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Serial Number: 07/765,615
Date Filed: September 25, 1991
INTRANASAL SCOPOLAMINE PREPARATION AND METHOD

This invention relates to a new method and preparation for intranasal delivery of scopolamine and provides a safe and effective treatment for motion sickness and other conditions requiring anticholinergic therapy.

The new method and preparation has been found superior to the prior alternative drug delivery systems. The intranasal delivery is usually by nose drops, nasal mist spray as a metered dosage delivery, or aerosol mist, although gel or ointment preparations can be made. The intranasal delivery provides high bioavailability without the drawback of drug induced amnesia by intravenous delivery. The intranasal delivery can be performed by the patient without the necessity for an invasive intravenous administration. The intranasal preparation is inexpensive to formulate in multiple dose quantities as needed by the patient.

Scopolamine is prepared in a buffered saline solution at the desired dosage rate for effective anticholinergic response. A dose of 0.4 mg is a satisfactory rate. Doses up to at least 0.6 mg may be used. The solution is adjusted to pH 4±0.2. This formulation may be modified into other forms by adaptations known by those skilled in the art of pharmaceutical preparations. The scopolamine formulation is a nonirritant solution to the nasal cavity. The preparation requires no special storage conditions or formulation equipment.

Inventors: Lakshmi Putcha and Nitza M. Cintron
Employer: NASA Johnson Space Center
Evaluator: Deborah L. Harm, Ph.D.
INTRANASAL SCOPOLAMINE PREPARATION AND METHOD

**Origin of the Invention**

The invention described herein was made by employees of the United States Government and may be manufactured and used by and for the Government of the United States of America for governmental purposes without payment of any royalties thereon or therefor.

**Field of the Invention**

The invention is a highly effective preparation and method of administering scopolamine with an intranasal dosage. Scopolamine is an anticholinergic and is used as a treatment for motion sickness, as a pre-operative drug to inhibit body secretions and for other disorders requiring anticholinergic therapy. The intranasal dosage is more effective than oral doses and safer and easier to administer than intravenous doses.

**Background of the Invention**

Scopolamine is an anticholinergic agent which affects the parasympathetic nervous system. Anticholinergics are well known and understood by pharmacologists and are substances that inhibit and have a highly selective blocking action on effector organs innervated by postganglionic cholinergic nerves. This nervous system controls bodily secretions such as saliva and digestive juices. Scopolamine has known antiemetic and antinausent properties and has been used to treat motion sickness by oral administration and topical patch. Also, scopolamine is used as a preoperative treatment, generally administered intravenously, to inhibit secretions during anesthesia and surgery.
When administered orally, the bioavailability of scopolamine is significantly diminished because it is broken down by the liver. The intravenous administration of scopolamine has drawbacks, because although the bioavailability is high, the large dose can cause drug induced amnesia in the patient. Alternative routes of scopolamine administration have been explored including skin patches and buccal absorption. The skin patch technique is exemplified in U. S. Patent Nos. 4,262,003 and 4,436,741, both issued to Urquhardt et al. on April 14, 1981 and March 13, 1984, respectively. The patch effects transdermal absorption of the drug, and the patient is recommended to apply the patch about 3 hours prior to need. However, some studies have indicated that transdermal scopolamine must be used 8 hours prior to need. The manufacture of the patch is expensive adding cost to the administration of the drug. Buccal administration has also been used and, although individual absorption rates of scopolamine vary greatly, the individual adsorption by buccal and oral ingestion is not significantly different.

Summary of the Invention

A new method and preparation for scopolamine for intranasal delivery has been developed and found superior to the prior alternative drug delivery systems. The intranasal delivery is usually by nose drops, nasal mist spray as a metered dosage delivery, or aerosol mist, although gel or ointment preparations can be made. The intranasal delivery provides high bioavailability without the drawback of drug induced amnesia by intravenous delivery. The intranasal delivery can be performed by the patient without the necessity for an invasive intravenous
administration. The intranasal preparation is inexpensive
to formulate in multiple dose quantities as needed by the
patient.

