CHAPTER II
LITERATURE REVIEW

1. Incidence of Adverse Drug Reactions and Drug Allergy

Adverse Drug Reactions (ADRs) are common drug- related problems which are an important cause of hospital admissions worldwide and occurred in 7.8- 8.1% of all DRPs related to hospital admissions (Hallas et al., 1990; Blix et al., 2004). Many studies had estimated the incidence of ADRs, which found that around 5.3- 6.5% of all admissions to hospitals are due to ADRs (Einarson, 1993; Pirmohamed et al., 2004; Kongkaew et al., 2008). ADRs are leading to patient morbidity and mortality. The study by Lazarou et al. (1998) was a meta-analysis which reviewed 39 prospective studies from US hospitals investigated ADRs in hospitalized patients excluding possible ADRs and ADRs cause by errors in administration, noncompliance, overdose, drug abuse, or therapeutic failures. The overall incidence of serious ADRs (occurred in hospitals and admission to hospitals) was 6.7% [confidence interval (CI) 5.2, 8.2] and of fatal ADRs was 0.32% (CI 0.23, 0.41) of hospitalized patients, making these reactions to be among the fourth and sixth leading cause of death.

Studies of ADRs in hospitalized patients tend to categorized patients into two groups including ADRs related to hospital admission and hospitalization. One previous study used database from MEDLINE, Index Medicus, and International Pharmaceutical Abstracts, synthesized ADRs data which published in 36 articles from 1966 through 1989. Admissions associated with ADRs resulted from patients' noncompliance or unintentionally inappropriate drug use, were included into the study. Excluding cases were involved in drug abuse, alcoholism, suicide attempt, intoxication, or inadequate prescribing. The results from meta- analysis found that the prevalence of admissions related to ADRs was 5.1% (CI 4.4, 5.8), of which 71.5%, 16.8, 11.3%, and 0.4% were side effects, excessive effects, hypersensitivity reactions, idiosyncratic, respectively. ADRs were causes of death for 3.7% of total ADRs admissions (Einarson, 1993).

A recent UK prospective observational study was conducted from November 2001 to April 2002 in two large general hospitals in Merseyside (Hospital A and Hospital B), 18,820 patients, who aged over 16 years and admitted to hospitals over six months were included into the study. They assessed causes of admissions related to ADRs (definition by Edwards and Aronson), types of ADRs (classification by Rawlins and Thompson), and avoidability of the ADRs (definition by Hallas et al., 1990). The results demonstrate that 6.5% of admissions were due to ADRs, most of them (95%, CI 93, 96) were type A ADRs. Over 70% 0f ADRs were classified as avoidable. The causality assessments used in this study were Naranjo method and Jones method, demonstrated that most admissions were classified as "probable" (Naranjo method: Hospital A 69.5%, Hospital B 68.1%; Jones method: 55.9%, 66.1%). Moreover, this study found that ADRs were accounting for 4% of hospital bed capacity and resulted in projected annual cost to the National Health Service (NHS) of £466 million (€706 million, $847 million). The study also found that the overall fatality was 0.15%. Most reactions were either definitely or possibly avoidable. Drug most commonly implicated in causing these admissions included low dose aspirin, diurectics, warfarin, and non-steroidal anti-inflammatory drugs other than aspirin, with the most common reaction being gastrointestinal bleeding (Pirmohamed et al., 2004). The others two studies estimated that ADRs may lead to an additional $1.56 to $4 billion in direct hospital cost per year in the US (Classen et al., 1997; Bates et al., 1997).

Later, Kongkaew et al. (2008) performed a systemic review of prospective studies through electronic sources of Cumulative Index to Nursing and Allied Health literature, Embase, and Medline, to determine the prevalence of hospital admissions associated with ADRs. The studies used the World Organization ADR definition were included into the study. The results showed that an overall median of ADRs prevalence was 5.3% (interquartile range [IQR] 2.7 - 9.0%). Antiinfective drugs were most common related to ADRs admissions in children; cardiovascular drugs were most common related to ADRs admissions in adults and elderly patients.

The preventable ADRs were more serious and more costly than the unpreventable one. Most ADRs were predictable from the known pharmacology of the drug or known drug allergy (Lazarou et al., 1998; Pirmohamed et al., 2004). The

retrospective study of hospital admission resulting from preventable ADRs reviewed charts of 437 ADRs in a university hospital over 11 months. The admission related to probably or highly probably ADRs was 154 (35.24%) of all cases. Potentially preventable ADRs were considered to be 96 (62.3%) of those cases, with 23 (24%) considered severe to life-threatening. Characteristics associated with these ADRs included documentation of a toxic drug concentration or abnormal laboratory value (80%), inadequate monitoring of a patients' drug therapy (67%), inappropriate dose (51%), patient noncompliance (33%), drug-drug interaction (26%), contraindication to therapy (3%), and documentation allergy (1%). (McDonnell, Jacobs, 2002).

In Thailand, Dansirikul et al. (2005) performed a prospective observational study to determine the incidence, rate and factors related to preventable ADRs. They did intensive hospital monitoring to 1,408 patients who admitted in medical ward. This study found that 62 (4.4%) patients experienced ADRs which 38 (2.7%) patients were preventable ADR cases based on Schumock and Thornton Criteria. Most of ADRs were pharmacology effects of the drugs (75.7%), hypersensitivity reactions (16.2%), and drug- drug interaction (8.1%). Preventable ADRs resulting in antidote or other treatment was required (32.4%), increased length of hospitalization 20.3%, stopped or changed the drugs (17.6%), life- threatening 8.1%, and death 1.4%.

Choppradit (2000) explored ADRs and their associated costs in 320 patients who developed ADRs during their stay as inpatient in Samutsakhon Hospital. The incidence of ADRs was 0.07% of the total patients and 98.16% of the suspected cases. Preventable ADRs was 17.50% of all ADRs cases. Skin and appendages disorder were the most common organ system affected by ADRs. ADRs related extended length of stay in hospital was 3.91 days and for preventable ADR cases was 5.92 days. The total direct medical costs of ADRs treatment were 162,100 Baht and the average cost per case was 506.56 Baht. The 22.31% of total direct medical cost was accounted for the preventable ADR cases.

Similar results were found by a prospective study in the medical ward patients at Hatyai hospital. ADRs were the cause of admission to hospital 3.6% of the patient and 3.6% of the patients developing ADRs during hospitalization. ADRs significantly increased the length of stay for 5.46 days (P= 0.01, CI 0.035, 7.40). The

cost per ADR was 2087 Baht, while the cost per preventable ADR was 5568 Baht. (Songsiriphan, 2002).

