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Template-based Data Entry for General Description in Medical Records and Data Transfer to Data Warehouse for Analysis

Yasushi Matsumura[a], Shigeki Kuwata[b], Yuichiro Yamamoto[a], Kazunori Izumi[c], Yasushi Okada[c], Michihiro Hazumi[c], Sachiko Yoshimoto[a], Takahiro Mineno[a], Munetoshi Nagahama[a], Ayumi Fujii[a], Hiroshi Takeda[a]

[a] *Department of Medical Informatics, Osaka University Graduate School of Medicine, Japan*
[b] *Department of Medical Informatics, Tottori University Medical School, Japan*
[c] *Medical Systems Division, NEC Corporation, Japan*

Abstract

General descriptions in medical records are so diverse that they are usually entered as free text into an electronic medical record, and the resulting data analysis is often difficult. We developed and implemented a template-based data entry module and data analyzing system for general descriptions.

We developed a template with tree structure, whose content master and entered patient's data are simultaneously expressed by XML. The entered structured data is converted to narrative form for easy reading. This module was implemented in the EMR system, and is used in 35 hospitals as of October, 2006. So far, 3725 templates (3242 concepts) have been produced.

The data in XML and narrative text data are stored in the EMR database. The XML data are retrieved, and then patient's data are extracted, to be stored in the data warehouse (DWH). We developed a search assisting system that enables users to find objective data from the DWH without requiring complicated SQL.

By using this method, general descriptions in medical records can be structured and made available for clinical research.

Keywords:

medical records system, template, structured data entry, data warehouse, XML

Introduction

Recently, electronic medical record systems have been implemented and are used in many hospitals [1,2]. The medical staff expects data entered into electronic medical records (EMR) to be linked with a knowledge base for decision support, or used for assessment of medical activities and clinical research [3-5]. Medical records include patient profile data, diagnosis, chief complaints, patient histories, physical examinations, progress notes, records of orders, examination reports, operation reports, summaries and so on. Some of the patient profile data, diagnosis, records of orders, and laboratory test results are originally structured data, and have thus been stored in the clinical data warehouse (DWH) and previously used for clinical research [6-8]. However, most general descriptions in medical records are diverse and complicated, thus they are entered as free text. The valuable data for clinical research (e.g. stage of cancer, tissue type, side effects of medicine etc.) are usually entered as free text. Analysis of data in free text format is difficult. If these data are not available, the data in EMR declines in value.

In order to analyze the entered data, it must be structured, i.e. the description should be expressed by the assembly of data elements that consist of item and values with codes [9-11]. To get data into this format, an input template is the most practical method [12]. By using input templates, the entered data can be stored in the database and made available for data analysis. The descriptions in medical records are so diverse and complicated, however, that the template method is difficult to adopt. To overcome this problem, we developed a tree-structured template named 'dynamic template', whose basic concept was reported in 1998 [13].

It is usual to adopt a strategy of making templates based on their own database files [14,15]. This strategy makes it possible to analyze the data easily. Because of the lack of productivity and flexibility, however, it is difficult to produce templates for any possible description that might arise within broad specialties.

In this paper, we report on the dynamic template module and the method for analyzing the entered data by the template. In our method, the contents of the templates are independent of the database schema, thus the template can be easily produced and freely revised. We have produced many templates in broad specialties in every department. Furthermore, any data entered by the templates can be searched through DWH with the assistance of the searching system.

Methods

Structure of descriptions in medical records

In this paper we term a cluster of descriptions a 'describing object', which is a record about a certain property of a patient at a certain point in time. A medical record can be

considered as an aggregate of describing objects about one patient. A describing object has the attributes of patient ID, object name, observation time, description time, writer, department, and contents. In our model, contents of a describing object are expressed by the assembly in tree structure of data elements consisting of items and values.

Template module

We developed the input template module to get the data in this structure. The template contents can be considered as a union of the possible descriptions of patients regarding a certain describing object, i.e. each description of a patient is a subset of the template contents. Thus the structure of the template must be the same as that of the describing object.

The template content is the assembly of data elements consisting of items and options or text boxes, which are arranged in a tree structure. The template module displays all the elements in the same layer at once. When a value that has some subordinate elements is selected, these elements are displayed under the selected value. Because the template form changes according to the selected values, we call it 'dynamic template' (Fig. 1).

Although the structured data is processed easily by computer systems, it is difficult for users to understand. Therefore, we adopted a strategy of converting the structured data into narrative form, using the following rule: Each item and value has 4 types of character string: prefix, body, conjunction, and suffix. Linefeed can be set after each character string. If several values are selected for one item, conjunction is set between these values. If there are several items linked with one value, conjunction is set between these pairs of item and value, and the suffix of the value is set after those [16].

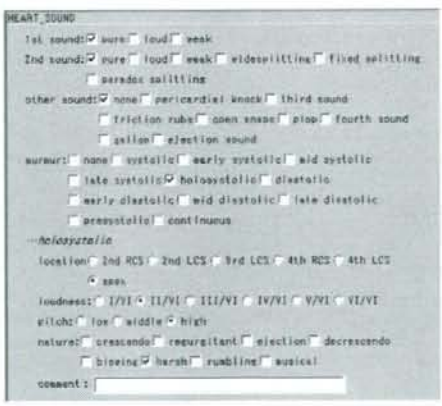
We adopted XML for the expression of the template contents master. This master includes the information about a structure of describing element, a way for expression on template of these elements, and a way for conversion of entered data to narrative form.

The main part of the elements in DTD of the template master is as follow.

```
<!ELEMENT ATOM-LIST (ATOM-
STYLE,ATOM*)>
<!ELEMENT ATOM (ATOM-TYPE,DISPLAY-
STRING,DOCUMENT-STRING,VALUE-LIST?)>
<!ELEMENT VALUE-LIST (VALUE-
STYLE,VALUE*)>
<!ELEMENT VALUE (VALUE-TYPE,DISPLAY-
STRING,DOCUMENT-STRING,ATOM-LIST?)>
<!ELEMENT DOCUMENT-STRING (DOC-
BODY?,DOC-PREFIX?,DOC-CONJUNC-
TION?,DOC-SUFFIX?)>
<!ELEMENT DOC-PREFIX (#PCDATA)>
<!ELEMENT DOC-BODY (#PCDATA)>
<!ELEMENT DOC-CONJUNCTION (#PCDATA)>
<!ELEMENT DOC-SUFFIX (#PCDATA)>
```

DISPLAY-STRING is the character string expressed on the template. DOCUMENT-STRING is the character string on the narrative form, which consists of DOC-PREFIX, DOC-BODY, DOC-CONJUNCTION and DOC-SUFFIX. ATOM is an item of the describing element. ATOM-LIST includes ATOM, and ATOM includes VALUE-LIST. VALUE-LIST includes VALUE, and VALUE includes ATOM-LIST. In this format, the nested structure is presented.

Because the entered patient data is sometimes recalled with the original template and then revised, we adopted a method in which entered patient data is included in the template contents master. We put the SELECTED attribute of VALUE-LIST element in the template master. Before the value is selected, no is set to SELECTED attribute. When the value is selected, it changes to yes. When a character string is entered in a text box, it is set as the element of DISPLAYSTRING and DOCUMENT-STRING of VALUE-TYPE.



Narrative form

1st sound pure, 2nd sound pure, no other sound

holosystolic murmur (apex Levein II/IV high pitch harsh)

diastolic murmur (2nd LCS Levein I/IV high pitch regurgitant)

Figure 1 - An example of the dynamic template.

When the user selects "holosystolic" in " murmur", then the portion under "...holosystolic" appears. After data is entered by this template, the narrative form is generated.

Storage of data into the EMR database

In the EMR database, all kinds of patient data are stored. We call a cluster of information a 'medical event', which is stored in one record of the database. The describing object is one of the medical events. The data in XML and narrative text data are stored in each field, respectively.

EMR database is not suitable for data analysis, because the procedure for such analysis affects the response of the daily online transaction procedure. Furthermore, the patient data is included in the XML. Thus, in order to

search the objective data, all the records have to be checked. To overcome this problem, the data in EMR is transferred to the DWH. In this process, the XML data is parsed to extract patient data, which is stored in the database of DWH (Fig. 2). The structure of the database of DWH is quite simple. One record is made to correspond to one value. The main fields of this database file are as follows: patient ID, date, template name, xPath name, xPath code, value code, value name, suffix. The xPath code and the xPath name indicate the traced items and values in the tree structure. The xPath code (or the xPath name) is expressed by the traced items and values codes (or names) connected with "\", e.g. \A01\V0101\A02.

