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Lending String:

Patron: TN: 383052

Journal Title: Clinical therapeutics

Volume: 6 **Issue:** 5

Month/Year: 1984**Pages:** 577-91

Article Author: Finkel MJ

Article Title: Phenytoin revisited.

Imprint:

ILL Number: 53446678



Call #: Clinical therapeutics

Location: jstks

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Editorial Comment

Phenytoin (formerly referred to as diphenylhydantoin) has been in general and effective therapeutic use for epileptic seizures for several decades. It is less hypnotic than phenobarbital. During the years, its beneficial effects in numerous other disorders have been observed and reported.

In response to inquiries about other uses, the office of Orphan Products Development, Food and Drug Administration, conducted a review of approximately 8,000 published reports. "Phenytoin Revisited" is an extensive critical evaluation of this literature by competent scientists. Use of the drug seems probable for several indications and possible for others. Under present laws and regulations, demonstrations by controlled clinical trials are needed for recognition of these new claims.

This review is a constructive contribution to therapeutics.

George E. Farrar, Jr., M.D., F.A.C.P.
Editor-in-Chief

Phenytoin Revisited

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ABSTRACT

Phenytoin has a wide range of pharmacologic effects other than its anticonvulsant activity. It has been the subject of more than 8,000 published papers, which include clinical reports of its usefulness in approximately 100 diseases and symptoms. In the United States the only indications for use in the official labeling for phenytoin are various types of seizures. An advisory committee of the Food and Drug Administration recently recommended the addition of certain cardiac arrhythmias to the labeling. To determine whether other uses should be added to the labeling and whether additional clinical trials should be encouraged, an in-depth review of the published literature was undertaken.

This review revealed that, on the basis of controlled studies, phenytoin is probably useful in the continuous muscle fiber activity syndrome, myotonic muscular dystrophy, and myotonia congenita. In addition, phenytoin appears to be potentially useful in recessive dystrophic epidermolysis bullosa, intermittent explosive disorder, anxiety disorder in which anger and irritability are prominent features, and, topically, in

burns and refractory skin ulcers. Additional clinical studies are needed before definitive conclusions can be drawn. Clinical trials of phenytoin in most of these disorders are ongoing or are contemplated. Any labeling changes will await results of the studies.

Based on phenytoin's pharmacologic effects in animals, controlled trials of the drug appear to be warranted in cerebral ischemia and stroke, spinal cord injury, angina pectoris, and fractures in which the rate of healing is poor.

INTRODUCTION

In the United States the only indications listed in the official labeling for phenytoin are the control of grand mal and temporal lobe seizures and the prevention and treatment of seizures occurring during or after neurosurgery. Approximately 90% of phenytoin prescriptions written in the United States are directed to these indications and to the prevention and treatment of seizures due to other causes. Cardiac arrhythmias account for about 1% of all use of the drug, and a variety of other disorders account for the remainder.¹

In 1981 a book by Jack Dreyfus, *A*

*Remarkable Medicine Has Been Overlooked,*² was published. The primary aim of this book was to bring to the attention of the public the vast amount of research on phenytoin that has been performed over the years and the indications other than epilepsy for which the drug has been reported to be useful. Approximately a decade earlier, a bibliography on phenytoin was distributed by the Dreyfus Medical Foundation to US physicians. Updated bibliographies were distributed in 1975 and 1983.³

The bibliographies include references to the use of phenytoin in a number of cardiovascular, neurologic, neuromuscular, psychiatric, endocrine, allergic, cutaneous, collagen, and other disorders. The drug has been the subject of over 8,000 published papers and has been reported to be useful in approximately 100 diseases and symptoms. Dreyfus does not claim that phenytoin has been shown to be effective for all the indications for which its use has been reported, but, rather, that the drug has a broader range of usefulness than the treatment of epilepsy.

