A summary of clinical results of the phosphodiesterase inhibitor ICI 63,197 in a variety of disease states

AUTHOR(S): Bayliss P F C

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Submitted by: P.F.C. Bayliss

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A SUMMARY OF CLINICAL RESULTS OF THE PHOSPHODIESTERASE INHIBITOR ICI 63,197 IN A VARIETY OF DISEASE STATES

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INTRODUCTION

ICI 63,197 was initially selected to go to clinical trial upon the basis of its anti-bronchoconstrictor effect in animals. Further work revealed that it had a variety of effects in animals suggestive of a possible central nervous system action. Clinical trials were begun in a variety of disease states in addition to studies in normal volunteers. At an early stage it became obvious that the agent had a variety of unpleasant side effects (nausea, vomiting, dizziness, flushing) at low doses (1 - 4 mg.) which made clinical trials difficult to conduct. At a later stage the agent appeared to induce angina pectoris in two patients with no previous history of the complaint. Because of this, and the fact that no beneficial effect had been seen in pilot studies, it was decided that no further work should be done with the agent and that existing trials with the agent should be wound up.

This report summarises the results seen in various areas of medicine. The appendix contains a brief description of each trial carried out, together with what results we possess. It will be appreciated that because of the severe side effects, lack of beneficial effect and difficulty in predicting a target disease state in which ICI 63,197 might be effective it was only possible to study small numbers of patients, most trials being stopped or abandoned rather than reaching completion.

SUMMARY OF RESULTS

1. Respiratory system

No evidence of protection against histamine induced bronchospasm (aerosol or i/v histamine) could be shown. No potentiation of the bronchodilator effects of isoprenaline or salbutamol were shown.
2. **Cardiovascular system**

No consistent effect was seen upon the blood pressure of either normotensive or hypertensive subjects. No consistent effect on pulse rate was seen. No evidence of potentiation of the effects of isoprenaline on heart rate were shown. Angina pectoris seems to have been induced in 2 subjects.

3. **Psychiatric disorders**

No beneficial effect was seen in patients with anxiety, depression or schizophrenia. In depression there was a suggestion that there was a worsening of the depressed mood.

4. **The endocrine system**

ICI 63,197 did not produce any effect in thyroid or adreno-cortical function. In one female subject there was a surge in LH levels. No consistent effect was produced upon a standard intravenous glucose tolerance test. There was a suggestion that ICI 63,197 suppressed the rise in insulin levels following an oral glucose load.

5. **Obesity**

No effect on body weight was shown.

6. **Pharmacokinetics**

The halflife of ICI 63,197 was between 1½ and 3½ hours.

7. **Side effects**

Nausea, vomiting and dizziness were commonly seen with ICI 63,197 at 1 mg. unit doses and above. Angina pectoris appeared on chronic dosing of 2 mg. TDS in 2 patients after 4 and 6 weeks respectively. Capillary fragility with a positive Hess's test was seen in one subject.
APPENDIX

Summaries of all clinical trials
CLINICAL PHARMACOLOGICAL STUDY OF ICI 63,197 IN NORMAL VOLUNTEERS
(PROFESSOR J. CROOKS, DUNDEE)

PROTOCOL

Fit, healthy University students were selected for the study. Informed consent was obtained from each volunteer. Subjects were not on any other medication at the time of the test.

Each subject took on one occasion a dose of ICI 63,197 of between 0.25 and 8 mg., when the following parameters were measured:

a) Blood level of ICI 63,197 at 1, 2, 3, 4, 5, 6, and 8 hours after the dose.

b) Pulse rate and blood pressure at -10 minutes, 0 and 1, 2, 3, 4, 5, 6, and 8 hours and 3 days after the dose.

c) Plasma L.H., P.B.I. and cortisol at -10 minutes and 1 hour after a dose.

d) A blood sample was taken at -10 minutes and 4 hours and 3 days after the dose for Hb, WBC, diff, ESR, alkaline phosphatase, bilirubin, SGOT, 5 NT, urea, sodium, potassium chloride, albumin and globulin.

e) A urine sample was tested at -10 minutes and 4 hours after the dose for protein (album tint) and sugar (clinistix).

f) Two 24 hour urine collections, one immediately before and one immediately after dosing.

