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ORIGINAL ARTICLE

A survey of therapeutic drug monitoring services in Malaysia

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Abstract In Malaysia, therapeutic drug monitoring (TDM) service was started in the 1980s. Since then, the number of hospitals that offer the service has increased. In this paper, we report the findings of a nationwide survey describing the practice of TDM in these hospitals. Questionnaires were mailed to 128 government hospitals. Data were collected for general characteristics of the hospitals, administrative, and laboratory activities related to TDM service. One hundred and twenty-one hospitals responded to the survey. Thirty-four hospitals (28.1%) provided the service with their own TDM laboratories, 44 hospitals (36.4%) provided the service using other hospitals' laboratories and 43 hospitals (35.5%) did not provide the service at all. TDM services were more likely to be offered in larger hospitals with various medical specialties. Since it is managed entirely by hospital pharmacists, these pharmacists assume an important role in ensuring optimum use of the TDM service.

1. Introduction

Therapeutic drug monitoring (TDM) is a useful clinical tool in drug therapy. Nationwide surveys of TDM service in other countries have been reported (Murphy et al., 1996; Morris, 1998; Thomson et al., 1998; Pedersen et al., 2000). In Malaysia, TDM service was first provided by the Hospital Universiti Sains Malaysia (HUSM) in 1984 (Hassan, 1993). Later, other hospitals in the country started to provide this service as part of drug monitoring service to their patients (Matnor, 1996; Othman et al., 1996). In 1987, four hospitals provided the TDM service and the number of hospitals with the service increased steadily to 73 in 2005 (Ministry of Health, 1988, 1992, 2002, 2005). Gentamicin was the first drug to be monitored when the service was first introduced (Hassan, 1990; Ismail, 1990). Since then, the service has been expanded to include antiepileptic drugs, digoxin and theophylline.

The total number of cases monitored by TDM services for the whole country increased from 25,756 in 1998 to 61,907 in 2005 an increase of 140.4% within seven years (Ministry of Health, 1988, 1992, 2002, 2005). In this survey, we have attempted to determine the current practice of TDM among

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government hospitals in Malaysia by identifying the availability of clinical and analytical components of the service.

2. Methods

A cross sectional study design was used to obtain information on TDM from the hospitals in Malaysia. The questionnaire was developed based on various studies, surveys and review articles on TDM service from different countries like the USA, UK and Australia (Murphy et al., 1996; Morris, 1998; Crawford and Santell, 1994; Howard et al., 1994; Morris and Lam, 2002; Perez et al., 2006).

The target hospitals were all government hospitals in Malaysia. Addresses and telephone numbers of the hospitals were obtained from the website of the Ministry of Health, Malaysia (Ministry of Health, 2006). A self-addressed stamped envelope together with the questionnaire was mailed to the targeted hospitals. The questionnaire was written in English language with a covering letter that explained the aim of the study. The cover letter and a questionnaire were addressed to the chief pharmacist of each hospital. The first mailing of the questionnaire was in May 2006. The first reminder with a copy of the questionnaire was mailed two months later in July 2006. The second reminder was done one month later to non-responding hospitals by phone calls between September and October 2006.

The questionnaire sought to identify the following information: general and demographic information, TDM service operational hours, drugs monitored, number and source of samples, and reporting procedures. In addition, the questionnaire asked about physicians' acceptance toward the pharmacist therapeutic recommendations. A section of the questionnaire was dedicated to laboratory activities, which asked about the location of the TDM laboratory in the hospital, and type of assay technique used. This section also asked about the availability of a quality assurance (QA) program in the laboratory. The draft survey was reviewed and evaluated by two pharmacists with extensive experience in TDM service in Malaysia. The questionnaire was pretested in March 2006 at three hospitals with TDM services. It consisted of multiple-choice and open-ended questions.