Dreyfus's book generated widespread public interest, including that of physicians. In letters to the Dreyfus Medical Foundation, physicians praised the book and indicated that the writers had found phenytoin effective in a variety of diseases. Inquiries to the American Medical Association (AMA) asked why the Food and Drug Administration (FDA) had not added additional indications to the labeling and whether it was true that the drug was effective for many indications other than epilepsy. The AMA referred several of these inquiries to the FDA (JA Ballin, personal communication).

In this context, the FDA's Office of

Orphan Products Development recently undertook an in-depth review of available medical publications on the pharmacologic and clinical effects of phenytoin. This work was performed as part of the Orphan Products Office's basic responsibilities, which include (1) a continuing review of the literature to determine whether acceptable controlled studies exist to permit the addition of new uses to drug labeling and (2) support or stimulation of research on new uses for marketed products when such uses involve serious diseases and when at least some data from controlled studies demonstrate the potential effectiveness of the drugs.

The present report contains the results of this review. The report begins with a brief summary of the pharmacologic effects of phenytoin, which is followed by a description of the disorders for which phenytoin (based on controlled studies) appears to be useful or has the potential for being useful. Information on the status of those indications, with regard to labeling and ongoing clinical research, is provided, and, largely on the basis of interesting findings in animal studies, suggestions are made for clinical trials for other indications.

PHARMACOLOGIC PROPERTIES OF PHENYTOIN

It is well known that phenytoin has antiarrhythmic properties in addition to its anticonvulsant properties. It is less well known, however, that it has a much wider range of pharmacologic effects. Phenytoin dilates coronary, pulmonary, renal, and peripheral arteries. It stabilizes muscle and nerve membranes; relaxes smooth muscle; decreases collagenase

activity; affects the secretion and metabolism of various hormones, including insulin; protects against cerebral ischemia, neurologic deficit after spinal cord trauma, shock lung, and corticosteroid-induced myopathy; accelerates healing of fractures; has antihypertensive properties; decreases the duration of rapid-eye-movement sleep; increases plasma concentrations of high-density lipoprotein (HDL) cholesterol; and has other actions.³ This multiplicity of actions may not be tied to a single mechanism, but many of them are probably due at least in part to the effect of phenytoin on cation transport across cell membranes. Many studies have shown that phenytoin increases intracellular potassium and blocks sodium and calcium influx under various conditions.

It is important to note that the pharmacologic effects of phenytoin have been identified almost entirely in animals and in *in vitro* studies and, in some cases, under conditions that may not be clinically relevant. Some of the most interesting effects have not been studied to determine their clinical relevance. Interesting effects that have been studied have often been the subject of uncontrolled studies or of "controlled" studies that would not meet present-day standards, thus making it impossible to draw conclusions about effectiveness. The large number of uncontrolled or inadequately controlled studies reflects the fact that phenytoin is an "old" drug; most of the studies were performed in an era when the importance of controls was not as well appreciated. There are, however, a sufficient number of controlled studies to demonstrate phenytoin's usefulness or potential usefulness (to be established by further evidence) in a number of diseases.

INDICATIONS FOR WHICH PHENYTOIN APPEARS TO BE USEFUL

Cardiac Arrhythmias

The antiarrhythmic effect of phenytoin has long been recognized. About a decade ago, the foremost US manufacturer of phenytoin submitted an application to the FDA to allow the addition of certain cardiac arrhythmias to the labeling. The available clinical data were reviewed by the FDA's Cardiorenal Drugs Advisory Committee. The committee acknowledged the antiarrhythmic properties of phenytoin, but decided that the published and unpublished data did not include well-controlled studies that would permit a labeling change.

Recently the firm submitted an updated application. This time the committee noted several controlled studies supporting the effectiveness of phenytoin. The precise nature of the labeling change was left to the manufacturer and the FDA to determine.

