Oral Abstract Session 4

New Faces to Drug Allergy

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OAS-34

Analysis of 10-Year Drug Allergy Reports in a Single Institution

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Background: Drug allergy should be paid on attention by physicians and patients since it often recurs on re-exposed to the culprit drugs or drugs with similarity. Therefore, it is important to know the current status of drug allergy in real practice.
Methods: We reviewed the 2009-2018 database of individual case safety reports of the Seoul National University Hospital. The age, sex, underlying disease, causative drugs, symptoms, severity, causality, and clinical course were analyzed. Drugs were classified as ATC Classification System and symptoms were classified as WHO Adverse Drug Reaction Terminology. WHO-UMC causality assessment system were used.
Results: In total of 66,621 assessed reports of adverse drug reaction (ADR), 11,634 cases (17.5%) were type B ADRs including 9,793 cases (14.7%) of drug allergy. Among 650 kinds of drugs reported as culprits of drug allergy, L01X (Other anti-neoplastic agents, 15.7%) and J01D (Other beta-lactam anti-bacterials, 11.1%) were the most commonly reported drug categories including oxaliplatin (7.6%) and vancomycin (5.0%), respectively. According to involved organs, drug allergy mainly presented as skin (72.8%) but 20.5% developed as whole general (20.5%) disorders including 431 patients cases of anaphylaxis (4.4%). Mortality related with drug allergy was 0.1%. The proportion of severe and serious cases were higher in drug allergy group than other ADR. (12.7% vs 6.0%, $p < 0.0001$, 17.2% vs. 8.7%, $p < 0.0001$) In the case of multiple drug allergy episodes, using drugs of similar chemical characteristics revealed more serious outcomes than using the same culprit drug of allergy. (Moderate to severe symptoms: 80.6% vs 54.6%, $p=0.0024$, serious adverse events: 36.1% vs 17.8%, $p=0.0069$)
Conclusion: Drug allergy has more severe consequences compared to other types of ADR. Using drugs with similar chemical characteristics of causative one was also has risk of serious drug allergy.

Key Words: Drug hypersensitivity, Drug-related side effects and adverse reactions

OAS-35

Development of Practical Oxaliplatin Desensitization Protocols Using 2 Bags System

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Background: Oxaliplatin is a widely used drug in chemotherapy for colorectal, pancreatic, gastric and ovarian cancers. However, hypersensitivity reaction (HSR) to oxaliplatin is not rare in clinical practice. Desensitization have been proven for prevention of HSR, but there are some barriers in this procedure. As differently diluted solutions and multiple administration are the essential requirements, the workload is real huddle to settle this procedure. We developed a more simplified desensitization protocol using 2 diluted concentrations of oxaliplatin, and validate the protocol in this study.
Methods: A retrospective observational study was carried out between January 2017 and March 2019. 138 oxaliplatin desensitization cases in 36 Patients was reviewed. Our new desensitization protocol consisted of increases in infusion rate every 15 minutes using only 2 bags (a 1:100 diluted solution and full concentration). We compared HSRs during chemotherapy using 2 bag desensitization protocol to using our old 4 bag desensitization protocol.
Results: Of the 36 patients who used 138 oxaliplatin desensitization procedure, 10 (27.8%) patients [(36 (26.1%) cases)] used 2 bag desensitization protocol and the others used 4 bags protocol. Total 9 (25%) patients suffered HSRs during desensitization and 2 (5.6%) patients stopped chemotherapy including oxaliplatin. However, there was no difference in development of HSRs (20% vs. 26.9%, $p > 0.999$) and interruption of chemotherapy (0% vs. 7.7%, $p > 0.999$) between 2 and 4 bags protocol.
Conclusion: This new practical oxaliplatin desensitization protocol is not inferior to our old 4 bag protocol in the prevention of HSR and safety.

