1950

Mesantoin in the treatment of epilepsy

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MESANTOIN IN THE TREATMENT OF EPILEPSY

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SENIOR THESIS

PRESENTED TO THE COLLEGE OF MEDICINE

UNIVERSITY OF NEBRASKA

Omaha, 1950

INTRODUCTION

Epilepsy has been known since the earliest of times and, beginning with the Arabs and Hebrews, ancient medical writers recognized the seriousness of seizures. The earliest discussion is by Hippocrates about 400 B.C.( ). While there is yet no cure for epilepsy, new medicines for treatment and modern opinions of the nature of seizures have altered greatly the outlook for the future of the epileptic person.

PURPOSE OF THESIS

The purpose of this thesis is to evaluate the effectiveness of the drug Mesantoin (3-methyl 5, 5-phenylethyl hydantoin) in the treatment of epilepsy. However, to a lesser degree, the purpose of obtaining more knowledge about the subject of epilepsy is also attained. Last, the fulf. ing of the requirement of writing a thesis is accomplished.

EPILEPSY

Incidence. Epilepsy is a rather common disease and figures ranging from 500,000 to 700,000 persons of both sexes in the United States have been estimated, many of them adolescents and younger children. Selective Service reports that among more than 9,000,000 men from 18 to 45 years of age in this country who received physical exam-

inations through selective- service boards from April I942 to December I943, five of each thousand, or 45,000 men were rejected because they were diagnosed as having epilepsy. In addition, recent statements from the Army and Navy have shown that for every thousand men in all the armed services, between I.0 and I.5 cases of epilepsy were diagnosed (24). Interestingly enough, it can be said that this is about the same number that have active tuberculosis or diabetes (3).

Types. The Grand Mal Seizure is the well known generalized convulsion which may be preceded by an aura. Consciousness is lost. Generalized hypertonicity and rigidity of muscles occur and are accompanied by apnea and cyanosis. Symmetrical, clonic convulsive movements involving the whole body follow. Sweating occurs, accompanied by increased heart rate and blood pressure, salivation, and often by tongue biting and relaxation of sphincters. Finally, the patient's muscles relax, his breathing is resumed, cyanosis disappears and he fails into a deep sleep. He awakes feeling sore of muscle and spirits, often with a headache and with nausea and vomiting. Occasionally certain patients are found to have a feeling of extraordinary well-being on recovering consciousness (I4)(37).

Jacksonian Seizures ere described by the English neurologist, Jackson, and are characterized by clonic convulsive movements or sensations of parasthesia which begin in a hand or foot and spread upward in a "march" while consciousness is retained. The seizures may then end, or continue into a grand mal, with loss of consciousness. This type is uncommon in post-traumatic epilepsy (I4)(37).

Focal Seizures (Convulsive Seizures with Localizing Symptoms) are a grand mal type of convulsion which are predominantly or wholly one-sided, often with initial turning of the head and eyes to one side (adversive movement), or which has a warning, such as a peculiar odor, which indicates the part of the brain where the seizure starts. The "march" seen in Jacksonian epilepsy is not present (I4)(37).

Psychomotor Seizures are characterized by a period of amnesia, without clonic movements and with or without tonic spasm or contortion of the trunk muscles. Muscular hypertonicity, when present, may be accompanied by some cyanosis and drooling. The person may appear confused or he may mutter, make chewing motions, fumble with his clothes, or have a "running fit". He may become violent, especially if physical restraint is attempted. The manifestations of this type are extremely variable and often lead to the mistaken diagnosis of hysteria. The patient

has no memory of events during the attack and may be unaware that the attack has occurred (14)(37).

Pykno-epilepsy does not involve a convulsion. It consists of a transient loss or impairment of consciousness (lasting five to thirty seconds) with immobility or with rhythmic twitching of eyelids, facial muscles, or head. Attacks usually recur several to many times a day, every day (14).

Myoclonic Jerks are single shock-like jerks of arm or trunk muscles, without apparent loss of consiousness.

Akinetic Seizures ("Lack of Motion"Epilepsy) are a sudden postural collapse of muscles, with consequent nodding of the head, or, if the collapse is generalized, a fall. The seizures are apt to recur frequently (14).

These last three types of seizures are sometimes spoken of as the "Petit Mal Triad".

