CLINICAL TRIAL OF WIN 14,098: A NEW ANALGESIC AGENT

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PETHIDINE was the first potent synthetic analgesic agent. Numerous other compounds have since been prepared, one of the more recent being WIN 14,098 (ethyl 4-phenyl-1-[3-(phenylamino)propyl] piperidine-4-carboxylate ethanesulphonate).

Structurally similar to pethidine (fig. 1), WIN 14,098 was synthesized by Elpern (1954).

In rats and monkeys WIN 14,098 was found to be a more potent analgesic than pethidine, yet causing less respiratory depression.

Clinical trials have been carried out at the Sterling-Winthrop Research Institute and reports of other clinical studies have been published in the American literature by DeKornfeld and Lasagna (1959), Groeber and Ziserman (1959) and Sadove et al. (1960). These reports concern only the oral or intramuscular administration of the drug and confirm its potent analgesic activity.

New synthetic analgesic drugs are made available and tested in the hope that they may possess the following properties: potent analgesic action; minimal sedative effect; minimal effect on respiration; absence of other side effects.

The present investigation was performed in order to make a preliminary evaluation of WIN 14,098 in relation to these properties. The limitations of this study are appreciated, since no comparison between WIN 14,098 and other drugs is reported, and further work is being undertaken to establish its potency in relation to morphia.

METHOD

Three groups of patients were used. The first consisted of 100 patients with postoperative pain severe enough to indicate the use of a potent analgesic. These patients were given a standard dose of WIN 14,098 (20 mg) by intramuscular injection. One hour later they were asked: "How is your pain?" and were offered a choice of the following five assessments: "gone", "much better", "better", "same", "worse". They were then asked: "Did
you notice any other effects of the injection?" Leading questions were not asked. The injections were given by the nursing staff who were invited to comment on the action of the drug.

WIN 14,098 was given only to patients who had fully recovered from anaesthesia and it was not given within 4 hours of any other analgesic or sedative agent. There were 55 males and 45 females in this group and their average age was 49.7 years. The youngest patient was aged 14 years and the oldest 81 years. All had undergone major surgery, the operative procedures being listed in table I.

<table>
<thead>
<tr>
<th>Operative procedure</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracotomy</td>
<td>45*</td>
</tr>
<tr>
<td>Upper abdominal operations</td>
<td>9</td>
</tr>
<tr>
<td>Lower abdominal operations</td>
<td>11</td>
</tr>
<tr>
<td>Herniorrhapy</td>
<td>4</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>8</td>
</tr>
<tr>
<td>Orthopaedic operations</td>
<td>17</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>9</td>
</tr>
<tr>
<td>Total</td>
<td>103†</td>
</tr>
</tbody>
</table>

*Including 28 pulmonary resections.
†Three patients underwent double procedures.

In the second group 20 healthy young adults received an intramuscular injection of WIN 14,098 (20 mg), together with atropine 0.6 mg as premedication 1 hour prior to anaesthesia for minor surgical procedures. The degree of sedation was observed.

A third group of 7 fit women aged between 22 and 45 years and weighing between 92 and 145 lb. (41.4–65.2 kg) received atropine 0.6 mg only, prior to anaesthesia for minor gynaecological surgery. Anaesthesia was induced with a small dose of thiopentone (300–425 mg) and was maintained with nitrous oxide and oxygen (6 l./min and 2 l./min) and halothane 0.9 per cent. When anaesthesia had been stabilized an intravenous injection of WIN 14,098 0.05 mg/lb. (0.45 kg) as a 0.1 per cent solution was given. The effect on respiration was observed. Other apparent effects were also noted.

RESULTS

WIN 14,098 for relief of postoperative pain.

Figure 2 summarizes the results in this group of patients. WIN 14,098 appeared to be a potent and generally reliable analgesic agent.

In reply to the question: "Did you notice any other effect of the injection?" 78 of the 100 patients said they had not.

Sleepiness was reported in 21 cases, nausea in 2, sweating in 2 and dryness of the mouth in 2. (Various other symptoms, each encountered in one case only, were not apparently significant.)

The nursing staff reported 3 cases of oversedation, 2 of sweating and 2 of nausea and vomiting apparently associated with the injection of WIN 14,098. The combination of absence of drowsiness with satisfactory analgesia was remarked in 13 cases.

![Figure 2](image-url)

**Figure 2**

Effect of WIN 14,098 20 mg on postoperative pain in a series of 100 cases.

None of the cases gave rise to concern and there was no instance of local reaction to the injection.

Premedication with WIN 14,098.

Of the 20 patients none appeared at all drowsy. On being asked: "Do you feel sleepy?" 8 said they did not and 12 indicated slight subjective sedation. Induction of anaesthesia appeared smoother than is usual when premedication consists of atropine alone. Induction of anaesthesia with thiopentone produced no more than the usual degree of respiratory depression.

Intravenous WIN 14,098.

Figure 3 shows the respiratory rates of the 7 patients before the intravenous injection of WIN 14,098 and afterwards at the time of maximum
respiratory depression. The mean of these results is indicated. The respiratory rate fell by an average of 77 per cent. Apnoea occurred in 2 cases. Respiratory depression appeared rapidly and in 5 patients was maximal within 3 minutes of the injection.

About 10 minutes after the administration of WIN 14,098, and after maximum respiratory depression had been observed, nalorphine was given with good effect in all cases. A nalorphine:WIN 14,098 ratio of 2:1 (w/w) was found to be appropriate.

No significant effect on pulse rate was observed. In 3 patients the rate increased by up to 9 per cent and in 4 it fell by up to 10 per cent. The mean result was a fall of 4 per cent. Blood pressure changes were minimal. The greatest rise was from 110/75 mm Hg to 130/80 mm Hg and the greatest fall from 100/70 mm Hg to 90/60 mm Hg.

No other general or local effects were observed. Clinically, recovery of consciousness appeared to be delayed and there was an average interval of 19 minutes between the end of anaesthesia and the time at which sensible answers could be given to simple questions. (Note that, as stated, these patients had received nalorphine.)

**DISCUSSION**

The response of those patients given WIN 14,098 for the relief of pain confirms that this agent is a powerful analgesic. Clinical observation indicates that a 20-mg dose of WIN 14,098 is about as potent as pethidine 100 mg. The age and physical condition of these patients varied greatly and they had undergone a variety of surgical procedures. In no case did the response to the standard 20-mg dose of the drug cause concern and this indicates that WIN 14,098 is a safe agent. The hypnotic effect is not marked and other side effects are minimal. In particular nausea and vomiting are not provoked. Considerable respiratory depression followed the intravenous administration of the drug, however, and care is necessary when it is given by this route.

WIN 14,098 appears to be worthy of further clinical trial and a more critical study of the analgesic properties and side effects of the drug, in comparison with morphine and a placebo, is being undertaken.

**SUMMARY**

One hundred patients received WIN 14,098 in 20-mg doses intramuscularly for relief of post-operative pain, 20 patients were given the same dose prior to anaesthesia, and a further 7 received an intravenous injection of 0.05 mg/lb.

WIN 14,098 produced good analgesia. Side effects were minimal in the first two groups of patients, but, in the third, marked respiratory depression occurred.

Further trial of this drug is suggested but care is recommended when it is given intravenously.

**ACKNOWLEDGMENTS**

I should like to thank the surgical consultants concerned for the opportunity to study their patients and the nursing staff of King's College Hospital and The Brook Hospital for their excellent co-operation.

Generous supplies of WIN 14,098 were provided by Messrs. Bayer Products Ltd.

**REFERENCES**


