RELATIVE PHARMACOLOGICAL EFFECTS OF A SERIES OF QUATERNARY ALKALOIDS ISOLATED FROM MAGNOLIA AND COCCULUS PLANTS

KIRO SHIMAMOTO, KUNIO INOUE AND KIKUO OGIU

Department of Pharmacology, Faculty of Medicine, Kyoto University, Kyoto

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The present report deals with the pharmacological properties of a series of quaternary tetrahydrobenzylisoquinoline, phenylethylamine and phenanthropyridine alkaloids, isolated from Magnolia and Cocculus plants by Prof. Tomita et al. (1). Marsh et al. (2) reported that some of the quaternary alkaloids isolated from the Cocculus plants showed a considerable curare-like activity. Ogiu and Morita (3) showed that magnocurarine and salicifoline, the tetrahydroisoquinoline and phenylethylamine derivatives of the alkaloids revealed potent curare-like actions on the extirpated rectus abdominis muscle of frog, which resembled to d-tubocurarine type of action. Laurifoline (4) and menisperine (5, 6), the phenanthropyridine derivatives of the alkaloids proved to have a potent ganglion blocking property.

I. Materials

All the quaternary chlorides used in the experiments, obtained through the courtesy of Prof. Tomita. The names, chemical formulae, melting points and the plants from which they were isolated are listed in Table 1. As control drugs d-tubocurarine chloride, papaverine methiodide (PV), hexamethonium bitartrate (C;2) and decamethonium bichloride (C;16) were used.

II. Curare-like Action

A. Sciatic-Gastrocnemius, Sciatic-Soleus and Fibularis-Anterior Tibialis Preparations of Rats in Situ

Rats, weighing 150 to 200 g, were used under urethane anesthesia (1 g/kg intraperitoneal). The preparations were made according to Inoue's method (7). For the supramaximal stimulation of the nerve, the square wave stimulator was used. The stimulus was 6/min in frequency and 1 msec in duration. The contraction of the muscle in response to the stimulus was recorded on a kymograph via an isotonic lever. The drugs tested were all injected into the jugular vein. Most of the experiments were made under artificial respiration.

1) Curare-like action of MS and LF

The preparation did not respond to the first administration of MS or LF below the dose of 1 mg/kg. The administration of 2 to 3 mg/kg of either drug depressed the response of
TABLE 1. Names, chemical formulae, melting points and the plants from which they were isolated.

<table>
<thead>
<tr>
<th>Names</th>
<th>Chemical formulae</th>
<th>Melting point</th>
<th>Name of plants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnocurarine (MC) chloride</td>
<td>CH₃O-</td>
<td>200 (decomp.)</td>
<td>Magnoliaceae: Magnolia aborea Thunb.</td>
</tr>
<tr>
<td></td>
<td>HO-</td>
<td></td>
<td>Magnolia salicifolia Maxim.</td>
</tr>
<tr>
<td></td>
<td>CH₃-</td>
<td></td>
<td>Magnolia denudata Desr.</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td></td>
<td>Magnolia lilifora Desr.</td>
</tr>
<tr>
<td>Salicifoline (SF) chloride</td>
<td>HO-CH₂CH₂N-</td>
<td>260-261 (decomp.)</td>
<td>Magnoliaceae: Magnolia salicifolia Maxim.</td>
</tr>
<tr>
<td></td>
<td>(CH₃)₂</td>
<td></td>
<td>Magnolia Kobus DC.</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td></td>
<td>Magnolia siduida Maxim.</td>
</tr>
<tr>
<td></td>
<td>OH</td>
<td></td>
<td>Magnolia denudata Desr.</td>
</tr>
<tr>
<td></td>
<td>CH₂O-</td>
<td></td>
<td>Magnolia lilifora Desr.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Magnolia grandiflora L.</td>
</tr>
<tr>
<td>Laurifoline (LF) chloride</td>
<td>CH₃O-</td>
<td>253 (decomp.)</td>
<td>Menispermaceae: Coccus laurifolius DC.</td>
</tr>
<tr>
<td></td>
<td>HO-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N&lt;CH₃-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CH₂O-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menisperine (MS) chloride</td>
<td>CH₃O-</td>
<td>219 (decomp.)</td>
<td>Menispermaceae: Menispernum dauricum DC.</td>
</tr>
<tr>
<td></td>
<td>CH₂O-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>N&lt;CH₃-</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>OH</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CH₂O-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnoflorine (MF) chloride</td>
<td>CH₃O-</td>
<td>248-249 (decomp.)</td>
<td>Magnoliaceae: Magnolia grandiflora L.</td>
</tr>
<tr>
<td></td>
<td>HO-</td>
<td></td>
<td>Magnoliaceae: Coccus trilobus DC.</td>
</tr>
<tr>
<td></td>
<td>N&lt;CH₃-</td>
<td></td>
<td>Siomonium actum Rehd. et Wils.</td>
</tr>
<tr>
<td></td>
<td>Cl</td>
<td></td>
<td>Coccus laurifolius DC.</td>
</tr>
<tr>
<td></td>
<td>CH₃H₂</td>
<td></td>
<td>Parazyceles insularis</td>
</tr>
<tr>
<td></td>
<td>ClH₂</td>
<td></td>
<td>Berberidaceae: Berberis Thunb. DC.</td>
</tr>
<tr>
<td></td>
<td>OH</td>
<td></td>
<td>Berberis amurensis</td>
</tr>
<tr>
<td></td>
<td>CH₂O-</td>
<td></td>
<td>Mahonia japonica DC.</td>
</tr>
</tbody>
</table>

the muscle to about 10 to 20% for a while. The minimal paralytic dose was subjected to a good deal of individual variation. The maximal depression on the muscle in response to 5 to 6mg/kg of either drug appeared 2 to 3 minutes after the injection and recovered gradually to normal within 10 to 20 minutes. The depression of the muscle to the above dose of the drug extended to about 50 to 100%. The respiratory exercise of the animal, including those of diaphragm, was similarly depressed or rather arrested after the adminis-
tration of the drugs in the above doses. The recovery from the respiratory paralysis was always delayed compared to that of the muscular paralysis. To prevent the asphyxia resulting from the respiratory paralysis, artificial respiration was required. Under artificial respiration the dose of either drug required to obtain complete suppression of the response of the muscle was 8 to 10mg/kg. The response of the muscle to the direct stimulation was not modified in any dose of the drugs. Table 2 shows the minimal paralytic dose, ED 50 and relative values of the drugs in the sciatic-gastrocnemius preparation.

