# Treatment of Migraine

## Results with Dihydroergocornine Methanesulfonate (DHO-180) and Other Ergot Derivatives

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*SUMMARY*

*A comparison of nicotinic acid, a non-narcotic analgesic and a series of injectable and oral ergot preparations tested by various methods in treating 40 patients with typical migraine indicate that ergot alkaloids are far superior in producing symptomatic relief.*

*A comparison of ergotamine tartrate, dihydroergotamine (DHE-45) and dihydroergocornine (DHO-180) indicated that ergotamine tartrate is the most effective and perhaps the most toxic, DHE-45 is slightly less effective and considerably less toxic, and that DHO-180 is the least effective but also the least toxic. When given orally, these alkaloids were about half as effective as when given by injection. EC-110 (ergotamine nitrate with caffeine) was the most effective.*

*DHO-180 in liquid form, given daily for one month, had a marked preventive effect on migraine attacks.*

IT is estimated that 8 per cent of the population of this country, over 10,000,000 persons, have migraine. Of those who have the disease, 61 per cent have family history of it.

During the past decade two important contributions were made to the understanding and treatment of this disease. One was the work of Wolff[16] and his associates who extensively studied the mechanism and localization of migraine. Their conclusions can be stated briefly as follows:

1. Migraine has a biphasic mechanism:

(a) The vasoconstriction or prodromal phase, in which the intracranial vessels (especially some of the branches of the internal carotid artery), are involved, is responsible for scotoma, paresthesia, etc.

(b) Then follows the vasodilatation phase in which the extracranial vessels, chiefly the branches of the external carotid artery, are implicated with concomitant increase in the amplitude of pulsations which corresponds to the actual headache.

2. Pain fibers in the vessel walls and the neighboring part of the meninges are the afferent fibers of the fifth, ninth and tenth cranial and the first three cervical nerves.

3. After the vasodilatation of the vessels has lasted awhile, edema of the vessel wall results, at which time vasoconstrictor drugs can no longer exert an optimum action.

The other major contribution was the introduction of ergotamine tartrate in the treatment of migraine by Stoll and his associates from Basle, Switzerland.

Ergotamine has, unlike other ergot derivatives, a minimal oxytocic and maximal sympatheticoparalytic action. This statement is not equivalent to saying that the latter action is necessarily adequate to control migraine headache. However, as nearly 90 per cent of patients with migraine get some definite benefit from this drug,[3] the statement is fundamentally correct.

Unfortunately this form of symptomatic treatment is not without annoying side-reactions in some cases. Nausea, vomiting and prostration are the chief corollary reactions. The following question then presented itself: How could one eliminate the toxic effect of this drug to allow a larger, expectedly more adequate dosage for the relief of headache?

Stoll, Hofmann and Petrzilka[14] showed that ergotoxin is not a uniform chemical substance but consists of three individual alkaloids, ergocornine, ergocristine and ergocryptine. Hydrogenation of the double bond in the lysergic acid component of these alkaloids yielded dihydroergocornine, dihydroergocristine and dihydroergocryptine. These are known as the dihydrogenated alkaloids of the dimethylpyruvic acid group. The dihydrogenated alkaloids of ergot have pronounced sympathicolytic or adrenolytic action in animals with only slight direct stimulating effect on the smooth muscle.

Rothlin[13] and Brügger[2] found in the isolated seminal vesicle of the guinea pig a method of biological assay to compare the various ergot variants according to their epinephrine-inhibiting effect on that particular preparation. This led to the tabulation of their respective sympathicolytic effects. Using ergotamine tartrate as the basis with a sympathicolytic

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index of one, the other preparations compare with one another in the following manner:

| | Index |
|---|---|
| Ergotamine I—Dihydroergotamine (DHE-45) | 7 |
| Ergocornine II—Dihydroergocornine (DHO-180) | 25 |

Due to this especially high sympathicolytic index, dihydroergocornine appeared to be particularly suitable for a clinical trial in the treatment of migraine, and its toxic effect was expected to be far below the previously used ergotamine tartrate and dihydroergotamine methanesulfonate (DHE-45).

## MATERIAL

The 40 patients employed for the past two years in this study were carefully selected. The number was believed to be large enough to permit statistical evaluation. The two-year period was estimated to give sufficient time for comparative evaluation of the various drugs. It should be pointed out that all the patients could qualify as having "typical" migraine. The criteria used for selection were:

(a) The absence of organic disease as determined by careful physical and special neurological as well as laboratory work-up supplemented by x-ray of the skull, electroencephalogram and, in some cases, pneumoencephalography.

