BENZOCTAMINE—A STUDY OF THE RESPIRATORY EFFECTS OF ORAL DOSES IN HUMAN VOLUNTEERS AND INTERACTIONS WITH MORPHINE IN MICE

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SUMMARY

A double-blind trial has been performed to investigate the respiratory effects of low oral doses of benzoctamine, and to compare them with diazepam and a placebo. The displacement of the carbon dioxide response curves indicated that whilst diazepam caused respiratory depression, benzoctamine had a variable effect. Some volunteers showed depression, but most showed stimulation. Peak respiratory effects were seen 1 hr after oral administration, returning to normal 2–3 hr after administration. It is suggested that oral drugs given for premedication need to be administered at least 2 hr before operation to obtain maximum sedative effects at a time when respiratory effects are returning to normal. In animal experiments it has been shown that the analgesic actions of morphine are diminished by concurrent administration of benzoctamine, and that the depression of respiratory rate caused by morphine is enhanced.

There is a need for a tranquillizer, which can be used before surgery and in the intensive care unit, that will not depress respiration. It is also desirable that it should not potentiate the respiratory depression or diminish the analgesic properties, of drugs used for premedication, pain relief or anaesthesia.

One of the more recent tranquillizers, benzoctamine, a dibenzobicyclo-octadiene, has been reported to cause respiratory stimulation (Geisler and Rost, 1970). The possibility that the drug may have analgesic properties has been investigated both in animals (Jacques and Helfer, 1971) and in man (Rizzi et al., 1971).

To our knowledge, no previous human study has been carried out in which the respiratory effects of low oral doses of minor tranquillizers have been compared using a double-blind technique. Therefore we set out to evaluate benzoctamine in this manner, comparing it with diazepam, a drug already widely accepted in clinical practice.

Interactions between morphine and benzoctamine with regard to analgesia and respiratory depression have been examined in mice.

METHOD

Clinical trial

Eight healthy volunteers, four of each sex, were used in the trial. The age range was from 25 to 40 yr, and weight from 55 to 80 kg. No subject was taking any medications during the period of the trial, and the volunteers were asked to abstain from alcohol on the night before each measurement. At least 1 day was allowed to elapse between successive tests. All tests were carried out in the morning, at least 2 hr after a light breakfast, and no smoking was permitted on the morning of the trial.

Control values of heart rate, arterial pressure, minute volume (V), tidal volume (VT), respiratory rate (f) and carbon dioxide responses were measured after each subject had been sitting quietly for half-an-hour. Systolic and diastolic arterial pressures were measured using a standard mercury column sphygmomanometer. The same arm was used for all readings, and as far as was possible, the same observer made all the measurements.

A bell closed-circuit spirometer (Morgan), with the cylinder filled with air, was used to measure V, VT and f. Gases were sampled at the mouthpiece and measured continuously by an infra-red carbon dioxide analyser (Hartmann & Braun, URAS4). This was recorded by a Rikadenki single-channel pen-recorder, and the end-tidal PCO₂ was calculated.

The carbon dioxide response was measured after the method of Read (1967). The soda-lime cannister was removed from the circuit and the cylinder of the spirometer was filled with 5% carbon dioxide in oxygen. Following a maximal expiration, the subject was connected to the spirometer and, after an initial deep inspiration, was allowed to breathe quietly into
the spirometer. The carbon dioxide concentrations in the circuit increased gradually and a carbon dioxide response was obtained in which each breath could be matched with the appropriate end-tidal carbon dioxide value. Rebreathing took place for not more than 5 min. Minute volume was plotted against end-tidal Pco₂. After the 1st min, which allowed for equilibration, the plot was linear. The slope of each line was calculated by ΔV/ΔPco₂ after the line of best fit had been drawn by eye through the points plotted. The displacement of each line relative to control values was expressed by reading the Pco₂ at 30 litre/min and subtracting this from the control value at 30 litre/min. 30 litre/min was chosen because this value intersected the lines from all subjects without the need for extrapolation.

