THE RESPIRATORY EFFECTS OF A POTENT ANALGESIC (GPA 2087)* IN MAN

BY

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SUMMARY

The respiratory depressant effects of a potent analgesic (GPA 2087) were compared with morphine in a randomized double-blind cross-over study in human volunteers. Using a rebreathing technique, carbon dioxide response curves were plotted automatically with a special-purpose analog computer. The respiratory depressant relative potency of GPA 2087 to morphine was found to be 1.21 with lower and upper 95 per cent confidence limits of 0.88 and 2.04. Our best estimate based on the displacement of the respiratory response curve is that GPA 2087 8 mg is the equivalent of morphine 10 mg in our population of volunteers.

The search for potent clinically useful analgesics is currently directed towards those with minimal dependence liability and respiratory depression. The realization that nalorphine, a morphine antagonist, was itself a potent analgesic with low-abuse potential led to the association between antagonism, analgesia, and low-dependence liability. Some of the recently studied narcotic antagonists, which had low-abuse potential and were potent analgesics, retained the unfortunate characteristic of respiratory depression. Since animal data suggested that narcotic antagonism might reside in just one of the optical isomers, racemic mixtures of potent analgesics were resolved to their constituent isomers in a search for those which might retain the analgesic potency of the parent compound but be low in both abuse potential and respiratory depression (May and Eddy, 1966).

GPA 2087† is the laevo-racemate of a benzazocine derivative, which is a dependence-producing potent analgesic known as NIH 7856 (Lasagna, DeKornfeld and Pearson, 1963). The chemical structure of GPA 2087 is shown in figure 1. After toxicology and efficacy studies in animals and acute toxicity studies in man, GPA 2087 was submitted to a clinical trial‡ and found to be a potent analgesic (Beer, E. G., et al., unpublished data). The respiratory effects were investigated by an indirect bioassay and the results are reported here.

![Fig. 1](https://example.com/fig1.png)

**Fig. 1** Structural formula of GPA 2087. It is the hydrochloride of l-6, 11a-diethyl-1,2,3,4,5,6-hexahydro-3-methyl-2,6-methano-3-benzazocine-8-ol.

**METHOD**

The effects of morphine and GPA 2087 were compared in human volunteers. Respiratory...
effects were assayed in terms of alveolar ventilation and end-tidal carbon dioxide. This is one of the more sensitive indices of respiratory stimulation or depression. The basic method has been described elsewhere (Bellville et al., 1963) and represents a modification of the rebreathing technique of Eckenhoff, Helrich and Hege (1956). Essentially, the method involved plotting respiratory response curves automatically with an analog computer while the subject breathed in a closed system. In plotting alveolar ventilation ($\dot{V} A$) and end-expiratory carbon dioxide ($P E' C O_2$) simultaneously we make two assumptions which are considered appropriate in normal volunteers (Clark, 1968; Read and Leigh, 1967): (1) $P E' C O_2$ accurately reflects chemoreceptor carbon dioxide although there is a slight difference, and (2) this difference remains constant from control through post-drug measurements.

The volunteer subjects for the study were six healthy adult male graduate students. Two doses of morphine (5 and 10 mg) and two doses of GPA 2087 (6 and 12 mg) were administered intramuscularly to each subject on four separate occasions. Dosages were dispensed randomly and under double-blind conditions. There was at least one week between each experimental trial. Since all subjects received both doses of each drug, they served as their own controls. For each experiment, the subject sat in a semi-recumbent position and was fitted with a rubber noseclip and metabolic mouthpiece. In this position he breathed room air through the open circle system for 2 minutes until he became accustomed to the apparatus. The system, whose reservoir bags had previously been filled with 10 litres of oxygen, was then closed and rebreathing commenced. Rebreathing continued for several minutes until an alveolar ventilation in excess of 30 l./min was achieved. After two, or if necessary three, control runs the medication was given and the response curves were determined at 0.5, 1, 2 and 3 hours. A best-fitting straight line was drawn through the upper linear portion of each curve. Two respiratory parameters were measured: (1) the parallel displacement of each post-drug respiratory response curve from the mean of the two controls at an alveolar ventilation of 20 l./min and (2) the change in slope of each post-drug response curve from the mean of the two controls.
Displacement and change of slope mean values for subjects, medication and time were calculated. Analysis of variance was done and a relative potency was computed. Figure 3 shows a typical control curve with the post-medication curve displaced to the right. It was not taken from this study.

Results

The displacements of the post-medication respiratory response curves for each drug, subject, and time are shown in table I. Respiratory depression was indicated by a shift of the curves to the right. An overall weighted mean was calculated for each medication, weighting the first two measurements half as much as the later hourly readings and thus correcting for the half-hour observation. At the doses studied, mean effects for GPA 2087 were higher than for morphine. With both drugs the high dose produced a greater displacement than the low dose.

