British Journal of Anaesthesia **96** (**5**): 614–19 (2006)
doi:10.1093/bja/ael073 Advance Access publication March 24, 2006

BJA

PAEDIATRICS

Reflex pupillary dilatation in response to skin incision and alfentanil in children anaesthetized with sevoflurane: a more sensitive measure of noxious stimulation than the commonly used variables

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Background. Estimation of analgesia in anaesthetized children is often imprecise, and consequently, anaesthesiologists commonly evaluate children's response to surgical stimulation by movement or haemodynamic changes. In adults reflex pupillary dilatation has been demonstrated to be a very sensitive measure of noxious stimulation, correlated with opioid concentrations. The autonomic nervous control changes with age, raising the hypothesis that mechanisms involved in pupillary autonomic functions regarding both sympathetic and parasympathetic components may also differ between adults and children. In this pilot study, we tested the hypothesis that the pupillary reflex dilatation might allow assessment of noxious stimulation and analgesic effect of alfentanil in children under sevoflurane anaesthesia, as an alternative to haemodynamic and bispectral measures.

Methods. After sevoflurane induction, 24 children were maintained in steady-state conditions at 1.5 MAC of sevoflurane in O_2–N_2O (50–50). An intense noxious stimulation was provided by standardized skin incision on the lower limb. A bolus of alfentanil (10 $\mu g\ kg^{-1}$) was administered either 1 min (n=16) or 2 min (n=8) after skin incision. Haemodynamic values, bispectral index (BIS) and pupillary diameter (PD) were recorded just before stimulation and at 30–60 s intervals during 4 subsequent minutes.

Results. In all children PD increased significantly after noxious stimulation [+200 (40)%, at 60 s]. In contrast, mean heart rate and blood pressure increased only 11 (7)% and 10 (8)% respectively, 60 s after stimulation. BIS did not change significantly. In all children, alfentanil injection induced a rapid decrease of PD and restored pre-incision values in 2 min.

Conclusion. PD is a more sensitive measure of noxious stimulation than the commonly used variables of heart rate, arterial blood pressure and BIS in children anaesthetized with sevoflurane.

Br J Anaesth 2006; **96**: 614–19

Keywords: anaesthesia, depth; anaesthetics volatile, sevoflurane; children; eye, pupil; pain, acute

Accepted for publication: February 21, 2006

A traditional description of anaesthesia is a state of hypnosis, analgesia and lack of movement to surgical stimulation. Some monitors of depth of anaesthesia measure hypnosis, such as the bispectral index (BIS), which is now available for children.[1] BIS is correlated with the expired concentration of volatile anaesthetics or with the plasma concentration of hypnotic drug, according to the EEG effect of these agents. However, pain and effects of opioids are poorly assessed by these EEG-based monitors. Consequently, estimation of analgesia in anaesthetized children is imprecise and anaesthesiologists have to evaluate children's response to surgical stimulation by movement or haemodynamic changes.

Noxious stimulation dilates the pupils in both anaesthetized and non-anaesthetized adults.[2–4] In adults, Larson and colleagues[5] have demonstrated that alfentanil blocks reflex

pupillary dilatation in response to noxious stimulation. Thus, in adults the pupillary dilatation reflex may be used as an indirect indicator of analgesia. Portable infrared pupillometers are now available to allow continuous accurate quantification of the pupillary diameter (PD) in the anaesthetized subject. In anaesthetized children there is no study assessing the PD changes during noxious stimulation and the possible effect of opioids. Young children are known to have less-active pupillary reflexes than adults.[6] Moreover, there are important age-dependent changes in the cardiovascular autonomic control raising the hypothesis that the mechanisms involved in pupillary autonomic functions regarding both sympathetic and parasympathetic components may also differ between adults and children.

Therefore, in this pilot study, we tested the hypothesis that pupillary changes in anaesthetized children may provide an assessment of noxious stimulation during surgery. To evaluate this hypothesis, we studied the dynamics of the pupillary response to noxious stimulation in children anaesthetized with sevoflurane and the effect of alfentanil on the pupillary response. We compared the changes in pupil size with the changes in haemodynamic variables and BIS values to assess the sensitivity of these parameters to noxious stimulation.

