese)
7. Kishida M. Clinical aspects and related issues of β_2-stimulants. Japanese Journal of Pediatric Allergy and Clinical Immunology. 2004;18:426. (in Japanese)
8. Japanese Society of Pediatric Allergy and Clinical Immunology Committee on Asthmatic Death. 2001 report of the Committee on Asthmatic Death. Japanese Journal of Pediatric Allergy and Clinical Immunology. 2002;16:248–260. (in Japanese)
9. Lipworth BJ, Struthers AD, Mcdevitt DG. Tachyphylaxis to systemic but not to airway responses during prolonged therapy with high dose inhaled salbutamol in asthmatics. Am Rev Resp Dis. 1989;140:586–592.
10. Bremner P, Woodman K, Burgess C, et al. A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. Eur Respir J. 1993;6:204–210.
11. Higgins RM, Cookson WOCM, Lane DJ, et al. Cardiac arrhythmias caused by nebulised beta-agonist therapy. Lancet. 1987;2:863–864.
12. Nicklas RA, Whitehurst VE, Donohoe RF, et al. Concomitant use of beta adrenergic agonists and methylxanthines. J Allergy Clin Immunol. 1984;73:20–24.
13. Harris L. Comparison of the effect on blood gases, ventilation, and perfusion of isoproterenol-phenyle-phrine and salbutamol aerosols in chronic bronchitis with asthma. J Allergy Cl Immunol. 1972;49:63–71.
14. Lipworth BJ, Clark RA, Fraser CG, et al. The bio-chemical effects of high-dose inhaled salbutamol in patients with asthma. Eur J Clin Pharmacol. 1989;36:357–360.
15. Martin LE, Hobson JC, Page JA, et al. Metabolic studies of salbutamol-3H: A new bronchodilator, in rat, rabbit, dog and man. Eur J Pharmacol. 1971;14:183–199.
16. Heap E, Kalra D, Moore A, et al. Emergency asthma inhalers in schools. Arch Dis Child. 2003;89:590.

A Brief Overview of CMAAO and Its Recent Activities

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Key words CMAAO, WMA, Countermeasures for infectious diseases, Asia, Oceania

The Confederation of Medical Associations in Asia and Oceania (CMAAO) consists of 16 medical associations in Asia and Oceania. It is an affiliated association of the World Medical Association (WMA). The current Secretariat of CMAAO is located at the Japan Medical Association (JMA), which takes on the responsibility of supporting such activities of the organization as communication exchange with the hosting medical association for congresses and council meetings, and information gathering including infectious diseases in this area to be put on its web site.

The Establishment and Organization of CMAAO

The first CMAAO Congress in Tokyo, in 1959, marked the beginning of the practical activities of the organization. Prior to 1959, there was an organization called the Southeast Asian Medical Confederation. In 1956, this organization changed its name to the Confederation of Medical Associations in Asia and Oceania. At that time, Dr. R.P. Gonzalez of the Philippine Medical Association served as the first president, whose appointment was followed by that of Dr. Taro Takemi of the JMA at the first congress in 1959. At this congress, discussions were held on the constitution and membership fees among other issues. Furthermore, it was resolved that the JMA and the Philippine Medical Association make annual contributions of 1,000 US dollars and 500 US dollars, respectively, as an initial source of finance.

At the time of the first congress, the member medical associations numbered 6, including Australia, Burma, Republic of China (Taiwan), Indonesia, the Philippines, and Japan. Subsequently, CMAAO expanded its membership, and at the time of the 24th CMAAO Congress held in Seoul, Korea in September 2005, the number of its member medical associations had grown to 16, with Australia, Bangladesh, Cambodia, Hong Kong, India, Indonesia, Japan, Korea, Macau, Malaysia, Nepal, New Zealand, Philippines, Singapore, Republic of China (Taiwan), and Thailand.

The initial headquarters was established in the Philippines, followed by Malaysia and Thailand. In 2001, it was moved to the JMA.

Objectives of CMAAO

The major objective of CMAAO is, as stated in its constitution, to improve the level of medical education, clinical practice, and medical ethics in the region as much as possible. CMAAO also strives to deepen mutual cooperation and friendship among all member associations in Asia and Oceania.

