Brief Communication

Therapeutic drug monitoring pattern of the antiepileptic drugs in developed and developing countries

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Therapeutic drug monitoring (TDM) was introduced in the early 1960's as a method to improve antiepileptic drug (AED) therapy. Since then, different software programs have been introduced in this field for dose optimization of monitored drugs by utilizing their plasma concentrations. However, in developing countries, the situation is entirely different. The availability of a TDM service is still considered a novel tool. The medical staff working in these fields are not necessarily professionally trained in TDM applications and dose optimization of measured drugs.[1,2] The AEDs are preferred as prophylactic treatment in clinical practice. Most of them have a narrow therapeutic window. The invention of TDM in the 1960's assumed an important place in the patient's management of plasma drug level and their effects.[1] Further, the need for TDM in epilepsy treatment is due to difficulties in detecting and interpreting the clinical symptoms and signs of toxicity, in addition intermediate physiologic markers of clinical effects or toxicity of AEDs are also not available. However, it is still a relatively new practice in most developing countries. The main goal of TDM is to optimize drug therapy by individualizing the dose according to the serum concentration and the clinical effects. It is also frequently used to assess drug toxicity and patient compliance. Despite the wide acceptance of TDM, there is some debate regarding its cost effectiveness and usefulness in clinical decision making. Currently, great efforts have been made to use TDM more effectively and to avoid unnecessary assays.[2-4] Though a number of new AEDs are available, phenytoin, carbamazepine, and phenobarbitone are still commonly used in clinical practice. Hence, in the present study the TDM pattern of these 3 commonly used drugs was assessed. The plasma levels of drugs were categorized into 3 different levels as therapeutic, subtherapeutic, and toxic. A retrospective analysis was carried out to compare the TDM pattern between developed and developing countries.

A systematic literature search was carried out for the period from July 1966 to July 2006 in PubMed, Medline, EMBASE, and the Cochrane Library using the search words: TDM pattern, antiepileptic, and so forth. A reference list of original reports and review articles was screened for desired studies. We also manually searched related journals in the National Medical Library (New Delhi), library of the institute, and recent conference abstracts for 2003-2005 of international societies of epilepsy.

Studies mentioning antiepileptic level (therapeutic, subtherapeutic, and toxic) patterns were selected. The samples were determined using the high performance liquid chromatography (HPLC) technique. The HPLC technique can measure phenytoin, carbamazepine, and phenobarbitone samples simultaneously when all are present in the same sample, and is considered the best method available for drug level estimation. We included studies related to TDM pattern of different AEDs: phenytoin (10-20 mg/L), carbamazepine (4-10 mg/L), and phenobarbitone (15-40 mg/L). Studies were selected that satisfied the following inclusion criteria: studies published from a tertiary center in developed and developing countries, studies including TDM pattern of commonly used AEDs, for example, phenytoin, carbamazepine, phenobarbitone, and studies reporting the TDM pattern for more than one year. Studies that did not mention the selected AED level (therapeutic, subtherapeutic, and toxic) were excluded. The selection criteria remains same for developed and developing countries.

Data were extracted in a specially designed format. The outcome measure was expressed in percentage of level of different AEDs, and categorized into therapeutic, subtherapeutic, and toxic level. Data were entered in the Excel computer program and analyzed by SPSS 10.0 version. Data were expressed in percentage of different levels from developed and developing countries and and difference of therapeutic, subtherapeutic and toxic levels were calculated. A p-value <0.05 was considered significant.

Thirty articles were cited in total, among which, 7 articles were irrelevant, and 23 articles were selected for further screening. Out of the 23 articles, only 5[2-4,6,7] were selected for analysis and the remaining 18 articles were rejected due to incomplete data or different drugs selected for analysis. Tertiary centers were selected from developed (Scotland, Egypt, Saudi Arabia, and Turkey) and developing countries (India), and data were divided into 2 categories. In India, data from PGIMER, Chandigarh, was included.[3,4] The entire blood samples were received for the TDM from 1998 to 2004. A total of 3534 blood samples of patients were received and analyzed by HPLC for the drugs phenytoin, carbamazepine, and phenobarbitone.

Studies from Scotland,[7] Egypt,[2] Saudi Arabia,[2] and Turkey[6] evaluated the pattern of TDM from their centers (**Table 1**). Overall assessment showed values of cumulative TDM to be therapeutic in 68% for carbamazepine, 49% for phenytoin, and 56% for phenobarbitone, subtherapeutic in 25% for carbamazepine, 41% for phenytoin, and 24% for phenobarbitone, and toxic in 7% for carbamazepine, 5% for phenytoin, and 20%

Table 1 - Different antiepileptics drug levels reported from various centers from developed and developing countries.