A note was made of any adverse effects encountered.
RESULTS

Details of subjects studied

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**Blood levels of ICI 63,197**

These are shown below (µg/ml.):-

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\(\text{ND} = \text{not detected, i.e.} \leq 0.004 \text{ µg/ml.}\)

The half life varies from 1½ - 3½ hours in this series.
Effect on pulse rate and blood pressure

Pulse rate (beats/min.)

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<td>4</td>
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Effect on plasma, L.H., protein bound iodine and cortisol

**L.H. levels (m.IU/ml.)**

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**Protein bound iodine**

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**Cortisol level**

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Effect on 24 hour cyclic Amp levels (μ moles/24 hours)

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Blood tests

Hb, WBC, diff.ESR, alkaline phosphatase, bilirubin, SGOT, 5 NT, urea, sodium, potassium, chloride, albumin and globulin levels at 4 hours and 3 days did not differ significantly from the pre-dose figures.

Urine tests

Neither protein nor sugar were detected in the urine at 4 hours or 3 days.
Possible side effects

These are shown below:

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<th>Dose (mg.)</th>
<th>Possible side effects</th>
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<td>Nil.</td>
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<tr>
<td>2</td>
<td>0.5</td>
<td>Mild nausea and light headedness.</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>Nausea at 1 hour.</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>Severe dizziness at 15 minutes. Felt as if he had taken &quot;pep pills&quot; from 1 - 4 hours.</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>Mild nausea.</td>
</tr>
<tr>
<td>6</td>
<td>2.0</td>
<td>Nil.</td>
</tr>
<tr>
<td>7</td>
<td>2.0</td>
<td>Dizziness and sweating at 30 minutes followed by some nausea.</td>
</tr>
<tr>
<td>8</td>
<td>3.0</td>
<td>Dizziness and nausea marked 1 - 2 hours.</td>
</tr>
<tr>
<td>9</td>
<td>3.0</td>
<td>At 30 minutes dizzy, pale, sweating. Nausea marked.</td>
</tr>
<tr>
<td>10</td>
<td>4.0</td>
<td>Nausea and flushing at 15 minutes. Vomited at 30 minutes. Light headedness for 2 - 3 hours.</td>
</tr>
<tr>
<td>11</td>
<td>4.0</td>
<td>Dizziness, flushing of face, sweating from 1 - 2 hours.</td>
</tr>
<tr>
<td>12</td>
<td>8.0</td>
<td>At 30 minutes sweaty, flushed and light headed. Vomited at 2 hours.</td>
</tr>
</tbody>
</table>

CONCLUSIONS

No clearly defined results emerged from this study, although certain suggestive ones were seen. The following points may be made:

1. The half life of ICI 63,197 in the human, following a single oral dose is between 1½ and 3½ hours.

2. No clear effect was seen on pulse rate, although a slight fall was seen in some subjects. Similarly, no clear effect was seen on blood pressure, although in some subjects a fall was seen in the 2 - 4 hour period.
(3) One female subject (on the lowest dose) showed a surge of L.H. at 1 hour that was back to normal by 2 hours. No effect was seen on P.B.I. No regular effect was seen on cortisol levels although in some subjects there was a fall at 1 hour.

(4) The 24 hour urinary excretion of cyclic AMP rose in subjects after ICI 63,197, although in others it fell.

(5) The agent was poorly tolerated at doses above 1 - 2 mg. Nausea, vomiting, dizziness, sweating and flushing were complained of.
EFFECT OF ICI 63,197 UPON THE ENDOCRINE SYSTEM IN NORMAL SUBJECTS

(DR. D. DAVIES, MANCHESTER)

PROTOCOL

Fit, healthy University students who are on no drugs (including the contraceptive "pill") were chosen for this study. They gave informed consent to participation.

Subjects were studied in the fasting state. Blood samples were taken immediately before and at ½, 1, 1½, 2, 3, 4, 5, and 6 hours after a single oral dose of 2 mg. ICI 63,197. Blood samples were assayed for:

a) Growth hormone
b) Insulin
c) Cortisol
d) Thyroxine iodine
e) Glucose
f) L.H. and F.S.H.
g) Blood level of ICI 63,197 (at 0, 1 and 2 hours)

A note was made of any adverse reactions complained of. A cup of coffee was taken by the volunteers between ½ and 1 hours, a light meal between 1½ and 2 hours and a cup of tea between 4 and 5 hours.
RESULTS

Details of subjects studied

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<th>Day of cycle</th>
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<tr>
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<td>6/28-35</td>
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Blood levels of ICI 63,197 (µg/ml)

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ND = not detected, i.e. 0.004 µg/ml.
### Effect on Human Growth hormone

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ND = not detected i.e. less than 1 m. I.U./ml.
**Effect on F.S.H. (milli.I.U./ml.).**

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ND = not detected i.e. less than 1 m.I.U./ml.