TABLE 2. Minimal curarizing doses, ED 50 and relative values of the drugs in the sciatic-gastrocnemius preparation of the rat in situ.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Effect of initial injection</th>
<th>Minimal curarizing dose (mg/kg)</th>
<th>ED 50 (mg/kg)</th>
<th>Relative value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>Curare-like</td>
<td>2.0</td>
<td>5.0</td>
<td>1</td>
</tr>
<tr>
<td>LF</td>
<td></td>
<td>3.0</td>
<td>6.0</td>
<td>0.7</td>
</tr>
<tr>
<td>MC</td>
<td></td>
<td>5.0</td>
<td>8.0</td>
<td>0.4</td>
</tr>
<tr>
<td>MF</td>
<td></td>
<td>8.0</td>
<td>10.0</td>
<td>0.25</td>
</tr>
<tr>
<td>SF</td>
<td></td>
<td>10.0</td>
<td>15.0</td>
<td>0.2</td>
</tr>
<tr>
<td>PV</td>
<td></td>
<td>15-18</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>d-Tubocurarine</td>
<td></td>
<td>0.63</td>
<td>0.65</td>
<td>100.0</td>
</tr>
<tr>
<td>C10</td>
<td>Acetylcholine-like</td>
<td>0.65</td>
<td>4.6</td>
<td>—</td>
</tr>
</tbody>
</table>

2) Repeated administration

The repeated administration of MS or LF at the intervals of 10 to 20 minutes gradually increased the depressive effects. Fig. 1 shows the response of the gastrocnemius muscle to the repeated injection of MS. Similar results were obtained with d-tubocurarine, MS, SF, MF and C10 and also between each drugs. To compare the action of these drugs in the same preparation, the interval between each administration of the drug was necessary.

![Fig. 1. Effects of the initial and the repeated injection of LF (7.9 mg/kg) on the responses of the soleus and the gastrocnemius muscles to indirect stimulation. Supramaximal stimulation, 6/min in frequency, 1 msec in duration with square waves.](image-url)
over 30 minutes.

3) Differences of the responses of the red and white muscle to MS and LF

The effects of the administration of MS or LF in doses of 5 to 7 mg/kg on the response of the gastrocnemius, soleus and tibialis anterior muscles to indirect stimulation were comparatively studied. The results revealed that the depression by the drug was strongest in the soleus and weakest in the tibialis anterior muscle. The administration of 6 mg/kg of MS or LF depressed the response of the soleus muscle completely, while depressing that of the gastrocnemius about 70 to 80%, and that of the tibialis anterior about 60 to 70%. The administration of \textit{d}-tubocurarine revealed qualitatively similar effects to MS or LF on the responses of the muscles.

4) Effects of the administration of various drugs on the curare-like action of MS or LF

\textit{Eserine salicylate:} The administration of 0.05 to 0.5 mg/kg of eserine did not affect or only slightly potentiated (about 20%) the contraction of the muscle for 2 to 5 minutes. The depressive response of the muscle, as well as that of respiratory exercise to MS or LF was quickly interrupted with a return to normal response by administration of eserine in the above doses. The complete depression of the muscle induced by the administration of a large dose of MS or LF was also similarly affected. The extent of the antagonistic action of eserine against the curare-like action of MS or LF related to the doses of either drug administered. The depressive effect by MS or LF was also inhibited after the administration of eserine. Therfore the cumulative effect of the curare-like action of these drugs by repeated injection was not observed. The curare-like actions of \textit{d}-tubocurarine, MC, MF and SF were subjected to be similarly effected qualitatively by eserine.

It was frequently observed that the repeated injection or the administration of above 0.9 mg/kg of eserine, potentiated the curare-like action of these drugs.

\textit{Prostigmine chloride:} The administration of 5 to 10 mg/kg of prostigmine did not affect or slightly potentiated the response of the muscle to indirect stimulation. But depressive effect of MS or LF was also antagonized by prostigmine in the above doses. The antagonizing action of prostigmine was more potent than that of eserine. The repeated injection of prostigmine revealed always a similar antagonistic effect. The depressive effect of MS or LF which was not antagonized after the repeated injection of eserine, was easily antagonized by prostigmine.

\textit{Berberine bisulfate:} Berberine, in the dose of 0.1 to 0.3 mg/kg, also antagonized the curare-like action of MS or other drugs. The antagonizing action of berberine manifested gradually and was temporary. Also the repeated injection of the drug did not effect or slightly modified decreasingly the curarizing effects.

\textit{C_{10}:} The initial administration of \textit{C}_{10} (0.1 to 1.0 mg/kg) potentiated the response of the muscle to indirect stimulation about 10 to 20% for 2 to 5 minutes. The succeeding administration of the drug either revealed no effect or showed a slight depression of the response which continued for a long while. After the initial injection of \textit{C}_{10} in the dose of 0.5 to 0.6 mg/kg, the curare-like action of MS or LF was strikingly depressed or occa-
sionally reversed. But the succeeding administration of C₃₀ in the same dose potentiated the curarizing action of MS or LF.

B. Extirpated Rectus Abdominis Muscle of the Frog

The extirpated rectus abdominis muscle of the frog was immersed in frog-Ringer solution and the responses of the muscle to the curarizing drugs and the effects of the drugs on the response of the muscle to acetylcholine were observed.

![Graph showing effects of drugs on muscle response](image)

**FIG. 2. Effects of d-tubocurarine (5×10⁻⁷) and MS (2×10⁻⁷, 5×10⁻⁵) on the response of the rectus abdominis muscle to acetylcholine (2×10⁻⁶).**

**TABLE 3. Percentage depression of the extirpated rectus abdominis muscle of the frog in response to 2×10⁻⁵ of acetylcholine by the application of the drugs in the concentration of 10⁻⁵.**

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Concentration of the drug to induce 80% depression</th>
<th>Relative value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>2×10⁻⁵</td>
<td>1</td>
</tr>
<tr>
<td>LF</td>
<td>3×10⁻⁶</td>
<td>0.7</td>
</tr>
<tr>
<td>MC</td>
<td>5×10⁻⁶</td>
<td>0.4</td>
</tr>
<tr>
<td>MF</td>
<td>7×10⁻⁵</td>
<td>0.3</td>
</tr>
<tr>
<td>d-Tubocurarine</td>
<td>10⁻⁷</td>
<td>100.0</td>
</tr>
</tbody>
</table>

1) Effects of MS, LF, MC, MF and SF

These drugs, except SF did not reveal any action in concentrations between 10⁻⁷ to 10⁻⁴. SF always contracted the muscle at concentrations above 10⁻⁴.

