ORIGINAL ARTICLE

Causality Assessment of Cutaneous Adverse Drug Reactions

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Background: Cutaneous adverse drug reactions (ADRs) are the most common adverse reactions attributed to drugs. A systematic and effective approach to a patient with suspected drug eruption allows for prompt recognition, classification and treatment of cutaneous ADRs. A standardized and effective approach for objective causality assessment is necessary to make consistent and accurate identification of ADRs. **Objective:** Although the Naranjo algorithm is the most widely used assessment tool, it contains many components which are not suitable for clinical assessment of ADRs in Korea. The purpose of this study is to compare correlations of the Naranjo algorithm and the Korean algorithm to evaluate usefulness of both algorithms in order to make a causal link between drugs and cutaneous ADRs. In addition, this study classifies the clinical types and causative agents of cutaneous ADRs. **Methods:** The authors retrospectively reviewed the clinical types and laboratory findings of patients who were diagnosed with cutaneous ADRs in the dermatology clinic at Gil hospital. One hundred forty-one patients were enrolled in this evaluation. The causal relationship of ADRs was assessed by using the Naranjo algorithm and Korean algorithm (version 2.0). **Results:** A cross-tabulation analysis was applied to the Naranjo algorithm and Korean algorithm (version 2.0). Simple correlation analysis and a Bland-Altman plot were used for statistical analysis. Correlation analysis confirmed that the two assessment algorithms were significantly correlated. Exanthematous eruptions (68.8%), Stevens-Johnson syndrome (10.6%), and urticaria (8.5%) were the most common types of cutaneoues ADRs. The most common causative agents were antibiotics/antimicrobials, antipyretics/non-steroidal anti-inflammatory drugs, and central nervous system depressants. **Conclusion:** The Naranjo algorithm and Korean algorithm (version 2.0) were significantly correlated with each other, and thus reliable assessment methods to determine cutaneous ADRs. **(Ann Dermatol 23(4) 432~438, 2011)**

-Keywords-
Cutaneous adverse drug reactions, Korean algorithm, Naranjo algorithm

INTRODUCTION

Cutaneous adverse drug reactions (ADRs) are defined as noxious, unintended, morphologic skin changes, with or without systemic involvement, that develop after local or systemic administration of drugs in dosages commonly used for prevention, diagnosis, or treatment of diseases or modification of physiologic functions[1-3]. There is a wide spectrum of cutaneous ADRs, varying from transient maculopapular rashes to fatal toxic epidermal necrolysis[4,5]. The pattern of cutaneous ADRs and the drugs responsible for the ADRs change every year.

Most cutaneous ADRs are mild, self-limited, and usually resolve after the offending agent has been discontinued, but some severe cutaneous reactions may result in serious morbidity, and even death[6-9]. Since quick and careful attention to the diagnosis and treatment of cutaneous ADRs is required, a standardized approach is necessary to establish a final decision of causality to result in a consistent,

accurate and reproducible identification of ADRs.

In Korea, many types of drugs are prescribed at the same time and people take oriental medicines frequently[10,11]. During the past few years, as more new drugs have been produced, cutaneous reactions have occurred more frequently. Further, established drugs have also been reported to cause new eruptions not previously reported[10-12]. This study was designed to survey the cutaneous ADRs amongst patients who visited a particular dermatologic clinic during the past three year period and to compare the accuracy of the Naranjo[13] algorithm and Korean algorithm (version 2.0)[14] to evaluate causal association between drugs and cutaneous ADRs.

MATERIALS AND METHODS

Materials

The authors examined 141 patients with cutaneous ADRs who attended the dermatology clinic at Gil hospital from January 2006 till December 2008. Mean age was 45 years (range, 1~90 years) and the majority of the patients belonged to the 41~50 year age group, followed by the 51~60 and 31~40 year age groups. Sixty-three patients (44.7%) were males and 78 patients (55.3%) were females (Table 1).

Methods

The diagnosis of cutaneous ADRs was primarily based on detailed histories and the correlation between drug intake and the onset of the ADR. The diagnosis was confirmed by observing the resolution of signs and symptoms after discontinuation of the suspected offending drugs. Medical histories and physical examinations were performed by one of the authors. A careful history of symptoms, other skin and systemic diseases, medical history, and a family history of drug eruptions or any other disease was obtained. A thorough clinical examination was carried out. The skin, hair, nails, and mucosa (eyes, oral, and genital) were examined. Complete blood cell counts, liver function tests, and renal function tests were carried out.

