MEDICINE ELSEWHERE

Prepared by

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Valdizan EM, Garcia AP, Armijo JA. Time course of the GABAergic effects of vigabatrin: Is the time course of the brain related to platelet GABA-transaminase inhibition? Epilepsia 1999; 40:1062-1069.

Vigabatrin is a selective inhibitor of brain 4-aminobutyrate-2-ketoglutarate aminotransferase and increases GABA levels in the whole brain of mice and rats.

The aim of this study was to investigate the time courses of brain GABA concentration, GABA-T inhibition in brain and platelets, brain GAD activity and vigabatrin plasma concentrations in rats after a single dose of 200 mg/kg of vigabatrin, and after 3 and 8 days of treatment with 200mg/kg/day.

Both single and multiple doses significantly decreased brain and platelet GABA-T activity. Inhibition of platelet GABA-T was greater and longer after multiple doses. Platelet GABA-T activity reflects the time course of the increase in GABA better than does brain GABA-T after multiple doses of vigabatrin in rats. On the other hand, brain GABA increased after both therapies. Elevation of GABA in brain occurred quicker with single dose and longer with multiple doses. Plasma concentration of vigabatrin reached a maximum at 4 h and rapidly decreased after a single dose. Three and 8 days of vigabatrin produced a similar time course for plasma concentration, but mean concentration at 4 h was significantly higher than after a single dose.

Bragin A, Engel J, Wilson CL, et al. Hippocampal and entorhinal cortex high-frequency oscillations (100-500 Hz) in human epileptic brain and in kainic acid-treated rats with chronic seizures. Epilepsia 1999; 40:127-137

Ripples, 120-200 Hz field oscillations in hippocampal and parahippocampal areas of normal rats, are produced by inhibitory postsinaptic potentials occurring during high-frequency bursts of inhibitory interneurons and reflect a state of network synchronization. Recordings of electrical activity were taken in hippocampus and entorhinal cortex of normal rats, kindled rats, rats injected with kainic acid and patients with mesiotemporal lobe epilepsy. Ripple activity was found in CA1 and entorhinal cortex of all groups. Surprisingly, higher frequency oscillatory activity ranging from 200 to 500 Hz and 10-100 ms in duration was termed as fast ripples and recorded only in patients with epilepsy and kainic acid-treated rats. Fast ripples were found adjacent to the epileptogenic lesion in hippocampus, entorhinal cortex and dentate gyrus. Unaltered presence of ripples in epileptic animal models and patients indicates that inhibitory mechanisms are preserved in epilepsy. In addition, fast ripples appear to represent excitatory synaptic activity generated by abnormal synchronous pyramidal cell burst firing. If the fast ripple activity is unique to tissue capable of generating spontaneous seizures, it may become a useful marker for identification of the epileptic region in patients who are surgical candidates.

Fattore C, Cipolla G, Gatti G, et al. Induction of ethinylestradiol and levonorgestrel metabolism by oxcarbazepine in healthy women. Epilepsia 1999; 40:783-878.

Oxcarbazepine, a new anticonvulsant agent, differs from carbamazepin in pharmacokinetic behaviour and biotransformation profile. The effect of oxcarbazepine on the kinetics of ethinylestradiol and levonorgestrel was evaluated in a randomized double-blind placebo-controlled study in healthy women. The protocol was approved by the Ethics Committee of the center. Twenty-two healthy women aged 18-44 years were required to use a reliable nonhormonal contraceptive method throughout the study. A placebo or oxcarbazepine (1200 mg/day) was administered in randomized sequence for 26 days with a washout period. A steroid oral contraceptive containing 50 µg ethinylestrodiol and 250 µg levonorgestrel was given for the first 21 days of each cycle. Plasma steroid concentrations were determined by using a gas chromatography-mass spectrometry method. Compared with placebo, oxcarbazepine treatment induced a significant reduction in the plasma concentrations of both steroids. Peak plasma concentrations of ethinylestradiol were reduced by 30% during oxcarbazepine treatment, whereas peak concentrations of levonorgestrel decreased to a lesser

extent. Reduction in plasma concentrations of both steroids by oxcarbazepine may lead to a decreased efficacy of contraceptive agents. These patients should preferentially be given a high-dose steroid preparation. Alternative contraceptive methods may also be considered in women receiving oxcarbazepine.

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The Ethics Committee of the American Society of Reproductive Medicine. Sex selection and preimplantation genetic diagnosis. Fertil Steril 1999;72:595-598.