Neurologic and Neuromuscular Disorders

Phenytoin has been reported to be effective in treating trigeminal neuralgia and other neuralgias, choreoathetosis, Sydenham's chorea, Gilles de la Tourette's syndrome, Parkinson's disease, and various conditions characterized in part by muscle spasm. Of these, two conditions for which reasonable evidence of effectiveness is available, based on controlled trials, are the continuous muscle fiber activity syndrome and

myotonic muscular dystrophy. By extrapolation, it appears reasonable to conclude that phenytoin may also be useful in myotonia congenita. Currently, no drugs are labeled for use in these diseases.

The myotonia in myotonic muscular dystrophy and myotonia congenita is the result of a muscle membrane disorder leading to muscle hyperirritability. It is characterized by delayed relaxation of muscle after voluntary or mechanically induced contraction. The continuous muscle fiber activity syndrome is the result of a peripheral nerve disorder involving continuous abnormal discharge, but it, too, is characterized by delayed relaxation of muscle after voluntary contraction and, in addition, by a state of continuous muscle contraction at rest. These three diseases are quite rare, so that performance of conventional controlled clinical trials is difficult. Because of the rather clear-cut nature of the therapeutic response, however, only a small number of patients would be required.

Some clinical evidence of the effectiveness of phenytoin in myotonic muscular dystrophy and myotonia congenita has been presented by Munsat.⁴ He performed a double-blind controlled crossover trial of the effects of phenytoin, procainamide, and placebo in seven patients with myotonic muscular dystrophy and in two patients with myotonia congenita. There was a clear difference in response to active drugs and to placebo. Patients who improved when given either of the active drugs generally reported that procainamide had a somewhat greater effect, but this drug produced a much higher incidence of side effects. In addition, of four patients with cardiac conduction defects (a common compli-

cation of myotonic muscular dystrophy), three showed an increase in the degree of block while taking procainamide. Because procainamide can impair myocardial conduction, phenytoin would appear to be preferable in patients with myotonic muscular dystrophy.

The data on continuous muscle fiber activity syndrome consist of detailed case reports. The primary aim of most of the published papers on this disease appears to be to describe clinical and electromyographic findings, including the acute response of the electromyogram (EMG) to various interventions. Because the cases are carefully described, the effectiveness of phenytoin would seem to be obvious if there were agreement that spontaneous remissions—all of which happened to coincide with the administration of phenytoin—were unlikely occurrences. Patients, all of whom had symptoms of long standing, were said to respond dramatically (often within a day), to be able to return to work and other activities of which they had no longer been capable, and to experience an immediate relapse (in one or two days) upon withdrawal of the drug, with remission after resumption of its use. In addition, in patients receiving phenytoin the excessively elevated basal metabolic rate that occurs in this disease (due to the continuous muscle activity) reverted to normal and ventilatory capacity improved. A marked effect on the EMG was also seen. Some patients had been tried on many other drugs prior to phenytoin, eg, procainamide, cortisone, diazepam, phenobarbital, and mephenesin carbamate, and were found unresponsive to them. Typical descriptions of patient responses to phenytoin may be found in reports by Isaacs,^{5,6} Isaacs and Frere,⁷ and Wallis and colleagues.⁸

The mechanism of action of phenytoin in the myotonias and in continuous muscle fiber activity syndrome has not been definitely established. Su and Feldman⁹ have demonstrated that phenytoin stabilizes the excitable membrane of both muscle and motor nerve terminals. This stabilization may be the result of phenytoin's ability to block sodium influx, calcium influx, or both. Ferrendelli and Daniels-McQueen¹⁰ suggest that, at least with regard to nerve tissue, phenytoin's main therapeutic effect is related to its inhibitory effect on sodium uptake, although the effect on calcium uptake may be contributory.

The FDA recently asked its Peripheral and Central Nervous System Drugs Advisory Committee whether the clinical data permit addition of these diseases to the labeling. Although they were impressed by the findings of Munsat,⁴ all committee members agreed on the need for a confirmatory study in myotonic muscular dystrophy and myotonia congenita. The committee was split on the question of whether there was substantial evidence of the effectiveness of phenytoin in continuous muscle fiber activity syndrome, and it therefore recommended that a placebo-controlled trial be conducted. Parke-Davis, the manufacturers of Dilantin®, volunteered to support new studies of these diseases. The studies are in progress.

