Brit. J. Psychiat. (1967), 113, 1413–1418

Hexafluorodiethyl Ether (Indoklon) Convulsive Therapy: A Pilot Study

By D. R. GANDER, P. J. BENNETT and D. H. W. KELLY

In 1957 Krantz, Truitt, Ling and Speers found that the inhalation of small amounts of hexafluorodiethyl ether (Indoklon) produced convulsions in animals, and it was later used as a therapeutic convulsant for the treatment of psychiatric patients (Krantz, Truitt, Speers and Ling, 1957).

There have been many favourable reports in the American literature (Krantz, Esquibel, Truitt, Ling and Kurland, 1958; Karliner and Padula, 1960; Nussbaum and Kurland, 1962; Kurland, 1963; Karliner, 1965), but so far it has not been investigated in this country. It has been administered by inhalation and intravenously, and Karliner and Padula (1960) considered it to be superior to E.C.T. in the treatment of schizo-affective and paranoid schizophrenia and equally effective in depressive disorders. Rosenberg (1962) found that it was preferred to E.C.T. by most patients and it has been claimed to be safer than E.C.T. (Esquibel, Krantz, Truitt, Ling and Kurland 1958; Krantz and Truitt, 1959).

The present investigation was designed to evaluate Indoklon in terms of (*a*) therapeutic action and safety in comparison with E.C.T., (*b*) technique of administration, (*c*) side-effects, (*d*) convulsant properties.

Method

In order to compare the immediate therapeutic response of Indoklon with E.C.T., and also to compare the side-effects, the two forms of treatment were alternated. Each patient therefore started with one form of treatment and this was followed seven days later by the other form, and the pattern continued until maximum improvement was achieved. Thus each patient received either one or other form of treatment once weekly. The patients consented to have a new form of treatment, but they did not know which of the two they had at any given time.

Patients

The patients selected for this form of treatment were broadly speaking those who would otherwise have been treated with E.C.T. All patients attending the clinic who were physically fit, under 65 years old and had not had E.C.T. in the preceding month were accepted for this study. A total of 16 patients were treated, 15 with depressive illnesses and one with schizophrenia.

Technique of Administration

Anaesthesia was induced with 500 mg. of thiopentone preceded by 1 mg. of atropine intravenously. Muscle relaxation was produced by suxamethonium injected from a separate syringe; usually 40 mg. (female patients), 50 mg. (male patients). This was succeeded by a standard E.C.T. procedure using an Ectron machine, or the patient was inflated intermittently with Indoklon to produce a convulsion. In the latter case, a two litre bag filled with oxygen was connected to an anaesthetic mask via a stopcock. A metal chamber containing a piece of gauze was interposed between the bag

https://doi.org/10.1192/bjp.113.505.1413 Published online by Cambridge University Press

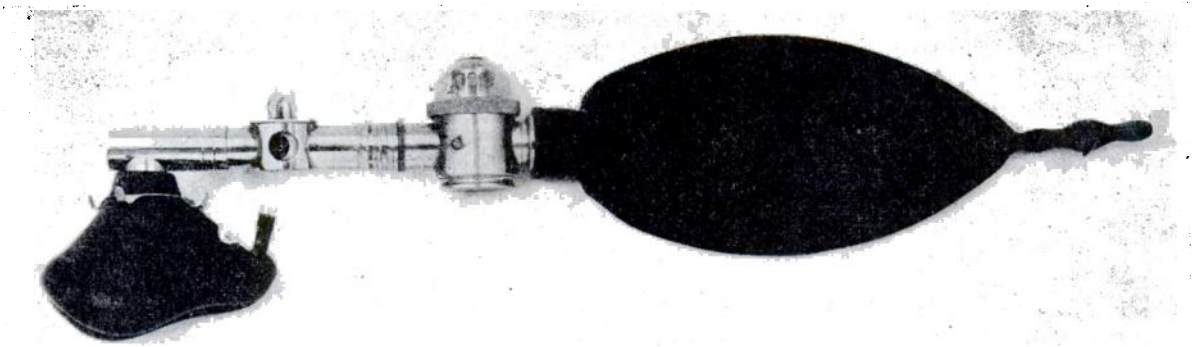


FIG 1.

and the mask and Indoklon introduced into this chamber, using a 2 ml. syringe. See Fig. 1. The dosage of Indoklon for "large dose" series A was 1·5 to 3 ml. The patient was inflated intermittently up to 10 times, but with this method, fits of unpredictable length were produced. In "small dose" series B, a standard dose of 0·5 ml. of Indoklon was used, and the patient inflated intermittently for up to 20 times, when either a fit appeared or the procedure was repeated after more suxamethonium and oxygenation. Ten patients received 32 large doses of Indoklon and nine patients 20 small doses of Indoklon.