2) Effects of the drugs on the action of acetylcholine

The contraction of the muscle in response to 2×10⁻⁵ of acetylcholine was depressed by the application of the drugs in concentrations of above 10⁻⁵. Table 3 shows the percentage depression of the muscle in response to 2×10⁻⁵ of acetylcholine by the application of the drugs in the concentration of 10⁻⁵. Only SF potentiated the response of the muscle to acetylcholine.

C. Head Drop Test in the Rabbit

Head drop doses of the curarizing drugs, according to the method of Holaday (8), were
as follows. The respective ED 50 were 1.8 mg/kg for MS, 2.0 mg/kg for LF, 6 mg/kg for MC and 0.023 mg/kg for d-tubocurarine.

III. Effects on Circulation

A. Hypotensive Action

Rabbits, weighing about 2 kg (urethane 1g/kg intraperitoneal anesthesia), cats weighing 2 to 3 kg (evipan sodium 150 mg/kg intraperitoneal anesthesia) and dogs weighing 5 to 10 kg (amytal sodium 50 to 70 mg/kg intraperitoneal anesthesia) were used. Arterial pressure was recorded on a kymograph from the carotid or the femoral artery with a mercury manometer. All the drugs tested were injected into the femoral vein.

1) Effects of the administration of MS, LF, MC, MF and SF

The administration of MS or LF (0.05 mg/kg in the dog and 0.1 mg/kg in the cat and rabbit) caused a fall of the blood pressure of about 5 to 10 mm Hg. The hypotensive response appeared within 30 to 50 seconds after injection, reached maximal response 1 to 3 minutes later and returned to normal within 5 to 10 minutes. The extent in fall and duration of the hypotensive action of the drug depended upon the dose administered and the initial height of the blood pressure. The hypotensive response to 2 to 3 mg/kg of MS extended to about 50 to 80 mm Hg, but the response to a larger dose resulted not in a further fall but a longer duration of action. Coinciding with the hypotensive action of the drugs dilation of the capillaries in the skin, especially in the ear of rabbit was observed. The administration of MC, MF, PV, SF and C; revealed similar effects as MS or LF. Table 4 shows the amounts of the drugs needed to induce a fall of blood pressure about 70 mm Hg in the dog.

2) Effects of the drugs on the various autonomic regulatory mechanism

The hypotensive action of these drugs was not modified by either bilateral vagotomy, full atropinization nor artificial respiration, but was somewhat potentiated by bilateral extirpation of the carotid body. The rise of blood pressure in response to bronchial occlusion or to occlusion of bilateral carotid artery was slightly depressed by these drugs in considerably larger doses. The spinal cord section between C1 and C2 under ether anesthesia reduced the hypotensive action of these drugs significantly.

3) Effects of the drugs on the response of blood pressure to various autonomic drugs

Adrenaline and noradrenaline: The hypertensive action by the administration of adrenaline or noradrenaline in doses of 1 to 5γ/kg, was strikingly potentiated after the administration...
tion of the drugs in doses above 1.0 mg/kg. The potentiating effect on the action of these amines manifested stronger in cats and dogs than in rabbits, with LF being stronger than MS. The same effect was stronger in spinal animal compared to the intact animal.

Acetylcholine: The hypotensive response of blood pressure to acetylcholine (1 to 2µ/kg) was not modified by the administration of 0.5 to 2.0 mg/kg of these drugs.

Pilocarpine: The hypertensive action of pilocarpine was markedly reduced or almost abolished, while the secondary hypertensive action was markedly potentiated after the administration of the drugs in doses above 0.1 mg/kg.

Large dose of acetylcholine in the atropinized animal: The hypertensive action of large dose of acetylcholine in full atropinized animal was blocked completely after the administration of MS in dose of 0.5 mg/kg, while depressed about 80% by the same dose of LF or C3. The duration of the depressive action was longest in C3, which continued for 30 to 60 minutes. The duration of the action of MS or LF continued for 20 to 30 minutes.

Nicotine: The hypertensive response of blood pressure to nicotine was subjected to a good deal of individual variation. The rise of blood pressure in response to 0.5 mg/kg of nicotine was completely depressed by 2 to 3 mg/kg of MS or LF. The similar effect was also observed by C3, which was superior to MS or LF in duration of action.

4) Effects of the drugs on preganglionic autonomic nerve stimulation

Stimulation of the cut peripheral end of the cervical vagus nerve: The right cervical vagus nerve of the cat or dog was exposed and prepared for stimulation with square waves. The stimuli were submaximal in intensity, 10/sec in frequency and 1 msec in duration. As shown in Table 5, these drugs depressed or blocked the hypotensive response to nerve stimulation. The depressive effect of C3 was also superior to that of other drugs in duration of action.

Stimulation of the cut peripheral end of the splanchnic nerve: The left splanchnic nerve was exposed extraperitoneally in the dog and cat. The peripheral end of the cut nerve was stimulated under the same conditions as in the vagus nerve. The hypertensive response of the blood pressure to nerve stimulation was obtained uniformly on the same animal even if the stimulation was repeated. The depressive effect of MS or LF on the response to nerve stimulation was not inferior to the similar effect of C3. But the duration of action of the drugs were always shorter than that of C3. The results are shown in Fig. 3.

B. Extirpated Auricular Preparation of Rabbit

The auricle of rabbit was extirpated and prepared for recording of the rhythmical contraction in Ringer-Locke solution at 30°C according to Bölbbring and Burn's method (9).
1) Effects of the drugs

The rhythmical contraction of the preparation was not affected by the application of the drugs in concentration of 10^{-7} to 10^{-4}.