Methods

After approval by the local ethics committee and informed consent from the parents, a total of 24 children undergoing short orthopaedic procedures on the lower limb, were prospectively included in this pilot study. No patient received any anti-cholinergic drug. After premedication, anaesthesia was induced with sevoflurane 6% in a mixture of oxygen and nitrous oxide (50:50); this inspired concentration was maintained up to tracheal intubation. Tracheal intubation was performed using a cuffed tracheal tube after placement of the i.v. line, and soon after visualization of pupils in central position. After placement of the tracheal tube, the lungs were mechanically ventilated with a tidal volume of 10 ml kg^{-1} at a rate of 20 min^{-1} (Aestiva, Datex-Ohmeda), then inspired concentration was reduced to obtain 1.5 MAC of sevoflurane in the presence of 50% of nitrous oxide of alveolar gas and this expired concentration was maintained for 15 min to obtain steady-state conditions.[7] The skin incision was performed at the end of this period. Sixteen patients [group 1, mean age 9.7 (2.3–15.3) yr, mean weight 32.8 (19.7) kg] were enrolled and received an i.v. bolus of alfentanil (10 $\mu g\ kg^{-1}$) 1 min after skin incision. An additional group of eight children [group 2, mean age 7.5 (3.2–15.5) yr, mean weight 30.7 (26.4) kg] was enrolled after completion of the study. Patients in this group received the i.v. bolus of alfentanil (10 $\mu g\ kg^{-1}$), 2 min after skin incision. This additional group was deemed necessary to discriminate the effect of alfentanil from the effect of time and to eliminate a spontaneous decrease of PD.

Pupil size was monitored and recorded using an infrared pupillometry system (Synapsys SA France, Marseille), consisting of a camera, infrared light source, video monitor and video processing software, capturing pupil diameter as a real-time analogue signal (rate of 25 Hz).[8] The camera was fixed in front of one eye which was kept opened and humidified, during the study, with a mask. The other eye was closed, and both eyes were prevented from light and maintained in darkness. This system illuminates the pupil with a low level infrared source tracking the pupil as it moves within the recording field and quantifying PD from an image of the subject's eye on a video monitor. For each patient the experimenter calibrated the system. Calibration was performed by placing two black dots of known size immediately adjacent to the target pupil and calculating a linear correction function.

PD, systolic and diastolic blood pressure (SBP and DBP), heart rate (HR) and BIS were recorded before induction of anaesthesia, just before skin incision, then every 30 s up to the end of the fourth minute after skin incision.

Data analysis

Post-stimulation values of PD, HR, SBP, DBP and BIS were compared with the pre-stimulus values using paired *t*-tests. One way ANOVA was performed for comparison of the data from the two groups measured 1 min after skin incision, between children <10 yr of age and children >10 yr of age (Statview v 5.0, Abacus Concept, Inc.). *P*-values less than 0.05 were considered as significant. Data are expressed as mean (SD).

Results

Twenty-four children aged from 2 to 15 yr, were included in the study. Figure 1 illustrates the pupillary response and the HR response to the surgical stimulation under sevoflurane. At 1.5 MAC of sevoflurane in N_2O–O_2 (50:50), just before skin incision (control period), pupils were constricted in all patients: 2.3 (0.3) mm in group 1 and 2.1 (0.2) mm in group 2. In the two groups, the PD increased rapidly after the start of surgical stimulation reaching more than 160% at 30 s and about 200% at the end of the first minute ($P<0.001$). In group 2, changes from the first to the second minute after stimulation, were limited to an additional +10% of the 1 min-PD. After alfentanil injection, maximal decrease of PD was observed in the first 30 s reaching 65% of the maximal size in the two groups. In the two groups, the pre-stimulation values of PD were restored 2 min after alfentanil injection. In contrast with the pupillary response, 1 min after surgical stimulation, the maximum increases in HR triggered by noxious stimuli were only 11 (10)% and 12 (7)%, respectively, in groups 1 and 2, the SBP responses were also very limited—9 (5)% and 12 (8)%. Although these haemodynamic changes were small they were statistically significant in both the groups ($P<0.001$). In the two groups, the pre-incision values of HR and SBP, were restored 2 min after alfentanil injection.