Assessment of ADRs

Each case was assessed for its causality using the Naranjo algorithm[13] (Table 2) and Korean algorithm (version 2.0)[14] (Table 3). The Naranjo algorithm consists of ten questions and is scored as follows: scores of 9 or 10 indicate that an event is 'definitely' an ADR, scores of 5~8 rate the likelihood of an ADR as 'probable', scores of 1~4 are 'possible' ADRs, and scores of less than 1 are 'doubtful' ADRs[13]. The Korean algorithm (version 2.0) consists of eight questions with scores as follows: greater than 9 is 'certain' for an ADR, 6~8 is 'probable/likely' for an ADR, 3~5 is 'possible' for an ADR, 1~2 is 'unlikely' for an ADR, and less than 0 is 'contradictory' for an ADR[14].

Statistics

Statistical Package for the Social Sciences (SPSS, SPSS Inc., Chicago, IL, USA) 12.0 was used for comparative analysis on the Naranjo algorithm and Korean algorithm (version 2.0). To assess the correlation between the two values, a simple correlation analysis, Pearson's simple correlation coefficient, and intra-class correlation coefficient (ICC) were used. A Bland-Altman plot was used to assess the reliability of the two values.

RESULTS

Assessment of causal association

Cross-tabulation analysis was performed to assess the correlation and reliability of the Naranjo algorithm and Korean algorithm (version 2.0) (Table 4). Simple correlation analysis yielded a Pearson's simple correlation

Table 1. Age and sex distribution

Age (years)	Male	Female	Total	%
0~10	5	3	8	5.7
11~20	5	3	8	5.7
21~30	7	11	18	12.8
31~40	7	12	19	13.5
41~50	12	21	33	23.4
51~60	9	17	26	18.4
61~70	8	8	16	11.3
71~80	7	1	8	5.7
81~90	3	2	5	3.5
Total	63	78	141	
%	44.7	55.3	100	

Table 2. Naranjo algorithm

Question	Answer			Score
	Yes	No	Un-known	
1. Previous report?	+1	0	0	—
2. Event after drug?	+2	−1	0	—
3. Event abate on drug removal?	+1	0	0	—
4. +Re-challenge?	+2	−1	0	—
5. Alternative causes?	−1	+2	0	—
6. Reaction with placebo?	−1	+1	0	—
7. Drug blood level toxic?	+1	0	0	—
8. Reaction dose-related?	+1	0	0	—
9. Past history of similar event?	+1	0	0	—
10. ADR confirmed objectively?	+1	0	0	—

ADR: adverse drug reaction.

Table 3. Prototype of Korean algorithm for ADR causality assessment (ver. 2.0)

| Items	Questions	Answers	Assessment (score)		Remark
Chronologic relationship	Is there any information of chronologic relation of medication and ADR?	Yes No	Appropriate chronologic relationship Contradictory chronologic relationship	(+3) (−3) (0)	Timing of interval following initial administration
Dose reduction or stop	Is there any information of reduction or stop?	Yes No	Clinical response after dose reduction Clinical progress irrespective of the dose reduction, stop was seen Dose reduction or removal of suspected drug has not been done	(+3) (−2) (0) (0)	If, non reversible had occurred, the score would be zero.
Past history of ADR	Have you ever experienced ADR by the same or similar drugs?	Yes No No information		(+1) (−1) (0)	
Combined medication	Is there any information of the drugs being taken in combination?	Yes No	In case the ADR can't be caused by the drug used in combination In case the drug used in combination alone can cause ADR In case data are available by interaction with suspicious drug In case of no available data in combination	(+2) (−3) (+2) (0) (0)	
Drug-unrelated cause	Is there any information of drug-unrelated cause?	Yes No	ADR can't be provocated by non-drug cause ADR can be provocated by non-drug cause	(+1) (−1) (0)	
Any unveiled information of drugs			Indicated in the permission materials (label, insert, etc.) Not indicated, but there existed case reports Unknown	(+3) (+2) (0)	
Re-challenge	Is there any information of re-challenge?	Yes No	Similar response to re-challenge No response to re-challenge No challenge	(+3) (−2) (0) (0)	
Specific tests	Specific tests such as provocation tests, plasma drug level monitoring?	Yes No	Positive Negative Unknown	(+3) (−1) (0)	
Total (highest point 19~lowest points -13) :				points	

ADR: adverse drug reaction.