INDICATIONS FOR WHICH PHENYTOIN APPEARS TO BE POTENTIALLY USEFUL

Psychiatric Disorders

On the basis of observations of aggressive actions and affective disturbances

in patients with psychomotor (temporal lobe) and other forms of epilepsy, abnormal electroencephalograms (EEGs) in children and adults with behavior and personality disorders, and reported improvement of concomitant emotional disturbances in epileptic patients treated with phenytoin, a number of investigators have studied the effect of phenytoin in nonepileptic patients with various psychiatric symptoms.

Improvement in children with behavioral problems and in adults with neurotic disorders has been reported in uncontrolled studies by several investigators.¹¹⁻¹³ In an open study,¹⁴ the anticonvulsant drug carbamazepine was reported to control violent episodes in hospitalized patients with severe schizophrenia.

Placebo-controlled studies in juvenile delinquents^{15,16} have failed to demonstrate a beneficial effect of phenytoin. Results of a controlled study of the drug in anxiety disorder¹⁷ were also negative, but this study was sparsely described, with no explanation for a large number of dropouts in the phenytoin group. The findings in controlled studies of hospitalized patients with psychiatric disorders have been conflicting. In a study of schizophrenics with symptoms of hostility, agitation, and/or anxiety and tension,¹⁸ which included some patients described as extremely hostile, a statistically significant difference in hostility between patients receiving phenytoin and those receiving placebo was noted at four weeks but not at eight weeks. Of patients dropped from the study because of assaultive behavior, approximately equal numbers had received phenytoin and placebo. In another placebo-controlled study of schizophrenic patients with similar symptoms,¹⁹ phenytoin-treated patients exhibited significantly

less agitation and irritability; they tended to show decreased hostility but more disruption of their thought processes. The report¹⁹ did not state whether the sample included patients who were violently aggressive.

Because the aforementioned controlled studies involved heterogeneous samples, a significant drug effect in a subsample could have been missed. The following studies report benefits of phenytoin in certain carefully selected types of patients. The most dramatic results have been described by Maletzky and Klotter²⁰ in patients with intermittent explosive disorder (episodic dyscontrol). This is a disorder characterized by violent outbursts and acts of aggression, often with little provocation, against people or property. Bach-Y-Rita and associates²¹ and Maletzky²² have described the histories and physical findings of patients with intermittent explosive disorder. There is often a history of head trauma and of hyperactivity or febrile convulsions during childhood. Alcoholism, violence, and psychiatric illness are common in parents and siblings. Violent episodes often follow intake of alcohol. Various aurae often precede, and headache and drowsiness often follow, the episodes. Patients report a lack of control over their violence, and most express extreme remorse for their actions. Many have brief episodes of an altered state of consciousness (usually staring), noted by family members. Anxiety, depression, and suicidal ideation are common. About half have abnormal EEG findings, most commonly in the temporal lobe. The incidence of temporal lobe abnormalities could be higher, however, inasmuch as activity in the depth of the temporal lobe usually is not visible at surface recording sites.²¹

The first study by Maletzky²² was uncontrolled. His patients had a high incidence of all the characteristics described above and a history of numerous seriously violent acts, including homicide. The patients had failed to respond to psychotherapy or to phenothiazines, and half of those who had received benzodiazepines experienced an increase in violence. Phenytoin produced an excellent response (close to a 100% decrease in the frequency and severity of violent episodes) in 15 of 22 patients and a good response (approximately a 75% decrease) in four. At the end of 12 months, none of the responders had had a violent episode. In view of these patients' poor response to psychotherapy and other drugs, Maletzky was surprised by the marked response to phenytoin. Maletzky and Klotter²⁰ then performed a double-blind placebo-controlled study in 24 patients carefully screened for characteristics of intermittent explosive disorder. They reported a significant difference in the frequency and severity of attacks in patients receiving phenytoin and those receiving placebo. The limited size of the Maletzky and Klotter study and some problems with the statistical analyses and reporting methods render the results less than definitive, but the findings merit the performance of additional trials.