In 1994, the Ethics Committee of the American Society and Reproductive Medicine concluded that preimplantation sex selection is appropriate for avoiding the birth of children with genetic disorders, but it is not acceptable when used solely for nonmedical reasons. Interest in sex selection has a long history. Methods have varied from special modes and timing of coitus to the practice of infanticide. Medical technologies have only recently made it possible to attempt sex selection of children before their conception or birth. For example, screening for carriers of X-linked genetic diseases allows potential parents not only to decide whether to have children but also to select the sex of their offspring before pregnancy or before birth. Methods now available for prepregnancy and prebirth sex selection are (1) prefertilization separation of X-bearing from Y-bearing spermatozoa; (2) preimplantation genetic diagnosis (PGD), followed by the sex selection of embryos for transfer; and (3) prenatal genetic diagnosis, followed by sex-selective abortion. Preimplantation genetic diagnosis is used with assisted reproductive technologies to identify genetic disorders, but it can also provide information regarding the sex of embryos either as a by-product of testing for genetic disorders or when it is done purely for sex selection. Whatever its methods or its reasons, sex selection has encountered significant ethical objections throughout its history. More recently, concerns have focused on the dangers of gender discrimination in contemporary societies. Although the actual use of PGD for sex selection is still infrequent, its potential use continues to raise important ethical questions. But important advantages can be achieved through this technique; the medical advantage of preventing the transmission of sex-linked genetic disorders such as hemophilia A and B, Lesch-Nyhan syndrome, Duchenne-Becker muscular dystrophy, and Hunter syndrome. It is sometimes argued that PGD and sex selection of embryos for transfer is a lesser evil than the alternative of prenatal diagnosis and sex-selected abortion. The weighing of opposing attitudes regarding PGD and sex selection depends on an assessment of the strength of the reasons given for and against it. PGD has the potential for serving sex selection in varying categories of cases, each of which raises different medical and ethical questions. Information about the sex of an embryo may be obtained (a) as an essential part of or by-product of PGD performed for other medical reasons, (b) through a test for sex identification that is added to PGD performed for medical reasons, (c) a patient who is undergoing IVF procedures as part of fertility treatment may request PGD solely for the purpose of sex selection and, (d) a patient who is fertile may request IVF and PGD, both solely for the purpose of sex selection. Each of these situations calls for a distinct medical and ethical assessment. There presently is little debate over the ethical validity of PGD for sex selection when its aim is to prevent the transmission of sex-linked genetic disease. It is less easy to eliminate concerns regarding PGD and sex selection when it is aimed at serving social and psychological goals not related to the prevention of disease. Ethical arguments against sex selection appear to gain strength as the categories of potential cases descend from (a) to (d).

Recommendations therefore follow from an effort to respect and to weigh ethical concerns that are sometimes in conflict namely, the right to reproductive freedom, genuine medical needs and goals, gender equality, and justice in the distribution of medical resources. The Committee recommends the following:

1- PGD used for sex selection to prevent the transmission of serious genetic disease is ethically acceptable.

2- In patients undergoing IVF, PGD used for sex selection for nonmedical reasons holds some risk of gender bias, harm to individuals and society, and inappropriateness in the use and allocation of limited medical resources.

3- The initiation of IVF with PGD solely for sex selection holds even greater risk of unwarranted gender bias, social harm, and the diversion of medical resources from genuine medical need. It should be discouraged.

4- Ethical caution regarding PGD for sex selection calls for study of the consequences of this practice.

Creinin DM, Lisman R, Strickler RC. Screening for factor V Leiden mutation before prescribing combination oral contraceptives. Fertil Steril 1999;72:646-651.

Hypercoagulability can be inherited or acquired. The most common cause of acquired hypercoagulability in women of reproductive age in developed countries is the use of a combination of oral contraceptives (OCs). Most of these women use combination OCs that contain ethinyl estradiol, a synthetic estrogen that results in an increased risk of venous thromboembolic disease (10-30 in 100,000). The most common cause of congenital hypercoagulability known today is factor V Leiden mutation, which is estimated to be responsible for 50% of cases of familial venous thrombosis and 30% of venous thromboembolic events. The inherited factor V Leiden mutation is a single base pair substitution in the coding sequence for factor V that renders it unable to be inactivated by activated protein C (APC). This shifts the balance toward hypercoagulability. Factor V Leiden mutation is present in 4.85% of white women in the United States. Because the prevalence of factor V Leiden mutation is high compared with other inherited causes of hypercoagulability, recent discussions in the medical literature have suggested that prescreening new users of OCs for this congenital form of APC resistance may be advisable to identify a high risk group who should avoid the use of combination OCs. To decide whether it is feasible to screen for factor V Leiden mutation in women in the United States before prescribing combination OCs, cost-effectiveness analysis is performed to calculate the cost of preventing one venous thromboembolic event and one death in users of combination OCs. Establishing limits of cost-effectiveness is, in itself, potentially controversial; interventions that cost $50,000 or less per year of life saved are generally acceptable, whereas those that cost $50.000-$100.000 are borderline, and those that more than $100.000 are not cost-effective.