In Southeast Asia, there is another confederation of medical associations called the Medical Association of South East Asian Nations

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Vice-Chair of Council	Ross Boswell	(New Zealand)
Treasurer	Yee Shing Chan	(Hong Kong)
Secretary General	Nobuya Hashimoto	(Japan)

(MASEAN). It was established in 1980, and includes 10 member medical associations. Some of these medical associations are also members of CMAAO. However, JMA is not a member of MASEAN. The CMAAO not only covers Asia but also the Oceanic nations of Australia and New Zealand, a wider area than MASEAN does.

The original mission of CMAAO was to utilize the organization to represent physicians in Asia and Oceania to the WMA. Currently, the JMA serves as the Pacific Regional Secretariat for the WMA. In this respect, the JMA is playing a role as a liaison between WMA and CMAAO. Therefore, it can be said that CMAAO not only promotes the solidarity of medical associations in the region, but is also a foundation to reflect the voices of the region to larger world organizations.

Recent Activities

Countermeasures for infectious diseases

CMAAO holds symposiums at each of its annual meeting to discuss various issues facing each country in the region, such as countermeasures for infectious diseases, medical education, patient safety, and insurance system. Infectious diseases have been a critical issue in the Asian region for some time, beginning with the recent outbreak of SARS and avian influenza. The CMAAO has been providing a forum for discussion on such issues common to member countries.

Due to the urgency of SARS, a proposal was introduced to establish a network allowing each member medical association and the CMAAO Secretariat (JMA) to exchange SARS related information. The SARS Network was established on the website of CMAAO, and member countries have contributed information on SARS. We are currently enlisting the cooperation from some medical associations and other sources to provide information on SARS and other related data. We are also working to improve the website to provide information on not only SARS and avian influenza, but also the conditions and countermeasures of infectious diseases which are deeply related to the CMAAO member countries.

Taro Takemi Memorial Oration

Commemorating Dr. Taro Takemi, former President of the JMA and contributor to the establishment of CMAAO, "The Taro Takemi Memorial Oration" has been given by prominent medical experts of hosting countries at every congress since 1991. At the congress held in Taiwan in 2001, Minister of the Department of Health, Dr. Ming-Liang Lee, spoke on medical education. More recently, at the congress held in Seoul in 2005, Dr. Tai Joon Moon, Honorary President of the Korean Medical Association, delivered his presentation about recent health environment of Korea. (Fig. 1)

Support for disaster victims of the Indian Ocean tsunami

To support the disaster victims of the Indian Ocean tsunami in December 2004, CMAAO, in keeping with its international agenda, has been collecting donations from its member countries and is preparing to donate the funds to the disaster-affected countries.

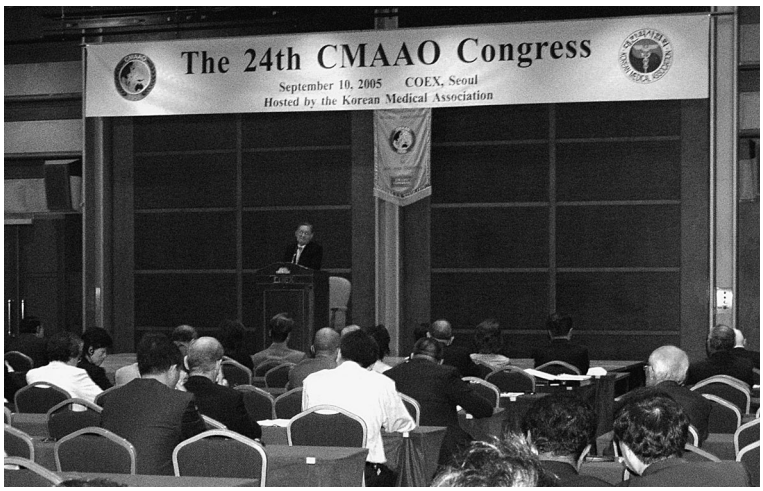

Fig 1. The 24th CMAAO Congress held in Seoul, 2005

Proposals on the Future of CMAAO

CMAAO's member countries exhibit great disparity in terms of GDP. How we understand this difference and make necessary adjustments in matters such as membership fees is one of several issues facing the future of CMAAO. Fostering a cooperative relationship with WMA to accelerate the activities of CMAAO is also one of the utmost important problems.

