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EVALUATION OF BLOOD SAMPLING TIMES AND INDICATIONS FOR THERAPEUTIC DRUG MONITORING SERVICES

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The appropriateness of sampling times and indications for monitoring of serum drug concentrations for the purpose of therapeutic drug monitoring (TDM) were evaluated at three hospitals on the east coast of Malaysia. Appropriateness criteria for indication and sampling were adapted from previously published criteria and with input from local TDM pharmacists. Six drugs were chosen, namely gentamicin, digoxin, carbamazepine, phenobarbital, phenytoin, and valproic acid. A total of 265 TDM requests were evaluated. Appropriateness of the indication for TDM ranged from 77.4% to 82%, while that for sampling ranged from 34.2% to 62.1%. There were no significant differences between the three hospitals in both categories of appropriateness. Among different drug groups, the percentage of appropriate indication was found to be highest with antiepileptic drugs. Antiepileptic drugs, however, had the lowest rate of appropriate sampling. Overall, findings from the three hospitals showed very encouraging results with almost 80% of the requests considered as appropriately indicated. However, the percentage of appropriateness of sampling was lower, and thus may require further investigation.

Keywords: *Therapeutic drug monitoring, Sampling times, Indication, Malaysia*

INTRODUCTION

TDM has contributed substantially to the management of patient drug therapy and has become an important tool in clinical medicine. However, concerns have been raised with regard to its appropriate use and impact on patient outcomes (Tonkin and Bochner 1994; Ensom *et al*. 1998; Schumacher and Barr 2001). Previous studies documenting inappropriate measurements and indications have found that a significant proportion of resources spent on TDM may be wasted (Beardsley, Freeman and Appel 1983; Pitterle, Sorkness and Wiederholt 1985). Consequently, to optimise its use, several guidelines have been developed that include guidelines on sampling time, correct indication and correct utilisation of the serum drug concentrations (SDCs) (Wing and Duff 1989; Kraus, Calligaro and Hatoum 1991).

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In Malaysia, the TDM service first started in the early 1980s (Hassan 1990; Ismail 1990) with gentamicin being the first drug to be monitored. Since then, the service has been expanded to include the antiepileptic drugs digoxin and theophylline. Later, other hospitals in the country started to provide TDM service as part of their routine drug monitoring in patient care (Matnor 1996; Othman, Abd. Ghani and Aziz 1996), where these services are run by the pharmacy department at each hospital. The attending physician usually orders the test and completes the TDM request form, which is sent together with the blood sample to the TDM laboratory. In some hospitals, pharmacists may suggest that TDM be initiated during clinical rounds with the health care team. The TDM pharmacist interprets and provides consultation services regarding the SDCs, and, where necessary, may request additional tests to be performed throughout the patient's drug therapy in the hospital.

The increase in the availability of TDM services in Malaysia is most likely due to an increasing awareness of its clinical benefits, and the availability of simple, fast and automated analytical techniques. While the use of these services has increased, there has not been any evaluation of TDM utilisation in this country. This study evaluated the appropriateness of drug level monitoring at three government hospitals on the east coast of Malaysia.

METHODS

Study Location

The study was conducted over a two-month period at three hospitals on the east coast of Malaysia: (1) Hospital Kuala Terengganu (HKT), a general hospital managed by the Malaysian Ministry of Health with a 761-bed capacity and nearly 50,000 admissions annually; its TDM service was started in 1989, and at this hospital, a TDM pharmacist recommends and provides consultations regarding SDCs; (2) Hospital Kota Bharu (HKB), which is located about 160 km from HKT, is also managed by the Malaysian Ministry of Health with a 920-bed capacity and has approximately 50,000 admissions per year; its TDM service was started in 1985, and at this hospital, a TDM pharmacist routinely performs patient care rounds with physicians and suggests drug level measurements when appropriate and provides consultation regarding SDCs; (3) Hospital Universiti Sains Malaysia (HUSM), which is approximately 10 km from

HKB, is the only university teaching hospital on the east coast under the administration of the Malaysian Ministry of Education, with approximately a 700-bed capacity and about 30,000 admissions per year; its TDM service was started in 1984, and like HKT, the TDM pharmacist provides consultations regarding SDCs.