In Singapore, a 2-year prospective study by Thong et al. (2003) using a network-based electronic notification system to describe the incidence, manifestations, and outcome of drug allergy in hospitalized patients. They collected all newly cases who developed confirmed or suspected as drug allergy. The results showed that of a total 90,910 admission patients, 310 cases were reported as drug allergy. After a review and adjusting for underreporting, the incidence of drug allergy was 4.20 per 1,000 patients (CI 2.93, 5.46). Hospitalized patients developed drug allergy 2.07 per 1,000 (CI 1.45, 2.69), and the incidence of mortality associated to drug allergy was 0.09 per 1,000 (CI 0.06, 0.12). Antimicrobials and anti-epileptic drugs accounted for the most frequently reported drugs causing drug allergy (75%). Cutaneous manifestations were the most common clinical presentation (95.7%) which maculopapular rash was the most common morphology. Serious adverse reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and generalized exfoliative dermatitis occurred in 11 (5.2%) patients.

In Thailand, Puavilai and Choonhakarn (1998) performed a 1-year study to evaluate the types of drug eruption and the causative agents in inpatients and out patients consulting for drug eruptions at Ramathibodi Hospital Medical School. The diagnostic criteria were: Definite (The eruption occurred after rechallenge of the suspected drug. The test dose was one tablet of suspected drug per day for 1-3 days. If no eruption occurred, they waited for 3 days and started another suspected drug until the eruption appeared), Probable (Only one drug was administered during the few weeks before the eruption occurred. Other probable causes of eruption were excluded with certainty), and Possible (more than one drug were administered during the few weeks before the eruption occurred. The previous incidences of drug eruption were obtained from literature. Other probable causes of eruption were excluded with certainty). One hundred and thirty two patients were included in the study. The diagnosis were definite (19.6%), probable (43.9%), and possible (34.8%). The three most common causative drugs were antimicrobial agents (60.8%), antipyretic/ anti-inflammatory agents (9.8%), and drug acting on the central nervous system (7.7%). The most common skin lesion was maculopapular rash (60.2%), followed by fixed

drug eruption (9.0%), and urticaria (6.0%). One patient developed two episodes of drug eruptions: maculopapular rash from Phenobarbital and Stevens-Johnson syndrome from valproic acid. One patient with exfoliative dermatitis died from septisemia.

A restrospective study of potentially life- threatening drug allergies which were Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), was performed in patients who were admitted to Siriraj Hospital between 1981 and 1990 to determine the drug etiology. There were 58 and 20 cases of patients who were diagnosed with SJS and TEN, respectively. Eight patients initially had an SJS-like aspect, which subsequently evolved into TEN. A suspected drugs were determined in 60 patients (77%), included the following: 32 cases (53.3%) of antibiotics, 9 cases (15.0%) of anticonvulsants, 8 cases (13.3%) of antitubercular drugs, 4 cases (6.7%) of analgesics, 2 cases (3.3%) of sulfonylurea, 5 cases (8.4%) of others. The mean time from first drug administration to onset of SJS or TEN was 6.8 +/- 6.5 days (range, 1 to 28 days). The most frequent underlying diseases justifying the ingestion of one or more drugs in our patients were infections (52.7%), followed by pulmonary tuberculosis (10.8%), and by seizures (8.1%). The total mortality rate was 14%; 5% for SJS, and 40% for TEN. The types of suspected drugs were not affected to mortality (Leenutaphong et al., 1993).

Later, Jantararoungtong et al. (2009) conducted a retrospective study to identify drugs which were associated with the cause of SJS or TEN in hospitalized patient and to evaluate the clinical outcome of these serious reactions. The patients whose diagnostic records were SJS or TEN during 1995 to 2008 at Srinagarind Hospital, Khon Kaen University, Thailand were included into the study. A total of 132 cases of SJS and 29 cases of TEN were identified. The average age of the patients was 36.6 ± 20.4 years. More than three-quarter (77.0%) of cases were possibly caused by drugs. The suspected drugs were included the following; anticonvulsants (38.7%), antibiotics (38.7%), anti-gout (8.1%), anti-tuberculosis (4.8%) and non-steroidal anti-inflammatory drugs (4.8%). In addition, the common drug implicated as the cause of SJS/TEN was carbamazepine (24.2%), sulfonamides (21.0%) and allopurinol (8.1%). The onset of SJS and TEN after the first exposure to the suspected drugs was 9.56 ±

9.47 days. Length of hospitalization was 13.19 ± 12.79 days. The mortality rate was 1.86% (2 cases of SJS and 1 case of TEN).

Since the ADRs monitoring system was implicated in Thailand, aimed at gathering ADRs reports for post-marketing drug surveillance, important information was essential for improving ADRs prevention program in health care service. A 2-year retrospective study was conducted to identify repeated drug allergy in three provinces: Pichit, Petchaboon, and Pitsanulok (Network 9/10). A total of 358 ADRs reports including adverse product reactions and positive rechallenge histories were reviewed. The results showed that of all 224 repeated ADRs reports, 173 (77.2%) reports were repeated drug allergy. Severity of drug allergy was evaluated, non-serious symptoms were most frequently reported (67.1%), followed by: prolonged hospitalization (19.6%), intervention required (6.4%), life- threatening (5.8%), and death (1.1%) (Kidkeukarun, 2005).

2. Risk factors for drug allergy

Drug allergy is immune-mediated reaction which may result in multi-factorial disorder. Epidemiologic studies had explored risk factors for drug allergy which may relate to drugs, treatment regimen, and patients (Adkinson, 1984; Britschgi et al., 2003; Guglielmi et al., 2006; Demoly et al., 2007; Demoly et al., 2008; Apter et al., 2008).

2.1 Drug-Related Aspects

The chemical property of the drugs, largely its protein reactivity is probably the most important factor (Adkinson, 1984; Guglielmi et al., 2006; Demoly et al., 2008). It is well established that a substance with molecular weight more than 1,000 daltons e.g. drugs, behave as haptens which bind to carrier proteins and develop an immunologic response. Certain drugs were not reactive, but they can still be immunogenic by direct non-covalent binding to immune receptors (pharmacological interaction concept) (Britschgi et al., 2003).

2.2 Treatment regimen

The dose and duration of treatment as well as the route of administration influence the frequency of reactions (Adkinson, 1984; Guglielmi et al., 2006; Demoly et al., 2008). A publication by Cetinkaya and Cag (2004) had studied 147 children age between 6 and 13 year-old who had had received a penicillin preparation at least three times in the last 12 months, to establish the prevalence of positive penicillin skin tests among outpatients without any drug reaction history. Children were invited for penicillin skin test during a healthy period. Total 15 (10.2%) subjects of the tested children had positive penicillin skin tests. They concluded that frequent expose to penicillin leads to sensitization.