The success experienced by these investigators in patients with intermittent explosive disorder may be due to the facts that their patients had most of the personal and family history associated with the disorder and that they had a high incidence of temporal lobe abnormalities, evident in EEGs. Although these patients are not epileptics, they may have some form of "temporal epileptic equivalent." Maletzky concluded that the patients

may have an anterior temporal or amygdalar focus triggered by mild frustration that results in a nongeneralized seizure manifested by violence.

Careful selection of patients was also undertaken by Stephens and Shaffer²³ in their studies in neurotic outpatients. First they administered phenytoin in an open study to a group of unselected patients and found that those reporting a favorable response had pretreatment symptoms of irritability, explosive temper, or anxiety. In a double-blind controlled crossover study in a different group of patients screened for these symptoms, statistically significant differences between patients receiving phenytoin and those receiving placebo (actually a minute dose of phenytoin) were noted in global effect and in rating factors related to anger, irritability, impatience, and anxiety. Next they performed a placebo-controlled crossover study in responders from the original uncontrolled study.²⁴ Most of these responders had a history of hot temper for which they had sought relief. Phenytoin was significantly superior to placebo in global ratings and in anger, irritability, and tension-anxiety factors.

Although Stephens and Shaffer²³ found an overall difference between patients' responses to phenytoin and placebo, not all patients responded to phenytoin. The investigators were unable to discover any variable that would predict which patients would respond.

Additional controlled studies are desirable in patients with anxiety disorder in which anger and irritability are prominent features. Studies in other types of patients with anger, eg, those with depression and the symptom of anger, might also be of interest. We are not aware of any studies being conducted

or planned in these conditions. The availability of a relatively safe therapy other than the benzodiazepines for patients with anxiety accompanied by anger is desirable because benzodiazepines, in addition to their dependence-producing potential, sometimes produce or may exacerbate pre-existing anger and rage.^{22,25,26} Further studies of phenytoin in patients with intermittent explosive disorder are warranted, particularly since there does not appear to be any clearly defined therapy for this condition. Several studies have reported that lithium is of value in patients exhibiting violence, but it is not clear that it would be effective in true intermittent explosive disorder. In addition, side effects of lithium are common and have resulted in a large number of dropouts. The FDA is considering methods for the performance of a study in intermittent explosive disorder.

Another possible subset of patients who might respond to phenytoin is illustrated by a study by Looker and Conners.²⁷ These investigators observed dramatic responses to phenytoin in a small open study in children with attention deficit disorders (minimal brain dysfunction) characterized in part by periodic outbursts of violent temper. These children had failed to respond to stimulant drugs; in fact, their behavior had worsened while they were taking stimulant drugs. In a subsequent placebo-controlled crossover trial in other children with attention deficit disorders, there were no important group differences between patients receiving phenytoin and those receiving placebo. The investigators reported in a subsequent study that all of the children from the placebo-controlled study showed a positive response to dextroamphetamine or methylphenidate. They hypothesized that children who

respond to phenytoin may be those whose condition deteriorates in response to stimulant drugs, thus suggesting an approach for further study.

Disorders of Collagen Production

Although phenytoin has been reported to be useful in patients with systemic and localized linear scleroderma, these studies were uncontrolled or poorly controlled. There is a theoretical possibility that phenytoin could have an adverse effect on scleroderma by enhancing the collagen overproduction found in this disease.

A controlled study has been performed in patients with recessive dystrophic epidermolysis bullosa (RDEB), a rare genetic disease of the skin and mucous membranes characterized by severe blistering after minor injury. It is often fatal within the first three decades of life. No drugs have been labeled as effective in its treatment.

