PUPILLARY EFFECTS OF ALFENTANIL AND MORPHINE

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SUMMARY

We have measured the onset and extent of the miotic effect of morphine and alfentanil in conscious patients. Forty unpremedicated ASA I and II patients were allocated randomly to four groups to receive either i.v. saline (control group), morphine 0.1 mg kg\(^{-1}\), alfentanil 4.0 \(\mu\)g kg\(^{-1}\) or a combination of these doses, and pupil diameters were measured for the next 30 min. There were no significant differences in the control diameters. In the opioid groups, a significant decrease in diameter (about 1 mm), occurred 4 min after administration of the drug and persisted throughout the study. The opioid groups behaved similarly for 25 min. After 10 min the mean diameter of the alfentanil group began to increase, but this did not reach statistical significance until after 25 min.

KEY WORDS


Miosis, analgesia and respiratory depression are typical mu agonist actions of morphine and alfentanil [1]. Changes in autonomic signs, including pupil size, are often used to assess adequacy of anaesthesia. Knowledge of the pupillary response to opioids in the unanaesthetized patient would help in its interpretation. Furthermore, there may be an interaction in the miotic effects when two mu agonist drugs are given in combination. An inhibitory interaction in analgesic effect has been reported when morphine and alfentanil were given in combination to mice [2], and there may be interactions in other mu effects.

Most studies on the effect of opioids on pupillary size have involved anaesthetized patients. However, it is not clear how anaesthetic drugs have contributed to the observed effects.

The object of this study was to determine the onset and extent of pupil diameter changes with morphine and alfentanil in conscious patients. A secondary object was to assess if additional miotic changes occur as a result of an interaction between alfentanil and morphine.

METHOD AND RESULTS

The study was approved by the local Ethics Committee, and all patients gave written consent. We studied 40 unpremedicated inpatients (ASA I and II) undergoing orthopaedic surgery. Patients suffering from eye diseases or receiving medication acting on the eye or autonomic nervous system were excluded.

In the anaesthetic room a cannula was inserted into a vein and routine monitoring commenced. The left pupil diameter was measured using a calibrated pupillometer (accurate to 0.1 mm) which itself provided standard lighting conditions [3].

Patients were allocated randomly to four groups of 10 patients according to the drug administered. Group S received saline 4 ml i.v., group M received morphine 0.1 mg kg\(^{-1}\) i.v., group A received alfentanil 4 \(\mu\)g kg\(^{-1}\) i.v. and group AM received morphine 0.1 mg kg\(^{-1}\) and alfentanil 4 \(\mu\)g kg\(^{-1}\) i.v.

Measurements of pupil diameter were made at 0, 2, 4, 6, 8, 10, 15, 20, 25 and 30 min after the injections which were given at time 0. All measurements were made by one of the authors who was aware of the patient's group allocation.

The pupil diameters were analysed using analysis of variance (ANOVA) and Bonferroni's
correction applied for multiple comparisons, \( P < 0.01 \) being considered significant. Other data were analysed using paired \( t \) tests, and chi-squared tests as appropriate, and \( P < 0.05 \) was considered significant.

The pooled data mean age was 31.8 yr and pooled mean weight 69.7 kg. The intergroup values for age, weight and frequency of brown eyes were not statistically different. The sex ratios of the groups were different (\( P < 0.05 \)); there was an absence and excess of females, in groups A and AM, respectively.

The pooled monitoring data on all patients during the study showed heart rates of 64–78 beat \( \text{min}^{-1} \), systolic arterial pressure of 126–111 mm Hg and ventilatory frequencies of 10.8–15.7 b.p.m.

There were no significant differences between the control pupil diameters in the four groups at time 0 (fig. 1). The main changes in pupil diameter occurred within 4 min of injection in the opioid groups, with minimal change in the saline group. After 4 min the pupil diameter curves in the opioid groups clustered between 2.8 and 3.2 mm. The curve for the saline group exhibited a downward trend, starting above 3.9 mm and decreasing to 3.7 mm over the last 26 min. In addition, after 10 min, the alfentanil group pupil diameter curve began to separate from the other opioid group curves, but this did not achieve statistical significance.

Analysis (ANOVA) of the pupil diameters in the groups at each time interval after 4 min showed that the three groups receiving opioids formed a population which was statistically distinguishable from any other combination of three groups. In addition, the analysis showed that the groups receiving opioids (A, M, AM) behaved as one homogeneous population for 25 min, which was significantly different from the control group (S) (fig. 1).

**COMMENT**

The decrease in pupil diameter, about 1 mm, in the opioid groups was almost complete by 4 min. This is interesting, in view of the relatively long onset time of the analgesic action of morphine. This may suggest that miotic effects occur at a lower brain concentration than analgesic actions.

There are few data on the duration of the miotic effect of morphine or alfentanil [4, 5]. Although the effect of alfentanil started to decrease after 10 min, it was still significant at 30 min. As the alpha half-life of alfentanil is about 3 min [6], these results suggest that the miotic effect of alfentanil is not related directly to its plasma concentration. These observations could be explained also by: action of metabolites, specific receptor effects and the polar nature of morphine, which delays its return from the CNS to the plasma.

Continuous measurement of pupil diameter with the pupillometer is unacceptable to patients, because of eye discomfort, but a 2-min measurement interval was acceptable to our patients. Taking this into account, the onset of miotic effect of morphine was similar to that of alfentanil. Unfortunately, the duration of the experimental period precluded estimation of the duration of miotic effects.

Our results do not support the generalization of the hypothesis that there is significant antagonism between morphine and alfentanil [2], at least as far as pupil diameter is concerned. This lack of antagonism could result from interspecies differences in pharmacokinetics and pharmacodynamics, or differences in pain and pupillary control mechanisms. Furthermore, as none of the patients developed pin-point pupils, it is unlikely that the ceiling of opioid miotic effects was reached; therefore, had an important interaction occurred, it would have been observable.

Changes in pupillary accommodation in con-
scious subjects could increase the variability of pupil diameter measurements; accommodation presumably does not occur during anaesthesia. The pupil diameters in the saline group decreased throughout our study. A similar but less pronounced effect was seen in Asbury's study [3] in anaesthetized patients. We see no obvious explanation for this effect.

REFERENCES