A composition for curing a Sjogren syndrome disease is disclosed. The composition comprising derivative of spirooxathiolane-quinuclidine of the following formula (I), (see formula I) wherein Z is =CR₁R₂, wherein R¹ and R² may be the same or different and each represents hydrogen, alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, or alkyl which may be substituted by one or more aryl groups, or an acid addition salt thereof, or an acid addition salt thereof, as an effective component. Especially effective is an administration of a hydrochloric acid addition salt of 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine.
ABSTRACT OF THE DISCLOSURE

A composition for curing a Sjoegren syndrome disease is disclosed. The composition comprising derivative of spirooxathiolane-quinuclidine of the following formula (I),

\[
\begin{array}{c}
\text{O} \\
\text{Z} \\
\text{S}
\end{array}
\]  \hspace{1cm} (I)

wherein Z is =CR^1R^2, wherein R^1 and R^2 may be the same or different and each represents hydrogen, alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, or alkyl which may be substituted by one or more aryl groups, or an acid addition salt thereof, or an acid addition salt thereof, as an effective component. Especially effective is an administration of a hydrochloric acid addition salt of 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine.
TITLE OF THE INVENTION

COMPOSITION FOR CURING SJÖEGREN SYNDROME DISEASE

BACKGROUND OF THE INVENTION

Field of the Invention:

The present invention relates to a composition for curing Sjögren syndrome diseases, comprising a derivative of spirooxathiolane-quinuclidine or an acid addition salt thereof as an active ingredient.

Description of the Background Art:

Sjögren syndrome, which is a xerotic disease caused by chronic inflammatory destruction of exocrine glands, occurs either independently or accompanied by various types of collagen diseases such as, for example, rheumatoid arthritis, systemic lupus erythematosus, progressive systemic sclerosis, polymyositis-dermatomyositis, or the like. It is an autoimmune disease which takes various pathologic forms. In addition, this disease is known to accompany lymphatic malignant tumors or quasi lymphomas at the final stage. Thus, this is a difficult-to-cure disease which attracts a great deal of attentions from medical experts. In Japan, the disease was designated as a specified disease (a difficult-to-cure disease) in 1976 by the Ministry of Health and Welfare. More recently, Tokyo metropolitan government also designated this disease as a specified disease (a difficult-to-cure
disease). According to the survey made by a study team of the Ministry of Health and Welfare, the number of the patients of this disease was estimated to be 17,669 as of 1976. Nowadays, the patients is considered to have increased several times as many as in 1976, i.e., about 100,000. The disease is characterized by the fact that the number of female patients are predominant; above 90%, or the ratio of female and male patients being 38.8:1.

Irrespective of complications, the major clinical symptoms of Sjoegren syndrome are xerostomia, xerophthalmia, and xerotic keratoconjunctivitis.

There is no effective method of curing these symptoms. Symptomatic treatments, such as administration of artificial saliva, artificial tear, or respiratory tract secretion promoters, are practiced as main countermeasures. Steroidal drugs which are dosed for suppressing immune reactions are reported to be almost ineffective to these symptoms. In addition, they have unfavorable side effects. On the other hand, the systemic (e.g., oral or intravenous) administration of parasympathetic nerve (cholinergic) stimulants, conventionally known saliva and tear secretion accelerators, is gradually phasing out due to their extensive side effects. Even bethanechol, the only one cholinergic system stimulant currently used, cannot be used at all for the Sjoegren syndrome disease due to its
comprehensive side effects such as headache, hot flush, palpitation, intrathoracic agony, nausea, emesis, diarrhea, abdominal discomfort, pyrosis, stomach discomfort, diaphoresis, and the like. Such a current medical situation gives the patients suffering from the Sjoegren syndrome disease conspicuous difficulty and inconvenience in carrying out the basic daily activities of living; eating, speaking, and seeing.

The object of the present invention is therefore to provide a drug for curing Sjoegren syndrome diseases which is safe and exhibits minimal toxicity as opposed to bethanechol which has extensive side effects.