**Possible side effects**

These are shown below:

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<tr>
<th>No.</th>
<th>Possible side effects</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Nausea and flushing 10 mins. after tablet. Cone by 1½ hours but fainted at 2 hours.</td>
</tr>
<tr>
<td>2</td>
<td>Flushing and slight nausea noted at 10 minutes.</td>
</tr>
<tr>
<td>3</td>
<td>Flushing and slight nausea noted at 1½ - 3½ hours.</td>
</tr>
<tr>
<td>4</td>
<td>Nausea present ½ - 3 hours.</td>
</tr>
<tr>
<td>5</td>
<td>Nausea 30 minutes. Vomited at 45 minutes.</td>
</tr>
<tr>
<td>6</td>
<td>Marked nausea 1 - 1½ hours.</td>
</tr>
<tr>
<td>7</td>
<td>Flushed, sweating and restless at 1 hour. Nausea throughout.</td>
</tr>
<tr>
<td>8</td>
<td>Sweating at 1 hour.</td>
</tr>
</tbody>
</table>
CONCLUSIONS

(1) ICI 63,197 did not have any significant effect upon any parameters measured, in the setting of the study.

(2) Every subject experienced some type of adverse reaction, especially nausea and flushing.
EFFECT OF ICI 63,197 UPON ORAL & INTRAVENOUS GLUCOSE TOLERANCE TESTS

DR. D. DAVIES, MANCHESTER.

PROTOCOL

Two fit, healthy young volunteers were chosen. They gave informed consent to taking part in the study. They underwent a glucose tolerance test (GTT) on 4 occasions each. Twice the GTT was an oral one, once with a placebo tablet and once with a single dose of 2 mg. ICI 63,197, and on the other two occasions the GTT was an intravenous one, again both with placebo and 2 mg. ICI 63,197. Tests were carried out at 7 day intervals.

Blood samples were taken 60 mins., 30 mins. and immediately before the glucose load was given and for the intravenous test 2, 5, 10, 20, 30, 40 and 60 minutes after, and for the oral test 30, 60, 90, 120 and 150 minutes after.

Blood samples were assayed for:

(a) Glucose
(b) Insulin
(c) Free fatty acid levels.

Possible side effects were noted.

RESULTS

Two male subjects were studied.
### Oral GTT

#### Effect of Glucose levels

<table>
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<tr>
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<th>60</th>
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#### Effect on Insulin levels

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#### Effect on FFA levels (mg/dl)

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### Intravenous GTT

#### Effect on Glucose levels

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#### Effect on Insulin levels

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#### Effect on FFA levels (mEq/l)

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Possible side effects

No side effects were seen.

CONCLUSIONS

Although only 2 subjects were used, ICI 63,197 seemed to suppress the insulin rise following the glucose load in both subjects in the oral test.
EFFECT OF ICI 63,197 IN HISTAMINE INDUCED BRONCHOSPASM IN ASTHMATIC PATIENTS

(DR. J.W. KERR, GLASGOW)

PROTOCOL

Allergic asthmatic patients with reversible airways obstruction were chosen for the study. Pregnant women and patients under 18 or over 45 years were excluded.

Patients were studied on the occasions when they took either ICI 63,197 2 mg. orally, or an identical placebo tablet, in a double blind randomised fashion. 2 hours later, bronchospasm was induced with an intravenous injection of histamine, and the forced expiratory volume in seconds (FEV₁) and the vital capacity were measured before and at 5, 10, 15, 20 and 25 minutes thereafter.

A note of possible side effects were made.

RESULTS

Details of patients studied

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<th>Diagnosis</th>
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### Effect on FEV₁ (litres)

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### Effect on vital capacity (litres)

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### Possible side effects

Two patients complained of nausea following ingestion of ICI 63,197 and one was sick. No side effects were noted during the placebo periods.

### CONCLUSIONS

No evidence was obtained from these 4 patients to show that ICI 63,197 gave any protection from the falls in FEV₁ and VC induced by intravenous histamine.
PROTOCOL

Asthmatic patients between the ages of 18 and 45, who had reversible airways obstruction, were included in the study. Pregnant women were excluded. The aim of the study was to look for possible potentiation of the effect of salbutamol upon bronchospasm induced by an aerosol of histamine.

