CARDIOVASCULAR EFFECTS OF 2-(O-CHLOROPHENYL)-2-METHYLMAMINOCYCLOHEXANONE (CI-581)* IN RATS

BY

P. CHANG, K. E. CHAN AND A. GANENDRAN

SUMMARY

2-(O-chlorophenyl)-2-methylaminocyclohexanone (CI-581), a derivative of phencyclidine, was shown to depress the cardiovascular system in conscious rats and in rats anaesthetized with pentobarbitone and urethane. In pithed animals, however, there was a substantial rise in blood pressure, suggesting that CI-581 may act on the central cardiovascular regulatory mechanisms. The pressor response to CI-581 in pithed animals was considerably reduced by phenoxybenzamine and phentolamine. In reserpinized animals, the pressor response to CI-581 was abolished but could be restored by infusions with noradrenaline. Thus, CI-581 may act indirectly by releasing catecholamines from peripheral stores. In adrenalectomized rats, the increase in blood pressure elicited by CI-581 was abolished by pre-treatment with reserpine. The data indicate that the peripheral release of catecholamines by CI-581 may be derived from more than one storage site.

CI-581 or 2-(O-chlorophenyl)-2-methylaminocyclohexanone is a derivative of phencyclidine (Sernyl). The anaesthetic properties of CI-581 were investigated in laboratory animals and in man by McCarthy and Chen (1965), Chen, Ensor and Bohner (1966), and Domino, Chodoff and Corssen (1965). These workers found that CI-581 produced a rapid and smooth surgical anaesthesia of short duration. Unlike phencyclidine, CI-581 is said to have no sedative, hypnotic or convulsive properties. However, as with phencyclidine, CI-581 at anaesthetic dose levels affects many other physiological processes including the cardiovascular system. For example, Chen, Glazko and Kaump (1967), reported that an intravenous injection of CI-581 resulted in an initial transient fall in arterial pressure followed by a prolonged pressor response in anaesthetized and unanaesthetized dogs. The heart rate was also substantially increased. In anaesthetized rats, an injection of CI-581 could result either in a fall or rise in blood pressure. In man, CI-581 considerably increased both the systolic and diastolic pressures and the heart rate (Domino, Chodoff and Corssen, 1965) and these effects are likely to preclude its widespread clinical acceptance (Robertson, 1967). The mechanisms underlying the cardiovascular changes brought about by CI-581 are not clear, although it has been suggested that it may act on the central cardiovascular regulatory mechanisms (Chen, Glazko and Kaump, 1967).

It is important therefore, to define the cardiovascular effects in order to anticipate possible clinical conditions in which the use of such an anaesthetic might be precluded or indicated. An investigation on the cardiovascular effects of CI-581 in rats is reported here.

METHODS

Male rats of the Sprague-Dawley strain weighing between 200 and 300 g were used. Conscious rats were prepared under short ether anaesthesia and they were kept in restraining cages after recovery from the anaesthetic. Anaesthetized rats were either given pentobarbitone 30 mg/kg or urethane 1 g/kg intraperitoneally. Pithed rats were prepared by the method of Brown and Gillespie (1957). Bilaterally adrenalectomized rats were either given pentobarbitone 30 mg/kg or urethane 1 g/kg intraperitoneally. Pithed rats were prepared by the method of Brown and Gillespie (1957).
TABLE I

Effects of intravenous injections of CI-581 on the heart rate and blood pressure of rats.

Values are means with SE.

<table>
<thead>
<tr>
<th>Experiments</th>
<th>Heart rate (beats/min)</th>
<th>Blood pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control (2 mg/kg)</td>
<td>Change (%): SE</td>
</tr>
<tr>
<td>Conscious rats</td>
<td>408 ± 40</td>
<td>-55 ± 8</td>
</tr>
<tr>
<td></td>
<td>353 ± 45</td>
<td>-55 ± 8</td>
</tr>
<tr>
<td>Rats treated with</td>
<td>426 ± 58</td>
<td>-74 ± 13</td>
</tr>
<tr>
<td>pentobarbitone</td>
<td>350 ± 62</td>
<td>-74 ± 13</td>
</tr>
<tr>
<td>Rats treated with</td>
<td>386 ± 68</td>
<td>-60 ± 18</td>
</tr>
<tr>
<td>urethane</td>
<td>326 ± 41</td>
<td>-60 ± 18</td>
</tr>
</tbody>
</table>

* Significance of difference (t test) compared with the corresponding control values.

animals were prepared under ether anaesthesia 3 days before the experiments. The adrenalectomized rats were fed on normal laboratory diet and given a solution of 1 per cent NaCl to drink. Rats were treated with reserpine (Serpasil, Ciba) by giving 2.5 mg/kg intraperitoneally on 3 successive days. Experiments were performed on the 4th day. When adrenalectomized rats were given reserpine, this was done on the 4th postoperative day. They were given reserpine 1.0 mg/kg on the 5th day and 0.5 mg/kg on the 6th and 7th days. Experiments on these animals were made on the day following the last dose of reserpine.

