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ORIGINAL RESEARCH

Intensive Adverse Drug Reaction Monitoring Program Improves Detection of Phenytoin-Induced Adverse Drug Reactions

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Video abstract

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Purpose: To compare the outcomes of routine versus intensive adverse drug reaction (ADR) monitoring programs among adult in-patients initially treated with phenytoin, and to identify risk factors associated with severe cutaneous adverse reactions (SCARs).

Patients and Methods: This retrospective cohort study recruited phenytoin-naïve patients treated at a general hospital in Northern Thailand. Potentially eligible admissions were identified through the electronic medical record by extracting all medication orders for phenytoin during October 2018 to May 2021. Patients were consecutively enrolled and divided into routine adverse drug reaction monitoring (n = 500, rADRM) and intensive adverse drug reaction monitoring (n = 500, iADRM) allocated based on ward-based monitoring models. All participants received standard counseling regarding phenytoin dosing and administration. The rADRM group underwent ADR monitoring during routine follow-up visits, while the iADRM group received additional individualized instruction on ADR recognition and access to a direct pharmacist contact for reporting suspected ADRs. Multivariable logistic regression was performed to identify independent risk factors for SCARs.

Results: Patients in the intensive adverse drug reaction monitoring group had a significantly higher detection rate of phenytoin-induced ADRs compared with those in the routine adverse drug reaction monitoring group (OR 2.301, 95% CI 1.091:4.853, p = 0.029), as well as a greater patient-initiated reporting (OR 4.527, 95% CI 2.274:9.010, p < 0.001). Type B ADRs occurred in 3.6% of patients, with the iADRM group documenting more SCARs (36.84% vs. 5.88%, p = 0.044). Discontinuation of phenytoin and prolonged hospitalization were observed in both groups (42.1 vs. 52.9%, p = 0.045). Multivariable logistic regression identified iADRM (OR 13.304, 95% CI 1.183–149.581, p = 0.036), comorbidities (OR 12.935, 95%CI 1.514:110.48, p =0.019), omeprazole use (OR 57.112, 95%CI 9.569:340.875, p <0.001), and increased age (OR 0.940, 95%CI 0.893:0.989, p =0.023) as significant risk factors associated with SCARs.

Conclusion: Intensive ADR monitoring facilitates earlier detection and reporting of phenytoin-associated ADRs including SCARs. Comorbidities, concomitant omeprazole use, and older age were associated with SCARs. Intensive monitoring programs may enhance patient engagement and improve medication safety by enabling timely recognition and management of adverse reactions.

Keywords: phenytoin, intensive adverse drug reaction monitoring, severe cutaneous adverse reactions, pharmacists, patient involvement

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Introduction

Severe cutaneous adverse drug reactions (SCARs) are a serious concern in modern medicine, posing a significant threat to patient safety and well-being. These reactions are characterized by extensive skin involvement, often accompanied by mucosal and internal organ manifestations. The morbidity and mortality associated with SCARs are alarming, with reported mortality rates ranging from 1–5% for Stevens-Johnson syndrome (SJS) to 25–30% for toxic epidermal necrolysis (TEN).[1] Common medications implicated in SCARs include anticonvulsants, antibiotics, and allopurinol.[2,3] Early recognition and prompt intervention by healthcare professionals are crucial for minimizing tissue damage and improving patient outcomes.[2]

Phenytoin is particularly known for its potential to induce a spectrum of ADRs, ranging from commonly encountered side effects like dizziness and gum hyperplasia to the more severe and potentially life-threatening cutaneous reactions.[4,5] A report from VigiBase® revealed that, among cases from Asian countries, phenytoin was the second most frequently implicated agent in SCARs, accounting for 29.45% of the cases analyzed.[4] Recent advances in pharmacogenomics have identified specific human leukocyte antigen (HLA) alleles that are strongly associated with an increased risk of developing SJS/TEN with phenytoin.[6] Pre-emptive genetic screening for these at-risk HLA alleles before initiating phenytoin therapy can significantly reduce the incidence of SJS/TEN.[7] However, because genetic testing remains costly and not widely accessible in many settings, additional approaches to mitigate phenytoin-related ADRs are still needed. Importantly, several non-genetic risk factors have also been reported, including Chinese ancestor among Thai patients,[8] concomitant use of other antiseizure medications - particularly aromatic agents such as carbamazepine and lamotrigine,[4] and comorbid conditions such as HIV infection or autoimmune diseases.[9] These patient- and treatment-related factors may help identify individuals at higher risk of SCARs and support the development of practical monitoring and prevention strategies where pharmacogenetic testing is not routinely available.

