ABSTRACT

Monitoring levels of psychopharmacological agents for the purpose of optimising treatment is being recommended for increasing number of situations in routine psychiatry practice by some western authors. As a result most psychiatrists in developed countries advise drug assays for many patients on psychopharmacological treatment. Even in developing countries like India, therapeutic drug monitoring (TDM) is being advised more frequently, thus creating a demand for facilities. This paper reviews the need & feasibility of TDM in developing countries focussing on cost effectiveness, ethnopharmacological and sociocultural issues. Recommendations are made for using TDM in developing countries only in certain specific & selected clinical situation. Cost-effectiveness of strict serum lithium monitoring is discussed from a community health point of view.

Key Words: Therapeutic drug monitoring, ethnopsychopharmacology, sociocultural, serum lithium

Therapeutic drug monitoring (TDM) for optimising drug treatment in psychiatric patients is being recommended more and more frequently in developed countries. In a detailed review Preskorn et al. (1993) recommended drug assay in a wide variety of clinical situations, implying a more or less routine use. Various indications cited are optimising dosage, checking compliance, for differentiating between depression and neuroleptic induced akinesia, for known cases of toxicity, for medico-legal and consumer purposes and for ensuring drug wash out to avoid overlap drug interaction, among several other situations. In developing countries, already more and more psychiatrists are resorting to drug assays not only for lithium and anticonvulsants, but also for antidepressants and neuroleptics. This is gradually creating a demand, at least in big cities, for this sophisticated and costly laboratory facility.

It is submitted that developing countries need to assess the need, feasibility and cost effectiveness of T.D.M. under different sociocultural conditions. This paper examines these issues under following headings:-

1. Cost considerations
2. Availability of TDM
3. Reliability of laboratories
4. Interracial differences with bearing on TDM
5. Cultural issues
6. Need and recommendations for developing countries

Cost considerations

Psychotropic drugs are present in very small concentrations in blood and assaying them requires sophisticated technology. TDM by nature is costly. Cost of a single plasma level of tricyclic antidepressant is several times a psychiatrist's consultation fee and therefore requires strict justification. Total cost of
treatment of depression for individual and community will go up considerably if TDM is used routinely, since depression is the commonest disorder in psychiatry practice constituting over 50% of patients. Cost is daunting even for other drugs.

Cost of single drug assay (figures for India)

1. Lithium  Rs. 150
2. Carbamazepine  Rs. 500
3. Tricyclic antidepressants  Rs. 400
4. Neuroleptics  Rs. 400
5. Psychiatrist's consultation  Rs. 100

In case of certain drugs like haloperidol and carbamazepine, active metabolites may need to be measured additionally, and in case of decanoate neuroleptic preparations, periodical levels need to be done. These factors further increase the cost. Cost gets further escalated if cost of transport or of special containers for sending samples is considered since facilities for doing plasma levels are few and far between, in most developing countries.

Availability of TDM

Even if affordable as a routine procedure which it is not and even if useful, availability of TDM is a serious problem at present in most of the developing countries. Taking the example of Punjab which is one of the most prosperous states of India, there is not a single government or private laboratory capable of handling plasma assay for TCA or neuroleptics. Serum lithium estimations are done in few laboratories, which are attached to medical colleges and at some private laboratories in big cities. Twelve out of seventeen district head quarters do not have facilities for lithium estimations; carbamazepine drug assays is possible in three out of seventeen districts in few private laboratories.

At a rough estimate, if TDM is advised routinely in the present condition of availability, each patient or his sample in special containers will travel an average of 150 kms every time blood level needs to be done.

Reliability of laboratories

Even when affordable and available, how reliable are the laboratories?

USA has a Clinical Laboratories Improvement Act of 1972 which states that all clinical laboratories should be subject to external proficiency testing in addition to internal control system and local exchange of standard sample. In a survey called American Association for Clinical Chemistry TDM Programme, which included 80 laboratories, it was reported that “result of these surveys to date indicate that the analysis of antidepressants is significantly less well developed and controlled than the analysis of other drugs that are monitored for therapeutic purpose. The coefficient of variation among the laboratories for TCA was in excess of 30%” (American Psychiatric Association, 1985).

In most other countries, where there are no such statutory provisions, situation is much worse, errors are much higher and are not talked about or even known.

Even if errors in peripheral laboratories in other countries pertaining to TCA are taken to be around 30% (and they are likely to be much higher), the levels lose their relevance for crucial dose titration and would be relevant only for grossly noncompliant cases or cases of acute toxicity. Even if levels are not expected to be etched on stone, an error of more than 10% would render the fine tuning of dose titration meaningless. There is a strong need to ensure quality control before the profession recommends TDM, as a routine.

Inter-racial differences with bearing on TDM

1. Dosage of beta-blockers required for treating hypertension in Asians as compared to Caucasians (Zhou et al., 1989) are much less, cause is difference in sensitivity of adrenoceptors (Kalow, 1989). It is a
pharmacodynamic and not a pharmacokinetic difference.