Key Words: Oxaliplatin, Desensitization, Protocol

OAS-36

Analysis of Individual Case Safety Reports of Drug-induced Anaphylaxis in Korea Adverse Event Reporting System Database

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Background: Anaphylaxis is a severe, life-threatening systemic reaction and drugs account for 20% to 40% of anaphylaxis. However, little is known about the characteristics of drug-induced anaphylaxis (DIA) in Korea.
Objective: To identify causal drugs and clinical features of the drug-induced anaphylaxis by using the Korea Adverse Event Reporting System (KAERS) in Korea.
Method: Among Individual Case Safety Reports (ICSRs) in KAERS from January, 2008 to December 2017, cases of drug-induced anaphylaxis were analyzed for demographics, causative agents and fatal cases resulting in death. The domestic drug labeling, Micromedex® and United States FDA (USFDA) drug package insert were reviewed to check that the labeling information of suspected causative agents contains anaphylaxis.
Results: A total of 5,873 cases of DIA were analyzed. The mean age was 49.77±18.55 years, 3,234 patients (55.1%) were females. DIAs were mainly caused by antibiotics (24.4%), non-steroidal anti-inflammatory drugs (14.2%), contrast media (9.7%), and antineoplastic agents (8.3%). Cephalosporins accounted for majority (57.0%) of antibiotic-induced anaphylaxis, followed by penicillins (18.2%) and quinolones (7.5%). There were 44 fatal cases (0.7%); antibiotics (13 cases), contrast media (10 cases), and antineoplastic agents (5 cases) were the most common causative drug categories related with mortality. Among 440 drugs reported at least two times, domestic drug labeling of 98 drugs did not reflect anaphylaxis. Micromedex® adverse event information of 73 drugs and USFDA package insert of 32 drug did not reflect anaphylaxis. There were 23 drugs repeatedly reported as a causative agents of anaphylaxis that did not reflect anaphylaxis in all three type of information.
Conclusion: A 10-year analysis of KAERS showed that antibiotic was the major cause of DIA and mortality rate was 0.7%. In 5.2% of suspected drugs, anaphylaxis was not mentioned in any of the drug labeling.

Key Words: Drug-induced anaphylaxis, Pharmacovigilance, Drug labeling

OAS-37

Unique Clinical Characteristics and Prognosis of Allopurinol-Induced Severe Cutaneous Adverse Reactions

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Background: Allopurinol is the most common cause of severe cutaneous adverse reactions (SCARs) in Korea due to relatively high prevalence of HLA-B*58:01 genotype (8-13%). We aimed to reveal the clinical characteristics and risk factors for death in allopurinol-induced SCARs in Korea.
Methods: We retrospectively reviewed medical records of 106 subjects with allopurinol-induced SCARs and 639 subjects with other drugs-induced SCARs who were enrolled in Korean SCARs Registry (collected from 34 nationwide medical institutions) from January 2010 to December 2015.
Results: Subjects with allopurinol-induced SJS/TEN were older and had more comorbidities, longer latent period, longer disease duration, more deranged laboratory findings and increased disease severity resulting in higher mortality rate (17.6% vs. 7.6%; P=0.020) compared to the subjects with other drug-induced SCARs. There were no significant differences in age and mortality in DRESS. Subjects with allopurinol-induced SJS/TEN were older and had shorter latent period and higher mortality (17.6% vs. 3.7%; P=0.044) than those with allopurinol-induced DRESS. In allopurinol-induced SJS/TEN, chronic renal insufficiency, ICU admission, increased BUN level at admission day, serum peak eosinophil count, baseline and peak creatinine, and peak ALT, and decreased lowest platelet count and baseline ALT were significant risk factors for death. In allopurinol-induced DRESS, ICU admission and increased glucose level at admission day were significant risk factors for death.
Conclusions: Allopurinol-induced SCARs have unique characteristics and poor prognosis with important predictive factors of death.

Key Words: Allopurinol, Severe cutaneous adverse reaction

OAS-38

Genetic Risk Markers of Carbamazepine-Induced Severe Cutaneous Adverse Reactions: New Candidates in Koreans