Measurements

(*a*) Clinical Assessment

The patients were seen before each treatment, their degree of improvement assessed, and any side-effects from the preceding form of treatment noted. Degree of improvement between one form of treatment and the next was assessed on a 5-point scale. The number of points allocated on each occasion to each patient was compounded from the patient's own opinion of his degree of improvement, the opinion of a friend or relative and that of the assessor. Thus a patient with subjective and objective evidence of complete resolution of symptoms scored 5 points, whereas one with subjective and objective evidence of no improvement scored 0. Side-effects were separately classified as early, if they occurred within four hours of treatment, and late.

(*b*) Type and duration of fit.

(*c*) Blood pressure and heart rate were measured at ½ minute intervals after the injection of thiopentone and measurement was continued after the fit until normal values were again obtained.

(*d*) ECG monitoring was used on 17 occasions.

(*e*) Serum glutamic oxalacetic transaminase (SGOT) estimations were made on each patient before the series started and again after treatment by Indoklon.

(*f*) Side-effects.

RESULTS

Clinical Improvement

The degree of improvement was similar after treatment with E.C.T. or a low dosage (0·5 ml.) of Indoklon. After a total of 44 E.C.T. treatments there was a total of 38 points of improvement on the five-point rating scale, and after 20 low dose Indoklon treatments there were 20 points of improvement (Table I). The patients treated with a high dosage of Indoklon showed less improvement. After 32 treatments there were only 17 points of improvement.

Type and Duration of Fit

With E.C.T., the fit is characterized by a tonic contraction followed by clonic movements. After Indoklon there is a gradual onset of myoclonic movements which precede the tonic phase, and this in turn is followed by clonic contractions. The length of fit was always longer when using large doses of Indoklon than that produced by E.C.T., but this effect was considerably diminished when 0·5 ml. was used

https://doi.org/10.1192/bjp.113.505.1413 Published online by Cambridge University Press

(Table II). On two occasions fits lasted five minutes, using large doses of Indoklon. However, these longer times may be partly due to the difficulty in detecting the end of the Indoklon fits, which often faded into restless movements and shivering. With 0·5 ml., the longest fit lasted 2¾ minutes as compared with 45 seconds for E.C.T. In practice, with small doses, these fits presented no difficulty in management as breathing returned early on.

TABLE I

Clinical improvement and side-effects of 16 patients treated alternately with Indoklon and E.C.T.

		Indoklon High dose	Indoklon Low dose	E.C.T.
No. of treatments		32	20	44
Degree of improvement after treatment		17	20	38
Side-effects:				
Early	Restlessness	6	2	0
	Confusion	6	2	0
	Dysphasia	4	0	0
	Headache	4	1	1
	Dizziness	1	1	1
	Vomiting	2	0	0
	Unreality	3	0	1
	Other	2	0	0
Late	Dysmnesia	5	3	5
	Headache	1	3	2
	Other	0	1	0
		34	13	10

Blood Pressure and Heart Rate

The induction of a fit, however produced, was always attended by a rise of systolic blood pressure, ranging from 10 mm. to 110 mm. with E.C.T., and 20 mm. to 120 mm. with Indoklon. Using the large doses of Indoklon this rise was always higher than that produced by E.C.T., and because of its prolonged effect—up to four minutes—this is a strong feature of the drug. Using 0·5 ml. doses, however, this marked difference disappears. The results of the measurements of blood pressure rise are presented in Table III, each patient acting as his own control.

TABLE II

Length of fit in minutes. Each patient acts as own control, and Indoklon treatment in high and low dosage is compared with E.C.T.

High Dose Patient	Indoklon Max.	Indoklon Mean	E.C.T. Max.	E.C.T. Mean
BO	3·0	2·25	0·75	0·75
BL	2·75	2·0	0·5	0·5
DE	2·5	1·75	0·3	0·25
DY	1·8	1·5	0·6	0·5
FA	3·0	2·3	0·5	0·3
FO	1·8	1·75	0·4	0·3
HO	5·0	5·0	0·5	0·5
LA	5·0	5·0	0·5	0·5
SC	2·4	2·25	0·16	0·16
TH	3·0	1·5	0·3	0·25
Low Dose				
CO	2·8	2·8	0·7	0·7
DA	0·5	0·5	0·5	0·5
DE	0·2	0·2	0·5	0·25
DY	1·5	1·2	0·7	0·5
DR	1·5	1·4	0·125	0·125
HO	1·5	0·8	0·8	0·5
NO	0·2	0·125	0·4	0·4
PA	1·0	0·8	0·5	0·5
ST	1·9	1·9	0·25	0·25

TABLE III

Systolic blood pressure changes in mm. mercury. Each patient acts as own control, and Indoklon treatment in high and low dosage is compared with E.C.T.

