Cycloserine

Cycloserine in the Treatment of Human Pulmonary TB
Israel Epstein, KGS Nau & Lenn J Boyd
Trans. XIV Conf. on TBC, V.A., Feb. 1955
VA Reg. Off. Atlanta, Ga. pp 326-331

29 pts. 1.0 → 1.5 Gm. /day (250 mg Caps) (about 25 mg/kg)
2 pts – EPE
2 pts = Hist of schiz → "change in personality, progressive
overright mental depress after month of therapy,
depressive state overlaid descontinuance of Rx
2 pts → hyperreflexia

of Weld et al / overbroke Med- 2/55
Epstn et al

Commercial Solvents Corp: H.N. Spencer
Cycloserine = Seromycin

Trifluoperazine — Parkinson
SKF 5019

9/57

Refs.

CP more Effective than Res. Shepherd & Watt J. N., N.S., P. 19: 232, 1956

Extrapyr. syndrome is sine qua non — CP, Tril > Prom, mepazine } Denber.

CP + diethazine → inc Δ.

Benactyzine: EES Effect
Jacobsen = Ugeskrift
Coady & Jewesbury. Br M J

EEG Jour:

Reserpine: 8: 1956, p 150 — delta prod or increased activates seizures.
(1) Arellano & Jeri
(2) Liberson: 8: 523 — no chg or theta range, no inc in fast.
(3) Gonnard, Schmitt, etc 8: 708 → sleep record (a) desynchron. (b) ~~[illegible]~~ delta

CP: Affects Br stem reticular formation → burst Bradley & Hance
8: 700

Reserpine: Legg & Schneider 9: 419: activates br stem → desynch; ~~[illegible]~~ produces seizures.

COPY

Clinical Release

PRODUCT

Combination of 'Thorazine' and Diparcol (SKF #1026-A)
Diparcol alone

FORMULAS	mg/cap.	mg/cap.
SKF #1026-A (Diparcol)	250.0 mg.	250.0 mg.
'Thorazine' HCl	50.0 mg.	----
Magnesium Stearate	2.0 mg.	----
Lactose	200.0 mg.	300.0 mg.

USE

Restricted Medical Utility Studies - Dr. Herman Denber

TOXICITY

Acute Intravenous Toxicity - The intravenous acute toxicity of a combination of SKF #1026-A ('Diparcol') and 'Thorazine' in the ratio of 5:1 was determined. Intravenous LD_{50}'s in male mice (CF_1) were determined for SKF #1026-A, 'Thorazine' and a combination of SKF #1026-A and 'Thorazine' in the ratio of 5:1. The mice were observed for a 24 hour period, at which time all surviving mice appeared normal.

Combination significantly more toxic than SKF #1026-A (T.R. = 1.2)

'Thorazine' not significantly more toxic than combination. (T.R. = 1.13)

'Thorazine' significantly more toxic than SKF #1026-A (T.R. = 1.36)

The acute intravenous toxicity in mice of a combination of 'Thorazine' and 'Diparcol', in the ratio of 1 part of 'Thorazine' to 5 parts of 'Diparcol', did not differ significantly from that of 'Thorazine' alone. Such a comparison is valid since the slopes of the toxicity curves are parallel. The combination is significantly more toxic than 'Diparcol' alone, but the comparison is subject to criticism that the slopes of the toxicity curves are not parallel.

December 9, 1955

C
O
P
Y

DIPARCOL

In answer to your request an attempt has been made to find data comparing the anticonvulsant activity of Diparcol (Diethazine, SKF #1026) with that of other phenothiazine derivatives: Phenergan (SKF 1498), 'Thorazine' (SKF 2601), Promazine (SKF 3406), 'Compazine' (SKF 4657), SKF 5277 and SKF 5116. No such studies have been done in our laboratory. The only SKF lab report on Diparcol gives its toxicity as LD_{50} = 31.2 mg/Kg I.V. as compared with 22.9 mg/Kg I.V. for 'Thorazine'.

Balestrieri (1955) compared Diethazine, Phenergan, Parsidol and chlorpromazine with respect to their protective action against electroshock and Metrazol seizures in rabbits. Phenergan and chlorpromazine showed no anticonvulsant action against electroshock seizures; Diethazine, 5 mg/Kg I.V. protected 2/5 animals and at 10 mg/Kg I.V. 3/5 animals. Parsidol protected 2/5 animals at both doses. These results confirm SKF data obtained using maximal electro-shock seizures in mice which showed no anticonvulsant activity for SKF 1498, 2601, 4657 or 5116. SKF 3406 did protect mice against seizures; the ED_{50} was 155 mg/Kg p.o. SKF 5277 also demonstrated anticonvulsant activity with an oral ED_{50} of 71.0 mg/Kg.

