COST-BENEFIT ANALYSIS OF AN INTENSIVE ADVERSE PRODUCT REACTIONS MONITORING PROGRAM OF INPATIENTS IN THAILAND

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Abstract. The objective of this study was to analyze the costs and benefits of the intensive adverse products reactions (APRs) monitoring program of inpatients in medical wards at Nakhon Ping Hospital, Chiang Mai, Thailand. The data were retrospectively collected from inpatients who had APRs during admission period from November 16, 2004 to March 31, 2005. Products included were drugs, electrolyte solutions, bloods and blood derivatives. Only direct medical costs were considered using provider's perspective. The results showed that there were 1,407 admitted patients during the study period. Adverse products reactions were found in 31 patients. Of those, three patients had two APRs. Therefore, a total of 34 APRs were found yielding the APRs incidence rate of 24 per 1,000 inpatients. Of the APRs found, 20 were reported after the symptoms had begun, but the remaining APRs were preventable. Drugs were the main causes for APRs (94.12%). Cost of intensive APRs monitoring was US$1,426.37 and included US$939.44 for labor costs, US$12.5 for material costs, US$29.07 for capital cost and US$445.36 for APRs treatment and investigation. The program cost saving excluding the cost of hemodialysis was US$3,090.85. Net benefit was US$1,664.48 and benefit to cost (B/C) ratio was 2.17. When one time hemodialysis cost was included, cost saving increased to US$4,040.85. Net benefit and B/C ratio were US$2,614.48 and 2.84 respectively. The results of sensitivity analysis represented that net benefit and B/C ratio were increased when duration of digoxin intoxication was prolonged. However, net benefit and B/C ratio were decreased when pharmacist labor cost was increased. Results indicate that intensive APR monitoring is a cost beneficial program and should be continuously implemented.

INTRODUCTION

Adverse Drug Reaction Monitoring (ADRM) has had a great impact on value of life and health of populations. Since 1983 the Thai Food and Drug Administration (TFDA), Ministry of Public Health together with collaboration of hospitals have established centers to network in development of ADRM for the whole country. This service has since been included in the Sixth National Economic and Social Development Plan (1987-1991). To date, there are 23 centers in Thailand which help gather, analyze Adverse Drug Reaction (ADR) reports and distribute to the TFDA. The scope of monitoring has been expanded to include non-medicinal products such as narcotic substances, food, cosmetic, medical supplies, and dangerous substances for home use. Therefore, the name of the center was changed to be the Adverse Product Reaction Monitoring (APRM) Center. The system used to report Adverse Product Reactions (APRs) is classified into two pathways. First, APRs found will be reported by healthcare team to APRM Center. This is called a voluntary spontaneous reporting system. The other system is the safety monitoring program which moni-

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tors the safety of new drugs including new chemical entities, new indicators, new combinations, and new delivery systems (Akaleephar *et al*, 2004; Thai Food and Drug Administration, 2005).

APRs result in transient or permanent morbidity or even mortality, as well as economic burden to patients, health care institutions, and society as a whole. Pharmacists can work with other healthcare teams to decrease the frequency and cost of preventable adverse drug events (ADEs) (Johnson and Bootman, 1997; Bond *et al*, 2000; Nesbit *et al*, 2001). Most ADR research in Thailand has focused on determining ADR incidence and reported 1.7-22.6% of ADR incidence (Pongwecharak, 1991; Anuwong, 1993; Tragulpiankit, 1995; Dhana, 1997; Pongwecharak *et al*, 1999; Siriruttanapruk, 1999; Chiewchantanakit, 2000; Indrachai-ea, 2000; Yaemphaka, 2000; Pomyen, 2002; Khunkaewla and Permsuwan, 2004). However, there is little in terms of research evaluating ARD-related cost. Two studies in Thailand described cost avoidance of preventable ADRs accounted for 21,428-36,157 baht (US$ 536-904) (Panrong, 1999; Choppradit, 2000). Little work has been conducted on cost benefit analysis. To our knowledge, only one study evaluated the cost benefit analysis of ADRM at the Lerd Sin Hospital in Bangkok, Thailand (Prommeenate, 2000). This study which was focused mainly on the adverse reaction resulting from the use of medicine, showed the benefit to cost ratio to be 1.12.