2) Effects of the drugs on the response of the preparation to adrenaline, noradrenaline, pilocarpine and acetylcholine

The stimulating response to adrenaline or noradrenaline (10^{-7} to 10^{-6}) and the depressive response to acetylcholine or pilocarpine (10^{-7} to 10^{-6}) were almost not influenced or slightly inhibited by MS or LF in the concentration of 10^{-7} to 10^{-6}.

3) Effects of the drugs on the response to nicotine

The stimulating response of the preparation to 10^{-6} to 5 \times 10^{-6} of nicotine was completely depressed after the application of MS or LF in concentration of 10^{-7} to 5 \times 10^{-7}. The depressive effect on the action of nicotine remained for a while even after the preparation was washed with Ringer solution repeatedly. C\textsubscript{i} also revealed a similar effect as MS or LF qualitatively and also quantitatively.

C. Perfusion of the Extirpated Rabbit's Ear Vessels

The extirpated ear vessels of the rabbit was perfused with Ringer solution according to Krawkow-Pissemski's method. The drug to be tested were injected to the rubber tube, to which the perfusion cannula was connected, and the volume of the perfusate was recorded on a kymograph by use of a drop timer.

1) Effects of MS and LF

The injection of LF or C\textsubscript{i} in the dose of 0.1 c.c. of 10^{-3} revealed no effects, while the injection of MS in dose of 0.1 to 0.3 c.c. of 10^{-4} showed an increase of the perfusion drops. The effect was magnified according to the increase of the dose. The injection of atropine (10^{-4}, 0.1 c.c.) not only depressed or blocked the dilatatory effect but also reversed the effect of MS. A similar constrictor effect on the vessels after the injection of atropine was also observed by LF (10^{-5}, 0.5 c.c.) but not by C\textsubscript{i} in any doses.

2) Effects of the drugs on the responses of the vessels to adrenaline and nicotine

The constrictive response of the vessels to adrenaline (10^{-8}, 0.1 c.c.) was depressed after the administration of MS (10^{-3}, 0.1 c.c.), while the same response to adrenaline was potentiated by LF in the same dose. The constrictor response of the vessels to nicotine (10^{-5},
IV. Effects on the Alimentary Tract Function

A. Effects on the Intestinal Movements in Situ

Rabbit or cat was anesthetized and was fixed on its back. The abdomen was incised and the rhythmical movements of a part of the ileum or jejunum was recorded on a kymograph via lever according to Trendelenburg's method. The drugs were injected into the ear or the femoral vein.

1) Effect of MS and LF

The administration of MS or LF in doses of 0.5 mg/kg increased the rhythmical contraction and the tone of the preparation. The effects appeared 30 seconds after the injection, reached its maximum within 2 to 3 minutes and recovered in 5 to 6 minutes. MS showed a stronger effect than LF. One-tenth to 0.3 mg/kg of atropine abolished the responses to both drugs.

0.1 c.c.) was blocked after the administration of LF or MS in the dose of $10^{-5}$. The response to nicotine recovered gradually within 10 to 20 minutes.
2) Effects of MS or LF on the action of adrenaline and acetylcholine

The administration of adrenaline in doses of 1 to 5 \( \mu \)g/kg induced an inhibition of the rhythmical movement and tone of the intestine, while the administration of acetylcholine in the dose of 1 \( \mu \)g/kg induced an increase of the intestinal activity. The administration of LF or MS in doses of 0.5 to 2.0 mg/kg did not affect the response of the preparation to adrenaline or to acetylcholine.

3) Effects of the drugs on the action of nicotine

The administration of nicotine in a dose of 0.01 mg/kg increased the intestinal activity. Also the response to nicotine was subjected to a considerable individual variation and a good deal of tachyphylaxis, the response to the same dose of nicotine at an interval of 20 or 30 minutes resulted in a uniform effect. 1.0 mg/kg of MS or LF abolished the response to nicotine. Doses of 2 to 3 mg/kg of C\textsubscript{1} was required to abolish the response to the same dose of nicotine.

4) Effects of the drugs on the response of the preparation to stimulation of the cervical vagus nerve

The effects of the drugs on response of the preparation to stimulation of the cervical vagus nerve was comparatively studied. The stimulus, applied on the nerve was the same as in the blood pressure experiment. The response of the preparation to stimulation of the nerve was completely abolished after the administration of MS, LF or C\textsubscript{1}, the dose required being 1.0 mg/kg for the former two drugs and for the latter 2.0 mg/kg. The depressive action of MS or LF was short in duration compared with that of C\textsubscript{1}.

5) Effects of the drugs on response of the preparation to stimulation of the splanchnic nerve

The effects of the administration of MS or LF on response of the preparation to stimulation of the splanchnic nerve, which was adjusted as previously mentioned, was studied. After the administration of either drug in doses of 2.0 mg/kg the stimulating effect of the
nerve was abolished, but gradually recovered to normal response within 20 minutes. C; revealed a similar intensity of action, but longer duration of action.

B. Effects on the Intestinal Movements in Vitro

E. Effects of the drugs

The response of an extirpated segment of the ileum, of which movements were recorded on a kymograph according to the originally Magnus' method, to the drugs and the effects of the drugs on the action of acetylcholine, adrenaline and nicotine were studied. The response of the intestine to the drugs and the minimal effective doses are shown in Table 6. Pretreatment of the drugs did not affect the responses of the ileum to adrenaline ($10^{-7}$) or to acetylcholine ($10^{-7}$). But the pretreatment of the intestine with the drugs each abolished or depressed the stimulatory action of nicotine ($10^{-7}$).

C. Effect of the Drugs on Salivary Secretion

Dogs, weighing 5 to 15 kg, were used under amytal sodium anesthesia. Wharton's duct, Rivinus' duct and Stensen's duct were usually cannulated bilaterally. The unilateral chorda tympani or the Jacobson's nerve was stimulated electrically with the square wave stimulator. The stimuli applied were 10/sec in frequency, 1 msec in duration and submaximal in intensity. The secretory volume was recorded on a kymograph by use of a drop recorder, electrically operated.

