Etomidate-® Lipuro is associated with considerably less injection pain in children compared with propofol with added lidocaine

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Background. Propofol is associated with a high incidence of injection pain in children, even if given together with lidocaine. A new lipid formulation of etomidate (Etomidate-® Lipuro) has been found in adults to cause very little discomfort during i.v. injection. The aim of the present prospective, double-blind, randomized trial was to compare the incidence of injection pain during i.v. induction of anaesthesia between propofol with added lidocaine (previous standard) and this new etomidate formulation in paediatric patients.

Methods. A total of 110 paediatric patients, aged 2–16 years, scheduled for outpatient surgery were planned to be included in the study. The primary end point of the study was the incidence of injection pain during induction of anaesthesia as assessed by a four-point scale as described previously. The occurrence of myoclonic muscular activity was registered as a secondary end point (four-point scale). An interim analysis after 80 patients was requested by the Ethics’ Committee.

Results. The study was stopped after the inclusion of 80 patients. A significantly lower incidence of injection pain was found in the Etomidate-® Lipuro group as compared with the propofol–lidocaine group (5.0% vs 47.5%, P<0.001). The use of etomidate was associated with a significantly higher incidence of myoclonic activity compared with propofol–lidocaine (85.0% vs 15%, P<0.001).

Conclusions. The use of a new lipid formulation of etomidate is associated with significantly less injection pain than propofol with added lidocaine in children. This finding may warrant a change in clinical practice in order to avoid unnecessary pain in children.

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Propofol is increasingly being used for both induction of anaesthesia and short-term sedation for various procedures in children. The reason for the increasing popularity is mainly its short duration of action that will allow for rapid emergence combined with minimal residual sedation. However, despite various attempts at reducing the often serious pain on injection that accompanies the use of propofol,¹–³ the incidence of this unwanted side-effect in children is still 20–39%, even after pre-mixing propofol with lidocaine.⁴–⁶

This incidence of pain on injection in children is in our view not acceptable and an alternative to propofol that has a similar duration of action and is not associated with pain on injection is, thus, highly desirable.

Etomidate, a substituted imidazole anaesthetic with a short duration of action and associated with a high degree of haemodynamic stability, is now available in a new pharmaceutical formulation that in adults completely relieves pain on injection.⁷–⁹ In this new formulation, etomidate is dissolved in a fat emulsion of medium- and long-chain...
triglycerides (Etomidate® Lipuro, B. Braun, Melsungen, Germany).

The aim of the present prospective randomized controlled single-centre double-blind trial was to compare the incidence of pain on injection in children undergoing day-case surgery between Etomidate® Lipuro and our current standard propofol-Diprivan® with added lidocaine.

Material and methods

Following written parental consent, combined with patient consent in appropriate cases, 110 patients listed for various types of outpatient surgery were scheduled to be included (age range: 2–16 years). The study used a single-centre prospective, randomized, double-blind controlled design. Randomization was based on computer generated random numbers. The study was approved both by the Regional Ethics Committee and the Swedish Medical Products Agency. The study adhered to Good Clinical Practice (GCP) guidelines.

Exclusion criteria were an allergy to lipid emulsions or a primary or secondary dysfunction (e.g. secondary to steroid medication) of the adrenal cortex.

After appropriate application of an EMLA® patch (AstraZeneca, Macclesfield, UK) an i.v. catheter (22 G, B. Braun, Melsungen, Germany) was placed on the dorsum of the hand in the paediatric day stay unit. All patients were given midazolam 0.05 mg kg⁻¹ i.v. as premedication before transfer to the surgical unit. One parent was allowed to accompany the child until anaesthesia had been induced.

The syringes containing the study drugs were prepared by the hospital pharmacy to assure a proper blinding procedure. The coded syringes contained either Etomidate® Lipuro 2 mg ml⁻¹ or propofol-Diprivan® 20 mg ml⁻¹ with lidocaine 2 mg ml⁻¹, and syringes were prefilled to contain 11 ml for blinding purposes (no visual difference could be detected between syringes). Following attachment of standard non-invasive monitoring anaesthesia was induced by the injection of 0.15 ml kg⁻¹ of the study drug (propofol 3 mg kg⁻¹ or etomidate 0.3 mg kg⁻¹). The injection was made manually and was accomplished in 5–10 s.

