Experimental studies

Excitative effects in anaesthetized rabbits from subarachnoidally injected iso- and hyperosmolar solutions of iohexol and metrizamide*

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Summary. Equimolar doses of iohexol and metrizamide (0.48 mmol/kg body weight = 185 mg I/kg), administered in solutions iso- and hyperosmolar to the CSF, were injected subarachnoidally into rabbits under pentobarbital anaesthesia. No excitative effects of iohexol were observed in the behaviour of the rabbits during a 3-h period immediately after the injection. Metrizamide caused significant, severe excitative effects, ranging from hyperexcitability to repeated generalized seizures. The frequency and severity of excitative effects were independent of the osmolality of the metrizamide solutions injected.

Key words: Contrast media - neurotoxicity - chemotoxicity - osmolality - subarachnoid injection

Introduction

Iohexol (Omnipaque®) – a monomeric non-ionic contrast medium – is presently being clinically tested for myelography. After injections into the subarachnoid space of animals, iohexol has been shown to cause significantly fewer and less severe adverse reactions than metrizamide, iopamidol, and ioglu- nide (P297) [1-4]. After subarachnoid administration of iohexol, no paroxysmal EEG activity, seizures, or excitative effects on animal behaviour have been reported.

Large doses of hyperosmolar contrast media had to be used in these studies to produce the adverse reactions at a higher frequency than they occur clinically. Hyperosmolality alone may, however, decrease the irritative effects of contrast medium molecules on electrophysiologic events in the central nervous system (CNS) [5, 6]. Thus, it is important to exclude the possibility that some superimposed depressive effect of hyperosmolality could have been responsible for the total absence of excitative effects of iohexol in the above-mentioned animal experiments.

The aim of the present study was to investigate whether hyperosmolality or a large volume of contrast medium solution injected into the subarachnoid space increases or decreases the excitative effects that are produced by contrast medium molecules. Excitative effects were evaluated for 3 h in rabbits injected subarachnoidally with iso- and hyperosmolar solutions of iohexol and metrizamide. It was desirable to preserve a hyperosmolar contrast medium bolus within the intracranial subarachnoid space for as long a period as possible. Therefore the animals were anaesthetized in order to prevent movements that might accelerate mixing and dilution of the contrast medium bolus by the cerebrospinal fluid (CSF).

Material and methods

Fifty-two albino rabbits (Swedish Land) of both sexes weighing 1.1–2.2 kg (median 1.3 kg) were used for the investigation. Rabbits with blood-stained CSF after the puncture or those with a subdural deposition of contrast medium were excluded and replaced (totally 18 rabbits).

During the entire experiment, which lasted for 3 h, the animals remained under light intravenous pentobarbital anaesthesia (Mebumal®) with the corneal reflex preserved. No puncture of the subarachnoid space was performed on the 7 rabbits in the control group. The remaining 45 rabbits, after
Table 1. Scores of excitative effects caused by subarachnoid injection of equimolar doses of iohexol and metrizamide per kg body weight in rabbits anaesthetized with pentobarbital

<table>
<thead>
<tr>
<th>Contrast medium</th>
<th>Control</th>
<th>Iohexol</th>
<th>Iohexol</th>
<th>Metrizamide</th>
<th>Metrizamide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration (mg I/ml)</td>
<td>-</td>
<td>144</td>
<td>370</td>
<td>166</td>
<td>370</td>
</tr>
<tr>
<td>Osmolality (mmol/kg H₂O)</td>
<td>-</td>
<td>300</td>
<td>980</td>
<td>300</td>
<td>580</td>
</tr>
<tr>
<td>Dose (ml/kg animal)</td>
<td>-</td>
<td>1.28</td>
<td>0.50</td>
<td>1.11</td>
<td>0.50</td>
</tr>
<tr>
<td>Dose (mmol/kg animal)</td>
<td>-</td>
<td>0.48</td>
<td>0.48</td>
<td>0.48</td>
<td>0.48</td>
</tr>
<tr>
<td>No. of animals</td>
<td>7</td>
<td>10</td>
<td>15</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Excitation score

| Score | 0- No effect | 1- Hyperexcitability: a slight touching of the animal evoked a muscular response of abnormal intensity | 2- Spontaneous jerks with the head or local muscular twitching | 3- One generalized seizure or myoclonic jerks of the whole body | 4- More than one generalized seizure, recovery within 3 h | 5- Many seizures without recovery within 3 h |
|-------|--------------|---------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|----------------------------------------------------------|

anaesthetization, were fixed in the right decubitus position with a belt around the pelvis on a plexiglass table with the head end lowered 40° to ensure replacement of the CSF within the intracranial subarachnoid space by the hyperbaric contrast media solutions. A suboccipital puncture of the cisterna magna was performed with a 25-gauge needle (Butterfly®, Abbott A.B.) and, after achieving a free flow of clear CSF from the needle, contrast medium was injected with an infusion pump at a rate of 0.4 ml/min. Both contrast media – iohexol and metrizamide – were injected in solutions iso-osmolar to CSF (144 and 166 mg I/ml, respectively) and in hyperosmolar solutions (370 mg I/ml) at volumes adjusted to ensure that the rabbits received the same number of contrast medium molecules per kg of body-weight, i.e., 0.48 mmol contrast medium/kg.

Except for the 7 animals in the control group, the rabbits were randomly injected with the following contrast media preparations: iso-osmolar iohexol (10 animals, 144 mg I/ml, 1.28 ml/kg), hyperosmolar iohexol (15 animals, 370 mg I/ml, 0.5 ml/kg), iso-osmolar metrizamide (10 animals, 166 mg I/ml, 1.11 ml/kg), hyperosmolar metrizamide (10 animals, 370 mg I/ml, 0.5 ml/kg), (Table 1).

During the contrast medium infusion, one series of films was exposed in submento-vertical projection over the head and in antero-posterior projection over the spine using an AOT film changer (Siemens-Elema A.B.) and a 0.1 mm focal spot to study the replacement of the CSF by contrast medium within the subarachnoid space. Following completion of the infusion, a lateral roentgenogram of the head and spine was made and studied immediately to exclude those animals in which the contrast media were deposited subdurally. The animals were then placed in the right decubitus position with the head at the same level as the spine for behavioural observations.

Signs of excitation in animal behaviour were observed during a 3-h period after the injection of the anaesthetic in the control group or of the contrast medium in the remaining anaesthetized animals. The observer had no knowledge of the suboccipital puncture and/or of the contrast medium preparation injected. Limb jerks were noted and recorded with respect to side difference (right or left). The excitative effects were ranked according to a predetermined scoring system:

**Excitation Score**

0- No effect
1- Hyperexcitability: a slight touching of the animal evoked a muscular response of abnormal intensity
2- Spontaneous jerks with the head or local muscular twitching
3- One generalized seizure or myoclonic jerks of the whole body
4- More than one generalized seizure, recovery within 3 h
5- Many seizures without recovery within 3 h

Statistical analysis of the scores obtained was performed with the two-sided Wilcoxon rank sum test. *P* < 0.05 was considered a level of significance.