It has been nearly 50 years since the establishment of CMAAO. The current pressing issue is to enrich the organization and its activities. To accomplish this goal, we need concrete measures to seek cooperation with WMA as well as effort to implement the measures by drawing on our past activities and accomplishments.

Medical ethics and education for the physicians are some of the themes, which can be discussed and shared among all countries in spite of large differences in social and political systems. Furthermore, the issue of infectious diseases, which is unique in this region, needs the devoted efforts of the member countries.

As a Secretariat of CMAAO, we hope that from these efforts, the uniqueness of CMAAO will not only be nurtured, but also that our efforts will continue to be actively engaged in the activities to fulfill our responsibilities as the Pacific Regional Secretariat for the WMA.

Inhaled Glucocorticosteroid Therapy
—A recent asthma treatment

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Key words Bronchial asthma, Inhaled corticosteroid therapy

Introduction

Recent research has highlighted the prevalence of chronic inflammation of the airways in clinical bronchial asthma. It is also widely recognized that inhaled steroids are the most effective long-term management medicine in the treatment of airway inflammation. The recently published "Global Initiative for Asthma (GINA)"[1] as well as "Asthma Prevention and Management Guideline 2003, Japan",[2] recommend the use of inhaled steroids.

In this report, drawing upon the Japanese guidelines and the recently published results of large-scale clinical trials, we will indicate the method of inhaled steroid use.

Process and Penetration of Inhaled Glucocorticosteroid Use in Japan

Inhaled glucocorticosteroids were developed abroad and introduced to Japan. The Metered Dose inhaler of Beclomethasone dipropionate (BDP) was released in 1972 and introduced in Japan in 1978. Subsequently, the Metered Dose inhaler of Budesonide (BUD) and Dry Powder inhaler were released abroad in 1981 and 1988, respectively. The Dry Powder inhaler was introduced in Japan in 2002. Furthermore, the Fluticasone propionate (FP) rotadisk was released abroad in 1993, followed by the diskhaler in 1994. In Japan, the rotadisk was introduced in 1998, followed by the diskhaler in 2002, and the Metered Dose inhaler in 2003. In Japan, the basic ingredient for Beclomethasone dipropionate was changed from one prepared with chlorofluorocarbon (CFC) to one with hydrofluoralkane (HFA)(Qvar) in 2002.

Twenty years ago Beclomethasone dipropionate was the only inhaled glucocorticosteroid available in Japan. Therefore, the penetration of the medicine to general physicians was retarded as compared with other countries. The reasons for this are as follows: 1) the dosage limit for inhalation was low with 400 μg/day (later on this increased to 800 μg/day), 2) since it required daily inhalation of 4 times, compliance was inadequate, 3) the method of inhalation was difficult, requiring a spacer, and 4) there were many antiallergic agents already developed and available in Japan. However, after the release of Fluticasone propionate in 1998, the dosage limit for the inhalation was lessened. With administration of the inhalant twice a day and the easing of the inhalation procedures, its effectiveness became widely recognized by general physicians.

However, in Japan in 2000, 2 years after the release of Fluticasone propionate, as a result of the 130,000-patient study Asthma Insight & Reality in Japan (AIRJ),[3] in the past year the percentage of patients who experienced asthma

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episodes were as follows: 36% of adult patients and 58% of children experienced an emergency visit, and 30% of adults and 53% of children experienced work/school absence. These results indicate that the daily lives of the patients were considerably limited. Therefore, current asthma treatment does not sufficiently control asthma. In this study, the use of inhaled steroids was low with 12% in adults and 5% in children. The disparity with Europe is quite evident with 22% of adult Europeans and 23% of children using inhaled steroids according to a similar study, "Asthma Insights and Reality in Europe (AIRE)".[4] However, the use of inhaled steroids has been increasing in Japan since 2000 with the penetration of the guidelines.

