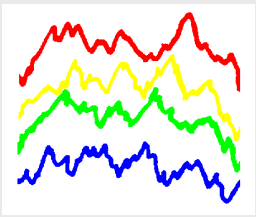


Comment: The Role of Therapeutic Drug Monitoring

Dansk Epilepsi Selskab
Forårsmøde Kolding 7.- 8. marts
2008

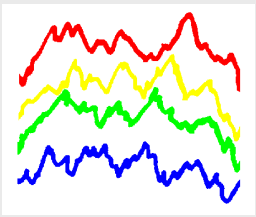


TDM and resistance

- TDM is indispensable for the establishment of pharmacoresistance
- But it needs to be done adequately

Bourgeois (1992): *“To demonstrate that the patient is indeed receiving the highest tolerated dose, some evidence of toxicity at the next higher dose must have been previously documented, at which point the dose was then promptly reduced just enough for this toxicity to subside.”*

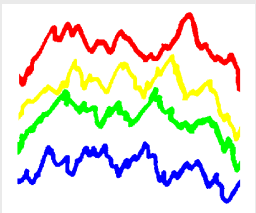
Alternatively, *“the dose under consideration is associated with evidence of beginning toxicity which is still acceptable to the patient”.*



“Therapeutic ranges” (TRs)

TRs are a pestilence

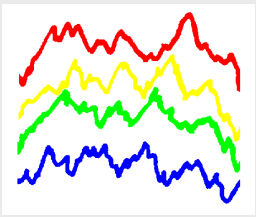
- TDM became counterproductive when patients’ drug levels started to come with reference to “therapeutic ranges”
- Virtually every non-specialist misunderstands these as a norm within which the patients should be placed and nothing more needs to be done
- These ranges are only informative; the individual needs can be higher or lower
- Very few people understand this



New guidelines on their way

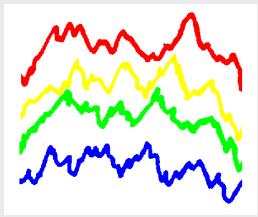
- The ILAE Commission on Therapeutic Strategies has finished a state-of-the-art paper on the correct use of TDM
- This has been accepted as an official document of the ILAE
- It is right now being edited in response to some critique from the ILAE EC and peer review
- It can be expected in EPILEPSIA later this year