While genetic screening is a key strategy in the prevention of severe cutaneous adverse reactions (SCARs), pharmacists also play a pivotal role in minimizing patient risk. Through careful medication review and patient counseling, pharmacists can help reduce the use of multiple anticonvulsants, particularly those with overlapping risk profiles for SCARs, thereby contributing significantly to safer anticonvulsant therapy.[10,11] Gradual dose initiation of phenytoin, following recommended guidelines, is essential to minimize the risk. Additionally, therapeutic drug monitoring (TDM) can help ensure adequate seizure control while avoiding excessive drug levels.[12] In some cases, alternative medications might be preferred in certain patients who have potential risk factors to SCARs.[13] Beyond individual patient management, hospital pharmacists are central to the detection, monitoring, reporting, and prevention of ADRs. Evidence from pharmacovigilance programs shows that approximately 60% of ADRs are preventable, underscoring the importance of pharmacists' expertise in pharmacotherapy and clinical monitoring.[14,15] Active or Intensive ADR monitoring systems led by hospital pharmacists have been implemented in several countries to enhance detection beyond traditional spontaneous reporting models. Studies from Korea, Iran, and Peru have demonstrated that pharmacist-led active surveillance significantly increases ADR identification and reporting rates compared with passive systems.[16–18] Such structured pharmacovigilance programs have been associated with improved early detection of serious adverse reactions and enhanced patient safety in hospital settings. These international experiences support the importance of structured ADR monitoring systems and provide a broader context for evaluating intensive monitoring models in resource-limited settings. In addition, based on real-world practice reports submitted to the FDA Adverse Event Reporting System database, over 77,789 cases were identified as SCARs. Of these, 78% were reported by healthcare professionals including pharmacists, while 12% originated from consumers.[3] Pharmacist-driven interventions can help reduce recurrence and guide safer prescribing practices.

A retrospective study conducted from 2007 to 2015 identified 47 cases of SCARs among patients admitted to Phrae Hospital, consisting of 39 SJS cases, 6 TEN cases, and 1 Drug reaction with eosinophilia and systemic symptoms (DRESS) case.[19] During this period, the reporting of ADRs still relied on a spontaneous reporting system, which may underestimate the true incidence of ADRs.[20] Between 2015 and 2018, five cases of SCARs associated with phenytoin were reported at the hospital, and all resulted in prolonged hospitalizations. In response, a close monitoring system was implemented in fiscal year 2019, which in Thailand began on October 1, 2018. This monitoring program aims to improve medication safety and encourages active patient participation. By reducing the incidence of severe medication-related complications and improving

patient outcomes, this initiative contributes to the reduction of premature mortality from non-communicable diseases, as promoted in Sustainable Development Goal 3.4. Therefore, this study aimed to compare the outcomes of a pharmacist-managed phenytoin monitoring system in two different follow-up strategies, close monitoring (Intensive ADR monitoring program: iADRM) and routine monitoring (spontaneous ADR monitoring program: rADRM), in new patients starting phenytoin therapy and to identify factors associated with the development of SCARs.

Methods

Study Design and Samples

This retrospective cohort study was conducted at Phrae hospital, a tertiary hospital which is located at the northern Thailand. We collected data of inpatients who were prescribed phenytoin for any indication between October 1, 2018, and May 31, 2021. Inclusion criteria were: (1) patients aged 18 years or older, and (2) those receiving phenytoin for the first time or within the first six months of ongoing therapy. Exclusion criteria were: (1) patients who discontinued and then resumed phenytoin during the study period, (2) cases with insufficient medical records for follow-up, and (3) Patients who died within six months from causes determined to be unrelated to phenytoin exposure or suspected adverse drug reactions, including deaths due to progression of underlying disease or other acute medical events, based on medical record review, were excluded from analysis.

Sampling and Sample Size

Eligible patients were identified from the hospital electronic medical record system (HosXp version 4) using prescription data for newly initiated phenytoin between October 1, 2018 and May 31, 2021. Consecutive eligible patients were selected using a computer-generated random number sequence, and group allocation was determined by ward-based pharmaceutical care practice rather than randomization. The internal medicine ward was selected for routine ADR monitoring (rADRM) assessment because it has a routine clinical pharmacy team and medication workflow, facilitating consistent prospective identification and assessment of rADRM events. In contrast, intensive ADR monitoring (iADRM) assessment was conducted across other inpatient units because expanding iADRM assessment across multiple units improved generalizability of inpatient ADRM burden.

The sample size was calculated based on a previous study, which reported ADR prevalences of 0.21 and 0.32 in the presence or absence of pharmacists, respectively.[21] Using a two-sided test with a significance level of 0.05 and 90% power, each group required 463 participants. To account for potential attrition, the sample size was increased by 10%, resulting in a minimum of 500 participants per group.

Procedures

Group 1 was patients admitted to the internal medicine ward who underwent routine phenytoin adverse drug reaction monitoring program (rADRM) by the clinical pharmacist in the ward who provided 5–10 minutes counseling on phenytoin indications and administration, with ADR monitoring conducted during scheduled visits. This process refers to spontaneous ADR monitoring. Group 2 comprised patients admitted to inpatient units other than the internal medicine ward —including the neurology, surgery, orthopedic, and intensive care units— who participated in an intensive adverse drug reaction monitoring program (iADRM), in which S.D., the research pharmacist, delivered more intensive pharmaceutical care to the rADRM group, requiring approximately 20–30 minutes per patient. In addition to routine counseling, patients in the iADRM group received further counseling on the importance of adherence, potential side effects, early signs of SCARs, and the process for direct patient reporting, either by telephone call to the pharmacist or by hospital visit. They were also provided with medication alert cards. During the first three months of therapy, follow-up reminders were scheduled so that S.D. could monitor ADRs by interviewing patients about any occurrences during their scheduled follow-up visits with the physician.

