Editorial

Therapeutic drug monitoring (TDM) pitfalls and limitations

Abstract

Therapeutic Drug Monitoring (TDM) is a valuable tool to assess treatment and lessen side effects of drugs; yet it should be done professionally to get its maximum benefit.

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Aim

TDM is a very important and widely used technique throughout the treatment process. Analysis is done for a range of drugs in blood for the following reasons:

a) To establish baseline values during therapy.

b) When a patient is refractory to therapy.

c) Non-compliance suspected.

d) When toxicity is suspected (similar symptoms of toxicity and under treatment) e.g. arrhythmia in digoxin, seizures in phenytoin…

e) Modifying dosage or concomitant therapy.

f) To achieve maximum therapeutic benefit and decrease unwanted effects.

We use the fact that when there is a sufficient relationship between the plasma level of the drug and its clinical effect, it is then useful to measure this level. If such a relationship does not exit, TDM is of little or no value. Based on this fact, the TDM will be of maximal benefit when:

i. Low therapeutic index of a drug.

ii. The drug metabolites in plasma have a relation to its pharmacological or toxic effects.

iii. We cannot determine the therapeutic effect relying on the clinical observation.

iv. There is an individual variation which is great in steady state.

v. Plasma concentration exists at any given dose.

vi. Appropriate analytical techniques are readily and easily present.

Subsequently, the TDM is not done for:

A. Drugs with large therapeutic index e.g. cephalosporin's.

B. Drugs with serum concentration not related to the clinical response.

C. When we can measure the clinical response directly e.g. blood pressure, blood glucose.

So now the concept is clear. What are the drugs that are suitable candidates for TDM technique?

a. Digoxin

b. Quinidine

c. Carbamazepine

d. Phenobarbitone

e. Phenytoin

f. Valproic acid

g. Gentamycin

h. Vancomycin

i. Cyclosporine

j. Theophylline

k. Acetaminophen.

l. Tricyclic antidepressants

m. Acetyl salicylic acid.

But sometimes we face problems. What to look for when you get an unexpected serum concentration?

I. Is there a non-compliance

II. Is the dose correct

III. Does the patient suffer from mal-absorption

IV. Does the drug has a low bioavailability

V. Look for concomitant drugs that could affect the dose of the drug in question

VI. Make sure of good hepatic or renal conditions

VII. Diseases related to genetic factors affecting drug metabolism.

If you face these abnormalities, what is the solution for these problems? We can start with a dosage adjustment. We can use the following formula for linear drugs.

$$New\ dose = Old\ \ dose \times \frac{desired\ \ concentration}{old\ \ concentration}$$

We then must be aware of the factors leading to pitfalls. These could be summarized as:

A. Timing of Sample collection

B. Dosage regimen

C. Infusion length

D. Disease state

E. Effect of age

F. Pregnancy

G. Others

Let us discuss some of these in more details.

Discussion

Timing of sample collection

The importance of proper timing of a sample is not given sufficient attention while ordering measurement of a plasma concentration. Ideal timing should be 4 to 5 half-lives (time to reach steady-state).

Dosage regimen

We have to revise thoroughly the regimen of the treatment given, regarding the dose and frequency, specially the last dose before the test.

Infusion length

Please refer to the following (Table 1) for determination of the peak serum level.

Table 1 Determination of the peak serum level

Infusion	Dose	Interval	Peak level
30min	500mg	8hrs	26.8
60min	500mg	8hrs	25.3
120min	500mg	8hrs	22.5

Effect of disease states

Revision of the pharmacokinetics of the drug in question is important to know the effect of acute or chronic disease states on its clearance patterns.

Effect of age

There is a great variability in response to drugs at extremes of age. As an example, elderly patients are more sensitive to the CNS depressant effect of drugs but are less sensitive to cardiovascular effects of Propranolol. It is well known that children are more sensitive to morphine.

Pregnancy

Many drugs can be affected by pregnancy state. As an example, drug levels of phenytoin and phenobarbitone are lower during pregnancy.

Other TDM precautions

This is a rule of thumb! We have to rule out errors before accepting out-of-range data.

What are the most common pitfalls and error sources?

a. Time of administration of the drug is not accurate.

b. Dose administration error.

c. Inaccurate time of sampling, or timing was before steady-state is reached

d. Wrong site of sampling.

e. Lab assay error.

f. Pharmacy dispensing error

Conclusion

Lastly, the TDM is a very useful method for achieving a highest benefit of a drug and avoiding most of its side effects if done properly. Avoiding its pitfalls will gain us the maximum benefit of the procedure.

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Conflict of interest

The author declares no conflict of interest.