Blood pressure was monitored from the common carotid artery via a Statham pressure transducer (P23AC) coupled to a Grass Polygraph (Model 5). The heart rate was determined from e.c.g. records. The drugs in solution were injected via a femoral vein.

The drugs used were 2-(O-chlorophenyl)-2-methylaminocyclohexanone hydrochloride (CI-581, Parke-Davis), phenoxybenzamine hydrochloride (SKF), phentolamine hydrochloride (Ciba) and noradrenaline bitartrate (Sigma). The concentrations referred to in the text are in terms of these salts. Drugs were dissolved or diluted in normal saline solution immediately before use.

RESULTS

Effects of CI-581 on arterial pressure and heart rate.

Throughout the study, a dose of 2 mg/kg of CI-581 was used in the investigation. At this dose level, two patterns of responses were observed.

Vasodepressor response. This was observed in five animals in each of the various groups; they were the conscious rats, rats under urethane anaesthesia and those under pentobarbitone anaesthesia. As shown in table I, an intravenous injection of CI-581 caused the arterial pressure of conscious rats to fall by a mean value of 13.0 mm Hg (SE 3.0) and the heart rate by a mean of 55 beats/min (SE 8). This fall in blood pressure was transient (fig. 1). In the pentobarbitone treated rats, CI-581 injection caused a significant fall in arterial pressure, the mean fall being 30.6 mm Hg (SE 11.5; P<0.05). The heart rate was not significantly decreased, although there was a mean drop of 76 beats/min (SE 13). The results are shown in table I and figure 1b.

The arterial pressure of animals under urethane anaesthesia also fell significantly following an injection of CI-581, as in the case of pentobarbitone treated rats (table I and fig. 1c).
blood pressure decreased by a mean of 17.0 mm Hg (SE 4.6; P<0.05) and the heart rate by a mean of 60 beats/min.

Vasopressor response. This was observed in pithed rats. In these animals (5), CI-581 produced a marked and prolonged rise in arterial pressure (fig. 1d). The mean rise of pressure was 57.7 mm Hg which is an increase of more than 60 per cent over the control (P<0.01, table II).

<table>
<thead>
<tr>
<th>TABLE II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of intravenous injections of CI-581 on the blood pressure of pithed rats (mean and SE).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure (mm Hg)</th>
<th>Control</th>
<th>Treated 2 mg/kg</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>84.4 ± 12.0</td>
<td>142.1 ± 10.5*</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

* Significance of difference (t test) compared with the control values (P<0.01).

The following experiments were carried out to investigate the mechanism(s) of vasopressor activity of CI-581 in pithed animals.

Effect of α-adrenergic receptor blockers on the pressor action of CI-581 in pithed rats.

Pretreatment of pithed animals with phenoxybenzamine (2 mg/kg), given by slow intravenous injection, markedly reduced the pressor activity of CI-581 (P<0.001, table III). This reduction was observed in five experiments and was also obtained with phentolamine 4 mg/kg (fig. 2).

Effect of reserpinization on the pressor action of CI-581 in pithed rats.

The pressor response to CI-581 in five pithed animals was virtually abolished when they were pretreated with reserpine (table IV and fig. 3).

<table>
<thead>
<tr>
<th>TABLE III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effect of α-adrenergic receptor blockers on the pressor action (mm Hg) of CI-581 in pithed rats (mean and SE).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Control</th>
<th>CI-581 (2 mg/kg)</th>
<th>After phenoxybenzamine (2 mg/kg)</th>
<th>CI-581 (2 mg/kg)</th>
<th>After phentolamine (4 mg/kg)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>59.0 ± 3.1</td>
<td>145.0 ± 6.2*</td>
<td>62.5 ± 2.6†</td>
<td>–</td>
<td>70.5 ± 3.5</td>
<td>5</td>
</tr>
<tr>
<td>66.0 ± 2.3</td>
<td>136.3 ± 7.3*</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5</td>
</tr>
</tbody>
</table>

* Significance of difference (t test) compared with the control values (P<0.001).
† Significance of difference (t test) compared with values obtained in the absence of an α-adrenergic receptor blocking drug (P<0.001).
However, after infusion with noradrenaline 10 μg/kg over a period of 5 minutes, and when the arterial pressure had returned to its previous levels, the same intravenous injection of CI-581 again caused a rise in blood pressure. The data obtained suggest that noradrenaline was taken up into storage sites and was released again by CI-581.