These guidelines strongly recommend individualized use of TDM



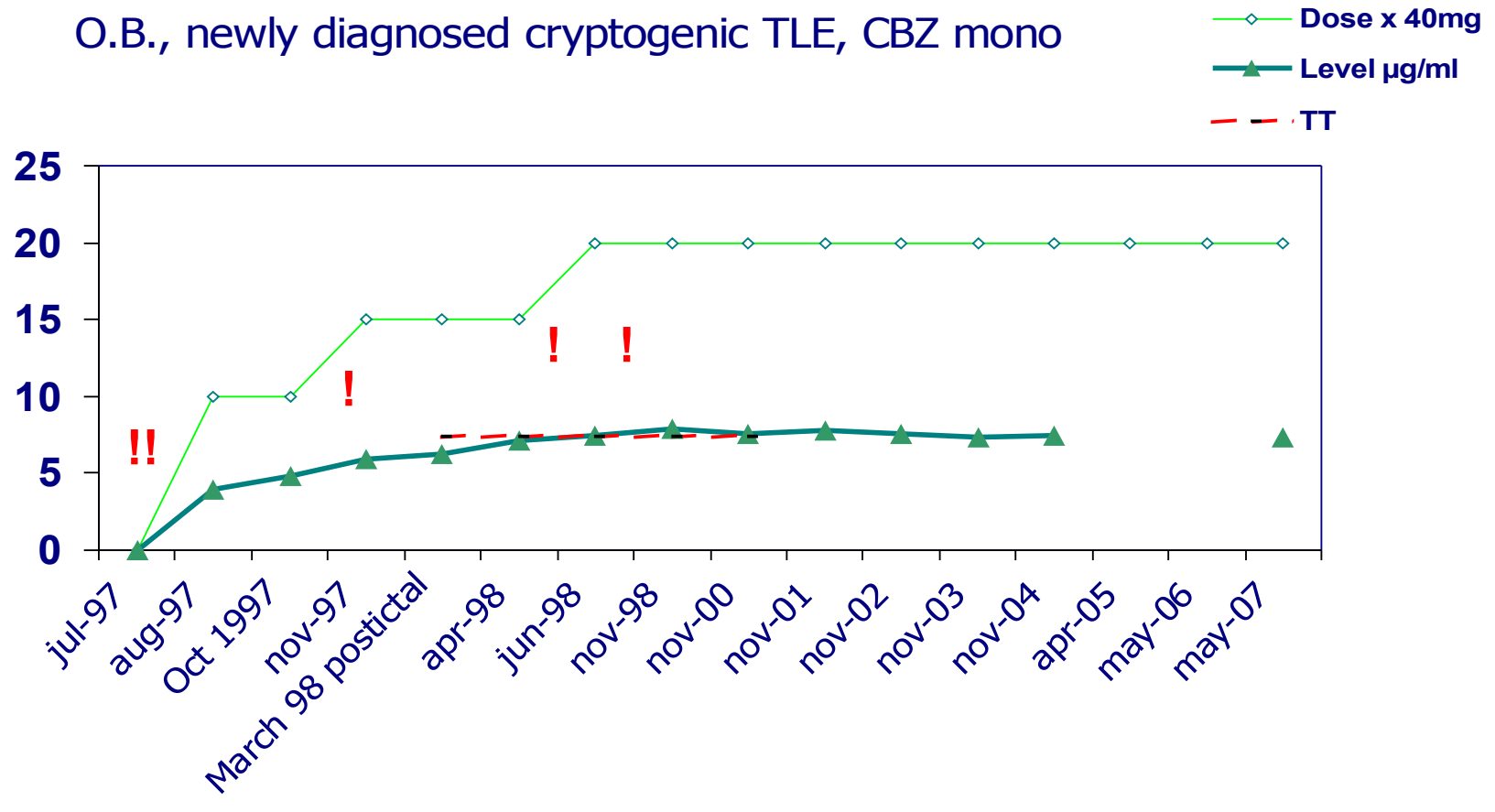
Individualized TDM: an example

- It is useful for every patient by TDM to define the plasma level which needs to be maintained to keep him/her above the individual therapeutic threshold (TT)
- In the case of an unexpected ("breakthrough") seizure, a post-ictal drug level will elucidate the situation:
- Value as expected: TT is actually higher than assumed, therapeutic level needs to be redefined
- Value below established TT: find the reason (non-adherence, PK interactions, preparation shift etc.)

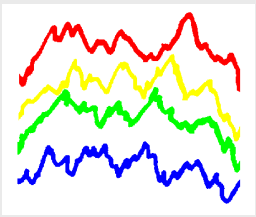


The therapeutic threshold is an individual measure

O.B., newly diagnosed cryptogenic TLE, CBZ mono

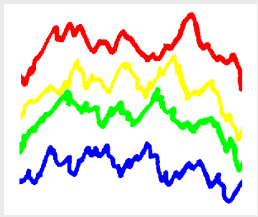


It serves as a reference for TDM in the patients' management



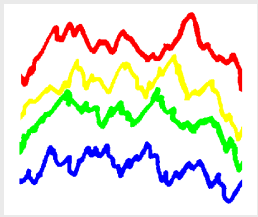
TDM with new-generation AEDs?

- It was a marketing strategy that started with the quasi-simultaneous introduction of Vigabatrine and Lamotrigine, to state that TDM was not necessary with these drugs.
- In the case of VGB this is true, otherwise not
- In the case of LTG, argument that plasma levels in seizure free patients and resistant patients were not different (M. Brodie)
- Wrong method: different populations are not comparable



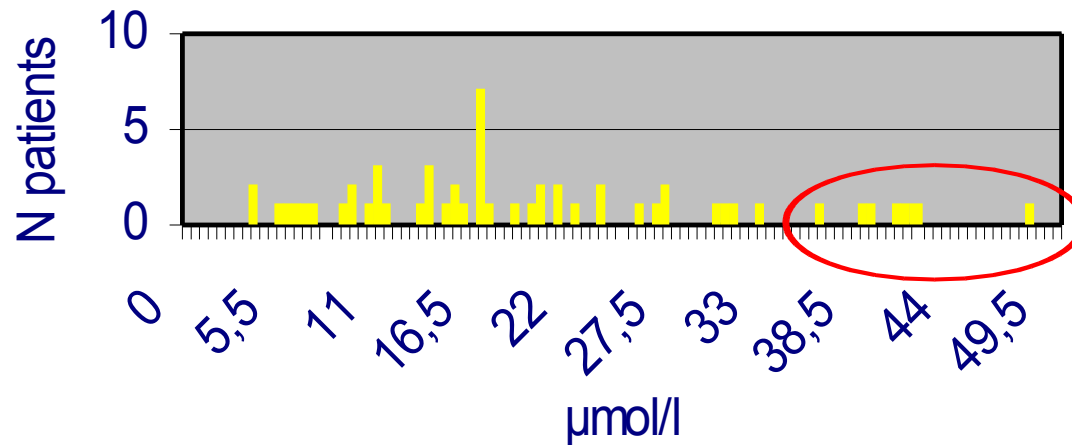
TDM with LTG

- Fröscher W et al. Epileptic disorders 2002: level dependent therapeutic and toxic effects shown
- Hirsch LJ et al. Neurology 2004: level dependent toxicity in large population of treated ptt.
- TDM fundamentally is an improved quantification of dose-dependent effects of a drug (both therapeutic and toxic)
- A useful way to demonstrate this is the investigation of therapeutic thresholds (TT)
- TT: mean of highest subtherapeutic and lowest therapeutic plasma level (or dose)

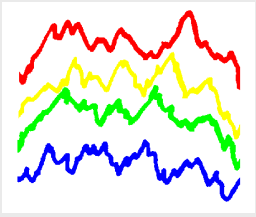


DTG therapeutic thresholds

Distribution of therapeutic thresholds of serum concentration in 55 patients on monotherapy with Lamictal



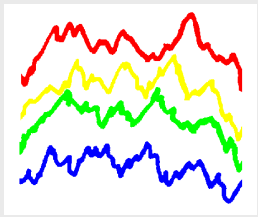
All patients seizure free without serious side effects
 7 patients (12.7 %) have a narrow therapeutic index (threshold > 35)



New AEDs where TDM is considered useful

- Oxcarbazepine
- Lamotrigine
- Levetiracetam
- Topiramate
- Zonisamide

(Perucca 2000; Johannessen & Tomson 2006)



Conclusion

There are intelligent ways to apply TDM and there are stupid ways

Intelligent, individualized TDM is still to be considered as the gold standard for the establishment of pharmacoresistance

This includes most of the newer AEDs