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Adverse Drug Reactions Associated with Dimenhydrinate, Thailand, 1993-2016

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Abstract

In 1984, the Health Product Vigilance Center of Thailand was established and has continuously collected adverse drug reaction (ADR) reports across the country. Severe drug-induced skin reactions with dimenhydrinate can result in death in some cases. All ADRs with dimenhydrinate from 1 Jan 1993 to 31 Dec 2016 were reviewed. Characteristics and system organ class ADRs from 7,282 patients were described. Most patients had no history of allergy (77%) and no underlying disease (83%) and the majority were female (75%). Skin appendage ADRs were the most commonly reported (52%) events and 1,431 reports were severe skin ADRs, including bullous fixed drug eruption (89%) and Stevens-Johnson syndrome (9%). Among patients who received dimenhydrinate and had ADRs, 63% completely recovered and 0.18% died. Multivariate regression analysis revealed that patients aged more than 65 years or having a history of allergy were more likely to have a serious ADR than those in the other groups. Dimenhydrinate must be avoided or used with vigilance when prescribed to the elderly or patients with a history of allergy due to its seriousness.

Keywords: dimenhydrinate, adverse drug reactions, severe drug-induced skin reactions

Introduction

The Thai national adverse drug reactions surveillance center (entitled Health Product Vigilance Center) was established in 1984. The center is responsible for gathering, administering and analyzing individual adverse drug reaction (ADR) case reports, which are submitted from health professionals across the country. Reporting methods are voluntary and spontaneous, involve post marketing studies and intensive monitoring programs. Data were collected in a database called the Thai Vigibase. The information derived from this database was used as baseline data for the Thai Food and Drug Administration (FDA) in regulatory decision-making processes.[1,2]

An ADR is a noxious, unintended response which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function. The seriousness of an ADR outcome was measured in four scales: mild, moderate, severe and fatal. The incidence of fatal ADRs is relatively low at around 0.32%.[3-5] Severe drug-induced skin reactions such as Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), generalized bullous fixed drug eruption (GBFDE), acute generalized exanthematous pustulosis (AGEP) and drug reaction with eosinophilia and systemic symptoms (DRESS) most result in a serious outcome, defined as a severe or fatal ADR.[6,7] SJS and TEN are rare immune-mediated cutaneous adverse reactions and are often drug-induced and mostly result in serious skin reactions.[8] The clinical manifestation of SJS is defined by fever, erosive stomatitis, ocular involvement, purpuric macules on the face and trunk with less than 10% epidermal detachment. TEN symptoms have similar features as SJS but have more than 30% epidermal detachment and high mortality has been reported.[9] Antibacterial sulfonamides, anticonvulsants, non-steroidal anti-inflammatory drugs and allopurinol are the drug or drug groups commonly implicated for serious skin reactions.[10] DRESS is atypical form of drug-induced allergic reactions and developed later, usually 2 to 8 weeks after therapy is started.[11]

Dimenhydrinate is an antihistamine that blocks H1 receptors and is used mainly to prevent motion sickness, to treat nausea and vomiting, and is also used in the treatment of vestibular disorders. The drug may be used alone or combination with other drugs.[12] Antihistamines are not supposed to cause hypersensitivity reactions because they are the keystone of allergy therapy, thus awareness of the problem would reduce its misdiagnosis.[13] Drug-induced events which have resulted in serious skin reactions with dimenhydrinate are rare and unexpected.[14]

The significant drug safety concern would lead to regulatory measures to mitigate the risk in the population. Drug risk management is the current method used to weigh the benefits and risks of treatment with regulatory measures of all drugs through their life cycle. A serious outcome from an adverse drug reaction can result in the utmost regulatory action, such as the withdrawal of a drug from the market.[15] Other actions after marketing, such as a post authorization safety study, are used to gather additional safety monitoring information for planning further risk management.[16]

We describe the adverse drug reactions associated with the use of dimenhydrinate including drug-induced serious skin reaction reports. In addition, we also explore factors associated with serious outcomes in order to identify at-risk subgroups.

Methods

The retrospective ADR case reports associated with dimenhydrinate which were sent to the Health Product Vigilance Center from 1 Jan 1993 to 31 Dec 2016 (study period) were analyzed.

Data Source

The individual ADR reports associated with dimenhydrinate during the study period were retrieved from the Thai Vigibase.

