

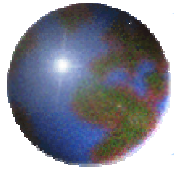
Purpose

< 1 >

In the daily medical practice and hospital/insurance pharmacy activities it is not rare to encounter scenes in which patients complain of early symptoms of adverse drug reactions.

In such a circumstance, each medical institution is worried about prompt and efficient responses within the short examination/dosing time, but more importantly this would be considered the core of risk management of patients.

In this situation we have built a database that links adverse reaction terms in the package inserts to drugs with expressions of early symptoms of adverse reactions patients complain of for efficiency of identifying the causal drugs.



Flow to Discoveries of Adverse Drug Reactions

< 2 >

Rx.

- 1) Drug A 3 tablets a day after each meal for 7 days
- 2) Drug B 1 tablet a day after breakfast for 30 days



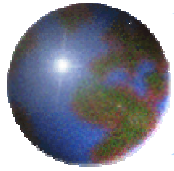
I have developed **rashes** since I started taking a drug....

Investigate package inserts to respective drugs prescribed

It takes too much time to investigate each package insert to each drug prescribed

Drug A is the cause?!

<Package insert to Drug B>
<Package insert to Drug A>
Serious adverse drug reaction:
Stevens-Johnson syndrome



Comparison with Conventional Approach < 3 >

Conventional

Developed a database of adverse drug reaction early symptoms

Complaint of early symptom of an adverse drug reaction from patient/family/helper

Check details of prescription

Investigate the adverse drug reaction in the package inserts to respective drugs prescribed

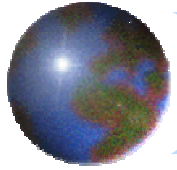
Identify the causal drug

- 1) Enter terms based on the complaint
- 2) Output early symptoms of serious adverse reactions of the prescribed drugs

Identify the causal drug

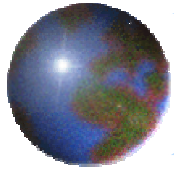
Protect patients from serious risks by providing convenient and swift response, and appropriate drug-taking guidance !



