OORSPRONKELIJKE ARTIKelen

Relative bioavailability of chloral hydrate after rectal administration of different dosage forms

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Summary

Relative bioavailability of chloral hydrate (CH) after rectal administration of different dosage forms was investigated.

Several types of rectioles and suppositories, containing 1000 mg CH each, were prepared and tested technically. For the in vivo studies the following material was chosen:

- Rectiole with CH dissolved in sesame oil, a rectiole with CH dissolved in PEG 300, a suppository with CH in Estarine D base and a suppository with CH in a base of PEG 1540/6000 (4:1). Preparation procedures are described in detail. The in vitro disintegration times were determined for the suppositories.

The dosage forms were administered to healthy, male volunteers. Blood concentrations of trichloroethanol (TCE), the active metabolite of CH, were determined at fixed time intervals by gas chromatography with electron capture detection employing head space analysis. Relative bioavailability was calculated by taking the area under the blood concentration-time curve from t = 0 to t = ∞ (AUC) and comparing it to the AUC obtained with the PEG suppository (100%). The mean value found for the suppository with Estarine D was 61%, for the PEG rectiole 84% and for the rectiole with sesame oil 60%. Consequently the lipophilic bases are found less effective CH delivery systems in comparison to the PEG bases. Absorption rates from the suppository bases were quite fast and peak levels were attained after 1/2-2 hours.

The conclusion reached was that in general practice the PEG suppository is the preferable dosage form for rectal administration of chloral hydrate.

Sammenvatting

De relatieve biologische beschikbaarheid van chloralhydraat (CH) na rectale toediening van verschillende doseerformen werd onderzocht. Verscheidene soorten rectioles en zetpillen (1000 mg CH) werden bereid en aan een serie proefnemingen onderworpen voor de in vivo studies. De in-vitro-proeven werden de volgende preparaten gekozen: een rectiole met CH opgelost in sesamolie, een rectiole met CH opgelost in polyethylenglycol (PEG) 300, een zetpil met CH in Estarine D en een zetpil met CH in PEG 1540/6000 (4:1). Bijzonderheden over de bereidingswijze worden in dit artikel beschreven. Van de zetpillen werd de uiteenvatting in vitro bepaald.

De doseerformen werden toegediend aan gezonde vrijwilligers van het mannelijk geslacht. De concentraties in het bloed van trichloorethanol (TCE), de werkzame meta-

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Introduction

Chloral hydrate has been used for more than a century in hypnotic and sedative drug therapy. It is considered as a relatively effective and safe sleep-inducing agent (Sharpless, 1970). After oral administration of the drug in water solution, rapid absorption from the gastrointestinal tract takes place (Marshall and Owens, 1954). However, the compound is irritating to the gastric mucosa and sometimes causes nausea and vomiting (Martindale, 1972). Therefore it is generally recommended to administer the drug orally, well diluted with water or milk. Another possibility to avoid this unwanted side effect is to give the drug rectally in solution (enema) or in a suppository. This route is also advantageous in children and infants as it avoids the irritant and bad taste of oral preparations. Infantile convulsions are being treated effectively in this way (Loevelt de Haas and Noach, 1968).

Despite the widespread use of rectal application of chloral hydrate no data on the effectiveness of rectal absorption or on the bioavailability have appeared so far. The purpose of this investigation was to study the absorption
of chloral hydrate by the rectal route. Four different pharmaceutical formulations, two types of suppositories and two types of enemas were chosen to measure the relative bioavailability and absorption rate and to establish the influence of vehicle composition. As chloral hydrate (CH) is very rapidly reduced to trichloroethanol (TCE) in the body (Butler 1948; Marshall and Owens 1954), so that no unchanged CH can be measured (Breimer et al. 1973), the TCE blood concentration is determined. The absorption of CH is slower than the conversion of chloral hydrate into TCE and therefore the initial rise of TCE blood concentration reflects very well the absorption rate of chloral hydrate. Bioavailability calculation is also based on TCE blood concentrations.

**Choice of Dosage Forms**

A review of various dosage forms for rectal administration of chloral hydrate (CH) has been previously published in this journal (Cox 1971). These dosage forms have been compared on the basis of the requirements as far as data were available at that time.

For the present study CH enemas (rectioles) were prepared containing 1000 mg CH per 3 ml dissolved in sesame oil or dissolved in polyethylene glycol (PEG) 300. The method of preparation was that described by Cox (1971).