(b) A family history of "sick headaches."

(c) Recurrent attacks consisting of prodromal manifestations such as nervous irritability, visual disturbances, numbness in certain limbs, and the whole array of phenomena believed to be vasospastic in origin—followed by

(d) Usually unilateral headache accompanied by nausea, vomiting, photophobia.

(e) Ending with rapid elimination of urine and/or sleepiness.

The subjects ranged in age from 17 to 61 years with an average of 33.5 years. The ratio of females to males was four to one. Duration of the periodic headaches ranged from five to 31 years with an average of 11 years. The total monthly headache hours when untreated was 680, or an individual average of 17 hours. This was used as a control. Total number of individual attacks was 127 or an individual average of 3.5 in each month.

It should be pointed out that the author is very much convinced of the importance of the psychological factor in the causation or at least in the precipitation of attacks of headache. The final conclusions of this study, therefore, should not be construed as a recommendation that the only form of therapy in migraine is drug therapy. On the other hand, it is strongly believed that had the study included psychiatric appraisal of these patients, whether for diagnostic or therapeutic purposes, an element of direct or indirect suggestion would have been hard to avoid. However, this would have introduced a new variant in the evaluation of drug therapy, which, after all, was the only objective of this work. The patients were at no time told that any of the treatments would help them, but rather—and this was emphasized—that they *might* or *might not*. The 40 patients, therefore, were submitted to a tedious experimental situation. Six patients were taken out of the series (and others substituted) because of poor cooperation.

Since there are some excellent summaries in the literature concerning the various theories about the mechanism and etiology of migraine—Graham and Wolff,[6] Lennox and von Storch,[9] Palmer[11] and von Storch[15]—these references are eliminated in this presentation. The fact remains that in spite of some very cogent observations and attractive speculations, the etiology of this condition is still not completely known. It is known, however, that thus far only symptomatic management of migraine can be termed as satisfactory.

When this study was begun two years ago, only pharmacological data were available on DHO-180. Since then Popkin[12] reported encouraging results in peripheral vascular diseases. Freis, Stanton and Wilkins,[5] and, more recently Bluntschli and Goetz,[1] have found this drug useful in hypertension and they extensively studied its effect on circulation in man. Imfeld,[8] who worked with a sister preparation (DHE-45), offered the following rationale for the use of the latter drug, which may be worth quoting since it is said that DHO-180 has identical action:

"Such a drug (DHE-45) inhibits the sympathetic stimulation acting upon the end organ or else it depresses the ways of excitation carrying a physiological or pathological sympathetic impulse." Further in the text he observed that "adrenergic stimulants originating not only in the ganglionic chain but also in the peripheral, autonomous, terminal reticulum can be inhibited or depressed."

## RESULTS

Previous to the use of ergot preparations, following the method of Friedman and Brenner,[4] the 40 patients were treated with nicotinic acid, 100 mg. intravenously, or with nicotinic acid, 150 mg. in 12 hours by mouth.

The results were as follows:

| | Relief | No Relief |
|---|---|---|
| Nicotinic acid injected | 9 | 31 |
| Nicotinic acid by mouth | 5 | 35 |

In order to get a collective impression, the patients were instructed to carefully record the duration of headache. The aggregate result:

| | Hours per month | Reduction | Average |
|---|---|---|---|
| No treatment | 680 | | 17 |
| Nicotinic acid injected | 570 | 16.2% | 14.25 |
| Nicotinic acid by mouth | 595 | 12.5% | 14.87 |

In general it can be said that the severe cases were the least likely to respond to nicotinic acid.

While Wolff's claim that the pre-headache phenomena are due to vasoconstriction of intracranial vessels is generally accepted, it has to be stated that the two phases cannot always be sharply separated, as overlapping of scotoma into headache is not rare and in many patients vasoconstrictor phenomena

are not noted at all. Of course it is entirely possible that vessels may be contracting in "silent" areas of the brain. Be that as it may, one would expect prompt abortion of the headache by the use of vasodilators in the constrictor phase. Sixteen of the patients in this series consistently complained of scotoma preceding headache. The administration of nicotinic acid intravenously one-half hour to four hours prior to the expected headache had the following effect:

| Abortion of Headache | Mild Headache | No Effect |
|---|---|---|
| 11 | 2 | 3 |

The patients with mild headache said they felt as if "several layers of headache had been removed." Since it is not common to find patients with constant prodroma of a vasoconstrictor nature, and since persons able to give intravenous injections are not always available, this form of treatment has little practical merit.