Nakhonping Hospital is a tertiary care government hospital with 531 beds located in Chiang Mai, the north of Thailand. It has 550 item lists of medicines available. A spontaneous reporting system and an intensive APR monitoring system have been used to report APR incidents. In 2003, 110 APRs were reported. Of those, 60% were found in inpatients. Presently, there is no published data regarding economic evaluation related to APR in Nakhonping Hospital. Therefore, this study was conducted to broaden the scope of monitoring to include non-medicinal products by using an economic evaluation method to describe the cost benefit of APRM.

The objective of this study was to examine net benefit and benefit to cost ratio of APRM from the provider point of view.

MATERIALS AND METHODS

Costs and benefit based on pharmacy service in terms of APRM were prospectively collected from inpatients with APRs who were admitted to medical wards in Nakhonping Hospital, Thailand during November 16, 2004 to March 31, 2005. The analysis took into account the perspectives of provider. Costs and benefits were evaluated in the year 2004.

Costs

Costs were confined to direct medical cost comprised of labor cost, material cost, capital cost, and costs related to APRs diagnosis and treatment in cases where APRs had begun before they were discovered by pharmacists. There were three trained pharmacists working for APRM in different wards. Labor cost was calculated by multiplying the working time for APRM by individual salary and other fringe benefits. Material cost was the expenditure for supplies that were used in the program. Capital cost was the depreciation cost calculated using straight line method with a 3% discount rate (Lipscomb *et al*, 1996). APRs diagnostic costs were laboratory expenditure and chest X ray cost. APRs treatment costs were composed of medicines, medical supplies, and medical services.

Benefits

The benefits considered in this study derived from early investigation of preventable APRs by trained pharmacists working in the medical wards. Benefits were converted to a monetary value. Given the dearth of data on the monetary value of APRs benefit, several as-

Table 1
APRs incidence.

	Number of APRs	APRs incidence (per 1,000 inpatients)
Total admitted patients	1,407	
Total APRs found	34	24
APRs were found after APRs symptoms had begun	20	14
Preventable APRs	14	10

sumptions in this study were made as followed.

1) Cost saving from early investigation of preventable APRs was calculated by multiplying APRs duration by the daily unit cost of APRs treatment.

2) APRs duration values were based on literature review. APRs continued to occur until medicines were eliminated from the body, which generally lasted five half lives (Winter, 1994; Rowland and Tozer, 1995).

3) If hemodialysis was required for APRs treatment, patients would receive it only once during admission period.

4) Discounting was not considered because benefits and costs occurred in the same time period.

Net benefit and benefit to cost ratio

Since both cost and benefit were in the monetary unit, the calculation could be performed in both the difference (net benefit) or the ratio between benefit and cost (benefit to cost ratio).

Sensitivity analysis

To test the robustness of the base case results, a one-way sensitivity analysis was undertaken by varying each uncertain parameter. The net benefit and benefit to cost ratio were recalculated on each occasion to determine if there was a significant impact of final outcomes.

RESULTS

Based on the total of 1,407 admitted patients, APRs were found in 31 patients. Three patients showed APRs twice. They were counted twice because their causes were from different medicines or they would occur at different time period. Pharmacists, however, could investigate and found five APRs before they actually occurred. One APR was lasted for five days before it was found in one patient who received Warfarin for deep vein thrombosis treatment. Therefore, there were a total of 34 APRs. Of those, 67.74% were found in patients aged more than 60 years. Average age of APRs patients were 67.42 years. All patients did not have APRs history.