Secondly, suppositories containing 1000 mg CH were prepared for the present study. For CH suppositories a fatty base (Gstirner 1960) or a PEG base (Union Carbide Chemicals Comp. 1962) are generally used. As CH is more or less soluble in the base, resulting in a decrease of the melting point, the preparation of suppositories containing 1000 mg CH often gives rise to difficulties, especially if this amount is to be incorporated into a fatty base. In addition, the possibility of crystallization of CH has to be taken into account.

For the preparation of suppositories with CH in a fatty base, different types of bases were used, separate or in combination, each containing a mixture of mono-, di- and triglycerides of saturated fatty acids, but with different melting ranges (Estarine BC, Estarine C, Estarine D; melting range resp. 33.5-35.5°C, 36-38°C, 40-42°C). An attempt was made to find an easily reproducible method of preparation for this type of suppositories, with CH either suspended or dissolved in the base. For suspension-suppositories sufficiently fine particles were obtained by grinding the crystals down, after mixing with 0.5% colloidal silica (Aerosil 200), and passing the mixture through a sieve with 150 μm mesh length. The powder was mixed with the melted base (temperature just above the melting point in order to prevent substantial dissolution of CH in the base) and then the mass was poured into moulds. After the preparation of solution-suppositories the mass was examined through a microscope for CH crystallization. Also the weight-ratio between CH and base was varied by using 2.25 and 2.85 ml moulds.

With suspension-suppositories of 2.85 ml an attempt was made to stabilize the suspension by adding up to 2% colloidal silica. It turned out, however, that suppositories of passable hardness were obtained only by dissolving CH in Estarine D up to 2.85 ml. At room temperature it takes about 2 hours to reach this hardness. Crystallization of CH in this base could not be excluded with certainty.

For the preparation of suppositories with CH in a PEG base, the following bases, separate or in combination, were tested: PEG 1540, PEG 4000, PEG 6000 and hexane-1,2,6-triol. CH dissolved rapidly and completely in the melted bases. An easily reproducible method was sought for the preparation of suppositories with CH dissolved in a suitable base which were sufficiently hard and nevertheless had a short disintegration time in water at 37°C. The congealed mass was also examined for CH crystals. The weight-ratio between CH and base was varied by using 2.25 ml and 2.85 ml moulds. It turned out that suppositories with satisfactory hardness and with the shortest disintegration time in vitro, were obtained by using a combination of 4 parts PEG 1540 and 1 part PEG 6000 and 2.85 ml moulds. At room temperature it took about 2 hours to achieve this hardness. Crystallization of CH could not be definitely excluded with certainty.

Both types of rectioles and suppositories can be kept at room temperature for at least 2 months. Results of an initial investigation on the stability are published elsewhere in this journal (Cox 1973).
EXPERIMENTAL

Materials
Chloralhydrate (ch) and Sesame Oil (so) used in this study were of Dutch Pharmacopoeia vi grade.
Polyethylene Glycol 300 (Jefferson, Houston, USA).
Polyethylene Glycol 6000; Carbowax 6000 (Union Carbide Chemicals Company, Division of Union Carbide Corporation, New York, N.Y. 17, USA).
Polyethylene Glycol 1540 (Hoechst, Germany).
Estarine D (Edelfettwerke Werner Schlüter, Hamburg-Eidelstedt, Germany). Specification supplied by the manufacturers: melting range 40-42°C, congealing range 38-40°C, specific gravity at 20°C: 0.955-0.975, iodine number less than 3, saponification value 220-230, hydroxyl value 30-40.

Preparation of dosage forms

Chloral Hydrate Sesame Oil Rectiole 1000 mg (CH-so rectiole)
Chloral Hydrate 1.10 g
Sesame Oil (2.16 g) to make 3.0 ml
Powder ch in a wedgewood mortar. Dissolve the powder in so in a stoppered glass container heating gently. Cool down to room temperature. Fill into the rectiole. Screw the canula until it fits tightly.

Chloral Hydrate Polyethylene Glycol Rectiole 1000 mg (CH-PEG rectiole)
Chloral Hydrate 1.10 g
Polyethylene Glycol 300 (2.67 g) to make 3.0 ml
Preparation as with CH-so rectioles.
The rectioles contain 100 mg of CH in excess, as it was estimated that this is about the amount which is left behind after administration.
Protect rectioles from light.