The estimated risk of a venous thromboembolic event for those women who have factor V Leiden mutation and use combination OCs is 140 in 100,000. The risk of death for users of combination OCs is, 3 in 1 million. If the user of combination OCs has factor V Leiden mutation, the risk of death is increased to 14 in 1 million. Screening for factor V Leiden mutation involves 2 tests. An initial screening test will identify individuals who are at high risk of having factor V Leiden mutation. In women who screen positive for factor V Leiden mutation, DNA mutation is confirmed by polymerase chain reaction.

The number of women who would require testing for factor V Leiden mutation to prevent one death resulting from venous thromboeombolic disease varies from 1.9 million to>20 million depending on ethnicity. The annual cost to prevent one death resulting from venous thromboembolic disease if a policy of screening all users of combination OCs were enacted would be more than $300 million. It does not seem cost-effective. But dollar amounts cannot stand alone without weighing the individual impact of the disease in question.

Given that>50% of venous thromboembolic disease is unreleated to factor V Leiden mutation, the best screening tool is taking a thorough personal and family history. Women with a positive history should not necessarily be screened for factor V Leiden mutation, for deficiencies of protein C, protein S, or antithrombin III or any other factor to show that they can or cannot safely use combination OCs. These patients can use progestin-only methods. As a conclusion, given the prevalence of factor V Leiden mutation in the U.S. population, screening for this inheritable defect before prescribing combination OCs is not a cost-effective use of U.S. health care dollars.

Gruber DM, Berger UE, Sator MO, Horak F, Huber JC. Computerized assessment of facial hair growth. Fertil Steril 1999;72:737-739.

Androgen-releated disorders in women such as hirsutism, are difficult to objectify. Monitoring of either biochemical responses or the patients subjective assessment is not always sufficent, and an additional objective measure of hair growth is necessary for full assessment. Different objective and reproducible scoring systems have been used in the past. In the study a computer assisted method is documented. In 1961, Ferriman and Gallwey developed a score for semiquantitative assessment of body hair growth suitable for clinical use in hirsute women. The Ferriman-Gallwey score is used most often in clinical studies, where hirsutism is indicated by a score of>8 and the absence of hirsutism by a score of<8. Another means of assessing facial hirsutism is with the use of the Bardin and Lipsett, criteria. This is considered to be the best method for clinical use so far devised. There are also other scoring systems. No method has been presented that fulfills the criteria of precision, objectivity, and reproducibility for assessing clinical hair growth in patients with hirsutism. The lack of an accurate technique makes it difficult to objectively document the therapeutic success of medication used to treat hirsutism.

In this study facial hair growth was monitored with video equipment in four men, three hirsute and three nonhirsute women. Measurements were performed on

four regions of interest on the face (left and right cheeks, upper lip, and chin) on day 0 and day 21. In the men, a steady and marked increase in beard hair over the 20-day period was observed. This increase corresponded with the daily growth rate of beard hair. Similarly, significant growth of facial hair in the hirsute women was observed. In the nonhirsute women only minimal changes in facial hair growth was seen.

In the discussion it is said that computerized methods enable for the first time the measuring of hair growth objectively in men and women and its documentation over a specific period.

Investigators say that this method can easily be adopted by other investigators. The minimal equipment includes a microscope with a fixed focus, a video camera, a digital framegrabber and a Digi Trace-Macro for image analysis. This method has been shown to measure the growth of hair and, requires a suitable scoring system. With the help of such a system, it should be possible to achieve an objective and non-investigator dependent evaluation of hirsutism.

MEETINGS

19 - 20 April 2000, Port Sunlight

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ANNOUNCEMENT

Marmara Medical Journal is happy to announce the winners of the 1999 "Young Scientist" award:

Belgin Küçükkaya

Department of Biochemistry, School of Medicine, Marmara University, Istanbul for the excellent work on
**"NMDA receptor activity and its modulation by sulfhydryl compounds:
Chemiluminescence measurements in rat brain cortical synaptosomes"**

AND

Deniz Ertem

Sub-department of Pediatric Gastroenterology, Department of Pediatrics, School of Medicine,
Marmara University, Istanbul for the excellent work on
"Complications of intravenous deep sedation in pediatric endoscopy"

NMDA RECEPTOR ACTIVITY AND ITS MODULATION BY SULFHYDRYL COMPOUNDS: CHEMILUMINESCENCE MEASUREMENTS IN RAT BRAIN CORTICAL SYNAPTOSOMES

Belgin Küçükkaya / Goncagül Haklar / A. Süha Yalçın. Marmara Med. J. 1999;2:70-73.

