PHARMACOLOGICAL ACTIONS OF TWO NEW PETHIDINE ANALOGUES

BY

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The behaviour of two new analgesics, benzethidine and fur ethidine, in a number of different tests has been compared with that of pethidine. Some differences in side-effects at equi-analgesic dosage were observed, particularly a reduction in histamine release.

The synthesis of a number of N-substituted derivatives of pethidine has recently been reported by Frearson and Stern (1958) and Frearson, Hardy and Stern (1960). Many of these compounds have been shown by Millar and Stephenson (1956) and by Blair and Stephenson (1960) to have marked analgesic activity. Two potentially useful analgesics of this series have now been compared with pethidine. These compounds are benzethidine (I; ethyl 1-(2-benzyloxyethyl)-4-phenylpiperidine-4-carboxylate) and fur ethidine (II; ethyl 4-phenyl-1-(2-tetrahydrofurfuryloxyethyl)-piperidine-4-carboxylate).

![Chemical Structures](I and II)

**METHODS**

Analgesia.—The elevation of pain thresholds in a group of 10 weanling rats (4 to 6 weeks old) was measured 30 min. after the subcutaneous injection of the analgesic, or 1 hr. after oral administration, by a modification of the method of Green and Young (1951). The pain threshold of each rat was determined before and after administration of the drug; a squeak rather than struggle was taken as the end point. Any animal in which the pain threshold was raised to double or more than that of its initial value was judged to be showing significant analgesia. The ED50 and 95% limits of error were calculated using a standard probit analysis.

Respiration.—The respiratory depressant action on unanaesthetized rats was determined by measuring the frequency of respiration before and 30 min. after the subcutaneous injection of the drugs. The mean respiratory frequency per min. of groups of 10 young rats was determined by counting the respiratory rate of the animals very loosely restrained in a perspex tube.

The effect upon respiratory minute volume and respiratory rate was studied in anaesthetized dogs, cats and rabbits by the method of Paton (1949). The cats and dogs were lightly anaesthetized by intraperitoneal injection of pentobarbitone sodium 35 to 40 mg./kg. Rabbits were anaesthetized with urethane 1.5 g./kg. injected intravenously.

Cardiovascular System.—The direct effect of the drugs on the blood pressure of the anaesthetized rabbit, cat and dog was studied. Heart rate and electrocardiogram were recorded with a direct writing Ediswan electrocardiograph. The effect of the drugs on the normal vascular responses to noradrenaline, adrenaline, histamine, acetylcholine, nicotine and vasopressin was recorded.

Behaviour and Activity.—The effects on normal behaviour and activity of the mouse, rat, cat, dog and monkey were studied. Mice in which hyperkinesia had been induced by ββ-iminodipropionitrile after the method of Thuillier and Burger (1954) were treated with benzethidine, fur ethidine and pethidine and the effect on activity was recorded semi-quantitatively using a jiggle cage.

Antitussive Action.—Cough was induced in cats lightly anaesthetized with pentobarbitone sodium (35 mg./kg.) either by electrical stimulation of the superior laryngeal nerve (Green and Ward, 1955) or by mechanical irritation by means of a polythene tube passed down the trachea as far as the carina. The cough was recorded with a spring-loaded writing lever on a kymograph by means of thread tied to the abdominal wall in the region of the xiphisternum.

Prolongation of Barbiturate-induced Sleep.—Mice were injected subcutaneously with twice the analgesic ED50 20 min. before the intraperitoneal injection of
75 mg./kg. of hexobarbitone sodium. The time from injection of the hexobarbitone to the recovery of the righting reflex was taken as the sleeping time.

Anticonvulsant Action.—Convulsions were induced in mice by the intravenous infusion of leptazol 20 min. after the subcutaneous injection of the ED50 of the analgesic.

Emetic Action.—The drugs were injected in ascending doses into the gluteal muscle of mongrel dogs 0.5 hr. after feeding. The criterion of vomiting was taken as the expulsion of stomach contents.

