THERAPEUTIC DRUG MONITORING - A REVIEW

T.F. Ashavaid and A.J. Dheraj

P.D. Hinduja National Hospital & Medical Research Centre, Mumbai.

HISTORY

Therapeutic Drug Monitoring (TDM) is defined as the use of drug measurements in body fluids as an aid to management of patients receiving drug therapy for the cure, alleviation or prevention of disease. Traditionally the dosage of drugs has been adjusted according to the pharmacological response which can be easily established by clinical means (e.g. antihypertensive drugs, analgesics, hypnotics) or by laboratory markers (e.g. anticoagulants, lipid lowering agents, hypoglycemic drugs etc.). For drugs whose action cannot be easily assessed clinically (e.g. drugs used for prophylaxis of seizure or antidepressant drugs) and where toxic effects cannot be easily detected unless they are irreversible (e.g. ototoxicity, nephrotoxicity) TDM is essential. TDM optimises therapy and along with clinical criteria can help in individualization of therapy.

TDM started out in 1970 and since then this concept is well accepted. The availability of appropriate analytical methods with commercialisation of enzyme immunoassay techniques helped enormously in educating scientific, medical and the common people to the advantages of TDM.

In 1997, a definition of TDM was developed by the Joint C - TDM IATDMT CT / IFCC committee and was published as: " TDM is

a measurement made in a laboratory of a parameter which, with appropriate interpretation, will directly influence prescribing procedures. Commonly the measurement in a biological matrix is of a prescribed xenobiotic, but it may also be of an endogenous compound prescribed as a replacement therapy in an individual who is physiologically or pathologically deficient in the compound".

IS TDM NECESSARY?

There are some drugs where the desired effect cannot be assessed clinically but it is related to the amount of drug in the body and this is dependent on drug concentration which can be achieved at the site of action. The steady state concentration of a drug cannot be predicted from the standard dose, due to inter-individual variation in the processes which are involved between prescribing a drug and that drug achieving an effective concentration at its site of action.

METHODS FOLLOWED FOR THERAPEUTIC DRUG MONITORING

There are various methods followed for TDM services. The gold standard used for most drugs is High Performance Liquid Chromatography (HPLC) but it is cumbersome and requires skilled manpower to maintain operation. The introduction of immunoassays have helped greatly in the easy availability of drug levels. Radioimmunoassays, Enzyme

Author for correspondence:

Dr. T.F. Ashavaid, Ph.D, F.A.C.B, Consultant Biochemist, at above address

Immunoassays (EIA), Enzyme - Multiplied Immunoassay Technique (EMIT), Fluorescence Polarization Immunoassays (FPIA) and Chemiluminescence have proved to be the cornerstone for the wide spread adoption of immunoassays for drugs in clinical laboratories.

CRITERIA FOR VALID TDM

Poor correlation between dose and effect due to wide inter-individual pharmacokinetic variation is a valid criterion for TDM. Secondly, a narrow interval between therapeutic and toxic effects where the margin between desirable and toxic concentration is very small, monitoring is valuable in achieving effective concentrations without systemic toxicity. Thirdly, plasma concentrations must correlate well with effect. If an effective relationship between concentration and effect is to be demonstrated, the intensity and the duration of the pharmacodynamic response to a drug must be temporarily correlated with the receptor site (1).

INTERPRETATION

Even if an appropriate specimen is taken and an accurate analysis is obtained, the whole exercise is valueless unless the result is correctly interpreted and any necessary action taken. Interpretation of drug concentrations requires knowledge of pharmacokinetic and pharmacodynamic factors. But without effective education programmes users of TDM service frequently 'interpret' results by comparing them with the therapeutic range. This can be harmful if the clinician just tries to bring the levels close to the quoted range forgetting that the aim of TDM is to ameliorate the patients symptoms rather than to get drug levels in a particular range (2). The

therapeutic range is a synthesis of two concepts - the minimum effective concentration for a drug and the maximum safe concentration. There is evidence that drugs can be effective in some patients at supposedly 'subtherapeutic' concentrations (3).

PRACTICAL ASPECTS OF TDM

An appropriate specimen is the prime necessity for effective TDM. The time taken to reach steady state is determined by the elimination half-life of the drug. It is frequently stated that 5-6 half-lives must elapse before plateau concentrations are achieved. The most reproducible time to take measurements is immediately pre-dose (trough concentration) when the lowest level in the cycle will be obtained. Peak concentrations are generally more relevant to the diagnosis of toxicity and the samples should be taken one hour post intramuscular or intravenous injection or 1 - 2 hours post oral dosing. Samples should be collected in plain vacutainer tubes and never in tubes containing serum separator gel as the gel is known to bind the drugs and give spuriously low values. The body fluid of choice for TDM is serum though TDM is possible on urine, saliva, meconium and hair (4).

Thus TDM services add value to providing effective patient management and conserving resources and the true challenge lies in providing accurate analysis backed by high quality interpretative expertise which can then allow some prospective studies of the value of well conducted TDM services to be undertaken.

In 1995, we conducted a survey of the TDM facilities offered in major cities of India (5).

We could identify about 35 such centres in various cities. Out of the 35 centres identified 31 centres were monitoring antiepileptic drugs while about 17 centres conducted digoxin monitoring (Fig.1). Theophylline and cyclosporine were the other drugs monitored by some centres and only 1 centre monitored antibiotics and antineoplastic

drugs. The methodologies followed by the various centres for the different drugs are given in Fig. 2 where EMIT and FPIA are the most favoured methodologies probably due to ease of using these techniques and reproducibility of the results.

% Distribution

Fig. 1 Drugs monitored by TDM facilities.

Fig. 2 Methodologies followed by TDM centres in India.

Fig. 3. Demand for TDM facilities.

Our own centre started TDM services in 1989. From doing around 1000 tests in the first year, we have performed to around 5000 tests / year (fig. 3). The drug which is monitored the

most being antiepileptics like phenytoin and carbamazepine and ironically the drugs which are monitored the least are the aminoglycosides and antisthmatic drugs.

REFERENCES

1. Hallworth, M. and Capps, N. (1993) Therapeutic drug monitoring and clinical biochemistry. ACB Venture Publications, USA, p. 1-28.
2. Editorial (1985) What Therapeutic drugs should be monitored? Lancet II, 309-310.
3. Shorvon, S.D. and Reynolds, E.H. (1982) Early prognosis of epilepsy. Brit. Med. J. 285, 1699-1701.
4. Ashavaid, T.F. (1999). Laboratory's role in poisoning. Associated Physicians of India. Technical series (In press).
5. Ashavaid, T.F. (1995). Therapeutic drug monitoring and clinical toxicology in India. (Abstract). Proc. IVth International conference of TDM and clinical toxicology, Vienna.