Patients may be subject to seizures of two or more types, and assortments of attacks are common (6). Grand mal and Petit mal seizures may be present in the same patient, as also may Psychomotor seizures. Hence, the variety or varieties of seizures the patient is having must be carefully established by history, observation and electroencephalography.

Diagnosis. The clinical diagnosis of epilepsy is highly

probable if a history of recurring seizures without any obvious cause is obtained. If there is a preceding aura and there is a family history of a tendency to seizures, the diagnosis is all but certain (37). However, there are a number of various seizure phenomena which are non-epileptic. These include syncope, episodes which resemble syncope but are due to an irritable carotid sinus, periods of unconsciousness or amnesia due to hysteria, convulsions which occur in the course of toxemia of pregnancy, or uremia, or which are directly due to hypoglycemia, or the ingestion of a convulsant drug. Isolated convulsions which occur with fever in childhood are not epilepsy, although they have something like a ten to twenty percent chance of becoming so. Excluded also are certain conditions which have some superficial resemblance to convulsive episodes but do not possess the cardinal feature of lost consciousness. Examples are tetany or spasmophilia, chorea, sudden muscular collapse (cataplexy) which occurs in patients subject to narcolepsy, or inability to move on entering or leaving sleep (sleep paralysis).

The diagnosis of epilepsy is made chiefly by exclusion (eliminating each of the above mentioned possibilities through a careful history and appropriate

examination). In addition, positive evidence may be supplied by the E.E.G., when this is available (14).

The final diagnosis of epilepsy may be completed or confirmed by special test procedures such as electroencephalography (E.E.G.), pneumoencephalography (P.E.G.), water and pitressin test, hyperventilation of the lungs (for Petit mal), and by the therapeutic test. If any of these special diagnostic procedures, other than the last, is to be carried out, it will depend upon the availability of facilities and upon the necessity for additional information in a particular case.

The most informative and least rigorous test, so far as the patient is concerned is the first (E.E.G.). The second procedure (P.E.G.) is indicated only in the case of suspected anatomic lesions. The water and pitressin test is of special use in the diagnosis of grand mal epilepsy when seizures occur only at widely separated intervals and when the brain waves are normal throughout most of the free periods. Voluntary hyperventilation of the lungs for from forty seconds to several minutes will induce petit mal attacks in twenty to twenty-five percent of patients subject to this type of seizure (37).

Definitions. For a better understanding of the subject matter herein, a few definitions are necessary. They are as follows:

Epilepsy: This word is derived from the Greek "epilepsia" which means, "a taking hold of, and and something seizing the subject as though that 'something' were outside itself"(3). Lennox states that anyone who comes to his physician with the story of repeated sudden loss of consciousness, possibly with accompanying involuntary muscle movements or peculiar actions, is by definition an epileptic.

Mesantoin: 3-methyl 5,5-phenylethyl hydantoin. It is also called "Phenantoin", or "Hydantoin".

Hydantal: A combination of mesantoin (0.1 Gm.) and phenobarbital (0.02 Gm).

Idiopathic epilepsy: Also called cryptic, essential, or genetic epilepsy. The cause is unknown or due to an hereditary tendency.

Acquired epilepsy: Also called organic or symptomatic epilepsy. The cause is known.

Status epilepticus: This is a complication of epilepsy, and is rare. Seizures recur at frequent intervals and the patient remains unconsious in the interparoxysmal periods.

Grand Mal Seizures: See under types.

Petit Mal Seizures: See under types.

Jacksonian Seizures: See under types.

Psychomotor Seizures: Is also called Psychic variant or Epileptic Equivalent, and is explained under types.

Aims. The aim of treatment is to prevent attacks and to maintain well being (6). Prevention has priority over remedial treatment and applies to both genetic and acquired causes. As for genetic prevention, electroencephalography is a potential aid in the detection of a transmitted predisposition to seizures. Brain wave tracings provide at least one leg for eugenics to stand on and give to the present day physician a certain degree of confidence when he is asked to advise about marriage and children. Finally, the potential epileptic, one with subclinical seizure discharges, may be given drug therapy for the prevention of possible seizures (13). Since the aim of therapy is complete cessation of attackes, treatment may have to cover a wide range, including surgery, psychotherapy, and education as well as the practical problem of finding the drug or combination of drugs which will give the greatest degree of control.

