Drug Hypersensitivity in Phramongkutklao Hospital

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Objective: *To evaluate the prevalence of drug hypersensitivity, clinical manifestations, type of drugs involved, severity, and patients demographic data.*
Study design: *A cross-sectional descriptive study.*
Material and Method: *The study was performed from January 1st, 2008 to December 31th, 2008 at Phramongkutklao Hospital. Data were collected from Pharmaceutical Department, Dermatology Unit, Department of Medicine including adverse events reported by pharmacists. All records of in-patients and out-patients including gender, age, causative drugs, type of drug hypersensitivity and severity of hypersensitivity were collected.*
Results: *A total of 140 patients who had drug hypersensitivity were recorded. The most common drug hypersensitivity was due to antimicrobial agents which penicillin group was the most frequently involved. Of 61 patients (43.57%), 27 (19.28%) received anti-inflammatory and muscle relaxant drugs and 18 (12.85%) had drugs acting on the central nervous system. The most common manifestration of drug allergy was maculopapular rash (34.99%), followed by nonspecific erythrematous rash (16.42%), fixed drug eruption (9.28%) and Stevens-Johnson syndrome (8.57%), respectively. Majority (80.71%) of drug hypersensitivity was mild in severity. Moderate, severe and lethal hypersensitivity accounted for 8.51%, 10.0%, 0.71% respectively. Female were 51.77% while 48.22% were male. The mean age was 47.0 years (ranged from 8-100 years). There were 57 (40.71%) patients over 50 years of age and 103 (73.57%) patients had taken more than one medication.*
Conclusion*: Antimicrobial agents were the common cause while maculopapular rash was the most frequent clinical manifestation of drug hypersensitivity.*

Keywords: *Drug hypersensitivity, Maculopapular rash, Antimicrobial agents*

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Drug hypersensitivity is one of the most important medical problems. It affects patients unpredictably and serious condition leads to hospitalization and possibly death. Many risk factors such as genetic susceptibility[1], immunosuppression (chemotherapy), connective tissue disease[2], HIV infection, chronic illnesses, malnutrition play role in the development of drug hypersensitivity.

Drug hypersensitivity encompass all adverse events related to drug administration, regardless of etiology. Drug hypersensitivity has been classified by immunologic and nonimmunologic reactions. The majority of adverse drug reactions are caused by predictable, nonimmunologic effects[3], while the remaining are caused by unpredictable effects that may or may not be immune mediated[4].

Drug hypersensitivity[5] is defined as an immune-mediated response to a drug agent in a sensitized patient that have been classified by Gell and Coombs Classification, namely, Type I reactions (IgE-mediated), Type II reactions (cytotoxic), Type III reactions (immune complex) and Type IV reactions (delayed, cell-mediated). However, some drug hypersensitivity reactions are difficult to classify because of a lack of evidence supporting a predominant immunologic mechanism. These included certain cutaneous drug reactions such as maculopapular rashes, erythroderma, exfoliative dermatitis, and fixed drug eruption[6,7].

Adverse drug reactions affect 10-20% of hospitalized patients and more than 7% of the general population. Severe reactions including anaphylaxis, drug hypersensitivity syndromes, Stevens Johnson syndrome and toxic epidermal necrolysis are also

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associated with significant morbidity and mortality[8]. Thong et al (2003) reported 210 cases of drug hypersensitivity. About 95 patients (95.7%) had cutaneous manifestation, 30% caused by systemic manifestations and 5.2% caused by serious adverse reaction such as Stevens-Johnson Syndrome, toxic epidermal necrolysis (TEN) and general exfoliative dermatitis[9].

Puavilai et al (2005) reported that the most common causative drugs were antimicrobial agents of cephalosporin group. Maculopapular rash was the most common type of drug hypersensitivity, followed by urticaria and photosensitivity reaction, respectively[10]. Sitakalin et al (1999) reported that drug hypersensitivities were divided into six groups of rashes: fixed drug hypersensitivity (36%), exanthematous drug eruption (33.83%), Stevens Johnson syndrome (9.38%), urticaria (5.5%), eczematous drug eruption (4.25%), and photosensitivity eruption (3.5%), respectively. The causative agents were able to be identified in about 63.13% of all drug hypersensitivities and the most common ones were antibiotics (59.80%), non-steroidal anti-inflammatory agents (11.49%), anti pyretic and analgesic (10.50%), drugs acting on the central nervous system (8.12%) and beta-adrenergic blocking agents (0.59%)[11].

