

REGIONAL INSULISATION IN THE TREATMENT OF SCHIZOPHRENIA*

By A. L. Gwee, P. Ngui, T. S. Yeoh and Y. F. Tay

SYNOPSIS

Insulin coma has been used with effect in the treatment of schizophrenia, but hypoglycaemia with coma is serious risk. If it were possible to give insulin selectively to the brain, then a high regional insulin level could be attained without the difficulties of coma. Theoretically, this may be achieved by giving insulin directly into the carotid artery.

Animal studies showed that the technique was feasible and safe, and the systemic effect of insulin is the same for both routes.

A clinical study is made in six cases of selected chronic schizophrenia. The results show improvement. Regional insulin would seem to be a feasible and promising method in the treatment of schizophrenia.

Insulin coma has been advocated for the treatment of schizophrenia, (Sakel, 1930), and enjoyed popularity for a time, until its replacement in the recent decade by electro-convulsive therapy and psychotropic drugs. However, its value has been attested to by many psychiatrists who have had experience with this treatment, and even today some psychiatric practices still resort to insulin coma from time to time.

However, insulin coma is both troublesome and risky, for a case in hypoglycaemic coma requires careful nursing and has a definite mortality. Aspiration, brain damage and irreversible coma have been frequent enough to make insulin coma a grave procedure. Now if insulin treatment is beneficial, the value may be due to one of two reasons: firstly, the benefit arises as a result of systemic hypoglycaemia with the resultant coma; or secondly, the insulin may have exerted a direct beneficial effect on the brain. Both of these views have their adherents (Sakel, 1930). One of us (Gwee) reasons that if the benefit is a direct one on the brain, then the benefit may be dose-dependent to a degree, and if insulin is introduced regionally via the common carotid, then the brain can be exposed to a higher dose without the

patient having to run the risk of a dangerous coma. Since the cephalic circulation is only a quarter or less of the total, then giving 100 units of insulin intravenously would result in the following:—

100 units . . . dilution in bloodpool . . . $\frac{1}{4}$ in cephalic circulation (25 units) . . . $\frac{1}{8}$ ($12\frac{1}{2}$ units) in both carotid territories . . . $\frac{1}{16}$ ($6\frac{1}{4}$ units) in each carotid territory; i.e. each carotid territory inclusive of the cerebrum and the cephalic musculature is exposed to only 6 to 7 units of insulin. This is a small dose of insulin but the total amount of 100 units would be sufficient to cause severe hypoglycaemia including coma in a good proportion of the cases. If however, 20 units of insulin be injected directly into one common carotid, then the brain on that side will in fact be exposed to a higher dose level (three to six times), while the total amount is barely felt systemically. Theoretically, therefore, direct regional insulin can have two advantages:

1. A high dose level can be selectively achieved with ease.
2. The troublesome hypoglycaemia and coma would be avoided.

Studies have shown that insulin has no direct toxicity on the brain tissue (Sakel), although the mode and site of insulin action are still controversial points. Animal experiments were accordingly done by us using rabbits to see if there is any change in the hypoglycaemic action of insulin after its passage through the brain.

METHODS

Adult rabbits weighing between 1.4 to 1.5 kilogram were fasted for 24 hours prior to the experiment, but they were allowed to drink water. In all cases the rabbits were anaesthetised with

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A. L. GWEЕ, M.D., F.R.C.P., Former Head, Medical Unit III, Outram Road General Hospital, Singapore.

P. NGUI, M.B., B.S., M.R.C.Psych., D.P.M., Former Deputy Medical Superintendent, Woodbridge Hospital, Singapore.

T. S. YEOH, M.B., B.S., Ph.D., Associate Professor, Department of Pharmacology, University of Singapore.

Y. F. TAY, M.B., B.S., M.D., Lecturer, Department of Pharmacology, University of Singapore.

a 5% solution of sodium pentobarbitone administered intravenously through the marginal ear vein. Blood was sampled for fasting sugar level immediately prior to administering insulin and thereafter at the 15th, 30th, 60th, 90th, 120th, and 180th minutes. Blood sampling was done by a cut in the opposite marginal ear vein and 0.05 ml. sampled using a calibrated microcapillary tube (Microcaps). The common carotid artery was exposed for injection of insulin (40 units per ml.) or saline. A 100 UI Hamilton syringe fitted with a 26 G needle suitably bent was used for the injection. A clamp was placed proximal and distal to the site chosen for injection. After the needle had been introduced into the lumen of the artery, the distal clamp was temporarily released and the injection made. The proximal clamp was then similarly released to allow flow of blood rostrally for 10 seconds after which both clamps were reapplied. Both clamps usually could be removed after 3 minutes.