THE DRUG MESANTOIN

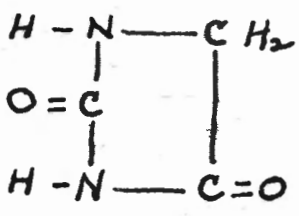
History. The history of drug therapy in epilepsy falls into three main eras. The first began about 1858 when Sir Charles Locock used bromides in the treatment of epilepsy on the hypothesis that a sedative would decrease the number of attacks. This medication reduced the incidence of epileptic attacks, but often caused the undesireable side effects of bromism. The second era began about 1919 when Hauptman introduced phenobarbital as a substitute for the bromides. Seizures were more effectively controlled and unpleasant side effects were less frequent and less severe. The third era began about 1938 when Merrit and Putnam introduced sodium diphenyl hydantoinate. They found that the reduction in the number of seizures was out of proportion to the degree of sedation caused by bromides and phenobarbital. The barbiturates seemed to have a therapeutic effect which they chose to call "anticonvulsant" in contrast to the "sedative" effect as evidenced in preventing electrically induced convulsions in cats. The Sandoz Chemical Works, Inc., started laboratory investigations of hydantoins. Many different hydantoins were prepared and thoroughly studied pharmacologically; Mesantoin (3-methyl 5,5-phenylethyl hydantoin) was found to be most effective and best tolerated. Clinical invest-

igations atarted, and much has been reported in the literature on its use (5)(13)(19)(21)(22)(23)(24).

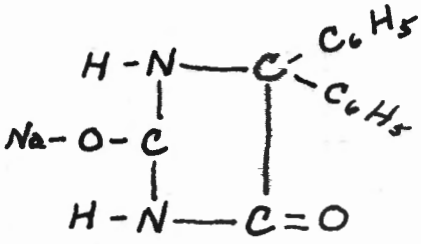
Chemistry and Composition. The chemical formulas of the various anti-convulsant drugs are similar. Dilantin and Mesantoin are both derivatives of hydantoin, but differ in that mesantoin has an ethyl group in place of one of the phenyl groups on carbon number 5 of dilantin and also has a methyl group on nitrogen atom number 3 (2). Futhermore, dilantin is in the form of a sodium compound, while mesantoin is sodium free and has the chemical characteristics of a weak acid (18). Both of these hydantoinates are considered derivatives of a cyclic condensation product of urea and acetic acid. Phenobarbital is a derivative of the cyclic condensation product of urea and malonic acid (18)(25).

Tridione is not a hydantoin derivative but is related in structure to mesantoin in that an oxygen atom has been sustituted for the number 1 nitrogen of mesantoin and two methyl groups have been substituted for the ethyl and phenyl groups on carbon number 5 (2).

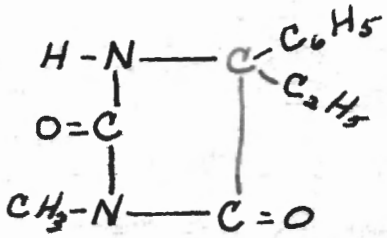
The following structural formulas show the close chemical similarity between some of the most commonly used anticonvulsants.



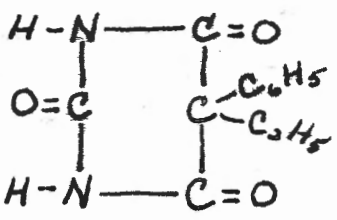
Hydantoin



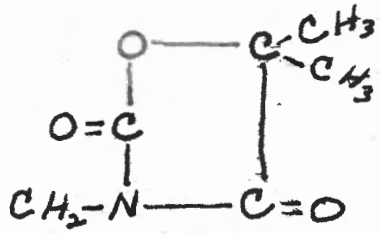
Dilantin



Mesantoin



Phenobarbital



Tridione

(1)(7)(12)(18)(25)

PHARMACOLOGY

Physiologic Actions. A survey of the literautre on mesantoin revealed nothing of its physiological actions, but Aird in his work states, "Aside from the slow absorption of Mesantoin, and the studies by Von Fischer and Staub (foreign) on the distribution and elimination of Mesantoin, little is known as to the physiology, biochemistry or pharmocological mechanism of action of the hydantoin on the central nervous system. Although clinically, the hydantoins have but a slightly depressent effect on the brain, their anticonvulsive action and their related benficial effect on behavior disorders of childhood, and on the behavior of many epileptics is striking" (1).

