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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.

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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.

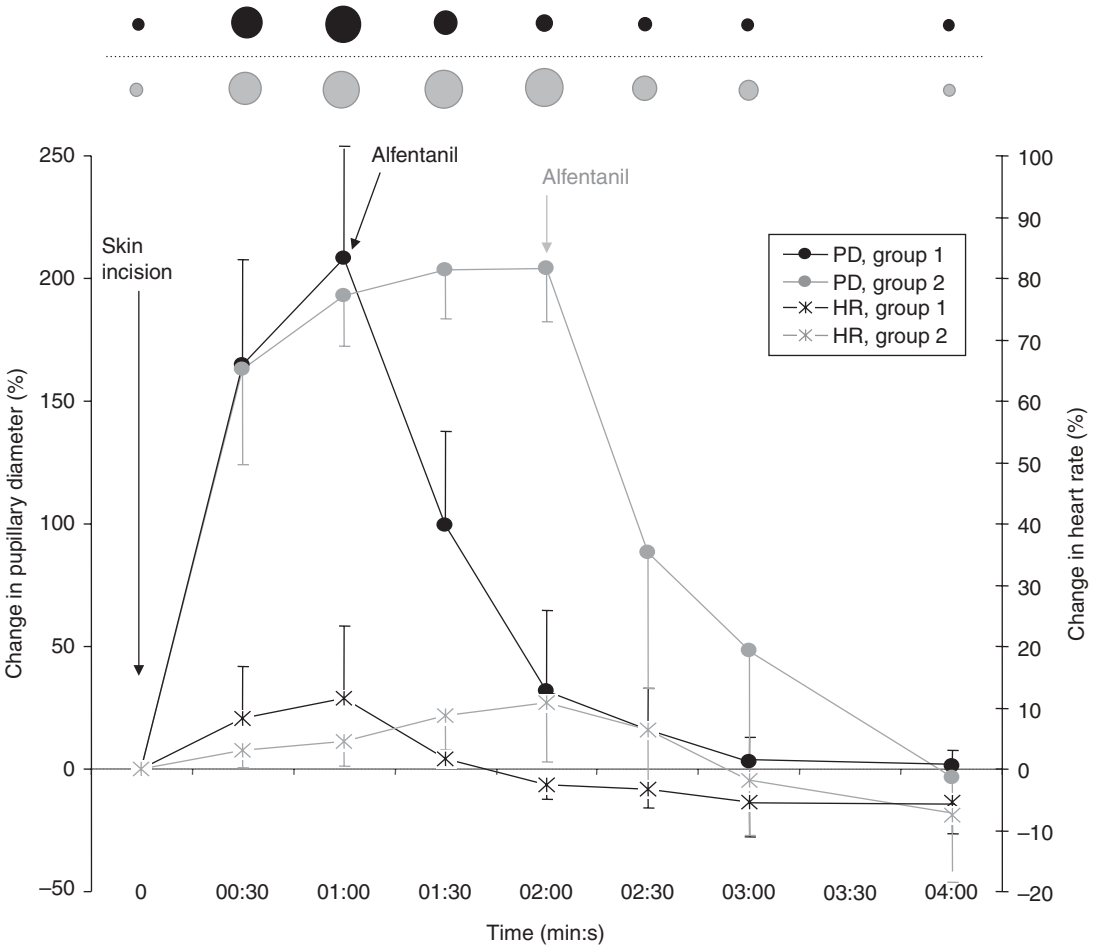

Fig 1 Changes in PD and HR measured after skin incision and alfentanil injection at 1 min (group 1, black circles) and 2 min (group 2, grey circles), expressed in percentage of pre-stimulation values [(mean (SD)]. The pupillary size corresponding to each studied point in the two groups, is illustrated on the top portion of the figure.

Changes of BIS associated with noxious stimuli or alfentanil injection, were not significant.

Figure 2 illustrates the individual changes (n=24) between control and 1 min after skin incision, in PD, HR, SBP and BIS.

In the 24 subjects, when measured just before skin incision and 1 min after, HR values were higher in children <10 yr of age [n=12, 5.2 (2.3) yr] compared with children >10 yr of age [n=12, 13.7 (1.7) yr], P<0.01, while PD values were similar in the two age-populations (Fig. 3).