Inclusion Criteria

Reports of at least 1 dimenhydrinate-related ADR either as a suspected, concomitant or interaction with other drugs were included in this study. Adverse drug reaction minimum criteria were: name of patient, name of suspected drug (dimenhydrinate), and adverse drug reaction term(s).

Causality assessment of ADRs is a method used for estimating the strength of relationship between drug exposure and occurrence of an ADR.[17] The causality assessment tool that is widely used in Thailand is Naranjo's algorithm.[18] The causality is classified as "certain", "probable", "possible" or "unlikely". In this study, we included drug-ADR reports assessed by Naranjo's algorithm with "certain", "probable" and "possible" classifications.

Exclusion Criteria

We excluded any report in which the drug-ADR causality assessment was evaluated as "unlikely" and if there was any missing of important patient characteristic (hospital number, patient code, name, age, and gender).

Data Extraction

The date of extraction was 11 May 2017. Patient's demographic characteristics, history of allergy, co-morbidities, drug dosage, dosing regimen, ADR seriousness and outcome information were extracted from the reports.

Data Cleaning

Totally, there were 11,813 reports with complete data. After elimination of duplicate records, 11,058 reports from 7,282 patients remained (Figure 1). Imputation was not applied to the missing data.

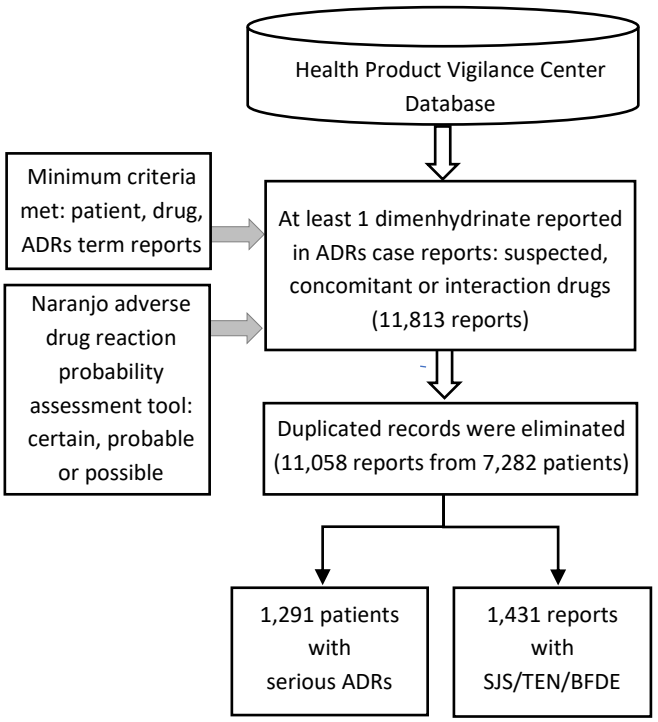

Figure 1. Concept framework diagram for data extraction

Data Analysis

Variables were presented descriptively using means with standard deviations for continuous variables and frequencies with percentages for categorical variables. The units of analyses for patients' characteristics, trend, treatment outcomes, and potential risk factors were patient, and for system organ class and severe drug induced skin reaction were report.

An analytic cross-sectional design is used to explore potential risk factors for seriousness of ADR. A serious ADR is defined as a drug reaction that caused any of the following six conditions to the patient: 1) death, 2) a life-threatening situation, 3) hospitalization, 4) persistent or significant disability/incapacity, 5) congenital anomaly/birth defect, and 6) a medically significant situation. Selection of variables for the multivariate logistic regression analysis was based on the ones which were statistically significant based on the 95% confidence interval (CI) from the univariate analysis.

Results

A total of 11,813 ADRs were reported to the Health Product Vigilance Center during the study period. During data cleaning, 755 duplicated reports were removed, resulting in 11,058 ADRs being reported from 7,282 patients. Trends in the number of patients and reports with dimenhydrinate-related ADRs are presented in Figure 2. From 1993 to 2009, the number of patients and reports with an adverse reaction involving dimenhydrinate gradually increased with a large peak occurring in 1996. From 2009 to 2016, the number of patients and reports gradually decreased.

