Random total antiepileptic drug levels and seizure control during pregnancy

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ABSTRACT

Objective: To study the correlation of randomly-tested total antiepileptic plasma levels and seizure control in a retrospectively collected group of pregnant epileptic Saudi women.

Methods: The medical records of 30 Saudi epileptic female patients were reviewed during their subsequent pregnancies (total of 50). The type of antiepileptic drugs used during each pregnancy, the dose of each drug and the corresponding total plasma levels were noted. Antiepileptic drugs assay were carried out randomly during pregnancy either by TDX or a sensitive high performance liquid chromatography method.

Results: A total of 50 pregnancies were studied. The most common seizure type in these women was complex partial seizure followed by primary generalized epilepsy, myoclonic seizures and of least occurrence was the simple partial seizure with secondary generalization. All patients were received antiepileptic drugs, including either carbamazepine, phenytoin, valporic acid, phenobarbitone or clonazepam. In a total of 24 pregnancies (48%), the serum levels of antiepileptic drugs were subtherapeutic during the first trimester. Recurrent seizures occurred in a total of 20 pregnancies (40%) especially in the 3rd trimester.

Conclusions: It is concluded that subtherapeutic serum levels of antiepileptic drugs correlated highly with the increased frequency of seizure in these pregnant women. Monitoring of state of seizure control in epileptic pregnant women should be made regularly during the course of their pregnancies.

Keywords: Epilepsy, pregnant women, antiepileptic drug levels.

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Epilepsy is the clinical phenomena resulting from spontaneously recurring seizures. Seizure is an intermittent stereotype disturbance of consciousness, behavior, emotions, motor function, perception or sensation that results from cortical neuronal discharges. The incidence of epilepsy is 0.05% per year (50/100,000) according to the Rochester study with the prevalence rate of 4-10 per 1000.[1] Male gender, extreme age group and single marital status have been shown to be associated with higher mortality.[2,3] It has been estimated that 0.3–0.4% of children today are born to mothers suffering from epilepsy.[4] Pregnancy in women with epilepsy may, however, be more complicated than that of their healthy counterparts since pregnancy may affect seizure control by altering the pharmacokinetics of antiepileptic medications.[5] Also, the rate of obstetric complications are higher. Antiepileptic drugs have also been reported to increase the risk of birth defects.[4] Treatment of epilepsy, in general must be based on a correct clinical diagnosis supplemented by electroencephalography (EEG) and neuroimaging. The use of antiepileptic drugs is usually associated with good response resulting in a seizure remission rate of 60-75% of all epileptic cases.[6] Pregnant

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women with epilepsy, similar to those that are not pregnant, should be treated according to the usual therapeutic rules and whenever possible they should be controlled with a single antiepileptic drug at the lowest possible effective dosage.[6] If a patient needs a change in the medications, this should be made, as far as possible, before the beginning of pregnancy. None of the antiepileptic drugs (carbamazepine, valporic acid, phenytoin and phenobarbitone) are known to cause less fetal abnormalities than any other. Also, none of the newer antiepileptic drugs (felbamate, gabapentin, lamotrigine, vigabatrin) are presently licensed for use during pregnancy, since the safety of the latter drugs have not yet been documented.[7] Recent studies suggest that total carbamazepine serum levels are slightly lower during the 3rd trimester as compared with baseline, whereas the unbound pharmacologically-active concentration remains essentially unchanged. In contrast, while total phenytoin serum levels decrease steadily as pregnancy progresses, unbound levels decrease far less. Total valproate serum levels also decrease as pregnancy proceeds, but the change in unbound concentrations may be insignificant. Therefore, adjustment of the dose of antiepileptic drugs should be based on the clinical condition of the patient and seizure control.[8] As far as I am aware, no studies in Saudi Arabia have investigated the state of seizure control during pregnancy and its correlation to the plasma levels of the commonly used antiepileptic drugs. Therefore, in the present study, I investigated the seizure control and its relation to these drugs levels in pregnant Saudi women.