Today, more drugs are emerging and distributed worldwide for treatment of many diseases and disorders due to advanced technology and scientific discoveries. Thus, the administration of drugs is increasing. As newer drugs are being experimented and used in addition to older ones, we are at possible risk of developing more drug hypersensitivity from all of these, plus their cross reactions. Therefore, the records concerning drug hypersensitivity is vulnerable to change. As a result, we collected and analyzed drug hypersensitivity information from all the databases available, which included cutaneous drug eruptions such as maculopapular rashes, erythroderma, exfoliative dermatitis, fixed drug reactions etc, and anaphylaxis. Our report not only offers an update on patients' drug allergy records for patients' benefit in Phramongkutklao Hospital, but also provide newly modified base for medical references in the future.

Material and Method

A cross-sectional analytical study was conducted after the approval of the ethical committee, Medical Department, the Royal Thai Army. We collected data from three different sources in the In-Patient Department (IPD) and in the Out-Patient Department (OPD) in Phramonkutklao Hospital between January 1st, 2008 and December 31th, 2008. The first involved a record of subjective history of drug allergy notified by patients to the in-house pharmacy. The second consisted of feedback of adverse drug events by physicians from all departments to the Pharmaceutical Department, and the third came from consultations and dermatologists recorded of drug hypersensitivity. Due to possible overlapping of these cases from the three groups, data collection process was further screened to ensure that no single case was repeated record. Data collection included gender, age, history of drug hypersensitivity, causative drug, type of drug hypersensitivity and severity of hypersensitivity (Table 1).

Results

A total of 141 patients were included in this study. Dermatology Clinic contributed to the highest number of recorded data (45.71%) (Table 2). There were 35 (25%) patients from in-patients. Seventy three patients (51.77 %) were female while 68 (48.22%) were male. The mean age for both genders was 47.0 years (ranged from 8 to 100 years). Of these, 57 patients (40.71%) were over 50 years. There were 103 pateints (73.57%) who had taken more than one medication before the clinical onset of drug hypersensitivity. The prevalences of drug hypersensitivity were caused by

Table 1. Severity of drug hypersensitivity

Severity	Detail
Mild ADR*	Not necessary for systemic treatment or prolonged hospitalization.
Moderate ADR	need some medications or specific treatment or prolonged hospitalization.
Severe ADR	Life threatening, may cause disability or need close monitoring.
Lethal ADR	ADRs that lead to death.

*ADR adverse drug reaction

Table 2. Sources of data

Sources of data	n (%)
Database of dermatology clinic	64 (45.72%)
Database of pharmacy department	48 (34.28%)
Adverse event reports from pharmacist	28 (20.00%)

Table 3. Causative drugs

Causative drugs	n (%)
Antimicrobial agents	61 (43.57%)
Anti-inflammatory and muscle relaxant drugs	27 (19.28%)
Drugs acting on the central nervous system	18 (12.85%)
Unknown	8 (5.67%)
Others[A]	7 (5.00%)
Drugs acting on cardiovascular system	7 (5.00%)
Antirheumatic drugs	5 (3.57%)
Radiocontrast agents	4 (2.85%)
Antihyperlipidaemic agents	2 (1.42%)
Chemotherapy	1 (0.71%)

A = Glipizide (1), levonorgestrel + Estinyl estradiol (1), esomeprazole (1), omeprazole (1), risedronate (1), methimazole (1), Granulocyte colony-stimulating factor (1)

Table 4. Type of hypersensitivity

group of skin lesions	n (%)
Maculopapular rash	49 (34.99%)
Erythematous rash not-specified	23 (16.42%)
Fixed drug eruption	13 (9.28%)
Stevens-Johnson syndrome	12 (8.57%)
Angioedema	11 (7.85%)
DRESS**	8 (5.71%)
Urticaria	3 (2.14%)
Anaphylaxis	5 (3.57%)
Photosensitivity	7 (5.0%)
Toxic epidermal necrolysis	3 (2.14%)
Hyperpigmentation	2 (1.42%)
Eczematous	1 (0.71%)
Lichenoid	1 (0.71%)
Acute generalized exanthematous pustulosis	1 (0.71%)
Exfoliative dermatitis	1 (0.71%)

**DRESS = Drug Rash with Eosinophilia and Systemic Symptoms

Table 5. Antibiotics that caused of drug hypersensitivity

Antibiotics	n (%)
Penicillin	15 (24.59%)
Cephalosporin	10 (16.39%)
Quinolone	6 (9.83%)
Clindamycin	6 (9.83%)
Sulfonamide	5 (8.19%)
Antiretroviral drugs	3 (4.91%)
Glycopeptide	3 (4.91%)
Anti TB drugs	3 (4.91%)
Antifungal drugs	2 (3.27%)
Macrolide	2 (3.27%)
Aminoglycoside	1 (1.63%)
Tetracycline	1 (1.63%)
Carbapenem	1 (1.63%)
Metronidazole	1 (1.63%)
Unknown	1 (1.63%)
Other	1 (1.63%)