Experimental Data. In a study of the anticonvulsant properties of 5,5 Phenyl thienyl hydantoin in comparison with Dilantin and Mesantoin, Goodman and co-workers found in animal experiments that Mesantoin has the highest protective index by the maximal electroshock test. Dilantin has the lowest and the thienyl compound is intermediate. In contrast to Mesantoin, neither Dilantin nor its thienyl homolog elevates the threshold for minimal electroshock seizures or afford protection against metrazol-induced convulsions. All three compounds are capable of elevating the experimentally lowered (hydration) electroshock threshold; Mesantoin is the most effective by this test, Dilantin next and the thienyl derivative least.

All three hydantoins modify the pattern of electroshock seizures in man. As also occurs in animals, the tonic component of seizures in characteristically abolished. Indeed, the tonic clonic seizure may be entirely replaced by a "missed shock", especially when Mesantoin or the thienyl compound has been administered. Such "missed shocks" more nearly resemble psychomotor seizures. The doses of the three hydantoins necessary to modify electrically-induced seizures in nonepileptic subjects are in the upper range employed for the control of grand mal epilepsy. No toxic effects

were noted from these doses. The results obtained with 5,5 Phenyl thienyl hydantoin differ from those with dilantin in that the convulsions were entirely replaced by psychomotor seizures and pure clonic convulsions were not observed. Mesantoin was intermediate in this respect (8).

Comparative studies on the anticonvulsive and toxic action of Mesantoin have been made in experimental animals by Swinyard and Goodman. These authors state that this agent has a protective index (ratio of toxic dose to protective dose) of 12, as compared to a protective index of 2 for Dilantin. Mesantoin raised the convulsive threshold to electric shock by 37 percent, whereas they obtained only 2 percent change with dilantin (1).

Toman and others state that Mesantoin and Dilantin in non-toxic doses rank high in ability to modify the pattern of electroshock seizures. Phenobarbital, Sodium Bromide and Mebarol are effective, but only in doses which occasionally produce side effects. Tridione is ineffective in modifying the electroshock pattern when given in doses more than adequate to control petit mal epilepsy (∞).

Swinyard and Goodman reported Mesantoin to be the least toxic and the most effective of the hydan-

toin derivatives in controlling the threshold to electroshock in rats (25).

Tainter, et al, in a study of several drugs to determine the relationship of dosage to effect over considerable ranges of tolerated doses, found that Mesantoin was similar in potency to Dilantin and required approximately the same dosage. The authors state that the choice of a drug for antagonizing epileptic attacks, would depend, in part at least, on the nature and extent of their side effects, such as hypnosis, tissue changes, etc., especially after continued administration (4).

Indication. The indications for the use of Mesantoin are grand mal, Jacksonian and Psychomotor types of epilepsy, since experimental work and clinical trial by various observers have indicated it to be a valuable drug to control especially these types of seizures. Mesantoin is of great benefit in the treatment of psychomotor epilepsy and in cases of grand mal and Jacksonian where the illness has not been completely controlled by maximum tolerated doses of Dilantin or Phenobarbital, or where, because of intolerance, the patients have not been able to take enough of the drugs to eliminate their attacks (9). Side effects which

prove troublesome with Dilantin, hypertrophy of gums, extreme ataxia, and hirsutism are not observed with Mesantoin (15) and hence is an indication for its use.

Intractable cases of epilepsy of any type, in which treatment of other sorts has been in vain, should be tried on Mesantoin.

The lack of distressing side effects as seen with the use of Mesantoin is in itself an indication for trial in epileptic seizures. Swinyard and Goodman have noted that Mesantoin is less toxic than Dilantin in rats, and Kozol has reported the ingestion of 7.2 grams of Mesantoin in a suicidal attempt without any serious results (2).

Used as a substitute for other hydantoins, when clinical evidence reveals a necessity to stop such drugs or convert to another, Mesantoin can be resorted to readily.