The dose of insulin used was 2 units per kilogram either given intravenously via the ear vein or the common carotid artery. In the animals which received insulin intravenously, a similar volume of saline was injected into the carotid artery and vice-versa.

Blood sugar was estimated using the glucose oxidase method, (Sigma Tentative Technical Bulletin, No. 510, January 1967).

The results show that the hypoglycaemic effect of I.V. insulin and intra-carotid insulin is practically identical, suggesting that the additional passage through one carotid territory which includes half of the cerebrum and the cranial musculature does not cause any detectable changes as judged by the hypoglycaemic effect of insulin (Figs. 1, 2 and 3).

A trial of regional insulin was arranged in chronic schizophrenia. The method is as follows:—

Six schizophrenic patients from the chronic ward of the mental hospital were selected for the trial. Consent from the next of kin was obtained before inclusion in the trial. All six were male patients between the ages of 20 to 40 years.

The average duration of their illnesses was 10.3 years, the shortest was 5 years, and the longest was 18 years.

The six patients had received varying numbers of electro-convulsive therapy with a minimum of 6 treatments to a maximum of 44 treatments over the years. One patient (P6) had insulin coma treatment over 17 years ago.

5 patients were on maintenance dose of one of the major tranquillisers (trifluoperazine or

chlorpromazine) which were continued throughout the trial period. One patient was not on drugs.

The operation was carried out in the minor theatre and consisted of an injection of 20 units of soluble insulin into the common carotid artery (except for the first injection when only 10 units were given in the first case for the first instance).

Blood sugar was taken before the intra-carotid injection of insulin and at 30 minutes and at 1 hour after the injection. A lumbar puncture was done at 1 hour after the intra-carotid injection and a sample of the C.S.F. was taken. This was examined with particular attention to the glucose content.

Pulse and blood pressure readings were taken before and after as well as a complete neurological examination being made.

Each patient had 3 injections (unsuccessful attempts excluded):

1. Injection of 20 units of soluble insulin into the right common carotid artery.
2. Injection of 20 units of soluble insulin into the left common carotid artery.
3. A control where the procedure was repeated with an injection of saline into the subcutaneous tissues around the region of the common carotid.

ASSESSMENT

The patients were assessed by the psychiatrist before the trial, a global assessment was made as well as an assessment with the use of a rating scale. A psychiatric rating scale for chronic schizophrenia modified by Hamilton and adapted from a multidimensional scale for rating psychiatric patients (Lorr Scale) was used, (Appendix I). This scale measured 18 items of various delusional expressions; hostility; disturbance of speech, thought, posture and mannerisms; disturbed affect, including apathy and objective evidence of hallucinations. This was a single blind assessment as only the patient was kept ignorant of the treatment.

The patients were also assessed on behaviour in the ward by a psychiatric nurse assigned to each patient. The nurse rating scale consisted of 8 items of behaviour on a 5-point rating scale (Hamilton), (Appendix II). This was double-blind as the nurse was also kept in the dark regarding the treatment received.

The items on behaviour included attitude to work, attention to dress and person, relation to other patients, relation to medical and nursing staff, behaviour at meals, toilet behaviour, activity and speech.