In patients with RDEB there is increased collagenase activity and resultant collagen degeneration in the blistered skin. On the basis of studies by Eisenberg and coworkers,²⁸ suggesting that phenytoin inhibits collagenase activity, Bauer and associates²⁹ treated patients with RDEB and found a significant decrease in new lesions during treatment periods versus control periods. These investigators found that phenytoin appears to decrease collagenase synthesis or secretion. Because of the potential importance of these findings, the FDA has asked the American Academy of Dermatology to design and conduct a controlled multi-clinic trial. The Academy has agreed, and the study is ongoing.

Wounds

The stimulation by phenytoin of fibrous tissue and collagen formation has been demonstrated in vitro and in vivo and is a well-recognized effect of the drug. Although there were a few clinical reports almost 20 years ago on the use of oral phenytoin to accelerate healing, this use of the drug was ignored until recently, when Rodriguez Noriega and associates^{30,31} studied the effect of phenytoin powder applied topically in chronic leg ulcers and burns. The investigators observed a 50% reduction in the healing time of leg ulcers. In patients with second-degree burns, the time to healing or graft was reduced from 30 days in the control group to approximately 22 days in patients given oral phenytoin and to 16 days in patients receiving topical phenytoin powder. Moreover, topical phenytoin appears to have an analgesic effect. In patients with bilateral burns, in whom phenytoin powder was applied to one side, the time between application and marked improvement or the disappearance of pain was five to 25 minutes on the treated side and 12 to 15 hours on the untreated side. Additional controlled clinical trials of phenytoin in these conditions are being conducted by the same investigators and by others.

INDICATIONS THAT APPEAR TO JUSTIFY THE INITIATION OF CLINICAL TRIALS

Fractures

Several investigators³²⁻³⁴ have shown in rodents and rabbits that systemically administered phenytoin increases the rate of healing of fractures, the tensile

strength of healing fractures, and the breaking strength of healed fractures by enhancing fibrous tissue proliferation and, probably, collagen formation. Although osteomalacia has been reported in patients receiving long-term phenytoin therapy, perhaps by means of an effect on vitamin D metabolism, this adverse effect is clinically irrelevant to the short-term use that would be required to promote fracture healing. If the beneficial effects on fracture healing can be replicated in a larger animal model, then controlled clinical trials of oral phenytoin in patients with delayed union of fractures who are poor surgical risks would seem to be warranted.

Prevention of Neurologic Deficit after Cardiac Arrest and Stroke

Phenytoin has been used clinically to ameliorate brain damage after a stroke or cardiac arrest. To our knowledge, no well-controlled studies of its use in these conditions are under way. Such studies of the drug are justified on the basis of its effects on brain metabolism in ischemia and stroke models. In cerebral ischemia there is a loss of potassium ion from brain cells and a replacement by sodium ion, with resultant intracellular edema; a decrease in glucose, glycogen, and adenosine triphosphate; an increase in lactate and free fatty acids, the latter resulting in interference with mitochondrial oxidation and an increase in blood coagulability; and a decrease in norepinephrine, dopamine, and 5-hydroxytryptamine.³⁵ After restoration of cerebral circulation, there are increases in brain catecholamine synthesis, with resultant stimulation of glycolysis and worsening of lactate accumu-

lation, and increases in cerebral oxygen consumption, lipolysis, and proteolysis.

Phenytoin has been shown to decrease potassium efflux³⁶⁻³⁸ and to decrease lactate and increase glucose and glycogen levels^{39,40} after ischemia. Although there have been a few reports that phenytoin increases cerebral blood flow, other workers have shown that the increase is selective in location or does not occur. The evidence suggests that this is not an important effect of phenytoin and could not account for phenytoin's protective action following ischemia.