The experiments of Balestrieri showed chlorpromazine to be inactive in protecting rabbits against Metrazol seizures. Phenergan was inactive at 5 mg/Kg I.V. but a 10 mg/kg I.V. protected 4/5 animals. Diethazine protected 4/5 animals at 5 mg/Kg and 5/5 at 10 mg/Kg. Parsidol protected 5/5 animals at both doses.

No similar SKF data are available.

Balestrieri, A. Anticonvulsant action and molecular structure of phenothiazine derivatives. Arch. Int. Pharmacodynam. 103:1-11, 1955

HLM:pz

hc

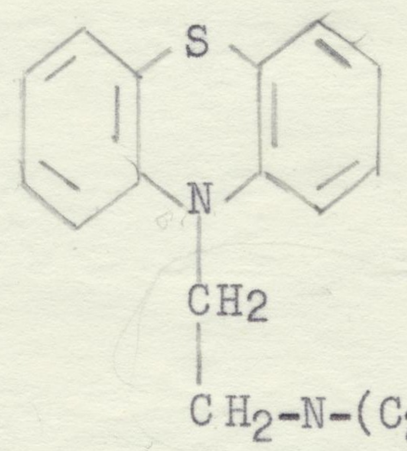
COPY

PHARMACOLOGY REPORT

November 8, 1956

Compound: SKF No. 1026-A — 10-(2'-Diethylaminoethyl)-Phenothiazine
Code No. Lot No. 99 — Hydrochloride OR (Diparcol)

Structure:



Origin: Dr. R. T. Conner - Specia

Tested for: Dose Range Studies in mice after intravenous administration (11/10/55)

Dose mg/kg	Observations
2.5	No side effects
5.0	2/2 slight depression, loss of pinnal reflex
10.0	2/2 ataxia, sl. depression, loss of pinnal reflex, 'Thorazine' walk.
15.0	2/2 ataxia, marked depression, dyspnea, 'Thorazine' walk, loss of pinnal reflex.
20.0	6/6 clonic convulsions, apnea, prostration, ataxia after recovery, hypotonicity, 3/6 dead
25.0	2/2 clonic convulsions, apnea, prostration, ataxia after recovery, hypotonicity

Note--all animals recovered from prostration within 60 minutes.

Summary: SKF #1026-A exhibited 'Thorazine'-like side effects after intravenous administration in mice. Slightly higher doses were required to produce depression than with 'Thorazine' and the depression produced was of shorter duration.

Activity: 'Thorazine'-like

Charge: Biological screening

GW/DS/EM/mh

LILLY LABORATORY FOR CLINICAL RESEARCH
INDIANAPOLIS GENERAL HOSPITAL INDIANAPOLIS 7, U. S. A.

December 29, 1956

Max Fink, M.D.
Hillside Hospital
75-59 263rd Street
Glen Oaks, New York

Dear Dr. Fink:

In answer to your recent request, Storey et al. (Antibiotic Med. & Clin. Therapy, 3:258, September, 1956), though they do not report electroencephalogram findings, do discuss the behavioral effects of cycloserine. There have been no publications, to my knowledge, reporting EEG findings in patients receiving 'Seromycin' (Cycloserine, Lilly).

The Veterans Administration hospitals have been doing EEG tracings but their reports have not yet been published. They will probably present their data at the Veterans Administration Conference on the Chemotherapy of Tuberculosis to be held in St. Louis in February.

If we may be of any further assistance, please do not hesitate to w rite us.

Very truly yours,

R. S. Griffith, M.D.
Clinical Research Division

mlw

Form 90a-Adm.

TELEPHONE: LEHIGH 4-1300

JOHN H. TRAVIS, M. D.
DIRECTOR

State of New York
Department of Mental Hygiene

MANHATTAN STATE HOSPITAL

Ward's Island, New York City 35, N. Y.

IN ANSWERING REFER TO_____ June 20, 1957

Dr. Max Fink
Hillside Hospital
75-59 263rd Street
Glen Oaks, N. Y.

Dear Max:

I should like very much to include your findings on the 'Diparcol' in the final paper that I am writing on Chlorpromazine-Diethazine Treatment of Depression. Could you send me a brief note indicating, in general, the effects of I.V. diethazine on the EEG? Were there any concomitant psychological effects? I will note this, of course, under the reference of "personal communication."