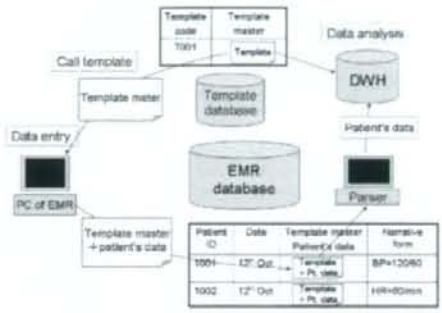


Figure 2 - Flow of template master and patient's data

Search assisting system

We developed an application system for searching the objective data from this database of DWH. In this system, users easily designate the objective data using a GUI. When users select an objective template, the system shows the names of items and values in the template. Thus, users can easily set the combination of search conditions in one template. The character string entered in the text box can also be the object of a search. In the case of numerical values, the conditions "more than" or "less than" can be set. The application system makes a SQL request according to the user's designation and searches the objective data from the DWH database. When the system finds the description that meets the condition, a progress note including the description is shown. Additionally, the system shows the progress notes of other days for the same patient.

Results

Availability of template

Preparation of input templates that are useful and convenient for every member of the hospital staff is essential before a hospital initiates an EMR system. The task is so large for each hospital that we formed an organization to support the preparation of template contents and their supply. The template contents that are developed for hospital use are then stored in the database, from which the staff of the hospital can select useful ones for their practice. The dynamic template module is used in 35 hospitals as of October 2006. Different styles of templates were sometimes produced for a concept. As of that time, 3725 templates (3242 concepts) had been produced and stored in the database. The numbers of template in each class are shown in Table 1. In the description of progress notes, the number of templates for "physical findings" is much greater than the numbers for "symptom", "assessment" or "plan". Not only doctors, but also nurses, pharmacists and nutritionists used templates. Templates are frequently used in examination reports, operation reports, and summaries.

Table 1 – The classification of templates

Classification of Template	No. of Concepts	No. of Template
Symptom	37	46
Physical finding	399	494
Assessment	157	168
Plan	24	26
Disease relating description	618	766
Patient history	184	211
Summary	62	64
Examination report	267	313
Operation report	55	62
Medical checkup	79	92
Description for rehabilitation	134	157
Description by social worker	23	23
Description by nurses	956	1013
Description by pharmacists	12	12
Description by nutritionists	44	44
other	191	234
Total	3242	3725

We examined 100 templates randomly selected from the database. When we count the same item linked with multiple values as 1, the average number of items in one template is 34.8. The average number of layers in one template is 8.1. We examined the maximum depth of layers in one template, and found 1 layer in 17%, 2 layers in 43%, 3 layers in 24%, 4 layers in 25%, and 6 layers in 1% of templates. The total number of items in the database is estimated as about 112,800.

Data warehouse and search assisting system

The DWH and search assisting system were implemented in Osaka University Hospital, and their usefulness was

evaluated. Without the search assisting system, users have to examine the xPath code of the value they want to search beforehand. Furthermore, it is quite difficult to write SQL for a combination of search conditions in one template. Contrasted with this, users can now search the objective data easily by this searching system.

Discussion

General descriptions in medical records, such as progress notes, examination reports, operation reports and summaries, are so diverse and complicated that these data are generally entered as free text in EMR. In order to use these data for research, clinical evaluation and so on, natural language processing is one of the possible methods [17,18]. However, to achieve good results by this method, all of the words in the entire medical field, including abbreviations and frequent typing errors, have to be entered into this system beforehand. This would entail tremendous amount of work.

The strategy of template-based data entry is a practical method from the viewpoint of data analysis [12]. The simple templates that are generally adopted, however, limit what users wish to express, and users have no choice but to tolerate these limitations.

Descriptions in medical records are the observation records of patients. When the observation object is normal, the user just enters "nothing particular". However, when something abnormal is found, they describe the object in detail. For the observation records, a tree structure is suitable: an abnormal object is described by several features, which may be further described by other properties [19,20]. Thus, a tree structure is necessary for the template. If the structured data is expressed as it is in EMR, it is not acceptable for users because it is quite different from the expression in free text. A person prefers an expression in which obviously understandable words are omitted, rather than a strictly redundant expression. To overcome this problem, we convert the structured data into narrative form [16]. By using this template, users can enter what they want to record in shorter time without the risk of typing errors. This strategy is quite acceptable for users.

The dynamic template is implemented in the EMR system produced by NEC and 35 hospitals actively use this module. Before starting to use EMR system, hospital staff prepared templates useful for their daily practice. During operating the EMR, templates were revised and new ones were added according to the users' requirement. More than 3725 templates have been produced and more than 100,000 items were entered in the template master. More templates about physical findings or examination reports have been produced than those about symptoms. Template-based data entry is suitable for actively acquired data. On the other hand, it is not suitable for passively acquired data such as symptoms. The concept, which has many options (e.g. portion of skin in dermatology), is difficult to handle with templates. Although the dynamic template is not effective for every type of description in medical records, its popularity and practical accomplishments show that the strategy of dynamic templates, i.e. tree-structured template and conversion of structured data into narrative form, is acceptable in many fields.

For general descriptions in medical records, many types of template have to be prepared. To bring this about, trial and error is inevitable, even after active use in daily practice [21]. Thus, it is necessary to have a system that enables users to produce templates easily and revise them even after releasing. Generally a template is made based on its own database file [14,15], which must be set on each occasion to produce a new template. If the template is revised, the corresponding database file must also be revised. Because this method disperses a patient data in many database files, it is not suitable for EMR system, which must enable users to refer quickly to any patient data.

In our method, the template content master that regulates the content of a template and the patient's data are simultaneously expressed in XML. After entering patient data by the template, the XML data and the narrative form of patient data are stored in the EMR database. Although this schema is practical for EMR systems, data analysis is virtually impossible. Thus, we developed a parser system that retrieves the data in XML from the EMR database and extracts patient data from it. The parser system then stores the patient data in the DWH database, in which one record corresponds to one value. Because patient data is originally in tree structure, xPath code and name is used to designate each property. This database schema is independent from the template contents; therefore, the user can produce and revise templates freely without thinking of the database schema.

Using this DWH, data entered by the template can be used for analysis. It is, however, difficult for users to find the xPath code of the objective data. Furthermore, in this database schema, it is difficult to execute combined search conditions in one template. Accordingly, we developed a search assisting system which assists in finding the xPath code in the template, and thus enables the user to easily set combinations of search conditions. Although this database schema is not the best for data analysis, the user can search the objective data from the database with the support of the search assisting system.

By using this method, general descriptions in medical records can be structured and analyzed. Although it has been said that structured data entry is essential for advanced functioning in EMR, there are a few reports that it succeeded when limited to a few a fields [14,15,22] or a few department [23,24]. We achieved active use of the structured data entry system in every department in many hospitals.

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Address for correspondence

Yasushi Matsumura MD, PhD.
Department of Medical Informatics, Osaka University Graduate School of Medicine.
2-15 Yamada-oka, Suita, Osaka 565-0871, Japan
Tel: (+81)6-6879-5900, Fax: (+81)6-6879-5903
E-mail: matumura@hp-info.med.osaka-u.ac.jp

The Application of an Institutional Clinical Data Warehouse to the Assessment of Adverse Drug Reactions (ADRs)

Evaluation of Aminoglycoside and Cephalosporin Associated Nephrotoxicity

Q. Zhang[1], Y. Matsumura[1], T. Teratani[1], S. Yoshimoto[1], T. Mineno[1], K. Nakagawa[1], M. Nagahama[1], S. Kuwata[2], H. Takeda[1]

[1]Department of Integrated Medicine, Medical Informatics, Graduated School of Medicine, Osaka University, Osaka, Japan

[2]Medical Informatics Division, Tottori University Hospital, Tottori, Japan

Summary

Objectives: To apply an institutional clinical data warehouse (CDW) to the assessment of adverse drug reactions (ADRs) and demonstrate its utility through a specific example.

Methods: We modeled the process for assessing ADRs through retrospective cohort design by using CDW at the Osaka University Hospital as follows: 1) We defined a drug X, an adverse drug reaction (ADR) Y, and a laboratory measurement Z to assess Y during a given study period; 2) we excluded those whose Z value exceeded the defined criteria or were not available at the inception of the cohort; 3) we divided the patients into two groups based on exposure or non-exposure to X; 4) we matched the patient characteristics between the two groups through stratification and randomization; and 5) we compared the frequency of patients who presented Y during the study period between the two groups. Aminoglycoside and Cephalosporin associated nephrotoxicity in pediatric inpatients was used as an example to demonstrate the usefulness of this approach.

Results: Our evaluation indicates that there is an increased risk of nephrotoxicity for pediatric inpatients who were prescribed cephalosporin either alone or in combination with aminoglycoside; further, aminoglycoside tends to increase the cephalosporin-associated nephrotoxicity.

Conclusions: Our findings are consistent with those drawn from other studies, indicating that the method of applying an institutional CDW is useful for assessing ADRs.