Data Collection Procedures

Data collection was conducted utilizing a standardized form to collect patients' data and outcomes of the ADRM. Patient demographics included age, gender, history of drug allergy, comorbidities, phenytoin indications and dosage regimen, concomitant medications, potential drug-drug interactions—specifically those affecting phenytoin metabolism, omeprazole co-administration, and specific dosing regimens. The ADRM outcomes were pre-specified and comprised three components: (1) identification and monitoring of phenytoin-related events, (2) assessment of confirmed phenytoin-related ADRs, and (3) intervention for phenytoin-related ADRs. Identification and monitoring outcomes included: (i) the number of patients with phenytoin-related DRPs; (ii) the number of patients with confirmed phenytoin-induced ADR events; and (iii) the number of patients who initiated telephone calls for suspected ADRs after discharge. Among patients with confirmed phenytoin-related ADRs, assessment outcomes included: ADR phenotype (SCAR vs non-SCAR), ADR seriousness (serious vs non-serious ADR), time from phenytoin initiation to ADR onset, and ADR probability score. Intervention outcomes were defined as the clinical management provided to patients with confirmed phenytoin-related ADRs and were summarized as the number of patients receiving each ADR treatment option and ADR-related pharmacotherapy.

Eligible patient data were extracted from the hospital's electronic medical record system via HosXp version 4, as well as from the pharmacy department's electronic database. These platforms provided comprehensive records of individuals prescribed phenytoin and those for whom phenytoin-related ADRs had been reported to the Health Product Vigilance Center within fiscal years 2019 to 2020. Supplementary information was obtained from medical records of patients with confirmed phenytoin-induced ADRs during the initial six months of phenytoin therapy. For all patients experiencing ADRs, causality was systematically assessed using Naranjo's algorithm. In cases of SCARs, further evaluation was performed utilizing specialized instruments, including the Algorithm of Drug Causality for Epidermal Necrolysis (ALDEN), the Score of Toxic Epidermal Necrosis (SCORTEN), and the EuroSCAR algorithm, thereby ensuring rigorous and objective determination of causal relationships. Potential drug-drug interactions were identified and classified according to the Drug Interaction Facts 2015, which organizes interactions into five levels: significant rating 1 (severity: major; documentation: suspected), rating 2 (severity: moderate; documentation: suspected), rating 3 (severity: minor; documentation: suspected), rating 4 (severity: major or moderate; documentation: possible), and rating 5 (severity: any; documentation: unlikely).[22]

Statistical Analysis

Statistical analyses were conducted using STATA version 16. Descriptive statistics summarized patient characteristics and outcomes. All outcomes were summarized as event counts and/or proportions, as appropriate. Comparisons between groups (iADRM vs. rADRM; SCARs vs. non-SCARs) utilized Student's *t*-test or Wilcoxon rank-sum test for continuous data and Chi-square or Fisher's Exact test for categorical data, with a significance threshold of $\alpha = 0.05$. Multivariable logistic regression was conducted to evaluate the impact of ADRM on clinical outcomes which included (1) occurrence of phenytoin-related drug-related problems (DRPs), (2) confirmed phenytoin-induced ADRs, and (3) patient-initiated telephone calls of suspected ADRs after discharge. Each outcome was treated as a binary variable for regression analysis. The primary clinical outcomes, The analysis adjusted for sex, age, presence of comorbidities, concomitant medication use, drug allergy history, co-administration of interacting drugs, and omeprazole dosage. Covariates were selected a priori based on clinical relevance. Additional candidate variables with evidence of association in univariable analyses ($p < 0.20$) were carried forward into the multivariable model to reduce residual confounding and to avoid excluding potentially important predictors.[23] Additionally, multivariable logistic regression was used to identify factors associated with the occurrence of SCARs, controlling the type of ADR monitoring program (routine vs intensive), age, comorbidities, number of concomitant medications, and use of omeprazole at a dose of 20 mg/day.

Ethical Considerations and Informed Consent

The study was approved by the Ethical Committee of Phrae Hospital (reg no. 37/2564). The requirement for patient consent was waived as the research relied solely on anonymized patient medical records and did not include any direct contact with participants.