A tablet of either benzoctamine 10 mg, diazepam 5 mg, or placebo was administered orally using a double-blind protocol. All readings were repeated at hourly intervals, until the carbon dioxide response lines had begun to return towards control values. In practice, this was never longer than 3 hr. Before each reading, subjects were asked for any subjective comments, and they were also followed up for the afternoon of the test.

Because of the variable results obtained with benzoctamine 10 mg, all subjects were asked if they would volunteer for another test. A dose of benzoctamine 20 mg was administered, but this part of the trial was no longer double-blind.

**Interactions with morphine—experimental mice**

Female mice of ASH XP strain, weighing 20-25 g were used in groups of not more than 16 and not less than eight.

Analgesic activity was tested using the hot-plate reaction time test (Beecher, 1957). The plate was maintained at a temperature of 55°C and the mice were placed on the plate in an open-ended glass cylinder. The time, in seconds, from the instant of placing the mouse on the plate, until a jump or distinct shake of a hind leg occurred, was measured. Any mouse nor reacting within 45 sec was removed from the plate to avoid possible tissue damage. Mice were tested at 15-min intervals for 90 min after the injection of drugs.

The respiratory rates of the mice were measured just before each hot-plate reaction time. The snout of each mouse was placed in a 5-ml syringe attached to a Bell and Howell transducer, in turn connected to a Devices single-channel pen-recorder.

The ataxic effect of benzoctamine was measured in mice using the rotating rod (Kinnard and Carr, 1957). Over a period of 3 days, the mice were trained to remain on the rotating rod. Those who consistently failed to remain on the rod for 2 min were discarded. Groups of 8–16 mice were injected with either benzoctamine or solvent and their performance on the rotating rod was monitored at 15-min intervals for the next hour.

Drugs used in this study were morphine hydrochloride, benzoctamine hydrochloride, dissolved in 10% polyethylene glycol 400, and benzoctamine solvent. Morphine was administered by the intraperitoneal route and benzoctamine by the subcutaneous route. All doses refer to the salts.

**Statistical tests**

The following tests were used where applicable: Student's paired or unpaired t test, Mann Whitney "U" test (non-parametric) and ratio of variance.

**RESULTS**

**Volunteer study**

The gross subjective effects are shown in table I. No comments were made until at least 2 hr after administration of the tablets. Most subjects given diazepam 5 mg felt either sleepy or relaxed, whilst those given the placebo made no comments at all. Only a few subjects had any remarks to make about benzoctamine 10 mg, but with the higher dose irritability, detachment and inability to concentrate were common features.

When compared with placebo changes, none of the drugs had any significant effects upon arterial pressure, pulse rate and unstimulated minute volume, tidal volume and respiratory rate.

Table II illustrates the mean slope of the carbon dioxide response lines obtained with each drug. No drug caused changes in slope significantly greater than those obtained in subjects who were given a placebo tablet. It appeared that certain subjects (1 and 8 in particular) tended to vary the slope of their carbon dioxide response line with successive tests, irrespective of the drug taken.

