Relationship of Morphine-Induced Miosis to Plasma Concentration in Normal Subjects

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Abstract □ The relationship between morphine plasma concentration and pupil diameter was evaluated 2–10 h following intravenous administration of morphine sulfate (10 mg). Seven healthy male volunteers received 10 mg of morphine intravenously following pretreatment for 4 d with either cimetidine (300 mg po four times a day) or placebo in a single blind, balanced crossover study. Pupil diameters were measured directly from contact prints using calipers and a photographed millimeter scale. Cimetidine pretreatment had no significant effect on pupil size either before or after morphine administration or on morphine pharmacokinetics. The relationship between morphine plasma concentration (2–10 h postdose) and pupil diameter was evaluated from the pooled data from both morphine treatment periods by perpendicular least-squares regression. In each individual, a strong relationship existed between morphine plasma concentrations and pupil diameter ($r = -0.76$ to -0.91; $p < 0.05$). Weaker correlations for both pupil diameter ($r = -0.65$; $p < 0.0001$) and the absolute change in pupil diameter from baseline ($r = 0.72$; $p < 0.0001$) for the grouped data probably reflect intersubject variation in morphine sensitivity. Thus, the miotic response to an intravenous dose of morphine varies in proportion to morphine plasma concentration.

Keyphrases □ Morphine—relationship of morphine-induced miosis and plasma concentration in normal subjects □ Miosis—morphine-induced, relationship to plasma concentration

In the initial 2 h following an intravenous dose of heroin, pupil diameter is directly related to plasma concentration of morphine equivalents in both naive and dependent subjects (1). After oral methadone administration, decreases in pupil diameter appear to follow the same time course as methadone plasma concentration (2). While investigating the effects of oral cimetidine on the disposition of intravenous morphine (3), serial measurements of the extent and duration of morphine-induced miosis were made. In this report are described the relationships observed in individuals between plasma morphine concentrations after an intravenous morphine dose and pupil diameter.

EXPERIMENTAL SECTION

Seven healthy male volunteers (weight, 65–98 kg; age, 20–38 years) participated in a single blind crossover study and were randomly assigned to receive either oral cimetidine (300 mg once every 6 h) or placebo for 4 d. On day four of each treatment period, the volunteers reported for testing after an overnight fast. Each subject received either cimetidine or placebo orally. One hour later, morphine sulfate (10 mg; 8.5 mg of free base) was administered intravenously over 2 min. Plasma was obtained at a series of times postinjection to determine the pharmacokinetics of morphine. Morphine concentrations were determined by radioimmunoassay (4). A 7-d interval separated morphine treatments.

Pupil diameters were measured prior to and at 2, 5, 7, and 10 h after each morphine dose by a photographic technique (5–8). Subjects were placed in a dimly lit room (4 foot candles) and allowed to sit quietly. Black and white photographs of the left eye of each subject were taken with a 35-mm single lens reflex camera[1] with ASA-125 film[2]. The camera was equipped with an electronic flash and a fixed-focus, close-up lens which produced a life size, (*i.e.*, 1:1 magnification) image on the negative. A millimeter scale was photographed under the same magnification. Pupil diameters were measured on the contact prints with calipers and the millimeter scale. A representative example of pupil measurements taken before and after morphine administration is depicted in Fig. 1.

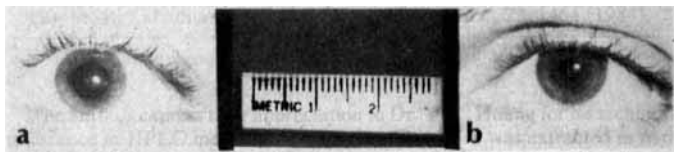

Figure 1—*Pupillary response to intravenously administered morphine sulfate (10 mg) in subject 4. Pupil diameter (5.9 mm) prior to morphine administration (a) is contrasted with pupil diameter 2 h following morphine administration (3.3 mm) (b).*

The relationships within and among individuals between morphine plasma concentration and pupil diameter were evaluated by perpendicular least-squares regression (9). Statistical comparison of pupil diameters as well as the slopes of the regression lines were done by using a paired Student's *t* test (9). All results are expressed as the mean ± *SD*.

RESULTS

Cimetidine pretreatment had no effect on baseline (premorphine) mean pupil diameter (placebo *versus* cimetidine, 6.4 ± 0.7 *versus* 6.3 ± 0.9 mm). A significant correlation existed between morphine plasma concentration and pupil diameter for each treatment period (placebo, $r = -0.69$, $p < 0.0001$; cimetidine, $r = -0.60$, $p < 0.001$). In addition, the mean of the slopes of the regression lines for each individual were not significantly different (placebo = −0.098, cimetidine = −0.110; $p < 0.05$).