Chloral Hydrate Estarine D Suppository 1000 mg (CH-Est. D suppository)
Chloral Hydrate 1.00 g
Estarine D 2.20 g
Powder ch in a wedgewood mortar. Dissolve the powder in Estarine D heated to 50-70°C in a stoppered glass container. Cool down to about 35°C and pour the mass into a 2.85-ml plastic mould.

Chloral Hydrate Polyethylene Glycol Suppository 1000 mg (CH-PEG suppository)

Preparation as with CH-Est. D suppositories.
Plastic suppository moulds have to be used because metal will be affected by CH.
Protect suppositories from light.

The content of the preparations used for this study was determined according to a modified method described by Schoorl (1929).
CH-so rectioles and CH-PEG rectioles of 1.1 g contained 100% and 101% respectively; CH-Est. D suppositories and CH-PEG suppositories of 1 g contained 96% and 102% respectively.

Determination of the disintegration time of the suppositories
The test has been performed using an Erweka Test Apparatus for suppositories being a part of the Erweka ‘All Purpose Disintegration Tester Type Z T 2’.
10 ml water of 37°C was put into a polyethylene bag (100 x 50 mm) and then the suppository was added. The bag was moved up and down with the aid of the apparatus in a waterbath of 37°C over 22 mm height between two horizontal sticks at 3 mm distance. The time elapsing until the suppository was completely melted was determined or, at a fixed moment, the fraction that had not yet liquified was determined by weighing.

In vivo studies
Dosage forms were used 2-6 weeks after preparation.
The subjects were male healthy volunteers, mainly medical students, ranging in age from 20-25 years and in weight from 75-83 kg. They had not taken any regular medication during the 4 weeks preceding initiation of the study. The subjects had been fasting overnight prior to the experiments and for 3½ hours after administration of the drug. At 9.00 A.M. the CH dosage form was introduced into the rectum and blood samples were taken from a forearm vein at ½, 1, 1½, 2, 3, 5, 7, 9 and 12 hours after administration. (Sometimes a sample was omitted due to organization problems.) The blood was drawn in tubes containing a small
drop of heparin solution as anticoagulant. There was in no instance early removal of the rectum contents by defaecation. For those subjects who participated twice in the investigation, there was at least an interim of 7 days between the two consecutive experiments.

**Determination of TCE in blood by head space analysis**

Immediately after taking the blood and mixing with heparin, 1.0 ml of whole blood was introduced into a 25.0-ml glass vial, containing 1 ml of lead acetate solution. This compound prevents the in vitro conversion of unchanged CH into TCE. The vial was equipped with a self-sealing silicon rubber cap and put into a water-bath (60°C) until equilibrium was reached between vapour and liquid phase. With a gas-tight Hamilton syringe a known amount of the head space vapour was taken and injected into a gas chromatograph with 63Ni-electron capture detection [Hewlett & Packard Model 402, column 1.80 m, i.d. 3 mm, Gas Chrom Q (80-100 mesh), 10% OV-17, 125°C]. The detector response was measured by peak height and the concentration was calculated by means of calibration curves. A typical gas chromatogram of TCE obtained by this procedure is shown in Figure 1. Details of the analytical procedure for the simultaneous determination of CH, TCE, TCE glucuronide and trichloroacetic acid in biological samples using head space analysis, will be published elsewhere (Breimer et al. 1973).

Sensitivity obtained for TCE in blood by this procedure is 0.5 mg/liter blood.

**Results**

The individual curves obtained are shown in Figure 2 (suppositories) and Figure 3 (rectioles). Unfortunately two subjects in the study with the rectioles and one with the suppositories were not able to participate more than once in the study. In Figure 4 the curves per individual, who received two different dosage forms, are given.

**Absorption rate**

There is quite a variation in absorption rates and plasma levels between the individuals per dosage form. Between lipophilic bases and PEG bases there are great differences in concentration values. A rapid initial rise in TCE concentration occurred in all subjects receiving a suppository. Absorption is fast and peak concentrations are reached between ½ and 2 hours after administration. If absorption is regular and takes place according to a first order process, as is often the case, the half life of absorption (t½) is characteristic for the absorption rate or rate of availability. In Figure 5 an example is given for chloral hydrate. The dose, the t½ and t½el determine the tmax and Cmax, which can be calculated.