In achieving this object, taking the advantage of the recent advancement in the research and development in parasympathetic nerve receptors, or cholinomimetic receptors, the inventors of the present invention synthesized and tested various chemical compounds possessing enhanced selectivity and specificity toward the central nervous system and the exocrine glands. As a result, the present inventors have discovered that derivatives of spirooxathiolane-quinuclidine, having the chemical structure of formula (I) shown below or their acid addition salts exhibit excellent effects.

SUMMARY OF THE INVENTION

Accordingly, an object of the present invention is
to provide a composition for curing a Sjögren syndrome disease comprising a derivative of spirooxathiolane-quinuclidine of the following formula,

\[
\begin{array}{c}
\text{O} \\
\text{\_\_} \\
\text{\text{\_\_\_\_}}
\end{array}
\quad \text{(I)}
\]

wherein \(Z = CR_1^1R_2^2\), wherein \(R_1\) and \(R_2\) may be the same or different and each represents hydrogen, alkyl, cyclopentyl, cyclohexyl, aryl, diarylmethylol, or alkyl which may be substituted by one or more aryl groups, or an acid addition salt thereof, as an active ingredient.

In a preferred embodiment of the present invention, said derivative of spirooxathiolane-quinuclidine, is a 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine hydrochloride.

In another preferred embodiment of the present invention, said derivative of spirooxathiolane-quinuclidine is a cis-isomer of 2-methylspiro(1,3-oxathiolane-5,3')-quinuclidine hydrochloride.

Other and further objects, features and advantages of the present invention will appear more fully from the following description.

**BRIEF DESCRIPTION OF THE DRAWINGS**

Figure 1 is a graph showing the relationship between the time after administration of quinuclidine...
hydrochloride (formula (II)) and the amount of saliva secretion in Example 2, wherein ** indicates that the administration brings about meaningful difference at a risk factor of 1%.

Figure 2 is a graph showing the relationship between the amount of quinuclidine hydrochloride (formula (II)) administered to the model mouse and the total amount of saliva secretion in Example 5.

Figure 3 is a graph showing the changes in the amount of saliva secretion with passage of time when the hydrochloric acid addition salt of quinuclidine (Formula II) was administered to the model mouse in Example 5.

**DETAILED DESCRIPTION OF THE INVENTION AND PREFERRED EMBODIMENTS**

In the present invention, the derivative of spirooxathiolane-quinuclidine represented by formula (I) is used as effective component in a composition for curing Sjoegren syndrome diseases. In said formula (I), as the alkyl group for R¹ and R², which constitute group Z, methyl, ethyl, n-propyl, and i-propyl are preferred, and phenyl group is preferred as the aryl group.

These compounds are known in the art; e.g., Japanese Patent Laid-open (kokai) No. 280497/1986. Of these derivatives of spirooxathiolane-quinuclidine, the following compounds are given as specific examples.
* 2-Methylspiro(1,3-oxathiolane-5,3')quinuclidine
* 2-Diphenylmethylspiro(1,3-oxathiolane-5,3')-quinuclidine
* 2-Methyl-2-phenylspiro(1,3-oxathiolane-5,3')-quinuclidine

These compounds include geometrical isomers, enantiomers, diastereomers, and racemates. The effective components for the composition of the present invention may be any one of these. Acid addition salts of these compounds include either inorganic or organic acid addition salts, such as those of hydrochloric acid, sulfuric acid, phosphoric acid, sulfamic acid, lactic acid, tartaric acid, succinic acid, maleic acid, and the like.