Keywords

Clinical data warehouse, relational database, retrospective cohort study, adverse drug reactions

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1. Introduction

Adverse drug reactions (ADRs) are common and important clinical problems; an estimated 5-15% of patients have adverse reactions to medications [1]. According to the medical literature from 1964 to 1996, the overall incidence of ADRs in hospitalized patients was 6.7% (range 1.2-24.1%) [2]. Assessing patient ADRs during hospitalization is crucial for better understanding the risk profiles of drugs. Most data on ADRs are gathered through spontaneous case reports, case-control studies, cohort studies, and randomized placebo-controlled trials. Each type of design has strengths and weaknesses. Spontaneous case reports can be useful for identifying ADR signals and may generate ideas for future studies. However, they are much less useful for quantifying the relative risk of different drugs of the same class and have no comparison group. Case-control studies are excellent for validation and assessment, but suitable control selection can be difficult and unsuitable controls can invalidate results. Also, recall bias may occur if cases and controls recall past events differently. Cohort studies can be prospective and are good at detecting effects; however, very large numbers are required and the studies are generally very expensive. Randomized placebo-controlled trials are considered to be the gold standard of clinical trials and can provide reliable evidence, but they tend to be extremely expensive and are conducted in pre-marketing (phases I-III) trials with relatively limited sample sizes [3-5]. Different study designs can be used to assess ADRs.

During the last three decades, rapid advances in information technology (IT) have allowed the storage of enormous volumes of patient information in electronic patient record (EPR) systems and clinical information systems (CISs). In the meantime, some large data collection systems were created as sources of information for research on ADRs. The Medimetrik database was an early example of a multi-sited hospital database that could support research on rare ADRs [6]. However, it was discontinued by 1988 due to the commercial inviability. Other leading CIS databases such as HELP [7], BICS [8], RMRS [9], and DHCP [10] have also been applied to ADR screening. Some of these either suffered from incomplete outcome assessment [9] or were used in pilot projects [11]. A recent observational cross-over study has evaluated the risk of antidementive drug-associated bleeding via the mediplus® database in Germany, in which patient demographic data, diagnoses, and prescription data were used [12]. The authors identified bleeding by the relevant ICD-10 codes. Although some ADRs should be evaluated by laboratory test data, few reports indicated that it was used for such assessments.

Hospital information system databases store a tremendous amount of clinical data, including prescription data, laboratory test results, etc. These databases are intended to meet the needs of clinicians in their daily practice. For research purposes, separate

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databases, typically called clinical data warehouse (CDW), need to be created and maintained to optimize the data for aggregate analysis, without putting clinical response time at risk. In recent years, the development of CDW has been extensively focused on design, technical and organizational issues [13-20], and applications to hospital administration, financial management [21-23], and quality assessment [24, 25]. Studies on the utility of clinical research are still limited [26-29]. In this paper, we will examine the possibility of an institutional CDW application for assessing ADRs.

As is well known, nephrotoxicity is a common ADR of physician concern. In surveys of the etiology of acute renal failure in hospitalized patients, about half of the drug-induced cases of renal toxicity were attributable to aminoglycosides (including combinations with cephalosporins) and the reported incidence rate was approximately 10% [30]. Cephalosporins are listed in the top 25 drug classes most frequently associated with ADRs [31]. Currently, most studies concerning this topic have been conducted among adults. Although some studies involved pediatric patients, they examined relatively limited sample sizes [32-43]. Thus, we chose the topic of aminoglycoside and cephalosporin associated nephrotoxicity in pediatric inpatients as an example to demonstrate our approach of applying the institutional CDW for assessing ADRs through the linkage of prescription and laboratory test data.

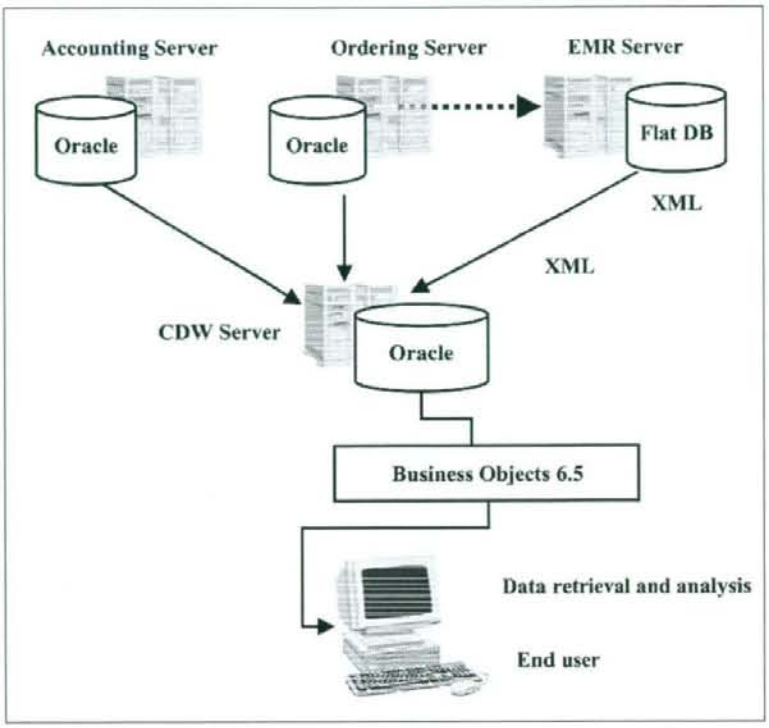

Fig. 1 System architecture of the clinical data warehouse in Osaka University Hospital

2. Methods

2.1 Outline of the Clinical Data Warehouse (CDW) at the Osaka University Hospital

Osaka University Hospital (OUH) is a 1024-bed tertiary national university teaching hospital in Japan. An integrated hospital information system [44], a computerized physician order entry system [45], and a comprehensive electronic patient record system [46] were developed and have been continuously updated and expanded. These systems were designed to collect patient care data, including information on admissions, discharges, transfers, clinic scheduling, patient demographics, diagnoses, laboratory test results, prescriptions, radiographic reports, procedures, progress notes, and billing. For research purposes, a CDW linked to the operational databases was built in 1995 [47]. Since then, the CDW has been used by different clinical research end-users for varied purposes, such as the epidemiological study of diabetes, auditing medication errors, and investigating drug expenditures [48-51].

The CDW in OUH is a subject-oriented database containing 12 tables with major dimensions such as basic patient information, prescriptions, diagnostics, laboratory tests, operations, medical images, blood transfusions, and others. The system configuration is as follows: the server (NEC: Express 5800/140Rc-4) consists of three CPUs (Intel Pentium Xeon MP Processor 2.20 GHz), 3.0 GB main memory, and a hard disc whose logical capacity is 73.2 GB (RAID 1). It is connected to a disc storage system (iStorage S100) whose logical capacity is 2.5TB (RAID 5) by a 2-fiber channel (2 Gbps transfer rate). The operating system is Windows 2000 Server and the database management system is Oracle 9i Enterprise Edition. Business Objects 6.5 was installed as an end-user access tool to enable users to interact with the CDW. The CDW is updated from the operational databases every 24 hours in the evening (Fig. 1). In order to use the data in this CDW, a project registration form must be submitted to the committee for clinical record administration.

2.2 Modeling the Process for Assessing ADRs through Retrospective Cohort Design

We modeled the process for assessing ADRs through retrospective cohort design

Source of Data	CDW Tables	Core Data Elements
Admission Registration System	Patient's Admission History	PatientNo AdmissionNo Age, Gender AdmissionDate DischargeDate FinalSatus
Laboratory Test Reporting System	Laboratory Test Results	PatientNo OrderNo Age, Gender CollectDate TestitemCode TestitemName Result
Order Entry System	Oral Prescription Injection Prescription	PatientNo OrderNo Age, Gender StartDate EndDate MedicationCode MedicationName Quantity, Unit, Times PrescribDays
Medication Master		MedicationCode MedicationName CatelogName

Table 1 Referred data sources, tables, and core data elements

by using CDW as follows: First of all, we defined a targeted drug X, an adverse drug reaction (ADR) Y and a laboratory measurement Z to assess Y in a given study period; then we excluded those whose Z value exceeded the defined criteria or whose Z value were not available at the inception of the cohort; next, we divided the patients into two groups based on the exposure or the non-exposure to the targeted drug X. In order to make the two groups comparable, we matched the patient characteristics through stratification and randomization, and then compared the frequency of patients who presented Y during the study period between the two groups and get the relative risk (RR) for X-associated problem Y [6].