Many thanks.

Sincerely yours,

HD

Herman C. B. Denber, M. D.
Director of Psychiatric Research

HD:SS

June 27, 1957.

Dr. Herman C. B. Denber,
Director of Psychiatric Research,
Manhattan State Hospital,
Ward's Island, N.Y.

Dear Hy:

It was a pleasure to spend some time with you and your wife in Atlantic City. I am sorry that we could not get together for "business" purposes - but Martha and I enjoyed our social visit very much. Jonathan was most taken with Michele, who is a very bright boy. But this you already know. As for our experience with Diparcol. Following your suggestion in Montreal, I obtained some intravenous material from SKF. In the last few months we have given it to six patients intravenously. Each subject had a course of electroshock therapy and the time of the experiment was at the height of the electroshock effect. In each instance high degrees of delta activity were present in the electroencephalogram. The setting for the test was the amobarbital test situation, in which I asked all the questions prior to the administration of the drug; and then repeated them after the administration. The drug dosage was 250 mgm. given at the rate of 50 mgm. a minute. Continuous recording following for about thirty minutes; and then discontinuous sampling for the next six to eight hours at the rate of ten minutes approximately every hour.

During the administration, each patient developed, between the second and fourth cc. an episode of coughing. There was some difficulty in breathing which was transient. This was the most untoward effect of the injection.

The electroencephalographic change appeared gradually but was most apparent within a few minutes after the completion of the injection. At this time delta voltages were reduced from a range of 150 to 200 microvolts to a range of 70 to 100 microvolts. The delta frequency was raised from frequencies 1½ and 2 cps. to a more general range of 3½ to 5 cps. The percent time delta, however, remained about the same. Such an effect persisted for one to two hours and in all instances in the samples taken about four to five hours later the delta activity was at the pre-injection level. In one of our patients the delta activity had been of the order of 4 to 6 cps. and in voltages of 40 to 70 U.V. Following the completion of the injection the delta activity was markedly reduced in percent time, and in voltage so that no delta appeared higher than 40 microvolts. There appeared superimposed

a clearly defined 25 cps. activity.

Behaviorally the records report the following. There was an "alerting" effect. This was manifested by an increased restlessness of the patient and a greater difficulty in having the patient maintain his eyes closed. The specific evidence for this alerting phenomena was the change in two patients from a positive amytal effect to a negative amytal. The changes in language after Diparcol were the reverse of the changes in language which we have experienced in the past after the administration of amobarbital. Since we use the identical questionnaire, we scored the changes in language in an identical fashion. In three instances the questions prior to the administration of Diparcol were negative and therefore it was impossible to evaluate the changes in language. In one instance the record changed from a "negative" response to an increase in language changes of the kind that we see with amobarbital. This discrepancy I cannot explain.

We are continuing this study and I would like to present the behavioral and electroencephalographic effects early in the fall to the Eastern EEG Association. These observations are, of course, exploratory and I am not sure ~~t~~BUT what the next batch of patients may not show us some other patterns. To the extent that this investigation has confirmed the observations of Lechner, I am most pleased.

I have no objection to your reporting some of this information in outline. If it is of any help to you, I will be pleased to see the paragraphs as you intend to report them and give you my reaction as to how they reflect our experiences.

My best regards,

Sincerely yours,

Max Fink, M.D.

Department of Experimental Psychiatry.

MF:JB

0+3
55.

Affect of Diethazine on EEG and Significance for Theory of Convulsive Therapy

Max Fink MD

Previous studies of the role of EEG changes in convulsive therapy have demonstrated the significance of the induced delta activity for the behavioral response. Investigations concerning the biochemical substrate of EEG delta in electroshock and convulsions have indicated significance for the cholinesterase - acetylcholine system. Recent reports by Ulett concerning the effects of atropine and scopolamine on the delta response of the EEG showed a reversal of the induced EEG patterns. Concurrent reports by Jeankner and Lechner on the effects of diethazine on normal EEG and that following trauma provided the stimulus for the study of the effects of this drug in electroshock.

Subjects:

Twenty psychiatric patients in an open-ward/psychiatric hospital have been tested to date. ~~Electroencephalograms have been obtained~~ at various times during treatment. During the recording, diethazine (Diparcol) is administered intravenously at the rate of 25 milligrams per minute until 250 milligrams have been administered.

---

from the Dept of E.P., HH, G.O., N.Y.