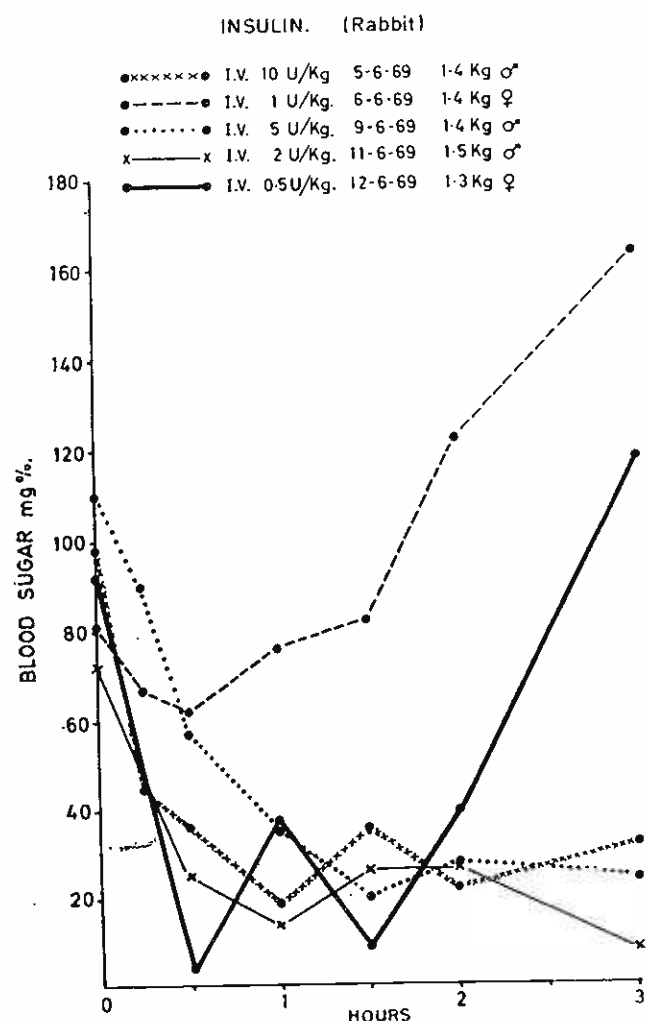


Fig. 1. Showing hypoglycaemic responses in the blood to different doses of insulin intravenously, the rabbits in comatose convulsion in all cases.

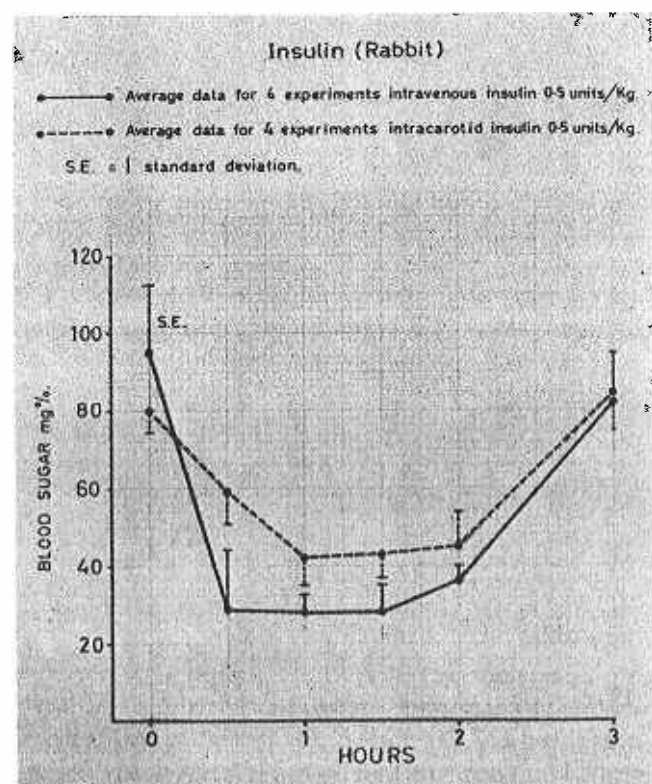


Fig. 2. Showing hypoglycaemic responses in the blood to intra-carotid and intravenous insulin with dosage of 0.5 units/kilo, with no convulsion in rabbits.