Table 2 sCr distributions by ages on admission for the exposure (n = 1055) and the non-exposure (n = 2895) pediatric inpatients (2000/1/1-2004/12/31)

Exposure	<6 years	6-12 years	12-18 years	Total
< 0.3 mg/dl	199	6	19	224
0.3-0.6 mg/dl	88	106	231	425
0.6-0.9 mg/dl	70	11	256	337
0.9-1.2 mg/dl	33	0	36	69
Total	390	123	542	1055
Non-exposure	**<6 years**	**6-12 years**	**12-18 years**	**Total**
< 0.3 mg/dl	603	114	11	728
0.3-0.6 mg/dl	613	556	214	1383
0.6-0.9 mg/dl	299	26	261	586
0.9-1.2 mg/dl	155	5	38	198
Total	1670	701	524	2895

2.3 Assessment of Aminoglycoside and Cephalosporin Associated Nephrotoxicity in Pediatric Inpatients

Based on the model described above, we first defined two classes of antibiotics – aminoglycosides and cephalosporins – as the targeted drugs X, nephrotoxicity as problem Y, and sCr ≥ 1.2 mg/dl at least once during hospitalization as the measurement to assess problem Y (nephrotoxicity), for pediatric inpatients who were admitted for at least two days (length of stay: LOS ≥ two days) between 2000/1/1 and 2004/12/31. Second, we excluded patients whose sCr was ≥ 1.2 mg/dl on admission or who were dead during hospitalization. Third, we divided patients into two groups based on exposure or non-exposure to the targeted classes of antibiotics. Fourth, we constructed tables to categorize patients in each group by stratifying their characteristics such as age and sCr levels on admission (Table 1). We then compared the number of patients identified in the corresponding categories between groups. In each category, we randomly selected patients from the group with a larger number to equalize the number of patients in each category and match characteristics. Finally, we compared the frequency of patients whose sCr was ≥ 1.2 mg/dl at least once during hospitalization between the two groups and calculated the RR for each comparison.

2.4 Data Extraction Processes

Five tables were referred to in the CDW; those contained the information about patient admission history, oral prescriptions, injection prescriptions, medication codes and categories and laboratory test results. The related data sources, CDW tables, and core data elements are shown in Table 2.

First, we obtained patient information from the admission history table by setting "Age ≤18", "2000/1/1 ≤ AdmissionDate ≤ 2004/12/31", "DischargeDate ≤ 2004/12/31", "LOS ≥2", and "FinalStatus ≠ dead" to identify those who were admitted for at least two days over 5-year periods.

Second, we used the identified patient IDs as primary keys (PK) to extract their sCr and BUN test results by setting "CollectDate" (from the laboratory test results table) ≥"AdmissionDate" and ≤"DischargeDate" (from the Admission History table), inputting their codes, and allowing the first "sCr Results <1.2" to recognize patients whose sCr concentration was <1.2 mg/dl on admission.

Third, we linked the table of admission history, the tables of oral or injection prescriptions, and Medication Master by the identified patient IDs and admission numbers as PKs, and the targeted medication codes (in the Medication Master) as foreign keys (FK). Then we let "StartDate (in the oral or injection prescriptions table) ≥AdmissionDate (in the admission history table)"and "EndDate (in the oral or injection prescriptions table) ≤DischargeDate" (in the admission history table) to identify patients in the exposure group. Next, by excluding the admission numbers of patients in the exposure group, we could identify those in the non-exposure group.

Fourth, we used the admission numbers of patients in the exposure group as a PK to link to the tables we formed in the second and third steps, and let "StartDate" ≤"CollectDate"≤"EndDate"and "sCr Results≥1.2" to find patients who were considered to suffer from nephrotoxicity. The same procedure was performed for the non-exposure group.

Finally, we counted the number of patients whose sCr was ≥1.2 mg/dl at least once during hospitalization in the exposure and the non-exposure group respectively. Then we identified those who were prescribed with aminoglycosides, cephalosporins, or combinations of both classes in the exposure group.

2.5 Methods of Assessment

Results are expressed as means ± standard deviations (SD), along with 95% confidence intervals (CI). The Student's unpaired t-test, the chi-square test (including Fisher's exact test, Yates's correction), and the relative risk were applied where appropriate. All P values were considered to be 2-tailed. Analyses were performed with Microsoft Access 2000, and SPSS11.0 Japanese version for Windows.

Table 3 Characteristics and laboratory test results on admission for the exposure (n = 1055) and the non-exposure (n = 2895) pediatric inpatients (2000/1/1-2004/12/31)

Parameter	Exposure	Non-exposure	P-value
Gender	566 M, 489 F	1515 M, 1380 F	0.46*
Age (years)	9.04 ± 6.94 (8.63-9.45)	5.70 ± 5.46 (5.50-5.90)	0.0001
BUN (mg/dl)	11.02 ± 4.78 (10.73-11.31)	11.20 ± 4.58 (11.02-11.38)	0.28
sCr (mg/dl)	0.48 ± 0.24 (0.47-0.49)	0.43 ± 0.25 (0.42-0.44)	0.0001

Note: M: male; F: female; * Chi-square test; numbers in parentheses stand for 95%CI

Table 4 Adjusted sample sizes and matched patients between the exposure (n = 1030) and the non-exposure (n = 1030) group based on sCr distributions by ages on admission (2000/1/1-2004/12/31)

Exposure	<6 years	6-12 years	12-18 years	Total
< 0.3 mg/dl	199	6	11	216
0.3-0.6 mg/dl	88	106	214	408
0.6-0.9 mg/dl	70	11	256	337
0.9-1.2 mg/dl	33	0	36	69
Total	390	123	517	1030
Non-exposure	**<6 years**	**6-12 years**	**12-18 years**	**Total**
< 0.3 mg/dl	199	6	11	216
0.3-0.6 mg/dl	88	106	214	408
0.6-0.9 mg/dl	70	11	256	337
0.9-1.2 mg/dl	33	0	36	69
Total	390	123	517	1030

Table 5 Characteristics and laboratory test results on admission after adjusting samples between the exposure (n = 1030) and the non-exposure (n = 1030) pediatric inpatients (2000/1/1-2004/12/31)

Parameter	Exposure	Non-exposure	P-value
Gender	555 M, 475 F	536 M, 494 F	0.40*
Age (years)	8.92 ± 6.98 (8.49-9.35)	9.23 ± 6.52 (8.84-9.62)	0.31
BUN (mg/dl)	11.03 ± 4.81 (10.74-11.32)	11.47 ± 4.65 (11.18-11.76)	0.04
sCr (mg/dl)	0.48 ± 0.24 (0.47-0.49)	0.48 ± 0.23 (0.46-0.49)	0.59

Note: M: male; F: female; * Chi-square test; numbers in parantheses stand for 95% CI

3. Results

3.1 Eligible Study Population

From 2000/1/1 to 2004/12/31, there were 7953 pediatric inpatient admissions with LOS ≥2 days in our hospital. 4095 (51.5%) patients had sCr tested and recorded on admission. Among these, we excluded 78 (0.98%) patients whose sCr levels exceeded 1.2 mg/dl on admission and 67 (0.84%) patients who died during hospitalization. Thus, 3950 (49.67%) patients were identified as the eligible population for this study. 1055 (566 male, 489 female) patients belonged to the exposure group and 2895 (male 1515, female 1380) to the non-exposure group. The group characteristics are shown in Table 3.

Table 6 Pediatric inpatients (2000/1/1-2004/12/31) who were observed to have sCr ≥ 1.2 mg/dl at least once during hospitalization after adjusting samples between the exposure (n = 1030) and the non-exposure (n = 1030) group of patients

sCr Level	Exposure	Non-exposure	Total
sCr ≥ 1.2 mg/dl	30 (2.91%)	12 (1.17%)	42 (2.04%)
sCr < 1.2 mg/dl	1000	1018	2018
Total	1030	1030	2060

Table 7 Prescriptions of aminoglycosides and cepholosporins to the exposure group of patients (n = 1030) either alone or in combinations

sCr Level	A	C	A + C	Total
sCr ≥ 1.2 mg/dl	1 (4.55%)	22 (2.37%)	7 (8.64%)	30 (2.91%)
sCr < 1.2 mg/dl	21	905	74	1000
Total	22	927	81	1030

Notes: A stands for the patients who were prescribed with aminoglycosides alone. C stands for the patients who were prescribed with cephalosporins alone. A + C stands for the patients who were prescribed with the combination of aminoglycosides and cephalosporins.

Table 8 Comparisons of the frequency of patients who were observed to have sCr ≥ 1.2 mg/dl at least once during hospitalization among the exposure group and between with the non-exposure group

	χ^2	P
A vs A + C	0.035	0.85[a]
C vs A + C	8.353	0.004[a]
A vs Non-exposure		0.24[b]
C vs Non-exposure	4.172	0.04[c]
A + C vs Non-exposure	20.725	0.0001[a]

Note: a: Chi-squared test with Yates's correction; b: Fisher's exact test; c: Chi-squared test

3.2 Adjusting the Samples and Matching the Characteristics of the Two Groups

From Table 3, we found that there were significant differences in age and sCr on admission between the two groups, which may make the two groups incomparable. In each category, we randomly selected patients from the group with a large number to equalize the number of patients in each category as in Table 4. After this procedure their characteristics were matched as expected as can be seen in Table 5.

3.3 Nephrotoxicity

Forty-two of 2060 patients (2.04%) were observed to have sCr ≥1.2 mg/dl at least once during hospitalization; 30 of 1030 (2.91%) in the exposure group and 12 of 1030 (1.17%) in the non-exposure group (Table 6). The RR between the two groups was 2.5 (95% CI: 1.29-4.86, P = 0.005).