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Background: Carbamazepine (CBZ) is the second most common cause of severe cutaneous adverse reaction (SCAR) in Korean. HLA-B*15:02 is a strong risk factor for CBZ-induced Stevens-Johnson syndrome in Han Chinese. However, HLA-B*15:02 is not a useful marker in Korea because of its very low frequency less than 1% of Koreans.
Objective: The aim of this study was to investigate genetic factors that increases the risk of carbamazepine-induced SCARs in Koreans.
Methods: We prospectively obtained blood samples from 41 carbamazepine-induced SCAR patients and 33 tolerant controls who took carbamazepine more than 60 days without hypersensitivity reaction. HLA-A, -B, -C, and -DRB1 genotyping was performed by direct DNA sequencing.
Results: HLA-B*15:02 was found in three out of 41 CBZ-induced SCARs and none of 33 tolerant controls (7.32% vs. 0%) but this difference did not reach statistical significance (P=0.249). HLA-A*31:01 was positive in 41.5% (17/41) of CBZ-induced SCARs but only in 12.1% (4/33) tolerant control (odds ratio (OR)=5.135, P=0.009). There were four more single HLA alleles which showed significant difference between CBZ-induced SCARs and tolerant controls: B*13:01 (OR=2.0, P=0.007), B*15:11 (OR=1.943, P=0.030), DRB1*12:02 (OR=11.733, P=0.009), and HLA-DRB1*04:05 (OR=0.249, P=0.026). If screened with presence of any of the following alleles: HLA-A*31:01, B*15:11, DRB1*12:02, or DRB1*09:01, sensitivity, specificity, positive predictive value, and negative predictive value were 83.0%, 75.7%, 80.95%, and 78.12% for the detection of CBZ-induced SCARs, respectively.
Conclusion: Although no single effective genetic marker to predict potential CBZ-induced SCARs is not available in Koreans, screening subjects for HLA-A*31:01, B*15:11, DRB1*12:02, and DRB1*09:01 prior to starting CBZ can be an option for the prevention of SCARs.

Key Words: Carbamazepine, Severe cutaneous adverse reaction, Human leukocyte antigen

OAS-39

Updates of a Korean Nationwide Registry of Severe Cutaneous Adverse Reactions 2010-2018

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Background: A life-threatening severe cutaneous adverse reactions (SCARs) such as Stevens Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), have genetic risk factor and ethnic difference. A nationwide registry-based study was performed to assess culprit drugs and clinical characteristics including morbidity and mortality of SCARs in Korea.
Methods: SCAR cases which occurred from 2010 to 2018 were recruited to a nationwide Korean SCARs registry from 36 tertiary referral hospitals. Demographics, causative drugs, causality, and clinical outcomes were collected after a thorough retrospective review of medical records.
Results: A total of 1,075 SCAR cases by 207 drugs were registered: SJS or TEN (n=544, 53±22 years), DRESS (n=531, 55±18 years). The rate of overall mortality and long-term sequelae were 6.8% and 7.5%, respectively. The complete recovery from SCAR was found in 84.1% of SJS, 65.4% of overlap, 55.8% of TEN, and 91.8% of DRESS cases. Major drug categories of culprit drugs were beta-lactam antibiotics (16.2%), non-steroidal anti-inflammatory drugs (NSAIDs) (8.7%), and anti-tuberculosis agents (6.8%) while the most common single culprit drugs were allopurinol (13.8%), followed by carbamazepine (9.3%), and vancomycin (4.7%). The main culprits of SCAR resulting in mortality were allopurinol (24.3%) and beta-lactam antibiotics (14.9%). The clinical course varied according to the causative drugs: mortality rate was 11.3% in allopurinol-induced SCAR patients while only 0.8% died in patients with carbamazepine-induced SCARs. The mortality risk increased with the age of the patient. (Exp(B)=1.033, p < 0.0001).
Conclusions: In Korea, allopurinol, carbamazepine, vancomycin, beta-lactam antibiotics, NSAIDs, and anti-tuberculosis agents were major cause of SCARs. Allopurinol and beta-lactam antibiotics were the most frequent causative drug of SCAR resulting in death.

Key Words: Severe cutaneous adverse reactions, Stevens Johnson syndrome, Toxic epidermal necrolysis, Drug react

OAS-40

HLA-B*13:01 and Dapsone-Hypersensitivity Syndrome in Korea

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Background: HLA-B*13:01 have been known to be an important risk factor of dapsone-induced severe cutaneous adverse reactions (SCARs) in Chinese and Thai. However, there have been no study concerning this association in Korean population. We aimed to reveal association of HLA-B*13:01 and dapsone-induced SCARs compared to general population in Korea.
Methods: We recruited 6 subjects who had experienced dapsone-induced SCARs through Korean Severe Cutaneous Adverse Reactions Consortium. We reviewed the medical records of them retrospectively, and obtained blood sample for HLA genotyping. In addition, HLA genotyping results of 485 general populations obtained in previous study were used for comparison of phenotype frequency.
Results: The HLA-B*13:01 carrier was frequently observed in dapsone-induced SCARs compared to that in general populations (66.7% vs. 4.1%; odds ratio [OR], 49.866; P < 0.001). The HLA-C*03:04 carrier (50.0% vs. 12.8%; OR, 7.147; P=0.008) and HLA-DRB1*12:02 carrier (50.0% vs. 6.4%; OR, 17.487; P<0.001) were also showed same trend; HLA-B*13:01 and these two alleles are well-known to be in linkage disequilibrium. In addition, HLA-A*02:01 carrier (83.3% vs. 29.9% with OR, 7.976 and P=0.005) and HLA-C*07:02 carrier (50.0% vs. 15.1% with OR, 5.533; P=0.019) were also frequently observed in dapsone-induced SCARs compared to that in general populations.
Conclusions: We demonstrated that HLA-B*13:01 carrier is frequently observed in dapsone-induced SACRs in Korea.

