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An efficient prediction model for OTC medicine effect with the package inserts information

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Abstract

In Japan, general public those who are not medical experts usually buy OTC medicine at a pharmacy, depending on their illness condition. In this case, it is difficult for them to consider how much the OTC medicine is effective for their symptom. The components of OTC medicine have been used as ethical medicines for a long period of time.
This is because the efficacy and safety of ethical medicine have been confirmed before being employed as OTC medicine. The information of those confirmed medicines is described in package inserts, which is aimed for medical professionals. Therefore, it is difficult for general public to understand what the package insert describes in terms of medical effects.
In this study, from the information which appears in the package inserts of prescription medicines, a method for estimating the effect of OTC medicine is investigated. Also, a method of estimating the effects of medicines without directly compared data is proposed, only by using the information of package inserts of ethical medicines.

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Keywords: Package Insert; Medicine; Effect range of medicine; Experimental configuration; Quantitative comparison reserarch; Text mining

1. Introduction

With the increase in medical expenditure in Japan, from the self-medication point of view, patients are inclined to buy OTC medicines by themselves. But patients find it difficult to get pharmaceutical information and apply

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them for their medical treatment. General people buy OTC medicine at a pharmacy depending on their illness condition. But general people do not have enough knowledge to understand the information of OTC medicines. OTC medicines are being purchased at a pharmacy, based on the pharmacist's advice.

Various information and knowledge are required in order to use the medicines, along with we have plenty of information for using the medicines. Component of OTC medicines are ethical medicines. Among the ethical medicines information, package inserts of medicines are medical information that is attached to each package of ethical medicines. The package inserts are published in home page of PMDA (Pharmaceuticals and Medical Devices Agency), and being available for anyone.

We have studied the possibility of effect comparison of each component from the package insert information of ethical medicines for components of analgesic that is widely used in general medicines.

With the information of package inserts, the effect of ethical medicine is comparable, but the difference in range of effect is wide.

Therefore, aligning the experimental system and by reducing the effect width, the possibility that the increase the accuracy of the effect comparison of ethical medicine has been reported.

In this study, we investigate further to consider the comparability of effects of the analgesics components, which are not compared directly from the information described in the package insert.

If it is possible to compare the effect of medicines only by publicly available information, people can infer the unfamiliar medical effect from package insert.

2. Related work

The text mining performs natural language processing on text documents with data mining techniques. This technique generates new knowledge based on the tendency, Co-occurrence or the characteristics among text document [1]-[4]. Kurohashi et al. also reported studies on analysis of the structure of the document [5] [6].

One of the applications of text mining method, Sugiyama et al. used text mining in order to prevent medical malpractice in a prescription ordering system of the hospital [7] [8]. They analyzed the contents on which prescription correction was made, the ordering system was changed the contents had much correction to improve the checking of prescription. They also reported the study for integrating the ordering system with a package insert of medicine. Since the statement of a package insert is complicated, construction of a database becomes complicated.

Some of the research analyzed text structure has been made about notes on the use of a package insert with text mining, so far. For example, Okuya et al. described cluster analysis of the information on medical supplies, and build the database of a package insert [9] [10]. Kimura et al. analyzed the document of the package insert in order to use a package insert [11][12]. Nabeta et al. analyzed the incident report with text mining [13]-[15]. Nabeta et al. reported studies to extract information from large amounts of data to enhance the safety of the medicine [16] [17]. Togashi et al. reported a study to create a database. Bisgin et al. reported a study utilizing topic models to the extraction of the Safety and therapeutic [20]. Although text mining is used in a medical area, the information, which anyone can obtain, is restricted. Among medical information, a package insert is public information and is the information, which can be used for analysis as information, which is easy to come to hand.

There is a report studied about the comparability of the effect of the medicines by which a direct comparison is not carried out using the text information on the package insert of a medicine. In this research, quantitative extraction of the relationship between ingredients was made using the text information indicated to the pharmacology of the ethical pharmaceutical package insert and the possibility of narrowing down of the effective range was examined in quantification of an effect. Ikoma et al. made effect comparison of medicines by which direct comparisons are not made with combining the information on the package inserts. Indicates relationship between effects of medicine. Ikoma et al. examine the effect comparison of the medicine with an

analgesic and antihistamine [22].

A report of the comparison of medicine effective using text mining, the width of the effective range is extensive. We suggest a method for increasing the accuracy of the effective range in the present work.