The total APRs incidence was 2.4%. Among the 34 APRs found, 20 APRs were found by pharmacists after APRs symptoms had begun and the remaining 14 APRs were preventable (Table 1). Of the 20 APRs found, based on Rawlins and Thompson ADR classification (Rawlins and Thompson, 1997), 16 were Type A and four were Type B APRs. When using Schumock and Thornton classification (Schumock and Thornton, 1992), 18 were non-preventable and two were preventable APRs. Based on Naranjo's algorithm (Naranjo *et al*, 1981), APRs were classified from most to least as probable, possible, and certain with 15, 3, 2 events, respectively (Table 2). Medicines, blood, and blood derivatives accounted for 94.12, 2.94, and 2.94% of APRs, respectively.

Total direct medical costs incurred by the provider in this analysis were US$1,426.37. Labor cost had the highest proportion of the

Table 2
The classification of APRs found after the symptoms had begun.

APRs classification	Number (n = 20)
Rawlins and Thompson (1997)	
Type A (Augmented) APRs	16
Type B (Bizarre) APRs	4
Schumock and Thornton (1992)	
Preventable	2
Non-preventable	18
Naranjo's algorithm (Naranjo *et al,* 1981)	
Certain	2
Probable	15
Possible	3
Unlikely	-

Table 3
Summary of direct medical costs incurred by provider used in this analysis.

Types of costs	Costs (US$)[a]
Labor cost	939.44
Material cost	12.5
Capital cost	29.07
APRs diagnostic cost	246.0
APRs treatment cost	199.36
Total	1,426.37

[a]US$1 was 40 baht (Thai currency unit)

total cost, followed by APRs diagnostic and treatment costs. On average, pharmacists spent 15% of their working time for the APRM which accounted for US$939.44 of labor cost. Material cost included in the analysis was the cost of office supplies such as papers, folders etc, which accounted for US$12.5. The annual depreciation cost of the building was US$290.70. The area that was used for APRM administration was 10% of the building. Therefore, capital cost accounted for US$29.07. Among 20 APRs found, 10 APRs did not incur any value because physicians immediately gave up the suspected products. The remaining 10 APRs incurred US$1,426.37 for total direct medical cost (Table 3).

There were a total of 16 preventable APRs. Of those, 14 were investigated and found before they actually occurred. The remaining two APRs from N-acetylcysteine, and drug interaction among nifedipine, sodium nitroprusside, and furosemide were found after APRs symptoms had begun. These two preventable APRs started after the working hours of the pharmacists. Digoxin intoxication and ceftazidime overdose were the most highly APRs found in this study and each accounted for 18.75% of total preventable APRs. APRs from ceftazidime and amikacin if they occurred required hemodialysis treatment which cost US$190 each time. Total cost saving was equal to US$3,090.85 and US$4,040.85 when excluding hemodialysis cost and including hemodialysis cost, respectively (Table 4).

Adverse product reaction monitoring incurred costs in exchange for a reduction in preventable APRs, and therefore reduced health resource costs to manage those APRs. Based on cost and cost saving in this analysis, net befit of APRM excluding hemodialysis cost and including hemodialysis cost were US$1,664.48 and US$2,614.48, respectively. The benefit to cost ratio excluding hemodialysis cost was 2.17 as compared with 2.83 when including hemodialysis cost.

Sensitivity analysis

Because the assumption of this study used five times of half lives for each medicine as APRs duration if APRs occurred, cost saving from preventable digoxin intoxication showed the highest value. This was due to prolonged APRs duration. Therefore, duration of digoxin intoxication was varied to test the robustness of base case result. Not until the duration of digoxin intoxication decreased to as low as one day was the net benefit less than zero when hemodialysis cost was included. Excluding hemodialysis cost, net ben-

Table 4
Summary of cost saving from APRs monitoring program used in this analysis.