Scopolamine is prepared in a buffered saline solution
at the desired dosage rate for effective anticholinergic
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justed to pH 4 ± 0.2. This formulation may be modified
into other forms by adaptations known by those skilled in
art of pharmaceutical preparations. The scopolamine
formulation is a nonirritant solution to the nasal cavity.
The preparation requires no special storage conditions or
formulation equipment.

**Brief Description of the Drawing**

Figure 1 is a comparison of bioavailability and
effect of scopolamine by intranasal and oral dosage.

**Detailed Description of the Invention**

The scopolamine or the salts of scopolamine are mixed
in an aqueous buffered solution. The formulation can be
used directly as nasal drops or packaged as a spray mist
with a metered delivery dosage with an appropriate vehi-
cle. Also, the formulation can be adapted for use as an
ointment, gel, or any other viscous delivery systems for
intranasal use. The invention generally involves the
effective delivery of scopolamine to the intranasal tis-
sue. Other intranasal preparations may be known and
developed by those skilled the art and not depart from the
disclosure, method or preparation of this invention.

An exemplary formulation includes the following
ingredients, prepared in the following manner. There are
known substitutions and equivalents to the ingredients
that may be used. A methylcellulose vehicle was prepared
by dissolving 20 mg of the methylcellulose in 800 ml of
sterile sodium chloride 0.9% and stirred until dissolved. To the methylcellulose vehicle 75 ml of the bacteriocide benzalkonium chloride 1:750 aqueous solution was added. Then 4000 mg of scopolamine hydrobromide was added by stirring until dissolved. The pH was adjusted to 4 ± 0.2 with 1:100 phosphoric acid buffer. The final volume was made up to 1000 ml with 0.9% sodium chloride. The dose amount is 0.4 mg scopolamine HBr per 0.1 ml 0.9% NaCl. This preparation has a long shelf life and does not require special storage conditions.

The formulation may be prepared with a dosage of 0.4 mg to at least 0.6 mg. The aqueous formulation may be used directly as nose drops and are nonirritant to intranasal tissue.

The therapeutic effectiveness of a medication is a function of its bioavailability after administration. The bioavailability of scopolamine by oral dosage was compared to intranasal dosage. In addition, scopolamine was administered intravenously. For the test, 0.4 mg of scopolamine was administered intravenously, orally, and intranasally to 12 healthy male subjects in a randomized crossover design test. Each treatment was two weeks apart.

Subjects fasted for 10 to 12 hours before scopolamine administration. Water was allowed ad libitum except for the period from three hours before to one hour after dosing. An Intracath® I.V. was placed in the antecubital vein of the subjects for blood sampling. Saliva samples were collected using Sarstedt salivettes. The samples were collected 2.5, 5, 10, 20, 30, 45, 60, 120, 240, 300, 360, 480, 600, and 720 minutes after administration of the designated dosage form.

Plasma levels of scopolamine were determined by combined reverse-phase liquid chromatography and radioreceptor assay. Area Under the Concentration Curve (AUC) was calculated from plasma concentration - time.
data. Salivary volume and pH were measured, and salivary flow rate (SFR) was calculated for each sample. The salivary gland secretions are inhibited by anticholinergic agents. Percent suppression of control effect and Area Under the Effect Curve (AUEC) were calculated from SFR-time data. Absolute bioavailability of intranasal and oral doses were calculated from the respective AUCs and AUECs.

TABLE 1 below is a summary of the data for each of the subject's scopolamine bioavailability calculated from plasma data showing the significant contrast between oral delivery characterized by low to negligible bioavailability and intranasal with high bioavailability. The data is summarized with mean and the standard error of the mean.