Analgesics were also tried. The patients were given tablets containing 0.65 gm. of acetylsalicylic acid and 1.3 gm. of caffeine. They were instructed to start out with two tablets, then one every hour for six doses if necessary. The results were as follows:

| Relief | Partial Relief | No Relief |
|---|---|---|
| 4 (10%) | 18 (45%) | 18 (45%) |

When expressed in monthly headache hours:

Untreated control ..... 680 hours
With analgesics ..... 620 hours, a reduction of 9 per cent

It can be concluded, therefore, that the action of this analgesic manifests itself not so much in shortening the period of headache, which was the case with nicotinic acid, but in making the headache less severe for some patients.

At this point oral and parenteral use of the various ergot preparations, such as ergotamine tartrate, dihydroergotamine methanesulfonate, and dihydroergocornine methanesulfonate, was begun. Results with injectable preparations given for one month each were as follows:

| Ergotamine | No. of Patients | Relief Pat's | Relief % | Partial Relief Pat's | Partial Relief % | No Relief Pat's | No Relief % | Toxic (Reaction) Pat's | Toxic (Reaction) % |
|---|---|---|---|---|---|---|---|---|---|
| Tartrate | 40 | 31 | 77.5 | 2 | 5 | 7 | 17.5 | 18 | 45 |
| DHE-45 | 40 | 29 | 72.5 | 6 | 15 | 5 | 12.5 | 6 | 15 |
| DHO-180 | 20 | 10 | 50 | 4 | 20 | 6 | 30 | 2 | 10 |

The results with the first two substances are largely in agreement with the already published findings. Ergotamine tartrate gives relief in a higher percentage of cases than does any other drug which has been tried, but the toxicity of it is relatively high. Of the 18 patients who had toxic reaction, seven were in the "relief" category, and the price they had to pay for the relief made discontinuance necessary in five of these seven patients. Toxic effects consisted of nausea, vomiting, weakness, pain in the legs, and dizziness.

DHE-45, although not quite as effective, is definitely less toxic and for that reason has an over-all advantage as compared to ergotamine tartrate. In only one case of the six in which there was toxic reaction were the effects of such an annoying nature as to necessitate discontinuance. Horton, Peters, and Blumenthal[7] reported that DHE-45 was just as effective as ergotamine tartrate, but toxic manifestations were noted three times more frequently with ergotamine than with DHE-45.

DHO-180 is less effective than either of the other two, but it is also the least toxic. In the one case in which toxic effect was shown, circulatory collapse occurred. (The patient responded in the same manner to other injectable ergot alkaloids.)

One conclusion from experience in this investigation was that unless subcutaneous injection of one of these ergot medications achieves control of the headache, this method is not warranted, since partial relief can be obtained by oral medication with less inconvenience. It should be noted also that in this series it was found that if a severe headache was not relieved at the first trial of one or another of these ergot preparations and a repetition within the hour had still no more effect, further trials consistently proved unsuccessful. The efficacy of these medications for an individual patient, therefore, could be canvassed on two trials given as close to the onset of headache as possible.

### ORAL ERGOT ADMINISTRATION

When the ergot preparations were given orally, two types of dosage schedules were used, with half of the patients following one schedule and half the other, but a breakdown of the figures does not show a significant difference between results obtained by the two schedules. The patients were instructed to take the medication at the first manifestation of headache. Those patients who were unable to swallow the first large dose of ergot alkaloid because of nausea or vomiting were given another trial and if nausea persisted they were given ergot preparations subcutaneously, but the results are not included in the data on results (Table 1).

The schedules were as follows:

| Drug | Initial Dose (mg.) | Subsequent Half-hour Dosage (mg.) | Maximum Total Dose (mg.) |
|---|---|---|---|
| **Schedule A** | | | |
| Ergotamine tartrate | 3 | 1 | 6 |
| DHE-45 | 6 | 2 | 10 |
| DHO-180 | 4 | 3 | 10 |
| EC-110* | 3 | 1 | 6 |
| **Schedule B** | | | |
| Ergotamine tartrate | 5 | 1 | 8 |
| DHE-45 | 8 | 2 | 12 |
| DHO-180 | 6 | 2 | 12 |
| EC-110 | 4 | 1 | 8 |

While the series was not large enough to permit far-reaching statistical evaluation, it can be concluded with safety that by and large the oral administration in the manner it was given was roughly half as successful as the subcutaneous use of the (first three) substances. While incidence of toxic manifestations was rather high, the reactions were much milder in nature and even negligible; they

*Composition: 1 mg. ergotamine tartrate with 100 mg. caffeine.