Product	APRs (if occurred)	Number of events [N]	APR duration (days) [D]	Daily unit cost of APRs treatment (US$) [C]	Cost saving (US$) [D*C*N]	
					Exclude hemodialysis cost	Include hemodialysis cost[a]
Digoxin	Digoxin intoxication	3	20.0	47.02	2,821.20	2,821.20
Ceftazidime[b]	Ceftazidime overdose (neuromuscular hypersensitivity, convulsion)	3	4.9	4.59	67.47	637.47
Amikacin[b]	Amikacin overdose (ototoxicity, nephrotoxicity, neuromuscular toxicity)	2	9.4	0.0	0.0	380
Enalapril	Enalapril overdose (hyperkalemia, hypotension)	2	7.6	8.75	133	133
Imipenam	Imipenam overdose (neuromuscular hypersensitivity, seizure)	1	0.5	4.59	2.30	2.30
Metoprolol	Bronchoconstriction, dypnea, wheezing	1	1	5.75	5.75	5.75
Furosemide	Hyperuricemia	1	0.2	5.25	1.05	1.05
Vancomycin	Vancomycin overdose (ototoxicity, nephrotoxicity)	1	8.9	6.75	60.08	60.08
N-Acetylcysteine[c]	Anaphylactoid reaction	1	0.0	6.29	0.00	0.00
Nifedipine, sodium nitroprusside, furosemide[c]	Hypotension	1	1.3	3.75	0.00	0.00
Total cost saving					3,090.85	4,040.85

[a]plus US$190 for hemodialysis cost for one APR event; [b]medicines that required hemodialysis if APRs occurred; [c]medicines when APRs were found after symptoms had occurred

efit became less than zero when duration of digoxin intoxication decreased to the eighth day (Fig 1). Labor cost was another key parameter that might show an impact on net benefit. The percentage of pharmacists' working time on APRM was varied. The net benefit was negative when pharmacists spent at least 42% of their working time if cost of hemodialysis was excluded. In case of including hemodialysis cost, the net benefit became less than zero when the percentage of their working time increased to 57% (Fig 2).

DISCUSSION

The cost benefit analysis in this analysis was based on the actual value of the data from Nakhonping Hospital. The benefit has to be converted into monetary value due to cost-benefit methodology. The benefit in this analysis was cost saving of investigated preventable APRs which were calculated by multiplying APRs duration times daily unit cost of APRs treatment. It is obvious that the actual duration of preventable APRs were not be fore-

Table 5
Cost and consequences of implementing adverse product reaction monitoring program.

	Cost (US$)	Cost saving (US$)	Net benefit (US$)	B/C ratio
Exclude hemodialysis cost	1,426.37	3,090.85	1,664.48	2.17
Include hemodialysis cost	1,426.37	4,040.85	2,614.48	2.83

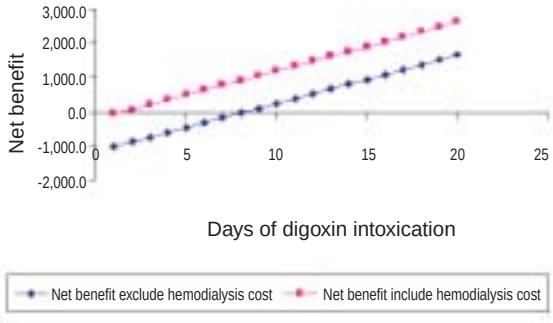

Fig 1–Sensitivity analysis of net benefit for various days of digoxin intoxication.

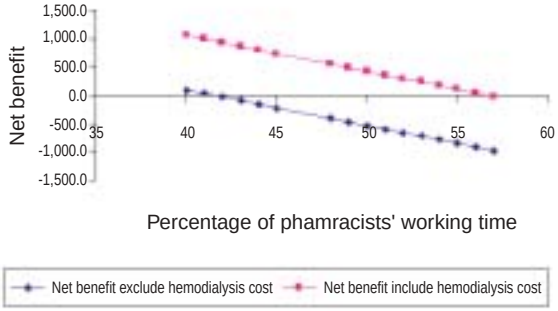

Fig 2–Sensitivity analysis of net benefit for various pharmacists' working time.

casted. Given the limited data at this point, several assumptions previously made in the analysis. The sensitivity analysis attempted to address the issue of uncertainty of suspected variables that might show an impact on the study results. These included duration of digoxin intoxication and labor cost.