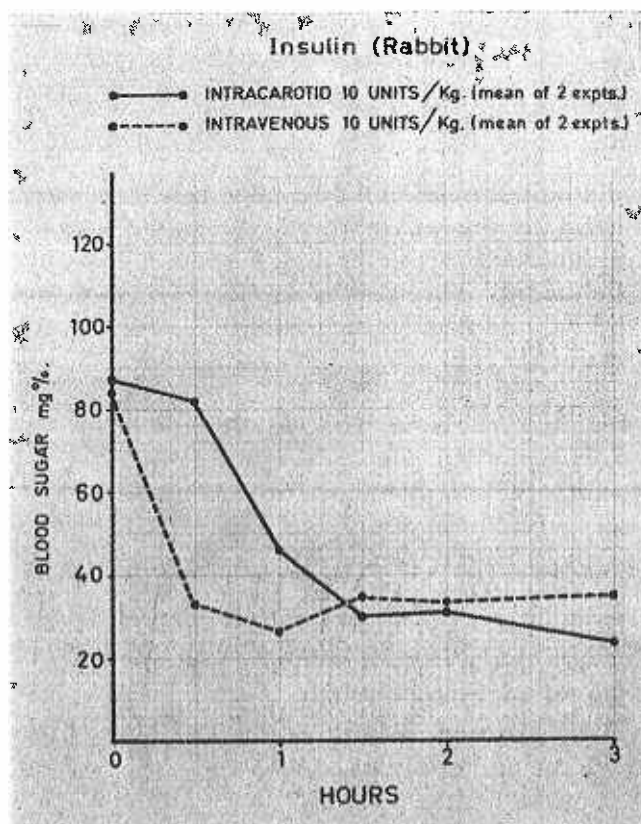


Fig. 3. Showing hypoglycaemic responses in the blood to intra-carotid and intravenous insulin with dosage of 10 units/kilo, with all rabbits in the intravenous cases, but only half of the intra-carotid cases in convulsions.

Age	Duration of illness	16-2	20-2	28-2	33-3	5-5	7-5	7-5	22-5	19-8	20-8	21-8	28-8	Final Status
P1	26	9yrs	P 12	N 16	0	0	0	0	0	0	0	0	0	0
P2	24	5yrs	P 20	N 8	0	0	0	0	0	0	0	0	0	0
P4	25	6yrs	P 10	N 11	0	0	0	0	0	0	0	0	0	0
P6	37	18yrs	P 4	N 12	0	0	0	0	0	0	0	0	0	0
P7	27	12yrs	P 2	N 12	0	0	0	0	0	0	0	0	0	0
P8	28	12yrs	P 26	N 17	0	0	0	0	0	0	0	0	0	0

P = Psychiatric Rating
 N = Nursing Staff Rating
 R = R Carotid
 L = Left Carotid
 U = Unsuccessful Injection
 C = Control Injection
 W = Worse
 B = Better
 S = Same

Fig. 4. Showing the responses of chronic schizophrenic cases to therapy.

B and darkened squares indicated improvement.

W and white squares indicated worsening.

S and dotted squares indicated unchanged status.

The ratings were made before the injections were given, the following day, 1 week after and on later occasions as specified in the chart. The difference between the first ratings made and the subsequent ratings would indicate the progress of the patient. Improvement was represented as a decrease in the score, and indicated by 'B'. Unchanged condition would have the same score and indicated by 'S', and worsening with an increasing score and indicated by 'W'.

RESULTS

From the analysis of the psychiatric and nurse rating scores, although the raw scores at the end of the trial showed improvement in 9 instances, worsening in 2, and no change in one out of a total of 12 scores, the differences were small, and in a disease like schizophrenia with its protean manifestations and changes, they were not put forward as being strongly significant. In general therefore, the evidence was as yet regarded as still inadequate to prove that intra-carotid injection of insulin had caused a significant change in the symptoms or behaviour of the patients. This was to be expected in view of the recalcitrant cases of schizophrenia in the sample, many of them had been ill for years and regarded as hopeless, after running through a gamut of all known treatment in an equipped psychiatric hospital. Nevertheless, the general improvement in the score in hitherto incurable cases is of interest.

Side effects observed after the intra-carotid injection were transient. These were mild hypoglycaemic reactions, and were detected in 3 patients. No untoward effect of significance was noted. One patient was obviously drowsy half an hour after the injection and had excessive sweating. He had also fluttering movement of the upper eyelids and appeared negativistic, resisting efforts to open his eyes. He was given oral glucose. Two other patients had excessive blinking of the eyes, one of whom had associated with it some sweating, but no interference was necessary. The conclusion therefore must be that intra-carotid insulin in that dose is safe.