Development of Appropriateness Criteria

Appropriateness criteria for indication and sampling times were adapted from the literature (Bussey and Hoffman 1983; Levine and Chang 1990; Aronson and Hardman 1992; Schoenenberger *et al*. 1995; Eadie 1998; Canas *et al*. 1999; Begg, Barclay and Kirkpatrick 2001) and revised by the authors and other TDM pharmacists from six hospitals, including the three study hospitals included here (Table 1). The appropriateness of TDM use was categorised as: (a) appropriateness of sampling, and (b) appropriateness of indication.

Data Collection

The study was conducted over a two-month period (February to March 2001). Each TDM request form for any of the six drugs (gentamicin, digoxin, phenytoin, carbamazepine, valproic acid and phenobarbital) was screened and evaluated for appropriateness of indication and sampling. The following request forms were excluded from the study: (a) requests from district hospitals or from other hospitals, (b) requests received after office hours and on public holidays, (c) forms with incomplete information, (d) except for Hospital Kota Bharu, those requested by the TDM pharmacist, and (e) requests for single daily dose gentamicin monitoring.

Data Analysis

Results were expressed as proportions and mean values. For comparison of appropriateness of drug level monitoring between hospitals, the Chi-square test was used. A p value of less than 0.05 was considered as statistically significant.

Table 1: Indication and sampling criteria for selected drugs.

Appropriate indication	Appropriate sampling
Gentamicin	
• As initial monitoring: within 24–48 h of therapy • Suspected toxicity: if repeated, should not be less than one half-life of previous sample. • No or inadequate response • After a change in dose regimen • Suspected drug-interaction	• At steady-state (at least four half-lives) • Pre sample: within 30 min of the next dose • Post sample: 30 min after 30 min IV infusion, or 30 min to one hour after IV bolus.
Digoxin	
• As initial monitoring for new patient • Suspected toxicity: if repeated, should not be less than one half-life of previous sample • No or inadequate response • Suspected noncompliance • Suspected drug-interaction • After a change in dose regimen	• At steady-state: eight days (normal renal function) • Trough: before next dose • At least 6 h after the last dose
Carbamazepine	
• As initial monitoring: after 2–4 weeks of initiation of therapy • Within 6 h after seizure recurrence • Suspected toxicity: if repeated, should not be less than one half-life of previous sample • No or inadequate response • Suspected noncompliance • Suspected drug interaction • After a change in dose regimen • Every 6–12 months in stable adults and every 4–6 months in stable children.	• At steady-state: 2–4 weeks after initiation of treatment or 3–5 days after change in dose regimen or 1–2 weeks after addition or discontinuation of a known enzyme inducer • Sampling: trough – within 2 h before next dose. • Anytime if toxicity is suspected.
Phenobarbital	
• As initial monitoring: after 2–3 weeks of initiation of therapy. • Within 6 h after seizure recurrence • Suspected toxicity: if repeated, should not be less than one half-life of previous sample. • No or inadequate response • Suspected noncompliance • Suspected drug interaction • After a change in dose regimen • Every 6–12 months in stable adults and every 4–6 months in stable children.	• At steady state: 2–3 weeks after initiation of treatment • Sampling: trough – within 2 h before the next dose. • At least 3 h after the last dose during the dosing interval. • Anytime if toxicity is suspected