High Dose Patient	Indoklon Max.	Indoklon Mean	E.C.T. Max.	E.C.T. Mean
BO	60	55	50	50
BL	100	75	50	40
DE	70	60	80	50
DY	80	50	25	20
FA	110	100	40	40
FO	60	50	30	25
HO	120	120	70	70
LA	65	65	50	40
SC	100	85	100	75
TH	25	25	20	20
Low Dose				
CO	70	50	110	70
DA	75	72·5	50	50
DE	20	20	50	50
DY	70	65	25	22·5
DR	100	70	20	20
HO	80	55	90	70
NO	45	35	20	15
PA	100	65	80	80
ST	40	40	30	30

https://doi.org/10.1192/bjp.113.505.1413 Published online by Cambridge University Press

The heart rate showed no regular pattern in either series and was obviously considerably affected by baroreceptor activity and CO_2 retention. There were no wild fluctuations.

ECG and S.G.O.T. Estimations

Continuous ECG monitoring was performed on 17 occasions. On six of these there were ECG abnormalities. In one patient a poor record only enabled the diagnosis of an irregular pulse two minutes after inhalation of Indoklon to be made. The other five abnormal records all occurred in the same patient; they consisted of frequent ventricular extrasystoles, and appeared following the intravenous thiopentone and suxamethonium, and before Indoklon was given in all but one instance, on that one occasion, after the inhalation of Indoklon. Indoklon was not therefore implicated. On one other occasion bradycardia was noted; this occurred when atropine was accidentally injected extravenously. There were no abnormal changes in S.G.O.T. after treatment with E.C.T. or Indoklon.

Side-Effects

The early side-effects were classified as restlessness, confusion, dysphasia, headache, dizziness, vomiting, unreality and others. The late ones were dysmnesia, headache and others. The side-effects after E.C.T. were less than those after a low dosage of Indoklon (Table I). About one quarter of the patients experienced some side-effects after E.C.T. compared with over half the patients who had low dose Indoklon. Using the small doses, a tendency to prolonged muscular twitching, and occasionally very quick awakening, were noted. These were ascribed to an analeptic property of the drug. Where a high dose of Indoklon had been employed the early side-effects were much more frequent and generally more severe. The late side-effects after high dosage of Indoklon were similar in frequency to those that followed E.C.T. In addition to the specific side-effects shown in Table I, two patients had a sore throat for several days after Indoklon, and in two other patients jerking movements of the limbs occurred intermittently up to thirty minutes after Indoklon administration. Four patients showed marked dysphasia after high dosage Indoklon. This side-effect was not experienced after low dose Indoklon or E.C.T.

Recurrence of Fit

In one patient in the large dose series there was a recurrence of a fit five minutes after the first fit.

Failure

Failure to induce fits was experienced four times in the early part of the series only. In the small dose series there were three occasions when an Indoklon treatment was repeated, and one where E.C.T. had to be repeated. In each case a successful fit was produced at the second attempt.

Serious Side-Effects

Three patients were very restless after Indoklon, one requiring further thiopentone to control him. Another patient had several runs of jerky movements, each lasting about 15 seconds. Four patients were severely disturbed after Indoklon; they were confused, disorientated, unintelligibly dysphasic and resisted violently any attempt at interference. Partial or total amnesia for this period was the rule after these episodes but one of these patients had subsequent distressing symptoms of unreality. Another had severe headache and giddiness for several days. The most alarming reaction was a five-minute fit following 3 c.c. Indoklon, after which the patient was restless, confused, disorientated, dysphasic, salivating and grinding his teeth. He remained like this for three hours and was then admitted to the ward, pyrexial (99·2° F.) with neck stiffness and epigastric tenderness. Lumbar puncture revealed no abnormality, and he settled after 24 hours. None of these reactions was directly related to dose of Indoklon.

Discussion

The main findings of this pilot study are that low dose Indoklon-induced convulsions produce

https://doi.org/10.1192/bjp.113.505.1413 Published online by Cambridge University Press

roughly the same clinical improvement as that obtained on the same patients by E.C.T. Side-effects were experienced in over 50 per cent. of cases following low dose Indoklon, compared with less than 25 per cent. after E.C.T. When a large dose was employed, the immediate side-effects were very much more frequent and more serious than when either small-dose Indoklon or E.C.T. were used. The numbers in this study are too small to compare with those of other investigators in the United States who have reported on its use. Comparison with other workers is also made difficult because of the varieties of technique employed. When the drug is given by inhalation, the effective dose depends not only on the amount of Indoklon in the vaporizer but also on the number of times the patient is reventilated with the mixture of Indoklon and oxygen. Padula and Karliner (1963) used 2 ml., but only ventilated the patient three or four times. In our "small-dose" series, which gave the best results, only 25 per cent. of this dose was used, but the patient was inflated up to 20 times.

