Case Study on Important Terms in Safety Investigations
- Survey and Evaluation of Safety Terms Appearing in
Literatures on a Hypocholesterolemic Agent, Lovastatine

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Abstract This paper describes survey and evaluation of important terms on drug safety. We used a case study on the pharmaceutical, Lovastatine for the survey, and an analysis of frequency of the terms for the evaluation. Four words, "adverse", "safety", "toxicity", "failure" were found at higher occurrence frequency rate in the records containing mainly description on safety than that in the records with little or no description on safety.

Key words safety, drug safety, literature survey, database, safety terms, online searching, Lovastatine, MEDLINE

1. Introduction

It has been reported that eosinophilia-myalgia syndrome(EMS), a newly recognized disease, is associated with ingestion of industrially synthesized tryptophan which contained trace amount of an etiologic contaminant¹⁾⁻³⁾. In the EMS problem, the importance of a quite small amount of an impurity have again directed our attention to the importance of safety control in consumer products. In this type of safety problem, analytical chemists should play an important role in the improvement of the safety measures.

Safety measures must be examined interdisciplinarily on the basis of information and knowledge in many fields concerned. It seems, however, difficult to make an effective access to the information on safety problems even in the adjacent fields because of the differences in sophisticated forms and in terminology among databases. In order to improve this situation, it will be helpful to make a new system of effective use of the huge amounts of safety information accumulated already in various databases. This will be done by the strategy of following steps:

- 1) to survey and obtain definitely the general idea of safety in each field
- 2) to collect comprehensively technical terms and related terms expressing the general idea of safety in each field
- 3) to rearrange and classify the terms obtained in the step 2)
- 4) to elucidate linkage between the terms obtained in the step 3) and the terms used in various databases, and
- 5) to rearrange and classify the safety terms in various different fields, and to make linkage among them for managing and utilizing databases.

To make a new system to utilize the various established databases in the aspects of safety, we have done a survey on safety in the pharmaceutical field, as the first example according to the above mentioned strategy, and will present here the outline.

2. Safety Terms in the Pharmaceuticals Field

Safety of pharmaceuticals has been investigated systematically in all the stages of research & development. The manufacturing/marketing/use and measures for safety have been well established after bitter experiences on safety. The large amount of information concerning about safety has been accumulated. Furthermore, interest on drug safety is very strong, because drug, although toxic, is used on the balance between risk and effect of relieving pains from disease. These points lead us to investigate the safety in the pharmaceutical field. This is the first case study on important terms in safety investigation.

In the pharmaceutical field, "adverse reaction" or "adverse effect" is the most representative term on safety. Its definition by the World Health Organization is as follows: "an adverse reaction is any response to a drug that is

noxious and unintended and that occurs at doses used in man for prophylaxis, and diagnosis or therapy, excluding failure to accomplish the intended purpose"⁴⁾ This definition expresses the most typical concept of safety and/or risk in the pharmaceutical field.

There are, however, many other terms concerned with the concept of safety on various toxicities, absorption/distribution/metabolism/excretion, and on quality such as contamination of impurities including criminal addition of poison. It is considered that concept of safety covers also the problems such as withdrawal of a product, change of indication, usage and/or package insert, dissemination of doctor letter, survey to elucidate casual relation, and presenting a case to the court, judgement and compensation. Terms concerned with the above-mentioned concept have been collected, rearranged and classified. The main terms are shown in Table 1.