Asthma Prevention and Management Guideline 2003, Japan[2]

Using the international guidelines as a base, the Japanese Guidelines categorize the severity of asthma into 4 steps, according to the characteristics of symptoms, peak expiratory flow rate, and forced expiratory volume in one second: Mild intermittent (Step 1), Mild persistent (Step 2), Moderate persistent (Step 3), and Severe persistent (Step 4). Patients are divided into these stratums, based on symptoms at the start of the treatment and past treatment and symptoms in the past. The inhaled glucocorticosteroid is the most effective long-term controller medicine and is the first-line therapy in long-term controllers for persistent asthma patients who are rated Step 2 or above (Table 1).

After achieving the desired treatment outcome with therapies in combination with a bronchodilator or a leukotriene modifier, including other long-term controller medicines, such as long-acting β2-agonists or theophylline, the guidelines indicate it is permissible to step-down the treatment after verifying the stability of control for a minimum of 3 months. If the symptoms are exacerbated or if the current treatment fails to control the symptoms sufficiently, it is necessary to step-up the treatment.

Currently, there are three types of inhaled glucocorticosteroids available clinically in Japan: Beclomethasone dipropionate (BDP), Fluticasone propionate (FP), and Budesonide (BUD). There are 2 types of inhalation methods: the pressurized Metered Dose inhaler (p-MDI) and the Dry Powder inhaler (DPI) with natural inspiration (Table 2).

All of these inhaled glucocorticosteroids have a high affinity with steroid receptors, high uptake quantity to organs and long retention time at the target regions. When excreted to the entire body, it has a characteristic of being swiftly inactivated by the liver enzyme. As for the comparison of effectiveness among medications, there are few comparative studies. Based on the international guidelines, the domestic guidelines advise setting the maximum dose in Step 4 to that permitted by health insurance, the maximum in Step 3 to be half of the maximum in Step 4, the maximum in Step 2 to be the half of the maximum in Step 3, and the rest in the same manner (Table 3).

The Results of Large-scale Clinical Trials on Asthma Treatment with Inhaled Glucocorticosteroids

The results of a large-scale Japanese clinical trial called the FINE study[5] was published in 2005. It was carried out in 510 primary care facilities nationwide, with the subjects being patients without previous continuous glucocorticosteroid use, including inhaled glucocorticosteroids. Asthma episodes due to the worsening of asthma symptoms for 6 months before and after the administration of Fluticasone propionate were investigated. 898 cases were studied. The occurrence of asthma episodes decreased from 62.9% before the administration to 24.9% after the administration, with a declining rate of 60.4%. The high declining rate was recorded regardless of patient age, severity of asthma, duration of asthma, or kinds of "add-on" long-term controllers. The percentage of patients who experienced the following episodes declined: hospitalization from 10% to 1.7%, emergency room treatment from 21.9% to 2.9%, unscheduled clinical visit from 49% to 19.1%, and work/school absence from 43.8% to 12.6%. This study validated the efficacy of inhaled glucocorticosteroids against asthma episodes.

The effects of early intervention with budesonide in mild persistent asthma have been investigated and reported abroad. One such study was a large-scale, international double-blind prospective study with approximately 7,000 subjects. The patients received either daily budesonide or a placebo once daily in addition to their usual

Table 1-1 Classification of asthma severity by clinical features before treatment

Severity	Step 1: Mild Intermittent	Step 2: Mild Persistent	Step 3: Moderate Persistent	Step 4: Severe Persistent
Characteristics of symptoms	●Asthma symptoms less than once a week ●Symptoms are mild and brief. ●Nocternal symptoms once or twice a month	●Symptoms more than once a week, but not every day ●Daily life or nocternal sleep disturbed more than once a month ●Nocternal symptoms more than twice a month	●Symptom daily ●As-needed use of short-acting inhaled β2-agonists nearly every day ●Daily life or nocternal sleep disturbed more than once a week ●Nocternal symptoms more than once a week	●Frequent exacerbation even under treatment ●Symptom daily ●Frequent nocternal symptoms
PEF FEV1.0	More than 80% of the predicted value, with less than 20% variability, or more than 80% of one's best PEF value	More than 80% of the predicted value, with variability of 20–30%, or more than 80% of one's best PEF value	60–80% of the predicted value, with more than 30% of variability, or 60–80% of one's best PEF value	Less than 60% of the predicted value, with more than 30% of variability, or less than 60% of one's best PEF value