Other factors which make the drug desirable, are its tastlessness and small size of the pills which are advantageous especially in treating aesthetic individuals and children.

Dosage and Administration. The drug is put out in tablets of 0.1 Gm. (1½ grains). The usual method is to have the patient take one tablet daily for the first week, then two tablets daily for the second week, and

so on, continuing to increase the daily dose by one tablet in weekly steps until the effective dosage level is reached. The object is to arrive at a dosage of the smallest number of tablets that will keep the patient entirely free from seizures.

For patients who have previously shown sensitivity to drugs, it is wise to follow a slower and more gradual method of therapy. Starting with one-half tablet daily for the first week, the dose is increased to one tablet the second week, then two tablets the third week, and so on until the effective dosage level is reached.

The minimum effective dosage varies somewhat with different patients. Four to six tablets daily are the doses most commonly needed for adults, although some may require as many as eight to ten tablets. Children require smaller amounts of the drug. The average dosage is one to four tablets daily. The dosage is increased the same as under the adult plan, but with smaller amount, frequently starting with one-half or even one-quarter tablet depending upon the age and weight of the patient. The drug is usually prescribed to be taken three times a day after meals and at bedtime in divided doses (5)(25).

The development of drowsiness is a factor that may limit the dosage. This can be corrected and alertness restored by giving Dexidrine sulfate in five milligram doses at breakfast and lunch without decreasing the therapeutic value. Other stimulants as caffeine and desoxyn may be used with equally good effects (6)(12).

Contraindication. Drowsiness is a fairly common complaint and patients taking higher dosages complain that they tend to fall asleep and are troubled with lethargy. In many instances this is slight and a sense of calm and relaxation is often welcomed by the patient. It can be counteracted without detracting from the anticonvulsant effect by the use of a stimulant as previously mentioned (5)(6). Some patients have stated that their drowsiness has diminished with the taking of the drug over a period of time (9).

A measles-like rash has been reported by observers in from four to ten percent of their patients. The drug in these cases has been stopped and the skin eruptions have subsided. Carefully regulated and graduated doses over a longer period of time have diminished these skin manifestations, even in patients who previously exhibited such reactions (5)(6)(1).

Aplastic anemia has been reported in patients

being treated with Mesantoin. Frank and Holland reported two such cases with recovery (7). A search of the literature revealed a case of fatal aplastic anemia, but Tridione was concomitantly used with Mesantoin and neither drug could be proved to be the etiological agent (10). Bloom and co-workers reported a case of Mesantoin poisoning with aplastic anemia and recovery following the use of transfusions, pencillin, streptomycin and various hematinic aids (2). It is suggested that patients receiving any of the hydantoinates should have hematologic studies once a month at least, and any sudden drop in the hemoglobin or granulocytes should be viewed with suspicion (1)(2)(26).

Clinical Application: The application of Mesantoin will vary with the patient, the severity, and the frequency of seizures. Hence, the plan of treatment must be flexible and designed to meet the needs of the individual patient (9). Some may experience excellent results and others will note side actions and be unable to use the drug. Thus the indications and dosage may vary much. Most patients, however, observe a change for the better in a few days. They state they are no longer listless, that they have new drives and are capable of thinking more clearly and are not near so

restless as formerly. The seizures are not as severe and become less frequent to a complete absence (25).

It is to be remembered that, if satisfactory results are not obtained with one drug, a combination of two or more of the commonly used drugs will yield much better results than the use of one alone. It is not infrequently found that one drug has been discarded as useless whereas in reality a slight increase in dosage would have resulted in a complete disappearance of all attacks (21).

W. G. Lennox reported his experience with Mesantoin and observed that one-third of his patients subject to frequent major seizures obtained the best results. The benefit in its substitution for other hydantoins resulted either in redution of the frequency of convulsions or in an absence of the unpleasant side effects of ataxia or gum hyperplasia (3).

H. L. Kozol studied Mesantoin in a series of epileptics, especially in resistant cases. Many of the patients were either greatly or moderately improved and the frequency of attacks was reduced ninety percent. The incidence of side effects was negligible (3)(11)(12)(15)(25).

K. O. Von Hagen reported his findings with Mesantoin combined with phenobarbital (hydantal) in the

treatment of grand mal epilepsy. He states that in the small series he has observed over a prolonged period, it was effective in the control of seizures, especially the grand mal type, and that toxic reactions were almost absent (3)(34).