**TABLE 1**  
**AREA UNDER PLASMA CONCENTRATION (AUC)**  
Time Curve of Scopolamine  
After Administration of a 0.4mg Dose

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Intravenous</th>
<th>Intranasal</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9515</td>
<td>920</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1814</td>
<td>2119</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>2854</td>
<td>1905</td>
<td>126.9</td>
</tr>
<tr>
<td>4</td>
<td>3823</td>
<td>4196</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>4732</td>
<td>2602</td>
<td>92.7</td>
</tr>
<tr>
<td>6</td>
<td>3013</td>
<td>2098</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3659</td>
<td>2146</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>2420</td>
<td>3221</td>
<td>65.3</td>
</tr>
<tr>
<td>9</td>
<td>3520</td>
<td>2345</td>
<td>329.2</td>
</tr>
<tr>
<td>10</td>
<td>1676</td>
<td>2000</td>
<td>135.7</td>
</tr>
<tr>
<td>11</td>
<td>4016</td>
<td>2301</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>4107</td>
<td>3114</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± Standard Error  
3762 ± 588  2414 ± 235  72.0 ± 26.2

TABLE 2 below is a summary of the data for saliva flow which is inhibited by scopolamine. The data shows comparable saliva flow decrease for intravenous and
intranasal delivery with significantly lower effect by oral delivery. The data is summarized with the means and standard error of the mean.

**TABLE 2**

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Intravenous</th>
<th>Intranasal</th>
<th>Oral</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>276.8</td>
<td>195.8</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>440.4</td>
<td>321.9</td>
<td>237.5</td>
</tr>
<tr>
<td>3</td>
<td>352.8</td>
<td>284.7</td>
<td>73.2</td>
</tr>
<tr>
<td>4</td>
<td>329.5</td>
<td>316.5</td>
<td>105.7</td>
</tr>
<tr>
<td>5</td>
<td>373.8</td>
<td>413.5</td>
<td>362.1</td>
</tr>
<tr>
<td>6</td>
<td>338.5</td>
<td>336.5</td>
<td>100.3</td>
</tr>
<tr>
<td>7</td>
<td>149.0</td>
<td>211.6</td>
<td>27.0</td>
</tr>
<tr>
<td>8</td>
<td>191.2</td>
<td>284.9</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>400.1</td>
<td>405.5</td>
<td>219.6</td>
</tr>
<tr>
<td>10</td>
<td>452.9</td>
<td>409.9</td>
<td>326.6</td>
</tr>
<tr>
<td>11</td>
<td>474.0</td>
<td>426.4</td>
<td>291.5</td>
</tr>
<tr>
<td>12</td>
<td>400.4</td>
<td>249.3</td>
<td>74.3</td>
</tr>
</tbody>
</table>

Mean ± 348.3 ± 19.0 321.4 ± 23.1 151.5 ± 43.7

Standard Error

Figure 1 is a summary comparison of the bioavailability (AUC) of intranasal and oral scopolamine from plasma levels of each dosage type. Figure 1 also shows a comparison of the saliva suppression (AUEC) data. The oral dose had lower than 10% bioavailability exhibiting less than 40% saliva suppression as compared to 90% bioavailability and 95% suppression of saliva for intranasal dosage. The standard deviation is represented by the "I" above each box of the graph.

Plasma concentration-time profiles of scopolamine after intravenous and intranasal administration were similar with comparable AUC values. Scopolamine plasma concentrations after oral dosage were significantly lower than intravenous or intranasal doses. The data showed
high bioavailability of intranasal as compared to oral scopolamine. Both intranasal and oral absorption of scopolamine was rapid with peak concentrations occurring within one hour after dosing. However, the percent bioavailability was drastically different with 90% of the intranasal dose bioavailable as compared to less than 10% of the oral dose bioavailable.

The pharmacodynamic effect as a function of route of administration was determined from saliva flow rate (SFR) measurements after dosing. The intranasal dose produced a maximum effect of 95% inhibition of SFR as compared to 99.7% produced by the intravenous route with similar duration and effect. The maximum inhibition by the oral dose was less than 40%. The maximum effect was 1.05 hours after intranasal dosage which correlates to its plasma concentration peak.

Results show that intranasal scopolamine is a highly bioavailable and effective source of scopolamine. It may be administered as a noninvasive, reliable, fast and effective treatment for motion sickness and for other disorders or conditions requiring anticholinergic therapy.
ABSTRACT

A new method and preparation for intranasal delivery of scopolamine provides a safe and effective treatment for motion-sickness and other conditions requiring anticholinergic therapy. The preparation can be in the form of aqueous nasal drops, mist spray, gel or ointment. Intranasal delivery of scopolamine has similar bioavailability and effect of intravenous delivery and is far superior to oral dosage.