Discussion

The pupillary responses to painful stimuli are far greater than the associated haemodynamic changes in children anaesthetized with sevoflurane and 50% nitrous oxide. In addition, alfentanil administration results in a rapid decrease of the pain-induced pupillary dilatation.

In awake subject the stimulus-induced dilatation (the ciliospinal reflex) is primarily sympathetically mediated. However, because this reflex is not present in organ donors, the neural pathway requires a supraspinal component for completion.[9] On the contrary, Larson and colleagues[10] have shown that pupillary dilatation in response to noxious electrical stimulation persisted after local alpha1 adrenergic blockade during desflurane anaesthesia, suggesting that sympathetic contribution to pupil size is negligible during the anaesthetized state.

Pupillary reflex dilatation is not diminished when isoflurane concentration is increased from 0.7 to 1.0 MAC[4] or when desflurane is increased from 0.6 to 1.1 MAC.[10] In our study noxious stimulation was performed at 1.5 MAC sevoflurane in N_2O and O_2 (50–50). We have chosen these conditions in order to be in a range of depth of anaesthesia allowing haemodynamic response because the chosen concentration is below the MAC^{11}_{BAR} and also ethically correct because the chosen concentration is above the MAC for surgical incision.[12] In our study, no patient moved at skin incision, and only two children showed an increase in either HR or SBP ⩾20% 1 min after skin incision, whereas all patients demonstrated at least a 125% increase in the PD. Our results, therefore, suggest