One patient showed a dramatic improvement soon after the injection which was however,

transient. This was a 26 year old hebephrenic (P1) with gross thought-disorder and marked retardation. He was initially almost mute and would remain in fixed posture with bowed head staring at the floor and replying only occasionally. He had marked echolalia. After the first injection of 10 units of insulin into the right carotid, there was no appreciable change. On the second injection of 20 units into the left carotid, he appeared more alert and conscious of his surroundings immediately after. He became more spontaneous in conversation, smiled appropriately and even asked for a cigarette. Six hours later, however, when reviewed, he had relapsed into his former almost inaccessible state.

There were two instances of gross variation in assessment between the psychiatrist's score and that of the nurse. This was because of the interesting situation that as the patient got more responsive, he revealed more disturbed thoughts, and hence came down in the psychiatric rating, but his increased accessibility created good nursing impressions resulting in a better score (Fig. 4).

CONCLUSION

Regional insulinisation via the carotid is feasible and safe. A trial in 6 cases of chronic incurable schizophrenia showed a dramatic response in 1 case transiently, and the general assessment score showed improvement although this was not regarded as conclusive. It is a new approach of treatment worthy of a further trial.

ADDENDUM

While the study is in progress, two cases of acute schizophrenia were encountered, and were given intra-carotid insulin with good results.

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APPENDIX I

Physician's Rating Scale for Chronic Schizophrenia

Adapted from the M.S.R.P.P. (Lorr Scale)

- P. 1. How direct and relevant are his responses to questions or to the topic discussed?
0 Direct and relevant.

- 1 Somewhat rambling and tangential.
2 For the most part irrelevant.
3 Wholly irrelevant.

- P. 2. Does he assume or maintain peculiar, unnatural or bizarre postures?
 0 None.
 1 For short periods.
 2 Throughout most of the interview.
 3 Throughout the entire interview.
- P. 3. Are his thoughts consistent with his mood, or is there a discernible lack of harmony between them?
 0 Consistent.
 1 A little disharmonious.
 2 Distinctly disharmonious.
 3 Appear totally unrelated.
- P. 4. Does he exhibit any repeated peculiar gestures, grimaces or mannerisms?
 0 None.
 1 Occasionally.
 2 Fairly frequently.
 3 Throughout the interview.
- N. 5. Does he tend to suspect or to believe on slight evidence or without good reason that people and external forces are trying to or now do influence his behaviour and control his thinking?
 0 No unjustified suspicion.
 1 Inclined to suspect.
 2 Believes others are trying to control him.
 3 Believes he is influenced or controlled.
- P. 6. Are the elements of his speech logically consistent and connected by some idea or relationship, or do they tend to be inconsistent and disconnected? (Rate what is most representative during the interview).
 0 Coherent and consistent.
 1 Slightly incoherent and inconsistent.
 2 Distinctly incoherent and inconsistent.
 3 Conspicuously scattered, disconnected or incoherent.
- N. 7. Does he bear little hostility or a high degree of ill will, resentment, bitterness or hate?
 0 No hostility.
 1 Slight hostility.
 2 Moderate hostility.
 3 Much hostility.
- P. 8. Does he have any insight into his hallucinations? (Score 0 for no evidence of hallucinations).
 0 Full insight.
 1 Possibly full insight.
 2 Some insight.
 3 No insight.
- P. 9. How frequently does he speak, mutter or mumble to himself, seemingly to carry on conversations with hallucinatory voices?
 0 Not at all.
 1 Occasionally.
 2 Fairly frequently.
 3 Throughout the interview.
- P. 10. Is there any evidence that the patient has auditory hallucinations?
 0 None.
 1 Doubtful.
 2 Probable.
 3 Certain.
- P. 11. Does the patient ever glance up as if listening to auditory hallucinations?
 0 Not at all.
 1 Doubtfully or occasionally.
 2 Fairly frequently.
 3 Throughout the interview.
- P. 12. Does he repeat certain words or phrases in a meaningless, stereotyped or mechanical fashion?
 0 Never.
 1 Occasionally.
 2 Fairly frequently.
 3 Almost constantly.
- P. 13. Is his speech irregularly interrupted, halted or blocked for varying periods of time because of difficulty in finding words for his thoughts?
 0 No speech blocks.
 1 A few interruptions.
 2 Many interruptions and conversation very difficult.
 3 Patient is mute or almost mute.
- N. 14. Does he have an exaggeratedly high opinion of himself, or an unjustified belief or conviction of having unusual ability, knowledge, power, wealth, or status?
 0 No exaggerated high opinion of himself.
 1 An exaggeratedly high opinion.
 2 Conviction of unusual power, wealth, etc.
 3 Conviction of grandiose or fantastic power, wealth, etc.