2.3 Patients-Related Factors

Multiple definable risk factors account for drug allergy included:

2.3.1 Age

Popescu et al. (1984) studied the incidence of drug allergy in 3 groups of subjects. The incidence in the first group was verified in terms of the subjects' age. The incidences were 1.8% in children up to 14 years old (323 subjects), 5.8% in middle-aged subjects (389 subjects) and 2.9% in the elderly (243 subjects). In the second partly selected group, drug allergy was studied in patients who were admitted to the 3rd Medical Clinic--Craiova between 2 Jan. 1981 and 31 Dec. 1982. Of the total 8,760 admitted patients, 103 patients developed drug allergic reactions (incidence rate 1.01%). The third group of previously selected cases consisted of 197 patients who complained of the present or past sensitivity to drug and visited the allergology service. The total number of patients was 336 selected or preselected from about 10,000 subjects. In terms of allergic drug, the most commonly reported drugs were penicillin, pyramidon-algocalmin, aspirin, iodine preparations, etc. The clinical syndrome which were frequently reported were the dermatologic syndromes types I, III and IV; syndromes of the "anaphylactic shock" type, "serum sickeness" bronchial asthma, angioneurotic oedema. The relevant result of age related to drug allergy was also found by Poon and Macy (2009) which antibiotic allergy was more commonly reported in both male and female as age increased.

2.3.2 Gender

Gender may influence susceptibility to drug allergy. Tran et al. (1998) conducted a study to identify gender-related differences in the types of symptoms, type and number of drugs reported to cause an adverse drug reaction, and positive skin or oral challenge testing results. They collected patient information at the Adverse Drug Reaction (ADR) Clinic at Sunnybrook Health Science Centre, Toronto, Ontario, Canada (now officially known as the Glaxo Wellcome-Sunnybrook Drug Safety Clinic) during April 24, 1986 to May 21, 1996. Of the total 4,894 adverse events assessed, 77.7% were experienced by female patients with the mean age of 43 ± 17 years. The most frequently reported adverse events overall by both male and female patients were skin disorders (49.0%), followed by allergic/immunologic disturbances (13.8%), and gastrointestinal disorders (8.7%). There were 381 severe adverse drug reactions defining as being potentially life threatening, causing permanent damage, or requiring intensive medical care, of which 77.2% were reported by female patients. Of the female patients, 47.6% were tested for skin or oral challenging, versus 41.6% of the male patients. The positive results were found 6.2% and 6.1% in female and male patients, respectively. Several factors that may involve with more reports of adverse event in female than male patients were pharmacokinetic and pharmacodynamic factors, hormonal influences, healthcare utilization, reporting bias, and increase use of medications in women.

Macy and Poon (2009) extracted drug allergy data from the electronic health records of the 411,543 patients cared for by Kaiser Permenente in San Diego who had more than 1 outpatients visit during 2007. Antibiotic allergy accounted for 54.2% of all drug allergy reports. Follows were narcotics (13.9%), NSAIDs (7.7%), ACE inhibitors (3.1%), non-ACE-inhibitor anti-hypertension medications (2.9%), radiographic contrast materials (2.3%), anti-cholesterol medications (1.7%), therapeutic proteins (0.8%), and local anesthetics (0.5%). Women tend to had more antibiotics allergy than men in all antibiotic classes evaluated and for all decades of life. The most commonly reported antibiotic allergy for females was penicillin (11.0% of the population) followed by sulfa (7.9%), macrolides (1.9%), others (1.7%), cephalosporins (1.7%), tetracyclines (1.5%), and quinolones (0.8%). For males it was penicillin (6.5%) followed by sulfa (2.4%),

cephalosporins (0.8%), macrolides (0.6%), others (0.5%), tetracyclines (0.5%), and quinolones (0.3%).

2.3.3 Concomitant Infection

Epidemiological data support information in concomitant infections associated to drug hypersensitivity (Guglielmi et al., 2006). Coopman et al. (1993) conducted a cohort study at The Brigham and Women's Hospital. Comparing the visiting rates correlated with skin conditions between HIV-infected patients and non-HIV-infected patients. For 34 months, they reviewed only the completed ambulatory care records of patients whose diagnosis was HIV infection. Of the total 684 HIV-infected patients, all drug-specific incidence data were confined to reactions occurring in 666 patients. A total of 2281 skin diagnosis were detected by dermatologist, of which 188 diagnosis in 125 patients were identified as cutaneous reactions to drugs. As compared with non-HIV-infected men, the men with HIV had visit rates that were at least 5 times higher for 18 of the 20 most common infection and inflammatory skin conditions and at least 15 times higher for 9 conditions. Most common drugs with high rates of cutaneous reactions (per 1000 courses) were sulfadiazine (200), trimethoprim-sulfamethoxazole (149), trimethoprim-dapsone (156), and aminopenicillins (93).

2.3.4 Concurrent Illnesses

Previous study had reported that sulfonamides were both a predisposing factor and as an exacerbating agent to drug allergy in Systemic Lupus Erythematosus (SLE) patients. Petri and Allbritton (1992) performed a case-control study to evaluated antibiotic allergy in SLE patients. A total of 221 members of The John-Hopkins Lupus cohort and 2 control groups, including 178 relatives and 186 best friends were enrolled for antibiotic allergy analysis. Drugs with most common allergic reactions were penicillin/ cephalosporin (27%), sulfonamide (31%), tetracycline (7%), and erythromycin (13%). Symptom most frequently reported was rash.

A case-control study was determined whether greater risk for anaphylactoid reaction from intravenous urographic contrast media exists in patients receiving beta-adrenergic blockers or in asthmatic patients. The total of 49 patients experienced moderate to severe anaphylactoid reaction during July 1987 to June 1988.

Medical records from these 49 reactors were compared with those from a control group matched for gender, age, and date and type of contrast study who received intravenous urographic contrast media without adverse reaction. Beta-blockers and asthma (39%) were significantly associated with adverse reactions when comparing to match control (16%) (OR, 3.43; 95% CI, 1.45 to 8.15; P = 0.005). After correction for beta-blocker use, asthma was also associated with increased risk for anaphylactoid reaction (odds ratio, 4.54; CI, 1.03 to 20.05; P = 0.046) (Lang et al., 1991).

2.3.5 Genetic Factors

A recent study had been discovered that genetic factors including polymorphisms in gene coding for drug metabolizing enzymes and immune responses response for drug allergy (Adkinson, 1984; Demoly et al., 2007). Apter et al. (2008) performed a case-control study to identify and correlate clinical and genetic risk factors of self-reported penicillin allergy. Complete data were available for 23 cases and 39 controls. Multivariable analysis showed that penicillin allergy was associated to family history of penicillin allergy in first-degree relatives and IL4 single nucleotide polymorphisms (SNPs).