Phenytoin given immediately after the production of ischemia in rabbits provided complete protection against necrotic lesions in the brain and was more effective in this regard than thiopental.⁴¹ When given immediately prior to ischemia, phenytoin again protected against necrotic injury. This protective effect was numerically but not statistically significantly different from that conferred by thiopental. Neurologic deficit scores, however, revealed highly significant differences between phenytoin and placebo and phenytoin and thiopental at 15 and 30 minutes after ischemia, differences that were still significant at 72 hours.⁴² A number of investigators have demonstrated that pretreatment of animals with phenytoin prolonged survival under hypoxic or anoxic conditions^{36,43,44} or permitted revival after more prolonged periods of ischemia than in control animals.³⁷

In a stroke model, phenytoin pretreatment prevented cerebral edema in rats,⁴⁵ but of greater interest is the finding in monkeys that phenytoin administered two to three hours after occlusion of the middle cerebral artery prevented cortical edema and necrosis and im-

proved the level of consciousness within 24 hours—although megadose methylprednisolone protected against infarction in other areas of the brain as well.³⁸

Why should clinical studies be conducted with phenytoin? Other drugs, eg, barbiturates, corticosteroids, and reserpine, have been found to exert various protective effects in the brain, and there is interest in clinical trials with calcium channel blockers such as nimodipine and nifedipine because of their ability to preserve cerebral blood flow after cardiac arrest.⁴⁶ Because few well-controlled studies have been conducted in this area, and no drug has been shown conclusively to be of value, controlled trials with phenytoin alone and combined with other drugs would seem to be warranted.

Spinal Cord Injury

Because ischemia is postulated to play a significant role in spinal cord dysfunction following injury, Gerber and colleagues⁴⁷ studied the effect of phenytoin on motor recovery after spinal cord injury in dogs. Animals received 20 mg/kg intravenously immediately following or 30 minutes after injury and an identical dose six hours later. An untreated group and one treated immediately after injury with dexamethasone were used as controls. Progress was charted over a six-week period. Recovery was much more rapid and profound in the three drug-treated groups than in the untreated group. By six weeks, none of the untreated controls could run or walk, whereas 40% of the dogs in the dexamethasone group could run with little motor deficit, and 80% to 83% of the animals in the phenytoin groups achieved this level of recovery. Microscopic

examination of the area of injury revealed almost 95% loss of spinal cord parenchyma in the untreated group, compared with approximately 50% to 60% in the dexamethasone and immediate-treatment phenytoin group and 60% to 70% in the delayed-treatment phenytoin group. These findings suggest that controlled clinical trials with phenytoin would be desirable in patients with spinal cord injury.

Angina Pectoris

Studies in dogs have revealed that phenytoin, at parenteral doses of 3.5 and 5 mg/kg, reduces coronary vascular resistance. This effect is due to a direct dilator action on the coronary arteries.^{48,49} There is a small decrease in myocardial oxygen consumption.⁴⁸ Phenytoin has been shown to inhibit calcium ion influx in cardiac muscle⁵⁰ and nerve tissue,¹⁰ and it is possible that its vasodilator effects may be the result of inhibition of calcium influx into vascular smooth muscle.

In a small double-blind placebo-controlled crossover trial,⁵¹ phenytoin was reported to decrease the frequency and duration of anginal attacks but to have no beneficial effect on exercise performance. In patients with more severe angina, phenytoin was preferred by the majority, with no patient preferring placebo.⁵¹ Problems in the design of this study have been well described by Davies,⁵² leading to the conclusion that the data were inadequate to ascertain the effectiveness of phenytoin in patients with angina pectoris. In another controlled study,⁵³ phenytoin was reported to decrease the number of anginal attacks as well as the consumption of nitro-

glycerin, but this study was quite small and not sufficiently described. Because phenytoin is well tolerated by most patients who take it, additional clinical trials would seem to be indicated in patients with angina pectoris.

Prevention of Stroke and Myocardial Infarction

Plasma HDL cholesterol levels have been found to be lower in persons with coronary heart disease than in those without the disease. Although Castelli and associates⁵⁴ have found that plasma low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglyceride levels are directly related to coronary heart disease, such an association is not as strong as the inverse association with HDL cholesterol.