For the exposure group, the observed rate of nephrotoxicity was 4.55% in the aminoglycoside (A) group (RR = 3.90, 95% CI: 0.53-28.71), 2.37% in the cephalosporin (C) group (RR = 2.04, 95% CI: 1.01–4.09), and 8.64% in the combination (A + C) group (RR = 7.42, 95% CI: 3.00-18.32) (Table 7).

Significant differences were found between the C group and the non-exposure group, and the A + C group and the non-exposure group, while no significant difference was found between the A group and the non-exposure group because of the small size of the A group. Also, there was no significant difference between patients prescribed A alone and A + C, but there was a significant difference between patients prescribed C alone and A + C. The P values for each comparison are shown in Table 8.

4. Discussion

Much attention has been focused on ADRs in hospitalized patients over the last three decades. However, most studies have been based on hospital reporting systems, which probably reflect only serious ADRs and therefore underreport the true incidence of ADRs. On the other hand, although some studies have involved large multi-sited databases, few publications have documented the frequency or rate of ADRs [31], and most of these involved data on prescriptions and diagnoses [12]. To our knowledge, patient laboratory test data have rarely been involved in such studies. For some ADRs, such as nephrotoxicity, laboratory test data is essential for its assessments. Thus, it should be used when addressing such issues.

Given the volume and toxicities of drugs used in the hospital, the need to assess ADRs persists. For research purposes, regional database systems incorporating information from multiple hospitals would provide large sample sizes and longitudinal information for individual patients; however, privacy regulations make access to and successful extraction of patient data across hospitals either problematic or infeasible. As a trusted third party policy for gathering clinical data from diverse data sources in Japan still remains in its infancy, institutional clinical data warehouses (CDW) may serve as an alternative solution for us to address such issues.

The application of CDW technology to conduct clinical research is by no means a new concept. However, there are few pragmatic clinically relevant examples of exploiting CDWs in the medical literature. In most cases worldwide, this avenue is only beginning to be exploited and few of the existing CDWs provide access to all data regarding patient care [19]. In this study, we provide a specific example of the use of a CDW to assess drug-associated nephrotoxicity using prescription and laboratory test data.

As discussed above, ADRs can be assessed by cohort studies, which provide reliable evidence. However, expense and time consumption are major flaws of the pro-

spective cohort design. To overcome these disadvantages, we adopted a retrospective cohort design. The basic principle of this study design is to assemble cohorts of exposed and non-exposed subjects from the pooled data, and then to collect outcome data for each case from the database. In the past, it has been argued that retrospective cohort studies have no reference cohort at all, or that the cohorts are not really comparable [12]. As the CDW holds much pooled data, we were able to mimic the process adopted by randomized control trials (RCTs) to stratify and randomly select patients in the exposure and non-exposure groups to match patient characteristics and to make the cohorts comparable.

Previous small studies have provided evidence from RCTs in the pediatric population. Among these, the largest study included 412 patients [38], and in seven trials [36-39, 53-55] more than 100 children were involved. Our study involved 2060 patients, which may provide more reliable evidence. Our data suggest that treatment with cephalosporins, either alone or in combination with aminoglycosides, contributed to nephrotoxicity, and that treatment with aminoglycosides tended to increase cephalosporin-associated nephrotoxicity. These findings are consistent with previous studies, which have implicated some cephalosporins in nephrotoxicity, both alone and in combination with aminoglycosides [33, 34]. In addition, our data indicate that the incident rate of nephrotoxicity with aminoglycoside/cephalosporin combinations is about 8.46%, which is consistent with other findings placing this rate at about 10% [30]. No study has reported the relative risk of cephalosporin-associated nephrotoxicity in pediatric patients. Our data indicate that this relative risk is 2.04 (95% CI: 1.01-4.09), which should provide a meaningful reference to clinicians. Due to the relatively limited sample size of the group treated with aminoglycosides alone, we could not interpret the data concerning the effects of aminoglycosides alone.

The gold standard test for assessing renal function is the glomerular filtration rate (GFR) (normal range: 80-120 ml/min) [56]. The practical marker is creatinine clearance, which measures the ability of the kidneys to clear creatinine from the circulation into the urine over a period of 24 hours. The Cockroft-Gault formula allows the calculation of the GFR without undertaking a 24-hour urine collection, but it requires the patient's body weight. In this study, we did not use creatinine clearance because the data for urine creatinine and body weight were limited. Some studies have used criteria such as an increase in the sCr of >0.4 mg/dl [57] or an increase in sCr of >50% from baseline [58] as definitions of nephrotoxicity. However, there is no international consensus on this issue. We used the upper limit of the normal range of sCr (1.2 mg/dl) adopted in our hospital for this analysis and defined nephrotoxicity as patients whose sCr had exceeded this level at least once during hospitalization.

There are several limitations of this study. 1) Our study design allowed us to determine association between variables, but not causality, because other confounding factors could have influenced creatinine levels between the two groups. Although we mimicked the process of stratification and randomization adopted by RCTs to reduce confounding factors, their presence could not be totally eliminated. Thus, these findings should not be construed as cause and effect. Nevertheless, the obtained relative risk could provide meaningful references for assessing ADRs. 2) The lack of a standard definition of nephrotoxicity adopted by other studies creates the possibility that differences in methodology could influence the conclusions. 3) Our CDW is a free-standing system rather than an integrated multiple national data warehouse across institutions. The size and composition of patient populations in individual hospitals tends to limit the ability to detect events of low incidence and produce generalizable results.

The method of applying the CDW to the assessment of ADRs in hospitalized patients using prescription and laboratory test data is not limited to the evaluation of antibiotic-associated nephrotoxicity. Other drugs with associated nephrotoxicity, including radiocontrast agents, nonsteroidal anti-inflammatory drugs (NSAIDs), angiotensin-converting enzyme inhibitors (ACEs), and anticancer agents can also be evaluated using this method. Moreover, the method can be expanded to investigations of drug–associated hepatotoxicity, immunotoxicity, or other types of ADR. In the future, we will further explore whether nephrotoxicity is associated with dosing, and what situations tend to cause nephrotoxicity. These types of study may require massive sample sizes based on nation-wide populations, incorporating data from many national hospitals' data warehouses.

5. Conclusions

Our evaluations indicate that an institutional CDW can be useful for assessing ADRs in a hospital setting.

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Correspondence to:
Yasushi Matsumura
Department of Integrated Medicine
Medical Informatics
Graduated School of Medicine
Osaka University
2-15 Yamada Oka, Suita City
Osaka 565-0871
Japan
E-mail: matumura@hp-info.med.osaka-u.ac.jp

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ORIGINAL PAPER

Analysis of Yearly Variations in Drug Expenditure for One Patient Using Data Warehouse in a Hospital

Yufeng Chen · Yasushi Matsumura · Katsuhiko Nakagawa · Shanmei Ji · Hirohiko Nakano · Tadamasa Teratani · Qiyan Zhang · Takahiro Mineno · Hiroshi Takeda

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Abstract Medical expense has grown rapidly in Japan. It could be caused by the increase of the patient number and the increase of medical expense per patient. We studied the latter factor on drug expenditure from 1996 to 2002 using the prescription data stored in the data warehouse of one hospital. We found that the drug expenditure per patient had increased 1.32 times. The mean number of prescriptions per patient increased 1.23 times and the mean expenditure of one medicine increased 1.08 times. These results demonstrated that drug expenditure for one patient had gradually increased. This was caused by both the rise in the number of medicines taken by one patient and the rise in the prices of medicines. The data warehouse in the hospital was useful for the analysis of the trends in medical expenditure for one patient.

Keywords Data warehouse · Prescription · Drug expenditure · Drug price · Medical cost

Introduction

The growth of medical expenditure is a common problem in the world. Medical expenditures in Western Europe increased by an average of 4.1% per year between 1970 and 1990, exceeding the overall 2.7% annual rate of economic growth during the same period [1]. In Japan, the universal national health insurance system was put in place in 1961. With the ongoing trend of the increase in the elderly population in recent years, national medical expenditures have risen on average about 3.8 % per year from 1992 to 2000, and the total expenditure amounted to about 30 trillion yen in 2000 [2]. Under the medical insurance system in Japan, people can visit any hospital and can be treated for their illnesses with expensive examinations, drugs and operations. Since the Japanese payment system is based on fee for service, expenditure is not a factor in deciding which medicines to use [3].

Recent studies of medical economics have clearly demonstrated that drug expenditures are increasing more rapidly than other health care spending [4, 5]. In the United States, spending on prescription drugs increased 122% from $US 50 billion in 1993 to $US 111.1 billion in 1999 [6]. There are two opinions as to the critical factors driving these increasing expenditures. One opinion is that rising prices are driving the growth of drug expenditures. A contrary view from RW Dubois's study states that volume growth is the largest driver of spending on drugs [7].