Key Words: Dapsone, Severe cutaneous adverse reaction, HLA allele

OAS-41

Who are at Risk of Development of Allopurinol-Related Severe Cutaneous Adverse Reaction among Patients with B*58:01?

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Background: HLA-B*58:01 is a high risk factor of allopurinol-induced severe cutaneous adverse reaction (SCAR) in Asian population including Koreans. However, SCARs develop in only a part of HLA-B*58:01 carriers but it is not known what determine their susceptibility.
Objective: To investigate the other genetic factor contributing the development of allopurinol-induced SCAR in addition to HLA-B*58:01
Method: A total of 25 HLA-B*58:01 carriers who were diagnosed as allopurinol induced SCARs (Stevens-Johnson syndrome, toxic epidermal necrolysis or drug reaction with eosinophilia and systemic symptoms) and 22 HLA-B*58:01 carriers who took allopurinol more than 90 days without any hypersensitivity symptoms were recruited from 8 different hospitals. Genotyping of HLA-A, -B, -C and -DRB1 was performed with the PCR-sequence-based typing method for high-resolution typing. Pearson's chi-square test and Fisher's exact test were used to analyses the risk of SCAR occurrence.
Results: The risk of allopurinol induced SCAR in HLA-B*58:01 carriers was significant higher if they had HLA-A*24:02 (odd ratio [OR], 4.327; 95% confidential interval [CI], 1.213-15.439; P=0.020; positive predictive value [PPV] 73.7%, negative predictive value [NPV] 60.7%). Coexistence of HLA-A*24:02-C*03:02 (OR, 4.875; 95% CI, 1.279-18.575; P=0.032; PPV 76.5%, NPV 60.0%) or HLA-A*24:02-DRB1*13:02 (OR, 11.813; 95% CI, 1.354-103.038; P=0.012; PPV 90%, NPV 56.8%) further increased the risk of SCAR when compared to those without these alleles. Coexistence of HLA-A*24:02-C*03:02-DRB1*13:02 presented the highest risk of SCAR in HLA-B*58:01 carriers (OR, 21.857; 95% CI, 1.179-405.191); P=0.004; PPV 100%, NPV 56.4%).
Conclusion: Additional secondary screening with HLA-A*24:02, -C*03:02 and -DRB1*13:02 can improve the predictability of SCAR development among HLA*-B*58:01 carriers taking allopurinol.

Key Words: Allopurinol, Severe cutaneous adverse reaction, Human leukocyte antigen

OAS-42

Challenge Test Strategy to Prevent Breakthrough Reaction in Patients with Iodinated Contrast Media Anaphylaxis

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Background: Once hypersensitivity reaction (HSR) to iodinated contrast media (ICM) develop, the risk of recurrence is high, especially in patients with severe reaction such as anaphylaxis. Although skin tests and premedication were used to prevent recurrence, their clinical usefulness was not proven.
Objective: To establish the optimal protocol to choose safe ICM in patients with a history of anaphylaxis.
Methods: A retrospective cohort study was performed with high risk patients who underwent re-exposure to ICM after their initial anaphylaxis to ICM. The skin test (skin prick and intradermal test) with ICM was conducted in order to choose non-reactive ICMs, which were re-evaluated with intravenous challenge tests before undergoing enhanced computed tomography (CT). Two different ICM challenge protocols were used; a low dose protocol (a maximal dose: 10 mL) and a high dose protocol (a maximal dose: 30 mL). Enhanced CT was performed using the ICM which was negative in the challenge test after pretreatment with antihistamine and systemic steroid one hour before.
Results: Among 36 patients with a history of ICM anaphylaxis, 53 skin tests were done without any HSR. With non-reactive ICM on skin test, 63 challenge tests were performed but 2 (3.2%) showed immediate HSR on intravenous challenge and the minimal challenge dose inducing HSR was 5 mL. A total 61 cases of ICM enhanced CT were done with ICMs which were negative in challenge test and 91.8% (56/61) of them completed without any HSR. According to challenge protocols, 9.3% (4 of 43 cases) in the low dose group had moderate to severe HSR such as hypotension or severe urticaria while only 5.6% (1 of 18 cases) in the high dose group had mild itching.
Conclusion: This study suggests that skin test and low dose challenge test is not sufficient to predict non-reactive ICM in patients with a history of ICM anaphylaxis. An establishment of a provocation protocol is needed for the safe reuse of ICM in high-risk patients.