Table 1-2 Recommended medications by level of severity: adults

Severity	Step 1: Mild Intermittent	Step 2: Mild Persistent	Step 3: Moderate Persistent	Step 4: Severe Persistent
Long-term controller medicines ●:Continuous use ●:Consider	●Consider the administration of either one of the following when experiencing asthma symptoms slightly more frequently, for instance once or twice a month, or an increase in the percentage of eosinophils in blood or sputum. • Inhaled glucocorticosteroid (minimum dose) • Sustained-release theophylline • Leukotriene modifier • Anti-allergic drugs	●Continuous use of inhaled glucocorticosteroid (Low dose) ●Or use continuously or combined with either one of the following: • Sustained-release theophylline • Leukotriene modifier • DSCG ●For nighttime symptoms or lasting airway closure in combination with inhaled glucocorticosteroid • Long-acting β2-agonists (inhalation/adhesive preparation/oral) ●For asthma patients due to allergies, in combination with either one of the above: • Anti-allergic drugs	●Continuous use of inhaled glucocorticosteroid (Medium dose) In combination with inhaled glucocorticosteroid, use either one or some of the following: • Sustained-release theophylline • Long-acting β2-agonists (inhalation/adhesive preparation/oral) • Leukotriene modifier ●Consider Th2 cytokine inhibitor	●Continuous use of inhaled glucocorticosteroid (High dose) In combination with inhaled glucocorticosteroid, use some of the following: • Sustained-release theophylline • Long-acting β2-agonists (inhalation/adhesive preparation/oral) • Leukotriene modifier ●Consider Th2 cytokine inhibitor ●When uncontrolled with the above: • Add oral glucocorticosteroid
In case of exacerbation	Short-acting inhaled β2-agonists, or short-acting oral β2-agonists, short-acting theophylline	Short-acting inhaled β2-agonists, etc.	Short-acting inhaled β2-agonists, etc.	Short-acting inhaled β2-agonists, etc.

(Asthma Prevention and Management Guideline 2003,[2] partially changed)

Table 2 Inhaled glucocorticosteroids currently permitted for clinical use in Japan

	p-MDI (Pressurized Metered Dose Inhaler)	DPI (Dry Powder Inhaler)
BDP (Beclomethasone dipropionate)	BDP-CFC (Aldecine etc) BDP-HFA (Qvar)	(−)
FP (Fluticasone propionate)	FP-HFA (Flutide Air)	FP-DPI (Flutide Diskus & Diskhaler)
BUD (Budesonide)	(−)	BUD-DPI (Pulmicort)

(Asthma Prevention and Management Guideline 2003[2])

Table 3 Estimated equipotent doses of inhaled glucocorticoids by classicication of asthma severity (adults)

Drug	Step 1 (Minimam dose)	Step 2 (Low dose)	Step 3 (Medium dose)	Step 4 (High dose)
BDP-CFC	200 μg/day	200–400 μg/day	400–800 μg/day	(800–1,600 μg/day)
BDP-HFA	100 μg/day	100–200 μg/day	200–400 μg/day	400–800 μg/day
FP-HFA	100 μg/day	100–200 μg/day	200–400 μg/day	400–800 μg/day
FP-DPI	100 μg/day	100–200 μg/day	200–400 μg/day	400–800 μg/day
BUD-DPI	200 μg/day	200–400 μg/day	400–800 μg/day	800–1,600 μg/day

(Asthma Prevention and Management Guideline 2003[2])

treatment. The daily budesonide dose was 400 μg for adults and 200 μg for children. The elapsed time to the first severe asthma-related event (SARE) was assessed. The results reported that in the budesonide group, the risk of developing SARE decreased 44% in 3 years (START study, 2003).[6]

The next study compared two therapies in their achievement level of total control: one with only Fluticasone propionate and the other with Fluticasone propionate in combination with salmeterol. The study was carried out with 3,416 uncontrolled asthma patients over 12 years of age. Based on their inhaled steroid dosage during the 6 months before screening, the patients were divided into 3 groups: stratum 1, previously corticosteroid-free, stratum 2, low-dose corticosteroid users, and stratum 3, moderate-dose corticosteroid users. Patients were administered with either a combination of Fluticasone propionate and salmeterol or only Fluticasone propionate. Treatment was stepped up every 12 weeks until a totally controlled condition was achieved. This totally controlled condition was defined as a condition with morning peak expiratory flow rate reaching 80% of the predicted value every morning, absence of daytime symptoms, nighttime awakenings, acute exacerbations, emergency visits, nor β2-agonist use. The achievement levels after 1 year were compared. As a result, in the group with the combination of Fluticasone propionate and salmeterol, approximately 40% (50% in stratum 1, 44% in stratum 2, 29% in stratum 3) of the patients achieved total control. Furthermore, the results also indicate that the group with Fluticasone propionate and salmeterol achieved total control with less dosage and in a shorter period of time (GOAL study, 2004).[7]