The increase of medical expenditure can be caused by two factors: one is the growth of the patient population and the other is the increase of medical expenditure of one patient. It is said that because of population aging, the growth of the number of patients is the major factor contributing to the rise of medical expenditure. On the other hand, there isn't sufficient data about concerning the rising of medical expenditure of one patient. The medical expenditure of one patient can be determined by the total medical expenditure being devided by the total patient number. However, because there is no national ID number in Japan, it is impossible to ascertain total patient number. Thus to ascertain the medical expenditure of one patient, the data in hospitals should be analyzed.

Y. Chen · Y. Matsumura (✉) · K. Nakagawa · S. Ji · H. Nakano · T. Teratani · Q. Zhang · T. Mineno · H. Takeda
Department of Integrated Medicine, Medical Informatics, Osaka University, Graduate School of Medicine 2-2, Yamada-oka, Suita, Osaka 565-0871, Japan
e-mail: matumura@hp-info.med.osaka-u.ac.jp

The hospital information system is used in many hospitals in Japan. The main purpose of this system is to save manpower in hospital management by having physicians directly enter the data. The data contained in this system can be used for data analysis. We developed the data warehouse in 1995, and the data used in the subsystems of the hospital information system have been stored in it. In this paper, we studied the drug expenditure of one patient and its yearly variations from 1996 to 2002 using this data warehouse and elucidated the contributing factors for its variation.

Methods

Construction of the data warehouse

We developed the data warehouse in 1995. The source data was moved from the databases of the subsystems in the hospital information system, including the order entry system, laboratory test results, the radiological examination report system, and the diagnosis entry system, and so on. The database in the data warehouse was constructed to be suitable for data analysis. The data with analytical value were extracted and transferred from the subsystem databases to the data warehouse (Fig. 1). The data warehouse contains 12 tables according to major dimensions such as patient demographic information, prescriptions, injections, diagnostics, laboratory tests, radiology examinations, operations, blood transfusions and others. The system configuration is as follows: the server (NEC: Express 5800/140Rc-4) consists of 3 CPU (Intel Pentium Xeon MP Processor 2.20 GHz), 3.0 GB main memory, and hard disk whose logical capacity is 73.2 GB (RAID 1). It connected with the disk storage system (iStorage S100) whose disk logical capacity is 2.5 TB (RAID 5) by the 2-fiber channel (2 Gbps transfer rate). The operating system of the server is Windows 2000 Server and the database management system is Oracle 9i Enterprise Edition. We adopted BusinessObject (6.5) to help users retrieve data from the data warehouse without using SQL. BusinessObject is the front user supporting tool to retrieve data from a data warehouse. The retrieved data can be exported into Microsoft Excel using the BusinessObject Info View application.

In this data warehouse, information about one drug in one prescription is registered in one record of the database file for prescription orders. Table 1 shows the field names of the database file for prescription orders.

The subjects were internal medicines prescribed for in patients and out patients of Osaka University Hospital from 1996 to 2002. Medicines used for examination were excluded. The total number of different drugs prescribed was 1241. In this data warehouse, there are 9,745,556 records from 1996 to 2002 in the database file for prescription orders.

Analysis of the data

The records were divided every year by the start date of the prescription. Data for medicine code, dosage, and number of days prescribed were drawn out of the data warehouse. We generated a master table which indicated the prices of each medicine. By linking each record to the corresponding price data, the drug expenditure on one medicine in one prescription, which corresponds to one record, was calculated by the following formula:

$$\text{Drug expenditure} = \text{Drug price} \times \text{Dosage} \times \text{Number of days prescribed}$$

To tally the total drug expenditure in one year (tDE), the expenditure data of all of the records was summed. The Japanese government has changed drug prices every two years. Therefore, governmental control affects drug expenditures. To obtain the actual expenditure, drug expenditures were calculated using the drug prices of each year. To eliminate the effect of the governmental controls, drug expenditure in each year was calculated using the drug prices in 2002.

The total number of patients who received at least one prescription in a year (tPN) was counted using the data warehouse.

The mean drug expenditure per patient per year (mDE/p) was arrived at by the following formula:

$$\text{mDE}/p = \text{tDE}/\text{tPN}$$

The total number of prescription days (tPD) per year, which indicates the total amount of medicine prescribed in a year, was calculated by summing the data of the prescription days in each record.

The mean number of prescription days per patient per year (mPD/p), which indicates the mean amount of medicine prescribed on a per patient basis, was arrived at by the following formula:

$$\text{mPD}/p = \text{tPD}/\text{tPN}$$

The mean drug expenditure of one medicine per day per patient (mDE/m.d), which indicates the mean virtual drug price, was calculated by the following formula:

$$\text{mDE/m}.d = \text{mDE/p/mPD}/P$$

To calculate the total drug expenditure for each group of medicines, we made a master table, which linked each medicine to a group. All medicines were placed into 11 groups: medicines for the central nervous system, medicines for the cardiovascular system, gastrointestinal drugs, vitamins, hematinic drugs and fluid drugs, metabolic drugs,

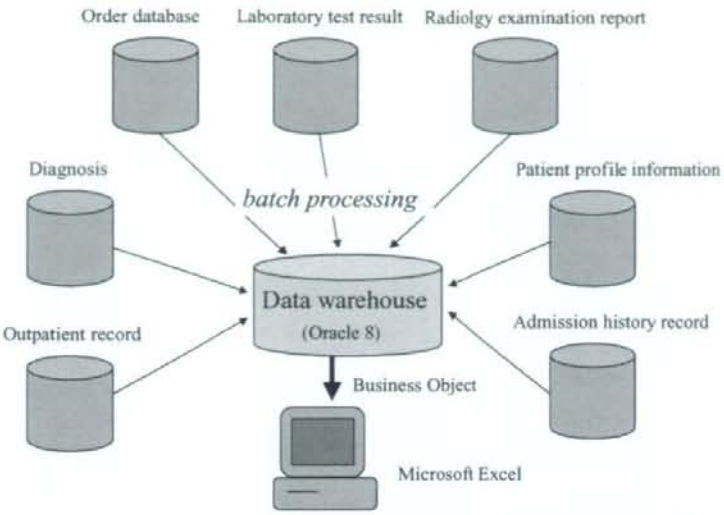

Fig. 1 The data flow to the data warehouse

anticancer drugs, antibiotic drugs, chemotherapeutic drugs, medicines for the respiratory system, and others. Medicines which belonged to more than two groups were linked to one of them. Furthermore, in the study of antihypertensive medicines, the drugs were divided into 5 subgroups: Ca antagonists, angiotensin-converting enzyme inhibitors, sympathomimetic antagonists, angiotensin-II receptor antagonists, and diuretic drugs.

Results

The total drug expenditure of the hospital was 2.50 billion yen in 1996. This amount did not change significantly through 1998, but after that it gradually increased until it reached 3.45 billion yen in 2002. These figures represent 38% increase over the seven years. When the expenditure was calculated using drug prices fixed at 2002 levels, we found that the expenditures had increased monotonically since 1996, reaching 1.80 times the initial level by 2002 (Fig. 2). The mean drug expenditure per patient shows a similar trend. Drug expenditure per patient started at 62.3 thousand yen in 1996 and rose to 82.6 thousand yen in 2002, representing an increase of 1.32 times. When recalculated based on the fixed drug prices, an increase of 1.73 times was observed (Fig. 3). In addition, the mean number of prescription days per patient gradually increased to 1.23 times (Fig. 4).

Table 1 An example of prescription data from the data warehouse

Order No	Patient No[a]	Start Date	End Date	Medicine Code	Medicine Name	Quantity	Unit1	Prescribe Days
44707	XXXX	2000/1/11	2000/1/24	210120	Luprac	1	T	14
53183	XXXX	2000/1/11	2000/1/14	210480	Asverin	15	MG	4
44197	XXXX	2000/1/11	2000/1/14	210910	Ebastel	1	T	4
58131	XXXX	2000/1/11	2000/1/11	210910	Ebastel	1	T	1
48667	XXXX	2000/1/11	2000/1/13	210940	Pentasa	12	T	3
44410	XXXX	2000/1/11	2000/1/11	211130	Aldactone A	2	T	1
52363	XXXX	2000/1/11	2000/1/11	211130	Aldactone A	1	T	1
49080	XXXX	2000/1/11	2000/2/9	211210	Gaster D	2	T	30
51523	XXXX	2000/1/11	2000/1/11	211210	Gaster D	1	T	1
57717	XXXX	2000/1/11	2000/1/11	211210	Gaster D	1	T	1
36328	XXXX	2000/1/11	2000/1/13	211640	Flomox	3	T	3
51523	XXXX	2000/1/11	2000/1/11	211800	Inteban	1	CA	1
50062	XXXX	2000/1/11	2000/1/11	211910	Ubretid	1	T	1
55951	XXXX	2000/1/11	2000/1/14	212260	Edecril	0.6	T	4
48761	XXXX	2000/1/11	2000/1/14	212680	Euglucon	1	T	4
44761	XXXX	2000/1/11	2000/1/13	213260	Cabaser	2	T	3