An analysis of variance was carried out on the weighted means over time for the 24 experimental trials. A typical example is shown in table II. The F-ratios for subjects and treatments were significant (P<0.005). Slope (a measure of mean morphine and mean GPA 2087 differences) was also highly significant (P<0.0005). Parallelism was not significant (P<0.9). These results indicate a valid bioassay; although, ideally, preparation effects should not be significant. This is not damaging, however, since the ranges of response for the two preparations overlap nicely (fig. 4).

On the basis of the displacement data, the relative potency was calculated (Finney, 1964;
TABLE II
Analysis of variance for displacement of the respiratory response curve in mm Hg
P_{E'CO_2} at V_A of 20 1./min.

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Degrees of freedom</th>
<th>Sum of squares</th>
<th>Mean squares</th>
<th>F ratio</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>5</td>
<td>74.56</td>
<td>14.91</td>
<td>10.54</td>
<td>0.0005</td>
</tr>
<tr>
<td>Treatments</td>
<td>3</td>
<td>99.56</td>
<td>33.19</td>
<td>23.46</td>
<td>0.0005</td>
</tr>
<tr>
<td>Slope (1)</td>
<td>1</td>
<td>76.93</td>
<td>76.93</td>
<td>54.37</td>
<td>0.0005</td>
</tr>
<tr>
<td>Preparations (1)</td>
<td>1</td>
<td>22.61</td>
<td>22.61</td>
<td>13.98</td>
<td>0.0005</td>
</tr>
<tr>
<td>Parallelism (1)</td>
<td>1</td>
<td>0.02</td>
<td>0.02</td>
<td>0.014</td>
<td>0.9000</td>
</tr>
<tr>
<td>Residual</td>
<td>63</td>
<td>89.18</td>
<td>0.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>71</td>
<td>263.29</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Gaddum, 1953) to be 1.21 with lower and upper 95 per cent confidence limits of 0.88 and 2.04 (see fig. 4). That is, as a respiratory depressant, 10 mg of morphine is roughly equal to 8 mg of GPA 2087, with confidence limits of 5 mg to 11 mg.

The changes in slope of the respiratory response curves from the control are shown in table III. Greater changes in slope occurred with morphine than with GPA 2087, although the magnitude of change between the two doses of morphine was less than between the two doses of GPA 2087. An analysis of variance carried out on these data shows that the F-ratios for subjects and treatments are highly significant (P<0.0005). Parallelism is not significant. For components of variance, slope was significant (P<0.0005), preparations were significant (P<0.0005), and parallelism was not significant (P>0.95). Again the responses for the two preparations overlapped nicely although the preparations effect was significant. On the basis of the change in slope data, the relative potency for respiratory depression was calculated to be 0.52. Finite limits were not obtainable.

DISCUSSION

Drugs may modify the response of the respiratory control mechanism to carbon dioxide; hence, the displacement of the carbon dioxide response curve has become an established technique for measuring the effect of drugs on respiration. The exact shape of the lower end of the carbon dioxide response curve is uncertain (Kellogg, 1964). The curve appears level at its base (i.e., in the region of normal breathing). This may apply to control and post-drug curves. Consequently, it is difficult to detect and measure accurately drug-induced respiratory changes in a subject breathing room air. However, at elevated alveolar carbon dioxide tensions, the relationship between alveolar ventilation and alveolar carbon dioxide tension...
becomes linear and the displacement of the after-drug response curve can be more accurately defined and measured. In the technique used in this laboratory, elevated alveolar carbon dioxide tensions were achieved by the rebreathing technique. Other methods are available. For a discussion of these and a review of the effect of drugs on the respiratory response to carbon dioxide the work of Bellville (Bellville and Seed, 1960) and Lambertsen (1964) should be consulted.

The interpretation of drug-induced changes on the ventilation v. end-tidal carbon dioxide response curves is discussed by Bellville (Bellville and Seed, 1960) and Tenney (1956). The curve may be altered by a shift in the resting point (displacement), by a change in the slope, or both. The data in table I show that for both doses of morphine and GPA 2087 the curve was shifted to the right. On a mg basis, GPA 2087 produced a greater displacement than morphine.

In dogs anaesthetized with pentobarbitone and subjected to a carbon dioxide challenge, GPA 2087 4 mg/kg could not be distinguished from saline, whilst morphine 4 mg/kg caused respiratory depression (DeMaar, 1970; personal communication). This would be regarded as unusual for a potent analgesic, since narcotics appear to exert respiratory depressant effects roughly proportional to their analgesic potency (Eckenhoff and Oech, 1960). In fact, our data indicate that GPA 2087 does cause respiratory depression. In terms of respiratory depression, the relative potency of GPA 2087 is 1.21; that is, GPA 2087 8 mg is equal to morphine 10 mg. This estimate was considered with the data from an analgesic bioassay using GPA 2087 and morphine in which patients with postoperative pain were studied (Beer et al., unpublished data). This analgesic assay suggested that GPA 2087 8 mg was equivalent to morphine 10 mg. Thus, there was reassuring consistency in the relative potency estimates for the two parameters assayed.