- N. 15. Does he tend to suspect or to believe on slight evidence or without good reason that some people are against him (persecuting, conspiring, cheating, depriving, punishing) in various ways?
- 0 No unjustified suspicions.
1 Inclined to suspect.
2 Inclined to believe.
3 Has firm conviction.
- N. 16. Does he tend to suspect or to believe on slight evidence or without good reason, that some people talk about, refer to, or watch him?
- 0 No unjustified suspicions.
1 Inclined to suspect.
2 Inclined to believe.
3 Has firm conviction.
- N. 17. Is there evidence of false ideas or beliefs? If present, are these ideas or beliefs (a) sufficiently plausible as to be accepted by a normal person uninformed as to the facts, (b) implausible but not impossible, (c) impossible or bizarre (e.g. mind controlled by radio waves, heart removed or dead)?
- 0 No evidence of false beliefs.
1 Plausible to the uninformed.
2 Implausible.
3 Impossible or bizarre.
- P. 18. Does the patient's mood and emotional response show blunting?
- 0 Not at all.
1 Slight blunting.
2 Severe blunting.
3 Complete apathy.

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APPENDIX II

Nurse's Rating Scale for Behaviour in Ward

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|---|---|
| <p>1. ATTITUDE TO WORK</p> <p>Normal attitude, co-operative - - - 0
Can do simple jobs only - - - 1
Requires some supervision - - - 2
Needs constant supervision and urging - 3
Refuses work, passively or actively - - 4</p> <p>2. ATTENTION TO DRESS AND PERSON</p> <p>Attends to clothes and appearance normally 0
Dresses himself, but looks untidy - - 1
Dresses himself, but needs adjustments - 2
Requires help to get dressed and cleaned - 3
Has to be dressed and washed - - - 4</p> <p>3. RELATION TO OTHER PATIENTS</p> <p>Helpful and friendly, co-operative in activities - - - - - 0
Occasionally talks or helps others - - 1
Will talk when spoken to - - - - 2
Will only say a word or so - - - - 3
Ignores other patients and may strike them 4</p> <p>4. RELATION TO MEDICAL AND NURSING STAFF</p> <p>As with 'other patients' - - - - 0
1
2
3
4</p> | <p>5. BEHAVIOUR AT MEALS</p> <p>Normal manners and behaviour - - - 0
Peculiar habits and unco-operative with others - - - - - 1
Stealing and snatching food - - - 2
Wolfing and gobbling food, seldom using cutlery - - - - - 3
Requires supervision or encouragement to eat - - - - - 4</p> <p>6. TOILET BEHAVIOUR</p> <p>Goes normally to lavatory - - - - 0
Requires to be taken or fetched out - - 1
Occasionally incontinent - - - - 2
Frequently incontinent - - - - 3
Smearing sometimes - - - - 4</p> <p>7. ACTIVITY</p> <p>Normal activity and mobility - - - 0
Lethargic Overactive - - - 1
<i>Tends to sit about</i> Restless - - - 2
Has to be moved Never still - - 3
Resistive and Rigid Rushing about - 4</p> <p>8. SPEECH</p> <p>Normal speech and conversation - - 0
Taciturn, inconsequential, no real conversation - - - - - 1
Says only a few words, or speech disorganised - - - - - 2
Occasional mumbles - - - - 3
Mute or incomprehensive speech - - 4</p> |
|---|---|