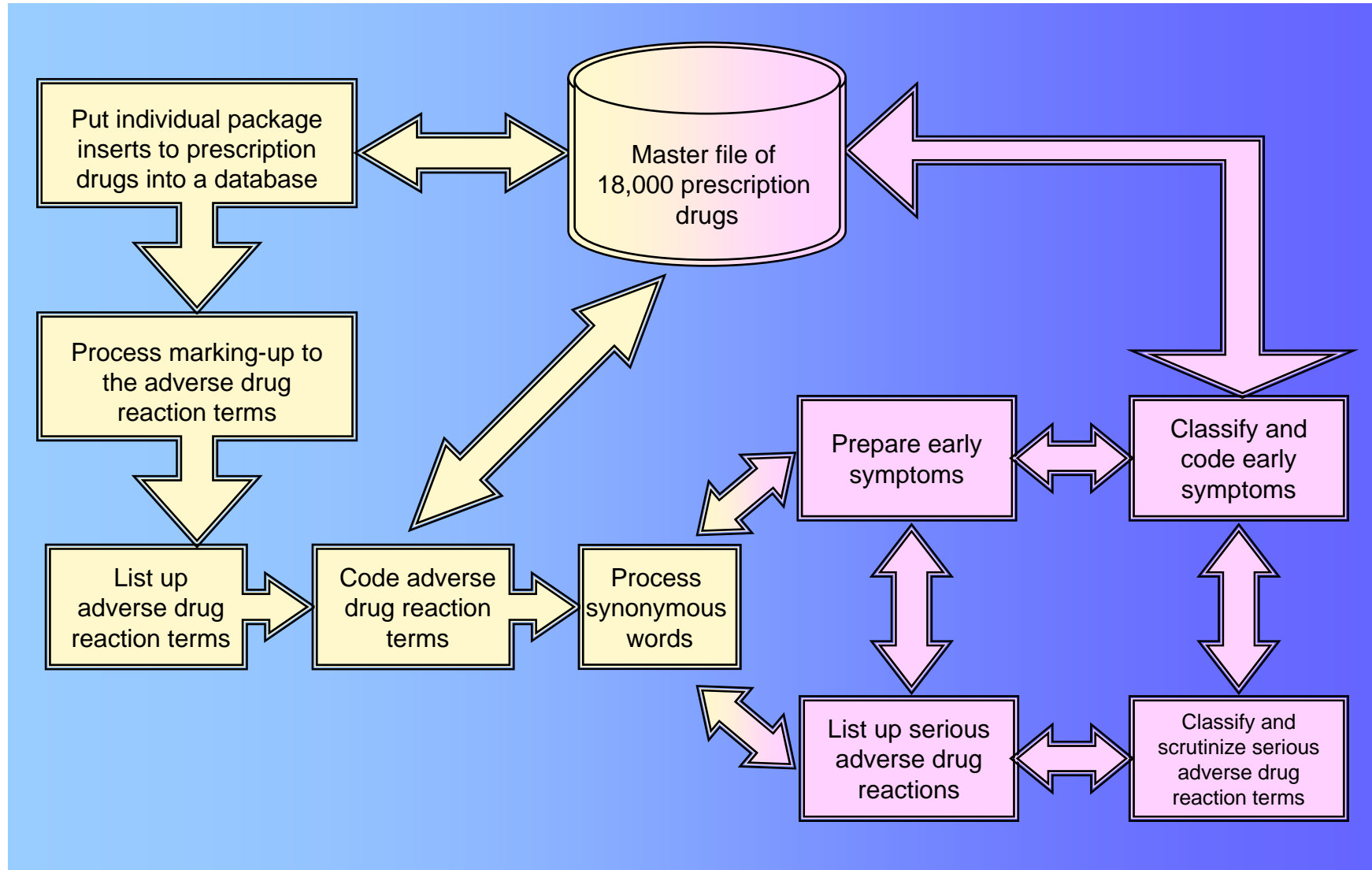


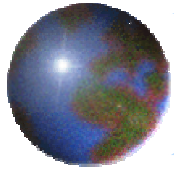
Features of Developed Database < 4 >

- ✦ Uniquely marked-up processing enables you to extract all adverse drug reaction information described in the package inserts to prescription drugs as terms.
- ✦ Extracted adverse drug reaction terms can be classified into “serious adverse drug reactions” and “other adverse drug reactions”.
- ✦ Early symptoms of an adverse drug reaction can be printed out and utilized as information for drug-taking guidance.
- ✦ Easily identify the causal drug from the complaint of early symptoms of an adverse drug reaction from patient/family/helper and take prompt responses.
- ✦ The database is structured to allow convenient and regular maintenance
- ✦ Highly convenient



System Flow





Process Steps for Database Structure (1) <6>

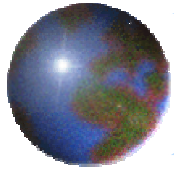
Mark-up processing of adverse drug reaction terms in package inserts put in a database

Package insert

(1) Serious adverse drug reactions
1) Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome)
Adequate observations should be provided, as oculomucocutaneous syndrome or toxic epidermal necrolysis may occur. If such a syndrome occurs, stop dosing and provide appropriate treatment.

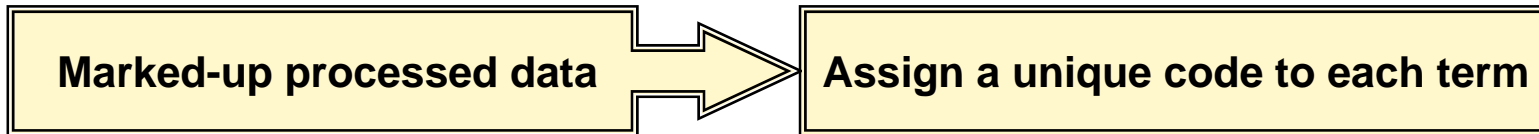
After mark-up processing

1. Serious adverse reactions
1). ¥61 Oculomucocutaneous syndrome (61 Stevens-Johnson syndrome) , 61toxic epidermal necrolysis (61Lyell syndrome): Adequate observations should be provided, as oculomucocutaneous syndrome or toxic epidermal necrolysis may occur. If such a syndrome occurs, 92 stop dosing == and provide appropriate treatment.