Data were analyzed using the Statistical Package for Social Sciences (SPSS®) program (Ver. 12.0). Descriptive statistics with frequencies, mean ± SD, median and range were used where appropriate. Percentages were calculated based on the number of respondents who answered each particular question. Mann–Whitney test was used due to skewed data to evaluate differences in the availability of TDM service based on hospital characteristics. An *a priori* P value of less than 0.05 was considered statistically significant.

3. Results

One hundred and twenty-three (96.1%) respondents returned the questionnaires. Two questionnaires were excluded (one was returned unfilled and the other stated that the hospital did not have inpatient service). Seventy-eight (64.5%) respondents reported providing TDM services at their hospitals. Thirty-four hospitals provided TDM services and performed their own drug assays. Forty-four hospitals provided the services but the drug concentration measurements were done in other hospitals. For these respondents, data are presented based on the number of respondents who answered each particular question in the survey. Forty-three hospitals did not provide the service at all and did not answer the remaining questions.

Hospitals that provided TDM service had significantly larger number of beds, higher number of clinical specialties, and higher number of pharmacists employed (Mann–Whitney test, $P < 0.001$). A similar trend was observed when comparing hospitals that had their own drug assay facilities with hospitals that did not have their own drug assay facilities (Table 1). The duration of providing TDM service ranged from less than a year to 22 years. Most respondents reported providing the service five days a week. In hospitals with drug assay facilities, 20 (58.8%) respondents said they provided the service during the normal working hours (8 h/day) and with an "on-call" pharmacist after the normal working hours. During "on-call" service, a pharmacist will be paged or called by the hospital when a TDM request is received. Two (5.9%) respondents said their hospitals provided 24-h service. One respondent from the hospital without drug assay facility said it provided an "on-call" service as well as during the normal working hours.

There was a wide variation in the types of drugs monitored by TDM services in these hospitals (Table 2). Aminoglycosides and antiepileptic drugs like phenytoin, carbamazepine and sodium valproate, were among the most commonly monitored drugs in these hospitals. On average, hospitals with their own drug assay facilities provided monitoring to about 10 different drugs whereas hospitals without the assay facilities monitored about five different types of drug only. The average number of blood samples received by hospitals with drug assay facilities was higher than that received by hospitals without the facilities. Respondents from hospitals with drug assay facilities also reported receiving blood samples from external sources (Table 3). In addition, 90.9% of these respondents said that the number of samples received had been increasing over the years. Fifty percent of the respondents in hospitals without assay facilities reported a similar trend.

When asked how the assay results were communicated to the doctors, the majority of respondents said that they gave their pharmacokinetic consultations and dosing recommendations to doctors by phone (84.4%) or using a TDM request form (88.9%). Four respondents from the hospital with drug assay facilities said they used the hospital's computerized system to report the assay results. Three respondents from the hospitals without assay facilities informed that they received both the assay results and pharmacist's dosing recommendation from the hospital that performed the drug assay for them. All respondents in both groups reported that doctors in their hospitals accepted the pharmacokinetic and dosing recommendations made by the pharmacists.

Survey recipients were asked in which department the TDM assay is done at their hospital. Of the 33 respondents, 23 (69.7%) reported that the drug assay was performed in the TDM laboratory of the pharmacy department, while 10 (30.3%) said the assay was done in the biochemistry department. Respondents reported using three different drug assays for TDM. Out of 31 respondents who answered this question, 25 (80.6%) reported using fluorescence polarization immunoassay technique (FPIA) and eight (25.8%) used enzyme-multiplied immunoassay technique (EMIT). High pressure liquid chromatography (HPLC) technique was reported by one respondent from a university hospital.

Twenty-four out of 31 (77.4%) respondents from hospitals with their own drug assay facilities reported having quality

Table 1 Characteristics of hospitals that provide TDM service.