Mydriatic Effect.—The pupil size of mice before and after subcutaneous and local application of the drug was determined by measuring the pupil diameter with a low power microscope.

Local Anaesthetic Action.—The local anaesthetic action was determined in guinea-pigs, after the intradermal injection of the analgesics, by the method of Bulbring and Wajda (1945), and compared with procaine as a standard. Qualitative assessments in man were also made.

Histamine Release.—The histamine-releasing power was determined in man by injecting the drugs in 0.1 ml. of normal saline intradermally into the skin of the volar surface of the forearm. The area of the weal produced was measured using squared paper (Bain, 1949). Weal area was plotted against log dose.

Gastro-intestinal Effects.—The antagonistic effects of the three drugs against contractions of the guinea-pig ileum induced by acetylcholine, histamine and barium chloride were determined. The preparation described by Trendelenburg (1917) was used to study effects on the peristaltic reflex.

The influence on intestinal motility in mice was studied by comparing the effects of injection of the drugs and a control solution on the weight of faecal pellets passed by 4 groups of 8 mice. A cross-over design was used and each group was given each treatment. The faeces from each mouse were collected over a period of 2 hr. and the means for each group compared statistically.

The effect on gastro-intestinal propulsion of the three drugs under test was also examined using the method described by Green (1959). For this test young rats were used and were kept on a diet of protein hydrolysate for 2 days, being starved for 2 hr. before the commencement of the experiment.

Antidiuretic Action.—This was determined using rats which had been loaded with water by stomach tube at 5% body weight and 1 hr. later with a further 5% body weight of 12% ethanol. The bladder and jugular vein were cannulated and the urine output was measured at 4 min. intervals. All drugs were given by intravenous injection. Antidiuretic potency was calculated by the method of Dicker (1953).

Acute Toxicity.—The LD50 of the three compounds was determined after intravenous injection in mice and oral and subcutaneous injection in rats.

Subacute Toxicity.—This was determined over a period of 12 weeks on 4 groups of 20 male rats. Newly weaned rats were injected daily with furethidine, 1 mg./kg.; benzedrine, 5 mg./kg.; pethidine, 25 mg./kg.; and normal saline, 4 ml./kg. by the intraperitoneal route.

Each animal was weighed daily and any gross toxic symptoms were recorded. Blood samples were taken from randomly selected rats every 2 weeks. The samples were examined and haemoglobin level, red cell count and total white cells determined. Differential white cell counts were performed for each group at the end of the eleventh week of the test.

After 12 weeks, 10 rats from each group were killed and sections of the liver, spleen, lung, kidney, adrenal gland, bone marrow of the femur and skin at the site of injection were examined for pathological changes.

RESULTS

Analgesia.—Both benzedrine and furethidine had a considerably greater analgesic action in rats than pethidine. The activity of the three compounds is compared in Table I. All these compounds showed a similar duration of action by either route. The ratios of analgesic activities by oral and by subcutaneous administration appear to be similar, and values obtained are in satisfactory agreement with those of Blair and Stephenson (1960).

Respiration.—All three compounds produced respiratory depression in unanaesthetized rats, and in the anaesthetized rabbit, cat and dog (Table II).

In unanaesthetized rats a linear relationship between log dose in mg./kg. and the log of the difference in respiratory rates before and after the drug was obtained. The dose-response curves for the three drugs showed no significant deviation from parallelism (P>1.0). Similar relationships between dose and respiratory depression were obtained when the effect on the minute volume of anaesthetized cats was studied. The relative potencies of the drugs as respiratory depressants are shown in Table II.

Nalorphine and levallorphan both reversed the respiratory depression which followed the administration of pethidine, furethidine, and benzedrine.