Nikkila and associates⁵⁵ have reported that patients with epilepsy under treatment with phenytoin have significantly higher HDL cholesterol levels than do age- and weight-matched controls. The difference was noted in both men and women and the degree of increase was correlated with serum phenytoin levels. In the other lipid and lipoprotein analyses carried out in this study, the only other significant difference consisted of lower levels of LDL cholesterol in female phenytoin users.

These investigators are conducting a small prospective study in patients with transient ischemic attacks to ascertain whether phenytoin can decrease the risk of stroke or myocardial infarction.⁵⁶ Although the size and design of the study are such that this question may not be answered adequately, it is interesting to note that before therapy the patients had significantly lower HDL cholesterol

levels than did healthy controls and that the levels rose to normal within a few months of the start of phenytoin therapy.

It would be of interest to determine whether phenytoin-treated patients with epilepsy have a less-than-expected risk of coronary heart disease and stroke. Available databases are currently being considered by the FDA for such an epidemiologic study.

DISCUSSION AND CONCLUSIONS

Phenytoin is probably useful for disorders other than seizures and certain cardiac arrhythmias. These include (1) the continuous muscle fiber activity syndrome, (2) myotonic muscular dystrophy, and (3) myotonia congenita. An FDA advisory committee has concluded that additional controlled studies are needed to reach definitive conclusions about the use of phenytoin in these conditions. These studies are ongoing.

On the basis of a limited number of controlled clinical trials, together with results from pharmacologic and other studies, phenytoin appears to be potentially useful in (1) recessive dystrophic epidermolysis bullosa, (2) burns (topical use), (3) refractory skin ulcers (topical use), (4) intermittent explosive disorder, and (5) anxiety disorder in which anger and irritability are prominent features. Studies are under way or are planned for most of these conditions so that definitive conclusions may be drawn and so that the patient subpopulations that may be expected to benefit can be identified, if possible.

On the basis of studies in animals, clinical trials appear to be warranted in stroke, postcardiac arrest, spinal cord

injury, and angina pectoris. If additional animal studies replicate the findings of earlier studies showing a beneficial effect on fracture healing, clinical trials might be considered in delayed union of fractures.

One of the questions in all of these potential indications, of course, is whether the dosage tolerated in humans is of sufficient magnitude to produce the beneficial effects observed in animals, and, in the case of neurologic deficit after stroke or cardiac arrest, whether the pharmacologic effects of phenytoin on the brain are sufficient to produce a clinical effect. The question of dosage is important. Studies have demonstrated an antihypertensive effect of orally administered phenytoin in spontaneously hypertensive rats, and rapid intravenous injection of phenytoin can produce hypotension in humans; a controlled clinical trial of the oral drug in patients with hypertension, however, revealed only a possible acute, transient lowering of systolic pressure and no beneficial effect of chronic administration.⁵⁷ The dosage used was the usual anticonvulsant dosage, 300 mg/day. Higher dosages often are not well tolerated.

With respect to the dozens of other clinical disorders in which phenytoin has been reported to be useful, the absence of well-controlled trials in these conditions limits the ability to draw substantiated conclusions. Based on its pharmacologic effects, however, phenytoin may well merit further study in disorders carefully selected from this group.

ACKNOWLEDGMENTS

Jerome Levine, MD, and Allen Raskin, PhD, of the National Institute of Mental Health, reviewed and made suggestions about the potential usefulness of phenytoin in psychiatric disorders; Marshall Urist, MD, of the University of California, Los Angeles, reviewed, and he and J.W. Frymoyer, MD, of the University of Vermont, made suggestions about the use of phenytoin in fractures; Gordon Pledger, PhD, and Lawrence Hauptman, PhD, of the FDA, reviewed the statistical analyses in the studies cited as references 20 and 23; and Esther Sigler provided secretarial assistance.

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