Hospital characteristics	Hospitals with TDM laboratory, *N* (%)	Hospitals without TDM laboratory, *N* (%)	*P* value[a]
Number of beds	*n* = 34	*n* = 44	< 0.001
< 200	1 (2.9)	35 (79.5)	
201–400	10 (29.4)	8 (18.2)	
401–600	5 (14.7)	0 (0.0)	
601–800	7 (20.6)	0 (0.0)	
801–1000	7 (20.6)	0 (0.0)	
> 1000	4 (11.8)	1 (2.3)	
Mean ± SD	681.0 ± 411.0	188.1 ± 377.9	
Median	654.0	109.5	
Range	114–2245	29–2600	
Number of pharmacists	*n* = 32	*n* = 43	< 0.001
0	0 (0.0)	1 (2.3)	
1	1 (3.1)	20 (46.5)	
2–5	6 (18.8)	22 (51.2)	
6–10	12 (37.5)	0 (0.0)	
> 10	13 (40.6)	0 (0.0)	
Mean ± SD	10.3 ± 5.9	1.9 ± 1.2	
Median	10.0	2.0	
Range	1–30	0–5	
Number of specialties	*n* = 33	*n* = 36	< 0.001
1	1 (3.0)	4 (11.1)	
2–5	0 (0.0)	17 (47.2)	
6–10	5 (15.2)	14 (38.9)	
11–15	24 (72.7)	1 (2.8)	
> 15	3 (9.1)	0 (0.0)	
Mean ± SD	12.4 ± 3.3	5.3 ± 2.8	
Median	13.0	5.0	
Range	1–17	1–11	

"*n*" indicates the number of respondents.
[a] Mann–Whitney test.

Table 2 Drugs monitored by TDM service.

Drugs monitored	Hospitals with TDM laboratory, *N* (%)	Hospitals without TDM laboratory, *N* (%)
Aminoglycosides	*n* = 33	*n* = 10
Gentamicin	32 (97.0)	7 (70.0)
Amikacin	24 (72.7)	0 (0.0)
Netilmicin	14 (42.4)	1 (10.0)
Antiepileptics	*n* = 33	*n* = 10
Carbamazepine	33 (100)	8 (80.0)
Phenytoin	33 (100)	8 (80.0)
Sodium valproate	32 (97.0)	8 (80.0)
Phenobarbitone	25 (75.8)	5 (50.0)
Other drugs	*n* = 34	*n* = 11
Paracetamol	30 (88.2)	5 (45.5)
Theophylline	29 (85.3)	3 (27.3)
Vancomycin	28 (82.4)	1 (9.1)
Digoxin	27 (79.4)	5 (45.5)
Cyclosporine	17 (50.0)	2 (18.2)
Aspirin	16 (47.0)	0 (0.0)
Methotrexate	6 (17.6)	0 (0.0)
Lithium	4 (11.8)	0 (0.0)
Tacrolimus	3 (8.8)	0 (0.0)
Opioids	1 (2.9)	0 (0.0)

"*n*" indicates the number of respondents.

assurance (QA) program in their hospitals. Six (25%) respondents participated in international QA programs. These international agencies included the International External Quality Assessment (RIQAS), The Royal College of Pathologists of Australia (RCPA) and United Kingdom National External Quality Assessment Service (UKNEQAS). The rest of the respondents reported that they participated in the hospital's internal QA programs and in those conducted by the Malaysian Ministry of Health.

4. Discussion

This study shows that TDM service is widely available in government hospitals in Malaysia. Sixteen hospitals started their service during the 1980s and the number of hospitals offering the service has increased significantly since then. Now, almost two-thirds of government hospitals provide this service. Hospitals that do not have the TDM service are generally those with smaller number of hospital beds, pharmacists and medical specialties. The findings from this study, to some extent, are similar to those reported elsewhere (Murphy et al., 1991; Howard et al., 1994; Morris, 1998). India started its TDM service by the late 1980s and the service was widely available in the 1990s to include more hospitals and centers (Gogtay et al., 2001).

Morris (1998) reported that not all hospitals in Australia performed drug assay measurements in their own laboratories. Drug assays for TDM are also performed by private laborato-

Table 3 Distribution of different sources of samples.