Cardiovascular System.—All three compounds produced a fall in blood pressure when injected intravenously into the anaesthetized rat, cat and dog. A qualitative difference was observed, however, when the drugs were given in the ratio of their analgesic doses. Pethidine produced an initial short-lasting rapid fall of blood pressure which was followed by a secondary more prolonged fall. With benzedrine and furethidine this secondary fall in blood pressure was much less, or frequently absent. Thus the fall in arterial
TABLE I
COMPARISON OF THE ANALGESIC ACTION OF BENZETHIDINE, FURETHIDINE AND PETHIDINE IN RATS
The limits of error (P=0.95) of the ED50's are shown in parentheses.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Subcutaneous</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ED50 mg./kg.</td>
<td>Duration (min.)</td>
</tr>
<tr>
<td>Benzethidine</td>
<td>0.92 (0.48-1.76)</td>
<td>60</td>
</tr>
<tr>
<td>Furethidine</td>
<td>0.45 (0.27-0.65)</td>
<td>60</td>
</tr>
<tr>
<td>Pethidine</td>
<td>7.2 (3.0-12.5)</td>
<td>60</td>
</tr>
</tbody>
</table>

TABLE II
COMPARISON OF THE EFFECTS OF BENZETHIDINE, FURETHIDINE AND PETHIDINE ON RESPIRATION
The relative potencies were calculated from the reduction in respiratory rate of rats, and from measurements of minute volume in the rabbit, cat and dog.

<table>
<thead>
<tr>
<th>Relative Potencies</th>
<th>Unanesthetized Rats (Subcutaneous)</th>
<th>Anaesthetized Rabbit (Intravenous)</th>
<th>Anaesthetized Cat</th>
<th>Anaesthetized Dog</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pethidine</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Benzethidine</td>
<td>2.8 (1.6-5.6)</td>
<td>5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Furethidine</td>
<td>24.3 (12.8-45.3)</td>
<td>16</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

TABLE III
INCREASE IN HEXOBARBITONE-INDUCED SLEEPING TIME
Subcutaneous injection in mice.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg./kg.)</th>
<th>Increase in Sleeping Time (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzethidine</td>
<td>5</td>
<td>63</td>
</tr>
<tr>
<td>Furethidine</td>
<td>1</td>
<td>130</td>
</tr>
<tr>
<td>Pethidine</td>
<td>20</td>
<td>265</td>
</tr>
</tbody>
</table>

blood pressure caused by pethidine was more rapid and long-lasting than that caused by benzethidine or furethidine.

A slight reduction in heart rate was observed with higher doses of all three drugs, but no changes in the electrocardiogram were observed. The drugs had no effect on the responses of the vascular system to injected adrenaline, noradrenaline, acetylcholine, histamine, nicotine or vasopressin.

**Behaviour and Activity.**—In doses producing analgesia, no sedative or hypnotic effects were seen in the mouse, rat, cat, dog or monkey. Higher doses of furethidine (4 mg./kg.), benzethidine (20 mg./kg.), pethidine (40 mg./kg.), that is, up to 10 times the analgesic doses, produced sedation in all animals except the cat which showed a pattern of excitation similar to that caused by morphine; lower doses produced no excitement.

No reduction in activity in mice made hyperkinetic with ββ-iminodipropionitrile was observed in analgesic doses; higher doses reduced the degree of hyperactivity although the animal still responded normally to nociceptive stimuli.

**Antitussive Action.**—All three compounds prevented artificially induced cough in anaesthetized cats: the minimal doses needed to abolish cough by intravenous injection were benzethidine, 0.5 mg./kg.; furethidine, 0.1 mg./kg.; and pethidine, 2.0 mg./kg.

**Prolongation of Barbiturate-induced Sleep.**—When given in doses producing equal analgesic effects, benzethidine and furethidine produced less prolongation of hexobarbitone-induced sleep than did pethidine (Table III).
Anticonvulsant Effect.—In doses twice the analgesic ED50, none of the three compounds showed any protective effect against leptazol-induced convulsions in mice.