**Table 4.** Naranjo and Korean algorithm v 2.0 cross tabulation

		Korean algorithm v 2.0			Total
		Possible	Probable/ likely	Certain	
Naranjo algorithm	Possible	5	29	5	39
	Probable	0	32	70	102
Total		5	61	75	141

coefficient of 0.682 (p-value=0.0) (Fig. 1), and the measurement of inter-rater reliability by ICC was 0.67 (0.57~0.75), which ascertains a signific ant correlation of the measured quantitative values of the two assessments. A Bland- Altman plot graph was used to determine if a difference existed between the measured quantitative values of the two assessments. The analysis showed that the values were widely spread on the x-axis, revealing the existence of various test variables, which indicates tha t the test was properly conducted. In addition, most values were distributed within +/− one standard variation, suggesting that the reliability between the two assessments was high (Fig. 2). The difference in the two values became greater in inverse proportion to the average, thus low scores required more scrutiny.
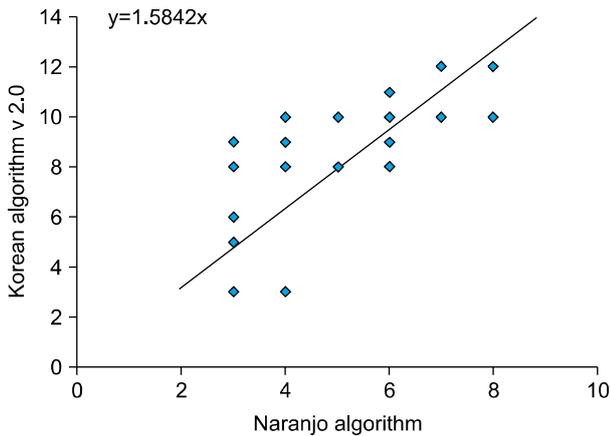
Fig. 1. The measured quantity values of the Korean algorithm (version 2.0) in the x-axis and the Naranjo algorithm in the y-axis are significantly correlated.
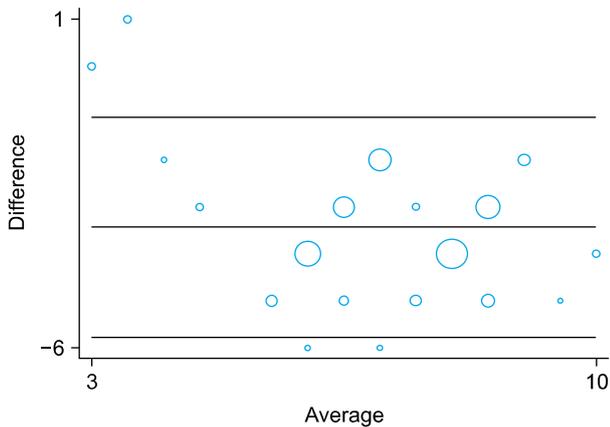
Fig. 2. The x-axis indicates the average of the two values, and the y-axis indicates the difference of the two values, being diffuse sideward means there are many experimental variables. The up-and-down lines in the graph mean a $+/-1$ standard variation, and the more the measured quantity values are within the two lines, the higher the reliability.

Clinical features & latent period

The cutaneous manifestations of ADRs in the order of frequency were as follows: exanthematous eruption, 97 (68.8%); Stevens-Johnson syndrome, 15 (10.6%); urticaria, 12 (8.5%); erythema multiforme, 9 (6.4%); fixed drug eruption, 4 (2.9%); toxic epidermal necrolysis, 2 (1.4%); bullous eruption, 1 (0.7%) and pustular eruption, 1 (0.7%) (Table 5).