3. Knowledge, Understanding and Attitude of the Patients in Drug allergy and Drug Allergy card

As a safety of the medication used, knowledge, understanding and attitude of the patients could be involved. Their perceivability and attitude toward the risk of prescription drugs are likely to affected treatment and compliance. Therefore, O'Brien et al. (1990) had surveyed 1,034 patients with ankylosing spondylitis (AS) by postal questionnaires to investigate their perceived causation and attitude toward the risk of medicines in general and non-steroidal anti- inflammatory drugs (NSAIDs). Patients who took NSAIDs, seemed to perceive serious ADRs more frequent than prescription drugs generally and those who had experienced previous ADRs (47%) judged ADRs to be more frequent ($P < 0.001$). About the likelihood of the causation of ADRs, patients perceived that inadequate drug information and inadequate patient follow up were most reported. Later, Bongard et al. (2002) found that the perception of risk of ADRs between health professionals and non health professionals had major differences.

Wyatt (1996) investigated the nature and accuracy of drug allergy information carried by patients. Two thousand five hundred adult patients at accident and emergency department of tertiary referral centre, who aged 16 years or over and ability to provide their drug allergy history were included in this study. Patients were questioned about their drug allergies. General Practitioners (GPs) were contacted to evaluate allergy information holding by them and those given by patients. The results showed that 242 (9.7%) patients claimed to have 276 drug allergies. The most frequent drugs related to drug allergy were: penicillin (151 allergies), cotrimoxazole (15), aspirin (12), amoxicillin (9), erythromycin (8), and mefenamic acid (6). Thirty eight patients claimed to have allergy to drugs which they could not recognize the drug name. The most commonly allergic reaction was rash. Only 7 of all 272 patients carried any evidence of their allergies on them: five carried a written note, two wore a bracelet. GPs were able to confirm 114 (41.3%) allergies, the others were unable to because 97 (35.1%) of them have no drug allergy record and 29 (10.5%) of them had records involved with a different drugs.

The ability of the patients to identify symptoms that possibly related to drugs is of real interest. A model for understanding patient attribution of adverse drug reaction symptoms had been studied. Self- administered questionnaires were sent to adults (aged over 18 year-old) who visited a family medicine clinic over a four week period. The questionnaire was formatted into two stages. First, subjects were asked if they had previously experienced ADRs. Those who reported an ADR experience were asked to briefly describe the reaction and descriptions were coded in terms of cause, identity, time, consequence, and cure when details of those elements were mentioned. The second stage explored the information of each element, included: the name of the involved drug, an estimation of the duration between drug administration and reaction occurred, duration of the drug reaction effect, the severity of drug- induced reaction, and how to treat or alleviate ADRs symptoms. Three hundred and thirty-eight questionnaires were returned. Over 53.4% of the sample reported that they had experienced ADRs, and 59% of the sample also known a person with ADRs history. Demographic data indicated significantly higher rate of response in women than men and dependent on education level ($p < 0.05\%$). Media exposure to drug effects was also studied. Response to television, radio, newspapers, and magazines were all $\geq$

50%, 47 participants cited healthcare professionals and books or literature about drugs and their effects, twenty-seven stated that they had had information from friends, relatives, and coworkers, and 87 subjects had additional sources of information. Healthcare professionals that people would contact regarding ADRs, subjects were most sought for physicians (93%), pharmacists (45%), and nurses (21%). The descriptions of ADRs by respondents including references to 5 prototype elements were cause of ADRs 77 (44%) cases, symptoms of ADRs 172 (98%) cases, onset or duration of the ADRs 17 (10%) cases, severity of the ADRs 43 (24%) cases, and treatment of the ADRs 6 (3%) cases. This study indicated that patients who experienced ADRs could easily categorize their information to those five prototype elements (Dewitt, Sorofman, 1999).

Implementation of self-reported drug allergy by the patient had been one of the method used to increase the prevalence of ADRs in pharmacovigilance post-marketing drug monitoring programs. Gomes et al. (2004) conducted a cross-sectional survey during the year 2002, using a self-administered questionnaire to estimate the prevalence of self-reported drug allergy in adults. They focused on 2,500 patients, included adults (mostly parents) living with children who were participating in the International Study of Asthma and Allergies in Childhood (ISAAC) phase three study in porto, who took Beta-lactam antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). Only 2,309 questionnaires were evaluated. The prevalence of self-reported drug allergy was 181 (7.8%) subjects which women were significantly more likely to have self- reported drug allergy (women 10.2%, men 5.3%; OR= 2.05, P< 0.001) and to be allergic to Beta- lactams (women 6.0%, men 3.0%; OR= 2.08, P= 0.001), but not significantly higher to NSAIDs (women 2.4%, men 1.5%; OR= 1.61, P> 0.05). Ninety six subjects (53.0%) considered themselves to be allergy to Beta-lactam, 37 (20.4%) to NSAIDs, and 8 (4.4%) to both. There were 171 subjects known how their allergies were diagnosed, 50 (29.3%) stated that they had been told by their doctors they were allergies. Route of administration of the drugs was investigated. Only 125 (69.1%) could remember how they take them, which were oral for 56%, parenteral for 40%, and both oral and parenteral for 4%. Recalling of the name of the drugs and clinical manifestation of drug allergy were evaluated. In the "allergy only to Beta-lactam" group, 21 (21.9%) subjects recalled the exact name of the drug that

caused reactions and the most frequently implicated was penicillin G or V (76.2%), followed by amoxicillin/ clavulanic acid (14.3%). In the "allergy only to NSAIDs group, 22 (59.5%) subjects could recall their allergic drugs which acetylsalicylic acid and ibuprofen were identified by 8 (18.2%) subjects. The most commonly recalled clinical manifestations were cutaneous (63.5%), followed by cardiovascular (35.9%), bronchial (14.4%), nasal/ ocular (12.7%), and gastrointestinal symptoms (11.6%). Parenteral route was significantly response for more reactions occurring within the first hour (58.7%, p= 0.017). Most subjects (86.8%, 138 out of 159 who answered this question) completely avoided taking drugs which caused allergies, while 20 out of 21 (13.2%) took it again and relapsed.

Cullen et al. (2006) had performed a prospective study over two time periods in September 2002 and May 2003. The medications under study were corticosteroids, proton pump inhibitors (PPIs), warfarin, non steroidal anti-inflammatory drugs (NSAIDs) and aspirin. They assessed 399 patients who were admitted on acute medical call during study period. Of those, 173 patients were taking at least one of the study medications which only 100 patients had the abbreviated mental test score (AMTS) less than or equal to 7 out of 10 were interviewed. All patients completed a visual analogue scale (VAS), where o indicates minimum and 10 maximum risk, indicating their perception of the safety of the study medications. A control group of 20 medical professionals was used for comparison. The results showed that corticosteroids were ranged most toxic drug by the patients (median score, 25^{th} - 75^{th} percentiles: 5.4, 2.9-8.7) while medical staffs ranged NSAIDs as highest risk (6.2, 4.0-7.5). Overall, patients underrate the risk of ADRs of their medications e.g. NSAIDs (including aspirin) (2.1, 0.7- 4.8). There is a good level of ADRs knowledge among patients using warfarin and aspirin, but a clear lack of knowledge was found among NSAIDs users, especially in relation to drug's effect to gastrointestinal tract.