11-5-57 — EAEEG

Observations:

a) Behavioral: All subjects respond by coughing, dryness of the mouth and thickness of speech. Feelings of weakness of extremities and illusory sensations are common. There is an increase in restlessness and difficulty in maintaining eyes closed. In patients who have had sufficient electroshock to manifest syntactic and orientation language changes indicative of altered cerebral function, there is a reversal of language patterns.

b) EEG: In all subjects there is desynchronization of frequencies and decrease in voltage. Alpha rhythms are less prominent. Occasionally, low voltage theta frequencies appear.

In patients with varying degrees of delta activity, voltage ~~is~~ in decreased, frequencies ~~de~~crease and burst activity disappears. Irregular alpha and beta frequencies of low voltage become ~~more~~ prominent.

c) The EEG and clinical effects persist ~~consist~~ for one to three hours, and gradually disappear.

Discussion:

The pharmacologic effects of diethazine are described as "anti-cholinergic" and "atropine-like," and in patients with altered brain function may be described as "allertig." The action of diethazine on electroshock induced EEG delta is similar to atropine and ~~scelpalomine~~ scopalomine (Ulett). ~~Also~~ These observations are similar to those in subjects with head injury (Jenker and Lechner).

Conclusion:

Based on this data, as well as the cerebro spinal fluid cholinesterase studies of Bornstein, and Tower and McEachern, it is concluded that: (1) diethazine ~~has a ready ability to~~ readily enter the central nervous system; (2) delta activity induced by electroshock and by trauma may have a similar biochemical substrate; (3) electroshock may be looked upon as a controlled method ~~to induce~~ of inducing cerebral dysfunction for its ~~induced~~ behavioral effects.

The significance of these observations for EEG studies of head trauma and the mode of action of ~~electro~~convulsive therapy will be discussed.

11-6-57

Effect of Diethazine on EEG and Significance for Theory of Convulsive Therapy

Previous studies of the role of EEG changes in convulsive therapy have demonstrated the significance of the induced delta activity for the behavioral response. Investigations concerning the biochemical substrate of EEG delta in electroshock and convulsions have indicated significance for the cholinesterase - acetylcholine system. Recent reports by Ulett concerning the effects of atropine and scopalomine on the delta response of the EEG showed a reversal of the induced EEG patterns, Concurrent reports by Jeankner and Lechner on the effects of diethazine on normal EEG and that following trauma provided the stimulus for the study of the effects of this drug in electroshock.

Subjects:

Twenty psychiatric patients in an open-ward/psychiatric hospital voluntary have been tested to date. Electroencephalograms have been obtained at various times during treatment. During the recording, diethazime (Diparcol) is administered intravenously at the rate of 25 milligrams per minute until 250 milligrams have been administered.

Observations:

a) Behavioral - All subjects respond by coughing, dryness of the mouth and thickness of speech. Feelings of weakness of extremities and illusory sensations are common. There is an increase in restlessness and difficulty in maintaining eyes closed. In patients who have had sufficient electroshock to manifest syntactic and orientation language changes indicative of altered cerebral function, there is a reversal of language patterns.

b) EEG - In all subjects there is desynchronization of frequencies and decrease in voltage. Alpha rhythms are less prominent. Occasionally, low voltage frequencies appear. In patients with varying degrees of delta activity, voltage is decreased, frequencies decrease and burst activity disappears. Irregular alpha and beta frequencies of low voltage become more prominent.

c) The EEG and clinical effects persist for one to three hours, and gradually disappear.

Discussion:

The pharmacologic effects of diethazine are described as "anti-cholinergic" and "atropine-like," and in patients with altered brain function may be described as "allertic." The action of diethazine on electroshock induced EEG delta is similar to atropine and ~~scolpalomine~~ scopalomine (Ulett). Also, these observations are similar to those in subjects with head injury (Jeanker and Lechner).

Conclusion:

Based on this data, as well as the cerebra^{0} spinal fluid cholinesterase studies of Bornstein and Tower and McEachern, it is concluded that: (1) diethazine has a ready ability to enter the central nervous system (2) delta induced by electroshock and by trauma may have similar biochemical substrate (3) electroshock may be looked upon as a controlled method to induce cerebral dysfunction for its induced behavioral effects.

The significance of these observations for EEG studies of head trauma and the mode of action of electroconvulsive therapy will be discussed.

Effect of Diethazine on EEG and Significance for Theory of Convulsive Therapy

Max Fink, M.D.

