Systemic absorption of ocular cyclopentolate in children*

Kimmo Lahdes 1, Risto Huupponen 2, Timo Kaila 2, Timo Ali-Melkkilä 3, Lotta Salminen 4, and Matti Saari 1

1 Department of Ophthalmology, 2 Department of Clinical Pharmacology, and 3 Department of Anaesthesiology, University of Turku, Kiinamyllynkatu 4-8, SF-20520, Turku, Finland,
4 Department of Ophthalmology, University of Tampere, Tampere, Finland

Abstract. Cyclopentolate plasma levels were quantitated and heart rate and pupil size were monitored after ocular application of the drug to juveniles. In all, 12 children were given one 35-μl eyedrop of either 1% cyclopentolate (n=6) or placebo (n=6) in randomized order in the lower cul-de-sac of one eye. A sensitive radioceptor assay was used to determine the systemic drug absorption. With the exception of one child, detectable cyclopentolate concentrations were seen in plasma as early as 3 min after the ocular drug application. There was a marked interindividual variation in peak plasma cyclopentolate concentrations ranging from undetectably low to 5.8 ng/ml (median, 2.9 ng/ml). In some children a second drug concentration peak was detected. Cyclopentolate increased the pupillary diameter from 4.8 ± 1 mm before drug application to 8 ± 0.9 mm at 30 min after administration, but the children’s heart rate did not alter.

Introduction

Cyclopentolate, a potent synthetic parasympatholytic drug, causes rapid, intense mydriasis and cycloplegia in the eye. Because of its intense and short duration of action, it is widely used in routine funduscopic and in testing of cycloplegia refraction. The usual concentrations of ocular cyclopentolate solutions range from 0.5% to 1%.

When ocular cyclopentolate was introduced into the clinical practice, in the early 1950s, it seemed to be virtually free of the undesirable systemic side effects frequently associated with the use of atropine in children [6]. However, during the past few decades many cases of central nervous system (CNS) disturbances have been reported in children following treatment with ocular cyclopentolate [1, 4, 13]; psychotic reactions may also occur in adults [12, 17]. Besides in the CNS, the systemic toxicity of ocular cyclopentolate may manifest in the gastrointestinal tract. Treatment with 0.5% cyclopentolate eyedrops has decreased both the secretion and the volume of gastric acid pre-term infants [9]. Even one fatality has been observed in a newborn that was given 1% cyclopentolate eyedrops [3].

Cyclopentolate is rapidly absorbed from eyedrops in adults [11]. We therefore quantitated cyclopentolate plasma levels after its ocular application to children. A control group was included for determination of the drug’s effects on heart rate and pupillary diameter.

Patients and methods

A total of 12 children (6 boys and 6 girls) hospitalized for strabismus surgery participated in the study. Written informed consent was obtained from their parents prior to the study. The study design was approved by the Ethical Committee of the University of Central Hospital of Turku. None of the eyes showed signs of conjunctival inflammation or excess tearing. The experiment was started at 8 a.m. on the day of surgery. The children received no topical or systemic medication during the 24 h prior to the trial.

After randomization, one 35-μl drop of 1% cyclopentolate (Oftan-Syklo; Leiras Pharmaceuticals Co., Tampere, Finland) or an equal volume of placebo (Balanced Salt Solution for ophthalmic use; Alcon Laboratories Inc., Fort Worth, Tex., USA) was instilled unilaterally into the lower cul-de-sac of the eye. Both the cyclopentolate and saline concentrations were determined by radioceptor assay. Measurements were performed 3 min after the eyedrop administration, and also 10, 15, 30, and 60 min later to determine the systemic absorption of cyclopentolate. The radioceptor assay was used to determine the systemic drug absorption. The level of cyclopentolate in the plasma was expressed as ng/ml; the determination was performed by a modification of the Clark and Clark method [1] using a sensitive radio receptor assay.

Table 1. Characteristics of the children in the cyclopentolate group

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>12</td>
<td>155</td>
<td>43</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>6</td>
<td>126</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>10</td>
<td>142</td>
<td>43</td>
<td>21</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>10</td>
<td>143</td>
<td>36</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>6</td>
<td>118</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>7</td>
<td>133</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td></td>
<td>9 ± 3</td>
<td>136 ± 13</td>
<td>33 ± 9</td>
<td>18 ± 2</td>
</tr>
</tbody>
</table>
Cyclopentolate and the placebo group consisted of six children. The eye-
drops were given with an adjustable Finnpipette. An antecubital
vein was cannulated and blood samples were drawn into tubes
containing ethylenediaminetetraacetic acid (EDTA) before admin-
istration of the eyedrops and at 3, 5, 8, 15, 30, 45, and 60 min
thereafter. The children remained recumbent during the experi-
ment. The body mass index (BMI) was calculated by dividing
the weight (in kilograms) by the height (in meters) squared. Char-
acteristics of the children in the cyclopentolate group are given in
Table 1. In the placebo group the mean age was 10 ± 3 years; the
mean height, 141 ± 22 cm; the mean weight, 39 ± 16 kg; and the
mean BMI, 18 ± 3 kg/m².