In Thailand, the experience and knowledge of drug allergy in people was studied by Lohasuphakarn (2000). A cross sectional study was conducted between August and October, 2000 using questionnaire which was tested in the Maesot General Hospital and was adjusted, collected data from Maesot's people. The volunteers were trained about basic knowledge of drug allergy, interviewing skill, and Maesot's districts zoning area. The cluster random sampling method was used, 1,341

questionnaires were received of which 1,200 (89.5%) questionnaires were valid. The results found that 15.25% of sample had some experience on drug allergy (8.08%, 2.17%, and 5.00% were allergic to one drug, more than two drugs, and could not remember, respectively). Most of the sample (96.17%) thought that it was important to remember name of the allergic drug and the drug allergy reaction, but only 48.63% was able to tell their name of allergic drug. Only 3.33% of the sample could choose all the correct answers of the questionnaires which indicated that the people in Maesot district were lack of drug allergy knowledge. It also found that there was no significant difference relationship among the knowledge and education level.

Later, Lebnak et al (2001) also surveyed the knowledge of drug allergy and the management of drug allergy in people of Muang district, Ubon Ratchathani Province. The questionnaire was used for collecting drug allergy data especially drug used for common cold and management when drug allergy occurred. The total of 951 samples was randomly selected into the study. More than half of the sample (53.6%) had moderate level of drug allergy and the management knowledge which was related to education level, direct drug allergy experience, and location of the people. Most of the sample (80.2%) could answer the correct management when drug allergy occurred which was immediately stop the allergic drug and consult healthcare professionals, 62.9% could answer the correct prevention of repeated drug allergy which were remembering name of the allergic drug and always informing drug allergy history to healthcare professionals. The major source of drug allergy information was drug store's pharmacists (62.9%) but the others (28.1%) did not sure that the informers were pharmacists or not.

4. The Pharmacists' Role in the Prevention of Repeated Drug Allergy

A case report of repeated drug allergy in Thailand found that the contributed causes were patient receiving causative drug from multiple sources and the deficit of drug allergy documentation in either of patient's medical profile and drug allergy card. These problems lead to the proper preventions of repeated drug allergy which were documentation of drug allergy information on patients' medication profile, providing drug allergy card to the patient, and encouraging healthcare professionals to ask patients for their history of previous drug allergy (Pithakthim, 2000).

Further investigation of problems and the method to prevent repeated drug allergy was studied by Kidkeukarun et al. (2008), who designed a descriptive and qualitative research to compare the incidence of prescribing errors in drug allergy patients and to study causes and method to prevent these problems at Buddhachinaraj Phitsanulok hospital. Root cause analysis was performed in the annual meeting of the fiscal year 2007, whom the attendees were doctors, nurses, and pharmacists. Qualitative assessment in repeated drug allergy used in-depth interview analysis from six doctors, one extern, one intern, three acute care nurses, two out-patient department nurses, and four pharmacists, covered three main points of study objectives; characteristics of the problems, causes of the problems, and suggestions to prevent the problems, during July to September, 2007. The results showed that there were significant difference in the incidence of prescribing error in drug allergy patients from 2004 to 2006 (2.02, 1.71, and 1.14 per 10,000 orders per each year, respectively; $P< 0.001$). The most incidences were from Otolaryngology, Surgery, and Orthopedic department (8.08, 5.11, and 5.6 per 10,000 orders, respectively). Causes of problems were human error (healthcare professionals neglected in following system protocol or did not know the importance information of drugs), working system (limited service time, inappropriate surveillance tools), patients (unawareness of drug allergy and drug allergy card carrying), communication (incomplete information transferring,), and other problems (familiarity to drug trade name, workload). Suggestions were tool amendment (changing the position of drug allergy information on doctors' order, more space for filling information, outstanding drug allergy card and easy to carry), innovation (drug allergy warning label to healthcare professional, wristband containing patients' name and allergic drugs' name), information improvement for concordant understanding, technology using, patient empowerment and system renovation (drug allergy testing system, modification of patient interview's technique).

In 2007, the joint Commission's Board of Commissioners declared the 2007 National Patient Safety Goals, of which the Goal 3 was to improve the safety of using medications (JCAHO, 2007). Therefore the collaboration between Thailand's Ministry of Public Health (MOPH) and WHO had launched First Global Patient Safety Challenge "Clean Care is Safer Care" campaign, emphasized on medication

administration system which included the principle for reducing serious ADRs and repeated drug allergy. The guidelines were systemically management/ surveillance of ADRM, lists of drug name for closed ADRs monitoring, drug allergy card distribution, and drug allergy POP UP ALERT program.

The American Society of Consultant Pharmacist (ASHP, 1995) also suggested that, in settings where applicable input into the design of ADR-monitoring and reporting program should be obtained from the medical staff, nursing staff, quality improvement staff, medical records department, and risk managers. The pharmacist should facilitate in

1. Analysis of each reported ADR,
2. Identification of drug and patients at high risk for being involved in ADRs,
3. The development of policies and procedures for the ADR-monitoring and reporting program,
4. A description of the responsibilities and interactions of pharmacists, physicians, nurses, risk managers, and other health professionals in the ADR program,
5. Use of the ADR program for educational purposes,
6. Development, maintenance, and evaluation of ADR records within the organization,
7. The organizational dissemination and use of information obtained through the ADR program,
8. Reporting of serious ADRs to the FDA or the manufacture (or both), and
9. Publication and presentation of important ADRs to the medical community.

Direct patient care roles for pharmacist should include patient counseling on ADRs, identification and documentation in patient's medical record of high-risk patients, monitoring to ensure that serum drug concentrations remain within acceptable therapeutic ranges, and adjusting doses in appropriate patients (e.g. patient with impaired renal or hepatic function).