Previous studies of the role of EEG changes in convulsive therapy have demonstrated the significance of the induced delta activity for the behavioral response. Investigations concerning the biochemical substrate of EEG delta in electroshock and convulsions have indicated significance for the cholinesterase - acetylcholine system. Recent reports by Ulett concerning the effects of atropine and scopolamine on EEG delta in electroshock showed a reversal of induced EEG patterns. Concurrent reports by Jenkner and Lechner on the effects of diethazine on normal EEG and that following trauma provided the stimulus for the study of the effects of this drug in electroshock.

Subjects:

Twenty psychiatric patients at various stages during treatment in an open-ward voluntary psychiatric hospital have been tested to date. During EEG recording, diethazine (Diparcol) is administered intravenously at the rate of 25 milligrams per minute, for a total of 250 milligrams.

Observations:

a) Behavioral: All subjects respond by coughing, dryness of the mouth and thickness of speech. Feelings of weakness of extremities and illusory sensations are common. There is an increase in restlessness and difficulty in maintaining eyes closed. In patients who have had sufficient electroshock to manifest syntactic and orientation language changes indicative of altered cerebral function, there is a reversal of language patterns.

b) EEG: In all subjects there is a desynchronization of frequencies and decrease in voltage. Alpha rhythms are less prominent. Occasionally, low voltage theta frequencies appear.

In patients with varying degrees of delta activity, voltages decrease, frequencies increase and burst activity disappears. Irregular alpha and beta frequencies of low voltage become prominent.

c) The EEG and clinical effects persist for one to three hours, and gradually disappear.

From the Department of Experimental Psychiatry, Hillside Hospital, Glen Oaks, N.Y.

11-5-57 - EAEEG

Discussion:

The pharmacologic effects of diethazine are described as "anti-cholinergic" and "atropine-like," and in patients with altered brain function may be described as "alerting." The action of diethazine on electroshock induced EEG delta is similar to atropine and scopolamine (Ulett). These observations are also similar to those in subjects with head injury (Jenkner and Lechner).

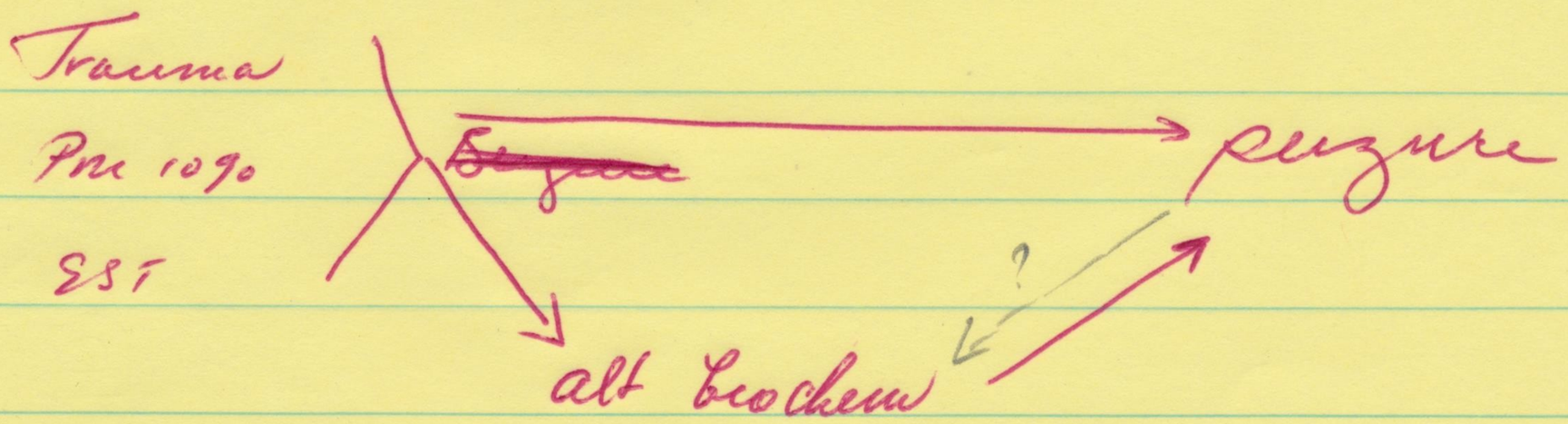
Conclusion:

Based on this data, as well as the cerebrospinal fluid cholinesterase studies of Bornstein, and Tower and McEachern, it is concluded that: (1) diethazine readily enters the central nervous system; (2) delta activity induced by electroshock and by trauma may have a similar biochemical substrate; and (3) electroshock may be looked upon as a controlled method of inducing cerebral dysfunction for its behavioral effects.

The significance of these observations for EEG studies of head trauma and the mode of action of convulsive therapy will be discussed.