In this study, we examined even the medicine of other effects whether an effect comparison was possible similarly.

3. Ethical pharmaceutical package insert

There are precautions in commentary book, Kusurino Shiori (Drag information Sheet), which is found in package insert and ethical medicine interview form as ethical medicine information.
Among ethical medicine package, insert medicine information is required for medical professionals such as doctor, dentist and pharmacist. It is briefly summarizing medical information, which is attached to the packaging unit of the pharmaceutical.

It is obliged to attach for every package unit of medical supplies. This document indicates ingredients, dosage and administration, pharmacology, pharmacokinetics, side effects, precautions for use and so on. Furthermore, an ethical pharmaceutical package insert is established the description items in the insert by Article 52 and 54 of the Pharmaceutical Affairs Law. It is used as a material in the reference at the time of use and prescribes for prescription medicine. It is aimed at the text information indicated to "pharmacology" among the information written in an ethical pharmaceutical package insert in this research. The section of "pharmacology" is briefly indicated the information such as the results of pharmacological tests from application to approval. In many cases, there is basic research with ethical pharmaceutical performed in a test tube or to an animal and clinical study performed to humans. The pharmacological test data are provided as text information. Moreover, as for test data, in addition to information, including the validity of ethical pharmaceutical, etc., relationship with other medicines may be indicated. In addition to information such as the efficacy of medicine, there is a relationship with the other medicine are described in the test data.

The medicine with which brand names differ from making into the main ingredients the medicine of an ingredient with which the patent term has expired. If the text information on the same ingredients is collected, it will become possible to put together as information on the same ingredient. The information acquired from each ethical pharmaceutical package insert for every ingredient is collected. The characteristics of an ethical pharmaceutical ingredient are verified.

Among them, it is possible to aggregate the data obtained by the same experiment, helps to promote, the precision of comparing the effects of medicines.

It is possible to estimate the effects of medicines without directly compared data, only by aggregating the results of the same experiment.

4. Analysis of ethical pharmaceutical package insert of Ethical Pharmaceutical

4.1 Effect comparison of Medicines by the package insert information

By analysing a package inserts with text mining showed that various information could be extracted as a last paragraph showed. Then, we focus on the document that compares the effect between the medicines in which the same effect is shown in this section. By analyzing these documents, text mining was carried out for the purpose of comparison of the effect among medicines. Many package inserts have described which compared the effect with the medicine put on the market previously, in order to verify the effect of a medicine.

This description is generally only comparison between two medicines of precedence medicine and the

medicine concerned. However, if the comparative information between two or more two medicines is combined, it is possible to make the effect comparison table between two or more medicines.

4.2 Filtering of the Effect Range

We have examined to extract the effect comparative information focusing to the medicine with an analgesic effect with text mining in section 4.1. However, mismatching occurred in the effect between each the component of the ingredients.

If we consider this result from a pharmacological viewpoint, the difference in test method will be considered to be a primary factor. For example, it is from the differences of the animals used in tests such as mice or rats.

Then, we investigate to narrow the range of effects by adjusting the experimental conditions,

Among the medicine with analgesic effect, we make a comparison with ibuprofen as test medicine for many package inserts. For a comparison of the effects with ibuprofen, following four ingredients were described in the package insert as follows:

- Aspirin
- Indomethacin
- Aminopyrine
- Oxyphenbutazone

Among them, aspirin was most compared with. Then, following eight experiment confirmations were extracted if we compared with the experimental configuration of the examination which compared ibuprofen with aspirin as follows:

Table 1 indicates the result of experiment configurations for each magnification of the effect on aspirin of ibuprofen. Even in the same experimental configuration, there is a range in magnification of the effect. Therefore, the table 4 indicates the range in magnification. From this result, the magnification of the effect on aspirin of ibuprofen is 6 to 9 times with the width of the fluctuation effect is 1.5 in experiment configuration of carrageenin dropsy. There was no effect of fluctuations in experiment configuration of lipoic saccharide for magnification of the effect was 4.0 as well. On the other hand, experiment configurations have an influence on the difference in the effect of two medicines. Table 2 indicates the result of the comparison of two same medicines called ibuprofen and aspirin.