The interval between the time the medication was administered and the clinical appearance of the ADR was 'less than a week' in 57 cases (40.4%), 'less than 24 hours' in 38 cases (27%), and 'after four weeks' in 17 cases (5%). Thirty of 48 cases (62.5%) caused by

Table 5. Clinical types of drug eruption

Clinical type	No. of patients	%
Exanthematous eruption	97	68.8
Stevens-Johnson syndrome	15	10.6
Urticaria	12	8.5
Erythema multiforme	9	6.4
Fixed drug eruption	4	2.9
Toxic epidermal necrolysis	2	1.4
Bullous eruption	1	0.7
Pustular eruption	1	0.7
Total	141	100.0

Table 6. Agents responsible for eruptions

Agents	No. of patients	%
Antibiotics/antimicrobials	48	34.1
Antipyretics/NSAIDs	38	27.0
CNS depressants	17	12.1
Anticancer agents	10	7.1
Radiographic dye	5	3.6
Gout preparation	4	2.8
Herb	4	2.8
GIT regulators/antacid agents	4	2.8
Antihypertensive drug	3	2.1
Antihemorrhagic agents	2	1.4
Diuretics	2	1.4
Others	4	2.8
Total	141	100.0

NSAIDs: non-steroidal anti-inflammatory drugs, CNS: central nervous system, GIT: gastrointestinal tract.

Table 7. Causative antibiotics & antimicrobials

Drugs	No. of patient	%
Penicilin group	12	25.0
Cephalosporin group (Gen I)	2	4.2
Cephalosporin group (Gen II)	4	8.3
Cephalosporin group (Gen III)	5	10.4
Quinolone	8	16.6
Antifungal agents	6	12.5
Antituberculous group	5	10.4
Macrolide group	2	4.2
Tetracycline	1	2.1
Aminoglycoside group	1	2.1
Others	2	4.2
Total	48	100

antibiotics/antimicrobials developed ADRs within one week, and 13 cases (27.1%) developed ADRs within a day. Five cases caused by radiographic dye developed within a day.

Causative agents

The precise history of ADR, including allopathic, ho-

Table 8. Comparison of four reports on cutnaeous ADRs

Reference	No. of patient	Highest incidence	Clinical types	Causative agents
Kim and Lee[12]	211 male 213 female	21 to 30 yrs	Exanthematous eruption (47.6%), Fxed drug eruption (25.7%), Urticaria (12.1%)	Antibiotics (40.4%), Antipyretics/NSAID (23.5%), Others (herb) (12.5%)
Shin et al.[11]	64 male 63 female	21 to 30 yrs	Exanthematous eruption (37.8%), Urticaria (28.3%), Erythema multiforme (11.1%)	Antibiotics (44.2%), Antipyretics/NSAID (29.5%), CNS depressants (16.8%)
Kim et al.[10]	147 male 123 female	31 to 40 yrs	Exanthematous eruption (49.3%), Fixed drug eruption (30.1%), Urticaria (10.0%)	Antibiotics (46.3%), Antipyretics/NSAID (32.2%), CNS depressants (6.3%)
Our study	63 male 78 female	41 to 50 yrs	Exanthematous eruption (68.8%), Stevens-Johnson syndrome (10.6%), Urticaria (8.5%)	Antibiotics (34.1%), Antipyretics/NSAIDs (27.0%), CNS depressants (12.1%)

ADR: adverse drug reaction, NSAIDs: non-steroidal anti-inflammatory drugs, CNS: central nervous system.

meopathic, and herbal remedies and self-medication was obtained from patients with cutaneous ADRs, and the imputability of each drug as a possible culprit was determined. The most common causative agents were antibiotics/antimicrobials (34.1%), followed by antipyretics/NSAIDs (27.0%), CNS depressants (12.1%), and anticancer drugs (7.1%) (Table 6).

Among the antibiotics/antimicrobials, penicillins and cephalosporins were responsible for causing the majority of cutaneous ADRs; amoxicillin was the most common causative antibiotics (Table 7). Five cases of cutaneous ADRs were caused by iodide, which is used for computer tomography, intravenous pyelography, and myelography. The other causative agents were allopurinol, herbs, antihypertensive drugs, and gastrointestinal tract regulators/antacids (Table 6).