ABSTRACT

Objective: We have used chemiluminescence (CL) measurements to investigate the effect of modulatory compounds on N-methyl-D-aspartate (NMDA) receptor activity in rat brain frontal cortex synaptosomes.

Methods: Freshly prepared synaptosomes (protein concentration: 5 mg/mL) were incubated with different modulatory molecules such as Zn^{++} (1 mM), Cd^{++} (1 mM), reduced glutathione, (GSH) (1 mM, 10 mM), oxidized glutathione (GSSG) (1 mM, 5 mM), dithiothreitol (DTT) (1 mM, 10 mM) and N-ethylmaleimide (NEM) (1 mM, 10 mM) for 5 minutes at room temperature. After preincubation, 0.1 mM NMDA was added either alone or in the presence of 65 mM KCl. CL measurements were taken with lucigenin as enhancer, at 10 second intervals for 1 minute.

Results: Synaptosomes showed a marked increase in CL upon addition of NMDA both in the presence and absence of KCl. When preincubated with the non-competitive NMDA receptor antagonist (Zn^{++}) or with the calcium channel blocker(Cd^{++}), CL formation was suppressed. DTT, a strong sulfhydryl group reducing agent, increased the activity of NMDA receptor, whereas NEM, a sulfhydryl group alkylating agent, decreased the NMDA receptor activity. Reduced and oxidized forms of glutathione decreased the receptor activity and were protective under excitotoxicity and depolarization conditions.

Conclusion: Our results demonstrated that endogenous and exogenous sulfhydryl compounds affect the redox modulatory site and play important roles in the generation of reactive oxygen species after activation of the NMDA receptor.

COMPLICATIONS OF INTRAVENOUS DEEP SEDATION IN PEDIATRIC ENDOSCOPY

Deniz Ertem / Ender Pehlivanoğlu. Marmara Med. J. 1999;3:126-129.

ABSTRACT

Objective: It is accepted that sedation during endoscopic procedures is mandatory in children, however the mode of sedation and choice of medication varies among gastroenterologists. The use of intravenous sedation in pediatric endoscopy offers a safe and effective way of either conscious or deep sedation.

Methods: In order to investigate the safety and efficacy of intravenous sedation with meperidine and midazolam in pediatric patients, 120 patients who underwent endoscopy were evaluated. Vital signs and any reaction to sedative agents were noted during and after the endoscopic procedure.

Results: The complication rate of sedation with this combination was 19.1%, and all were transient with no residual sequelae. The most common complication was allergic skin reactions (15.7%). Transient hypoxia was seen in 1.7% of patients. The recovery time was 74.8±15.8 min. The endoscopic procedure was not postponed in any of the patients due to the complication of sedation.

Conclusion: It was concluded that intravenous deep sedation with meperidine and midazolam when administered by an experienced pediatric gastroenterologist and monitored closely is safe and effective with a low risk of complication.

ANSWER TO PHOTO QUIZ

Diagnosis: Möbius sequence

Möbius sequence, a rare clinical syndrome, consists of congenital paresis or paralysis of the VIIth cranial nerve, frequently accompanied by dysfunction of other cranial nerves particularly N. Abducens. Dysmorphic features, limb and foot malformations may be seen in these patients.

Parents may not notice the facial weakness if it is subtle, and often the child is brought to medical attention solely because of an esotropia. When the disorder involves only ocular motility and the upper face, the major issues - strabismus surgery, amblyopia, corneal surface protection, and cosmoses - can be handled primarily by ophthalmologists and plastic surgeons. However, lower facial weakness may complicate an infant's ability to suck a bottle or nipple.

The etiology is not well understood. No one theory can satisfactorily explain all cases of Möbius syndrome, as the disorder has many possible causes. In one subset of patients, pathologic studies demonstrated aplasia or hypoplasia of cranial nerve nuclei, while in another group, abnormal peripheral portions of the cranial nerves were found. In the third subset, more widespread destruction of the brainstem, perhaps due to a prenatal vascular insult, has been suggested radiologically and neuropathologically. Neuroimaging in this group can demonstrate brainstem hypoplasia and calcification, and brainstem atrophy and mineralized necrotic foci have been found histopathologically. These studies support the hypothesis that Möbius syndrome in some cases could be the result of inutero brainstem vascular insufficiency. On the other hand, current chromosomal abnormalities as well as a locus on 3q21-22 and 10q were reported.

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