Methods. The clinical files of 30 Saudi women with epilepsy in the age range of 20-45 were reviewed retrospectively. Clinical data of their epilepsy and its control by the use of antiepileptic drugs were reviewed. The total levels of these medications, which were randomly determined during pregnancy were also noted. Ten patients had more than one pregnancy during the period of the retrospective study. This increased the number of recorded pregnancies to 50. The data was carefully analyzed to make note of the age for onset of the seizures, type of seizures and frequency of the seizure during the 1st, 2nd and 3rd trimester of pregnancy. The type of antiepileptic drugs used during each pregnancy, the dose range of each drug used and the corresponding drug plasma levels were all noted. The plasma levels of the antiepileptic drugs were determined in the Pharmacokinetics Unit in King Khalid University Hospital either via TDX or a sensitive high performance liquid chromatography method.

Results. The total number of patients studied were 30 Saudi pregnant women with epilepsy. They

Table 1 - Demographic data of patients.

Patient No.	Age of patient during pregnancy	No. of pregnancies reviewed	Patient No.	Age of patient during pregnancy	No. of pregnancies reviewed
1)	19, 23, 26, 19	4	16)	19	1
2)	27, 29, 35	3	17)	19	1
3)	29	1	18)	23	1
4)	28	1	19)	26	1
5)	20, 22, 24, 27, 33	5	20)	33	1
6)	23, 28	2	21)	32	1
7)	24, 26	2	22)	32	1
8)	23, 28	2	23)	32	1
9)	28, 29	2	24)	35	1
10)	25	1	25)	34, 35, 44	3
11)	22	1	26)	28	1
12)	25, 28	2	27)	27	1
13)	36, 37	2	28)	27	1
14)	38, 29, 44	3	29)	25	1
15)	20	1	30)	36, 37	2

Table 2 - Seizure classification, frequency and antiepileptic drugs used by women.

Type of seizure	No. of patients	Antiepileptic drug used	Seizure frequency/ pregnancy
Primary generalized tonic clonic seizures	6	Phenytoin Valproic acid, Phenobarbitone	5
Myoclonic seizures	7	Valproic acid, Phenytoin, Carbamazepine, Clonazepam	1
Complex partial seizure	14	Carbamazepine	13
Simple partial seizure	3	Carbamazepine	1

Table 3 - Antiepileptic drug distribution, doses and mean serum level.

Antiepileptic drug	No. of patients	Daily dose	Drug level (μg/ml) Mean ± SE
Carbamazepine	19	400-1200 mg	7.45 ± 0.5
Phenytoin	14	100-600 mg	12.50 ± 1.5
Valproic acid	5	400-1000 mg	18.80 ± 3.2
Phenobarbitone	3	25-100 mg	15.2 ± 1.3
Clonazepam	1	2 mg	Non determined

had a total of 50 pregnancies. Ten women had more than one pregnancy with the range of 2-5 pregnancies per woman. Fourteen patients had 14 complex partial seizures. In 20 out of the 50 recorded pregnancies, seizures occurred mostly in the 2nd and 3rd trimester of pregnancy. Major seizures occurred in labor in only 2 pregnancies. The plasma levels of carbamazepine were all in the therapeutic range (4-10 mg/ml) in all but 4 pregnancies. The plasma levels of phenytoin were subtherapeutic in 10 pregnancies and were in the therapeutic range in only 2 pregnancies. The most striking finding was that the plasma levels of valporic acid and phenobarbitone were subtherapeutic in all pregnancies. Nineteen patients received carbamazepine in a dose of 400-1200 mg/day while 14 patients received phenytoin in a dose range of 100-600 mg/day. Valporic acid was given in a dose range of 400-1000 mg/day to 5 women and the remainder of the patients received phenobarbitone at 25-100 mg/day. Only 1 patient had been treated with clonazepam at 2 mg/day. Combination therapy was given to 6 patients who had received both carbamazepine + phenytoin and 3 patients who had received carbamazepine + phenobarbitone while only one patient was treated with carbamazepine + valporic acid and another one with carbamazepine + valporic acid + clonazepam. The plasma drug levels were measured in the 1st trimester in all pregnancies. The estimated plasma levels of carbamazepine were in the range from 3.9 to 13.2 mg/ml (normal range = 4-10 mg/ml), that of phenytoin were in the range 3-9 to 25.6 mg/ml (normal range = 10-20 mg/ml), while the plasma levels of pharmabarbitone ranged from 15.9 to 21.9 mg/ml (normal range = 15-40 mg/ml) (Table 3). No seizures had occurred in 30 pregnancies. Out of the 50 pregnancies, one to 2 seizures were reported in 11 pregnancies. Nine pregnancies had more than 2 seizures during the 1st, 2nd and 3rd trimesters. Complex partial seizures were reported in 13 pregnancies, major tonic clonic seizures in 5 pregnancies while myoclonic seizures and partial motor seizures were noted in one pregnancy each. The seizures occurred in the 3rd trimester in 12 pregnancies and in the 2nd trimester in 8 pregnancies, while seizures occurred in 4 pregnancies during the 1st trimester. Seizures which were noted at labor occurred only in 2 pregnancies. Seven of the pregnancies which had seizures during the 3rd trimester had also seizures in the 2nd trimester. Seizures were noted during the 1st and 2nd trimester in only one pregnancy and in all trimesters in one pregnancy (Table 4).