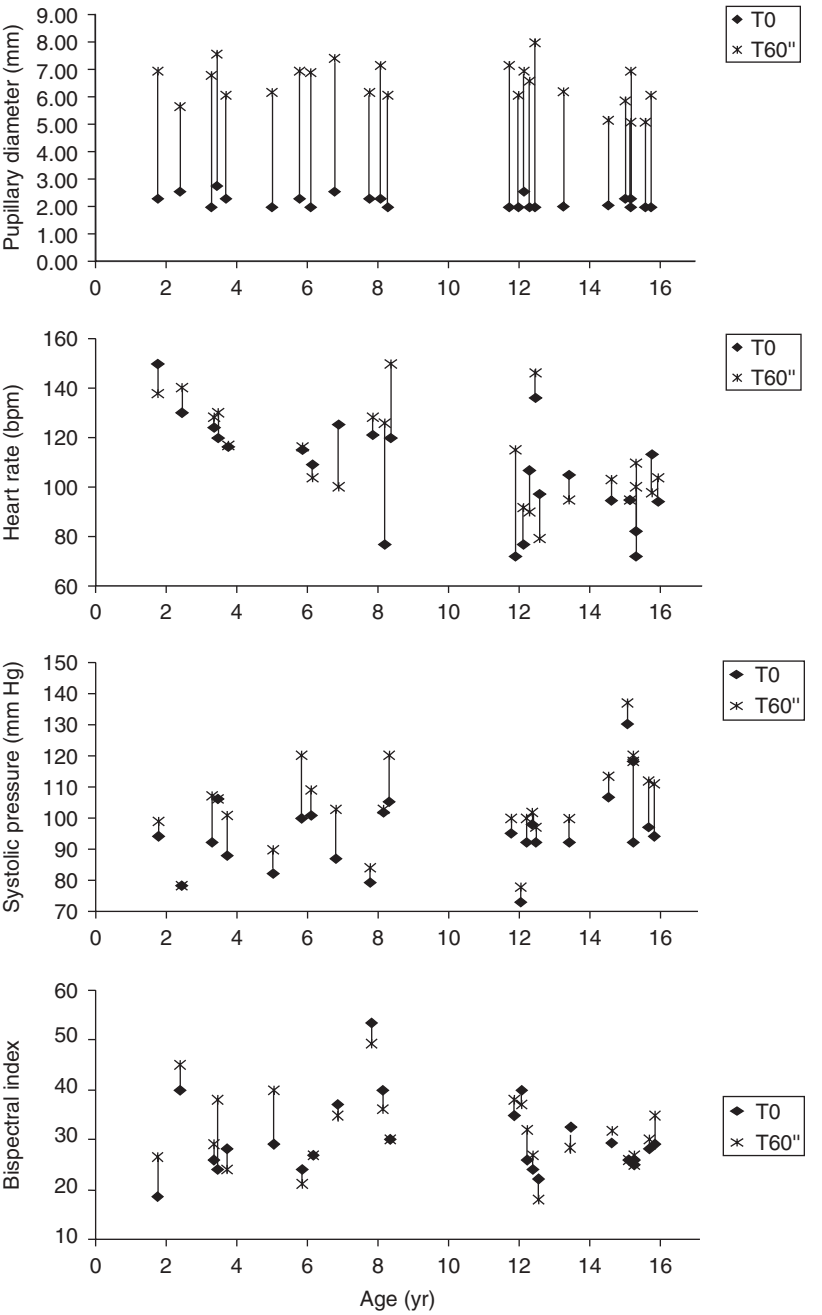

Fig 2 In all children (n=24), individual values of PD, HR, SBP and BIS, measured at baseline (♦) and 60 s after skin incision (⁎), and plotted against age.

that PD is a very sensitive index of nociception, more sensitive and faster than haemodynamic changes.

The sensitivity of the pupillary response to noxious stimuli has already been demonstrated in adults. In agreement with our results, Larson and colleagues[4] measured the changes in pupil size after electrical stimulus applied on the abdominal skin in adults anaesthetized with isoflurane or propofol and demonstrated that an intense noxious stimuli dilated the pupil approximately 200% in less than 1 min, the maximum rate depending on the hypnotic dose.

The effects of opioids and hypnotic agents on pupillary reflex dilatation differ significantly. Indeed opioids induce dose-dependent miosis.[13] The exact site within the central nervous system responsible for opioid-induced miosis is unknown, but seems to be dependent on the parasympathetic nervous system in animals.[14] Under desflurane, sevoflurane, isoflurane or propofol, opioids do not significantly decrease pupil size, as the pupil is already maximally constricted.[5,15] Opioids have been demonstrated to produce a substantial dose-dependant depression of pupillary dilatation after a noxious stimulus under anaesthesia.[5,16] In our study according to our routine clinical practice for short orthopaedic procedures, we used a single shot of a low dose of alfentanil. Despite the low dose of alfentanil the effect on pupillary