Table 1 Range in Magnification

Experimental Configuration	Min.	Max.
Lipoic saccharide	4	4
Ultraviolet erythema	16	32
Carrageenin edema	6	9
Adjuvant arthritis	5	10
Yeast suspension	20	20
Randall-Selitto method	30	30
Acetylcholine-induced writhing	28	28
T.T.G. Fever suppression	25	25

Table 2 Magnifications of an Effect for Hydrocortisone of Indomethacin

Experimental Configuration	Min.	Max.
Carrageenin edema	2	2.5
Granuloma method	4	4

Table 3 Magnifications of an Effect for Dicrofenac of Indomethacin

Experimental Configuration	Min.	Max.
Adjuvant arthritis	50	50
Carrageenin edema	5	5
Randall-Selitto method	5	5

Table 4 Effect Comparison Every Experiment Condition of the DL-Methyl Ephedrine Hydrochloride

Experimental Configuration	Experimental Medicine	Experimental animal	Max.
Guinea pig cough by the sulfurous acid gas inhalation	Codeine	Guinea pig	0.6
Guinea pig cough by the sulfurous acid gas inhalation	Ephedrine	Guinea pig	0.7

Furthermore, the result extracted from the experimental data for the diclofenac of indomethacin is as follows. The magnification of the experiment configuration and the effect of this experimental data are indicated in table 3. The same result was also confirmed in this examination. It was suggested that the experimental configuration was affected, the effect of a medicine as a result.

With the package insert of the medicine with an analgesic effect, we confirmed that there was a possibility of the effect range squeezing with extracting the magnification of an effect for every experimental configuration. Then, as for the medicine except analgetic, effective range squeezing was considered with same manner.

The package insert of the medicine classified into an antitussive medicine among ethical pharmaceuticals was accumulated.

Some of the experimental results were shown in below. It was confirmed that the experiments are carried out with various configuration even in antitussive medicine same as analgesics.

Among the medicine with antitussive, we make a comparison with dl- methyl ephedrine hydrochloride as test medicine for many package inserts. For a comparison of the effects with dl- methyl ephedrine hydrochloride, following two ingredients were described in the package insert as follows:

- Codeine
- Ephedrine

We can narrow down an effect range from information performed in same experiment system. Similar to an analgesic, it was found in the antitussive that a more correct effect comparison was possible by preparing experiment system. Furthermore, the effect comparison between the medicines that we do not compare directly by preparing experimental configuration is possible.

4.3 Effect prediction of Medicines by the package insert information

Medical evaluation data does not necessarily having taken in all the experimental conditions before getting approved.

We show the possibility of using the difference in effect of the medicines caused by the experimental conditions, for the guide to estimate the future experiments. Information on the effect in each of the package insert only describes results of experiments conducted for designated medicines. But we can infer the undescribed effects by merging medical information in attached documents. Therefore, we compared the text information in each package insert.

Information that has been described in the package insert of analgesics, were summarized for each experimental background and each medicine.

The same experimental conditions are categorized in the same dictionary in terms of experimental background, medicines, and stored the knowledge for the future comparison. If we have the same experimental background and the same range of effects data, we can infer the undescribed effects just by using the information written on package inserts.

Let us show an example. Suppose effects for indomethacin and carrageenan pleurisy for indomethacin and aspirin in kaolin paw edema in the pranoprofen are described in the package insert. On the other hand, effect against indomethacin in the carrageenan pleurisy amfenac sodium is being described. Since the effect on indomethacin in carrageenan pleurisy is equal, effect on indomethacin and aspirin in kaolin paw edema of the amfenac sodium can be thus estimated.

In the same manner, it is possible to infer the effects of, acemetacin and amfenac sodium which are not described in the package inserts. Thus, we can infer the undescribed effect by combining the information in the package inserts under the same experimental background.

Then we combine obtained data so far, such as analgesic and experimental system, we can infer the undescribed effects in the package insert. (Fig.1) This shows that we can infer the difference of effects caused by experimental background, with combining some attachments information, and also we can infer the comparison of any medical effect.