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Table 1: (*continued)*

Phenytoin	
• As initial monitoring: at least one week after initiation • Within 6 h after seizure recurrence • Suspected toxicity: if repeated, should not be less than one half-life of previous sample • No or inadequate response • Suspected noncompliance • Suspected drug interaction • After a change in dose regimen • Every 6–12 months in stable adults and every 4–6 months in stable children.	• At steady state: at least after 5–10 days • Sampling time: trough – within 2 h before next dose. • Anytime during the dosing interval. • After a loading dose: at least 2 h post loading. • Anytime if toxicity is suspected
Valproic acid	
• As initial monitoring: at least after 2–4 days of initiation • Within 6 h after seizure recurrence • Suspected toxicity: if repeated, should not be less than one half-life of previous sample. • No or inadequate response • Suspected noncompliance • Suspected drug interaction • After a change in dose regimen • Every 6–12 months in stable adults and every 4–6 months in stable children.	• At steady state: at least 2–4 days after initiation or change in dose regimen • Sampling time: trough – within 2 h before next dose or anytime if toxicity is suspected.

RESULTS AND DISCUSSION

TDM has been practiced in Malaysia for almost two decades. The use of TDM services in government hospitals is increasing throughout the country, with a total of 33,522 tests performed in 1999 and 48,878 tests in 2000 (Ministry of Health 1999; Ministry of Health 2000). Studies performed locally in Malaysia have reported improvement in therapeutic concentrations achieved and the number of physicians prescribing (Ismail, Sarriff and Ab Rahman 1990; Ismail *et al*. 1997). However, this is the first time an evaluation of the appropriate use of the service has been carried out in this country. The criteria for the evaluation of appropriateness that we used in this study have been adapted from the literature and with input from local TDM experts. Some of these criteria for sampling times and indications for TDM, which were used in this study, were similar to the existing guidelines available in their TDM services.

Two hundred and sixty-five requests for drug level determinations fulfiled the study criteria and were included in the analysis. Eighty-four requests were from HKT, 152 from HUSM and 29 were from HKB. Gentamicin, phenytoin and valproic acid accounted for over 75% of the requests (Table 2).

Nearly 80% of the requests from the three hospitals were considered appropriately indicated (Table 3). Other workers have found the rate of appropriate indication to be in the range of 27% to 85% (Pearce and Day 1990; Kraus, Calligaro and Hatoum 1991; Schoenenberger *et al*,.1995). HKB had the highest percentage of appropriate indication, 82.8%, followed by HUSM (77.6%), and HKT (77.4%). However, there was no significant difference among the three hospitals in term of appropriate indication.

On the other hand, our findings showed a lower rate of appropriate sampling compared to appropriate indication. The overall percentage of appropriate sampling was found to be 43.8%. HKB showed the highest percentage of appropriate sampling (62.1%), followed by HKT and HUSM (Table 3). Previous studies have reported that about 60% of SDC monitoring were appropriately obtained (Bussey and Hoffman 1983; Pitterle, Sorkness and Wiederholt 1985). In the three hospitals, it is a common practice for blood samples to be drawn by nurses acting on a

Table 2: Distribution of requests for drug level determination among the three hospitals.

Hospital	Digoxin	Genta-mycin	Antiepileptic drugs				Total request
			Carba-mazepine	Pheny-toin	Pheno-barbital	Valproic acid	
HKT	3	36	13	12	0	20	84
HUSM	22	14	7	50	14	45	152
HKB	4	10	1	6	1	7	29
Total number (%)	29 (10.9)	60 (22.6)	21 (7.9)	68 (25.7)	15 (5.7)	72 (27.2)	265 (100)

Table 3: Appropriateness of TDM among the three major hospitals.

	General Hospitals		Teaching hospital	Significance
	HKB N = 29	HKT N = 84	HUSM N = 152	
Appropriate indication	24 (82.8%)	65 (77.4%)	118 (77.6%)	NS
Appropriate sampling	18 (62.1%)	46 (54.8%)	52 (34.2%)	*P < 0.05

Notes: *Chi-square test; NS – not significant. Each request was evaluated for both appropriate indication and sampling

physician's order. It is possible that knowledge of sampling times among nurses may be lacking. Further studies should investigate the knowledge and attitude of nurses regarding selected aspects of the TDM service.