Females dominated the reports and patients aged 18-65 years were the most common age group (75%). The mean (standard deviation) age of all patients was 48.96 (0.24) years. Most had no underlying disease (83.41%) and no history of allergy (77.01%) as seen in Table 1. Among 6,682 patients who received dimenhydrinate and experienced an ADR, 63.48% recovered, 19.58% recovered with sequelae, 16.75% had not recovered, and 0.18% died (Table 2).

Table 1. Characteristics of patients with dimenhydrinate-related ADRs (n=7,282 patients)

Characteristic	Number (%)
Gender (n=7,248)	
Female	5,411 (74.66)
Male	1,837 (25.34)
Age [years] (n=6,795)	
Mean±SD	48.96±0.24
Age <18 years (n=482)	
Female	264 (54.77)
Male	218 (45.23)
Age 18-65 years (n=4,609)	
Female	3,460 (75.07)
Male	1,149 (24.93)
Age >65 years (n=1,704)	
Female	1,355 (79.52)
Male	349 (20.48)
History of allergies (n=5,821)	
Yes	1,338 (22.99)
No	4,483 (77.01)
Underlying disease (n=6,994)	
Yes	1,160 (16.59)
No	5,834 (83.41)
Serious ADR (n=1,219)	
Age <18 years	73 (5.99)
Age 18-65 years	752 (61.69)
Age >65 years	394 (32.32)
Non-serious (n=5,018)	
Age <18 years	299 (5.96)
Age 18-65 years	3,442 (68.59)
Age >65 years	1,277 (25.45)
Causality assessment (n=7,282)	
Certain	637 (8.75)
Probable	3,959 (54.37)
Possible	2,686 (36.89)

Note: ADR=Adverse drug reaction

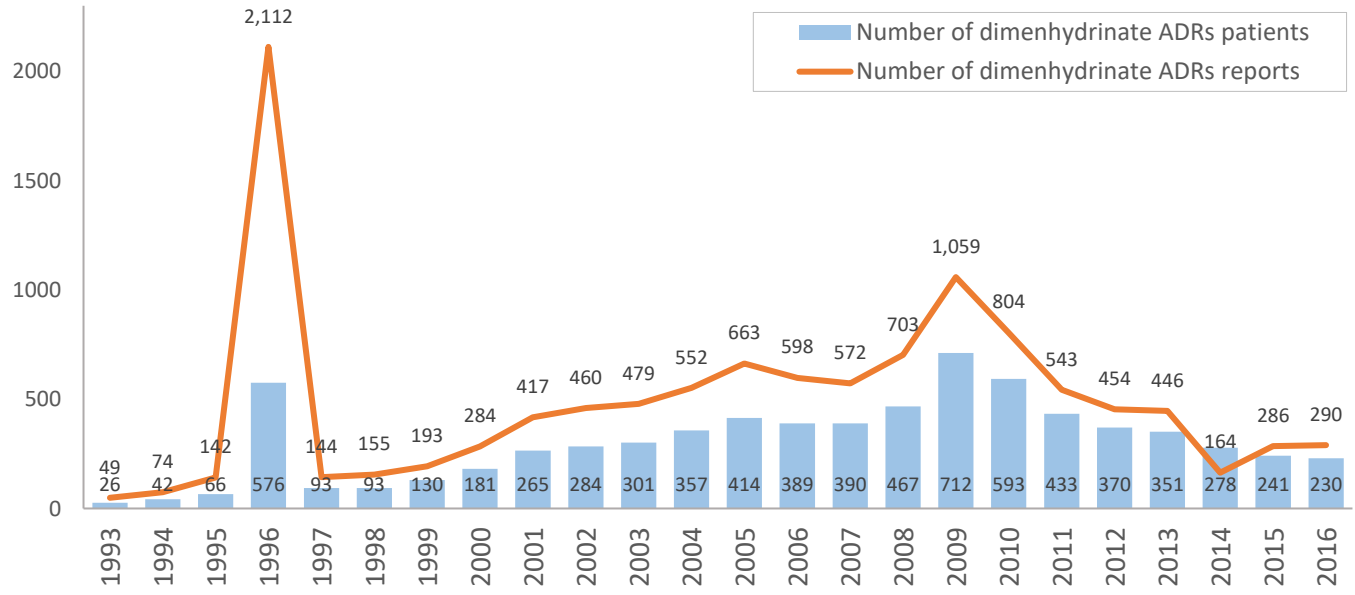

Figure 2. Yearly number of patients and reports with a dimenhydrinate-related ADR, 1993-2016