Emetic Action.—Merlevede and Levis (1958) claim to produce vomiting in 50% of dogs with an intramuscular injection of 10 mg./kg. of pethidine hydrochloride. No emesis was observed in dogs with benzethidine 2 mg./kg. injected intramuscularly or 5 mg./kg. orally or with furethidine 0.5 mg./kg. injected intramuscularly or 1 mg./kg. orally, but 10 mg./kg. of pethidine injected intramuscularly produced emesis in one dog out of three.

Pupillary Action.—Benzethidine, furethidine and pethidine produced mydriasis in the mouse, rat and cat, but myosis in the dog. The potency ratios are shown in Table IV.

Local Anaesthetic Action.—Both benzethidine and furethidine possess local anaesthetic properties and are approximately 3 times more potent than pethidine and procaine (Table IV). All 4 compounds had a duration of action of approximately 30 min. in the guinea-pig. When given intradermally in man, furethidine and benzethidine had a local anaesthetic action which lasted about 60 and 45 min. respectively.

Histamine-releasing Action.—Pethidine, like morphine, has been shown by previous workers to be capable of releasing histamine. When benzethidine and furethidine were compared with pethidine in doses producing an equal analgesic effect a striking difference in the histamine-releasing properties was apparent. Furethidine and normal saline produced weals of the same size and the amount of histamine released by benzethidine was very small.

Table IV shows the relative histamine-releasing properties of the three compounds as measured by the weal area produced by approximately equi-analgesic doses. The plot of weal area against log dose gave parallel lines.

Gastro-intestinal Effects.—In common with pethidine, benzethidine and furethidine showed a general, apparently non-specific depressant effect on smooth muscle. All three drugs inhibited the normal spontaneous contractions of isolated rabbit duodenum. They also antagonized the stimulant actions of acetylcholine, histamine and barium chloride on the guinea-pig ileum.

Table V

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mydriasis</th>
<th>Local Anaesthesia</th>
<th>Charcoal Meal Test</th>
<th>Inhibition of Peristaltic Reflex</th>
<th>Antagonism of Barium Chloride</th>
<th>Histamine Liberation</th>
<th>Analgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzethidine</td>
<td>1</td>
<td>3.5</td>
<td>5</td>
<td>6</td>
<td>0.6</td>
<td>0.15</td>
<td>8</td>
</tr>
<tr>
<td>Furethidine</td>
<td>20</td>
<td>3.5</td>
<td>10</td>
<td>14</td>
<td>32</td>
<td>0.02</td>
<td>16</td>
</tr>
</tbody>
</table>

Table VI

The Effect of Benzethidine, Furethidine and Pethidine on the Growth Rate of Rats

Each drug was injected intraperitoneally in a group of 20 male rats and compared with a similar group injected with saline.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg./kg.)</th>
<th>F Ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzethidine</td>
<td>5</td>
<td>1.4</td>
<td>&gt;0.10</td>
</tr>
<tr>
<td>Furethidine</td>
<td>1</td>
<td>1.0</td>
<td>&gt;0.50</td>
</tr>
<tr>
<td>Pethidine</td>
<td>25</td>
<td>1.1</td>
<td>&gt;0.25</td>
</tr>
</tbody>
</table>
Like all potent analgesics benzethidine and furethidine inhibited peristalsis in the isolated guinea-pig ileum preparation. All three drugs given subcutaneously reduced the quantity of faeces passed by normal rats. The potency ratios are given in Table IV.

**Antidiuretic Action.**—In common with all other potent analgesics tested pethidine, benzethidine and furethidine showed antidiuretic properties when injected intravenously in rats.

The antidiuretic responses of different rats of 200 g. body weight showed a wide variation; the total doses of drug to produce a 40% inhibition of urine output were benzethidine 11 μg., furethidine 30 μg., and pethidine 100 μg.

The antidiuresis appears to be due to the release of antidiuretic hormone as no antidiuretic response was observed during a saline diuresis.