Of those total 34 APRs found in the study, 32 events were due to medicines. The remaining two APRs were from blood and blood derivative. Therefore, ADR incidence was equal to 2.3% (32/1,407). Pharmacists were able to investigate and prevent 14 preventable APRs. Additional two APRs were preventable, but had occurred after pharmacist working time. Even though ADR incidence found in this study (2.3%) was in the range of 1.7-22.6% of ADR found from previous studies in Thailand (Pongwecharak, 1991; Anuwong, 1993; Tragulpiankit, 1995; Dhana, 1997; Pongwecharak *et al*, 1999; Siriruttanapruk, 1999; Chiewchantanakit, 2000; Indrachai-ea, 2000; Yaemphaka, 2000; Pomyen, 2002; Khunkaewla and Permsuwan, 2004), the rate was quite low. This might be because of differences in reviewers, institutional climate, process of reporting APR, or patient mix.

The results demonstrated the positive net benefit and benefit to cost ratio whether hemodialysis cost was included or not. Including hemodialysis cost into the analysis provided higher net benefit and benefit to cost ratio than those of excluding hemodialysis cost (US$2,614.48 and 2.83 *vs* US$1,664.48 and 2.17). These findings support those of previous study in Thailand (Prommeenate, 2000), which reported that APRM is a cost beneficial program to hospitals in Thailand. It can help reduce avoidable expenditures and improve patient outcome. The results were also relatively insensitive to variation of both suspected variables. The net benefit calculated was not sensitive to 60% and highly 95% reductions

in the duration of digoxin intoxication when excluding hemodialysis cost and including hemodialysis cost, respectively. Additionally, the net benefit calculated was robust to 180% and 280% increases in the percentage of pharmacist working time when excluding hemodialysis cost and including hemodialysis cost, respectively.

For most drug therapies in Thailand, diagnosis and prescribing remain the physician's responsibility. Pharmacists have contributed more to the pharmaceutical care of patients such as intensive APRM. However, due to a limited number of pharmacists in each hospital, it is very difficult for pharmacists to work both inpatient wards and pharmacy unit at the same time. Despite an implicit cost effectiveness, the costs and benefits of the provision of intensive APRM should be made explicit to convince policymakers of the value of enhanced intensive APRM. This has led to improved investigation and substantial reductions in preventable APRs leading to substantial cost-savings. The findings of this study demonstrate that by providing pharmacists working on intensive APRM become increasingly cost beneficial.

This analysis involved several limitations. Most important, there is a lack of empirical data on monetary value of benefit from APRM. Therefore, five times of half lives for each medicine were used as a proxy of APR duration if they had occurred. To strengthen our results, sensitivity analysis was performed (Jolicoeur and Jones-Grizzle, 1992; Bootman *et al*, 1999). Overall, the impact of this possible limitation is subsided because the results of sensitivity analyses when varied suspected variables help minimize the effect of this limitation.

As stated earlier, the cost and benefit estimations made in this analysis were limited to the direct medical costs incurred or benefit received by the provider. A more complete estimation based on a societal perspective would include more types of costs or benefits, especially costs or benefits that would occur to patients. Previous studies in the US indicated that indirect costs associated with medication noncompliance were two or three times the estimated direct costs (Sullivan *et al*, 1990; Johnson and Bootman, 1995).

Additional limitation is generalizability. Since most data were directly derived from Nakhonping database, the application of the study results would be limited only to similar settings.

In conclusion, the cost benefit analysis showed that APRM was a cost beneficial pharmacy service with positive net benefit or benefit to cost ratio.

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