Source of samples	Hospitals with TDM laboratory, *N* (%)	Hospitals without TDM laboratory, *N* (%)
Hospital departments	*n* = 34	*n* = 10
Inpatients	34 (100.0)	10 (100.0)
Outpatients	33 (97.1)	6 (60.0)
Accident and emergency department	11 (32.4)	0 (0.0)
Number of samples received per month	*n* = 31	*n* = 10
< 50	4 (12.9)	8 (80.0)
51–100	4 (12.9)	2 (20.0)
101–200	6 (19.4)	0 (0.0)
201–300	9 (29.0)	0 (0.0)
301–400	2 (6.45)	0 (0.0)
> 400	6 (19.4)	0 (0.0)
Mean ± SD	286.7 ± 279.9	23.4 ± 30.1
Median	240.0	5.5
Range	8–1200	1–90
External sources	*n* = 34	–
Other government hospitals	23 (67.6)	–
Other government clinics	19 (55.9)	–
Private hospitals	6 (17.6)	–
Private laboratories	2 (5.9)	–
Number of samples received from external sources/month	*n* = 23	–
< 50	12 (52.2)	–
51–100	4 (17.4)	–
101–150	6 (26.1)	–
> 150	1 (4.3)	–
Mean ± SD	66.2 ± 63.6	–
Median	30.0	–
Range	1–240	–

"*n*" indicates the number of respondents.

ries as well as laboratories in public hospitals (Morris and Lam, 2002; Norris et al., 2010). Unlike in Australia, our survey shows that hospitals that do not have their own drug assay facilities rely on other hospitals to perform drug assays. Smaller size hospitals rely on larger hospitals to provide the TDM service where patient samples are sent to and assayed by the latter. It is difficult to determine exactly the reasons for establishing a TDM service in smaller size hospitals despite not having drug assay facilities. It may be a combination of different factors such as the availability of additional pharmacists, or the demand from certain medical specialties in the hospital. Half of the respondents in such hospitals reported that the number of samples they received had increased over the years. If this trend continues, the pharmacy departments may be forced to allocate assay facilities at their own hospitals.

Almost all hospitals reported having only one pharmacist to manage the TDM service. Most of the hospitals reported providing the service only during weekdays. To provide a 24-h service will require additional pharmacists working in three different work-shifts. Therefore, the number of pharmacists involved in TDM service has to be increased. Providing 24-h service is common in developed countries (Koren et al., 1985; Vinks et al., 1992). In USA, Murphy et al. (1996) reported that TDM service was available for 24 h a day, 7 days a week in 11.9% of hospitals. In Europe, Thomson et al. (1998) reported that most of the TDM laboratories provided the service during the weekdays while 73% of them offered a 24-h service for emergency cases only and for specific types of drugs. Although not being able to provide a 24-h service, some hospitals in this country overcome this situation by providing an "on-call" TDM service. The "on-call" pharmacist is needed mainly for emergency cases, either after normal working hours or during weekends. The pharmacist does not have to be at the hospital at all times but will be contactable by phone when his/her service is required.

Larger hospitals are usually located in urban areas and cater for larger population size. They receive higher number of TDM samples because many of them also received samples from external sources like government clinics, private hospitals and clinics. A similar trend has been reported by Cridland (1994), that 70% of the TDM samples came from their hospital departments, while the rest came from 40 different institutions. Because of the larger number of patients and specialties, hospitals with their own drug assay facilities monitor more drugs than those without drug assay facilities. The two most common drugs monitored are antiepileptics and aminoglycosides. Drugs like lithium, methotrexate, cyclosporine and tacrolimus are infrequently monitored. These drugs are more expensive or are used in more specialized settings and that not all hospitals have these specialties.