Process Steps for Database Structure (2) <7>

Coding the terms tagged and carved out using Access

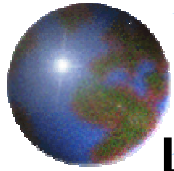


1. Serious adverse reactions

1). ¥¥61 **Oculomucocutaneous syndrome** (61 **Stevens-Johnson syndrome**), 61toxic epidermal necrolysis (Stevens-Johnson syndrome): Adequate cautions should be provided, as oculomucocutaneous syndrome or toxic epidermal necrolysis may occur. If such a syndrome occurs, 92 stop dosing == and provide appropriate treatment.

Coding

ref_code	wrd_code	wrd_name
	0150	Stevens-Johnson syndrome
0150	4143	Stevens-Johnson syndrome
0150		Oculomucocutaneous syndrome
0150	E912	Stevens - Johnson Syndrome



Process Steps for Database Structure (3) < 8 >

Linking synonymous words processing (hypernym/hyponym) with early symptoms of adverse drug reactions

Hypernym code (Processing of synonymous words)

Unique code

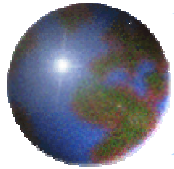
Adverse drug reaction terms marked up and extracted

Enter early symptoms of adverse drug reactions anticipated from adverse drug reaction terms

ref_code	wrд_code	wrд_name	contents
	0150	Stevens-Johnson syndrome	Develop a fever, feel dull, articular pain, headache, have no appetite, entire skin inflames and develops a rash, have a blister, mucous membrane such as in the mouth, in the nose or conjunctiva festers, have a red eye
0150	4143	Stevens-Johnson syndrome	
0150	6623	Oculomucocutaneous syndrome	
0150	E912	Stevens - J Syndrome	

Register early symptoms of adverse drug reactions, which are anticipated to be major and occur at a high frequency, in plain words

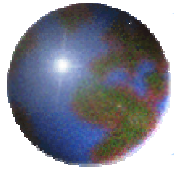
Individual expressions are made to carve out by compartmentalizing “, (comma)”



Classifying and Scrutinizing Adverse Drug Reaction Terms

< 9 >

- ✦ All adverse drug reaction terms were shortlisted into terms described in the 'serious adverse drug reactions' column: 2,083 words (as of August 2003)
- ✦ Serious adverse drug reactions were classified and scrutinized
 - Serious adverse drug reaction terms: 1,010 words
 - Symptom terms: 711 words
 - Test terms: 265 words
- ✦ Expressions of early symptoms were standardized and scrutinized
- ✦ Regional classification of early symptoms is now being developed in the light of convenience of use of information printed out from a system in clinical field



Database Structure (1)

< 10 >

Microsoft Access - [Early symptoms of adverse drug reactions K2: Tables]

File (F) Edit (E) Visual (V) Insert (I) Format (O) Record (R) Tool (T) Window (W) Help (H)

ref_code MS P Gothic 9 B I U

ref_code	wrd_code	wrd_name	contents	Subjective	Subjective/objective	Others	Test data
	0150	Stevens-Johnson syndrome	Develop a fever, feel dull, articular pain, headache, have no appetite, entire skin inflames and develops a rash, have a blister, mucous membrane such as in the mouth, in the nose or conjunctiva festers, redness in the eye	Feel dull, articular pain, headache, have no appetite	Develop a fever, entire skin inflames and develops a rash, have a blister, mucous membrane such as in the mouth, in the nose or conjunctiva festers, redness in the eye		
0150	4143	Stevens-Johnson syndrome					
0150	6623	Oculomucocutaneous syndrome					
0150	E912	Stevens - Johnson Syndrome					

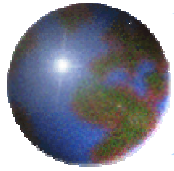
record : 1 / 4 (filter)

Datasheetview

*** Excerpt from package insert to "Diclofenac Sodium Tablet"**

(1) Serious adverse drug reactions (frequencies unknown)
The following adverse reactions may occur.
In this case, stop dosing and provide appropriate treatment.