11-19-57

Synch. seizures after EST, or PM 1090 (Ewalo)
are evidence for biochem. basis of seizures - not
the physical response to the trauma.



Biochemical Studies of Electroshock

(a) Ach - chol — Review

(b) Cont. - Conv. — Chol.

(c) EEG + Behav. — Dopacol.

Concl: Prev studies related to Learning in gen.

~~Judges~~ suggestion as to ECT confirmed for ECT.

Relation to Present concept of ECT.

Heymans, Estable + C. de Bonneveaux

Diparcol   Arch Int pharmacody. 1949

Dogs:

BP ↓ by peripheral vasodilator

Blocks vagal inhib. effect on heart

Prevents or suppresses	bradycardia	of	Ach
	bronchospasm		DFP
	Convulsions		Pilocarp
	fasciculation		nicotine
	salivation		

Protects heart ag. toxic effects of → (above)

Inhibits or inactivates (in vitro / in vivo) — serum cholin E.

without affecting true - cholinesterase

Induces mydriasis in normal + sympathect. eye

Form 90-Adm.

LAWRENCE C. KOLB, M. D.
DIRECTOR

New York State
Psychiatric Institute
722 WEST 168TH STREET, NEW YORK

December 4, 1957

Dr. Max Fink
Dept. of Experimental Psychiatry
Hillside Hospital
75-59 263rd Street
Glen Oaks, New York

Dear Max:

Our feelings about Saturday night are reciprocal. We thoroughly enjoyed the gracious company of you and Martha. With the intuitive perceptiveness of the female, Yetta informed me of a forthcoming event in your family, and we wish you the best of everything.

I indeed look forward to the reprints on your work which you described in your letter and our discussing them together. The next edition of the Kalinowsky and Hoch will be expanded to include tranquilizers, and I would also appreciate any reprints of yours in this area.

I have enclosed my own reprint on the clinical effects of Win-2299 and the basic paper by Luduena and Lands. As you will note, the compound is a peripheral anticholinergic and produces a "disorientative" reaction in cats by central action. Its psychotomimetic action in man appears basically to be an acute toxic reaction type. I would imagine that its central mechanism of action is similar to that of atropine (which also produces acute confusional states in high doses). Win-2299 is effective at much lower dosages than atropine. Possibly both atropine and Win-2299 both produce central effects by an anticholinergic action but, as far as I know, this modus operandi has not been pinned down crucially as far as the C.N.S. is concerned.

I would not expect all anticholinergic agents to be psychotomimetic, of course. Win-2299 is a tertiary amine. Monodral is a closely related drug, differing only by quaternization of the terminal nitrogen in Win-2299. It is Win-4369 in the paper of Luduena and Lands (p.283), i.e. the methobromide form. According to Winthrop-Sterling, it is a peripheral anticholinergic in man in doses of 5-40 mg. per day. Central or psychic actions are not mentioned in their account. Presumably, quaternization reduces central activity by reducing permeability.

I imagine that other agents in the Win series with central effects in cats might also be active as psychotomimetics in man. I am not familiar with the formula of diparcol and if you have it available would appreciate learning where to look it up. The drug is not covered by Goodman and Gilman. I would appreciate return of the Luduena and Lands paper when it has served your needs.

We gave the Win-2299 orally, the compound being supplied in tablet form. The drug was supplied as the racemic mixture, the asymmetric carbon atom being terminal in the aliphatic chain. Sterling-Winthrop may have it for intravenous use and I suggest that you write M. L. Tainter, M.D., Director, Sterling-Winthrop Research Institute, Rensselaer, N.Y. about it. Our oral supply was used up in the study.

As you know, all psychotomimetics not only create new symptoms in mental patients but also intensify or revive pre-existent symptoms.

Best of luck.

Cordially,

Harry

Harry H. Pennes, M.D.

HHP/ys
Encl.

12-6-57 O + E D.T. 7.5.

Effect of Diethazine on EEG and Significance for Theory of Convulsive Therapy

Max Fink MD

In a previous report to this society we noted the relationship between the degree of induced delta activity during the course of therapy and the behavioral response to electroshock. Those patients, in whom high degrees of delta activity were induced early, and were sustained, manifested the greatest degrees of behavioral change, as well as a significantly greater percentage of improvement and recovery than those patients in whom only low degrees of delta activity were induced (Fink and Kahn, 1957).