Table 1. Safety Terms in the Pharmaceutical Field

0. General Terms on "Safety"			Deficiency Deviation Disorder Disturbance Dysfunction Failure Hazard Impairment Impair Injury Reaction Symptom Death Defect Deformity Sensitivity Epidemiology Epidemiological Study Cohort Study Association Casual Relation Association Morbidity Mortality Intoxication Poisoning ADR Reporting Pharmacovisilance Case Control Study Quality of Life
Safety , Safe Risk			
1. Terms on "Toxicities"			
General Terms	Specific Terms		
Toxicity Toxic	Cardiotoxicity Cytotoxicity Hepatotoxicity Immunotoxicity Myelotoxicity Neurotoxicity Ototoxicity Reproductive toxicity Teratrogen Teratogenicity Antifertility Infertility Carcinogen Carcinogenicity Tumor Tumorigenicity Oncogenicity Mutagen Mutagenicity		
Toxicity Test	Acute Test Short Term Test LD-50 Subacute Test Chronic Test Long Term Test	3. Terms on Miscelneous "Safety Problems"	
		General Terms	Specific Terms
Tolerance		Scientific Misconduct Inspection Withdrawal	Ban Recall Remove Restricted Restriction Alert Precaution Information Change Data Sheet Change Indication Change Challenge Trial Court
Dependency	Physical Dependency Psychiatric Dependency	Warning	
Accumulation Bioavailability Bioequivalence		Suit Filed	
2. Terms on "Adverese Reactions"		Ignorance No-Fault Compensation Product Liability Abuse Accident Counterfeit Contamination	
General Terms	Specific Terms		Misuse
Adverse Drug Ractions(ADR)	Drug Related Effects Drug Related Changes Abnormality Abnormal Damage Debility Debilitation		
Adverse Effects Adverse Events			

3. Search and Classification of Literatures on Lovastatine

Lovastatine is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A. It is widely used as a hypocholesterolemic agent because of its inhibiting effect on the synthesis of a precursor of cholesterol. All the records on Lovastatine were searched in MEDLINE(1966-1990) which is a representative database in biomedicine. We obtained 475 records(1980-1990) on Lovastatine by use of "S LOVASTATNE" as

the search formula in one of the powerful online retrieval system , DIALOG.

These records were classified into a j groups on the research stages of the drug, and also into groups on the degree of description of safety. The results of classification are shown in Table 2. The degree 2 records which contain mainly the description on safety are 46 records, about 10% of all records, while the degree 0 records containing little or no description on safety are 245 records, 52% of all records. Among 46 records are contained 26 case reports on experiences of adverse reactions.

Table 2. Classification of 475 Searched Records by the Research Stages* and the Degree of Description on Safety**

	a	b	c	d	e	f	g	h	i	j	sum
0	2	0	35	53	36	7	0	1	99	12	245
1	1	12	55	31	6	4	8	0	26	2	145
2	26	3	1	8	0	0	7	0	1	0	46
5	4	0	7	20	2	0	0	0	2	4	39
sum	33	15	98	112	44	11	15	1	127	18	475

* Research Stages, a - j.

- a: clinical experience after marketing(case reports)
- b: post marketing surveillance and epidemiological studies
- c: clinical trials and/or clinical evaluations
- d: other miscellaneous clinical experiences(including reviews)
- e: pharmacological studies
- f: absorption/distribution/metabolism/excretion studies
- g: toxicological studies
- h: physiochemical and/or analytical studies
- i: biological and/or biochemical studies
- j: other miscellaneous studies

** Description Degree on Safety, 0 - 2 and 5

- 0: little or no description
- 1: some but insignificant description on safety
- 2: major and/or significant description
- 5: insufficient description to decide a degree of safety

4. Evaluation of Safety Terms

An attempt of evaluating the propriety of the safety terms shown in Table 1 was done by comparing the occurrence frequency rate of the safety terms between the degree 2 records and the degree 0 records. The comparisons in word by word were performed on the title field, the abstract field, and the index field, respectively. This is because the occurrence frequency rate became too small to be compared, due to the declension of a word, and also due to the variation of combination of words in a term. The occurrence frequency rate was calculated as the ratio of the occurrence frequency to the total of words.⁵⁾