Table 4 - Seizure distribution during pregnancy.

No. of seizures	SEIZURE OCCURRENCE			
	1st Trimester	2nd Trimester	3rd Trimester	Labor
30	4	8	12	2
← 1 → ← 7 → ← 1 →				
Total No of pregnancies = 50 One patient had seizures in first and second trimesters Seven patients had seizures in second and third trimesters One patient had seizures during all trimesters				

Discussion. An increased risk of seizures during pregnancy and immediately after labor had already been recognized in women with epilepsy.[8,9]

At constant drug dosage, the plasma levels of most antiepileptic drugs tend to decrease during pregnancy but return to pre-pregnant levels within the 1st month after delivery. Low plasma levels, however, may provoke seizures.[10] Therefore, limited information is available regarding the disposition of antiepileptic drugs during pregnancy.[11-15] Sodium Valproate is extensively bound to plasma proteins (90%).[16] This binding is significantly decreased in pregnant women. A two-fold increase in the unbound valporic acid fraction has been observed during pregnancy. Phenytoin is also extensively bound to plasma proteins with the unbound fraction reaching up to 10%. However, the unbound fraction for carbamazepine is 25% and for phenobarbitone is 50%. Consequently, the decrease in protein binding capacity during pregnancy results in increased plasma clearance of antiepileptic drugs leading to decreased total plasma levels.[16] Other changes which occur during pregnancy such as increased renal clearance, metabolic capacity, increased tissue binding, altered receptor sensitivity and increased body water may counteract the effect of altered drug binding.[5] Monitoring of unbound levels may be of advantage during pregnancy. Thus, it is not necessary to modify dosage of antiepileptic drugs according to changes in total concentration, but it is important to ensure patient compliance.[12,18] A recently published population-based study has shown than 55-65% of pregnant women with epilepsy had primary generalized epilepsy.[15] The most common seizure types which I observed in our patients were complex partial seizures (47%) and generalized tonic clonic seizures (30%). Schmidt (1982) had reviewed reports on 2165 pregnancies which have been published since 1980. He concluded that seizure frequency increased in 24%, decreased in 23% and remained unchanged in 53% of the cases he had studied. Also, status epilepticus was not reported in our patients. Knight and Rhind (1975) reported the risk of increased seizure frequency is higher in the 1st trimester of pregnant women while Remilland (1982) found the risk of seizure to be highest in the 3rd trimester. These latter results are in agreement with my present observations. The Helsinki study[21] found that convulsive (generalized tonic clonic seizures and complex partial seizures) increased in the 3rd trimester rather than during the 1st and the 2nd trimester of pregnancy, a finding which is in agreement with my present results. Although it is not clear whether any trimester is associated with the higher risk of seizure, it is undisputed that the period of labor carries a particular risk of seizure occurrence.[21] Seizure occurred at labor in 0.04% of the pregnant epileptic women studied. The patients follow up was not satisfactory as serial determinations of plasma drug levels and hence antiepileptic drugs dose adjustments were not performed according to seizure control. It is therefore concluded that the general recommendation would be to use monotherapy at the lowest possible antiepileptic drug dose but at plasma levels that would protect against tonic clonic seizures. Additionally, it is essential to monitor regularly the status of the pregnant epileptic women in order to achieve better seizure control.

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