The technique used and method of administration are of the greatest importance. With too large a dose, as we found in the "high-dose" series, the frequency and severity of side-effects was considerable. However, with modifications of technique and dosage it was possible to overcome a great many of these disadvantages. As with any other technique, a pilot study is clearly desirable so that imperfections of procedure may be overcome before a true comparison can be made between it and standard methods.

E.C.T. is such a safe, convenient, reliable and cheap method of inducing convulsions for therapeutic purposes that the advantages of any other method would have to be considerable to replace it. Indoklon by inhalation is more cumbersome, but it was possible, using 0·5 ml., to produce convulsions of manageable proportions regularly, and with effects on the E.C.G. and blood pressure which were comparable with those of E.C.T. Very large numbers of patients will have to be treated by both methods before it will be possible to say that the therapeutic advantages of Indoklon outweigh the safety, convenience and less frequent side-effects that follow treatment with E.C.T.

Summary

Hexafluorodiethyl ether (Indoklon) by inhalation was used to produce therapeutic convulsions and treatment alternated with E.C.T. It was found that, using 0·5 ml. of Indoklon, convulsions of manageable proportions could be produced regularly and with effects on the E.C.G., blood pressure and heart rate which were comparable with E.C.T. The clinical improvement was similar, but there was a higher incidence of side-effects after this dose of Indoklon. With a higher dosage of Indoklon, the side-effects were even more frequent and often severe and the clinical improvement was less. It is concluded that Indoklon is a satisfactory method of inducing therapeutic convulsions, but because it is more cumbersome and attended by more frequent side-effects it is unlikely to become a real alternative to E.C.T.

Acknowledgments

We wish to thank Dr. William Sargant for help and encouragement and permission to examine his patients, and Dr. Harry Churchill Davidson for most valuable assistance. We should like to express our gratitude to Ohio Chemical for supplies of Indoklon.

References

Esquibel, A. J., Krantz, J. C., Truitt, E. B., Ling, A. S. C., and Kurland, A. A. (1958). "Hexafluorodiethyl ether (Indoklon): its use as a convulsant in psychiatric treatment." *J. nerv. ment. Dis.*, **126**, 530–534.

Karliner, W. (1965). "Observations on the use of bis (2,2,2, trifluoroethyl) ether." *Int. J. Neuropsychiat.*, **1**, 139–143.

—— and Padula, L. J. (1960). "The use of hexafluorodiethyl ether in psychiatric treatment." *J. Neuropsychiat.*, **2**, 67–70.

Krantz, J. C., Esquibel, A., Truitt, E. B., Ling, A. S. C., and Kurland, A. A. (1958). "Hexafluorodiethyl ether (Indoklon): an inhalant convulsant: its use in psychiatric treatment." *J. Amer. med. Assn.*, **166**, 1555–1562.

—— and Truitt, E. B. (1959). "The pharmacologic and therapeutic properties of hexafluorodiethyl ether (Indoklon)." Honoris Causa Volume for Prof. G. Joachimoglu, Athens.

—— —— Ling, A. S. C., and Speers, L. (1957). "Anaesthesia, LV. The pharmacologic response to hexafluorodiethyl ether." *J. Pharmacol. and Exper. Therap.*, **121**, 362–368.

—— —— Speers, L., and Ling, A. S. C. (1957). "New pharmaco-convulsive agent." *Science*, **126**, 353–354.

https://doi.org/10.1192/bjp.113.505.1413 Published online by Cambridge University Press

KURLAND, A. A. (1963). "Implications of Indoklon for psychiatric research." *J. Neuropsychiat.*, **4**, 173–177.

NUSSBAUM, K., and KURLAND, A. A. (1962). "Intravenous hexafluorodiethyl ether (Indoklon) modified by succinylcholine chloride. Clinical studies in convulsive psychiatric treatment." *Curr. Ther. Res.*, **4**, 44–56.

PADULA, L. J., and KARLINER, W. (1963). "Inhalation Indoklon convulsive therapy." *J. Neuropsychiat.*, **4**, 182–183.

ROSENBERG, I. D. (1962). "Resistant psychosis treated successfully by Indoklon (1, 2, 3)." *Amer. J. Psychiat.*, **118**, 1050–1051.

D. R. Gander, M.B., M.R.C.P., D.P.M., *Consultant Psychiatrist, Queen Elizabeth II Hospital, Welwyn Garden City, Hertfordshire*

P. J. Bennett, B.Sc., F.F.A.R.C.S., *Registrar, Department of Anaesthetics, St. Thomas's Hospital, London, S.E.1*

D. H. W. Kelly, M.D., M.R.C.P., D.P.M., *Chief Assistant, Department of Psychological Medicine, St. Thomas's Hospital, London, S.E.1*

(*Received 15 December, 1966*)

https://doi.org/10.1192/bjp.113.505.1413 Published online by Cambridge University Press