Table 3. Occurrence Frequency Rate of Safety Words appearing in Abstract Field

Safety Words in Abstract field	Examples from Safety Terms in Table 1	Occurrence Frequency Rate*	
		degree 2	degree 0
acute	Acute Test	0.0018(7)	0.0001(6)
adverse	Adverse Drug Reactions	0.0039(15)	0.0000(1)
change, changes	Drug Related Changes	0.0026(10)	0.0012(52)
control, controls	Case Control Study	0.0008(3)	0.0022(91)
data	Data Sheet Change	0.0021(8)	0.0007(29)
drug, drugs	Drug Related Effects	0.0096(37)	0.0034(145)
effect, effects	Adverse Effects	0.0054(25)	0.0038(164)
events	Adverse Events	0.0016(6)	0.0001(3)
risk	Risk	0.0018(7)	0.0004(18)
safety	Safety	0.0016(6)	0.0001(5)
study	Epidemiological Study	0.0023(9)	0.0013(55)
symptoms	Symptoms	0.0013(5)	0.0000(1)
term, terms	Long Term Test	0.0013(5)	0.0002(9)
toxicity, toxicities	Toxicity	0.0021(8)	-----(--)
trial, trials	Trial	0.0026(10)	0.0002(13)

* Figure in each bracket indicates an occurrence frequency of a term

In the title field, it is unable to evaluate the propriety of words in Table 1 because the occurrence frequency is very low(1 - 2) in the records of degree 2. Among 46 records in the degree 2, there are 19 records with the description in the abstract field while 28 records have no description in the abstract field because these are letters to editor which are case reports on the experiences of adverse reactions.

In Table 3 are listed the words of which the occurrence frequency is more than 5 in the degree 2 records or equivalent occurrence frequency rate in the degree 0 records. The occurrence frequency rates of six words, "acute", "adverse", "events", "safety", "symptoms" and "toxicity" are more than ten times in the degree 2 records than in the degree 0 records. On the other hand, there is no word in Table 1, of which the occurrence frequency rate is over 10 times in the degree 0 records than in the degree 2 records.

Among above-mentioned six words, "acute", "events", and "symptoms" have no meaning on safety. Only three words, "adverse", "safety", and "toxicity" are, therefore, significant as safety terms in the abstract field. This is from the comparison of the occurrence frequency rate in the degree 2 records with that in the degree 0 records. The three words seem to be proved to be fundamental as safety words in the pharmaceutical field.

Concerning the index (MeSH term used in MEDLINE) field, similar analysis indicates that four words, "adverse", "acute", "failure", and "toxicity" appear in high occurrence frequency rate in the degree 2 records, as shown in Table 4. "Failure" also should be added to the above mentioned words as another fundamental safety words.

Table 4. Occurrence Frequency Rate of Safety Words in Index Field

Safety Words on Index Field	Occurrence Frequency Rate	
	degree 2	degree 0
acute	0.0063 (7)	0.0004 (3)
adverse	0.0368 (41)	0.0019 (16)
drug	0.0475 (53)	0.0333 (278)
effects	0.0502 (56)	0.0176 (147)
failure	0.0063 (7)	0.0001 (1)
toxicity	0.0099 (11)	----- (--)
trials	0.0045 (5)	0.0020 (17)

5. Concluding Remarks

In the present study of survey, "adverse", "safety", "toxicity", and "failure" have been found in higher occurrence frequency rate in the records containing mainly description on safety than in the records containing little or no description on safety. They are considered to be the fundamental safety terms in pharmaceutical field. Many other words in Table 1 are unable to be regarded as safety terms. It may be caused by the survey limited within a drug and a database, multi-meaning of a word, use of safety words in description irrelevant to safety such as description on experimental materials, and so on. We feel, however, that the method presented here may be useful in other areas for finding the safety-related literatures.

References and Foot Notes

- 1) White, K.E., et al. New Eng. J. Med. 323(6), p.357-65(1990).
- 2) MMWR. 39(34), p.589-91(1990).
- 3) Wygert, L.A., et al. J. Am. Med. Assoc. 264(13), p.1698-703(1990).
- 4) Karch, F.E. and Lasagna, L. J. Am. Med. Assoc. 234(12), p.1236(1975).
- 5) Occurrence frequency rate of term_i (OFR_i) is defined as follows.

$$OFR_i = \frac{f_i}{\sum_{j=1}^n f_j}$$

- n : number of kinds of terms appeared in a group(to a specified field)
 f_i : occurrence frequency of Term_i in a group(to a specified field)
 $\sum_{j=1}^n f_j$: Summation of occurrence frequency of all terms in a group (to a specified field)