1) Effects of the drugs on the response of salivary glands to stimulation of the secretory nerve

The administration of the drugs all depressed the submaxillary or parotid secretion in response to stimulation of the nerve. The depressive action on salivary secretion appeared quickly, within 10 to 30 seconds after the injection. The duration and intensity of the depressive action of the drugs depended on the dose administered. The minimal effective doses needed to depress the secretion are illustrated in Table 6. The duration of

![Diag. 7. Effects of MS (0.1 mg/kg) and LF (0.1 mg/kg) on the response of the submaxillary secretion induced by stimulation of the chorda tympani, and the antagonistic action of eserine. Submaximal stimulation with square waves, 10/sec in frequency and 1 msec in duration.](Image)
the abolishment of the salivary secretion in response to 0.1 mg/kg of MS or LF was 5 minutes and the duration of response to the same dose of C; was 10 minutes. The salivary secretion induced by stimulation of the Jacobsen's nerve was similarly depressed or abolished after administration of the drugs. The salivary secretion of the lingual gland in response to stimulation of the postganglionic nerve was not depressed even after the administration of the drugs in doses sufficient to abolish the submaxillary or the parotid secretion.

2) Antagonistic action of cholinesterase inhibitors on the depressive action of the alkaloids on salivary secretion

The depressive action of the drugs on salivary secretion induced by stimulation of the innervated secretory nerves was antagonized markedly by the administration of the cholinesterase inhibitors such as eserine, prostigmine and berberine. Although the administration of the inhibitors themselves augmented the salivary secretion, the depressive effect of the alkaloids on the salivary secretion was quickly antagonized by the injection of the non-effective doses of the inhibitors (20 to 30¿/kg for eserine, 5 to 10¿/kg for prostigmine and 50 to 100¿/kg for berberine). The depressive effect of the drugs on salivary secretion was also inhibited by the administration of these cholinesterase inhibitors. The depressive effect of atropine was not, while the effect of atropine-N-methylbromide was antagonized by the inhibitors. The antagonistic action of the inhibitors was strongest in prostigmine and weakest in berberine. The repeated injection of prostigmine revealed a similar intensity of the antagonistic action, while the same injection of eserine or berberine revealed a decrease of the antagonistic effect.

3) Effect of the drugs on secretory action of pilocarpine

The minimal effective dose to induce salivary secretion in the submaxillary gland was 10 to 20¿/kg. The secretory response to 30 to 50¿/kg of pilocarpine was usually depressed after the administration of MS or LF in doses of 0.05 to 0.1 mg/kg. Increasing the dose of the drugs an abolishment of the response to pilocarpine was not induced. Occasionally it was observed that the response to pilocarpine was augmented by MS or LF. These augmentative effects were observed in summer.

4) Effect of MS or LF on the sympathetically denervated gland

The effects of the administration of MS or LF or the response of the sympathetically denervated submaxillary gland, in which the superior cervical ganglion had been extirpated 10 to 14 days previously, to stimulation of the chorda tympani was studied. The results revealed that the depressive action of the drugs on the salivary secretion showed no difference of action compared to the control side.

5) Effect of MS or LF on salivary response of the submaxillary glands to stimulation of the cervical sympathetic nerve

Electrical stimulation of the cervical sympathetic nerve elicited a viscous secretion of the submaxillary gland, which decreased gradually in spite of continued stimulation. The response also disappeared after the administration of 1 to 2 mg/kg of MS or LF.

6) Effect of MS or LF on the secretory response to adrenaline
The administration of 10 to 20 μg/kg of adrenaline induced a mucinous salivary secretion of the submaxillary gland. The administration of MS, LF or C₃ in the doses of 0.1 to 2.0 mg/kg slightly potentiated the response of the gland to adrenaline.

7) Effects of the alkaloids on the action of acetylcholine in the atropinized animal

The submaxillary gland did not respond to the systemic administration of 1 to 2 μg/kg of acetylcholine, but the salivary response of the gland to large doses of the drug could not be repeated, because the muscarinic effects of the drug manifested markedly. The administration of 500μg/kg of acetylcholine to the atropinized animal caused a mucinous salivary secretion, which ceased after bilateral adrenalectomy and also after the injection of 1 to 2 mg/kg of MS, LF or C₃.

V. Effect of the Alkaloids on the Nictitating Membrane of the Cat

Cats, weighing 2 to 3 kg, were used under evipan sodium anesthesia. The bilateral or the unilateral contraction of the membrane in response to stimulation of the cervical sympathetic nerve was recorded on a kymograph via an isotonic lever, magnified 7.5 times. The stimuli applied to the nerve were the same as in the experiments of salivary secretion.

Effects of the Alkaloids

1) Continued stimulation of the preganglionic cervical sympathetic fibers

The nictitating membrane revealed a maximal contraction in response to stimulation of the preganglionic fibers of the cervical sympathetic nerve, which reached maximal contraction within 30 seconds and continued throughout the stimulation. The administration of the alkaloids all relaxed the contracted membrane. The doses of the drugs needed to cause an 80% relaxation of the membrane are shown in Fig. 8. The relaxing action of MS or LF was not inferior to that of C₃, but markedly inferior to the action of C₃ in duration.

2) Effect of the alkaloids on the response of the membrane to intermittent stimulation of the preganglionic cervical sympathetic fibers

After the contractive response of the membrane revealed a uniform reaction to preganglionic stimulation of the cervical sympathetic fibers for 10 seconds, the effects of the administration of various doses of the alkaloids on the response of the membrane were observ-
The results are illustrated in Table 7, concerning the doses of the drugs needed to relax the membrane about 100%, the duration of the action of the drugs and the relative efficiency of the drugs. The depressive action of MS or LF was superior to the action of Cs. MC, MF, and PV was markedly weaker than the action of MS. The duration of action of MS or LF was not inferior to that of Cs. The depressive action of the drugs manifested quickly, while the same action of Cs slowly.

### Table 7. Intravenous doses of the drugs needed to induce complete depression of the response of the nictitating membrane of the cat in response to stimulation of the cervical sympathetic nerve.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Dose (mg/kg)</th>
<th>Relative Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>LF</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>MC</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>MF</td>
<td>2.0</td>
<td>0.25</td>
</tr>
<tr>
<td>SF</td>
<td>5.0 50% depression</td>
<td>—</td>
</tr>
<tr>
<td>PV</td>
<td>5.0 10% depression</td>
<td>—</td>
</tr>
<tr>
<td>C₈</td>
<td>0.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

3) **Effects of the alkaloids on the response of the membrane to stimulation of the postganglionic cervical sympathetic nerve**

The administration of the alkaloids in doses of 1.0 to 2.0 mg/kg did not affect or slightly potentiated the response of the nictitating membrane to stimulation of the postganglionic fibers of the cervical sympathetic nerve.