4.1 Documentation of drug allergy

Among many strategies were designed to prevent repeated drug allergy, completing documentations of drug allergy by healthcare provider was one, used to detect potential ADRs. Shulman et al. (1982) used a two-card record system for three

years (1977-80) in North London pharmacy. One of the cards, retained by the pharmacy, contained history of the patient included any history of previous allergy to medications or major illnesses and ADRs. The other card was given to the patients, contained history of the patients. They enrolled all patients who were aged over 40 year-old and on multiple drug therapy, long-term medication (over three months), and received psychoactive drugs, corticosteroids, cardiovascular and antihypertensive drugs, anti-inflammatory agents, anticoagulant or antidiabetic drugs. Over a three years period, medication record cards were kept for 1,366 patients. Potential ADRs were identified for 86 cases, which 65 cases of them were detected using the record cards retained by the pharmacists. Of all potential ADRs, the prescriptions with drugs prescribed for patients known to be allergic to them were 15 (17.4%) cases which were all changed after pharmacist detection. Therefore, improving the role of the pharmacists in documentations of ADRs could be valuable in monitoring for potential drug reactions in general practice. However, a recent study found that 211 (70%) patients' charts had a completed drug allergy box of all 300 patients' charts presenting for elective surgery (Farooq et al., 2008).

Later, Ismail et al. (2008) performed a cross- sectional study, determined 3 strategies for preventing inpatient in Whittington Hospital from drug allergy. The strategies consisted of white wrist bands which identify patient's name for all patients, red wrist band for allergic patients contained name of the allergic drug, and the completeness of the allergy box response by the pharmacists. The study conducted 11-months apart, each study period included 186 and 250 patients respectively. The results showed that, the incomplete allergy box were significantly decreased between each period (24.7% and 5.2%, $P< 0.001$). The reasons response for such case were allergy status not transferred to new drug chart when chart finishes and is re- written, allergic status sought by doctor and documented in the notes but not on drug chart, failure to obtain allergy status from other source when patient unable to communicate, failure to ask about drug allergy, and patient's previous drug charts were missing. The proportions of patient who did not receive white and red wrist bands were not significant different between each study period: 12.9% VS 10.8% ($p= 0.499$) and 44.8% VS 30.4% ($P= 0.206$). These results indicated that the response of the

pharmacists in completed allergy documentation on patients' drug charts significantly increased use of this safety measure.

In Thailand, the prevention of recurrent drug allergy had been improved. Sirichai (2004) performed a study in outpatient department in Lerdsin Hospital. Starting in the year 2001, they specified only with penicillin and sulfa allergy. But at the end of the study in the year 2003, the entire medications were attended. Two types of patients were included. First, patients who had experienced drug allergy during their hospital stay. The pharmacist questioned about their drug history and provided causality assessment. Second, patients with history of drug allergy were asked to complete data of the allergic drug and reaction associated with drug allergy. Those patients' prescriptions were documented in details of the drug name and reaction associated to drug allergy and enclosed with drug allergy warning card. Then the information was collected in the computer. The doctors and the pharmacists were notified by drug allergy notes that appeared on patient's prescription to prevent repeated prescribing and administration those allergic drugs again. Moreover, they provided sticker with drug name that might cause the same reaction on drug package. This would urge patients to ask for information from the pharmacists. These prevention strategies showed effective results such as no patient return with recurrent drug allergy and decreasing prescriptions with known drug allergy by the doctors (year 2001, 115 prescriptions; year 2002, 117 prescriptions; year 2003, 94 prescriptions).

Nevertheless, the accuracy of drug allergy documentation was essential for optimizing drug allergy management. Improper documentation of drug allergies could withhold proper drug therapy, resulting in less effective prescribing, more toxic, or more expensive drug (Tripp, 1993; Pilzer et al., 1996). The accuracy of drug allergies documentations in medication profiles was assessed by pharmacist interviews. The patients' medication profiles were reviewed after discharges to identify the pharmacists' prevention of adverse effects or allergic reactions. Fourteen pharmacists interviewed 195 patients in 347 drug allergies reports, 53.0% of the allergies was related to anti-infective agents, followed by narcotics (18.0%), psychotropic medications (7.0%), non-steroidal anti-inflammatory drugs (6.0%), cardiovascular medications (5.0%), and others (11.0%). Pharmacists found that more than 80.0% of

beta-lactam and sulfonamides reports were either found or could not rule out true allergies, this was found in 31.0% of narcotics allergies. The cost-effectiveness of pharmacist interviews to clarify these documentations was assessed. Pharmacists intervened in four cases to prevent adverse reactions and a total of 4.4 additional hospital days, and in five instances the use of less suitable or more expensive drug was avoided (Pilzer et al., 1996).

A study at the university of Alabama hospital, Birmingham, was performed to determine the accuracy of true patient- related allergies to drugs, and to identify contributed factors to medication errors that involved drug allergies. Patients who were at least 19 year-old and had an allergy history to-lactam antibiotics, sulfonamides (including diuretic agents), and/or narcotics were included into the study. The total of 340 patients who were admitted to the hospital during November 24, 2000-February 26, 2001, was assessed for drug allergies documentation and contributing factors involving medication errors. The results showed that 133 patients (39%) reported allergies to at least one drug, but only 73 of these patients met the study criteria. The interviews determining the timing, nature, and the extent of the reaction, were available in 50 patients who reported allergy to one drug (46.0%), two drugs (40.0%), and more than 3 drugs (14.0%). From the total of 70 allergies, more than half of the assessed allergies (64.3%) listed in the computer system did not indicate a specific agent, but rather a class of the drugs. The most common drugs reported from total population were-lactam (12.6%), opioid narcotics (14.4%), sulfonamides (9.1%), and others (63.9%). True allergies were found in 50.0% and 60.9% of the reported allergies to-bactams and sulfonamides, whereas most of the reported allergies to opioid narcotics were determined to be intolerance of the drug (88.2%). The reactions which could not be ruled out as allergic reactions were found in 43.0%, 17.0%, and 12.0% of the reported allergies to-bactams, sulfonamides, and opioid narcotics. The total of 70 medication errors were identified in which a drug was prescribed to patients with documented of drug allergies, only 54 occasions were able to contact the prescribers. Contributing factors were classified as MD (prescribing physician) not aware of allergy (76.0%), MD think allergy not actual (9.0%), MD aware of allergy but benefit greater than risk (7.0%), MD not aware that agent was in same class (6.0%), and others (2.0%) (Jones, Como, 2003).