Patients were seen on 4 occasions, when one of the following were given:

a) 2 mg. salbutamol
b) 2 mg. ICI 63,197
c) 2 mg. salbutamol + 2 mg. ICI 63,197
d) placebo.

Drugs were given in a double blind manner in random sequence. Two hours after taking the tablet a dose of histamine by aerosol was given. This dose had been previously determined as one that would produce a measurable bronchospasm.

Before and at 1, 5, 15 and 30 minutes after the histamine the forced expiratory volume in 1 second (FEV₁), pulse rate and blood pressure were measured.

RESULTS

Only 2 patients were included in the study as in the second severe side effects occurred.

Details of the patients studied

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### Effect on pulse rate (beats/min.)

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Effect on blood pressure

Patient No. 1

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Patient No. 2

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Possible side effects

Patient No. 1 had no side effects during the study. Patient No. 2 took ICI 63,197 at the first sitting. 20 minutes after ingestion the patient complained of severe nausea, followed by copious vomiting. The patient was markedly agitated and restless and became pale, cold and clammy. These features slowly wore off over the next 2 hours. Because of these symptoms this patient was not given ICI 63,197 on a second occasion and the triallist was unwilling to expose further patients.

CONCLUSIONS

In both patients there was some evidence that the effect of histamine upon FEV₁ was reduced by ICI 63,197. In the one patient taking salbutamol there was clear protection against histamine bronchospasm but when combined with
ICI 63,197 this effect of salbutamol disappeared. The data is insufficient to draw any conclusions.

Severe nausea and vomiting occurred in one patient.
PROTOCOL

Patients with mild/moderate emphysema who were known to respond to inhaled isoprenaline by bronchodilatation were chosen for the study. They were tested on two occasions, upon which they took either a single dose of ICI 63,197 or an identical placebo in random order, double blind. Measurements were done on each occasion as follows:

Time (mins.)

0  ICI 63,197 or placebo tablet given.

60  Pulse rate, nitrogen washout and functional reserve capacity measured.

90  Pulse rate, nitrogen washout and functional reserve capacity measured.

120  As at 90 mins.

RESULTS

12 patients were studied.
### Effect on pulse rate

* = time after isoprenaline inhalation

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### Effect on Nitrogen washout

* = time after isoprenaline inhalation

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Effect on functional reserve capacity

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CONCLUSIONS

No effect of ICI 63,197 was demonstrated over and above placebo upon pulse rate, functional reserve capacity and nitrogen washout after the inhalation of isoprenaline. However, it must be noted that no effect of isoprenaline per se was detected. This is probably due to the fact that the first measurement at 30 minutes after inhalation was too late.
EFFECT OF ICI 63,197 IN ENDOGENOUS DEPRESSION (DR. D. ECCLESTON, EDINBURGH)

PROTOCOL

Patients with classical endogenous depression who were not on any other medication were chosen for the study. Patients under the age of 18 or over 60 were excluded. Patients were given 2 mg. ICI 63,197 TDS for 21 days and were to leave the trial at that time if no beneficial effect had been seen.

Depression was rated (Hargreaves scale) daily, as were possible side effects.

RESULTS

4 patients completed 21 days treatment each. The trial was then abandoned, due to side effects and a worsening of depression in all 4 patients, apparently due to ICI 63,197.

Detailed results are not available, but the triallist reported the following:-

1. All 4 patients became markedly worse over the 21 days of treatment. This worsening was considered more than would be expected from the natural history of their respective illnesses. They were all given ECT on stopping ICI 63,197.

2. In one patient the effect of ECT was considered to be greater than expected from the patient's clinical state.

3. All 4 patients complained of nausea in the first 3 - 5 days of the trial, although this wore off with no intervention.
(4) One patient developed a tendency to bruise with a positive Hess's test. The agent was withdrawn whereupon the capillary fragility disappeared over the next 3 - 4 days.
ICI 63,197 IN SCHIZOPHRENIA (DR. R.V. MAGNUS, BIRMINGHAM)

PROTOCOL

Chronic inpatient schizophrenics were chosen for the study upon the basis that they had sufficient symptomatology to show a significant change. Patients under 18 or over 50 years of age were excluded, as were pregnant women and people with physical illness.