With most asthma patients, the severity falls into two types: mild intermittent or mild persistent. The current guidelines (GINA) recommend continued administration of inhaled steroids to the Mild persistent asthma patients. In a study on mild persistent asthma patients, a comparison

was made between intermittent and continued use of inhaled glucocorticosteroids, and daily treatment with zafirlukast, a leukotriene-receptor antagonist. The one-year study was carried out with 225 mild persistent adult asthma patients. The patients were divided into 3 groups: one with Budesonide 400 μg/day and a placebo instead of zafirlukast, the 2nd group with zafirlukast 40 mg/day and a placebo instead of Budesonide, and the 3rd group with 2 placebos. In the event of exacerbation, the subjects were instructed to intake 1,600 μg/day of Budesonide for 10 days or oral prednisolone 0.5 mg/1 kg of body weight for 5 days. In the 3rd group with 2 placebos, glucocorticosteroids were given intermittently and their symptoms were compared to those with continued use. Morning peak expiratory flow rate (PEF), forced expiratory volume in one second (FEV_1) before and after the use of the bronchodilator, the frequency of exacerbations, the degree of asthma control, the number of symptom-free days, and the quality of life (QOL) were evaluated. Compared to the group with continued use of Budesonide and those with intermittent use, the daily budesonide therapy group experienced greater improvements in pre-bronchodilator FEV_1, bronchial reactivity, percentage of eosinophils in the sputum, exhaled nitric oxide levels, scores for asthma control, and the number of symptom-free days, whereas a significant difference was not seen in post-bronchodilator FEV_1 or in the quality of life. Moreover, no differences were observed between the zafirlukast group and the Budesonide intermittent treatment group. In addition, during the 400 days of observation from the start of the trial, no significant difference was seen in the 3 groups in the time leading up to the first exacerbation (IMPACT study, 2005).[8] This report has yet to be confirmed, but also from the point of medical cost, the results may serve to stimulate reconsideration of the current guidelines.

References

1. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. NHLBI/WHO Workshop Report. NIH Publication. Bethesda: National Heart, Lung and Blood Institute. 2002:102–106.
2. Makino S, Hurusho M, Miyamoto T, Nishima S. Asthma Prevention and Management Guideline 2003, Japan (Update from: JGL1998). Tokyo: Kyowakikaku; 2003:72–85.
3. Adachi M, Morikawa A, Ishihara K. Asthma insight & reality in Japan (AIRJ). Arerugi. 2002;51:411–420.
4. Rabe KF, Vermeire PA, Sorian JB, Maier WC. Clinical management of asthma insights and reality in Europe (AIRE) study. Eur Respir J. 2000;16:802–807.
5. Morita Y, Nagakura T, Suguro H, Miyagawa T, Miyatake A, Kubo H, et al. Comparison of asthma episodes, such as hospitalization and emergency room treatment for asthma exacerbation, before and after the administration of an inhaled steroid, fiuticasone propionate, in a large-scale national survey (FINE study). Allergology & Immunology. 2005;12:786–799.
6. Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, et al. Early intervention with budesonide in mild persistent asthma: a randomized, double-blind trial. Lancet. 2003;361:1071–1076.
7. Bateman ED, Boushey HA, Bousquet J, Busse WW, Clark TJH, Pauwels RA, et al. Can guideline-defined asthma control be achieved? The gaining optimal asthma control study. AJRCCM. 2004;170:836–844.
8. Boushey HA, Sorkness CA, King TS, Sullivan SD, Fahy JV, Lazarus SC, et al. Daily versus as-needed corticosteroids for mild persistent asthma. NEJM. 2005;352:1519–1528.