However, a careful analysis of the concentrations in the first few hours reveals that in most cases the absorption process cannot be described accurately by a first order kinetic process, and therefore it seems ill-advised to calculate these parameters. Consequently one can obtain only
an overall impression of the time necessary to reach the maximum concentration. It seems that both suppository bases are able to deliver the drug with approximately the same rate to the blood stream. With the rectioles there appears also to be rapid absorption in two subjects receiving the PEG rectiole, while in the other cases absorption is slower and takes place over a longer period of time. Although hardly any conclusion can be drawn on the basis of only two observations, the slow absorption from the SO rectiole is striking.
Relative bioavailability
Bioavailability refers to the fraction of the dose of a drug administered that reaches the general circulation intact. In the case of chloral hydrate the amount becoming available is related to TCE, as this is the compound measured in vivo.

The following may be derived:

\[ F \times D = k_{el} \int C \, dt = k_{el} \cdot AUC \]

in which:
- \( F \) = bioavailability (0 \( \leq \) \( F \) \( < \) 1),
- \( D \) = dose administered,
- \( C \) = blood or plasma concentration.
- \( k_{el} \) = total body clearance constant,
- \( AUC \) = area under the plasma concentration-time curve from \( t = 0 \) to \( t = \infty \).

The \( k_{el} \) of TCE can be determined only after intravenous administration and therefore the absolute bioavailability cannot be determined if only rectal data are available. Moreover, the dose in this case is related to chloral hydrate and not to TCE, so that the fraction of the dose that is converted to TCE also remains uncertain.

However, it is a reasonable assumption that in the same individual this fraction is constant and also that \( k_{el} \) for TCE remains constant. Then the relative bioavailability of chloral hydrate from a certain dosage form (I) can be determined by comparison to a reference dosage form (II) in the same subject.

The following now applies:

\[ F_{rel} = \frac{AUC_I}{AUC_{II}} \]

If the \( AUC \) is not determined to \( t = \infty \), then it must be corrected to include the undetermined \( AUC \). This is quite possible assuming that at the last data point, at time \( t = t' \), absorption has been completed, using Dost's law of corresponding areas (Dost 1968). The infinite area is given by

\[ \int_0^\infty C \, dt = \int_0^{t'} C \, dt + \int_{t'}^\infty C \, dt = AUC + C' \cdot t_{el} \]
in which \( \tau_{el} \) is the overall elimination time constant and \( C'' \) the last blood concentration measured for the determination of \( AUC \).

The \( AUC \)'s in the experiments of this investigation were determined by weighing the corresponding areas under the blood concentration-time curves up to 12 hours after administration. The remaining area was calculated by multiplying the concentrations at 12 hours by the overall elimination time constant \( \tau_{el} \). Because of irregularities in absorption it was not possible to determine an exact \( \tau_{el} \) (\( \tau_{el} = 1.44 \times t_{\frac{1}{2}} \)) in each subject and it was decided to take one value for all individuals: \( t_{\frac{1}{2}} = 10 \) hours \( \rightarrow \tau_{el} = 14.4 \) hours (Fig. 5). Results per individual will hardly be influenced by this assumption.

In Table 1 the results are given for the five subjects to whom two dosage forms were ad-

![Chloralhydride 1000 mg rectal supp. PEG](image)