Results

Overall, 1000 patients were included in the study. Males comprised 62.6% of the rADRM group and 73.0% of the iADRM group, with mean ages of 57.5 (17.4) and 52.7 (17.3) years, respectively. Both groups received an average daily phenytoin dose of 300 mg. Phenytoin was predominantly used for non-epileptic indications in the rADRM group (59.8%), but mainly for epilepsy in the iADRM group (93.0%). Prior drug allergy and comorbidities were more frequent in the rADRM group. A higher proportion of iADRM patients received phenytoin inhibitors and omeprazole. Level 4 drug interactions were notably higher in the iADRM group, while level 2 interactions were more prevalent in rADRM (Table 1).

Significantly fewer phenytoin-related drug problems were observed in the iADRM group compared to the rADRM group (24.6% vs. 32.8%, $p < 0.005$). The most common problem was inappropriate combination of drugs (22.3%), occurring more frequently in the rADRM group than the iADRM group (27.6% vs 17.0%). This was followed by inappropriate drug selection according to guidelines (44/312, 4.4%) and possible adverse drug event (36/312, 3.6%). In both groups, most cases of initial rash following drug initiation were detected by patients or their relatives (57.9% vs. 47.1%, $p = 0.605$). After discharge, the rate of phone calls reporting ADR was higher in the iADRM than the rADRM group (8.6% vs. 2.4%) ($p < 0.001$). Type B ADRs occurred in 3.4% of rADRM and 3.8% of iADRM patients ($p = 0.865$). SCARs were significantly less frequent in rADRM than in iADRM (0.2% vs. 1.4%, $p = 0.044$). Most ADRs were non-serious, especially in rADRM (88.2% vs. 42.1%, $p = 0.020$). Causality assessments indicated that the majority of ADRs in the rADRM group were deemed probable (70.6%), whereas most in the iADRM group were categorized as possible (52.6%). The median time to pharmacist detection of ADRs was 10 days (IQR: 4–38) for the rADRM group and 14 days (IQR: 10–30) for the iADRM group (Tables 2 and 3).

Table 1 Demographic and Clinical Characteristics

Characteristics	No. of Patients (%)		
	rADRM (n=500)	iADRM (n=500)	Total (n=1000)
Male	313 (62.6)	365 (73.0)	678 (67.8)
Age, years			
Mean (S.D.)	57.5 (17.4)	52.7 (17.3)	55.08 (17.5)
Median (IQR)	59 (45.5–70)	54 (41–64)	57 (43–67)
Indication of Phenytoin			
Epilepsy	201 (40.2)	465 (93.0)	666 (66.6)
Others	299 (59.8)	35 (7.0)	334 (33.4)
History of Adverse Drug Reaction	41 (8.2)	9 (1.8)	50 (5.0)
History of drug allergy	29 (5.8)	6 (1.2)	35 (3.5)
Presence of comorbidities	356 (71.2)	233 (46.6)	589 (58.9)
Hypertension	130 (26.0)	140 (28.0)	270 (27.0)
Diabetes	22 (4.4)	5 (1.0)	27 (2.7)
Alcohol Withdrawal Syndrome	17 (3.4)	4 (0.8)	21 (2.1)
Systematic Lupus Erythematosus	8 (1.6)	0 (0.0)	8 (0.8)
Infections	20 (4.0)	2 (0.4)	22 (2.2)
Number of co-administered drugs [median,(IQR)]	5 (5–8)	4 (3–6)	4 (3–7)
Co-administration of phenytoin-interacting medications[a]	310 (44.9)	380 (55.1)	690 (69.0)
Significant rating 2	106 (21.2)	60 (12.0)	166 (16.6)
Significant rating 4	166 (33.2)	319 (63.8)	485 (48.5)
Significant rating 5	38 (7.6)	1 (0.20)	39 (3.9)
Co-administration of Omeprazole	213 (42.6)	356 (71.2)	569 (56.9)
Omeprazole 20 mg/day	69 (13.8)	38 (7.6)	1.7 (10.7)
Omeprazole 40 mg/day	144 (28.8)	318 (63.6)	462 (46.2)

Notes: [a]Potential drug-drug interactions were organizes interactions into five levels: significant rating 1 (severity: major; documentation: suspected), rating 2 (severity: moderate; documentation: suspected), rating 3 (severity: minor; documentation: suspected), rating 4 (severity: major or moderate; documentation: possible), and rating 5 (severity: any; documentation: unlikely).

Abbreviations: iADRM, intensive adverse drug reaction monitoring; rADRM, routine adverse drug reaction monitoring; S.D., Standard Deviation; IQR, Interquartile Range.