We have been led to investigate the role of acetylcholine-cholinesterase metabolism in electroshock by ~~In the past few years,~~ a variety of recent reports, ~~relating~~ changes in free acetylcholine and cholinesterase in the spinal fluids of patients (Sachs, Ward) and animals (Bärnstein, Tower and McEachern) following head trauma, and the observations that anticholinergic ~~cholinalytic~~ agents ~~may~~ alter the EEG patterns induced by trauma (Bärnstein, Ward, Jenkner-Lechner) and by electroshock (Ulett), ~~led us to investigate the role of acetylcholine-cholinesterase metabolism in electroshock therapy.~~ Arising recent observations.

In 1956 Ulett reported that atropine and scopolamine, ~~when administered on a round the clock schedule~~ blocked the appearance of the delta activity we have come to associate with electroshock therapy. ~~Ulett noted, however,~~

From the Dept of G. P., H H, G. O., N.Y.
Read at the Eastern Conference of Electroencephalographers, New York, December 11, 1957.

~~that his patients suffered numerous undesirable side effects during these observations.~~ Previously, Ward (1950) following the suggestion of Bornstein, (1946) had noted that atropine altered both the EEG patterns and the neurologic signs induced in man by head trauma. In both these studies, ~~Here, too,~~ the side effects of the drugs were marked. In 1955, Jenkner and Lechner reported that EEG and behavioral effects similar to atropine were achieved by diethazine administered in patients with head trauma. They also reported the effect of diethazine in normal subjects.

(2)

It is the purpose of this report to describe the effects of intravenous diethazine on the EEG of patients during electroshock therapy; and to relate ~~their~~ these findings to the present neurophysiologic-adaptive hypothesis of the mode of action of convulsive therapy.

(4)

Diethazine is a soluble phenothiazine compound with pharmacologic properties similar to atropine. In experimental animals, Heymans et al (1949) have noted that diethazine blocks vagal slowing of the heart, suppresses the bradycardia, bronchospasm, salivation, ~~and~~ fasciculation and seizures induced by acetylcholine, DFP and pilocarpine; and induces dry mouth, mydriasis and hypotension.

Subjects: Twenty-two psychiatric patients, at various stages of electro-shock treatment in an open-ward, voluntary psychiatric hospital have been studied. ~~In these experimentas, experiments,~~ Subjects were tested in the EEG laboratory. Following a routine EEG recording, diethazine was administered intravenously at the rate of 25 mgm per minute, for a total of 200 to 250 mgm, depending upon the behavioral effects. Prior to the drug administration, an unstructured historical interview and a structured questionnaire period were tape-recorded. Following drug administration, both EEG recording and recorded interview periods were continued until the EEG record again manifested the pre-injection patterns on visual inspection.

Observations:

(a) Clinical: Initially, ~~All~~ subjects manifested spontaneous coughing ~~initially,~~ followed by a dryness of the mouth and a thickness of speech. They noted a feeling of lassitude and weakness of the extremities, which soon followed by increased restlessness and difficulty in maintaining eyelid closure.

Psychiatric phenomena were clearly manifested in some subjects. In the rest period between 15 and 30 minutes after drug administration, six subjects spontan-

eously voiced feelings of unreality, visual and haptic illusions, and delusional thoughts about their illness, the setting of the test procedures or our identity. Such patterns were transient and had disappeared by the termination of the experiment, ~~usually within three hours~~. In three subjects, increasing agitation and panic led to a cessation of the recording. ~~Here, too, restitution of pre-injection behavior was apparent within three hours~~.

Language Patterns

(b) In previous studies, we had noted the intimate relationship between changes in syntactic language patterns with alteration in cerebral function induced by electroshock. In subjects tested prior to electroshock, diethazine induced changes in syntactic pattern of an "alerting" variety. In subjects with EEG delta activity and with clinical syntactic patterns indicative of an alteration in cerebral function, diethazine induced a transient disappearance or minimzation of such language patterns. The period of changes in language was concurrent with changes in electroencephalogram.

(c) EEG Patterns: In all records, there is a decrease in voltage and desynchronization of frequencies. There is a decrease in prominence of prevailing rhythms. In patients without delta activity (pre-electroshock),

this dechronization and voltage decrease is occasionally accompanied by the appearance of small amounts of low voltage ~~6-7~~ 5-7 cps activity. These are demonstrated in Slides 1, and 2. The basic alpha rate does not appear to be altered. The build-up in voltages and appearance of slower frequencies with hyperventilation is blocked.

In patients with varying degrees of ~~induced~~ high voltage ~~delta~~ delta activity ~~resulting from convulsive therapy,~~ there is a decrease in voltage, both random and burst delta activity disappears, and irregular, low voltage alpha and beta frequencies become prominent. These changes are noted in Slides 3 and 4.