Key Words: Iodinated contrast media, Anaphylaxis, Skin test, Challenge test

OAS-43

Intradermal Testing with Radiocontrast Media to Prevent Recurrent Adverse Reactions

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Background: Adverse drug reactions (ADRs) to radiocontrast medium (RCM) are a significant social and economic burden and are difficult to predict. As some ADRs to RCM may be immunologically induced, a skin test has been used for prediction. However, the usefulness of the skin test to prevent recurrent ADRs to RCM has not been verified in practice.
Methods: This study enrolled 36 patients with history of immediate ADR to RCM who visited Allergy and Asthma Clinic of Severance Hospital. Patients underwent intradermal testing (IDT) with diluted (1:10) and undiluted (1:1) 5 different RCMs (iohexol, iobitridol, iopamidol, iopromide, iodixanol). Sensitivity and PPV of IDT for culprit RCM were calculated and compared. For subsequent CT with RCM, the RCM eliciting the least skin reaction in IDT was selected, excluding the previous culprit RCM.
Results: Sensitivity and PPV of IDT with 1:10 were 47.2%, 100% and Sensitivity and PPV of IDT with 1:1 RCM were 75%, 87%. Sensitivity and PPV was higher in cases of more frequent RCM use or more severe reaction. Twenty-two patients underwent another CT with the RCM selected based on IDT results; 21 (95.5%) did not experience an ADR.
Conclusions: IDT to prevent recurrent ADR should be performed with two RCM solution (1:10, 1:1) considering sensitivity and PPV. Selecting the RCM based on IDT results can be clinically useful to prevent recurrent ADRs to RCM.

Key Words: Radiocontrast media, Adverse drug reaction, Intradermal test

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Factors Affecting Skin Test Positivity to Iodinated Contrast Media

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Background: There is increasing evidence supporting the diagnostic specificity of iodinated contrast media (ICM) skin test in patients with a history of hypersensitivity reaction (HSR) to ICM. However, safety and efficacy of skin test-negative RCM need further validation and there is no recommendation on the choice among skin test-negative ICMs.
Objective: To evaluate the safety and potential risk of skin test-negative ICMs in patients with ICM HSR.
Methods: A retrospective cohort study was performed on patients who underwent ICM skin test (skin prick and intradermal test) as a post-test after the occurrence of ICM HSR. The positivity of ICM skin test was assessed according to the severity of index reaction and chemical similarity (Tanimoto coefficient).
Results: Among of 247 patients with a history of ICM HSR, 293 skin tests were performed. No systemic symptom occurred during skin testing. The overall positive rate was 39.2% (115/293) and positive rate to culprit agent was 62.0% (67/108). The median time interval from ICM HSR and skin testing was 3 weeks [IQR, 1.86-4.14 weeks]. Skin test positivity showed difference according to the severity of previous HSRs; 32%, 28.7%, and 52.8% in mild, moderate, and severe reactions ($p<0.0001$). In 77.4% (89/115) of skin test-positive cases, re-exposures to skin test negative ICM with premedication were performed. 15.7% (14/89) of these cases resulted in breakthrough reaction; 8.3%, 16%, and 17.6% in cases with mild, moderate, and severe index reaction. Cross-reactivity assessment based on skin test showed 47.0% of multi-positivity to different ICMs among skin test-positivity cases. Cross-reactivity rate showed correlation with Tanimoto coefficient ($r2=0.476$, $p=0.009$).
Conclusion: ICM skin test does not completely exclude reactive ICMs in high risk patients. Chemical similarity of ICMs were related with higher cross-reactivity between ICMs.

Key Words: Drug hypersensitivity, Hypersensitivity, Immediate, Contrast media, Immunologic test, Skin tests