Since the slope of the curve indicated the volume change in ventilation for each increment change in end-tidal carbon dioxide tension, it may be regarded as a measure of the sensitivity of the respiratory centre to carbon dioxide although many other factors can also affect this. Some studies suggested that morphine, in the doses used in clinical practice, shifted the respiratory response curve without appearing to change its slope (Loeschske et al., 1953; Seed et al., 1958), whereas others have reported significant changes in slope (Bellville and Green, 1965; Bellville, Cohen and Hamilton, 1964). Since change in slope may be small, differences in sensitivity of the methods used could explain the inability to
detect changes in slope in some studies. Our data show significant differences in slope and are consistent with reports by Bellville. Two parameters of drug effect were measured in this study—displacement and slope. Because no finite limits were obtained for the relative potency for change in slope, there is greater confidence in the relative potency estimate which was derived from the displacement data. Until further refinements are made in the measurements of change in slope, and until confidence in this has increased, displacement will continue to provide a more reliable estimate of respiratory depressant relative potency.

TIME-EFFECT CURVES FOR MEAN DISPLACEMENT FOR ALL SUBJECTS

![Graph](https://academic.oup.com/bja/article-abstract/43/12/1129/240471)

**Fig. 5**

Time-effect curve of morphine and GPA 2087.

The respiratory time-effect curves (mean 20 l. displacement v. time) for the four medications are shown in figure 5. They were based on the mean 20 l./min displacement at each of the four observation periods. The curves appear to differ in shape for the two drugs and would probably continue to do so, although less dramatically, even if the 30-minute mean displacement of GPA 2087 6 mg were regarded as spurious. The respiratory depression produced by morphine appeared to be of slower onset than that by GPA 2087. The morphine curves showed a trend towards a plateau with peak effect at approximately 120 minutes although this may be misleading since the true peak could have been missed. The sustained effect of morphine has been seen before (Bellville and Green, 1965; Beer, Forrest and Belville, 1971). With GPA 2087, the displacement was suggestive of more rapid onset, and peak effect appeared to be reached at 30 minutes for the low dose and 1 hour for the high. The effect did not appear to be sustained.

In a bioassay, lambda (λ), the ratio of the standard error to the common slope, is a measure of the experimental efficiency. The smaller the value of lambda, the greater the estimated efficiency (Finney, 1964). The lambdas for displacement and change in slope in this bioassay are 0.17 and 0.42 respectively. It is thus a relatively efficient assay since these values for lambda fall between those expected from in vitro laboratory studies (0.005–0.1) and those obtained in clinical bioassays of analgesics and sedatives (0.4–0.9). The efficiency of this study is probably attributable to (1) the sensitivity of the respiratory centres to small changes in drug concentration and (2) minimal patient variation when the respiratory control mechanism is under the positive stimulus of elevated alveolar carbon dioxide.

Calculation of lambda to monitor experimental efficiency in a bioassay is of more than just academic interest. In the evaluation of new drugs, efficient assays will yield reliable data from small populations, thus exposing as few volunteers as possible to the hazards of potent drugs. We believe this is an important ethical consideration.

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REFERENCES


**RESPIRATORY EFFECTS OF A POTENT ANALGESIC (GPA 2087)**

**RESPIRATORY EFFECTS OF A POTENT ANALGESIC (GPA 2087) CHEZ L'HOMME**

**SUMMARY**

The effects depressor of analgesics puissant (GPA 2087) on the respiration have been compared to those of the morphine in the frame of a study in double avenue with cross-over to subject human volunteers and preferably non-selected. By using a technique of rebreathing, the courses corresponded to the response of the carbon dioxide have been recorded automatically by the aid of an operator specially designed for analogous studies. On has constituted that the pouvoir depressor GPA 2087 on the respiration was 1,21 by rapport to that of the morphine, with an error inferior to 0,88 and superior of 2,04 for a confidence of 95%. Our estimation is the most favorable, based on the displacement of the course of the responses respiratory is 8 mg of GPA 2087 equivalent to 10 mg of morphine, in ce qui concerne notre population of subject volunteers.

**RESPIRATORISCHE WIRKUNG EINES STARKEN ANALGETIKUMS (GPA 2087)**

**BEIM MENSCHEN**

**ZUSAMMENFASSUNG**


**EFFECTS RESPIRATORIOS DE UN ANALGESICO POTENTE (GPA 2087)**

**EN EL HOMBRE**

**RESUMEN**

Los efectos depresivos respiratorios de un potente analgésico (GPA 2087) fueron comparados con la morfina en un estudio cross-over doble ciego al azar en sujetos voluntarios. Utilizando una técnica de rerespiración, las curvas de respuesta del anhidrido carbónico fueron proyectadas automáticamente mediante un computador análogo para fines especiales. Se encontró que la potencia relativa depresora respiratoria del GPA 2087 en comparación con morfina fue de 1,21 con un límite inferior y superior con 95 por ciento de confianza de 0,88 y 2,04. Nuestra mejor estimación basada en el desplazamiento de la curva de respuesta respiratoria es que 8 mg de GPA 2087 son equivalentes a 10 mg de morfina en nuestra población de voluntarios.