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Table 2 Comparison of Outcomes Between the rADRM and iADRM Groups in Phenytoin-Related ADR Management

Outcomes	No. of Patients (%)			p-value
	Total (n=1000)	rADRM (n=500)	iADRM (n=500)	
Identification and Monitoring of phenytoin-related events				
Patients with phenytoin-related problems	287 (28.7)	164 (32.8)	123 (24.6)	0.005[a]
The first- adverse event notifiers during hospital admission				
Patient/relatives	19 (1.9)	8 (47.1)	11 (57.9)	0.605[a]
Nurse	14 (1.4)	8 (47.1)	6 (31.6)	
Pharmacist	3 (0.3)	1 (5.9)	2 (10.5)	
Patient with confirmed Phenytoin-induced ADRs	36/77 (46.7)	17/18 (94.4)	19/59 (32.2)	<0.001[a]
Patient initiated telephone calls for suspected ADRs after discharge	55 (5.5)	12 (2.4)	43 (8.6)	<0.001[a]
Assessment of confirmed phenytoin-related ADRs				
Type B ADRs	36 (3.6)	17 (3.4)	19 (3.8)	0.865[a]
Non-SCARs[c]	28 (77.8)	16 (94.12)	12 (63.16)	0.044[a]
SCARs	8 (22.2)	1 (5.88)	7 (36.84)	
Seriousness of ADRs				0.020[a]
Non-serious	23 (63.9)	15 (88.2)	8 (42.1)	
Caused Hospitalization	7 (19.4)	1 (5.9)	6 (31.6)	
Prolonged Hospitalization	6 (16.7)	1 (5.9)	5 (26.2)	
Onset of ADRs (days) [median (IQR)]	12 (4–25.5)	7 (3–16)	13 (9–28)	0.222[b]
Median day of pharmacist identified ADR (IQR)	13.5 (6–30)	10 (4–38)	14 (10–30)	0.680[b]
Median day of ADR symptoms (IQR)	4.5 (3–10)	4 (3–5)	5 (3–12)	0.358[b]
Median day of hospitalization (IQR)	9 (3.5–13.5)	9 (5–12)	9 (2–20)	0.786[b]
ADR Probability Scale by the Naranjo's algorithm				
Possible (total score 1–4)	15 (41.7)	5 (29.4)	10 (52.6)	0.192[a]
Probable (total score 5–8)	21 (58.3)	12 (70.6)	9 (47.4)	
Naranjo's algorithm Probability Score [median (IQR)]	7 (5–8)	7 (5–8)	7 (6–8)	0.7553[b]
Intervention for phenytoin-related ADRs				
Treatment Options				0.045 [a]
Discontinued phenytoin and symptomatic treatment	8 (22.2)	4 (23.5)	4 (21.0)	
Discontinued phenytoin and admitted to hospital	6 (16.7)	0 (0.0)	6 (31.6)	
Discontinued phenytoin and initiated a new antiepileptic drugs	5 (13.9)	4 (23.5)	1 (5.3)	
Discontinue phenytoin and prolonged hospital admission for supportive treatment	17 (47.2)	9 (52.9)	8 (42.1)	
Pharmacotherapy in ADR patients	32 (88.9)	13 (74.5)	19 (100.0)	0.024[a]
Antihistamines	17 (47.2)	9 (52.9)	8 (42.1)	
Antihistamines and Corticosteroids	15 (41.7)	4 (25.5)	11 (57.9)	
Complete recovery without residual scars	30 (83.3)	16 (94.1)	14 (73.7)	0.182[a]

Notes: [a]Fisher's exact test; [b]Wilcoxon Rank-sum test; [c] maculopapular rash, urticaria, exfoliative dermatitis, erythema multiforme.
Abbreviations: iADRM, intensive adverse drug reaction monitoring; rADRM, routine adverse drug reaction monitoring; Severe cutaneous drug reactions; Non-SCARs, Non-severe cutaneous drug reactions; IQR, Interquartile Range.

Most cutaneous reactions were maculopapular rashes (24 cases; 66.7%) and Stevens-Johnson syndrome (6 cases; 16.7%) (Table 3). Notably, mucosal involvement (7 cases, 36.8%) and internal organ involvement (3 cases, 15.8%) were observed exclusively in the iADRM group. Both groups discontinued phenytoin and experienced prolonged hospitalization following the incidence of ADRs (52.9% in rADRM groupand 42.1% in iADRM group). Among patients in the iADRM group who experienced ADRs, 57.9% discontinued phenytoin and received antihistamines and corticosteroids as treatment for the ADRs. (Table 2).

After adjusting for confounding variables, multivariable analysis revealed that patients in the iADRM group were more than twice as likely to have phenytoin-induced adverse drug reactions (ADRs) detected compared to those in the rADRM group (OR 2.301; 95% CI 1.091:4.853; p = 0.029). Furthermore, the likelihood of initiating telephone consultations regarding suspected ADRs was 4.5 times higher in the iADRM group (OR 4.527; 95% CI 2.274:9.010; $p < 0.001$) (Table 4).