Assessments

Pain was measured using a four-graded scale (0: no pain, 1: verbal complain of pain, 2: withdrawal of the arm, 3: both verbal complain and withdrawal of the arm), as described previously (6). Pain was assessed by the same specially trained nurse anaesthetist (KvH) in all patients. The assessment was based on the patients’ response during the injection of the study drug. In order to preserve blinding the score was noted immediately after the patient lost consciousness, thus before possible myoclonic activity would potentially occur.

The incidence and the degree of myoclonic movements after loss of consciousness were also noted. The degree of such muscular activity was scored as follows: 0, no myoclonic movements; 1, minor myoclonic movements; 2, moderate myoclonic movements; 3, major myoclonic activity. When the assessment of myoclonic activity had been performed (within 1–2 min after induction of anaesthesia) the study was stopped and anaesthesia was thereafter handled as appropriate for the scheduled surgery.

Statistical analysis

The primary end point of the study was the presence (score 1–3) or absence (score 0) of injection pain. In accordance with our previous findings, the power calculation was based on a conservative 25% incidence of pain in the propofol–lidocaine group and an expected pain incidence of 5% in the Etomidate® Lipuro group. The alpha- and beta-values were set at 0.05 and 90%, respectively. With compensation for a limited number of potential drop-out cases the total number of patients was estimated at 110 (55 patients in each study group). However, the Ethics’ Committee demanded an interim analysis so that patients would not be subjected to unnecessary injection pain if there was a difference in pain incidence between the two study groups. Thus, it was decided to include an interim analysis following 80 patients and if a statistical difference at P<0.02 was present between the two study groups at this interim point the study should be stopped.

Non-parametric statistical procedures were used in all the analyses. The 95% confidence intervals (95% CIs) for proportions were calculated as given in Mendenhall.10 Classified data from two independent populations were compared using the Fisher’s exact test. P-values <0.05 were considered as statistically significant.

Results

Demographic data were similar between the two study groups [Etomidate® Lipuro vs propofol–lidocaine: sex (m/f): 12/28 vs 10/30; age (yr, median/range): 8.9/2.2–15.4 vs 9.6/2.8–15.9; weight (kg, median/range): 33.3/11.3–81.0 vs 30.0/15.0–65.0]. Because of the result of the interim analysis the study was stopped after inclusion of 80 patients.

The incidence of injection pain, the primary end point of the study, was significantly lower in the Etomidate® Lipuro group (5.0%; 95% CI 0.61–16.9%) compared with the propofol–lidocaine group (47.5%; 95% CI 31.5—63.9%) (P<0.001). The distribution of pain scores is shown in Figure 1.

A higher incidence of myoclonic activity was seen in the Etomidate® Lipuro group (85.0%; 95% CI 70.2–94.3%) compared with the propofol–lidocaine group (15.0%; 95% CI 5.7–29.9%) (P<0.001). The distribution of myoclonic movement scores is shown in Figure 2.
The main finding of the present study was that the use of
Etomidate-Lipuro for i.v. induction of anaesthesia in chil-
dren is associated with a very low rate of pain on injection
and that it is a significantly better alternative compared with
propofol with added lidocaine in this respect.

The present financial pressure to reduce anaesthesia turn-
over time has created a demand for an induction agent with a
rapid offset and minimal residual sedation, thereby mini-
mizing the time required for emergence and time spent in the
recovery room. Even if the issue of minimal postoperative
residual sedation is debatable in children, as a majority of
parents (75%) in fact prefer their child to be slightly calm
and sedated during the first day after operation,11 the use of
propofol as the drug of choice for i.v. induction of anaes-
thesia is steadily increasing also in children, especially in
outpatients.

A serious problem with the use of propofol in children is
the high incidence of pain on injection.1–6 A large number of
various attempts to lower the incidence of pain on injection
have been reported but have not been able to remedy this
clinical problem.1–3 The currently most common practice to
reduce this problem is by adding lidocaine to the propofol
solution, but despite this the incidence of pain on injection
remains unacceptably high (20–39%).1–6 Thus, an alterna-
tive to propofol that combines rapid emergence and minimal
residual sedation with no or a very low incidence of pain on
injection would be much welcomed.