Since cimetidine pretreatment appeared to have no effect on morphine pharmacokinetics (3) or on the relationship between morphine plasma concentration and pupil diameter, additional analysis of the combined data was performed. For the combined data, significant correlations were observed between pupil diameter and morphine plasma concentration at corresponding times. A significant correlation existed between the absolute change in pupil diameter from baseline (premorphine) and morphine plasma concentration ($r = 0.72$; $p < 0.0001$). The correlation coefficient for the grouped data (all observations) was −0.65 ($p < 0.0001$), whereas the correlation coefficients for the data from each subject, independent of pretreatment, ranged from −0.76 to −0.91 (Table I). The relationships between pupil diameter (in millimeters) and morphine plasma concentration for the subjects with the highest and lowest correlation coefficients (*i.e.*, subjects 4 and 6, respectively) are shown in Fig. 2.

Table I—Correlation Between Pupil Diameters and Plasma Morphine Concentrations in Healthy Volunteers [a]

Subject	Correlation Coefficient	Slope
1[b]	−0.86[c]	−0.120
2	−0.85[c]	−0.094
3	−0.77[c]	−0.065
4	−0.91[c]	−0.071
5	−0.78[c]	−0.089
6	−0.76[d]	−0.050
7	−0.82[c]	−0.066
Mean ± *SD*	−0.82 ± 0.06	−0.079 ± 0.02

[a] Pupil diameters are in millimeters, and plasma morphine concentrations are in nanograms per milliliter; $n = 10$ after a 10-mg iv infusion of morphine sulfate; data were collected before and at 2, 5, 7, and 10 h after morphine injection and were combined for placebo and cimetidine treatment periods (see text). [b] $n = 9$. [c] $p < 0.01$. [d] $p < 0.05$.

[1] Nikon.
[2] Plus-X.

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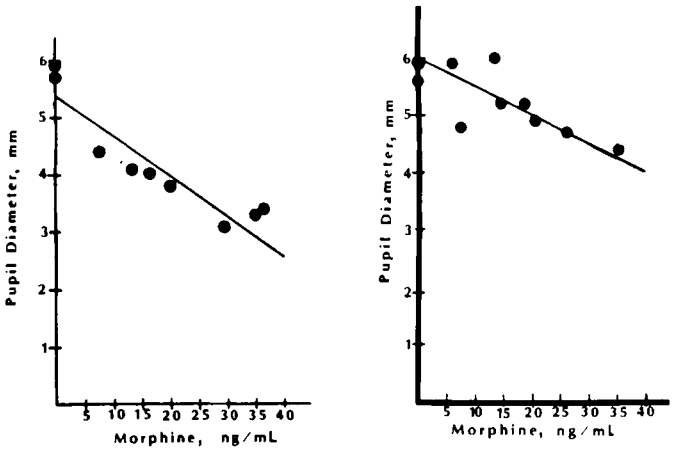

Figure 2—*Regression line derived from the data for subjects 4 and 6. These represent the subjects with the highest and lowest correlation coefficients. For subject 4 (left),* $y = -0.07x + 5.4$, $r = -0.91$, $p < 0.01$; *for subject 6 (right),* $y = -0.05x + 6.0$, $r = -0.76$, $p < 0.05$.

DISCUSSION

Recently, greater emphasis has been placed on evaluating the nature of the relationship between the pharmacokinetics and pharmacodynamics of an agent (10). The data from the present study establish the relationship between the miotic response to morphine and its plasma concentrations in the postdistributive phase. A difference in the magnitude of the correlation coefficients for individuals *versus* the group was observed. This is most probably accounted for by individual variation in pretreatment pupil diameter and sensitivity to morphine; evidence for the latter is the wide range of slopes described in Table I. Cimetidine exhibited no demonstrable effect on pupil diameter prior to or following morphine administration. These findings suggest that H_2-receptors have little role in the regulation of pupil size and are consistent with the lack of effect of cimetidine on morphine pharmacokinetics (3).

These data confirm and extend the previous observations of a relationship between plasma concentration of morphine equivalents following an intravenous dose of heroin and pupil diameter (1, 11). However, correlation coefficients were not reported in those studies, making comparison with the results obtained in this study impossible. Similarly, the time course of methadone-induced miosis appears to parallel methadone plasma concentrations (2).

Photographic pupillometry is an easily performed, readily quantifiable test which may have experimental and clinical utility for monitoring opiate activity. For example, tolerance to the miotic response to morphine has been demonstrated and used in the assessment of opiate dependency (7, 11). Further investigations are warranted to clarify the relationships between the serum concentrations of other opiate analgesics or other ocularly active agents and pupil diameter.

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