C. D. Aring states that Mesantoin is a useful drug in those patients who exhibit untoward reactions such as uncontrollable ataxia or gum hypertrophy (3).

P. Cohen states that Mesantoin may be substituted for phenobarbital or dilantin when the lack of therapeutic results or toxic reactions require a change.

A. E. Loscolzo studied Mesantoin combined with phenobarbital and reports that grand mal seizures were reduced sixty percent and improved emotional status was noted. Side effects were strikingly low (3)(18)(19)(25).

Combination therapy is often more successful than treatment with one frug, since it apparently is true that the anti-convulsive effects may be additive or synergistic, whereas the side reactions and intolerance of each of the combined drugs need not be (1)(4)(6)(34).

The use of phenobarbital with Mesantoin is recommended by some observers who state that the barbit-

urate enhances the effect (4)(5)(17)(23). Kozol states that it is inadvisable to give barbiturates with Mesantoin, unless small dosages of Mesantoin are being used, for Mesantoin has a substantial sedative effect (13).

Mesantoin as a supplement to Dilantin is of definite value, for in some cases side actions due to large Dilantin dosages are unpleasant or even toxic. By combining the two drugs excellent results may be obtained in controlling seizures through the sum of their anticonvulsant properties, while each neutralizes the side actions of the other (6)(9)(12).

COMMENTS

The symptoms of epilepsy can now be reduced or eliminated in a large majority of patients by the use of specific medication. Bromides, Phenobarbital, Dilantin, Tridione, and Mesantoin are effective drugs.

Mesantoin has been used in the control of convulsive seizures with some excellent results. Various observers indicate that it is effective in the treatment of epilepsy exluding Petit mal seizures, and that it is low in toxicity. However, it may cause serious side effects as reactions of the skin and changes in the blood in a small number of patients. The skin reactions are usually benign and respond quickly to cessation of treatment with the

drug. All patients should receive examinations of the blood while on treatment to prevent any possible blood changes.

When Mesantoin is being used, it should be administered in small initial doses and increased slowly and in small amounts as any other hydantoin.

The side effects of the drug Mesantoin are considered much less than any of the other anticonvulsants in comparison to the size of the dosages employed. This alone makes it popular in the treatment of epilepsy.

SUMMARY

1. Epilepsy is an age old disease, and is considered to be about as prevalent as diabetes or active tuberculosis.
2. The types of epilepsy are Grand mal seizures, Jacksonian seizures, Focal seizures, Psychomotor seizures, and the Petit mal triad (Pykno-epilepsy, Myoclonic jerks, and Akinetic seizures).
3. Diagnosis of epilepsy is by history, electroencephalography, pneumoencephalography, water and pitressin test, hyperventilation test, and therapeutic test. The use of these methods depend upon the availability of facilities and necessity for additional information.
4. The aim in the treatment of epilepsy is complete prevention of seizures and maintainence of well being.

5. Mesantoin was developed by the Sandoz Chemical Works, Inc., in a search for an anticonvulsive hydantoinate superior to any previously used.

6. Chemically, Mesantoin is a derivative of hydantoin and its composition is somewhat similar to Dilantin.

7. The physiologic action of Mesantoin is not clearly known, except that it has a slightly depressant effect on the brain.

8. Experimental work indicates th t Mesantoin is very effective in the control of convulsive seizures and is low in toxicity.

9. Indications for the use of Mesantoin are all types of epilepsy except Petit mal, intractable cases in which treatment of other sorts has failed, to mimimize distressing side effects, use as a substitute for other hydantoins, and also its tastelessness.

10. The drug is put out in tablets of 0.1 Gm. (1½grains), but the dosage and administration vary with the patient, the frequency and type of seizures. The average adult dose is 4 to 6 tablets per day, for children 1 to 4 tablets per day in divided doses.

11. Contraindications are a measles-like rash, and aplastic anemia. Extreme drowsiness may be considered as such although stimulants counteract it and don't interfere with therapeutic results.

12. Clinically the use of Mesantoin varies with the severity and frequency of seizures and it must be used to meet the needs of the individual patient. Satisfactory results may be increased by combinations of other drugs with Mesantoin.

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