Table III shows the mean displacement of the carbon dioxide response lines from pre-drug control values. When compared with placebo values, all drugs had significant effects upon the displacement of the carbon dioxide response lines, 1 hr after administration. The effects of diazepam were still demonstrable 2 hr after administration. Only diazepam displaced the response line consistently in one
TABLE I. Non-respiratory effects of oral diazepam, benzoctamine and placebo in human volunteers.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Wt. (kg)</th>
<th>Diazepam 5 mg</th>
<th>Benzoctamine 10 mg</th>
<th>Benzoctamine 20 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F 60</td>
<td>Sleepy at 2 hr</td>
<td>Slept all afternoon</td>
<td>Irritable at 3-4 hr</td>
<td>No comments</td>
</tr>
<tr>
<td>2</td>
<td>M 76</td>
<td>Relaxed, yawnig</td>
<td>No comments</td>
<td>Detached at 3-4 hr</td>
<td>No comments</td>
</tr>
<tr>
<td>3</td>
<td>F 51</td>
<td>Relaxed, yawnig</td>
<td>No comments</td>
<td>Irritable at 3-4 hr</td>
<td>Detached: difficulty in concentrating</td>
</tr>
<tr>
<td>4</td>
<td>M 80</td>
<td>No comments</td>
<td>No comments</td>
<td>No comments</td>
<td>No comments</td>
</tr>
<tr>
<td>5</td>
<td>F 57</td>
<td>No comments</td>
<td>No comments</td>
<td>As for 3</td>
<td>No comments</td>
</tr>
<tr>
<td>6</td>
<td>M 57</td>
<td>Relaxed, yawnig</td>
<td>No comments</td>
<td>As for 3</td>
<td>No comments</td>
</tr>
<tr>
<td>7</td>
<td>M 57</td>
<td>Relaxed, yawnig</td>
<td>No comments</td>
<td>No comments</td>
<td>No comments</td>
</tr>
<tr>
<td>8</td>
<td>F 53</td>
<td>Sleepy at 2 hr</td>
<td>Slept all afternoon</td>
<td>Detached 4-6 hr</td>
<td>Difficulty in concentrating</td>
</tr>
</tbody>
</table>

TABLE II. Effects of oral doses of diazepam and benzoctamine upon the slope of the ventilatory response to carbon dioxide in man.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Time</th>
<th>Slope $= \Delta V/\Delta P_{CO_2}$ (mean ± variance)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hr</td>
<td>1 hr</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.66±0.13</td>
<td>0.67±0.07</td>
</tr>
<tr>
<td>Diazepam 5 mg</td>
<td>0.56±0.04</td>
<td>0.55±0.05</td>
</tr>
<tr>
<td>Benzoctamine 10 mg</td>
<td>0.62±0.03</td>
<td>0.63±0.06</td>
</tr>
<tr>
<td>Benzoctamine 20 mg</td>
<td>0.51±0.08</td>
<td>0.50±0.06</td>
</tr>
</tbody>
</table>

Drug and placebo slopes were not significantly different using the variance test.

TABLE III. Effects of oral doses of diazepam and benzoctamine upon the displacement of the ventilatory response to carbon dioxide in man.

<table>
<thead>
<tr>
<th>Displacement (mm Hg measured at $V=30$ litre/min)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mean ± variance)</td>
<td>1 hr</td>
</tr>
<tr>
<td>Placebo</td>
<td>$-0.20±0.43$</td>
</tr>
<tr>
<td>Diazepam 5 mg</td>
<td>$-3.00±7.53^{*}$</td>
</tr>
<tr>
<td>Benzoctamine 10 mg</td>
<td>$+0.55±9.33^{‡}$</td>
</tr>
<tr>
<td>Benzoctamine 20 mg</td>
<td>$-0.13±2.42^{†}$</td>
</tr>
</tbody>
</table>

$^{*}P<0.05$; $^{‡}P<0.01$ = significantly different from placebo values using ratio of variance test; $^{*}P<0.05$ = significant negative displacement using Student $t$ test.

direction. This was a significant negative displacement, indicative of depression.

Some of the individual results are shown in figure 1. For comparison, graph A shows three consecutive carbon dioxide responses in a subject given a placebo. This demonstrates the reproducibility of the method. An extreme example of the effects of diazepam 5 mg is shown in B. At 1 hr, the carbon dioxide response line was displaced by $-8$ mm Hg $P_{CO_2}$, and the displacement was still $-3.6$ mm Hg at 2 hr after administration. In all but one subject, diazepam caused a negative displacement of the carbon dioxide response line.