- 1) Shock (chest distress, cold sweat, dyspnoea, coldness of limbs, hypotension, disturbance of consciousness, etc.), anaphylactoid symptoms (urticaria, angioedema, dyapnoea, etc.)
- 2) Hemorrhagic shock or gastrointestinal ulcer associated with puncture
- 3) Aplastic anemia, hemolytic anemia, agranulocytosis, thrombocytopenia
- 4) Oculomucocutaneous syndrome (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), erythroderma (exfoliative dermatitis)
- 5) Acute renal failure (nephritis interstitial, renal papillary necrosis, etc.)
(Symptoms/test findings: oliguria, haematuria, proteinuria, BUN, increased creatinine in blood, hyperkalemia, hypoalbuminemia, etc.), nephrotic syndrome



Database Structure (2)

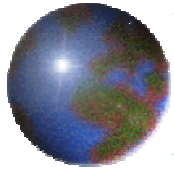
Early symptoms of adverse drug reactions K2: Tables							
ref_code	wrd_code	wrd_name	contents	Subjective	Subjective/objective	Others	Test data
	2576	Hypercalcemia	Feel dull, have no appetite, confused, have concentration problems, feel sick, feel numb, jumped pulse, have high blood pressure, feel thirsty	Feel dull, have no appetite, feel sick, feel thirsty	Have concentration problems, jumped pulse, feel numb	Confused	Have high blood pressure
*							

* Excerpt from package insert to "Calcitriol Injection"

(1) Serious adverse drug reactions

Hypercalcemia (28.1%): Measure serum calcium values regularly (at least once two weeks), as this product increases serum calcium. If the serum calcium value exceeds the upper limit of normal values of serum calcium set by the medical institution by 1 mg/dL, immediately suspend dosing. Be careful about appearance of symptoms (itching paraesthesia, the back teeth, etc.) considered due to hypercalcemia. Restart dosing only after the serum calcium values are confirmed to be lowered to the normal values of serum calcium set by the medical institution by suspension of dosing, and consider lowering the dose with reference to the dose level before suspension (Refer to the section of <precautions for use related to dosage and administration>).

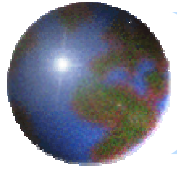
Note 2) If the compensated calcium value exceeds 11.5 mg/dL



Classification Criteria for Expressions of Early Symptoms

Item	Classification criteria
Subjective symptoms [457 expressions]	Early symptoms known only to patient <hr/> 5 senses (sensuous expressions; pain, itching, others) Desires (3 desires), etc.
Subjective/objective symptoms [654 expressions]	Early symptoms known to patient and family/helper <hr/> Including change in excretion such as urine and stool, temporal course of events such as “I became unconscious”, and symptoms cognizable as pointed out by others
Objective symptoms [75 expressions]	Early symptoms not recognizable by patient but known only to family/helper
Test symptoms [81 expressions]	Symptoms to be tested as laboratory values can only tell

* Number in [] as of March 2003



Review

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Quality medical service is in need although effectiveness of medical care is progressed, and recently 'Secure rights and safety of patients' has been established as an independent item for hospital function assessments. Specifically, in order to ensure that information on adverse drug reactions that serves as the central role of patient safety management is provided and that safety measures are promptly and certainly provided irrespective of experience of medical professionals, it is essential to utilize information technology. In this respect, this database is very helpful.

By loading this database to an application system easily usable by medical professionals and presentable to patients in an understandable way, verification will be performed in various medical fields to further improve the database on early symptoms of adverse drug reactions.