The heart rate was recorded simultaneously with blood sam-
ping. The pupillary size was measured before the administration
of cyclohexane and at 30 and 60 min thereafter using a plastic ruler
to estimate the mydriatic effect of cyclopentolate. The lighting
in the room was kept constant throughout the experiment. A radi-
ceptor assay originally described for ipratropium bromide in plas-
ma by Ensinger et al. [7] was used to determine the drug concen-
trations in plasma. The detection limit of the assay was 0.3 ng cy-
clopentolate in 1 ml plasma. The area under the curve (AUC) for
cyclopentolate was calculated by the trapezoidal rule. Analysis of
variance (ANOVA) for repeated-measures design and student's
paired t-test were used for statistical calculations.

Results

Cyclopentolate concentrations were below the detection
limit in the samples taken before drug application and
in all samples from the placebo group. After ocular ap-
lication, cyclopentolate rapidly appeared in blood.
With the exception of one patient, detectable drug con-
centrations were seen in the first sample at 3 min after
drug administration. At 5 min the cyclopentolate concen-
trations varied from undetectably low to 4.2 ng/ml
(median, 2.1 ng/ml). In three patients the highest drug
concentration in plasma was recorded at 5 min. In two
children the first drug concentration peak in plasma,
observed at 5 and 8 min after application (1.3 and
3.7 ng/ml, respectively), was followed by an even higher
second peak at 60 and 45 min (2.3 and 5.8 ng/ml, respec-
tively; Table 2).

The amount of cyclopentolate absorbed systemically
varied greatly between the patients. Peak drug concen-
trations in plasma ranged from undetectably low to
5.8 ng/ml (median, 2.9 ng/ml). The AUC (0–60 min) for
plasma cyclopentolate varied from 0 to 217 ng ml⁻¹ min
(median, 46 ng ml⁻¹ min). Patient 1 failed to show any
detectable drug concentration in plasma throughout the
study.

Cyclopentolate caused mydriasis in all patients, whereas
placebo had no effect (between-group difference,
P = 0.007; ANOVA for repeated-measures design).

Table 2. Cyclopentolate concentrations in plasma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time since eyedrop application (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>UD</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
</tr>
<tr>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean</td>
<td>1.1</td>
</tr>
<tr>
<td>±SD</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Cyclopentolate concentrations are expressed in ng/ml. UD, Unde-
tectable. patient 2 (mean, 3.9 ng/ml, respectively), was followed
by an even higher second peak at 60 and 45 min (2.2 and 5.8 ng/ml,
respectively; Table 2).

The amount of cyclopentolate absorbed systemically
varied greatly between the patients. Peak drug concen-
trations in plasma ranged from undetectably low to
5.8 ng/ml (median, 2.9 ng/ml). The AUC (0–60 min) for
plasma cyclopentolate varied from 0 to 217 ng ml⁻¹ min
(median, 46 ng ml⁻¹ min). Patient 1 failed to show any
detectable drug concentration in plasma throughout the
study.

Cyclopentolate caused mydriasis in all patients, whereas
placebo had no effect (between-group difference,
P = 0.007; ANOVA for repeated-measures design).

Table 2. Cyclopentolate concentrations in plasma

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time since eyedrop application (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>UD</td>
</tr>
<tr>
<td>2</td>
<td>1.1</td>
</tr>
<tr>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>4</td>
<td>0.6</td>
</tr>
<tr>
<td>5</td>
<td>2.1</td>
</tr>
<tr>
<td>6</td>
<td>0.9</td>
</tr>
<tr>
<td>Mean</td>
<td>1.1</td>
</tr>
<tr>
<td>±SD</td>
<td>0.8</td>
</tr>
</tbody>
</table>

Cyclopentolate concentrations are expressed in ng/ml. UD, Unde-
tectable. patient 2 (mean, 3.9 ng/ml, respectively), was followed
by an even higher second peak at 60 and 45 min (2.2 and 5.8 ng/ml,
respectively; Table 2).

The amount of cyclopentolate absorbed systemically
varied greatly between the patients. Peak drug concen-
trations in plasma ranged from undetectably low to
5.8 ng/ml (median, 2.9 ng/ml). The AUC (0–60 min) for
plasma cyclopentolate varied from 0 to 217 ng ml⁻¹ min
(median, 46 ng ml⁻¹ min). Patient 1 failed to show any
detectable drug concentration in plasma throughout the
study.