Graphs C and D show examples of the two types of response obtained with benzoctamine 10 mg. Five subjects had a positive displacement of the carbon dioxide response line (Nos. 1, 2, 4, 5 and 6) similar to that obtained for subject 4 in graph C. Two subjects, however, had a negative displacement (nos. 3 (fig. 1D) and 7). The results obtained with benzoctamine 20 mg were equally variable. Four subjects (nos. 3, 4, 7 and 8) had positive displacements whilst the rest showed no change or slight negative displacements.

Animal studies

Using the hot plate reaction time test (HPRT), benzoctamine alone had no significant analgesic activity in doses up to 10 mg/kg.

In figure 2A the effects of benzoctamine 2.5 mg/kg upon the analgesic action of morphine are shown. Benzoctamine significantly diminished the increase in reaction time produced by morphine 45 and 60 min after injection ($P<0.01$). A similar trend was seen with benzoctamine 1.25 mg/kg, whilst benzoctamine 10 mg/kg increased the reaction time of morphine-treated mice. However, mice treated with this dose of benzoctamine as well as morphine, were grossly ataxic and great difficulty was found in judging the end-point of the test. Benzoctamine solvent had no effects upon morphine analgesia.

The rotating rod test confirmed that doses of benzoctamine greater than 5 mg/kg induced ataxia.
The duration of the stay of these mice upon the rod was significantly less than that of solvent-treated control mice (P < 0.05). The mean times on the rod were 86 sec for control mice, 50 sec for mice treated with benzoctamine 10 mg/kg and 15 sec for mice treated with benzoctamine 20 mg/kg.

The minimum respiratory rates obtained in solvent- and benzoctamine-treated mice are shown in table IV. Benzoctamine 1.25 and 2.5 mg/kg caused significant slowing 15 and 30 min after injection (P < 0.05). Benzoctamine 10 mg/kg caused significant slowing over the whole time course (P < 0.01). Figure 2B shows that benzoctamine 2.5 mg/kg increased the depression of respiratory rate caused by morphine in the mouse. Similar results were found with benzoctamine 1.25 and 10 mg/kg.

**Table IV. Effect of benzoctamine on the respiratory rate of the mouse.** Solvent controls were measured concurrently. Results expressed as means ± SEM.

<table>
<thead>
<tr>
<th>Benzoctamine dose (mg/kg)</th>
<th>Minimum respiratory frequency per min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzoctamine</td>
<td>Controls</td>
</tr>
<tr>
<td>1.25</td>
<td>106 ± 7</td>
</tr>
<tr>
<td>2.50</td>
<td>114 ± 7</td>
</tr>
<tr>
<td>10.00</td>
<td>83 ± 5</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In the small number of subjects used in the volunteer trial, the change in slope of the carbon dioxide response lines appeared to be more an individual characteristic rather than a measure of drug effects.
Displacement of the carbon dioxide response lines appeared to be a better method of assessing our drugs. The respiratory depression caused by diazepam, when administered as an induction agent or during anaesthesia, has been well documented (McClish, 1966; Hunter, 1967). However, experimental studies, in man, on the effects of diazepam upon the ventilatory response to carbon dioxide has produced variable results. Steen and colleagues (1966) and Cohen, Finn and Steen (1969) found no significant displacement of the carbon dioxide response curve when diazepam, in doses up to 0.266 mg/kg, was administered by the intravenous route to human volunteers. However, Catchlove and Kafer (1971), also using the intravenous route, found that diazepam 0.14 mg/kg caused a depression of the ventilatory response to carbon dioxide in most subjects. Geisler and Rost (1970) reported similar findings when diazepam 20 mg was administered i.m. In the present study we have demonstrated significant respiratory depression with diazepam 5 mg, administered orally.

The results obtained from benzoctamine varied from subject to subject, most showing stimulation, but two showing depression. The possibility that an oral dose, larger than that used in the initial trial, would cause more consistent respiratory effects was not substantiated when the responses were repeated using twice that dose of benzoctamine. In fact, fewer subjects exhibited positive displacement. It is possible that, because this part of the trial was not double-blind, the results may have been influenced by subject awareness.