These derivatives of spirooxathiolane-quinuclidine can be easily prepared by a method disclosed, for example, in the above-mentioned Japanese Patent Laid-open (kokai) No. 280497/1986; i.e., by reacting 3-hydroxy-3-mercaptomethyl-quinuclidine with a carbonyl compound represented by the formula, R^1-CO-R^2, wherein R^1 and R^2 are the same as defined above, and separating the target compound from the reaction mixture. When the product is a mixture of optical isomers or other isomers, the isolation of each isomer can be carried out according to a method disclosed by said Japanese Patent Laid-open (kokai) No. 280497/1986 or Japanese Patent Laid-open
Among the derivatives of spirooxathioliolane-quinuclidine, especially preferred as active component of the composition for curing Sjoegren syndrome diseases is an acid addition salt of 2-methylspiro(1,3-oxathioliolane-5,3')quinuclidine of the following formula (II).

\[
\text{CH}_3

\text{O}

\cdot \text{HCl} \cdot \frac{1}{2} \text{H}_2 \text{O}

(II)

More preferred is a mixture of cis and trans isomers of this compound containing a larger amount of the cis isomer. The cis isomer is particularly preferred due to its high curing effect.

In a treatment of a Sjoegren syndrome disease with the present invention, said compound of formula (I) or a composition comprising said compound, as an effective component, and pharmaceutically acceptable carriers is administered to the patient. The composition is prepared into a form suitable for oral, parenteral, local, or rectal administration, e.g., into capsules, tablets, powder, granules, injection, ointment, eyedrop, suppositories, or the like.

As preparations suitable for oral administration, solid compositions, such as capsules, tablets, powder,
granules, or troches; and liquid compositions, such as syrups or suspensions, are given as examples.

These compositions for oral administration such as capsules, tablets, and granules are prepared according to conventional methods using vehicles, for example, starch, lactose, white sugar, mannitol, carboxymethylcellulose, corn starch, inorganic salts, and the like. In addition to these vehicles, binders, disintegrators, surfactants, lubricants, fluidity accelerators, flavorers, colorants, perfumes, and the like may be added as appropriate. Specific examples of these additives include the following materials.

<Binders>

Starch, dextrin, gum arabic, gelatin, hydroxypropyl starch, methylcellulose, sodium carboxymethylcellulose, hydroxypropylcellulose, crystalline cellulose, ethylcellulose, polyvinylpyrrolidone, and Macrogol (trade mark).

<Disintegrators>

Starch, hydroxypropyl starch, sodium carboxymethylcellulose, cross-linked sodium carboxymethylcellulose, calcium carboxymethylcellulose, carboxymethylcellulose, low-substituted and hydroxypropylcellulose.

<Surfactants>
Sodium lauryl sulfate, soybean lecithin, sucrose fatty acid ester, and Polysolvate 80 (trademark).

<Lubricants>

Talc, waxes, hydrogenated vegetable oils, sucrose fatty acid ester, magnesium stearate, calcium stearate, aluminum stearate, and polyethylene glycol.

<Fluidity accelerators>

Light anhydrous silicic acid, dry aluminum hydroxide gel, synthetic aluminum silicate, and magnesium silicate.

The compound of formula (I) may be administered in the form of a suspension, an emulsion, a syrup, an elixir, or the like, which may contain a flavorer and a colorant.

It is desirable that these compositions contain 1-95% by weight of the effective component.

Injections are given as examples of preparation for parenteral administration.

These compositions for parenteral administration can be prepared by a conventional method. Normally, distilled water for injection, physiological saline, an aqueous solution of glucose, vegetable oil for injection, sesame oil, peanut oil, soybean oil, corn oil, propylene glycol, polyethylene glycol, and the like can be used as a diluent. In addition, a bactericidal agent, a preservative, and a stabilizer may be added as required. From the aspect of preserving the stability, such
compositions for parenteral administration may be filled in vials or the like and freeze-dried by a conventional freeze-dry technique for removing water, and may be made into a liquid injection preparation immediately before use. In this instance, an isotonic agent, a stabilizer, a preservative, a soothing agent, and the like can optionally be added.

As an injection preparation, a preparation in which the active compound in a form of a salt is dissolved in conventional injection water, or a suspension or emulsion prepared using a mixture of such an active component and a pharmaceutically acceptable oil or liquid can be used. In this instance, an antibacterial agent (e.g., benzyl alcohol), an antioxidant (e.g., ascorbic acid), a buffer solution, an osmotic pressure modifier, a dissolution adjuvant, and the like may be added. It is preferable that such an injection preparation contain 0.1-5% by weight of the active component. Intravenous injection, intraarterial injection, intramuscular injection, or subcutaneous injection are applicable.