Laboratory findings

Liver function abnormalities, eosinophilia, and leukocytosis were present in 36.0% (31/86), 33.7% (29/86), and 15.1% of the patients (13/86), respectively. Leukocytosis was commonly present in patients with Stevens-Johnson syndrome and exanthematous eruption; liver function abnormalities were commonly present in patients with exanthematous eruptions, Stevens-Johnson syndrome, and erythema multiforme, but no cases of toxic hepatitis occurred.

Associated signs and symptoms

The major presenting complaint was itching (61.0%), followed by fever (9.2%) and myalgia (6.4%). Other symptoms included oral mucosal lesions (5.0%), including cheilitis, stomatitis, facial edema (2.8%), and gastrointestinal symptoms, such as diarrhea and vomitting (0.7%).

DISCUSSION

Two to three percent of hospitalized medical patients are reported to have cutaneous ADRs[15-17]. Fatal cutaneous ADRs occur in 0.1% of medical patients and 0.01% of surgical patients[15-17].

There are five reports on the incidence of cutaneous ADRs ranged from 2.6% to 8.9% assessed by dermatologist in Korea[10-12,18,19]. Kim and Lee[12] and Bang et al.[18] reported that 2.7% and 3.8% of patients visited hospitals because of cutaneous ADRs, respectively, and Shin et al.[11] reported that 8.9% of inpatients had cutaneous ADRs. Hahm[19] reported that 2.6% of inpatients with dermatology consultations were diagnosed with cutaneous ADRs. According to the report by Kim et al.[10], the incidence of cutaneous ADRs was 1.32% in the 1970s, 1.33% in the 1980s, and 1.78% in 1990s; the gradual increase in the incidence of ADRs has been attributed to diversification, abuse, and misuse of drugs. However, the incidence and type of cutaneous ADRs evaluated by dermatologist in 2000's has not been reported on. As the incidence of ADRs is increasing, people perceive ADRs with greater concern. Proper monitoring systems and causality assessment are required to prevent the severe cutaneous ADRs which cause death, threaten lives, affect fetuses, and lead to permanent disability[20,21]. Recently, an ADR monitoring system (pharmacovigilance research network) has been activated in Korea. Since cutaneous ADRs are the most common, it is highly desirable for dermatologist to actively participate in the network.

The algorithms for causality assessment that are widely used in foreign nations include the Naranjo algorithm[13], the French algorithm[22], and the RUCAM algorithm[23]. These algorithms are used in foreign countries with different genetic backgrounds, investigators, and level of aware-

ness for ADRs, and as such they might not suitable for use in Korea[12,14,22]. The Naranjo algorithm, which was established in 1981, is the most widely used assessment tool and consists of ten simple questions[13]. The merits of the Naranjo algorithm are that it is easy to apply, and assessment is possible with very little information and knowledge[13,14]. The downside of the Naranjo algorithm is the absence of a time-related detailed description (question 2), assessment for the response after administering a placebo that actually had not been carried out (question 6), and a non-concrete question (question 10), which may cause differences between investigators[13,14,21]. In fact, there was much difference between the researchers in studies undertaken to determine the causality assessment for ADRs of inpatients[24,25]. Similarly, the Naranjo algorithm contains many components that are not suitable for clinical assessment for ADRs in Korea and, when applied, the scores are mostly evaluated as 'probable'. Specifically, 102 cases (72.3%) were assessed as 'probable' in the current study.

Ultimately, Hong et al.[14] developed the Korean algorithm, and improved ambiguous descriptions of the clinical course by adding proportional dose-dependent responses, event abatement, and clinical appearance on drug removal[14,21,23]. Some questions were specialized for consistent assessment as the period between administration and symptom onset, risk factors, and drug- unrelated factors[14]. Finally, the Korean algorithm (version 2.0) was developed as the assessment of the causal association between the suspected drug and the cutaneous ADR, which can be properly applied to Koreans. The Korean algorithms (version 2.0) will be helpful for clinical use as items with a low response rate in Korea were excluded.

