INTRODUCTION

Retinopathy of prematurity (ROP) is a serious problem of preterm infants which may lead to impairment of vision and even to blindness if untreated. Routine eye examination is necessary for early diagnosis and treatment of ROP in preterm infants. Mydriatic eye drops (cyclopentolate, tropicamide and phenylephrine) are applied before the ophthalmic examination. These agents are rarely absorbed to systemic circulation and in some cases result with serious side effects like skin rash, tachycardia, feeding intolerance, discomfort, apnea, gastro-intestinal dilatation and ileus, despite different treatment models and dosage reducing strategies. We report here a preterm patient who died because of severe diffuse necrotizing enterocolitis (NEC) after topical application of 0.5% cyclopentolate and 1.25% phenylephrine during ROP screening to emphasize the serious side effects of these agents.

CASE REPORT

A 1050 gram female infant was delivered at 26 weeks of gestation by C-section and treated with early surfactant and nasal continuous positive airway pressure (nCPAP) for respiratory distress syndrome. She had normal haematologic and biochemical markers and a normal echocardiographic evaluation. No pathology was observed in abdominal and cranial ultrasonographic screening. The patient was weaned from nCPAP and transferred to room air by day 22. She had minimal enteral feeding beginning at day 7 and enteral feeding was increased quite slowly due to intermittent gastric retensions. The patient was on full enteral feeds at day 33. ROP screening was performed at day 37 (postnatal 6 weeks old). Haematologic, biochemical markers and the C-reactive protein levels were within the normal range on the same day just before the examination. Enteral feeding was discontinued 2 hours before the eye drops. She had no evidence of ROP at the eye examination. Approximately 4 hours after the examination while enteral nutrition was still off, cutis marmorata and tachycardia developed associated with abdominal distension (Figure 1a). A nasogastric tube was kept in site for free drainage while enteral feeding was still discontinued. Broad-spectrum antibiotic treatment besides pentoxifylline was ordered. The patient was intubated and put on mechanical ventilation because of tachypnea, tachycardia, increased oxygen need and desaturation. She developed leukopenia and neutropenia with normal platelet counts. Pneumatosis intestinalis was detected on abdominal radiography 12 hours after the examination (Figure 1b). The diagnosis of stage-III NEC led to surgery decision with the ongoing colour change of the abdomen, abdominal distension and fecaloid orogastric drainage. Necrotic intestinal tissue of 60...
centimeters from the small intestine and 20 centimeters from the colon was dissected (Figure 1c). She had cardiac arrest during operation and cardiopulmonary resuscitation was performed. The patient died 24 hours after the operation despite all efforts. All her cultures were reported as negative. Marked necrosis was observed at pathologic investigation in all layers of the intestine (Figure 2).

**DISCUSSION**

Screening guidelines for ROP have been previously defined in detail to prevent the undesired complications such as blindness. Several mydriatic eye drops are recommended for pre-examination period of ROP but also multiple side effects are reported during the neonatal period. Cyclopentolate and phenylephrine eye drops are most commonly used to achieve mydriasis. Cyclopentolate shows a parasympatholytic and an atropine like effect on the gut while phenylephrine is a sympathomimetic probably causing splanchnic vasoconstriction. All these side effects may be due to the stress during the ROP examination or to the toxic effect of the drugs with the systemic absorption.

Necrotizing enterocolitis (NEC) is one of the most important causes of morbidity and mortality among preterm infants. The incidence of NEC is inversely proportional with gestational age and birth weight. Mortality rates differ between 10 – 50% in infants who weigh less than 1500 grams. A 20 – 40% of NEC patients would undergo surgery and mortality rate is the highest for this particular group.

Multifactorial mechanisms play role in the pathophysiology of NEC. The most important risk factor is prematurity due to immature intestinal mucosa, decreased intestinal motility, immature immune system and insufficient antioxidant levels. During this process, while hypoxia and ischaemia are major risk factors for term infants; very early onset and rapid increase of enteral nutrition, abnormal intestinal colonisation and inflammatory mediators are accused for the development of NEC in the preterm group. The duration of the onset is rapid among term infants within a few days compared to the later and insidious onset within weeks in preterm infants.

Hermansen et al. demonstrated the risk of feeding intolerance following the ophthalmologic examination of neonates. In that study, all 50 premature infants received cyclopentolate 0.5% and phenylephrine 2.5% before the examination. More abdominal distention and gastric aspirates were detected in the period following the examination than in the period preceding the examination. One infant developed NEC during the 24-hour post-examination period.

Nair et al. reported 4 patients who developed NEC within 24 hours of ROP screening, one of whom had intestinal resection 6 hours after 2.5% phenylephrine and 0.1% atropine administration.

Siu et al. reported three monochorionic triamniotic triplets born at 28 (6/7) weeks undergoing ROP screening when they were 6 weeks old. While triplet-III had achieved full feeds and was on exclusively preterm formula, triplet-II had a quarter of her feeds with preterm formula and triplet-I was still on parenteral nutrition because of gut motility problem. All of them had received one drop of 2.5% phenylephrine and 1% cyclopentolate eye drops twice, one hour before ROP examination. Triplet-II required a second ROP screening at the 7th week and immediately after the application of the eye drops, she developed desaturation with bradycardia, requiring resuscitation. Eighteen hours after instillation of eye drops, her abdomen became stony hard and bowel sounds could not be heard. She was then transferred to surgical centre and laparotomy was performed 2 days later.

Bonthala et al. using a low compliance continuous perfusion manometric system, showed that although the number of antral motor contractions remained relatively constant throughout the study, duodenal motor contrac-
tions decreased nearly four-fold after the instillation of mydriatics in 11 preterm infants (p < 0.01). Gastric emptying was significantly delayed after the completion of the eye examination (p < 0.05). In order to minimize the side effects of the topical eye drops, the concentrations of the eye drops must be limited (cylopentolate concentration with 0.5%, phenylephrine with 2.5%). One eye drop must be applied once and from the medial corner of the eye directed to the lateral corner. The excess of the drug should be mopped. A slight pressure should be applied to the medial corner of the eye for 3 minutes to prevent the nasal mucosal absorption of the topical eye drop. If sufficient dilatation is obtained, repeated dose applications should be avoided. In a prospective study among 26 premature infants by Wheatcroft et al., 5 microliters microdrops had the same effect and fewer adverse effects with standard 26 microliters eye drops of cyclopentolate 0.5% and phenylephrine 2.5%. In preterm infants.

Elibol et al. showed that microdrops (mean drop volume 5.6 microl) produced similar increase in pupil diameter compared with standard drops (mean drop volume 35.4 microl) of cyclopentolate, phenylephrine and tropicamide. Mean blood pressure increased significantly in infants given standard drops but not in the group that was given microdrops.

Punyawattanaporn et al. reported pupil dilatations were adequate for the peripheral retina examination after receiving either a drop of mixture of 0.2% cyclopentolate and 1.0% phenylephrine single dose (group A) or triple doses of 10-minute interval (Group B).

This patient received two times 0.5% cyclopentolate and 1.25% phenylephrine eye drops diluted two-fold alternately with an interval of 10 minutes, but unfortunately had severe stage-III NEC and died 24 hours after the intestinal resection. We have started to use topical tropicamide and phenylephrine combination after this case and discontinued enteral feeding 4 hours before and after the eye examination. After this case, we have also started to drop the mydriatic agent directed from the medial corner of the eye to the lateral corner, remove the excess of the drug and slightly press to the medial corner of the eye for 3 minutes to prevent the absorption through the nasal mucosa.

REFERENCES