4) **Effects of the alkaloids on the tone of the nictitating membrane**

The administration of MS, LF, MC, MF and C₈ in doses of 1.0 to 3.0 mg/kg did not affect or slightly relaxed the membrane, while the administration of SF in doses of 0.025 to 1.0 mg/kg, which did not block the transmission in the superior cervical ganglion, relaxed markedly the membrane.

5) **Effects of the alkaloids on the responses of the membrane to adrenaline, noradrenaline, acetylcholine and pilocarpine**

The administration of the alkaloids in doses of 1.0 to 3.0 mg/kg potentiated the response of the normal and the denervated membrane to adrenaline or to noradrenaline. The effects were more marked in the spinal animal than in the intact animal. SF did not
effect the response of the membrane to both amines. The response of the membrane to acetylcholine or pilocarpine was almost not affected by these drugs.

6) Effects of the alkaloids on the contractive response of the membrane of the atropinized cat to large doses of acetylcholine

The response of the denervated membrane of the atropinized spinal cat to 500 \( \gamma /\text{kg} \) of acetylcholine was abolished by the administration of MS, LF or C; in doses of 2.0 to 3.0 mg /kg.

7) Effects of the alkaloids on the response of the membrane to splanchnic nerve stimulation

The responses of the normal and the denervated nictitating membranes of the spinal cat to stimulation of the peripheral end of the cut splanchnic nerve was also depressed after the administration of the alkaloids in doses of 1.0 to 3.0 mg/kg. The response of the normal membrane was more easily affected than the response of the denervated membrane. The depressive action of the three drugs, MS, LF and C; did not reveal any difference, but C; showed a surprising effect in duration.

VI. Effect of the Drugs on Uterine Movements in Vitro

The uterus of the mouse or rabbit was extirpated and the effects of the drugs on the uterine movements in vitro was investigated by use of Magnus' method. These alkaloids in concentration below \( 10^{-5} \) did not affect the uterine movements of the rabbit or mouse. Neither the response of the uterus to adrenaline \( (10^{-5}) \) nor to acetylcholine \( (10^{-6}) \) was affected by the application of the drugs in the above concentration.

VII. Acute Toxicity in Mice

The LD 50 of the alkaloids in mice are shown in Table 8. The acute toxic symptoms common to all the drugs were as follows. A few minutes later the intraperitoneal injection of the drugs a marked muscular paralysis was observed. The muscular paralysis appeared especially in the respiratory muscles. Just before or during the respiratory arrest a tonic convulsion, by which the animal were killed, was observed.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>LD 50 (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>12</td>
</tr>
<tr>
<td>LF</td>
<td>14</td>
</tr>
<tr>
<td>MF</td>
<td>19.6</td>
</tr>
<tr>
<td>MC</td>
<td>84.3</td>
</tr>
<tr>
<td>( \delta )-Tubocurarine</td>
<td>1.6</td>
</tr>
</tbody>
</table>

DISCUSSION

The pharmacological properties of a series of quaternary alkaloids isolated from Magnolia and Cocculus plants by Prof. Tomita et al. (1) were investigated.

I. Curare-like Action

The curare-like action of the drugs were investigated on the sciatic-gastrocnemius, -soleus and -tibialis anterior preparation of the rat in situ and on the extirpated rectus abdominis muscle of the frog. Paton and Zaimis (10) proved that the curarizing action of \( C_{10} \) is the least
sensitive and the same action of \( d \)-tubocurarine is the most sensitive in rats. The results in this experiment also proved a similar differential response to \( C_{10} \) and \( d \)-tubocurarine. The ED 50 of the curarizing action in rats revealed 50 \( \mu \)g/kg for \( d \)-tubocurarine and 4.0 mg/kg for \( C_{10} \). The administration of MS, LF, MC, MF, SF and PV all depressed the response of the muscles to indirect stimulation but not to direct stimulation. The activity of the drugs are in the following order: MS > LF > MC > MF > SF > PV. Even the curarizing action of MS, however, corresponded to one hundredth of the action of \( d \)-tubocurarine.

Paton and Zaimis (11), Zaimis (12), Hall and Parkes (13) showed that the characteristic figures of the curarizing action of \( d \)-tubocurarine consist in; i) the stronger respiratory paralysis in comparison to the curarizing action of the skeletal muscles, ii) the cumulative effect by the repeated injection of the drug, iii) more sensitive responses of the red muscles than those of the white muscles, iv) depression of not only the twitching of the muscle but also of the contracture of the muscles, v) antagonistic effect by the cholinesterase inhibitors, vi) antagonistic effect by \( C_{10} \), vii) Non-depolarizing action on the end-plate potential of the muscles. The results of the experiments here proved that the curarizing action of the drugs all agreed qualitatively to the same action of \( d \)-tubocurarine except the seventh point, which was not studied.

Several discussions on the action of tubocurarine may be found in the literature. Gray and Halton (14) showed that the administration of \( d \)-tubocurarine paralysed lastly the respiratory muscles. This was denied by Paton and Zaimis (10), and Unna et al. (15) in experiments in the cat, which is less sensitive to \( d \)-tubocurarine and in experiments in the rat, which is most sensitive to \( d \)-tubocurarine. Also according to the clinical evidence the spontaneous contraction of the diaphragm or the intercostal muscles are the most sensitive to \( d \)-tubocurarine, making respiratory arrest, the most feared side reaction (16). However, the respiratory paralysis does not result from paralysis of the respiratory centre, because the potential response of the phrenic nerve was not affected (10), and the asphyctic convulsion by the drugs did not appear under artificial respiration in this experiment.

The repeated administration of \( d \)-tubocurarine manifested a cumulative effect (15,17). The same effects were also obtained by the administration of the alkaloids. Kalow (18) indicated in 18 hours the urinary excretion of \( d \)-tubocurarine was only one-third of the amount of the drug administered, therefore the remaining amount of the drug in the body fluid raised the threshold to the action of the drug. The cumulative effect of the alkaloids were supposed to be resulted from a similar mechanism. That the cumulative effects of the alkaloids were not observed in regards to the ganglion blocking action of the drug described below, was because of a different response, in the affinity of the receptor substance of the ganglionic and the myoneural synapses. Holmes et al. (19) discussed the action of \( d \)-tubocurarine concerned with the regulatory process of diffusion and reversible dissociation between drug and receptors.