Eyedrops, ointments and suppositories are given as examples of the composition for local or rectal administration.

Ointments can be prepared by adding a base component which is usually used according to a conventional method. It is preferable that such an ointment composition
contain 0.5-30% by weight of the active component.

The suppositories may contain any carriers known in
the art, such as polyethylene glycol, lanoline, cacao
butter, fatty acid triglyceride, and the like. It is
preferable that the suppository contain 1-95% by weight
of the active component.

The above compositions for oral, parenteral, local
or rectal administration can be prepared by a known
method so as to regulate the rate of release of the
active component therefrom; i.e., they may be made into a
rapid release preparation, suspended release preparation,
or a slow release preparation.

A dose of the composition of the present invention
for curing the Sjogren syndrome disease varies depending
on the type of the composition, the manner by which it is
administered, the purpose of use, the age, weight,
symptoms, and the like of the patients. In general, a
suitable dose for an adult, in terms of the active
component contained in the composition is in the range of
about 1 mg to 1 g per day. The amount of the active
component in the composition can be determined depending
on the intended dose. If necessary, it is possible to
administer the above amount of the composition dividedly
several times a day.

Other features of the invention will become apparent
in the following description of the exemplary embodiment
which is given for illustration of the invention and is not intended to be limiting thereof.

EXAMPLE

Example 1

Toxicity Test

Groups of ICR (CD-1) male and female mice (age: 5 weeks, weight of male mice: 22.0-33.8 g, weight of female mice: 18.8-27.3 g), each consisting of eight mice, were used for the test. 2-methylspiro(1,3-oxathiolane-5,3′)quinoxylidine hydrochloride of formula (II) was orally, intravenously, or subcutaneously administered at different (high and low) doses. LD$_{50}$ (50% lethal dose) was determined by the observation of mice for two weeks thereafter. The results are shown in Table 1.

TABLE 1

<table>
<thead>
<tr>
<th>Administration route</th>
<th>Sex</th>
<th>LD$_{50}$ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Male</td>
<td>139.2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>167.3</td>
</tr>
<tr>
<td>Intravenous</td>
<td>Male</td>
<td>45.2</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>40.8</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Male</td>
<td>65.0</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>78.1</td>
</tr>
</tbody>
</table>
Example 2

Saliva secretion effect in rats

A pharmacological action test was carried out by using groups of Wistar male rats (weight: 150-250 g), each consisting of 5 rats. The rats were anesthetized with 40 mg/kg of sodium Pentobarbital, followed by intravenous injection of 2-methylspiro(1,3-oxathiolane-5,3′)quinuclidine hydrochloride of formula (II) in amounts of 0, 0.3, 1, 3, and 10 mg/kg. After 60 minutes, saliva secreted in oral cavity was collected by cotton balls to weigh the amount of the saliva. The results are shown in Figure 1.

Example 3

Saliva and tear secretion effects in dogs

2-Methylspiro(1,3-oxathiolane-5,3′)quinuclidine hydrochloride of formula (II), in amounts of 0, 0.5, 3, and 18 mg/kg, was orally administered to female beagle dogs (weight: 7.1-9.6 kg) of four groups, each consisting of four dogs, one time a day and for four weeks. The secretion of saliva and tear was observed at least four times a day and the observations were recorded.