Among the three hospitals, HKB consistently performed the best, both for appropriateness of indication and sampling. The presence of a TDM pharmacist, who routinely makes rounds together with the physicians at this hospital, may have some positive influence on the use of the TDM service. A clinical pharmacist's involvement in TDM has been shown to decrease inappropriateness and monitoring costs (Pearce and Day 1990; Kraus, Calligaro and Hatoum 1991). In the paediatric setting, inappropriate indications and samplings decreased from approximately 15% to 0% as a result of pharmacy input (Kraus, Calligaro and Hatoum 1991).

Table 4 shows distribution of the appropriate use of TDM among the different drugs monitored. There were 29 requests for digoxin, 60 requests for gentamicin, and 176 requests for antiepileptic drugs. Each request was evaluated independently for their appropriate indication (N = 207) and sampling (N = 116). Therefore, the total number of evaluations made (N = 323) did not equal the number of requests (N = 265).

Among different drug groups, we found that for antiepileptic drugs, the appropriateness of indication was the highest, but for appropriateness of sampling, this group was the lowest. With antiepileptic drugs, Schoenenberger *et al*. (1995) have found that 27% of the levels had an appropriate indication, yet half of these were not sampled correctly. Thapar *et al.* (2001) recently reported that only 26% to 47% of patients had their phenytoin levels appropriately checked. The

Table 4: Evaluation of appropriateness of indication and sampling among different drugs in all hospitals.

	Digoxin	Gentamicin	Antiepileptic drugs
Total number of requests from all hospitals	29	60	176
Appropriateness of indication	20 (69.0%)	34 (56.7%)	153 (86.9%)
Appropriateness of sampling	18 (62.1%)	37 (61.7%)	61 (34.6%)
Total number of evaluations made for each drug request	38	71	214

Notes: *Each request was evaluated for both appropriate indication and sampling.
The percentage of appropriateness was calculated based on the number of requests for each drug.

percentage of appropriateness of sampling time and indication for digoxin in our study was more than 60%, which is comparable with earlier studies (Bussey and Hoffman 1983; Canas *et al*. 1999). Canas *et al.* (1999) compared the appropriateness of digoxin levels in inpatients and outpatients. For inpatients, only 16% were found to be appropriately indicated and these were attributed to the commonly practiced once-per-day levels in their setting. A study by Clague, Twum-Barima and Carruthers (1983) reported a higher rate of appropriateness in sampling for digoxin. It seems that in their setting, good coordination between blood sampling by phlebotomist nurses and administration of the drug might have contributed to a satisfactory outcome.

The cost of performing TDM in a developing country is a constraint on a hospital's budget (Gogtay, Kshirsagar and Dalvi 1999), as reagents and maintenance costs are expensive. It is important for blood samples to be obtained and the results interpreted appropriately to contain the costs of health care. In some hospitals in Malaysia, TDM pharmacists initially screen the request form for appropriateness of indication and sampling. In cases which are considered inappropriate, the TDM pharmacist will advise the physician and ask for the blood sampling to be repeated. This method, however, still results in the waste of blood samples. Thus, intervention should be made before the blood sample is drawn. Studies to improve the use of TDM, including strategies for physician education, have been reported (Wing and Duff 1989; Pearce and Day 1990). Bates *et al*. (1998) have described efforts to improve TDM use at Yale University through the use of guidelines and digital reminders when the drug is ordered on-line. Since an on-line TDM request is not yet available in our setting, TDM pharmacists need to consider implementing more comprehensive and long-term educational programmes for both physicians and nurses.

CONCLUSION

Our study has shown that the rate of appropriateness of sampling and indication for SDC monitoring in the three hospitals examined here can still be improved. A TDM service with its pharmacist routinely conducting clinical rounds on patient care consistently performs the best, both for appropriateness of indication and sampling.

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