Table 3 Diagnosis of Drug-Related Problems and Cutaneous Adverse Reactions Associated with Phenytoin Use

Diagnosis	Number of Patients (%)		
	rADRM	iADRM	Total
Phenytoin-related problems[a]	**n=171**	**n=141**	**n=312[b]**
Untreated symptoms or indication	1 (0.2)	1 (0.2)	2 (0.2)
Adverse drug event possibly occurring	17 (3.4)	19 (3.8)	36 (3.6)
Unnecessary drug-treatment	1 (0.2)	2 (0.4)	3 (0.3)
Inappropriate drug according to guidelines	14 (2.8)	30 (6.0)	44 (4.4)
Inappropriate combination of drugs	138 (27.6)	85 (17.0)	223 (22.3)
Drug dose too low	0 (0.0)	3 (0.6)	3 (0.3)
Patient intentionally takes less drug than prescribed	0 (0.0)	1 (0.2)	1 (0.1)
Cutaneous adverse reactions	**n=17**	**n=19**	**n=36**
Non-severe cutaneous ADRs			
Maculopapular rash	14 (82.3)	10 (52.6)	24 (66.7)
Urticaria	1 (5.9)	0 (0.0)	1 (2.8)
Exfoliative Dermatitis	1 (5.9)	1 (5.2)	2 (5.5)
Erythema Multiforme	0 (0.0)	1 (0.2)	1 (2.8)
Severe cutaneous ADRs			
Stevens-Johnson Syndrome	1 (0.2)	5 (26.3)	6 (16.7)
Acute generalized exanthematous pustulosis	0 (0.0)	2 (10.5)	2 (5.5)

Note: [a]PCNE Classification for Drug-Related Problems V9.1; [b]Patients could have multiple DRPs.
Abbreviations: iADRM, intensive adverse drug reaction monitoring; rADRM, routine adverse drug reaction monitoring.

Table 4 Logistic Regression Analysis of the Impact of Adverse Drug Reaction Monitoring Program on Clinical Outcomes

Clinical Outcomes	Univariable Analysis			Multivariable Analysis		
	cOR	95% CI	p	aOR	95% CI	p
Occurrence of Phenytoin-related DRPs						
rADRM	1.000			1.000		0.150[a]
iADRM	0.668	0.507–0.881	0.004	1.315	0.906–1.910	
Confirmed phenytoin-induced ADRs						
rADRM	1.000			1.000		0.029[b]
iADRM	1.344	0.629–2.871	0.440	2.301	1.091–4.853	
Patient-initiated telephone calls after discharge						
rADRM	1.000			1.000		<0.001[c]
iADRM	3.826	1.992–7.348	<0.001	4.527	2.274–9.010	

Note: [a]Adjusted with age, presence of comorbidities, number of co-administered drugs, history of drug allergy, co-administration of phenytoin-interacting medications, and omeprazole dose. [b]Adjusted with gender, ages, presence of comorbidities, number of co-administered drugs, history of drug allergy, co-administration of phenytoin-interacting medications, and omeprazole dose. [c]Adjusted with gender, ages, presence of comorbidities, and history of drug allergy.
Abbreviations: cOR, crude Odds ratio; aOR, adjusted Odds ratio; 95% CI, 95% confident interval,

There was also a significant increase in the risk of phenytoin-induced severe cutaneous adverse reactions (SCARs) among patients receiving intensive ADR monitoring (OR 13.304; 95% CI 1.183:149.581; p = 0.036), those with comorbidities (OR 12.935; 95% CI 1.514:110.480; p = 0.019), and those prescribed omeprazole at a dose of 20 mg/day (OR 57.112; 95% CI 9.569:340.875; p < 0.001). Conversely, increased age was associated with a lower risk of SCARs (OR 0.940; 95% CI 0.893:0.989; p = 0.023) (Table 5).

Table 5 Univariable and Multivariable Logistic Regression Analyses of Factors Associated with Severe Cutaneous Adverse Drug Reactions

Factors	Number of Patients (%)		Univariable Analysis			Multivariable Analysis[a]		
	SCARs	Non-SCARs	cOR	95% CI	p-value	mOR	95% CI	p
iADRM	1 (87.5)	493 (49.7)	7.085	0.868–57.800	0.024	13.304	1.183–149.581	0.036
Male gender	8 (100.0)	670 (67.54)	NE	NE	NE	NE	NE	NE
Age (year) [mean (S.D.)]	44.75 (7.32)	55.16 (0.55)	0.967	0.929–1.006	0.101	0.940	0.893–0.989	0.018
Presence of comorbidities	6 (75.0)	583 (58.8)	2.105	0.423–10.479	0.364	12.935	1.514–110.48	0.019
Number of co-administered drugs [median,(IQR)]	5 (3.5–5)	4 (3–7)	0.930	0.716–1.209	0.591	0.877	0.625–1.228	0.445
History of drug allergy	0 (0.0)	35 (3.5)	NE	NE	NE	NE	NE	NE
Co-administration of phenytoin-interacting medications	7 (87.5)	683 (68.8)	3.167	0.388–25.851	0.282	NE	NE	NE
Significant rating 2	2 (25.0)	164 (16.5)	1.683	0.337–8.411	0.544	NE	NE	NE
Significant rating 4	5 (62.5)	480 (48.4)	1.778	0.423–7.479	0.433	NE	NE	NE
Co-administration of Omeprazole	7 (87.5)	562 (56.6)	5.356	0.656–43.695	0.117	NE	NE	NE
Omeprazole 20 mg/day	6 (75.0)	101 (10.2)	26.465	5.271–132.863	<0.001	57.112	9.569–340.875	<0.001
Omeprazole 40 mg/day	1 (12.5)	461 (46.47)	0.164	0.020–1.342	0.092	NE	NE	NE

Note: [a]adjusted with variables: ADRM program, age, presence of comorbidities, number of co-medications, using omeprazole 20 mg/day.
Abbreviations: iADRM, intensive adverse drug reaction monitoring; SCARs, Severe cutaneous drug reactions; Non-SCARs, Non-severe cutaneous drug reactions; cOR, crude Odds ratio; mOR, multivariable Odds ratio; 95% CI, 95% confident interval, NE, not estimable.