In mice, benzoctamine caused respiratory rate depression, and the depression which occurred in morphine-treated mice was increased by the addition of benzoctamine. Therefore, patients who respond to benzoctamine by respiratory depression may exhibit increased depression when morphine and benzoctamine are used in combination.

The alleged analgesic properties of benzoctamine were not supported by the animal work. Benzoctamine reduced the analgesic actions of morphine.

In our volunteers, the subjective effects of the drugs varied. With diazepam, the subjects who reported sleepiness or slowness did not notice the effects until the 2nd hr, although maximum...
respiratory depression occurred at 1 hr. It would seem reasonable to conclude from these observations, that diazepam, given orally for premedication, should be given at least 2 hr before operation.

Benzoctamine, especially in the higher doses, caused irritability. This supports the recent findings of McCaughey, Pandit and Morrison (1974) that it is a poor anxiolytic. It is probably, therefore, unsuitable as a premedicant or for use in intensive therapy, particularly if the antagonism of morphine's analgesia, seen in mice, also occurs in man.

REFERENCES


LA BENZOCTAMINE: ETUDE DES EFFETS RESPIRATOIRES DES DOSES ORALES SUR DES VOLONTAIRES HUMAINS ET INTERACTIONS AVEC LA MORPHINE CHEZ LES SOURIS

RéSUMÉ

Des essais à double inconnue ont été effectués pour rechercher les effets respiratoires des faibles doses de benzoctamine administrées par voie buccale et les comparer au diazepam administré aux placebos. Le déplacement des courbes de réponse du gaz carbonique a fait ressortir qu'alors que le diazepam provoquait une dépression respiratoire, la benzoctamine avait un effet variable. Certains volontaires ont accusé une dépression, mais la plupart d'entre eux ont montré une stimulation. Les effets respiratoires de pointe ont été constatés une heure après l'administration orale, mais ils sont retournés à la normale 2 à 3 heures après l'administration. On suggère que les drogues orales données à titre de prémédication soient administrées au moins deux heures avant l'opération de manière à obtenir les effets sédatifs maximaux au moment où les effets respiratoires retournent à la normale. Dans des expériences effectuées sur des animaux on a constaté que l'action analgésique de la morphine est diminuée par l'administration simultanée de benzoctamine et que la dépression du taux de respiration provoqué par la morphine est accentuée.

BENZOCTAMINE: EINE UNTERSUCHUNG DER WIRKUNGEN ORAL VERABREICHTER DOSEN AUF DIE ATMUNGSSVORGÄNGE BEI MENSCHLICHEN FREIWILLIGEN, UND DIE WECHSELWirkUNG MIT MORPHIUM BEI MÄUSEN

ZUSAMMENFASSUNG


BENZOCTAMINA: UN ESTUDIO DE LOS EFECTOS RESPIRATORIOS DE LAS DOSIS ORALES EN VOLUNTARIOS HUMANOS E INTERACCIONES CON LA MORFINA EN RATONES

SUMARIO

Se ha realizado una prueba a doble puerta cerrada para investigar los efectos respiratorios de las dosis orales pequeñas de benzoctamina, y para compararlas con el diazepam y placebos. El desplazamiento de las curvas de respuesta al dióxido de carbono indicaron que aunque el diazepam causaba depresión respiratoria, la benzoctamina tenía un efecto variable. Algunos voluntarios presentaron depresión, pero la mayoría de ellos recibían estimulación. Los efectos respiratorios máximos se observaron 1 h después de la administración oral, regresando al estado normal 2 ó 3 h después de la administración. Se sugiere que los medicamentos orales administrados para medicación preventiva tienen que administrarse por lo menos 2 h antes de la operación para obtener los máximos efectos sedativos en el momento en que los efectos respiratorios empiezan a normalizarse. En los experimentos con animales se ha demostrado que la acción analgésica de la morfina disminuye mediante la administración simultánea de benzoctamina, y se aumenta la depresión del ritmo respiratorio causada por la morfina.