Paton and Zaimis (11) showed that the response of the red muscles was more sensitive than that of the white muscles, and the dose of \( d \)-tubocurarine which paralysed the soleus
muscle in response to indirect stimulation inhibited the tibialis anterior muscle only to about 50%. The results in this experiment also revealed similar effects concerning the action of these alkaloids.

Blaschko et al. (20), Hobbiger (21), McFarlane et al. (22), Wescoe et al. (23), and Randall (24) concluded that there existed a correlation between the activity of the cholinesterase inhibitors and the decurarizing action of the inhibitors. The antagonistic action of such cholinesterase inhibitors as eserine, prostigmine and berberine to the action of the curarizing agents as was proved by Wescoe and Riker (25), Jacobsohn and Kahlson (26), were studied. The administration of the inhibitors during or after manifestation of the curarizing effect inhibited or blocked the effect. The activity of the inhibitors to antagonize the curare-like action of the drugs were in the following order. Prostigmine > eserine > berberine. The repeated injection of eserine potentiated the curarizing action of the drugs, while prostigmine and berberine revealed similar antagonizing effects. Bacq and Brown (27) concluded that the depressive effect by a large dose of eserine on the response of the muscle to indirect stimulation resulted from the cumulative effect of acetylcholine in the myoneural junction. It was supposed that the potentiating effect on the action of the drugs by a large dose or the repeated injection of eserine resulted from the direct action of the drug on the myoneural junction of the muscles, even if the suggestion by Riker and Wescoe (25) that the anticuscar action of cholinesterase inhibitors concerned with only the cholinesterase activity of the tissue is permitted.

The initial administration of C19 potentiated the response of the muscles in the cat (12) and in the rat (28). In this experiment the administration of C19 also temporarily potentiated the response of the muscle to indirect stimulation. The initial administration of C19 inhibited or antagonized the curare-like action of d-tubocurarine, MS, LF, MC or MF, as shown by Hutter and Pascoe (29), Wescoe and Riker (25), Paton (30), Hall and Parkes (13). The mechanism of the antagonizing action of C19 against the curarizing action of the drugs was supposed to result from the acetylcholine-like action of C19, as was concluded by the above authors.

It may be concluded that all the results described above showed that the curarizing action of the drugs belong to the d-tubocurarine type of action, and the mechanism of action consist in the competitive blocking at the myoneural sites.

II. Ganglion Blocking Action

The effects of the drugs on the autonomic nervous system was also investigated. The results revealed a potent ganglion blocking action of the drugs, as may be concluded from the results that the effect of stimulation of the preganglionic autonomic nerves were abolished, while the effects of stimulation of the postganglionic fibers of the nerves were not affected by the administration of the drugs.

The hypotensive action of the quaternary isoquinoline derivatives, which was concluded as a result of the ganglion blocking action, was reported by O'Dell et al. (31), Winbury (32), and Hjort et al. (33). Some of the derivatives revealed a ganglion blocking action about
7.5 times as strong as the action of TEA.

A. Ganglion Blocking Action on the Various Ganglia

1) Sympathetic ganglion

The response of adrenal to these drugs did not reveal a marked difference compared to the response of the superior cervical ganglion. When the endorgan, on which the response to the drugs tested, was chronically denervated as in the case of the nictitating membrane of the cat, it was always necessary to administer a large dose of the drug to block the response. The marked difference between the normal and the denervated endorgan consists in the different sensitivity of the endorgan to the transmitter substance, especially, those circulating in the blood stream.

2) Parasympathetic ganglion

Experiments were performed on the ganglia located in the intestine, the heart and the salivary gland. The ganglion the most sensitive to the drugs, was that of submaxillary gland in the dog. The administration of C, MS and LF even in the doses of 0.05 to 0.1 mg/kg depressed the submaxillary secretion in response to stimulation of the chorda tympani. The parasympathetic ganglion located in the intestine was the least sensitive. Oyaizu (34) proved that the response of the gastric contraction to stimulation of the vagus nerve was not abolished by the large doses of C, MS or LF. It may be supposed that the reason for the response of Trendelenburg's peristaltic reflex in vitro being more sensitive than the response of the cervical superior ganglion in situ resulted from the differences of experimental condition or resulted from the more sensitive response of the intestinal ganglion which control the peristaltic reflex.

3) Ganglion blocking activity and intensity of nerve stimulation

In the comparison of the ganglion blocking agents, the intensity of nerve stimulation gave rise to a discussion. The uniform stimulation of the nerve in the same intensity was performed in the same kind of animal, but not in the individual animal, because the response of the individual differed considerably. The reason why submaximal shock was used for stimulation of the nerve, was to maintain the preparation long lasting. The depressive action of the drug on the transmission of the ganglion was stronger by weak stimulation of the nerve than by strong stimulation.

B. Hypotensive Action

All the drugs tested induced a fall of the blood pressure. Although some of the alkaloids revealed a muscarinic action, the mechanism of the hypotensive action of the drugs may be induced by the blocking action on the sympathetic ganglia which maintained the tone of the vessels, because the hypotension caused by the drugs was not affected by bilateral vagotomy, full atropinization or bilateral resection of the carotid body. The facts that the hypotensive actions of the drugs were weaker in the spinal animal than in the intact animal and that the drugs blocked the transmission in the adrenal and in the superior cervical ganglion were also important evidence. The hypotensive action of the drugs differed from that of C, where the response developed and recovered quickly.
C. Antagonistic Effect Against the Action of Nicotine

Tripod (35) classified the sites of the action of nicotine, as i) on the ganglionic synapse, ii) on the central nervous system, and iii) on the postganglionic receptor. The stimulant action of nicotine on these receptors was abolished after the administration of ganglion blocking agents (10, 36). The nicotinolytic action of LF, which was not inferior to the same action of C, was proved by Maeda (4) in the blood pressure and the extirpated organ of the cat and rabbit. Similar results were obtained on the blood pressure, extirpated intestine, heart and vessels concerning the effect of the drugs. The action of MS or LF was as strong as the action of C. The fact that the stimulating action of nicotine on the extirpated vessels, which contained no ganglion cell, was also abolished by the drugs, showed the postganglionic site of nicotine, and also showed the response of the postganglionic receptors to the ganglion blocking agents as was concluded by Shimamoto et al. (37) and Kanauchi (38, 39).