TABLE 1.—*Results with Oral Administration of Ergot Preparations*

(20 patients followed Schedule A and 20 Schedule B)

| Drug | Schedule | Relief Patients | % | Partial Relief Patients | % | No Relief Patients | % | Toxic Reaction Patients | % |
|---|---|---|---|---|---|---|---|---|---|
| Ergotamine tartrate | A | 7 | 35 | 6 | 30 | 7 | 35 | 6 | 30 |
| | B | 8 | 40 | 6 | 30 | 6 | 30 | 7 | 35 |
| DHE-45 | A | 10 | 50 | 2 | 10 | 8 | 40 | 4 | 20 |
| | B | 12 | 60 | 4 | 20 | 4 | 20 | 4 | 20 |
| DHO-180 | A | 10 | 50 | 2 | 10 | 8 | 40 | 2 | 10 |
| | B | 12 | 60 | 3 | 15 | 5 | 25 | 5 | 25 |
| EC-110 | A | 11 | 55 | 5 | 25 | 4 | 20 | 2 | 10 |
| | B | 12 | 60 | 0 | 0 | 8 | 40 | 7 | 35 |

consisted chiefly of transient weakness, nausea and palpitation. No interruption was necessary and these side-effects were frequently absent on subsequent trials.

Comparison of the individual variants of the ergot alkaloid shows that ergotamine tartrate, given orally, was the least successful in producing relief but that partial relief was the highest with this drug. The other three were rather alike in their action, with EC-110 somewhat better than the rest. When EC-110 was given according to Schedule B and only when patient had an oncoming attack, by-effects were noted, consisting of light-headedness and palpitation. This was probably the result of the caffeine in that preparation. Roughly 50 to 75 per cent of patients got relief, total or partial, with one schedule or the other.

An interesting observation was that in a group of five patients who had several migraine attacks in one week, less and less DHO-180 was needed in successive attacks which were of equal intensity. This was not the case with other medications. On the other hand, in the group of patients who were treated with ergotamine and got no relief, there were three who had headache with greater frequency as time went by.

At this stage of the study DHO-180 was supplied in liquid (drop) form, each cubic centimeter containing 1 mg. of dihydroergocornine methanesulfonate, which permitted greater flexibility of dosage. Inasmuch as the toxicity of this drug when given according to Schedule A was low, and in view of the previously mentioned observation of decreasing need in subsequent attacks, this medication was given daily for one month in order to find out whether headaches could be prevented or the frequency of occurrence reduced. All 40 patients were used for this purpose. The individual dose was 5 to 20 drops thrice daily, but it was found that 10 to 15 drops was the most effective.

The results calculated in headache hours demonstrated pronounced reduction: In the untreated control the monthly total of headache hours was 680; when DHO-180 was given, 30 drops daily in three equal doses, headache hours aggregated 140 monthly, or a reduction of 79.4 per cent. When migraine attacks did occur they were in all cases milder.

When the drops were given according to Schedule A, the results were somewhat different, in that 32 of the 40 patients were completely or greatly relieved while five were not relieved. In aggregate, the frequency of attacks was reduced and headache was milder with fewer and less pronounced associated symptoms, although individually the attacks lasted as long as they ever did. Eleven patients had their first attack-free month in several years, although the following month they may have had recurrence.

As it was important to determine whether the same results could be obtained with some of the other ergot preparations, the whole group was given DHE-45 (dihydroergotamine) in tablets, each containing 2 mg., with a dosage schedule of one tablet thrice a day. The monthly total of headache hours was 510, a reduction of 25 per cent from the control total, as compared with the reduction of 79.4 per cent obtained with DHO-180.

Lennox[10] in 1934 demonstrated that daily administration of ergotamine tartrate had little or no effect. No effect was observed with 3 mg. daily and only a few attacks were skipped with 9 mg. daily. However, sublingual administration of this drug has proven effective in some cases. Now DHE-45 is added to the list of ergot preparations with a moderate preventive effect. DHO-180 appears to be, therefore, the first ergot variant which has something like a preventive effect on the frequency of migraine.