**Acute Toxicities.**—Table V shows the acute toxicities for benzethidine, furethidine and pethidine. The toxic effects of benzethidine and furethidine appeared to be a result of depression of the central nervous system; pethidine, on the other hand, produced excitation and clonic convulsions prior to death, symptoms not seen with benzethidine and furethidine.

**Subacute Toxicities.**—None of the drugs tested had any significant influence on the growth rate of male albino rats, when compared with a control group of rats treated with saline (Table VI). The mortality rate in the treated groups was not significantly different (P>0.1) from that of the control group.

No pathological changes attributable to the administration of the drugs were detected in any of the internal organs; slight necrotic areas were apparent at the injection site in 3 rats treated with pethidine and 2 from the group treated with benzethidine; no lesions were seen in the furethidine or the control groups.

Haemoglobin concentration, red cell count and differential white cell count were all within normal limits.

Tanabe and Cafruny (1958) have suggested that the development of tolerance to the analgesic action of morphine is accompanied by adrenal hyperplasia; in the present investigation, however, no significant difference (P>0.1) was found between the adrenal weights of the control and the treated groups.

**Discussion**

For many years it was believed (Braenden, Eddy, and Halbach, 1955) that for high analgesic potency the optimum substituent on the nitrogen atom in the pethidine series was a methyl group; within the last four years, however, many norpethidine derivatives with markedly higher potency than pethidine have been prepared. Little advantage is to be gained by increasing the potency of an accepted drug if this increase is paralleled by an increase in the incidence of undesirable side-effects. Present research is therefore aimed at achieving a reduction in side-effects caused by a drug administered at an adequate analgesic dose.

Millar and Stephenson (1956) and Blair and Stephenson (1960) have produced evidence that the dose-response curves for analgesia of a number of substituted norpethidine derivatives are not parallel with that of pethidine. Pethidine is an inadequate analgesic for severe pain, because increase of the dose above a certain level does not produce a corresponding increase in analgesia, that is, a plateau in the dose-response curve is reached. As the dose-response curves for furethidine and benzethidine appear to be steeper than that of pethidine a greater degree of analgesia may be possible with these drugs than with pethidine.

The increased analgesic potency of benzethidine and furethidine compared with pethidine appears to be accompanied by an increase in respiratory depression. Respiratory depression, however, only occurs in doses which are higher than those producing an adequate level of analgesia. Since benzethidine and furethidine are considerably more potent than pethidine, it may be possible to control severe pain with these drugs without causing excessive respiratory depression.

In equi-analgesic doses benzethidine and furethidine produce less potentiation of barbiturate-induced sleep in mice than does pethidine; this indicates that the latter drug may produce more general central nervous depression than benzethidine and furethidine. Reduced sedation has been found particularly useful in obstetric analgesia when it is desirable that the patient should remain unsedated and fully co-operative.

An interesting finding is that benzethidine and furethidine on intradermal injection release much less histamine from the skin than does pethidine in doses of equal analgesic potency. Gershon and Shaw (1958) have suggested that a number of the undesirable side-effects of morphine are due to its histamine-releasing properties and that many of these effects can be controlled by the administration of an antihistamine; thus it is possible that benzethidine, and furethidine in particular, may
show a decreased liability to produce these troublesome side-effects. In the limited experiments using dogs, no side-effects attributable to histamine release were produced by benzethidine and furethidine in effective analgesic doses.

In anaesthetized cats the fall in blood pressure which follows the intravenous injection of pethidine is greater than that with benzethidine and furethidine; part of this hypotensive response can be blocked by the administration of an antihistamine drug, and this lends further support to the finding that benzethidine and furethidine are less potent histamine liberators than is pethidine.

I should like to express my thanks to Dr. E. S. Stern for much valuable advice and discussion, to Mr. I. Beattie for the pathological investigations, to Mrs. F. Stothers for the antidiuretic estimations, to Miss M. D. Bradley for technical assistance, and to the directors of J. F. Macfarlan & Co. for permission to publish.

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