Study	Therapeutic level	Therapeutic	Subtherapeutic	Toxic
		n (%)		
Yamanturk et al, 2000 (Turkey)[6]				
Carbamazepine	4-10 mg/L	1504 (76.6)	332 (16.9)	126 (6.4)
Phenytoin	10-20 mg/L	415 (37.3)	564 (50.8)	132 (11.9)
Phenobarbitone	15-40 mg/L	509 (61.9)	228 (27.7)	85 (10.3)
McKee et al, 1993 (Scotland)[7]				
Carbamazepine	4-10 mg/L	692 (62.0)	112 (10.0)	317 (28.0)
Phenytoin	10-20 mg/L	383 (48.0)	247 (32.0)	168 (20.0)
Phenobarbitone	15-40 mg/L	234 (75.0)	75 (23.0)	7 (2.0)
EL Desoky et al, 2003 (Egypt)[2]				
Carbamazepine	4-10 mg/L	198 (77.0)	48 (19.0)	11 (4.0)
Phenytoin	10-20 mg/L	14 (20.0)	46 (19.0)	10 (14.0)
EL Desoky et al, 2003 (Saudi Arabia, 1996)[2]				
Carbamazepine	4-10 mg/L	480 (71.0)	118 (18.0)	75 (11.0)
Phenytoin	10-20 mg/L	85 (31.0)	140 (51.0)	51 (18.0)
EL Desoky et al, 2003 (Saudi Arabia, 2001)[2]				
Carbamazepine	4-10 mg/L	830 (82.0)	128 (13.0)	46 (5.0)
Phenytoin	10-20 mg/L	281 (34.0)	393 (49.0)	134 (17.0)
Vinu et al, 2006 (India)[3]				
Carbamazepine	4-10 mg/L	1045 (75.0)	268 (19.0)	86 (6.0)
Phenytoin	10-20 mg/L	662 (29.0)	1171 (52.0)	428 (19.0)
Phenobarbitone	15-40 mg/L	307 (56.0)	214 (39.0)	32 (6.0)
Garg et al, 2000 (India)[4]				
Carbamazepine	4-10 mg/L	93 (75.6)	22 (17.9)	3 (2.4)
Phenytoin	10-20 mg/L	38 (32.8)	63 (54.3)	12 (10.3)

for carbamazepine. In the developing countries,[3,4] the level of phenytoin was found to be 32% subtherapeutic, 51% therapeutic, and 17% toxic level in comparison with phenytoin, 48% subtherapeutic, 32% therapeutic, and 20% toxic levels in developed countries.[2,6,7] Carbamazepine levels in developing countries[3,4] were found to be 77% subtherapeutic, 17% therapeutic, and 6% toxic, in contrast to the developed counties data[2,6,7] of 62% subtherapeutic, 10% therapeutic, and 28% toxic. The phenobarbitone plasma level obtained were found to be 60% subtherapeutic, 32% therapeutic, and 8% toxic in developing countries,[3,4] but in the developed countries[2,6,7] it was 75% subtherapeutic, 23% therapeutic, and 7% toxic. The results (carbamazepine, phenytoin and phenobarbitone) obtained are almost comparable in developed and developing countries; however, increasing requests were noted in 2000 in the above developing country center for TDM.

The present analysis found only a few centers from developed and developing countries that reported their antiepileptic TDM pattern. In our study, we included only the most commonly used AEDs, such as phenytoin, carbamazepine, and phenobarbitone. Among the AEDs, phenytoin is still the most important anticonvulsant, and phenytoin kinetics have been thoroughly investigated in man. Studies reported frequent inter-individual variation in the plasma level/dose ratio for these drugs.[5] Plasma level monitoring can circumvent this. Dose changes during treatment mainly depend on dose dependent kinetics, as individual variations exist in the rate of metabolism, and several pharmacokinetic drug interactions. Carbamazepine, the other conventional tested drug, has first order elimination, and the rate of metabolism increases after a few weeks of treatment. The TDM was found to be beneficial due to drug interaction with other AEDs, or with the other classes of drug. Phenobarbitone is commonly used in epileptic treatment, however, due to its variable rate of elimination, TDM is required.

Though the chosen AEDs are extensively studied, there is limited data available on clinical pharmacokinetics and pharmacogenetic variations in the metabolism of different AEDs, and its racial difference in metabolism in Western and Asian populations, and therefore, the present study indicates that antiepileptic TDM patterns are similar in developed and developing countries, however, only a very few centers report their TDM patterns in the published literature.

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Errata

In the manuscript "Association between the functional independence measure and Glasgow coma scale regarding the rehabilitation outcomes of traumatic brain injury" Neurosciences 2009; Vol. 14 (1): 41-44, the author affiliation detail should have appeared as follows:

From the Departments of Physiotherapy and Rehabilitation Sciences (Nazzal, Maayah, Al-Jarrah), Neurosurgery (Jamous), Forensic Medicine and Toxicology (Azab), Jordan University of Science and Technology, Irbid, Jordan and the Physical Therapy and Rehabilitation Sciences Department (Al-Jarrah), University of Kansas Medical Center, Kansas City, Kansas, United States of America, and Hamad Medical Corporation (Nazzal), Qatar.

In the manuscript "Epidemiology of Bell's Palsy in Isfahan, Iran" Neurosciences 2009; Vol. 14 (2): 186-187, Reference number 5 should have appeared as follows:

5. Chen WX, Wong V. Prognosis of Bell's palsy in children--analysis of 29 cases. ***Brain Dev*** 2005; 27: 504-508.