taking the following drugs; antibiotics (43.57%), anti-inflammatory drugs including muscle relaxants (19.28%) and drugs acting on the central nervous system (12.85%), respectively (Table 3). The penicillins were responsible for most of the antibiotics group (Table 5). The most common types of drug hypersensitivity were maculopapular rash (34.99%), erythematous rash that was not specified (16.42%) (Table 6). There were 15 patients who suffered severe drug hypersensitivity from taking phenytoin, carbamzipine, celecoxib, ceftriaxone[1] cefazolin, mefenamic acid, vancomycin, allopurinol, erythromycin, sulfasalazine, nevirapine, and tolperisone. Unfortunately, one patient died from phenytoin hypersensitivity (Table 6).

Discussion

Patients' demographic data showed no difference of drug hypersensitivity preference for men or women (ratio F:M = 1:1). However it is still a controversy whether women are more susceptible to drug hypersensitivity than men[12,13]. A high percentage of the patients presented (73.57%) has received multiple drugs before the onset of drug hypersensitivity, suggesting drug interaction might play a role for drug hypersensitivity in some of these patients. Similar to other published studies[13,14], our study showed that antimicrobial agents such as penicillin and cephalosporins were the most common caused of drug hypersensitivity[7,10] followed by cephalosporins, quinolones, and clindamycin, respectively. Comparison with the other study[11], the prevalence of drug hypersensitivity in our study has been increased in some groups due to the use of newer antimicrobial agents, such as cephalosporin, quinolone and glycopeptides. Moreover, due to high incidence of HIV infection in Thailand, the use of antiretroviral agents and prophylactic drugs such as sulfonamide group against opportunistic infections, may contribute to higher drug hypersensitivity.The second most common drug hypersensitivity were anti-inflammatory

Table 6. Degree of severity of drug hypersentivity

Severity of drug hypersensitivity	n (%)	Causative drugs (n)	
Mild ADR	113 (80.71%)	Phenytoin (8)	Clindamycin (6)
		Unknown (6)	Diclofenac (5)
		Trimethoprimsulfamethoxazole (5)	Celecoxib (5)
		Etoricoxib (4)	Cloxacilin (4)
		Ceftriaxone (4)	Ibuprofen (4)
		Augmentin (4)	Amoxycillin (4)
		Ciprofloxacin (3)	Ioxitalmate (2)
		HCTZ (2)	Sodium Iopromide (2)
		Lopinavir/Ritonavir (2)	Aspirin (2)
		Ofloxacin (2)	Ethambutol (2)
		Vancomycin (2)	Glucosamine sulfate (2)
		Acetaminophen (1)	Felodipine (1)
		Aminoglycoside (1)	Fluvastatin (1)
		Amphotericin B (1)	Glipizide (1)
		Atenolol (1)	Grisiofluvin (1)
		Cefazolin (1)	Anti TB drugs (1)
		Cefdinir (1)	Losartan (1)
		Cefuroxime (1)	Meropenem (1)
		Chloroquine (1)	Methimazole (1)
		neomycin sulfate (1)	Metronidazole (1)
		Doxycyclin (1)	G-CSF (1)
		Enaril (1)	Nimesulide (1)
		Erythromycin (1)	Norfloxacin (1)
		Levonorgestrel/Estinyl estradiol (1)	Esomeprazole (1)
		Omeprazole (1)	Risedronate (1)
		Peniciilin (1)	Rosuvastatin (1)
		Piperacillin/Tazobactam (1)	Thalidomide (1)
		Prazosin (1)	
Moderate ADR	12 (8.57%)	Phenytoin (3)	Vancomycin (1)
		Allopurinol (1)	Erythromycin (1)
		Sulfasalazine (1)	Antibiotic (1)
		Nevirapine (1)	Trileptal (1)
		Mefenamic acid (1)	Tolperisone HCL (1)
Severe ADR	14 (10.0%)	Phenytoin (2)	Celecoxib (2)
		Sertraline (1)	Ceftriaxone (2)
		Unknown (2)	Carbamazepine (2)
		NSAID (unknown) (1)	Cefazolin (1)
		Cloxacilin (1)	
Lethal ADR	1 (0.71%)	Phenytoin (1)	

G-CSF = Granulocyte colony-stimulating factor

drugs and muscle relaxants, for example; celecoxib, ibuprofen, etc, which celecoxib was being used as the most common drug of these groups. The results were similar to the previous study[10]. The third group consists of drugs acting on the central nervous system, of which phenytoin was the leading causative agent. Higher prevalence of drug hypersensitivity was due to its narrow therapeutic range and its reactive metabolite structure which was capable of stimulating hypersensitivity reactions[15]. The most common clinical manifestations of drug hypersensitivity was maculopapular rash, exanthmatous rash that has not been specified and fixed drug eruption, respectively. which were similar to those reported from the previous studies[14,16,17]. The rashes that had not been specified were mostly exanthems which were not confirmed by

the dermatologist. The patients were lost to follow-up for evolution of the rash *e.g.* necrosis, bullous formation, or systemic involvement, which could end up in entirely different diagnosis. Another explanation for this unique category may be because of inappropiate medical records by non-medical team which caused precise allocation of specific drug reaction typing impossible. Non-specified drug exanthem groups had been reported often in our practice in comparison with other studies[9-11].