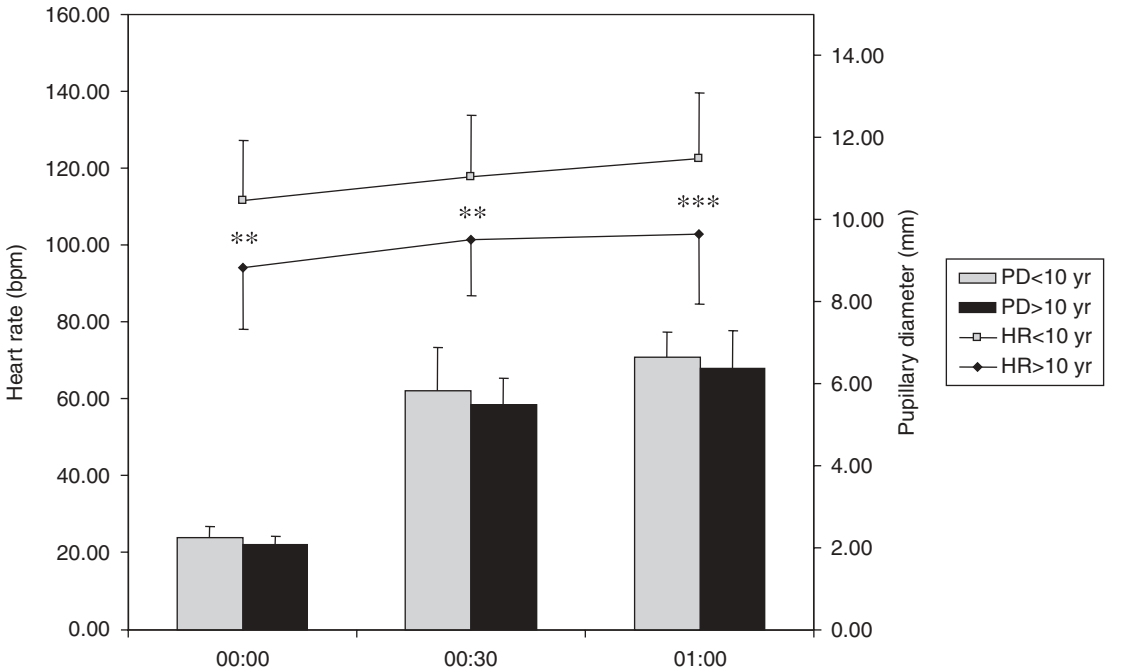

Fig 3 PD and HR in prepubertal children (n=12) compared with pubertal children (n=12) measured in the first minute after skin incision [mean (SD)]. $^{**}P<0.01$, $^{***}P<0.001$, prepubertal *vs* pubertal children.

reflex dilation was rapid and constant in all children restoring pre-stimulation values within 2 min after injection. The alfentanil injection 2 min after skin incision (group 2), demonstrated that the pupillary response did not regress spontaneously in the second minute after skin incision, and confirm that the decrease in PD is a result of the administration of alfentanil. In addition, constriction of pupils after alfentanil paralleled the HR and SBP decreases and is in keeping with the findings in adults[5] suggesting that pupillary reflex dilatation may be used to assess the analgesic effect and the duration of action of opioids in anaesthetized children. We cannot be completely sure that the effect of opioid on the pupil diameter is linked to analgesia and not to a pharmacological effect of the opioid itself. However, the parallel decrease of HR and SBP after alfentanil suggests that the inhibition of pupillary reflex dilatation is attributable to a reduction in the response to nociceptive stimulation.

Because of the maturation process, most physiological parameters differ between adults and children. Regarding the pupil diameter, optometric studies have shown that the normal values measured at ambient illumination, increase gradually and moderately with age up to adolescence, changing from 6 mm at 1 yr to 7.5 mm at 15 yr[17] and then declines slowly with age to reach routine values around 6 mm in the elderly.[18] Optic nerve myelination and maturation of the cell of the lateral geniculate body are not complete until approximately 2 yr of age[6] and young children are known to have less-active pupillary reflexes. The pupil reactivity improves, as the child becomes older, tightly linked to the maturation of distinct neural pathways. Regarding the light reflex a lower sympathetic contribution has been suggested in children under 10 yr of age.[19,20] The pupillary dilatation reflex in response to a noxious stimulus has not been investigated in children; however, Emery and colleagues[21] tested the pupillary dilatation reflex as a method of estimating the sensory level in children receiving combined isoflurane/caudal epidural anaesthesia. They showed that maximum pupillary dilatation in response to noxious stimulus with tetanic stimulation, was greater in children over 2 yr of age compared with children less than 2 yr of age. Regarding our data, the pupil diameter under sevoflurane before nociceptive stimulation and the dilatation response amplitude were very similar to those observed in healthy adult volunteers.[4,22] Moreover, when our data were re-examined to investigate the possibility of an age-related effect, it was found that basal values and response amplitude were strictly similar in children <10 yr of age and in children >10 yr of age.

In summary, we studied the effect of an intense noxious stimulus on pupil size in children anaesthetized with 1.5 MAC of sevoflurane and 50% nitrous oxide. We compared changes in PD to changes in HR, BP and BIS after surgical skin incision. In all cases, pupillary responses were far greater as compared with changes in BIS and haemodynamic parameters. Our data provide further evidence that in children, measurements of pupillary activity might enhance our ability to detect noxious stimulation and opioid effect during general anaesthesia. Moreover, the PD is a very sensitive index of nociception and seems to be independent of age at least in children over 2 yr of age.