[a]The patient number is omitted for the privacy of patient

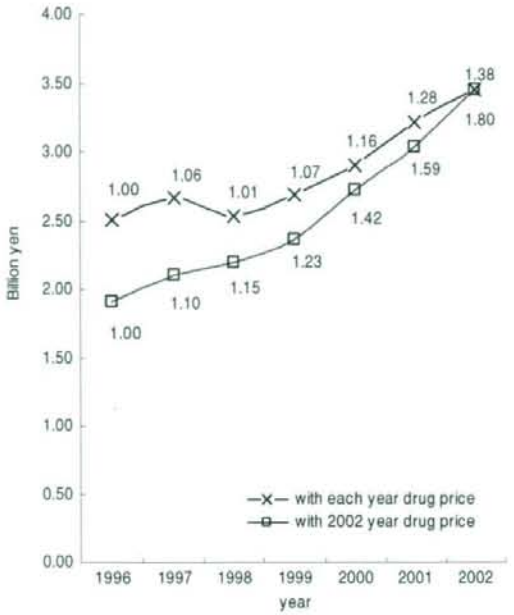

Fig. 2 Total drug expenditures

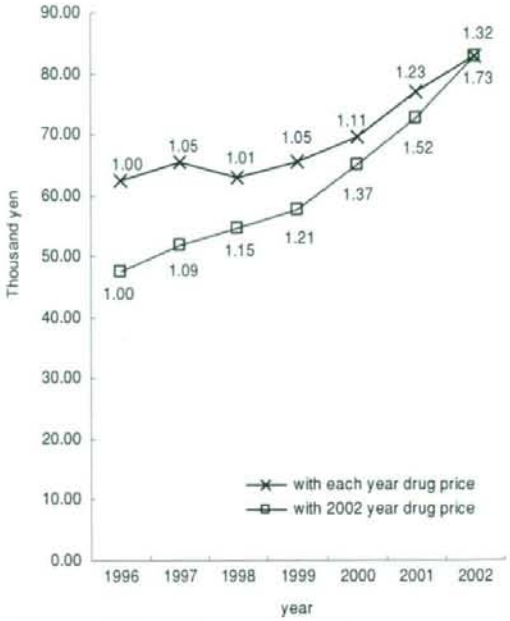

Fig. 3 The mean drug expenditure per patient

The mean expenditure of one drug per day per patient was 129 yen in 1996. This expense decreased to 0.91 of the initial value over the following 2 years, after which it then gradually increased to 1.08 times the initial amount at the end of the 7-year period. When the expenditure was calculated using the fixed 2002 prices, we found that the expense had increased monotonically since 1996, reaching 1.42 times by 2002 (Fig. 4). This increase may be due to the appearance of newer, more expensive medicines.

We calculated the percentage of the total drug expenditure that each group of medicines represented in 2002 (Fig. 5). Medicines for the cardiovascular system represented the largest percentage. Among these drugs, antihypertensive medicines were the largest fraction. Therefore, we selected the antihypertensive medicines as a representative example to analyze in detail. In the following research, drug prices fixed at the 2002 levels were used.

The total number of patients who received at least one prescription for an antihypertensive medication increased by 1.32 times (Fig. 6). The mean drug expenditure per patient for antihypertensive medication was 24.0 thousand yen in 1996. Since then, it has increased to 37.8 thousand yen as of 2002, which represents an increase of 1.57 times (Fig. 6). The mean number of prescription days per patient gradually increased to 1.28 times (Fig. 7). The mean drug expenditure for one medicine per day per patient was 83.9 yen in 1996. It has gradually increased to 1.23 times (Fig. 7). These results indicate that the increase in drug expenditure per patient is caused by both an increase in the number of medicines prescribed per patient and by an increase in the mean drug price. The latter factor may be caused by an increase in the prescription of newer, more expensive medicines.

New types of antihypertensive medicines were adopted in 1998, 1999, and 2000. Three of these were angiotensin-II receptor antagonists, and one was a diuretic drug. In 1998 0.15% of the total prescriptions were new medications, but this category gradually increased to 5.17% of total prescriptions in 2002. A similar trend was found in new medicines adopted in 1999 and 2000. New medicines adopted after 1997 represented 15.20% of the total prescriptions (number of prescription days) in 2002 (Fig. 8). These new medicines represented 28.79% of the total drug expenditure in 2002 (Fig. 9). These results demonstrate that prescription of new types of antihypertensive medicines has increased, and that this is one factor contributing to the total increase in drug expenditure per patient. The trend of the prescription days and the trend of the drug expenditure of each group of antihypertensive medicines are shown in Fig. 10 and Fig. 11, respectively. Expenditures on angiotensin-II receptor antagonists, which are a new type of antihypertensive medicine, had rapidly increased to reach 0.50 million prescription days and 100 million yen in 5 years (Fig. 11). Prescription days of the other types of medicine had also increased. Although the expenditures on diuretic drugs did not change during the 7-year period, the expenditures on Ca

Fig. 4 The mean drug expenditure on one medicine per day per patient and the mean number of prescription days per patient

antagonists, angiotensin-converting enzyme inhibitors, and sympathomimetic antagonists had also increased. These results demonstrate that although prescription of new medicines has certainly increased, they did not become substitutes for older medications. The number of prescriptions of antihypertensive medicines per patient has also increased. This is another essential factor contributing to the increase in expenditures.

Discussion

In Japan, medical expenses were about 30 trillion yen in 2000 [2]. Drug expenditure amounts to almost 20% of the total medical expense [8]. The contribution of drug expenditure to the total expenditure of the hospital is 19%. Tokita predicts that medical expenses will amount to more than 40 trillion yen by 2025 [9]. Expenditures on prescription drugs are the fastest growing component of the health care budget.

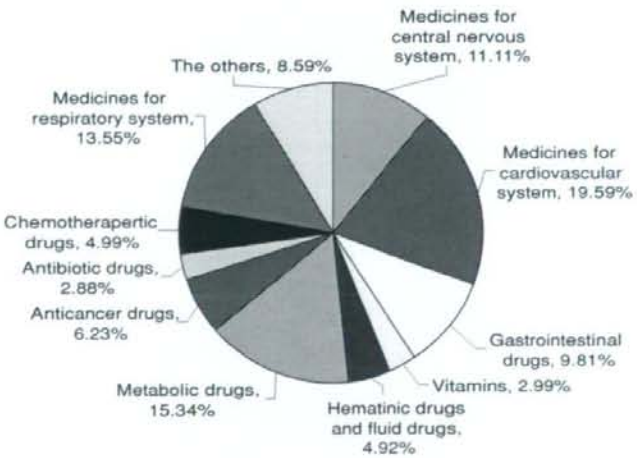

Fig. 5 The ratio of each group of medicine in drug expenditure in 2002

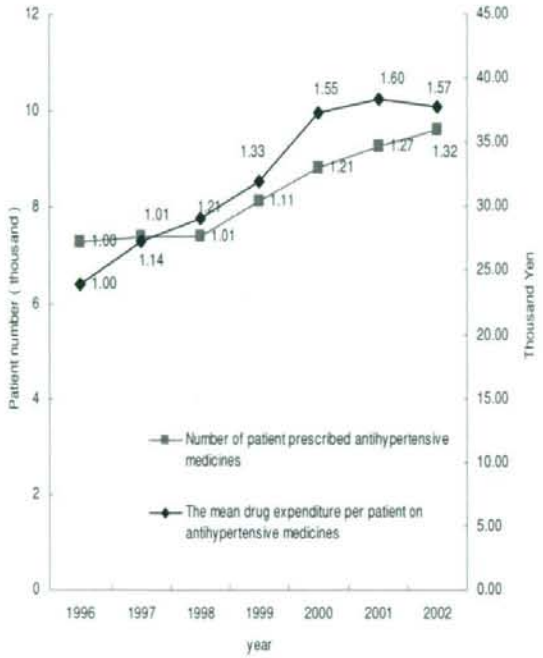

Fig. 6 The mean drug expenditure per patient on antihypertensive medicines and number of patients prescribed antihypertensive medicines

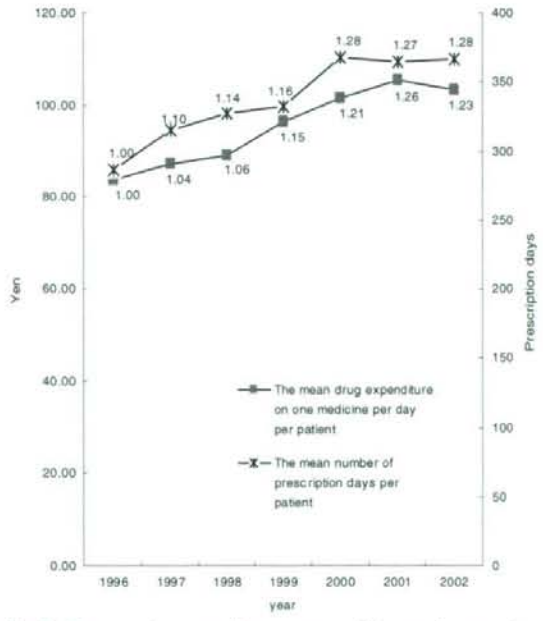

Fig. 7 The mean drug expenditure on one medicine per day per patient and the mean number of prescription days per patient for antihypertensive medicines