**Effect of bilateral adrenalectomy on the pressor action of CI-581 in pithed rats.**

Bilateral adrenalectomy (5) reduced but, did not completely abolish the pressor response to CI-581 (fig. 4a, b). There was a consistent rise of a mean of 11 mm Hg (SE 1.0) in arterial pressure (table V). This increase was, however, not seen in adrenalectomized rats previously treated with reserpine (fig. 4c, d). It thus appears that the release of noradrenaline and/or adrenaline which is responsible for the pressor action of CI-581 in pithed animals can come from several tissue stores including adrenal glands and sympathetic nerve endings.

![Graph](image)

**FIG. 4**

Effect of intravenous injections of CI-581 (CI at 2 mg/kg) on the blood pressure of pithed rats with bilateral adrenalectomy: (a) pithed rat; (b) pithed rat with bilateral adrenalectomy; (c) and (d) pithed rat with bilateral adrenalectomy being previously treated with reserpine. At S a volume of saline equal to that of CI-581 was injected.

**TABLE V**

<table>
<thead>
<tr>
<th>Control (2 mg/kg)</th>
<th>Treated Change</th>
<th>Change (%)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>55.0 ± 2.2</td>
<td>64.4 ± 3.0</td>
<td>+11.4 ± 1.0</td>
<td>+13.6 ± 1.7</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The results indicate that CI-581 depressed the cardiovascular system in conscious rats and in rats under pentobarbitone and urethane anaesthesia. However, CI-581 caused a marked rise in arterial pressure when the animal was pithed, suggesting that the cardiovascular depression produced by CI-581 in conscious and in anaesthetized animals may be centrally mediated. This view is shared by Chen, Glazko and Kaump (1967) who concluded from their studies in thiopentone treated rats that CI-581 depresses central cardiovascular regulatory mechanisms.

However, the reversal of these findings for CI-581 in pithed animals suggests that in addition the drug may possess a sympathomimetic activity. This pressor response to CI-581 was considerably reduced by the α-adrenergic receptor blockers, phenoxybenzamine and phentolamine. Interestingly, the pressor component of CI-581 in pentobarbitone treated dogs was also reduced, though not completely suppressed, by phenoxybenzamine (Chen, Glazko and Kaump, 1967). Furthermore, these workers showed that this pressor activity was blocked in conscious dogs pretreated with chlorpromazine, a drug known to possess strong adrenergic blocking activity.

The peripheral sympathomimetic action of CI-581 is probably due to release of catecholamines from tissue stores, since its action was abolished in pithed animals pretreated with reserpine which is known to deplete tissue catecholamine stores (Bertler, Carlsson and Rosengren, 1956; Eränkö and Hopsu, 1958; Shore, 1966). Furthermore, the pressor response to CI-581 was restored by infusing the animals with noradrenaline.

Bilateral adrenalectomy did not, however, appear to abolish completely the pressor action of CI-581 on the pithed animals. A small rise in blood pressure was consistently present in these animals. Evidently, CI-581 not only affects the release of catecholamines from adrenergic nerve endings but also partially from the adrenal glands. This suggestion is supported by the experimental findings.

**ACKNOWLEDGEMENT**

We are grateful to Drs. H. Breitkreuz and G. Lease of Parke-Davis (Far East) for gifts of CI-581.
REFERENCES


EFFETS CARDIOVASCULAIRES CHEZ LE RAT DU 2-(O-CHLOROPHENYL)-2-METHYLAMINOCYCLOHEXANONE (CI 581)

**SOMMAIRE**

Il a été démontré que le 2-(O-chlorophényl)-2-méthylaminocyclohexanone (CI 581), un dérivé de phencyclidine, inhibe le système cardiovasculaire chez le rat conscient et chez le rat anesthésié au pentobarbitone et urethane. Mais chez l’animal à moelle épinée sectionnée, il y avait une augmentation importante de la pression sanguine, et ceci suggère que CI 581 pourrait agir sur les mécanismes régulateurs cardiovasculaires centraux. Cette réaction d’hypertension par CI 581 chez les animaux à moelle sectionnée était considérablement réduite par phenoxybenzamine et phentolamine. Chez les animaux résépinisés, la réaction d’hypertension par CI 581 était coupée, mais pouvait être restaurée par des infusions de noradrénaline. Il est donc possible que CI 581 agit indirectement en libérant des catécholamines des stocks périphériques. Chez les rats adrénergectomisés, l’augmentation de la pression sanguine causée par CI 581 était éliminée par un prétraitement à la résépine. Les données indiquent que la libération périphérique des catécholamines par CI 581 peut trouver son origine dans plusieurs lieux de stockage.

ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN & IRELAND

The Association of Anaesthetists will be holding their Annual General Meeting in Manchester on October 2, 3 and 4, 1969. Full details will be circulated to members in due course.

Preliminary summaries of papers for the scientific sessions should be sent as soon as possible to:

The Hon. Secretary,

Association of Anaesthetists of Great Britain and Ireland,
at the Royal College of Surgeons, Lincoln’s Inn Fields, London, W.C.2.