**Fig. 5.** Blood concentration curve of TCE on semi-logarithmic scale following rectal administration of 1000 mg CH in a PEG suppository. From the descending part of the curve the elimination half life can be determined. The dotted line represents the absorption rate process. Apparently there is no lag time.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Dosage form</th>
<th>Dose (mg)</th>
<th>Dose/kg</th>
<th>AUC 0-12 hr (mg.hr/l)</th>
<th>conc. 12 hr (mg/l)</th>
<th>( \int_0^{\infty} C , dt ) (mg.hr/l)</th>
<th>Total ( AUC ) (mg.hr/l)</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P.W.</td>
<td>20</td>
<td>75</td>
<td>supp. PEG</td>
<td>1000</td>
<td>13.3</td>
<td>36.5</td>
<td>2.31</td>
<td>33.3</td>
<td>69.8</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>supp. Est. D</td>
<td>1000</td>
<td>13.3</td>
<td>22.2</td>
<td>1.30</td>
<td>18.7</td>
<td>40.9</td>
<td>59</td>
</tr>
<tr>
<td>G.E.</td>
<td>22</td>
<td>82</td>
<td>supp. PEG</td>
<td>1000</td>
<td>12.2</td>
<td>51.8</td>
<td>2.90</td>
<td>41.8</td>
<td>93.6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>supp. Est. D</td>
<td>1000</td>
<td>12.2</td>
<td>20.1</td>
<td>1.18</td>
<td>17.0</td>
<td>37.1</td>
<td>40</td>
</tr>
<tr>
<td>H.H.</td>
<td>22</td>
<td>75</td>
<td>supp. PEG</td>
<td>1000</td>
<td>13.3</td>
<td>41.0</td>
<td>2.60</td>
<td>37.4</td>
<td>78.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>supp. Est. D</td>
<td>1000</td>
<td>13.3</td>
<td>32.5</td>
<td>2.31</td>
<td>33.2</td>
<td>65.7</td>
<td>84</td>
</tr>
<tr>
<td>K.S.</td>
<td>21</td>
<td>67</td>
<td>rect. PEG</td>
<td>1000</td>
<td>14.9</td>
<td>45.4</td>
<td>3.40</td>
<td>49.0</td>
<td>94.4</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rect. SO</td>
<td>1000</td>
<td>14.9</td>
<td>27.2</td>
<td>1.43</td>
<td>20.6</td>
<td>47.8</td>
<td>51</td>
</tr>
<tr>
<td>W.B.</td>
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<td>83</td>
<td>rect. PEG</td>
<td>1000</td>
<td>12.0</td>
<td>33.4</td>
<td>2.40 (9 hr)</td>
<td>34.6</td>
<td>68.0</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>rect. SO</td>
<td>1000</td>
<td>12.0</td>
<td>19.6</td>
<td>1.61 (9 hr)</td>
<td>23.2</td>
<td>42.8</td>
<td>63</td>
</tr>
</tbody>
</table>

108-1973 *Pharmaceutisch Weekblad*
ministered. In all cases the PEG vehicles resulted in a higher bioavailability and they were considered as the reference dosage form.

These data show clearly a lower bioavailability per individual of the suppositories with Estarine D and the rectioles with sesame oil. The oily vehicle for the rectal administration of chloral hydrate seems to be an inferior delivery system compared to the hydrophilic PEG system.

In Figure 6 the mean plasma concentration curves for all four dosage forms are given and their bioavailability is calculated relative to the PEG suppository (Table II). Although the number of subjects is limited the conclusion may be drawn that the suppositories and rectioles with PEG are both quite efficient, whereas the Estarine D and sesame oil are both unsatisfactory. These data confirm the results in the individual subjects.

Disintegration in vitro
Disintegration of the CH-Est. D suppository means melting as the base is not water-miscible. Disintegration of the CH-PEG suppository is a combination of melting and dissolving in water. When trying to imitate in vitro the disintegration in vivo one has to use a limited amount of water, in accordance with the situation in vivo, to get

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**Table II** (mean values)

<table>
<thead>
<tr>
<th>No. subjects</th>
<th>Dosage forms</th>
<th>Dose</th>
<th>Dose/kg</th>
<th>AUC 0-12 hr</th>
<th>Conc. 12 hr</th>
<th>( \int C , dt )</th>
<th>Total AUC</th>
<th>F (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>supp. PEG</td>
<td>1000</td>
<td>13.7</td>
<td>44.4</td>
<td>2.62</td>
<td>37.7</td>
<td>82.1</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>supp. Est. D</td>
<td>1000</td>
<td>12.9</td>
<td>27.1</td>
<td>1.60</td>
<td>23.0</td>
<td>50.1</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>supp. PEG</td>
<td>1000</td>
<td>14.3</td>
<td>38.6</td>
<td>2.31</td>
<td>30.7</td>
<td>69.3</td>
<td>84</td>
</tr>
<tr>
<td>2</td>
<td>rect. so</td>
<td>1000</td>
<td>13.5</td>
<td>23.7</td>
<td>1.78 (9 hr)</td>
<td>25.6</td>
<td>49.3</td>
<td>60</td>
</tr>
</tbody>
</table>

---

Fig. 6. Average TCE blood concentration curves after rectal administration of the four dosage forms
comparable results. The method used fulfils this requirement (10 ml). The liquified PEG is not completely miscible with the amount of water available.