Patients were given 1 placebo tablet TDS for 6 days, followed by 1 mg. ICI 63,197 (1 x 1 mg. tablet) TDS for 7 days, followed by 2 mg. ICI 63,197 (1 x 2 mg. tablet) TDS for 7 days if the agent was tolerated. All tablets were identical.

On entry to the trial, the following were recorded:

(a) age, sex, weight
(b) diagnosis
(c) rating of schizophrenia
(d) blood sample for Hb, WBC, diff. ESR, urea, bilirubin, alkaline phosphatase and SGOT.

On days 6, 13 and 20, the following were recorded:

(a) rating of schizophrenia
(b) clinical assessment
(c) possible side effects
(d) pulse rate and blood pressure
(e) blood sample for the tests mentioned above.
RESULTS

Details of patients studied

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</tr>
<tr>
<td>4</td>
<td>WJ</td>
<td>54</td>
<td>M</td>
<td>150</td>
<td>Chronic schizophrenia</td>
</tr>
<tr>
<td>5</td>
<td>WH</td>
<td>52</td>
<td>M</td>
<td>-</td>
<td>Paranoid schizophrenia</td>
</tr>
<tr>
<td>6</td>
<td>SP</td>
<td>28</td>
<td>F</td>
<td>112</td>
<td>Chronic hebephrenic schizophrenia</td>
</tr>
</tbody>
</table>

Effect on clinical state

No patient showed any significant change in their schizophrenic state.

Their rating scores are shown below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Day 0</th>
<th>Day 6$^1$</th>
<th>Day 13$^2$</th>
<th>Day 20$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>15</td>
<td>13</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>17</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>14</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>21</td>
<td>21</td>
<td>20</td>
<td>25</td>
</tr>
</tbody>
</table>

1 = end of 6 day placebo period
2 = end of 7 days at 1 g. ICI 63,197 TDS
3 = end of 7 days at 2 g. ICI 63,197 TDS
**Possible side effects**

These are shown below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Possible side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>Slight nausea at 2 mg. TDS</td>
</tr>
<tr>
<td>3</td>
<td>Marked nausea at 2 mg. TDS</td>
</tr>
<tr>
<td>4</td>
<td>Nil</td>
</tr>
<tr>
<td>5</td>
<td>Nil</td>
</tr>
<tr>
<td>6</td>
<td>Nil</td>
</tr>
</tbody>
</table>

**Effect on pulse and B.P.**

These are shown below:

**Pulse (beats/min.)**

<table>
<thead>
<tr>
<th>No.</th>
<th>Day 0</th>
<th>Day 6</th>
<th>Day 13</th>
<th>Day 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>72</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>80</td>
<td>72</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>80</td>
<td>72</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>72</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>72</td>
<td>72</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>-</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**B.P. (mmHg)**

<table>
<thead>
<tr>
<th>No.</th>
<th>Day 0</th>
<th>Day 6</th>
<th>Day 13</th>
<th>Day 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120/70</td>
<td>120/70</td>
<td>130/70</td>
<td>140/75</td>
</tr>
<tr>
<td>2</td>
<td>130/75</td>
<td>120/70</td>
<td>120/70</td>
<td>130/80</td>
</tr>
<tr>
<td>3</td>
<td>130/90</td>
<td>120/70</td>
<td>120/70</td>
<td>130/70</td>
</tr>
<tr>
<td>4</td>
<td>130/80</td>
<td>120/70</td>
<td>130/70</td>
<td>130/80</td>
</tr>
<tr>
<td>5</td>
<td>135/70</td>
<td>120/70</td>
<td>140/80</td>
<td>130/70</td>
</tr>
<tr>
<td>6</td>
<td>130/70</td>
<td>-</td>
<td>130/70</td>
<td>130/80</td>
</tr>
</tbody>
</table>
Effect on blood tests

No significant effect was seen upon Hb, WBC, diff. ESR, urea, bilirubin, alkaline phosphatase or SGOT.

CONCLUSIONS

(1) ICI 63,197 had no effect upon the schizophrenic state.

(2) ICI 63,197 had no significant effect upon pulse rate, blood pressure on the blood tests used.

(3) 2 out of 6 patients complained of nausea at 2 mg. ICI 63,197 TDS.
PROTOCOL

Inpatients with established anxiety states were selected for the study. Those under 18 or over 50 years of age were excluded, as were pregnant women and people with overt physical illness.