Table 2. Treatment outcomes of patients with dimenhydrinate-related ADRs (n=6,682 patients)

Outcome	Number (%)
Recovering	127 (1.90)
Recovered without sequelae	4,115 (61.58)
Recovered with sequelae	1,309 (19.58)
Not recovered	1,119 (16.75)
Died	12 (0.18)

Table 3 presents the distribution of ADRs classified by system organ class. Of the 11,059 reports, 51.74% were skin appendage disorders, followed by 23.07% autonomic, central and peripheral nervous system disorders, and 6.35% were gastro-intestinal system disorders.

Table 4 shows the gender-stratified distribution of 1,431 reports of patients who experienced severe dimenhydrinate-induced skin reactions. Bullous fixed drug eruptions were the most commonly reported severe ADR (88.61%), followed by Stevens-Johnson syndrome (9.36%) and toxic epidermal necrolysis (2.03%). The proportion of females (79.59%) with severe dimenhydrinate-induced ADRs was higher than in males (20.41%).

Overall, 1,291 patients with a dimenhydrinate-related ADR (19.33%) had a serious outcome. Table 5 presents the factors associated with serious ADR. Patients aged more than 65 years (Odds ratio (OR)=1.31, 95% CI=1.14-1.52), and with history of allergy (OR=1.41, 95% CI=1.21-1.64) were more likely to experience a serious ADR compared to those aged <65 years and without a history of allergy, respectively.

Table 3. ADRs with dimenhydrinate by system organ class (n=11,058 reports)

System organ class	Number of reports (%)
Skin appendages disorders	5,722 (51.74)
Autonomic, central and peripheral nervous system disorders	2,551 (23.07)
Gastro-intestinal system disorders	702 (6.35)
Body as a whole-general disorders	679 (6.14)
Metabolic and nutritional disorders	445 (4.02)
Respiratory system disorders	324 (2.93)
Urinary system disorders	239 (2.16)
Vision disorders, hearing and vestibular, special sense disorders	149 (1.35)
Psychiatric disorders	88 (0.80)
Musculo-skeletal system disorders	46 (0.42)
Cardiovascular disorders, general	38 (0.34)
Liver and biliary system disorders	30 (0.27)
Reproductive disorders	21 (0.19)
Collagen disorders	8 (0.07)
Blood cell, platelet, bleeding and clotting disorders	8 (0.07)
Others	6 (0.05)
Foetal disorders	2 (0.02)

Table 4. Distribution of patients with severe dimenhydrinate-induced skin reactions (n=1,431 reports)

Severe drug induced skin reactions	Male (%)	Female (%)	Total (%)
Bullous fixed drug eruption	244 (19.24)	1,024 (80.76)	1,268 (88.61)
Stevens-Johnson syndrome	43 (32.09)	91 (67.91)	134 (9.36)
Toxic epidermal necrolysis	5 (17.24)	24 (82.76)	29 (2.03)
Acute generalized exanthematous pustulosis	0	0	0
Total	**292 (20.41)**	**1,139 (79.59)**	**1,431 (100)**

Table 5. Characteristics of patients comparing serious adverse reactions and non-serious reaction related to dimenhydrinate use (n=6,678 patients)

Characteristic	Serious ADR N (%)	Non-serious ADR N (%)	Crude OR (95% CI)	Adjusted OR* (95% CI)
Number of Patients	1,291 (19.33)	5,387 (80.67)		
Sex (n=6,644)	n=1,291	n=5,353		
Male	296 (22.93)	1,197 (22.36)	1.03 (0.89-1.19)	-
Female	995 (77.07)	4,156 (77.64)		
Age (n=6,237)	n=1,219	n=5,018		
Age >65 years	394 (32.32)	1,277 (25.45)	1.39 (1.22-1.61)	1.31 (1.14-1.52)
Age <18-65 years	825 (67.68)	3,741 (74.55)		
History of allergy (n=5,708)	n=1,209	n=4,499		
Yes	342 (28.29)	966 (21.47)	1.44 (1.24-1.67)	1.41 (1.21-1.64)
No	867 (71.71)	3,533 (78.53)		
Underlying disease (n=6,407)	n=1,250	n=5,157		
Yes	251 (20.08)	886 (17.18)	1.21 (1.03-1.42)	1.04 (0.88-1.23)
No	999 (79.92)	4,271 (82.82)		