2. Both the dosage and therapeutic concentration of lithium required for treatment and prophylaxis of mania have been consistently shown to be lower for Asian patients than for their Caucasian counterparts. Japanese patients required low therapeutic blood levels of 0.4-0.8 meq/l in contrast to Caucasians who require 0.7-1.3 meq/l (Stickland et al., 1993). However, no pharmacokinetic differences have been reported between these two races (Honda and Suzuki, 1979). Drug is metabolised in same manner and speed. The difference in response is because of differences in receptors' sensitivity.

3. Yamashita & Asano (1979) reported that doses of imipramine and amitriptyline prescribed in Asian countries (70-134mg/day) were much lower than in USA and also that depressed patients in Asia respond to fairly low steady state plasma concentrations of TCAs. The clear message from these studies is that since therapeutic and probably toxic levels for different races are likely to be different. TDM studies from West, where most of studies have been done, cannot be automatically applied to patient populations in East and before indigenous reports are available, TDM should not be recommended for routine use.

Cultural considerations

1. One of the major indications of TDM cited by Western authors is to monitor compliance (Preskorn et al., 1993). In most Eastern countries, because of extended families, compliance is comparatively less of a problem and even when patients are non-compliant, the fact of non-compliance is well known to family members obviating the need of plasma assay to assess compliance.

2. Another major indication for TDM cited by same authors is for medico-legal purposes. Because of cultural reasons, malpractice suits and to that extent TDM requirement, is less in Eastern societies. The Consumer Protection Act in India as applicable to medical care takes cognizance of negligence and not ordering a drug assay (except probably in a case of suspected toxicity) cannot be construed as negligence by any means.

Need and recommendations for developing countries

1. TRICYCLIC ANTIDEPRESSANTS

Only four TCAs have been subjected to clinical trials in which blood level measurements were made. These are imipramine, amitriptyline, desmethyl-imipramine and nortriptyline (Preskorn et al., 1993). Out of these desimipramine is rarely used and for amitriptyline there is poor co relation between concentration and efficacy in adults. Imipramine shows a linear, while nortriptyline shows a curvilinear relationship. There are no studies which clearly show that TDM driven dose adjustments were more effective than clinically titrated dose regimes. However there is a case for using TDM for TCAs in rare cases of particularly intractable patients and for detecting suspected toxicity.

2. SPECIFIC SEROTONIN REUPTAKE INHIBITORS e.g. fluoxetine

Since they have a flat dose-response curve, TDM will not increase effectiveness. They have a wide therapeutic margin so toxicity is not a concern. In view of very long half life, even compliance check is not possible since even noncompliant patients show some concentration. As such there is no indication for doing TDM of SSRIs in routine practice. However an unusual indication is to confirm drug washout of fluoxetine before a patient is subsequently put on a MAO inhibitor (Preskorn et al., 1993).
3. TRAZODONE

TDM with trazodone does not offer any advantage (Preskorn et al., 1993). No relationship is documented with efficacy. Priapism is idiosyncratic.

4. MAO INHIBITORS

Conventional TDM is not applicable to MAO in view of irreversible inhibition of MAO. Some studies have measured platelet MAO activity which is much costlier and cumbersome. There is need to take two samples. As such TDM for MAOI has not been recommended by any author.

5. LITHIUM

Lithium is the least controversial example of TDM. TDM has been widely documented as necessary part of standard care with lithium treatment and prophylaxis in view of its narrow therapeutic index and there is no reason not to do it routinely in all patients. However now that the profession has about thirty years experience with lithium, an important question needs to be addressed. The question is that in certain community situations where an experienced psychiatrist is available, should lithium prophylaxis for bipolar affective disorder be withheld? Such community situations are fairly common in developing countries and it is felt that some psychiatrists so placed are already successfully making the best of their clinical acumen. In the absence of facilities for lithium estimation over the last ten years, the author has treated over 2000, mainly rural, patients from remote areas who could not afford routine serum lithium estimations for reasons of either cost or distance. These patients of recurrent mood disorders have been maintained on lithium prophylaxis and doses have been adjusted clinically. Not a single case of toxicity has been seen. However it can be argued that had routine serum lithium estimation been done, prophylaxis of breakthrough episodes would have been even more effective. There is a clear need to study and report such experiences more systematically.

6. CARBAMAZEPINE AND SODIUM VALPROATE

No reports of TDM are available from studies on patients of affective disorder. All the reports are from seizure control studies (Preskorn et al., 1993). Even to assess and avoid potential adverse reactions, periodical blood counts and liver function tests would be more useful and much cheaper. However, TDM may be used in some cases of acute carbamazepine toxicity.

7. NEUROLEPTICS

There are no studies to recommend routine use of TDM in patients on neuroleptics. Effect is related to both dose and plasma levels up to particular limits beyond which neuroleptics are not additionally useful and cause side effects. Similarly, tardive dyskinesia is as much related to dose and duration as to plasma levels. TDM may be done for selected non-responders, patients who show serious unexpected side effects, or to check compliance.

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ANIRUDH K. KALA, M.D., M.N.A.M.S., Centre for Psychiatric Treatment, 95-A, Model Gram, Ludhiana-141002.