The number of animals frequently secreted saliva and tear during the four-week-period is shown in Table 2.
TABLE 2

<table>
<thead>
<tr>
<th>Animal Groups</th>
<th>Dose (mg/kg/day)</th>
<th>Number of tested animals</th>
<th>Number of animals secreted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0</td>
<td>4</td>
<td>0(0) 0(0)</td>
</tr>
<tr>
<td>Dose group</td>
<td>0.5</td>
<td>4</td>
<td>0(0) 0(0)</td>
</tr>
<tr>
<td>Dose group</td>
<td>3.0</td>
<td>4</td>
<td>3(75) 1(25)</td>
</tr>
<tr>
<td>Dose group</td>
<td>18.0</td>
<td>4</td>
<td>4(100) 4(100)</td>
</tr>
</tbody>
</table>

Example 4

Saliva secretion effects in human

2-Methylspiro(1,3-oxathiolane-5,3’)-quinuclidine hydrochloride of formula (II), in amounts of 5, 10, 20, 30, 40, 50, 60, and 70 mg, was orally administered to five men and five women, aged 20-50 years. The number of subjects who exhibited promoted secretion of saliva is shown in Table 3.

TABLE 3

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Tested subjects</th>
<th>Subjects showing promoted saliva secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>40</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>50</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>70</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

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Example 5

Saliva secretion effects in disease model mice

MRL/lpr mouse is a spontaneous autoimmune disease model mouse. The animal is known to exhibit lymphatic infiltration in salivary gland, the same symptom as the Sjoegren syndrome disease.

A pharmaceutical action test was carried out using groups of male MRL/lpr mice, 10 weeks of age and weighing 30-38 g, each group consisting of 8 animals. The mice were anesthetized by 50 mg/kg of sodium Pentobarbital, followed by intraperitoneal injection of the 2-methylspiro(1,3-oxathiolane-5,3′)quinuclidine hydrochloride of formula (II) in amounts of 1, 3, 6, and 10 mg/kg. Saliva was collected by a micropipette placed in animal’s mouth at an interval of 5 minutes for 30 minutes after the injection and an interval of 10 minutes between 30 and 60 minutes after the injection, to measure the volume of the collected saliva. The dose-dependent changes of the amount are shown in Figure 2 and the changes with passage of time are shown in Figure 3.

Example 6

Saliva secretion effects in a patient suffering from a Sjoegren syndrome disease

Five subjects diagnosed to be suffering from a Sjoegren syndrome disease according to the diagnosis
criteria made by the study team at the Ministry of Health and Welfare (M. Ofuji, Study Report Summary for 1977, the results for the year 1977 of Diagnostic criteria of Sjoegren’s syndrome (Ministry of Health and Welfare’s Sjoegren Investigational Research Group), M. Ofuji, Research Report of Ministry of Health and Welfare’s specific disease Sjoegren Investigational Research Group in 1977, 3-6, 1978). To each subject was administered said hydrochloric acid addition salt of quinuclidine of formula (II) at a dose of 10 mg, three times a day, each time one hour before meal, for 4 weeks (the first course); 20 mg, three times a day, each time one hour before meal, for 4 weeks (the second course); and 30 mg, three times a day, each time one hour before meal, for 4 weeks (the third course). The Saxon test (Kohler P. F., Winter M. E., Arthritis Rheum, 28, 1128-1132 (1985)) for measuring the saliva secretion was performed before the start of the first course, and after the completion of the first, second, and third courses. The results are shown in Table 4.
<table>
<thead>
<tr>
<th>Subject</th>
<th>First course Before*</th>
<th>First course After</th>
<th>Second course After</th>
<th>Third course After</th>
<th>Observation of the patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.65</td>
<td>1.08</td>
<td>2.05</td>
<td>3.90</td>
<td>Saliva secretion increased.</td>
</tr>
<tr>
<td></td>
<td>(1.66)</td>
<td>(3.15)</td>
<td></td>
<td>(6.00)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.73</td>
<td>1.24</td>
<td>2.54</td>
<td>4.50</td>
<td>A dry feeling of oral cavity and irritation in the eyes improved.</td>
</tr>
<tr>
<td></td>
<td>(1.70)</td>
<td>(3.48)</td>
<td></td>
<td>(6.16)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.76</td>
<td>1.45</td>
<td>1.56</td>
<td>3.85</td>
<td>The need for drinking water when taking food eliminated.</td>
</tr>
<tr>
<td></td>
<td>(1.91)</td>
<td>(2.05)</td>
<td></td>
<td>(4.80)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.43</td>
<td>0.65</td>
<td>1.65</td>
<td>2.89</td>
<td>Incidence of being awaken due to dry mouth at midnight improved.</td>
</tr>
<tr>
<td></td>
<td>(1.51)</td>
<td>(3.80)</td>
<td></td>
<td>(6.72)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.45</td>
<td>0.59</td>
<td>0.97</td>
<td>1.47</td>
<td>Saliva was felt like to secrete</td>
</tr>
<tr>
<td></td>
<td>(1.31)</td>
<td>(2.16)</td>
<td></td>
<td>(3.27)</td>
<td></td>
</tr>
</tbody>
</table>