*Note: *Number of observations included in the multivariate analysis was 5,246.*

Discussion

A study in the United States, concerning post-marketing surveillance of ADRs, found that a spontaneous reporting system could not detect ADRs that occurred from newly marketed drugs. In addition, there was a considerable amount of under-reporting. A spontaneous reporting system needs other ways to collect data concerning exposed and unexposed populations in order to evaluate the incidence of ADRs among patients.[19] Despite its limitations, a spontaneous reporting system is the most effective surveillance system for drugs. It allows rapid detection of potential alarm signals related to drug use. Improvements to the system through linking with the population's database will generate important recommendations related to ADRs such as updating of the product's safety profile or possibly other regulatory actions, including risk communication and other relevant risk minimization measures.

The Adverse Event Reporting System of the US Food and Drug Administration (US FDA) is the world's largest database of voluntary, spontaneous reports of adverse drug reactions. The US FDA established the MEDWATCH program for healthcare professionals to report adverse reactions related to drugs or other products regulated by the FDA. The MEDWATCH program is FDA's post-marketing drugs safety surveillance system, named after the FDA's promotional program to provide safety information to health professionals and encourage reporting of adverse events for drugs and other medical products.[20] The Food and Drug Administration Adverse Event Reporting System (FAERS) database is a database that contains adverse event reports submitted to the US FDA. The database is designed to support the post-marketing drugs safety surveillance program. In Thailand, the monitoring of adverse drug reactions after drug approval is also a voluntary, spontaneous reporting system. Thai Vigibase is the ADR database which gathers all ADR reports submitted from health professionals. The reports are evaluated for potential safety concerns for Thai patients. Unfortunately, both the FAERS database and the Thai Vigibase contain secondary data, therefore there are many missing values.

A study from the United Kingdom (UK) analyzed data collected by the Department of Health from all hospitals during 1998-2005.[21] Although the data was derived from patients admitted in UK hospitals and experienced an ADR within the previous 7 years, the number of ADRs increased by 45%. A French study of 197,580 ADR reports over a 16-year period found a similar increasing trend.[22] All ADR reports came from 31 regional pharmacovigilance centers around the country and were reported by health professionals.

In a study from Thailand, during 2000-2016, the total number of patients with ADRs was 671,774 and they mostly came from hospitals under the Ministry of Health (including outpatients and inpatients).[23] The trend was increasing over time until 2010 and then gradually decreased. Similarly, patients with dimenhydrinate-related ADRs followed the same trend of the total number of ADRs (Figure 3).

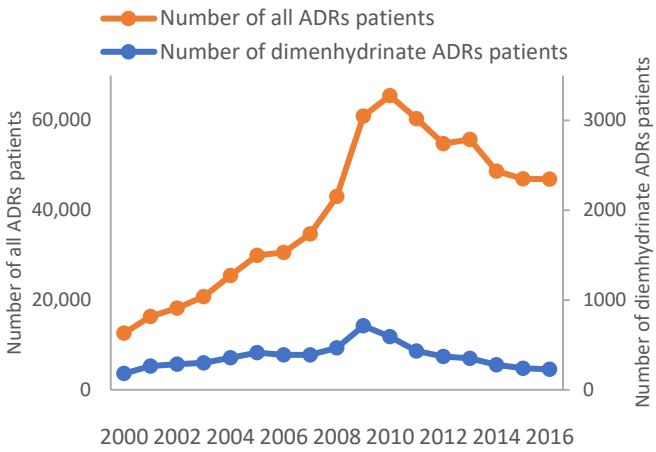

Figure 3. Annual number of patients with a dimenhydrinate-related ADR (blue line) and any ADR (orange line), 2000-2016

A higher number of dimenhydrinate-related ADR reports in 1996 was possibly due to the expanding scope of drug surveillance to other health products under the responsibility of the Thai FDA which included surveillance activities in the National Health Development Plan. In 2009, the Health Product Vigilance Center motivated spontaneous reporting by developing two research projects: Evaluation of the Thai Algorithm Usage for Adverse Drug Reaction Monitoring Project and Signal Detection for Thai Traditional Medicine Project. Those projects may also have enhanced the overall number of other drug-related ADRs in the Thai Vigibase besides dimenhydrinate.[23]