~~This~~ A change in ~~records~~ EEG patterns is manifest in all electroshock subjects. It appears during drug administration, and persists for ~~one~~ one-half to three hours. The behavioral and language changes occur concurrently with electroencephalographic ~~changes, are the behavioral and language patterns just described.~~ effects. Also, there with the ~~reconstitution~~ RESTITUTION of the pre-injection EEG patterns, the pre-injection behavioral and language patterns again appeared.

DISCUSSION:

These observations confirm the report of Jenkner and Lechner of the effects of diethazine in "normal" subjects. We have also noted that diethazine alters ~~records and with~~ electroshock induced delta activity in a fashion similar to atropine and scopolamine, as described by Ulett, without the attendant unpleasant side-effects. ~~Furthermore, these changes in electrical records in these patterns are similar to the effect of these anti-cholinergic compounds in records following head trauma.~~ Effects are immediate, both in the EEG and in behavior. ~~In these subjects, intravenous diethazine caused immediate changes both in the EEG and in behavior.~~ It is apparent, therefore, that diethazine readily affects the central nervous system, and the duration of its activity is most useful for experimental purposes.

The ~~previously cited~~ studies by numerous observers of nervous system effects of head trauma point to an intimate relationship between the degree of neurologic dysfunction, the degree of EEG alterations, and the level of free acetylcholine in the spinal fluid. The effect of atropine both on the EEG and ~~its~~ concomitantly on behavior in subjects with head trauma lends further support to the significance of ~~free~~ acetylcholine as the biochemical basis for the observed EEG patterns. In these studies of diethazine and electroshock, the intimate relationship between EEG patterns and behavior

have been reported. We note the parallel to the observations in head trauma. On the basis of these observations, as well as studies of spinal fluid cholinesterase levels (Tower and McEachern, Fink and Goldenberg), we would suggest that the biochemical substrate of the electroshock process is similar to that of head trauma. In this context, electroshock may be looked upon as a controlled method of inducing cerebral dysfunction for its behavioral effects.

Previous studies have demonstrated that alteration in cerebral function provides the physiologic basis for the behavioral changes in electroshock (Fink and Kahn, 1957). Such alteration in cerebral function provides the milieu for a change in the organism's adaptation to his environment. All aspects of behavior, as perception, language, mood, recall, memory, affect, etc. undergo change, and provide the basis for the therapist's evaluation of improvement. The studies of diethazine amplify this neurophysiologic adaptive hypothesis of electroshock by suggesting the type of biochemical substrate that underlies both the physiologic and the behavioral changes.

Summary:

Diethazine, a potent anti-cholinergic compound, was experimentally introduced intravenously in psychiatric subjects at various stages of convulsive therapy.

Electroencephalograms manifested a desynchronization of frequencies, and a decrease in voltage, ~~and observation of hyperventilation responses~~ in records without prior delta activity. Records with delta activity showed similar changes with disappearance of delta burst activity.

Concomitant with the electrographic effects, behavioral and language patterns indicative of a reversal of the electroshock effect were observed.

It is concluded that:

(a) Diethazine is a potent anti-cholinergic compound that readily enters the central nervous system upon intravenous administration.

(b) The biochemical basis for EEG changes in electroshock is similar to that of head trauma; and

(c) The biochemical basis of the mode of action of convulsive therapy may lie in the acetylcholine-cholinesterase system.

Research and Development Division

SMITH, KLINE & FRENCH LABORATORIES · PHILADELPHIA I

ESTABLISHED 1841

December 11, 1956

Max Fink, M.D.
Director of Research
Hillside Hospital
75-59 263rd Street
Glen Oaks, New York

Dear Doctor Fink:

My associate, Mr. C. W. French, has referred your letter of November 12 requesting a supply of diethazine to me for reply. It has taken me a little while to uncover sufficient supplies for the short clinical trial you want to conduct since our interest in diethazine alone and in combination with 'Thorazine' isn't too great at this time.

We do not have this compound available in 500 mg. capsules as you requested. It is only available in 250 mg. tablets. A supply of this strength has been sent to you together with a supply of the intravenous material so that you may observe the EEG effects on 10 to 15 patients.

Enclosed is all the literature we have available on diethazine. I hope this will be of some help.

Sincerely yours,

John F. Buckley hc

John F. Buckley
Research Associate
Medical Department

JFB:hc
Enclosures

P.S. Will you kindly sign the enclosed FDA card and return it to us so that we may keep our files up-to-date.