4.2 Patient counseling in drug allergy

Patients are increasingly willing to have information in all aspects of their healthcare, including drug information. Most patients wish to be informed about the adverse reactions that possibly associated to their medications (O'Brien et al., 1990; Cullen et al., 2006). Increasing patient education may reduce the incidence of ADRs but more importantly improving communication between patients and healthcare professionals is needed. Developing and implementing the drug allergy counseling service had been operated by Parkland Health and Hospital System (PHHS), which was a 964-bed teaching hospital in the Dallas County Hospital District. The counseling were provided for patient with history of severe allergic reactions included anaphylaxis, lalyngeal obstruction, angioedema, Steven-Johnson Syndrome, Toxic Epidermal Necrolysis, and severe hypersensitivity syndrome. Inpatient pharmacists were response for writing a two-part, standard patient notification form which contained name of the suspected drug that caused reaction and a brief description of the allergic reactions. One was given to the patient, the others was kept in the pharmacy. Then, pharmacist have to be ensure that allergic drug is not given to the patient again, update the medication profile to include the most recent allergic reaction, provide extensive counseling to the patients and their families about drug that cause allergy and its related reactions. Other information aids were given to the patients included a customized Medic I.D. bracelet (Custom ID Products, Seattle, WA), which identified patients' allergy, and a comprehensive list of drug names (brand and generic) that could cause similar problem, instructions if patient experiences another reaction, and explanation of the importance of notifying healthcare providers about their drug allergies. The patient is also advised to avoid filling medication from multiple pharmacies. Follow up the patients were operated by calling patient to ensure that all questions about their drug allergy had been answered and that the bracelet had arrived and contained accurate information. The drug allergy counseling program was proceeding from March 1999 to December 2000. The reports of Adverse Drug Event (ADE) included drug allergy were 46 cases. After they received drug allergy counseling, none of the 46 patients have been readmitted to the PHHS again. Even though the small number of the patients and lack of control group

were limitations of the program, this pharmacist- based counseling program yielded an effective result in the prevention of repeated drug allergy (Johnson et al., 2001).

4.3 Drug allergy card distribution to the patients

Many patients receiving prescriptions from multiple health care facilities: hospitals, clinics, or pharmacies. They seldom carried any information to warn others about their drug allergy reaction, which occasionally could brought to life-threatening event. The importantly of giving drug allergy information to the patient had been studied. Several education aids were designed to meet the important requirement in patient's perception, including drug allergy card. A previous study performed in Sheffield in an urban practice, using a short questionnaire which composed of two parts. Part I contained questions about patients' drug allergy which linked to another questions e.g. the name of the allergic drug, the reaction that occurred, and any warning tools to their allergy. Then part II of the questionnaire which examined the correlations of patient's reply with any warnings written on the cover of the patient's note and the evidence that confirmed in the reactions, was completed after each surgery. Over a 3-week period, 500 patients were questioned. The records of 75 patients had notes tagged which 51 (68%) patients could accurately name the suspected drugs. The drug allergy reports were found in 86 patients. Clarifying of patients who suffered from adverse reaction was made based on their descriptions and documentary evidences. There were 89 patients who probably or possibly had adverse reactions to 113 drugs. As for patient's drug sensitivity resources, most patients received information from doctors (76 subjects). Only 8 patients carried drug allergy warning such as a bracelet or SOS talesman. This study suggested that a plastic card, contained written information of their allergic drugs and reactions with management instruction, should be provided to the patient (Hannaford, 1986).

In Thailand, the allergy card was given to the patient with type B ADRs and serious type A ADRs by the pharmacists. Those serious type A ADRs were potentially life-threatening, causing permanent damage, or requiring intensive medical care (Adverse Drug Reaction Monitoring Center [ADRM], 2007). The role of the pharmacists on the management of patients with a history of drug allergy had been studied. A 10-month prospective descriptive study was conducted to inpatient at the

Department of Obstetrics and Gynecology, King Chulalongkorn Memorial Hospital. The pharmacist reviewed patient's medical history to assess the probability of drug allergy using Naranjo's algorithm. Then the pharmacist provided drug counseling and drug allergy card distribution. The results showed that among 10,100 inpatients admitted, 321 (3.2%) patients were reported with drug allergy whereas 185 (57.6%) patients received drug allergy cards from the pharmacists. Total counseling time was 139 hours and 6 minutes or 46 minutes per patient. Most patients (69.2%) received 5-8 scores (probably) in causality assessment by Naranjo's algorithm. The opinion of the patients after receiving drug allergy card from the pharmacists was evaluated. The average percentages for understanding in the cause of drug allergy of the pharmacist, the importance of drug allergy card, patient's satisfaction in drug allergy card issuing by the pharmacist, and the continuation of service by pharmacists were 77.2, 83.2, 85.2, 89.9, and 89.4 respectively. It was clear that patients who received drug allergy cards appreciated and hoped for continuation of this additional useful service (Laohapojanart et al., 2007).

Another evaluation of drug allergy card distribution to the patients had been studied. Wongpentak (2008) performed a prospective descriptive study in outpatients of Puttha Chinnarat Hospital. Patients who had history of drug allergy on computer-based were randomly selected, 172 volunteers were included. The two drug groups that caused ADRs most were anti-infective drugs (73.07%) and NSAIDs (11.54%). The adverse reactions associated with drug were assessed by Naranjo's algorithm. More than 136 (79.08%) reports were unable to evaluate, others were definite (score < 9), probable (score 5-8), possible (score 1-4): 2 (1.16%), 16 (18.61%), 16 (18.61%), and 2 (1.16%) respectively. The severity of drug allergy were serious (1.16%), non-serious (18.61%), and history of symptoms reporting by patient (80.23%). The perception of drug allergy history of the patients was determined, 104 (60.47%) of the patients knew the name of the drugs that cause the allergic reactions and 164 (95.35%) of the patients knew their allergic status. In term of patients' behavior after pharmacist counseling, four issues were reviewed. Firstly, drug allergy card carry by the patients were found 102 (59.3%) patients kept with themselves at all times, 14 (8.14%) patients occasionally carried them, 40 (23.26%) patients never carried them, and the other 8 (9.3%) patients had lost the drug allergy cards.

Secondly, the notifying of drug allergy history to health care providers was reported: always inform 102 (59.3%), occasionally inform 40 (23.26%), and never inform 30 (17.44%). Those reasons with non- inform drug allergy history were declared. Most patients thought that it was already recognized by the staffs 24 (33.33%) and no question were asked for their allergy 20 (27.78%). Thirdly, history of taking unknown drug were asked, 142 (82.56%) never did while the others did. Lastly was the behavioral of the patients in asking the name, indication, and administration of the given drugs. Sixty (34.88%) patients always did, fifty two (30.24%) patient occasionally did, and the rest of them never ask. The recurrent drug allergy was found in 7 (4.07%) patients. This study suggested that encouraging patients on drug allergy card carrying would directly emphasize patients to keep drug allergy card in hands and stimulating them to remember the drug name. In advance, these would improve patients' behavior when they seek for other health care facilities.