Discussion

Phenytoin is commonly used to treat partial and generalized seizures. Intensive monitoring enhances patient participation, medication adherence, and ADR surveillance, allowing pharmacists to detect phenytoin-related issues more effectively. Additionally, patient-related factors such as age, comorbidities, and concurrent use of omeprazole 20 mg/day have been associated with an increased risk of severe cutaneous adverse reactions (SCARs) in newly treated individuals receiving phenytoin.

In this study, implementation of an intensive ADR monitoring program (iADRM) for phenytoin therapy significantly improved detection of phenytoin-induced ADRs and enhanced patient self-monitoring. This improvement was attributed to emphasizing the importance of recognizing early signs of SCARs to patients, as well as providing a direct telephone line for patient reporting. A study in Thailand demonstrated that pharmacists' interventions—including assessment of patient-specific factors influencing treatment outcomes, addressing medication-related problems, providing education on medication management, and supplying patient booklets for recording appointments and documenting medication intake and adverse events—notably reduced seizure frequency (from 28.85% to 13.46%; $p<0.01$), prolonged seizure-free intervals (from 46.15% to 71.15%; $p<0.01$), and decreased medication-related issues (from 90.3% to 75.00%; $p<0.01$).[12] An additional hospital-based study demonstrated that pharmacist-led monitoring significantly enhances ADR detection. Following the integration of clinical pharmacists' in-service training into routine care, interconsultations for suspected ADRs increased by 168.4%. Reported ADRs to the national regulatory agency rose from 32 to 75, with severe ADRs increasing from 4 to 12.[18] In contrast, hospitals in the United States lacking pharmacist-managed anticonvulsant services reported a 1.55-fold higher mortality rate (OR 1.553; 95% CI 1.102–2.189) and a non-significantly higher incidence of cutaneous reactions and adverse effects compared to hospitals with dedicated pharmacist care.[21] Pharmaceutical care provided to patients receiving phenytoin improves seizure control, as it promotes better patient adherence and facilitates the identification of medication-related problems, including adverse drug reactions (ADRs) associated with anticonvulsant therapy.

Increased patient inquiries by telephone calls and ward alerts led to earlier identification and targeted management of severe reactions, thereby reducing their severity. Enhanced patient and caregiver education facilitated faster hospital visits for allergy confirmation. When pharmacists provide structured self-reporting tools, patients demonstrate a high level of engagement, as reflected by a 61% response rate, indicating strong willingness to participate in ADR monitoring when the process is guided and standardized by pharmacists. The system captured a substantial volume of ADR information, with 36.5% of all reported reactions classified as severe by patients' assessment, meaning that over one-third of identified ADRs required clinical attention.[24] Another study among epileptic patients found that 82% of patients who responded to a pharmacist's

telephone call reported experiencing adverse reactions to antiepileptic drugs. Of these, approximately 77% had these adverse reactions documented in their medical records by health professionals.[25] These findings emphasize the effectiveness of patient-initiated reporting systems and validate the role of pharmacist-facilitated self-monitoring tools in enabling early recognition of clinically significant reactions, including those suggestive of emerging SCARs.

This study identified age, comorbidities, and concomitant use of omeprazole as significant factors associated with SCARs, consistent with previous findings in Thai populations. Co-administration of omeprazole and phenytoin was found to significantly raise the risk of DRESS (adjusted OR = 9.21, p = 0.002).[26] This association is plausibly explained by omeprazole's inhibition of CYP2C9, which can elevate phenytoin plasma concentrations and thereby intensify the severity of SCARs.[27] Genetic predisposition has also been well documented: HLA-B56:02/04 and CYP2C193 have been implicated in DRESS, whereas SJS has been associated with Chinese ethnicity (adjusted OR 10.41, p = 0.0042) and the CYP2C9*3 allele (adjusted OR 5.40, p = 0.0097).[26] Further study conducted in a South-Indian cohort also demonstrated markedly elevated risks among carriers of CYP2C9*3, who exhibited a 12-fold increase in phenytoin-related cutaneous ADRs (OR 12.00; 95% CI 2.76–84.87) and a 12.45-fold increase specifically for SCARs (95% CI 1.14–136.20).[28] Additionally, patients older than 60 years were at higher risk for SJS/TEN (OR = 3.647; 95% CI, 1.193–11.147; P = 0.023).[8] Collectively, these findings underscore the multifactorial nature of phenytoin hypersensitivity, wherein both metabolic determinants (CYP2C9 variants), immunogenetic markers (HLA class I alleles), and clinical contributors play substantive roles. Although *HLA-B*15:02* screening is routinely conducted in Thailand to prevent carbamazepine-induced hypersensitivity reactions,[29] such procedure is not standard for patients prescribed phenytoin in general hospitals. Based on these findings, it is advisable to closely monitor new phenytoin recipients, particularly within the first six months of therapy. This is especially indicated for patients with risk factors including Chinese ethnicity, advanced age, comorbidities, and those receiving drugs that elevate phenytoin levels, such as omeprazole. Enhanced clinical vigilance in these high-risk groups can facilitate early identification and intervention for severe hypersensitivity reactions, ultimately reducing related morbidity and mortality.