This effect of DHO-180 cannot be explained easily or completely. In view of the high epinephrine-inhibiting index (25 with that of ergotamine tartrate taken as 1) it can be postulated that the effect is essentially sympatheticoparalytic, leading to an improvement of the vascular tone. Popkin demonstrated this effect in peripheral vessels by the improvement of color and increase in skin temperature of patients, and the duration of this reaction was three to four hours. There is no reason why a similar condition cannot occur in the vessels within and outside the cranium. Once the vascular tonus is improved, the vessels would be able to better resist the assault of whatever noxious stimuli there may be to unleash an attack of migraine. This protection is not complete, since some migraine did occur, but obviously a threshold effect seems to have been obtained. That the explanation is not simply one of inhibition of sympathetic action is demonstrated by the fact that the dihydrogenated ergot alkaloids in some cases produce favorable results in vasospastic conditions of the leg and of the head in patients in whom the sympathetic nerve supply has been surgically interrupted. That there cannot be any pain threshold-raising factor operating on pain mediating fibers of vessels was shown by Wolff, Hardy and Goodell,[17] who were unable to demonstrate such effect with their method when using ergotamine tartrate. The difficulty of explaining this action of DHO-180 is no different from the difficulty of accounting

for the mechanism of migraine, which is still not completely understood.

There is still no explanation for the coexistence of scotoma and pulsating headache which would indicate vasoconstriction in the branches of the internal carotid artery concurrent with vasodilatation in the branches of the external carotid artery. The difficulty of influencing these opposite mechanisms simultaneously is obvious. Both mechanisms, when extreme, may press upon pain fibers in the vessel wall and cause headache. Edema of the vessel wall after prolonged dilatation when the migraine is refractory to ergot medication has already been mentioned.

These are only a few factors impeding the final solution of the migraine problem.

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*Discussion by* ROBERT B. AIRD, M.D., *San Francisco*

The contributions of Dr. Bercel's study would appear to me to be as follows:

(1) The results with parenteral injections strongly suggest that DHO-180 is considerably less effective in the relief of migraine headaches than either of the older ergotamine preparations, that is, the tartrate or DHE-45. Although slightly more toxic than DHO-180, the DHE-45 compound gave appreciably better results than DHO-180. Although essentially as effective as ergotamine tartrate, DHE-45 was considerably less toxic. The practical import of this is that Dr. Bercel's results would appear to indicate that DHE-45 is the best all-around agent of the group for the relief of migraine. This is in agreement with our own observations and other reports, such as those of Horton and his coworkers. In making this point, it should be understood that such a statement has little significance insofar as the individual patient is concerned. What is best for one patient may be ineffective for the next.

(2) The studies on the oral administration of the ergotamine derivatives are also noteworthy in showing that EC-110, which is ergotamine tartrate in combination with caffeine, gave the most relief with the minimum of toxicity when used conservatively as indicated in "Schedule A."

(3) Dr. Bercel's most noteworthy contribution, however, is concerned with his observation on the prophylactic effect of DHO-180 upon migraine headaches when given regularly in doses of from 10 to 15 drops thrice daily.

With regard to the physiological mechanisms underlying migraine, I believe it is fair to postulate a vasoconstriction of the terminal branches of the internal carotid artery as being the primary event in a high percentage of cases, if not in all. That Dr. Bercel could abort migraine attacks partially or completely in 13 of 16 patients seems to me to be a striking point. In clinical studies one does not expect much better results than this. Considering one's inability to control all factors, as for example the possibility that an intravenous injection given relatively late might not be effective in aborting an attack, Dr. Bercel's positive results in 13 of 16 patients would seem to substantiate the point that vasoconstriction is the primary event in the abnormal physiology of migraine. Such a peripheral vasoconstriction intracranially would shunt considerable amounts of blood through the other main branch of the carotid artery. The dilatation and stimulus of this might be expected to initiate the strong pulsations of the branches of the external carotid, which in turn would stimulate the pain-sensitive fibers in the blood vessel walls and result in the unilateral, throbbing pain typical of migraine. Since the shunting effect would occur concomitantly with intracranial vasoconstriction, it is not surprising that the migraine attack might begin while the cerebral manifestations of vasoconstriction were still apparent in some patients, as may be observed occasionally and as was noted by Dr. Bercel. The prolongation of the migraine attack and ineffectiveness of the ergotamine derivatives when given late is best explained, as Dr. Bercel has stated, by the edema of the vessel wall and the perivascular swelling which has been termed "pipe-stem" arteries. This aspect of the problem has interested me a great deal inasmuch as this perivascular and edematous reaction would appear to be the result of, or associated with, an increased permeability of the vascular wall. In certain cases of headache, injections of the supra-vital dye, Trypan Red, have been beneficial. Since this dye stains the endothelial cells and tends to lower vascular permeability, its beneficial effect is presumably due to its action in aborting this perivascular and edematous reaction.