References

1 Murat I, Constant I. Bispectral index in pediatrics: fashion or a new tool? *Paediatr Anaesth* 2005; **15**: 177–80

2 Reeves AG, Posner JB. The ciliospinal response in man. *Neurology* 1969; **19**: 1145–52

3 Chapman CR, Oka S, Bradshaw DH, Jacobson RC, Donaldson GW. Phasic pupil dilation response to noxious stimulation in normal volunteers: relationship to brain evoked potentials and pain report. *Psychophysiology* 1999; **36**: 44–52

4 Larson MD, Sessler DI, Washington DE, Merrifield BR, Hynson JA, McGuire J. Pupillary response to noxious stimulation during isoflurane and propofol anesthesia. *Anesth Analg* 1993; **76**: 1072–8

5 Larson MD, Kurz A, Sessler DI, Dechert M, Bjorksten AR, Tayefeh F. Alfentanil blocks reflex pupillary dilation in response to noxious stimulation but does not diminish the light reflex. *Anesthesiology* 1997; **87**: 849–55

6 Catalano R, Nelson LB. *Pediatric Ophthalmology: A Text Atlas*. Connecticut: Appleton and Lange, 1994; 41–8

7 Katoh T, Ikeda K. Minimum alveolar concentration of sevoflurane in children. *Br J Anaesth* 1992; **68**: 139–41

8 Tilikete C, Hermier M, Pelisson D, Vighetto A. Saccadic lateropulsion and upbeat nystagmus: disorders of caudal medulla. *Ann Neurol* 2002; **52**: 658–62

9 Yang LL, Niemann CU, Larson MD. Mechanism of pupillary reflex dilation in awake volunteers and in organ donors. *Anesthesiology* 2003; **99**: 1281–6

10 Larson MD, Tayefeh F, Sessler DI, Daniel M, Noorani M. Sympathetic nervous system does not mediate reflex pupillary dilation during desflurane anesthesia. *Anesthesiology* 1996; **85**: 748–54

11 Katoh T, Kobayashi S, Suzuki A, Kato S, Iwamoto T, Bito H, Sato S. Fentanyl augments block of sympathetic responses to skin incision during sevoflurane anaesthesia in children. *Br J Anaesth* 2000; **84**: 63–6

12 Lerman J, Sikich N, Kleinman S, Yentis S. The pharmacology of sevoflurane in infants and children. *Anesthesiology* 1994; **80**: 814–24

13 Fedder IL, Vlasses PH, Mojaverian P, *et al*. Relationship of morphine-induced miosis to plasma concentration in normal subjects. *J Pharm Sci* 1984; **73**: 1496–7

14 Lee HK, Wang SC. Mechanism of morphine-induced miosis in the dog. *J Pharmacol Exp Ther* 1975; **192**: 415–31

15 Daniel M, Larson MD, Eger EI II, Noorani M, Weiskopf RB. Fentanyl, clonidine, and repeated increases in desflurane concentration, but not nitrous oxide or esmolol, block the transient mydriasis caused by rapid increases in desflurane concentration. *Anesth Analg* 1995; **81**: 372–8

16 Barvais L, Engelman E, Eba JM, Coussaert E, Cantraine F, Kenny GN. Effect site concentrations of remifentanil and pupil response to noxious stimulation. *Br J Anaesth* 2003; **91**: 347–52

17 MacLachlan C, Howland HC. Normal values and standard deviations for pupil diameter and interpupillary distance in subjects aged 1 month to 19 years. *Ophthalmic Physiol Opt* 2002; **22**: 175–82

18 Winn B, Whitaker D, Elliott DB, Phillips NJ. Factors affecting light-adapted pupil size in normal human subjects. *Invest Ophthalmol Vis Sci* 1994; **35**: 1132–7

19 Laor N, Korczyn AD, Nemet P. Sympathetic pupillary activity in infants. *Pediatrics* 1977; **59**: 195–8

20 Hasegawa S, Ishikawa S. [Age changes in pupillary light reflex. A demonstration by means of a pupillometer]. *Nippon Ganka Gakkai Zasshi* 1989; **93**: 955–61

21 Emery J, Ho D, MacKeen L, Heon E, Bissonnette B. Pupillary reflex dilation and skin temperature to assess sensory level during combined general and caudal anesthesia in children. *Paediatr Anaesth* 2004; **14**: 768–73

22 Tayefeh F, Larson MD, Sessler DI, Eger EI II, Bowland T. Time-dependent changes in heart rate and pupil size during desflurane or sevoflurane anesthesia. *Anesth Analg* 1997; **85**: 1362–6