* Before: before administration; After: after administration
** The parenthesized figures are ratios to the value before the administration in the first course.

Preparation Example 1

<Capsules>

Capsules having the following formulation was prepared according to a conventional method.
2-Methylspiro(1,3-oxathiolane-5,3')quinuclidine hydrochloride
(Formula II) 10 g

Low-substitution hydroxypropyl-cellulose 20 g

Cross-linked sodium carboxymethyl-cellulose 5 g

Magnesium stearate 2 g

Lactose q.s.

100 g

Preparation Example 2

<Tablets>

Tablets having the following formulation was prepared according to a conventional method.

2-Methylspiro(1,3-oxathiolane-5,3')quinuclidine hydrochloride
(Formula II) 20 g

Low-substitution hydroxypropyl-cellulose 10 g

Crystalline cellulose 15 g

Hydroxypropylmethylcellulose 10 g

Magnesium stearate 2 g

Lactose q.s.

100 g

Preparation Example 3

<Injection>

Injection for intravenous use having the following formulation was prepared according to a conventional method.
2-Methylspiro(1,3-oxathiolane-5,3')quinuclidine hydrochloride (Formula II) 1 g

Glucose 10 g

Distilled water for injection q.s.

200 ml

Obviously, numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the appended claims, the invention may be practiced other than as specifically described herein.
WHAT IS CLAIMED IS:

1. A composition for treating symptoms of a Sjoegren syndrome disease comprising a derivative of spirooxathiolanequinuclidine of the following formula (I),

\[
\text{O} \quad \text{Z}
\]
\[
\text{S}
\]

wherein Z is =CR\(^1\)R\(^2\), wherein R\(^1\) and R\(^2\) may be the same or different and each represents hydrogen, C\(_1\)-C\(_4\) alkyl, cyclopentyl, cyclohexyl, phenyl, diarylmethylol, or C\(_1\)-C\(_4\) alkyl which may be substituted by one or more phenyl groups, or an acid addition salt thereof, as the effective component and a pharmaceutically acceptable excipient.

2. The composition according to Claim 1, wherein said derivative of spirooxathiolanequinuclidine is a hydrochloric acid addition salt of 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine of the following formula (II)

\[
\text{O} \quad \text{CH}_2
\]
\[
\text{S}
\]
\[
\text{HC}1 \cdot \frac{1}{2} \text{H}_2 \text{O}
\]

3. The composition according to Claim 2, wherein said hydrochloric addition salt of 2-methylspiro(1,3-oxathiolane-5,3')quinuclidine is a cis isomer.
Fig. 1

- ○ control
- △ quinuclidine hydrochloride [formula (II)] 0.3mg/kg.i.v.
- ▲ quinuclidine hydrochloride [formula (II)] 1.0mg/kg.i.v.
- □ quinuclidine hydrochloride [formula (II)] 3.0mg/kg.i.v.
- ■ quinuclidine hydrochloride [formula (II)] 10.3mg/kg.i.v.

Amount of saliva secretion (mg/100g/min)

Administration

0 10 20 30 40 50 60 (min)
Fig. 2

Amount of saliva secretion (µl/hr/10g b.wt.)

Administered amount (mg/kg, i.p.)
Fig. 3

Amount of saliva secretion (μl/min/10g b.wt.)

Time after administration (min)

mg/kg
10
6
3
1