Table 5 Estimation of the effect of the experimental conditions and the comparison medicine 1

	kaolin paw edema		carrageenin pleurisy	
pranoprofen	Indomethacin Aspirin	Strong Strong	Indomethacin	Strong
amfenac sodium			Indomethacin	Strong

Table 6 Estimation of the effect of the experimental conditions and the comparison medicine 2

	Adjuvant		Carrageenan edema	
amfenac sodium	Diclofenac sodium Ketoprofen Indomethacin	Same、Strong Same、Strong Same	Diclofenac sodium Ketoprofen Indomethacin	Strong Same Same
Acemetacin			Indomethacin	Same

	carrageenan footpad edema assay	Haffner assay	Paper disk assay	Randall-Selitto assay	Tail pinch assay	adjuvant	kaolin paw edema assay	carrageenan-induced edema	carrageenin pleurisy	concanavalin A arthritis	bradykinin-induced	lipopolysaccharide fever	pressure stimulation assay	chemical stimulation	vascular permeability	acetic acid-induced stretching	pedal edema	Blow edema	electrical stimulation	granuloma formation	Quantity of effusion in the granuloma pouch	thermal stimulation	Tail-piece electrical stimulation	argentometric method
diclofenac sodium	●	○	○	●	●	●	○	○	○	○	○	●	○	○	●	●	○	○	○	●	○	○	○	○
ketoprofen		○	●	●	○	○	○	●	○	○	○	○	○		○	○	●	○	○	○	○	○	○	○
oxaprozin	●	○	○	●	○	●	○	○	○	○	○	○	○		○	○	○	○	○	○	○	○	○	●
ibuprofen	●	○	○	●	○	●	○	○	○	○	○	○	○		○	○	○	○	○	○	○	○	○	○
indomethacin	●		○	○	○	○															○			○
etodolac					○								○		○	○	○	○	○	●		○		
flufenamic acid aluminium	●			●	○	○		○													○			○
sulindac	●	○	○	○	○	●	○	○	○	○	○	○	○		○	○	○	○	○	○	○	○	○	○
zaltoprofen	○	○		○	○	○	○	○	○		●		○	○					○			○	○	○
mofezolac	●			○	○	○					●			○							●			○
tiaprofenic acid	○	○	○	●	○	●	○	○	○	○	○	○	○		○	○	●	○	○	●		○	○	○
eptazocine	○	○									●		●	○		○			○			○	○	
celecoxib	○	○	○	○	○	●	○	○	○	○	○	○	○		○	○	○	○	○	○	○	○	○	○
pentazocine hydrochloride	○	○		○	○	○	○	○	○	○	○	○	○			○			○			○	●	○
loxoprofen	○			○	○	●		○																○
tramadol hydrochloride M1		○		○		○		●																
tramadol hydrochloride	○	○		○	○	○	○	○	○	○	○	○	●	○		○							●	
naproxen	○	○	○	●	○	●	○	●	○		○	○	○			○			○		○	○	○	
pranoprofen	○	○		●	○	●	●	●	●	●										●				●
buprenorphine	○	○									○		●	●					●			●		
piroxicam	○	○		●	○	●	○	●									●	●		●				○
amfenac sodium	○	○	○	●	○	●	○	●	●	○	○	○	○		○	○	○		○	●	○	○	○	○
Ampiroxicam	●	○		●	○	●	○	○	○	○	○	○	○		○	○	○	●	○	●	○	○	○	○
flurbiprofen	○	○		●	○	●		○																○
mefenamic acid	○	○		○	○	●		○																○
dimetotiazine mesylate																								
epirizole	○	●	○	●	○	○	○	○	○	○	○	○	●	○		●			●		○	●	○	○
meloxicam	○	○		●	○	●	●	○	○	○														○
acemetacin	○	○		○	○	○	○	●	○	○	○	○	○		○	○			○			○	○	○
nabumetone	○	○	○	●	○	●	○	●	○	○	○	○									○	○	○	○
flurbiprofen axetil	○	○		●	○	●	○	○	○	○														●
lornoxicam	●	○		●	○	●	○	○	○	○														○

Fig. 1 Effect estimation of the drug by comparison medicine and experimental background

●: Text information exists in the package insert
○: Effect is expected from the other package insert information

5. Conclusion

It is possible to compare the effect of each component consisting of OTC medicines by mining the package insert information which comes with the ethical medicine. The range of effects usually become wider with all the information in the package insert, but the range can be reduced by satisfying the certain experimental conditions. By adjusting the experimental conditions, comparison between components which does not hold the direct corresponding data becomes possible and this leads to infer the range of effect magnification which appears in different experimental methods.

The range of effect magnification observed in several experimental methods can be used as a reference for the future experiments.

This result helps to improve the availability of the package insert information, and the difference in the experimental background can be used as a guide for the future experiments.

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