The correlation and reliability of the Naranjo and Korean algorithms (version 2.0) were assessed and analyzed in this study and it was found that the Korean algorithm (version 2.0) was significantly correlated with the Naranjo algorithm. The result of cross-tabulation analysis showed that 102 cases which were assessed as 'probable' based on the Naranjo algorithm were separated into 'probable/likely' and 'certain', and 39 cases assessed as 'possible' were separated into 'possible', 'probable/likely', and 'certain' (Table 4). Thus, these findings indicate that the Korean algorithm (version 2.0) can be used more properly in ascertaining risk factors earlier and reflecting prognosis.

There was no significant difference in the incidence of ADRs between men and women, which is in agreement with the results of the other studies (Table 8). ADRs increase with age, which may be due to the increased use of medications by the elderly, the increased potential for drug-drug interactions, and altered drug metabolism by the body. The majority of the patients belonged to the 41 ~50 year age group in our study, the 21~30 year age group in the studies by Kim and Lee[12] and Shin et al.[11], and the 31~40 year age group in a study by Kim et al.[10], respectively (Table 8).

The difference in various studies may be related to the regional variation in the health care-seeking behavior of the population.

The clinical types of cutaneous ADRs are classified into exanthematous eruption, urticaria, photosensitivity reaction, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, fixed drug eruption, purpura, lichenoid eruption, and bullous eruption[1-3].

Of patients with ADRs, Kim et al.[10] reported exanthematous eruptions in 49.3%, fixed drug eruptions in 30.1%, and urticaria in 10.1% as the most common patterns of eruptions. Of the various types of cutaneous ADRs seen in the current study, exthanthematous eruptions were the most common drug eruptions (68.8%), followed by Stevens-Johnson syndrome (10.6%) and urticaria (8.50%).

The most common latent period for cutaneous ADRs was 1~7 days, which corresponds with the symptom onset of exanthematous eruption, the most common clinical type of ADR.

The frequency of clinical types and causative agents were determined for outpatients by Kim and Lee[12] between 1969 and 1975, for inpatients by Shin et al.[11] between 1976 and 1985, and for outpatients and inpatients by Kim et al.[10] between 1989 and 1997. When compared to the present study, the most common causative agent for ADRs was salicylate in a study by Kim and Lee[12], ampicillin in a study by Shin et al.[11], amoxicillin in a study by Kim et al.[10], and amoxicillin in the present study (Table 8).

In the order of frequency of clinical types of ADR, there were differences between the reports (Table 8). The incidence of life-threatening cutaneous ADRs, such as Stevens-Johnson syndrome, was higher compared to studies reported in Korea and internationally, which may represent that those patients with severe reactions visited the hospital in question more often. Allopurinol was a common cause of Stevens-Johnson syndrome in this survey.

Leukocytosis, eosinophilia and liver function abnormalities are often observed in patients with ADRs[26-28]. Of patients with ADRs, Shin et al.[11] reported 42.0% had leukocytosis, 29.5% had eosinophilia, and 25.3% had liver function abnormalities; the corresponding abnormalities in laboratory findings in the present study were 15.1%, 33.7%, and 36.0%, respectively.

CONCLUSION

The Korean algorithm (version 2.0) was significantly correlated with the Naranjo algorithm and reflects prognosis properly when assessing Korean cutaneous ADRs. The findings of this study indicate that the Korean algorithm (version 2.0) can be used more properly than the Naranjo algorithm in ascertaining risk factors earlier and reflecting prognosis. Objective and consistent causality assessment is continuously required to detect the correlation of clinical index and cutaneous ADRs.

The clinical spectrum and causative agents of ADRs were similar to studies reported in Korea and internationally with minor variations. A wide clinical spectrum of cutaneous ADRs, ranging from mild maculopapular rash to serious Stevens-Johnson syndrome and toxic epidermal necrolysis were observed. The most common reaction pattern was an exanthematous eruption and the most frequent eliciting drug group was the antibiotics. Present findings on the most common reactions and eliciting drugs are in agreement with previous reports.