Nevertheless, single method might not be sufficient to resolve drug allergy issue. Applying various strategies in the prevention of repeated drug allergy with other healthcare provider cooperation was found to be usefulness. Choppradit (2004) conducted a 3-year period prospective descriptive study to reduce and prevent the re-occurrence of drug allergies in Samutsakhon Province. The strategies which were used in this study, involved with multidisciplinary cooperators such as hospitals, Samutsakhon Provincial Public Health, Pharmacies, health stations, school, and patients themselves. The ADRs reports were reviewed. Only reports with repeated drug allergy were selected and undergone root cause analysis. Strategies were assigned to three areas. Healthcare staffs were forced to ask patients about their history of drug allergy. Those with drug allergy history were recorded on OPD cards cover with "Drug allergy" stickers. Also the history was recorded in the computerized system to provide drug allergy information on their prescriptions in the future. Another participant included provincial health public, drug stores, health stations, and school. The meeting was arranged to inform and train those participants in the prevention of drug allergy. Lastly, variety medias were given to improve the knowledge in drug allergy of the patient e.g. brochures, and handbills. The drug allergy exhibition was set up for further education. Throughout the study period, the re-occurrence drug allergy was decreased from the fiscal year 2001 to 2003: 74

reports, 51 reports, and 42 reports respectively which related to the deceasing in direct medical costs to treat those reactions: 63,909 Baht, 13,465 Baht, and 12,690 Baht. The source of re-occurrence drug allergy also decreased in hospital setting (49, 31, 19 reports) whereas the result quite stable in outside hospital setting (25, 20, 19 reports). The most reported drugs were NSAIDs (27%), Penicillin group (21%), and Sulfa group (19%). The most allergic reactions were rash 23 (38%) reports, oedema periorbital 26 (16%) reports, anaphylaxis 21 (12%) reports, fixed eruption 15 (9%) reports, and other reactions 67 (40%). Causes of re-occurrence drug allergy were described in three domains; patients lacked in drug allergy knowledge and understanding and unawareness of repeated drug allergy hazard (47.0%), cross-drug allergy reaction/ combination drug regimen/ Ya-Chud (31.0%), and healthcare and system error (22.0%).

Later, Chaikoolvatana et al. (2006) performed a quasi- experimental, cross-sectional, pre-post study during June to November 2004 to investigate the effectiveness of the ADR Prevention Program at Rasrisalai Hospital and the attitude of the patients toward this program. The program consisted of providing basic knowledge of ADRs and management, distributing ADRs brochures, providing an ADR sticker on the patient tag, and collecting patient history data on the computer. In- and out- patients whose records showing drug allergy histories were included. The volunteers were requested to answer the questionnaires survey to assess their basic knowledge of adverse reaction three times: before, immediately after, and one month later after the ADRs prevention program implemented. A total of 65 volunteers were qualified. Comparison basic knowledge of ADRs between pre-and post-program immediately and one month later, some significant differences of mean scores were found in patient identification of the drug that cause reaction (Pre = 0.6 and Immediate = 0.9, and one month after = 0.9; P= 0.001 and P = 0.001) the prevention of recurrent adverse reaction knowledge (Pre = 0.6 and Immediate = 0.9, and one month after = 0.1; P = 0.001 and P= 0.001), and the advantage of drug allergy card (Pre = 0.3 and Immediate = 1.0, and one month after = 1.0; P = 0.001 and P = 0.001). Additionally, the mean total scores in post-test of both immediate (3.8) and one month later (3.9) were significantly higher than mean total score in pre-tests (2.4) ($p < 0.001$, $p < 0.001$ respectively). Some significant factors to immediate post-test mean

score were career, salary, and education level ($p = 0.002$). The educational levels, previous/ current medications and the severity of adverse reactions were significantly associated with the post-test mean scores obtained one month after the prevention program implementation ($p = 0.001$). Moreover, the pharmacist was positively satisfied (95%) towards the ADR prevention Program in terms of contents of the program and time spent (about 15-20 minutes). Limitations found in this study were short duration of the assessment of patient ADRs awareness and limited counseling time.

A comprehensive, continual ADRs program including repeated drug allergy prevention should consist of mechanisms for monitoring, detecting, evaluating, documentation, and reporting ADRs as well as intervening and providing educational feedback to prescribers, other health care professionals, and patients (ASHP, 1995; Pithaktim, 2000). Pharmacy profession is a part of healthcare professional team who directly contact to the patient especially medication aspect. Many strategies were established to manage the recurrence of drug allergy i.e. documentation of drug allergy on cards and retained both pharmacist and patient (Shulman et al., 1981) or in computers (Sirichai, 2004), identified wristband of drug allergy (Ismail et al., 2008), or pharmacist counseling of drug allergy to the patients and their family (Johnson et al., 2001). To ensure the patients' knowledge and understanding of drug allergy, pharmacists should exert leadership in the development, maintenance, and ongoing evaluation of such programs. Application of multiple strategies had been proved to be usefulness in the prevention of repeated drug allergy i.e. providing drug allergy card plus pharmacist counseling (Laohapojanart et al., 2007; Wongpentak, 2008), and providing educational tools such as ADRs brochure (Chaikoolvatana et al., 2006). Nevertheless, these tasks need to be cooperated with surrounding people, not only healthcare professionals and patients, but also the family members, friend, public (Choppradit, 2004).

Table 1 Strategies to prevent recurrent drug allergy

Researcher	Number	Strategies	Outcomes and results	P-value	Limitations
Shulman et al. (1981)	1,366 patients	a two-card record system of ADRs retained by pharmacy and patients	- ADRs detections: 65 potential ADRs (75.6%)	NA	None
Johnson et al. (2001)	46 patients	- a two-part, standard notification form of drug allergy - drug allergy counseling to patients and their family - a customized Medic I.D. bracelet identified the patients' drug allergies	- recurrent drug allergy: 0% - patients' knowledge and understanding of their drug allergy	NA	- pharmacists' workload
Sirichai (2004)	239,826 prescriptions	drug allergy documentation on prescriptions and computers	- Prescriptions of known previous drug allergy: 94 prescriptions (0.04%) - Recurrent drug allergy (0%)	NA	- drug dispensing overtime - incorrect patients' notification
Chaikoolvatana et al. (2006)	65 patients	- providing basic knowledge of ADRs and management - distributing ADRs brochures - providing ADRs stickers on patients' tag - collecting patients history data on the computer	- mean total scores of patients' knowledge of drug allergy and the prevention of recurrent drug allergy (Total score, 5): Pre-test (T_0); 2.4 Immediate post- test (T_1); 3.8 One-month after post-test (T_2); 3.9	P<0.001 ($T_{0,1}$) P<0.001 (T0,2)	- short duration of the assessment of patient awareness of ADRs - limited counseling time
Ismail et al. (2008)	Pre: 186 patients Post: 250 patients	- red allergy wristband for drug allergy patients - white notification wristband for all patients - completion of an "allergy box"	- The proportion of the drug allergy patients lacked of red wristbands: Pre-44.8%, Post-30.4% - The proportion of blank allergy box: Pre-24.7%, Post- 5.2%	P<0.206 P<0.001	- pharmacists were not available when patients' admitted