Patients were given 1 placebo tablet TDS for 5 days, followed by 1 mg, ICI 63,197 (1 x 1 mg. tablet) TDS for 7 days, followed by 2 mg. ICI 63,197 (1 x 2 mg. tablet) TDS for 7 days, if the patient could tolerate it. All tablets were identical.

On entry to the trial the following were recorded:-

(1) age, sex, weight
(2) diagnosis
(3) severity of anxiety
(4) anxiety rating using the Taylor Manifest Anxiety Scale
(5) blood sample for Hb, WBC, diff.ESR, urea, bilirubin, alkaline phosphatase and SGOT.

At the 5th, 12th and 19th days the following were recorded:-

(1) Taylor Manifest Anxiety score
(2) clinical assessment
(3) pulse rate and blood pressure
(4) possible side effects
(5) blood sample for tests above
RESULTS

Details of patients studied

<table>
<thead>
<tr>
<th>No.</th>
<th>Initials</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Diagnosis</th>
<th>Rating of anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>VM</td>
<td>18</td>
<td>M</td>
<td>154</td>
<td>Anxiety state</td>
<td>Severe</td>
</tr>
<tr>
<td>2</td>
<td>AC</td>
<td>32</td>
<td>F</td>
<td>112</td>
<td>Anxiety state</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>MN</td>
<td>24</td>
<td>F</td>
<td>116</td>
<td>Anxiety state</td>
<td>Moderate</td>
</tr>
<tr>
<td>4</td>
<td>RT</td>
<td>44</td>
<td>F</td>
<td>120</td>
<td>Anxiety state with obsession</td>
<td>Severe</td>
</tr>
<tr>
<td>5</td>
<td>KH</td>
<td>22</td>
<td>M</td>
<td>130</td>
<td>Anxiety state</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

Effect on anxiety

Clinically, patients No. 1 and 5 became somewhat worse on ICI 63,197, patients No. 2 and 3 showed no change while patient No. 4 showed an improvement. The Taylor scores are shown below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Day 0</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>31</td>
<td>31</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>22</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>3</td>
<td>29</td>
<td>29</td>
<td>29</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>36</td>
<td>35</td>
<td>29</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>22</td>
<td>36</td>
<td>25</td>
</tr>
</tbody>
</table>

1 = end of placebo period  
2 = end of 1 mg. TBS for 7 days  
3 = end of 2 mg. TBS for 7 days
Possible side effects

These are shown below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Possible side effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Vomited x 1 on 2 mg. TDS. Then settled.</td>
</tr>
<tr>
<td>2</td>
<td>Nil</td>
</tr>
<tr>
<td>3</td>
<td>Nil</td>
</tr>
<tr>
<td>4</td>
<td>Nausea on 2 mg. TDS. Maxolon 10 mg. TDS given with good effect</td>
</tr>
<tr>
<td>5</td>
<td>Nausea on 2 mg. TDS. Maxolon 10 mg. TDS given with good effect</td>
</tr>
</tbody>
</table>

Effect on pulse and blood pressure

Pulse rate and B.P. throughout the study are shown below:

Pulse rate (beats/min.)

<table>
<thead>
<tr>
<th>No.</th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 12</th>
<th>Day 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80</td>
<td>80</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
<td>80</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>80</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>88</td>
<td>-</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td>5</td>
<td>88</td>
<td>72</td>
<td>88</td>
<td>80</td>
</tr>
</tbody>
</table>

B.P. (mmHg)

<table>
<thead>
<tr>
<th>No.</th>
<th>Day 0</th>
<th>Day 5</th>
<th>Day 12</th>
<th>Day 19</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>140/80</td>
<td>130/70</td>
<td>130/70</td>
<td>130/70</td>
</tr>
<tr>
<td>2</td>
<td>130/70</td>
<td>130/70</td>
<td>130/70</td>
<td>130/70</td>
</tr>
<tr>
<td>3</td>
<td>120/70</td>
<td>120/70</td>
<td>110/70</td>
<td>110/70</td>
</tr>
<tr>
<td>4</td>
<td>140/70</td>
<td>130/70</td>
<td>130/70</td>
<td>120/70</td>
</tr>
<tr>
<td>5</td>
<td>130/60</td>
<td>120/70</td>
<td>130/70</td>
<td>130/70</td>
</tr>
</tbody>
</table>
Blood tests

No significant changes were seen in the values of Hb, WBC, diff. ESR, bilirubin, alkaline phosphatase, urea, and SGOT during this study.