REFERENCES

1. Shear NH, Knowles SR, Shapiro L. Cutaneous reactions to drugs. In: Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, editors. Fitzpatrick's dermatology in general medicine. 7th ed. New York: McGraw-Hill, 2008: 355-362.
2. James WD, Berger TG, Elston DM. Andrews' disease of the skin. 10th ed. Philadelphia: WB Saunders, 2006:115-138.
3. Knowles SR, Shear NH. Cutaneous drug reactions with systemic features. In: Wolverton SE, editors. Comprehensive dermatologic drug therapy. 2nd ed. Indianapolis: Saunders Elsevier, 2007:977-988.
4. Revuz J, Valeyrie-Allanore. Drug reaction. In: Bolognia J, Jorizzo J, Rapini R, editors. Dermatology. 1st ed. Philadelphia: Mosby, 2003:333-353.
5. Kwon KS, Kim BS, Jang BS, Kim MB, Oh CK, Kwon YW, et al. Clinical study of drug rash with eosinophilia and systemic symptoms (DRESS) on drug eruption patients over the last 10 years (1995～2004). Korean J Dermatol 2005;43:1164-1169.
6. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. N Engl J Med 1994;331:1272-1285.
7. Bachot N, Roujeau JC. Differential diagnosis of severe cutaneous drug eruptions. Am J Clin Dermatol 2003;4:561-572.
8. Roujeau JC. Treatment of severe drug eruptions. J Dermatol 1999;26:718-722.
9. Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. Arch Intern Med 1995;155: 1949-1956.
10. Kim KJ, Jeong MC, Yoo JH. Clinical study and skin tests of patients with drug eruption. Korean J Dermatol 1998; 36:887-896.
11. Shin KS, Cho KH, Lee YS. Clinical study of hospitalized patients with drug eruption during a 10-year reriod (1975-1985). Korean J Dermatol 1987;25:176-182.
12. Kim SN, Lee BH. Clinical study for drug eruptions. Korean J Dermatol 1978;16:377-381.
13. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-245.
14. Hong KS, Park BJ, Sin SG, Yang JS, Lee SM, Kim YN, et al. Development of a Korean algorithm for causality assessment of adverse drug reactions. Korean J Clin Pharmacol Ther 2002;10:129-142.
15. Franceschi M, Scarcelli C, Niro V, Seripa D, Pazienza AM, Pepe G, et al. Prevalence, clinical features and avoidability of adverse drug reactions as cause of admission to a geriatric unit: a prospective study of 1756 patients. Drug Saf 2008; 31:545-556.
16. Davies EC, Green CF, Mottram DR, Pirmohamed M. Adverse drug reactions in hospitals: a narrative review. Curr Drug Saf 2007;2:79-87.
17. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998;279:1200-1205.
18. Bang DS, Cho CK, Lee SN. Statistical study of dermatoses during the last 5 years (1976～1980). Korean J Dermatol 1983;21:37-44.
19. Hahm JH. A comparative study on clinical evaluation of inpatient dermatology consultation between 1976 and 1991. Korean J Dermatol 1992;30:651-658.
20. Becquemont L. Pharmacogenomics of adverse drug reactions: practical applications and perspectives. Pharmacogenomics 2009;10:961-969.
21. Lee SM, Hahn SK, Park BJ. Signal detection and causality evaluation for pharmacovigilance. Korean J Clin Pharmacol Ther 2005;13:121-133
22. Moore N, Biour M, Paux G, Loupi E, Begaud B, Boismare F, et al. Adverse drug reaction monitoring: doing it the French way. Lancet 1985;2:1056-1058.
23. Danan G, Benichou C. Causality assessment of adverse reactions to drugs--I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol 1993;46: 1323-1330.
24. Classen DC, Pestotnik SL, Evans RS, Burke JP. Computerized surveillance of adverse drug events in hospital patients. JAMA 1991;266:2847-2851.
25. Dormann H, Muth-Selbach U, Krebs S, Criegee-Rieck M, Tegeder I, Schneider HT, et al. Incidence and costs of adverse drug reactions during hospitalisation: computerised monitoring versus stimulated spontaneous reporting. Drug Saf 2000;22:161-168.
26. Hogan DJ. Morbilliform drug eruptions. J Am Acad Dermatol 2009;61:152.
27. Gerson D, Sriganeshan V, Alexis JB. Cutaneous drug eruptions: a 5-year experience. J Am Acad Dermatol 2008; 59:995-999.
28. Gendernalik SB, Galeckas KJ. Fixed drug eruptions: a case report and review of the literature. Cutis 2009;84:215-219.