Our survey shows that drug assays are performed either by the department of pharmacy or by the department of biochemistry. The setting of the TDM laboratories varies between different countries. Some reported that TDM services are performed in the pharmacy departments (Murphy et al., 1991; Vinks et al., 1992), while others reported that the analysis is performed in the biochemistry department with the pharmacology unit being responsible for providing the recommendations to doctors (Pou and Campos, 1992). Reports from South Africa, India and Turkey showed that the TDM laboratory is part of the pharmacology department (Cridland, 1994; Yamantürk et al., 2000; Gogtay et al., 2001). Some institutions in Australia have both practices, that the easier assays were performed in the clinical biochemistry or chemical pathology departments, while the more complex assays like cyclosporine were performed in the clinical pharmacology department (Morris, 1998).

Only two types of immunoassays are used by our hospitals, with FPIA being the most common. Similarly, FPIA seems to be the most common analytical method used in other countries (Cridland, 1994; Thomson et al., 1998; Yamantürk et al., 2000; Morris and Lam, 2002). The high usage of this technique by most hospitals probably reflects the ease of use of the system, which requires minimal maintenance and personnel training. However, the choice of drug immunoassays has been under scrutiny. Interference from drug metabolite and other endogenous substances in patient samples has been highlighted with drug assays for cyclosporine and digoxin (Morris, 2000; Rogers et al., 2010). Despite recommendations from the literature (Morris et al., 2002), a large percentage of laboratories still employ poor performing immunoassays (Norris et al., 2010). We did not determine how the choice of drug assay was made by each hospital, although cost is probably a major determinant. As with other developing countries, the main drawback of immunoassay is the high cost of reagents. In this survey we did not evaluate the cost per test. In India, the cost has been reported to be approximately £3–£4 per test (Gogtay et al.,

2001). Indonesia has not yet started its TDM service and the high cost of drug assays poses a major barrier toward implementing a TDM service in that country (Setiabudy, 2011). Like earlier reports, we found that chromatographic technique was not commonly used (Gogtay et al., 2001; Morris and Lam, 2002). This technique needs highly skilled personnel and long turnaround time to perform the assay. It is unlikely that this methodology is to be widely used in this country for the purpose of TDM.

The majority of respondents said they participated in quality assurance programs. The nature of these programs varies between different hospitals. One-third of those hospitals involved in the QA programs participate in international QA program schemes while the rest are carried out locally. Morris (1994) reported that 30% of CSA TDM laboratories in Australia participated in an external QA program and recent data showed an increase in the number of hospitals (71%) registered in an international testing scheme (Morris and Lam, 2002). Pedersen et al. (2000) reported that 29% of the hospitals in USA had a regular program to evaluate the quality of the clinical monitoring service provided. Participation in international QA programs helps to maintain the quality of TDM service, which is required for future accreditations.

Based on the findings from this survey, the following recommendations should be considered: (1) an increasing demand for TDM service will lead to an increase in hospital costs. Within the same hospital, policy makers must decide whether it is more economically favorable to consolidate resources in the pharmacy department and biochemistry department (Shenfield, 2001). (2) Commercially available assays are costly. The choice of assay methodology should not only take into account its cost but also assay cross-reactivity and performance. For example, hospitals that offer TDM of cyclosporine may benefit from recommendations in the guideline by Morris et al. (2002). At the same time, laboratories that perform drug assays should be encouraged to participate in quality assurance programs, and (3) appropriate use of TDM resources must be enforced. The presence of TDM guidelines alone does not guarantee compliance (Leong et al., 2006). Instead, TDM pharmacists should consider increasing their involvement in clinical activities as well. The presence of the pharmacist during clinical rounds has been shown to reduce inappropriateness and monitoring costs (Kraus et al., 1991; Ratanajamit et al., 2009).

5. Conclusions

TDM service is widely available in government hospitals in Malaysia. Although drug assay facilities are not always available in the pharmacy departments, pharmacokinetic consultations are performed by pharmacists. Thus, they have the responsibilities to ensure the optimum use of TDM to guide drug therapy in patients.

Conflicts of Interest

None.

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