CONCLUSIONS

(1) ICI 63,197 did not significantly affect anxiety
(2) ICI 63,197 did not significantly affect pulse rate, blood pressure or the blood tests used.
(3) ICI 63,197 produced nausea or vomiting in 3 out of 5 patients, all at 2 mg. TDS.
ICI 63,197 IN HYPERTENSION (DR. F.J. ZACHARIAS, EBBINGTON)

PROTOCOL

Patients with a sustained diastolic hypertension in the range 100 - 115 mmHg were chosen for the study. They were to be on no other drugs. Patients under 18 or over 60 years of age, and pregnant women were excluded.

Patients took ICI 63,197 2 mg. QDS for 4 weeks in the first instance, and this could be continued as clinically indicated.

On entry to the trial, the following were recorded:

(a) age, sex, weight
(b) diagnosis
(c) blood pressure (standing and lying)
(d) blood sample for Hb, WBC, diff.ESR, bilirubin, alkaline phosphatase, SGOT and urea.

At weekly intervals through the trial the following were recorded:

(a) blood pressure
(b) body weight
(c) possible side effects
(d) the blood tests mentioned above.

RESULTS

Details of patients studied

<table>
<thead>
<tr>
<th>No.</th>
<th>Initials</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Weight (kg)</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CCS</td>
<td>45</td>
<td>M</td>
<td>85.0</td>
<td>Hypertension</td>
</tr>
<tr>
<td>2</td>
<td>RJT</td>
<td>-</td>
<td>M</td>
<td>67.7</td>
<td>Essential hypertension with asthma</td>
</tr>
<tr>
<td>3</td>
<td>SN</td>
<td>64</td>
<td>M</td>
<td>77.3</td>
<td>Essential hypertension</td>
</tr>
</tbody>
</table>
Effect on blood pressure

The standing B.P.s (mmHg) during treatment with ICI 63,197 are shown below. There was no significant difference between standing and lying B.P.

<table>
<thead>
<tr>
<th>Week of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
</tr>
<tr>
<td>-----</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Effect upon body weight

No significant change was seen in body weight during treatment with ICI 63,197.

Possible side effects

These are shown below:

<table>
<thead>
<tr>
<th>No.</th>
<th>Possible side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nil</td>
</tr>
<tr>
<td>2</td>
<td>Severe indigestion, dizziness, flushing. Eventually refused to continue.</td>
</tr>
<tr>
<td>3</td>
<td>Nausea, severe heartburn, flushing. Agent finally stopped due to side effects.</td>
</tr>
</tbody>
</table>

Effect on blood tests

No significant change was seen in Hb, WBC, diff.ESR, bilirubin, alkaline phosphatase, SGOT or urea.
CONCLUSIONS

(1) ICI 63,197 did not significantly affect the B.P. of these hypertensive subjects.

(2) There was no effect on body weight on the blood tests used.

(3) 2 of the 3 had severe gastrointestinal side effects with dizziness and flushing.
EFFECT OF ICI 63,197 IN OBESE SUBJECTS

DR. D. DAVIES, MANCHESTER.

PROTOCOL

Patients in the age range 30 - 55 years with a body weight at least 30% over the ideal for their age, sex, height and build, were selected for the study. The trial was a double blind cross-over study of ICI 63,197 2 mg. TDS against identical placebo tablets given TDS, 6 weeks each. Patients were reviewed at fortnightly intervals when body weight, skin fold thickness, pulse rate and blood pressure were noted. A record of possible side effects was kept. Blood samples were taken at each visit for haemoglobin, white cell count, differential count, ESR, platelet count, bilirubin, alkaline phosphatase, SGOT, SGPT, Albumin, Globulin and urea. Urine was also checked for the possible presence of sugar, protein or blood.

RESULTS

Four patients had entered the study before it was discontinued, due to the appearance of angina pectoris in two patients while on the active preparation.