Cyclopentolate caused mydriasis in all patients, whereas
placebo had no effect (between-group difference,
P = 0.007; ANOVA for repeated-measures design).

The amount of cyclopentolate absorbed systemically
varied greatly between the patients. Peak drug concen-
trations in plasma ranged from undetectably low to
5.8 ng/ml (median, 2.9 ng/ml). The AUC (0–60 min) for
plasma cyclopentolate varied from 0 to 217 ng ml⁻¹ min
(median, 46 ng ml⁻¹ min). Patient 1 failed to show any
detectable drug concentration in plasma throughout the
study.

Cyclopentolate caused mydriasis in all patients, whereas
placebo had no effect (between-group difference,
P = 0.007; ANOVA for repeated-measures design).

Cyclopentolate caused mydriasis in all patients, whereas
placebo had no effect (between-group difference,
P = 0.007; ANOVA for repeated-measures design).

Cyclopentolate caused mydriasis in all patients, whereas
placebo had no effect (between-group difference,
P = 0.007; ANOVA for repeated-measures design).

Discussion

The toxic CNS symptoms associated with cyclopentolate
eyedrops often begin within the 1st h after ocular drug
application [4]. This clinical finding is in accordance
with the results of our study. Using a sensitive radiocor-
ceptor assay, we found cyclopentolate in plasma within
a few minutes after its ocular application. The time
course of the absorption in children closely resembled
that previously seen in adults [11]. We have previously
shown in adult patients that the systemic absorption of
two other anticholinergic drugs, atropine and scopol-
amine, is rapid from eye drops [14, 15].

The toxic CNS symptoms associated with cyclopentolate
eyedrops often begin within the 1st h after ocular drug
application [4]. This clinical finding is in accordance
with the results of our study. Using a sensitive radiocor-
ceptor assay, we found cyclopentolate in plasma within
a few minutes after its ocular application. The time
course of the absorption in children closely resembled
that previously seen in adults [11]. We have previously
shown in adult patients that the systemic absorption of
two other anticholinergic drugs, atropine and scopol-
amine, is rapid from eye drops [14, 15].

The exact site of the systemic absorption of topically
applied ocular drugs is not clear. Some absorption ob-
viously takes place via the capillaries within the conjunc-
tiva. In humans, the surface area of the conjunctiva is
about 17-fold that of the cornea [18], which enhances
the systemic absorption of drug in relation to its ocular
penetration. After drainage through the lacrimal sac
and nasolacrimal duct, ocular drugs could be absorbed
through the nasal mucosa or from even lower parts of
the gastrointestinal tract. By the obstruction of lacrimal
drainage, the systemic absorption of ocular timolol,
measured as the drug concentration at 60 min after eye-
drop instillation, could be reduced by > 60% [19]. We
found a mean reduction of similar magnitude when the
calculation was based on the AUC for timolol at up
to 90 min in plasma. In some subjects, however, the
initial absorption of timolol was even enhanced by lacrimal
drainage obstruction [10].

There was a marked inter-individual variation in the
magnitude and time of the peak plasma cyclopentolate
concentrations. Differences in the amount of drug reach-
ing the nasal mucosa might explain these variations. Us-
ing lacrimal scintigraphy, Chavis et al. [5] found that
the transit times of tears through the lacrimal drainage
system varied markedly, even in normal, asymptomatic
eyes. In one-third of the eyes examined, no tracer was
detected in the nose at 12 min after ocular application
[5]. The valve of Hasner has been suggested to form
a physiological obstruction at the level of the nasolacri-
mal duct, even in many asymptomatic lacrimal drainage
systems [2]. This physiological variation in the function of the lacrimal drainage system is certainly one factor explaining the interindividual variation of, or even the apparent lack of, systemic absorption of ocular cyclopentolate in our patients. The late systemic absorption of cyclopentolate in two children suggests the presence of drug, albeit without systemic absorption, in the nasolacrimal duct and its late access to the nose [16].

One eyedrop of 1% cyclopentolate did not affect the children's heart rate. A similar finding was previously reported in low-birth-weight infants, in whom no heart rate change was recorded within 1 hr after the administration of two drops of 0.5% ocular cyclopentolate [8]. Nevertheless, systemic side effects have been reported in some children following treatment with ocular cyclopentolate. Our results clearly show that the drug is rapidly absorbed into the systemic circulation from eyedrops. The development of a cyclopentolate formulation whose systemic absorption is low would increase the safety of ocular cyclopentolate therapy in children.

Acknowledgement. The expert technical assistance of Mrs. U. Heikonen is gratefully acknowledged.

References