Therapeutic drug monitoring (TDM) was not a routine test at our institution, as specimens were sent to an external laboratory. In practice, TDM was typically ordered in selected cases, such as when a concentration-related phenytoin ADR was suspected or when seizure control was suboptimal. In addition to intensive ADR monitoring, therapeutic drug monitoring (TDM) may further enhance phenytoin safety.[12,30] Integrating structured ADR surveillance with TDM services may provide a more comprehensive safety framework for high-risk anticonvulsants. Future studies could explore the combined impact of pharmacist-led monitoring and TDM on clinical outcomes.

The findings of this study demonstrate that intensive ADR monitoring is more effective than routine surveillance in detecting phenytoin-induced ADRs, enabling earlier recognition and intervention for emerging reactions. In parallel, the study identified key demographic and clinical factors—such as advanced age, comorbidities, and interacting medications—that contributed to the risk of SCARs among new phenytoin users. Expanding the number of pharmacists involved in intensive monitoring would support wider implementation of the iADRM system, allowing its benefits to reach a broader patient population, including both inpatients and outpatients and those receiving other high-risk aromatic anticonvulsants. Such expansion would strengthen early ADR detection, improve prevention of severe hypersensitivity reactions, and enhance overall patient safety.

This study has limitations. ADR follow-up was limited, particularly when patients transferred between healthcare facilities, which may affect the accuracy of ADR incidence estimates. In addition, the relatively low incidence of SCARs and the inability to obtain genetic confirmation of drug hypersensitivity may limit the generalizability of the findings. Nevertheless, the study did identify important clinical risk factors that can inform surveillance strategies in practice. Finally, patients were allocated by ward (rADRM vs iADRM) rather than randomized, introducing potential selection bias and unmeasured confounding. Therefore, findings should be interpreted as associations rather than causal effects. Given that severe cutaneous adverse drug reactions most commonly occur within the first three months of drug initiation,[31] future monitoring strategies should prioritize intensive surveillance during this period, especially for high-risk patients. Developing specific screening criteria to identify individuals at increased risk could further enhance the effectiveness of ADR surveillance. Furthermore, extending follow-up periods and broadening the range of drug classes studied in future research would refine risk factor identification and improve sample representativeness. Strengthening patient education regarding treatment and potential

ADRs, as well as implementing inter-hospital surveillance networks, may also improve early detection and overall care quality—particularly important given the limited access to genetic testing for phenytoin hypersensitivity in Thailand.

This study provides novel real-world evidence comparing routine and intensive ADR monitoring models within a hospital setting in Southeast Asia. While active pharmacovigilance systems have been evaluated in other contexts, data focusing specifically on phenytoin-associated severe cutaneous adverse reactions remain limited. The findings highlight the potential of pharmacist-led intensive monitoring to enhance ADR detection in settings where pharmacogenetic screening may not be routinely accessible.

Conclusion

Intensive ADR monitoring was associated with increased detection and reporting of phenytoin-induced ADRs compared with routine monitoring. This approach also enhanced patient engagement and enabled earlier pharmacist interventions. In addition to genetic markers, advanced age, comorbidities, and concomitant omeprazole use emerged as major clinical risk factors for SCARs in this population.

Abbreviations

SCARs, severe cutaneous adverse reactions; rADRM, routine adverse drug reaction monitoring; iADRM, intensive adverse drug reaction monitoring; OR, Odds ratio; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; HLA, human leukocyte antigen; TDM, therapeutic drug monitoring; SDG, Sustainable Development Goal; ALDEN, Algorithm of Drug Causality for Epidermal Necrolysis; SCORTEN, the Score of Toxic Epidermal Necrosis.

Data Sharing Statement

The data supporting the findings of this study are available from the corresponding author upon request.

Ethics Approval and Inform Consent

This study received approval from the Ethics Committee the Ethical Committee of Phrae Hospital (reg no. 37/2564). All procedures involving human participants adhered to the ethical standards of the 1964 Helsinki Declaration and its subsequent amendments or equivalent guidelines. Patient consent was waived because the study utilized anonymized electronic patient medical records and involved no direct participant recruitment.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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