Details of patients studied

<table>
<thead>
<tr>
<th>No.</th>
<th>Initials</th>
<th>Age (yrs)</th>
<th>Sex</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SMck</td>
<td>19</td>
<td>M</td>
<td>142.4</td>
</tr>
<tr>
<td>2</td>
<td>MT</td>
<td>50</td>
<td>F</td>
<td>166.0</td>
</tr>
<tr>
<td>3</td>
<td>AT</td>
<td>38</td>
<td>F</td>
<td>101.8</td>
</tr>
<tr>
<td>4</td>
<td>BA</td>
<td>33</td>
<td>F</td>
<td>83.0</td>
</tr>
</tbody>
</table>
Effect on body weight

| No. | Baseline | Placebo | | | | Active |
|-----|----------|---------|---|---|---|---|---|
|     |          | Week 2  | Week 4 | Week 6 | Week 2 | Week 4 | Week 6 |
| 1   | 142.4    | 134.0   | 134.8  | 134.2  | 140.6  | 138.0  | 138.0  |
| 2   | 166.0    |         |        |        | 161.0  | 163.7  | 160.6  |
| 3   | 101.8    |         |        |        | 103.8  | 106.2* |        |
| 4   | 83.0     |         |        |        | 82.0   | 82.8   | 83.3*  |

* trial stopped due to appearance of angina

Effect on skin fold thickness (cms.)

| No. | Baseline | Placebo | | | | Active |
|-----|----------|---------|---|---|---|---|---|
|     |          | Week 2  | Week 4 | Week 6 | Week 2 | Week 4 | Week 6 |
| 1   | R3.1 L3.3| R2.7 L3.1| R2.7 L3.0| R2.9 L3.1| R2.8 L3.1|
| 2   | 2.2      | 2.2     | 2.0    | 1.9    | 2.1    | 2.1    |
| 3   | R3.0 L3.1|         |        | R3.2 L3.1*|        |        |
| 4   | R3.0 L2.8|         |        | R3.0 L2.9| R2.7 L2.7| R2.7 L2.7*|

* trial stopped due to appearance of angina
R = right arm
L = left arm

Effect on pulse rate (beats/min.)

| No. | Baseline | Placebo | | | | Active |
|-----|----------|---------|---|---|---|---|---|
|     |          | Week 2  | Week 4 | Week 6 | Week 2 | Week 4 | Week 6 |
| 1   | 84       | 72      |        | 96     | 56    | 72    | 60    |
| 2   | 80       | 88      |        |        | 80    | 72    | 80    |
| 3   | 80       |         |        | 88     | 80*   |        |        |
| 4   | 72       |         |        |        | 64    | 72    | 72*   |

* trial stopped due to appearance of angina
Effect on blood pressure (mmHg)

<table>
<thead>
<tr>
<th>No.</th>
<th>Baseline</th>
<th>Placebo Week 2</th>
<th>Placebo Week 4</th>
<th>Placebo Week 6</th>
<th>Active Week 2</th>
<th>Active Week 4</th>
<th>Active Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>120/80</td>
<td>115/80</td>
<td>130/70</td>
<td></td>
<td>120/80</td>
<td>130/75</td>
<td>115/80</td>
</tr>
<tr>
<td>2</td>
<td>190/100</td>
<td>200/110</td>
<td></td>
<td>120/80</td>
<td>170/100</td>
<td>150/100</td>
<td>190/110</td>
</tr>
<tr>
<td>3</td>
<td>145/85</td>
<td></td>
<td>120/80</td>
<td>110/80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>110/70</td>
<td></td>
<td>110/70</td>
<td>110/70</td>
<td></td>
<td></td>
<td>120/75</td>
</tr>
</tbody>
</table>

Effect on blood tests

No abnormality was detected in Hb, WBC, diff., ESR, platelets, bilirubin, alkaline phosphatase, SGOT, SGPT, albumin, globulin or urine during the study.

Effect on urine tests

No abnormal urine findings were detected during the study.

Possible side effects

Three patients (Nos. 1, 2 and 4) complained of marked dyspepsia, flatulence and nausea while taking the active agent. In two patients (Nos. 3 and 4) classical angina of effort appeared for the first time ever while on the active regime. For this reason, the trial was abandoned.

Neither patient who took the placebo run had any side effects while on that regime.

CONCLUSIONS

As far as a possible anti-obesity effect is concerned this trial is inadequate to draw any conclusions. No effect was seen on pulse rate or blood pressure and blood and urine tests remained normal. Upper gastrointestinal
side effects were marked with the agent. The appearance of angina pectoris in two patients who had never had this symptom and in whom the cardiovascular system was clinically normal was apparently due to the compound. This view is strengthened by the fact that since withdrawal no more attacks have been recorded even on severe exercise. The mechanism whereby this was produced must be speculative but it could be due to the potentiation of endogenous catecholamines by ICI 63,197 on exercise, or perhaps the mobilisation of free fatty acid which could increase myocardial oxygen requirements.