The disintegration time for CH-Est. D suppositories was 6 minutes. This value had not changed significantly after storage for two months at room temperature. 50% of CH-PEG suppositories liquified in 10 minutes and 90% in 30 minutes. After storage for 6 months at room temperature these values were unchanged.

**DISCUSSION AND CONCLUSION**

The design and purpose of the study were for practical reasons very simple: comparison of the same dosage form, but with two different vehicles, in the same subject after rectal administration. This allows relative bioavailability measurement per individual under the assumptions mentioned. Unfortunately some of the volunteers were not able to participate in the study for a second time, so that only part of the design of the experiments could be realized. Nevertheless the results are sufficiently important to be reported, although the conclusions drawn must be considered against the background of a limited number of observations.

Some individual curves are given in Figure 4. Representation of the results in this way immediately gives an impression of the differences between dosage forms.

It is also important to give all the individual curves as this gives insight into the variability between different individuals. The differences are quite great as can be seen from Figure 2 and Figure 3. Often in the literature only the mean data are reported and these are then treated mathematically. The results of such a manipulation are given in Figure 6 and it may be noted that smoother curves are obtained in this way. Irregularities in absorption are not reflected in these mean curves, whereas they are obvious from the individual ones. Information is therefore lost by giving only mean values.

The results indicate a poor bioavailability of chloral hydrate from the lipophilic vehicles sesame oil and Estarine D, compared to the hydrophilic PEG. The fraction absorbed from PEG bases is about the same as obtained after oral administration of CH in a mixture (Breimer et al. 1973).

The reason for these differences is not clear: in the rectioles and probably also in the suppositories chloral hydrate is dissolved in the vehicle; consequently the differences cannot be due to particle size. Chemical incompatibilities with chloral hydrate are reported for many substances including sesame oil, Carbowax (a PEG brand) (Fairbrother 1973) and the suppository bases Witepsol and Imhausen (Petricič and Jalsenjak 1971) which are chemically related to Estarine D. It seems likely that 'chemical incompatibility' influences the extent of CH release from the different bases to varying degrees, probably depending on the nature of interaction between CH and the base. The in vitro disintegration results of the suppositories do not give any further explanation. On the contrary, as far as disintegration is concerned the in vitro results do suggest a better absorption from the lipophilic base.

Another important factor is the rate at which the active compound becomes available in the general circulation. Careful analysis of the concentrations in the first few hours reveals that in most cases the absorption cannot be described accurately by a first order kinetic process. Figure 5 is given merely as an example. One can obtain an overall impression of the time necessary to reach the maximum concentration. This seems to be shortest for PEG suppositories and longest for so rectioles. The absorption rate of PEG suppositories is indeed lower than after oral administration in a mixture. However, it is much higher than after administration of Chloraldurat Red capsules intended as a sleep-inducing dosage form (Breimer et al., to be published).

Central nervous system (CNS) depressant effects after administration of chloral hydrate in these dosage forms are difficult to assess objectively as the subjects received the drug in the morning, just after waking up. In general there was no evident feeling of CNS depression. However, two subjects (W.B., Fig. 3 and G.E., Fig. 2) did report subjective feelings of drowsiness at the time of peak concentration (8.5 and 7.5 mg/l respectively).

Generally there were no complaints about irritation of the rectum after administration of
the dosage forms and as already mentioned in no subject was the defaecation reflex initiated. To one subject, who was suffering from haemorrhoids, the Estarine D suppository was irritating while the PEG suppository was not.

Of the dosage forms we investigated in this study, rectioles and PEG suppositories are the easiest to prepare. From the stability point of view, so rectioles and PEG suppositories are preferable. The quantity administered, using the rectioles, is probably less exact.

As appears from the results of this study PEG suppositories are the best as far as absorption rate and bioavailability are concerned. If, moreover, PEG suppositories cause no irritation of the rectum this dosage form is preferable. By using this dosage form in children instead of the usual so rectioles, perhaps the dose can be reduced.

Acknowledgements
The technical assistance of Miss G. Freeke and Miss A. A. Ramondt in preparing and in vitro testing of the dosage forms, of Miss A. M. Slakhorst for the determination of the TCE blood concentrations and of Mrs. C. P. W. G. M. Verweij-Van Wissem for carefully taking the blood samples, is gratefully acknowledged. This investigation was supported in part by a grant from the Netherlands Organization for Medical Research Fungo.

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