D. Antagonistic Effect of the Cholinesterase Inhibitors to the Action of the Alkaloids

The ganglion blocking actions of the alkaloids including C, was antagonized by such cholinesterase inhibitors as eserine, prostigmine and berberine. The effect were mostly investigated on the submaxillary secretion in details. From the results, it was concluded that the site of the antagonistic action was the ganglionic synapses of the submaxillary ganglion. The activity of the inhibitors were in the following order. Prostigmine>eserine>berberine. The repeated injection of prostigmine had almost the same effect, while that of eserine was decreased by repetition. Koppanyi and Karczmar (40) denied the effect of cholinesterase inhibitors as DFP on the ganglionic transmission, but Marazzi and Jarvik (41), and Burgen et al. (42), postulated the augmentative effect of the inhibitors. The mechanism of the antagonizing effect consist in the competitive inhibition of the ganglion blocking agents, as was proved by Kamijo and Koelle (43) with TEA.

E. Chemical Constitution and the Ganglion Blocking Action

A significant rule between the chemical constitution and the ganglion blocking action was not obtained from the results. SF, which is a quaternary compound of epinine and is weak in the ganglion blocking action, revealed a weak sympathomimetic action on blood pressure and a weak nicotinic action on the rectus abdominis muscle of the frog.

It was supposed that the position of -OH or -OCH₃ in the phenyl ring modified the action of the alkaloids. The weak curarizing action of the drugs of this series was in striking contrast to the potent curarizing action of the decamethylene derivatives of bis-laudanosinium compounds which was proved by Taylor (44). The weak curarizing action of the drugs may be related to the absence of a long methylene chain, which according to Barlow’s concept (45) modifies the Van der Waals’ forces between the drug and the receptor. The inert action of PV showed the difference between pyridine and tetrahydropyridine nucleus in the isoquinoline ring.

III. Muscarinic Action of the Alkaloids

The administration of the alkaloids manifested a strong muscarinic action on the rhy-
thmical movement of intestine in the rabbit, which was abolished by atropine. The effects were not marked in the extirpated intestine. The stimulating effect of the drugs in vivo may be, in some parts, resulted from the ganglion blocking effects. The potentiating effect of PV on the submaxillary secretion in response to stimulation of the chorda tympani may result from the muscarinic action or the inhibiting action of the drug on the cholinesterase activity. The injection of MS dilated the perfused vessels of the rabbit ear, while LF and C3 did not. The dilatatory effect of MS was also abolished by atropine. The effect was also supposed to result from the muscarinic action of the drug.

IV. Nicotinic Stimulating Action of the Drugs

Although the administration of the drugs, with an exception of a few, dilated the ear vessels of the rabbit, the same injection of the drug after treatment of atropine constricted the vessels. Some of the drugs which did not dilate the vessels, also revealed the same response. The constrictor effect was supposed to results from similar mechanism as that of acetylcholine which was proved by Shimamoto et al. (46).

V. Effects on the Action of Pilocarpine

The hypotensive response to pilocarpine was inhibited and the hypertensive response was markedly potentiated by the drugs. The results well agreed with that of Root (47). Besides, the response of the submaxillary gland and the nictitating membrane of the cat to pilocarpine were depressed by the drugs. Shimamoto and Inoue (48) concluded that pilocarpine has three sites of actions, namely, ganglionic, postganglionic cholinergic and post-ganglionic adrenergic. Indeed, pilocarpine affects the adrenergic and ganglionic receptors. After the administration of the drugs the adrenergic effect of pilocarpine was potentiated and thus the hypertensive response to pilocarpine might be induced.

VI. Potentiating Effect of the Alkaloids on the Response to Adrenaline

The administration of the drugs potentiated the responses of the blood pressure, nictitating membrane, perfused vessels and pupils in response to stimulation of the sympathetic nerve and to adrenaline or to noradrenaline. The effects were supposed to result from the action on the postganglionic site of adrenergic nerves, which was masked under the normal condition (39–41). The administration of the drugs inhibited the depressor effect and so potentiated the pressor effect of adrenaline or noradrenaline. The weaker effect of MS in comparison to LF or C6 may be supposed to result from its muscarinic effect, which interferes with the action of both amines.

VII. Relaxing Action of the Nictitating Membrane of the Cat

Although SF relaxed the normal and the denervated nictitating membrane of the cat markedly, the response of the membrane to nerve stimulation or to adrenaline was only slightly affected. The mechanism of the relaxing action of SF could not be explained from the results in this experiment.
SUMMARY

The pharmacological actions of the quaternary alkaloids isolated from the Cocculus and Magnolia plants, namely, menisperine, laurifoline, magnocurarine, magnoflorine and salicifoline (all chlorides) were studied. The results obtained are summarized as follows.

1. These drugs showed d-tubocurarine-like curarizing actions on the sciatic-gastrocnemius preparation of the rat in situ and on the rectus abdominis muscle of the frog in vitro. The action of menisperine, which was strongest among the alkaloids, was as strong as one-hundredth of d-tubocurarine.

2. These drugs all revealed hypotensive effect on the dog, cat and rabbit, but the duration of the effect was shorter than that of Co.

3. These drugs all showed considerable ganglion blocking action on the various structures, among which the submaxillary ganglion was the most sensitive and the adrenal was least. Menisperine and laurifoline were most active and were as strong as Co, but the duration of action of the drugs was shorter than that of Co.

4. These drugs showed nicotinolytic activity. The effects elicited by menisperine or laurifoline were as strong as that by Co.

5. The ganglion blocking or the curarizing activities of the drugs were antagonized by the cholinesterase inhibitors such as eserine, prostigmine and berberine.

6. Some of these alkaloids showed muscarinic effects on the intestinal movements of the rabbit in vitro and in vivo, and perfused car vessels of the rabbit.

7. These drugs reversed the hypotensive action of pilocarpine and potentiated the hypertensive action of adrenaline.

From the results mentioned above, it was concluded that these drugs revealed ganglion blocking activity in common, and some of the drugs showed an effect as active as Co.

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