Moderate, severe and lethal ADR groups, phenytoin was the next most common drug (22.22%) followed by cephalosporin (11.11%). When compared with the previous study, sulfonamides and cephalosporin were the most common causative drug. Explanation could be that sulfonamides are being used at a much lower rate at present[18].

Most patients visited at the dermatology outpatient clinic while some were inpatients. Data collection was performed for a period of 1 year which many cases had incomplete information. Dermatoligical events were recorded by dermatologists and pharmacists which skin lesion was sometimes described as erythrematous rash not specified (16.42%). Elderly patients aged more than 50 years old mostly developed drug hypersensitivity (40%) because of having some underlying diseases and receiving multiple drugs. Thus, the tendency to develop drug hypersensitivity was more than other age groups.

Nowaday, antibiotics, NSAID, muscle relaxant could be obtained from physicians' prescription or purchased from the drug stores. Physicians and patients should be concerned about drug hypersensitivity and rationale drug use to decrease the occurrence of drug hypersensitivity and lethal drug reaction, especially in the elderly.

In conclusion, 80% of drug hypersensitivity had mild degree of severity with antimicrobial agents being the most frequently involved. The most common clinical manifestations of drug hypersensitivity were maculopapular rash and exanthematous eruptions that was not specified. There had been one death which was caused by phenytoin.

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Drug hypersensitivity ในโรงพยาบาลพระมงกุฎเกล้า

อธิก แสงอาสภวิริยะ, ธราธิป ประคองวงษ์, รัชยาณี คเนจร ณ อยุธยา

วัตถุประสงค์*: เพื่อทำการศึกษาการเกิดภาวะ drug hypersensitivity ความรุนแรง และลักษณะทางคลินิก, ชนิดของยาที่เกี่ยวข้อง*

การออกแบบ*: การศึกษาวิเคราะห์แบบตัดขวาง*

วัสดุและวิธีการ*: ศึกษาโดยการเก็บข้อมูลผู้ป่วยจากคลินิกผู้ป่วยนอกแผนกโรคผิวหนัง, กองเภสัชกรรม โรงพระยาบาลพระมงกุฎเกล้า ตั้งแต่ 1 มกราคม พ.ศ. 2551 ถึง 31 ธันวาคม พ.ศ. 2551 ได้เก็บรวบรวมข้อมูลจากผู้ป่วยนอกโรงพยาบาล, ผู้ป่วยที่รับไว้ในโรงพยาบาล โดยรวบรวมข้อมูลเกี่ยวกับอาการทางคลินิก, ความรุนแรง, ชนิดของยา, เพศ, อายุ*

ผลการศึกษา*: ผู้ป่วยจำนวน 140 ราย มีภาวะ drug hypersensitivity จากยาปฏิชีวะกลุ่มเพนิซิลินมากที่สุดจำนวน 61 ราย (42.57%) ยาในกลุ่ม NSAID, ยาคลายกล้ามเนื้อ จำนวน 27 ราย (19.28%) และยาในกลุ่มที่ออกฤทธิ์ต่อระบบประสาทส่วนกลาง 18 ราย (12.85%) ตามลำดับ อาการที่สำคัญทางคลินิกพบว่าเกิด Maculopapular rash มากที่สุด จำนวน 49 ราย (34.99%), non specified erythrematous จำนวน 23 ราย (16.42%), fixed drug eruption 13 ราย (9.28%) และ Steven Johnson syndrome 12 ราย (8.57%) ตามลำดับความรุนแรงของการเกิด drug hypersensitivity ชนิดรุนแรงน้อย 113 ราย (80.71%) รุนแรงปานกลาง 12 ราย (8.57%) และรุนแรงมาก 14 ราย (10.0%) เสียชีวิต 1 ราย (0.7%) อายุเฉลี่ยผู้ป่วย 47 ปี เป็นเพศหญิงและชายในอัตราใกล้เคียงกัน*

สรุป*: ยาปฏิชีวนะเป็นสาเหตุสำคัญที่พบบ่อยที่สุดของการเกิด drug hypersensitivity*