Although the Thai Vigibase has collected many ADR reports, without continuous encouragement, the number of reports would probably decline. In a six-week survey of reporting ADRs in UK hospitals, reporting rates increased after prescribers who reported ADRs received reimbursement and rates declined significantly after reimbursements were stopped.[24]

Adverse drug reactions involving skin appendages were mostly reported among all other system organ classes associated with dimenhydrinate, followed by autonomic central nervous system, which were consistent with previous studies. Moore et al aimed to assess the frequency and cost of drug reactions causing

or prolonging hospitalization in a six-month prospective study. He found that allergic skin reactions were the most ADRs reported and was associated with longer stay in hospital. Orthostatic hypotension (autonomic central nervous system organ class) from using antihypertensive drugs or neuroleptic antidepressants was the second-most common reaction in elderly patients staying in hospital, often due to falls, and resulting in a hip fracture with a fatal outcome.[25]

In this study, among patients who experienced severe drug induced skin reactions with dimenhydrinate, the majority were bullous fixed drug eruption followed by SJS and females predominated. A retrospective analysis evaluated patients with fixed drug eruption in a referral center in Taiwan for period of 11 years and showed no significant difference in the proportion of males and females but a trend in male predominance was noted.[26] Another study found that patients with SJS/TEN had a slight tendency to be female but the association did not reach statistical significance because of the small sample size.[27] Unlike in our study, which included data from a secondary database, most of these studies used retrospective data collected from a single institution.

SJS and TEN are rare, drug-induced skin reactions. There are limited data on the mechanism of action for dimenhydrinate and SJS.[28] H1-antihistamines are probably the most frequently used drugs in allergies, with widely established efficacy, tolerance and safety. However, there is limited information on dimenhydrinate-induced skin reactions with serious outcomes.[28,29]

Our findings indicated that those aged more than 65 years were 31% more likely to have serious adverse reactions after dimenhydrinate use. Another study exploring the incidence and predictors of all and preventable ADRs among frail elderly persons admitted to US hospitals indicated that older age was one of the potential risk factors. Other associated risk factors were multiple medications, severe renal insufficiency, and a prior ADR.[30]

In a prospective multicenter study based on intensive pharmacovigilance in Germany, increasing age correlated with increasing number of ADRs. In patients aged 65-75 years the ADR odds ratio was 2.32 (95% CI=1.54-3.48) which was consistent with our study.[31]

Another significant risk factor of serious ADR from dimenhydrinate in our study was history of allergy. A review of articles published between 1966 and 2010 describing the current evidence-based knowledge of the epidemiology, prevalence, incidence, risk factors and genetic associations of drug allergy found that the true incidence of drug allergy is unknown. The majority of currently available epidemiologic studies have been on ADRs rather than drug allergy specifically. Drug allergies are frequently encountered in patients with HIV infection, particularly to drugs such as cotrimoxazole, abacavir and nevirapine. It is likely that a complex interaction between the host underlying immune status and genetic factors predisposes patients to these allergic drug reactions.[32]

In a prospective cohort study in hospital settings, multiple medication use was identified as a significant ADR risk factor, especially in the elderly. Independent risk factors for all ADRs were number of medications (adjusted hazard ratio=1.07; 95% CI=1.05-1.10 per medication).[30] Unfortunately, data of multiple medications were not available in our study.

Conclusions and recommendations

A higher proportion of adverse reactions associated with dimenhydrinate was found in females. Among the system organ classes, skin appendage disorders were the most commonly reported ADR and one-fifth of patients had severe skin ADRs, including bullous fixed drug eruption and Stevens-Johnson syndrome. Serious or life-threatening outcomes were more likely to occur in older patients and those with a history of allergies. As dimenhydrinate is widely used and may be prescribed with other drugs, it must be used with vigilance when prescribed to the elderly or patients with a history of allergy. Due to the nature of the Thai national adverse drug reactions surveillance system, which is spontaneous, the number of dimenhydrinate-related ADRs are likely to be under-reported. This surveillance system should be periodically evaluated in a systematic way.

Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research and/or publication of this article.

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