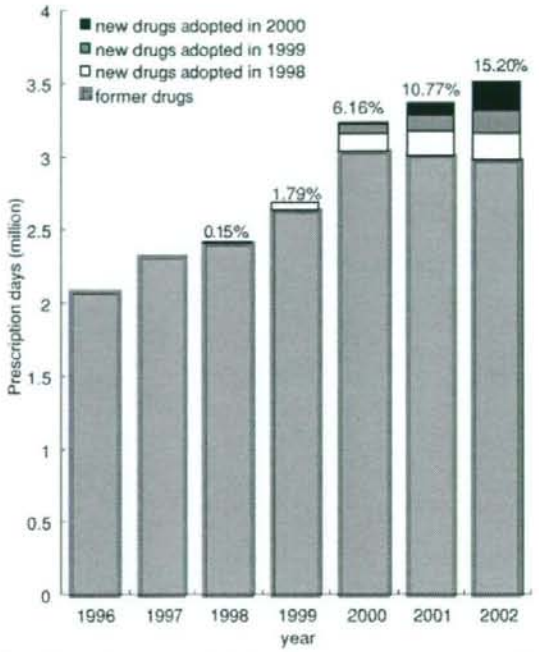

Fig. 8 The ratio of the number of prescription of newer medicines to total prescriptions for antihypertensive medicines

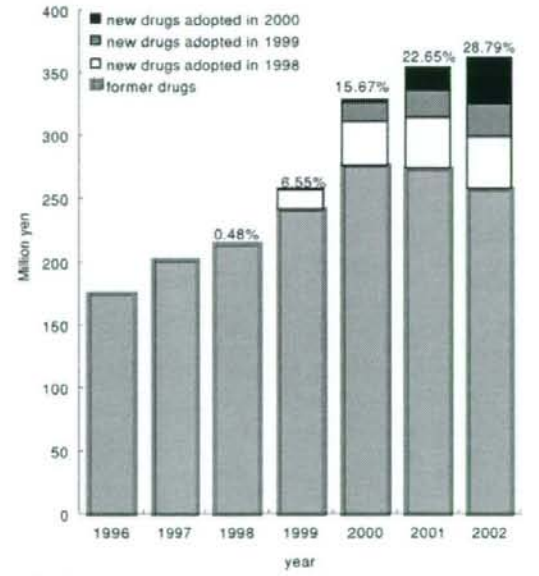

Fig. 9 The ratio of expenditures on newer medicines to total expenditures for antihypertensive medicines

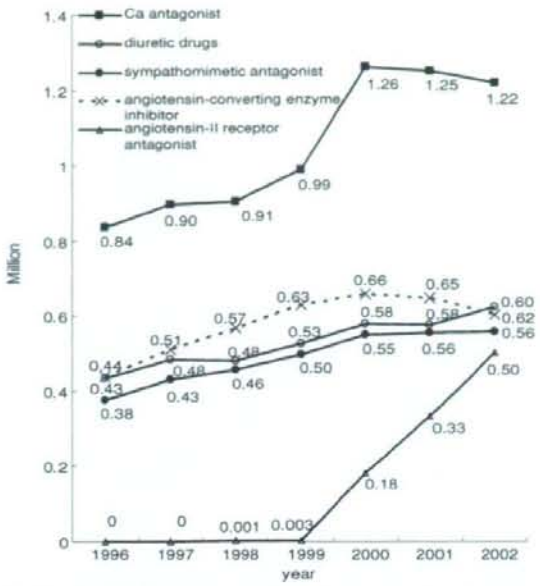

Fig. 10 The trend of prescription days of each group of antihypertensive medicines

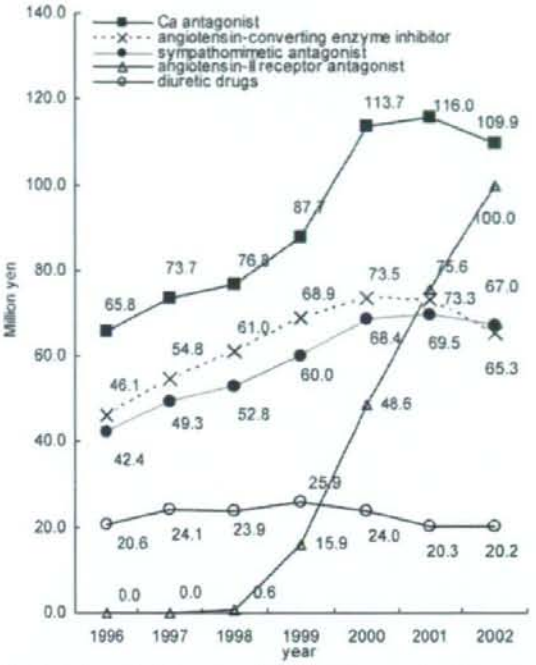

Fig. 11 The trend of drug expenditure of each group of antihypertensive medicines

Japan spent more than $300 per capita on pharmaceuticals [10]. There are two factors behind these rising medical expenses. One is an increase in the number of people who need medical treatment because of a demographic increase in the elderly population The proportion of the population over age sixty-five doubled between 1980 and 2000 to reach 17.1% and is projected to rise to 26.2% by 2020 [11]. Another reason for the rise of medical expenses is increased expenditure per patient due to improvements in medical treatment. However, this factor is difficult to estimate quantitatively. Before 1999, the Ministry of Health, Labor and Welfare had lowered the price of medicines in order to decrease the marginal profits of drug sales. Such profits lead to an increase in the number of prescriptions [12]. However, after 1999, the price of medicine has not been lowered dramatically, leading to a steady increase in drug expenditure per patient.

There are two possibilities which may help explain the rise in mean drug expenditure per patient. The first is an increase in the price of prescribed medicines, since doctors like to prescribe newer, more expensive medicines. The second is an increase in the number of medicines prescribed per patient. In order to separate these two factors, we examined the number of prescriptions by summing up the prescription days of each medicine in each prescription. We regard one day's dosage of one medicine as one unit, because some medicines need to be taken several times a day, while others need be taken only once. Therefore, comparison of the price per pill is meaningless. To calculate the mean number of prescriptions per patient, the total prescription days per year was divided by the number of patients who took at least one medicine during that year. The mean drug expenditure for one medicine in one day, which indicates the virtual mean drug price, can be calculated by dividing the total drug expenditure per year by the total prescription days per year. We found not only an increase in the virtual mean drug price, but also an increase in the mean number of prescriptions per patient.

To investigate this phenomenon in detail, we closely examined the antihypertensive medicines, which were the most frequently prescribed in our hospital. According to the National Survey on Nutrition, 15.3 million people of 30 years and older potentially have hypertension [13]. Medical expenses for hypertension were 1,700 billion yen, and accounted for 7.4% of total medical expenses in 1998 [14]. We supposed that the trend of expenditures on hypertensive medicines may be similar to the trend of expenditures on medicines in general.

Angiotensin-II receptor antagonists are the most recent antihypertensive medicines [15]. In the Sixth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, angiotensin II receptor antagonists were noted to be first choice medicines as they are effective for the treatment of hypertension and have relatively few side effects [16]. Our research indicates that the expenditure of angiotensin-II receptor antagonists has risen to 100 million yen in 5 years. This is one

factor causing the increase in the mean virtual drug price of antihypertensive medicines, though it is not sufficient to completely explain the increase. Several studies have suggested that the target blood pressure should be lower than previously believed. Therefore, the target blood pressure in the guidelines was lowered in 1999 [17]. This may lead to multi-medicine prescriptions, resulting in an increase in the number of prescriptions per patient. Furthermore, this supposition may be applicable to all internal medicines. There have been some studies which demonstrated that more strict control of a disease resulted in a more beneficial outcome. Reports of beneficial effects of medicines may therefore induce greater usage, leading to an increase in drug expenditure.

The data used in this study came from the data warehouse in one hospital. Generally speaking, analysis of data from one hospital may be biased. For example, the total expenditures of medicines in a hospital include the patient number, which partially reflects the popularity of the hospital rather than the prevalence of medical problems in the area. However, analysis of medical activity on a per patient basis is less prone to hospital bias, because it reflects the generally accepted treatment at the time. Furthermore, yearly variations of the data are thought to be more universal. Using the original prescription data allows precise data analysis. In this way, significant results can be obtained by analyzing data from one hospital.

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