Etomidate is a well-known substituted imidazole induc-
tion agent that shares most of the beneficial characteristics
of propofol (e.g. rapid onset/offset and minimal residual
sedation) and is also associated with a very high degree
of haemodynamic stability.12 Although etomidate causes
adrenocortical suppression, a single injection to induce
anaesthesia will only produce a transient and clinically
insignificant interference with adrenocortical function.13–16

In a study by Schenarts and colleagues17 the use of etomi-
date for the induction of anaesthesia in the emergency
department, as compared with midazolam, was associated
with a reduced cosyntropin stimulation test response (30% of
the control group response) at 3 h after administration.
However, the cosyntropin stimulation test response was
back to normal at 12 h after the administration. Furthermore,
despite the reduced adrenal response to cosyntropin during
the early phase after administration, the serum cortisol lev-
els remained within the normal laboratory reference ranges
during the limited period of adrenal inhibition.

A problem with previous preparations of etomidate was
that the solvent used also caused pain on injection.7–9 Eto-
midate is now available as a lipid emulsion (Etomidate-
Lipuro, B. Braun AG, Melsungen, Germany) and is a
registered drug in a number of European countries. In adults
this preparation is associated with significantly less pain on
injection than propofol.18 To our knowledge the present
study is the first randomized clinical trial comparing this
new preparation of etomidate with propofol regarding the
occurrence of pain on injection in children.

The use of Etomidate-Lipuro was found to significantly
reduce the incidence of pain on injection compared with
propofol–lidocaine (5% vs 47.5%; P<0.001) (Fig. 1).
Although the incidence with etomidate was as expected
in the power calculation the rate of pain on injection with
propofol was higher than the conservative figures used for
the power calculation. Thus, the higher observed incidence
than predicted resulted in a highly significant result in favour
of etomidate already at the interim analysis. As dictated by
the ethics committee the study was stopped at this point.

It could be argued that the reason for the higher than
expected incidence of pain on injection in the propofol–
lidocaine group may be because of the use of a 2% propofol
solution as compared with a 1% solution. As is alluded to in
the Material and methods section this was done in order to
produce adequate blinding conditions for the study and was
judged reasonable as Pellegrini and colleagues19 in a previ-
ous study did not find any significant difference in the inci-
dence of injection pain between 1 and 2% propofol solutions.
Furthermore, the incidence of injection pain for propofol
was not to any major extent different compared with figures reported by our group in a previous study
using propofol 1% with added lidocaine (39%).6
As it is not realistic to expect any drug that is injected i.v. in children to be associated with a zero incidence of injection pain it is perhaps reasonable to say that the use of Etomidate-C210/Lipuro from a clinical perspective has solved the problem with injection pain during i.v. induction of anaesthesia in children.

As both propofol and etomidate are associated with the occurrence of myoclonic movements this was also registered as a secondary end point of the study. In agreement with previous literature the use of etomidate was found to be associated with a higher incidence of myoclonic activity than propofol.\textsuperscript{18} The myoclonic movements were also judged to be more pronounced than those associated with the use of propofol–lidocaine (Fig. 2).

There may be at least two possible explanations for the observed difference between the drugs concerning myoclonic activity. First, etomidate appears to be especially potent in causing such movements.\textsuperscript{9} Second, it can be speculated that the addition of lidocaine to the propofol solution may reduce the excitability of the central nervous system, which is the cause of the myoclonic movements. Whether addition of lidocaine to the Etomidate-C210/Lipuro preparation is capable of reducing the occurrence of myoclonic movements deserves further study.

Previous studies in adults have also shown that the incidence of myoclonic movements can be reduced either by premedication with fentanyl\textsuperscript{20} or by preinduction priming with a subanaesthetic dose of etomidate.\textsuperscript{21} However, as the time between the loss of consciousness and the occurrence of myoclonic activity is quite short in certain patients (20–30 s) it is advisable to inform an accompanying parent that this may happen and that it is not a sign of insufficient anaesthesia and rapidly escort the parent out of the operating room immediately after the loss of consciousness.

In conclusion, the use of a new lipid emulsion of etomidate is associated with significantly less pain on injection than propofol with added lidocaine during induction of anaesthesia in children.

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