PHARMACOLOGICAL PROPERTIES OF 3-(*p*-CHLOROBENZYL) QUINOLIZIDINE TARTARATE (QB-1), A NEW OXYTOMIC

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On the pharmacological investigation of quinolizidine derivatives, it was discovered that one of them had marked oxytomic activity. The chemical structure of this compound [3-(*p*-chlorobenzyl) quinolizidine tartarate; QB-1] is as follows:

This compound was synthesized by Matsuo *et al.* (1). It is a colorless crystal consisting of two isomers, isomer A (m.p. 98–103°C) and isomer B (m.p. 93–96°C). The ratio of isomer A to isomer B is 6 : 4.

The present paper describes oxytomic activity of QB-1 together with other pharmacological properties.

METHODS

1. Toxicity

1) Acute toxicity

i) Subcutaneous administration

Male mice, *ddY* strain, six weeks of age, were divided into groups and received subcutaneous injection. Mortality was observed 48 hours after the injection. Calculation of LD₅₀ was according to Behrens-Kärber-Guadum modification.

ii) Intravenous administration

LD₅₀ by intravenous injection in female mice (age 8 weeks, *ddY* strain) was determined in the same way as above. Up and down method was employed to determine LD₅₀ by intravenous injection in male *ddY* strain mice (age 5 weeks), and in male and female Donryu strain rats weighing 130 to 180 g and 130 to 150 g respectively.

2) Subacute toxicity

Studies on subacute toxicity were carried out on female, *ddY* strain mice, and female Donryu strain rats. The mice were administered intravenously 25, 12.5, 5.25, 3.13 and

1.56 mg/kg of QB-1 for 10 days, respectively. The rats received subcutaneous injection of 60, 30, 15 and 7.5 mg/kg of QB-1 for 30 days, respectively. Control group received a corresponding volume of physiological saline solution.

2. Behavioral change

General toxic symptoms were observed in mice, rats, rabbits and dogs after the intravenous injection of large doses of QB-1 or sparteine sulfate.

3. Effects on uterus

1) *In vitro* experiment

Using the excited uteri of Wistar strain, 10-week-old rats in diestrus, contracting potency was comparatively determined following the method reported by Kumagai *et al.* (2). Strips were obtained from the excised uteri which had been stored for 24 hours at 5 to 10°C in a refrigerator in a low calcium modified Lock-Ringer solution, and then suspended in an organ bath consisting of the same solution. The bath was kept at a constant temperature of 20°C to prevent spontaneous movement of the uterine strip. No attempt was made to standardize the contraction height, thus the contraction height (mm) on the smoked paper was measured directly and regarded as response. The result of 2×2 parallel line assay were subjected to the calculation for the true relative potency of QB-1 to sparteine sulfate.

2) *In vivo* experiment

Mature female rabbits weighing 2.0 to 3.8 kg were used in this experiment. Under urethan or pentobarbital anesthesia, a thin rubber balloon (5 mm in diameter and 70 mm long) was inserted into the uterus. The balloon was filled with water and connected with an aqueous manometer under the pressure of 10 to 15 cm H₂O. The uterine activity was recorded on a smoked paper (3). For the purpose of comparison the area under the tracing was measured using a planimeter until the contraction curve showed almost the same figure as before medication. The drugs were injected to the femoral vein at the intervals of 25 minutes. The relative potency of QB-1 to sparteine sulfate and ergometrine maleate was calculated by the same manner as *in vitro*.

4. Effects on small intestine

Strips of the jejunum obtained from male guinea pig were used in Magnus' method. The temperature of the organ bath was kept at 25°C.

The movement of the small intestine *in vivo*, was traced kymographically by Trendelenburg's method using adult female rabbits anesthetized with urethan (1.2 to 1.5 g/kg).

5. Effects on cardiovascular system and respiration

1) *Effects on isolated toad heart*

The experiments were carried out by the method developed by Yagi.

2) *Effects on the blood vessels*

Pithed toads were used for the hind limb blood vessel perfusion experiments in the usual manner according to Laewen-Trendelenburg's method (4). The effects of drugs were estimated by counting the number of drops flowed from the ventral venous. The pressure of inflow was controlled by the height of the Mariotte bottle.

3) *Effects on blood pressure and respiration*

The effects of intravenously administered drugs on the carotic arterial blood pressure and the respiratory movement of the anesthetized rats (280 to 300 g, male), rabbits (2.5 to 3.5 kg, male and female) and cats (2.5 to 3.6 kg, male and female) were studied. These animals were anesthetized with pentobarbital. Dogs were anesthetized with amobarbital, and blood pressure was recorded from the femoral artery. The carotic arterial blood flow was also recorded in dogs, using the bubble flow meter.

4) *Effects on electrocardiogram*

Electrocardiograms of two urethan anesthetized rabbits and three pentobarbital anesthetized cats were obtained after the intravenous administration of QB-1, sparteine sulfate and quinidine sulfate. All animals were placed in a shielded room and needle electrodes were set just under the skin. Standard lead II was taken in rabbits, and either of lead II or chest lead (V_2L or V_4R) in cats. Records were made by means of Type RS-15A Electrocardiograph (Fukuda Electro K.K.) with a speed of paper at 50 mm/sec and a sensitivity of 1.0 or 1.5 cm for the input of 1 mV. P-R, QRS, Q-T and R-R intervals were measured at various times after the intravenous injection of the drugs. Also, the R-R intervals of female rats (Donryu strain, 180 to 230 g) were measured by means of an oscilloscopic recorder at various times.

6. *Effects on central nervous system*

1) *Effects of pentobarbital on the acute toxicity of QB-1*

Female mice of *ddY* strains, 8 weeks of age, were divided into groups of five each and received various doses of QB-1 or sparteine sulfate intravenously 15 minutes after pretreatment with pentobarbital (35 mg/kg, i.p.). Mortality was observed 24 hours after this procedure.

2) *Effects on the EEG*

Cortical and subcortical EEG activity and blood pressure were recorded in curarized rabbits and cats under artificial respiration. In rabbits, the uterine motility was recorded simultaneously. The location of the inserted electrode tip was verified afterwards.

RESULTS

1. *Toxicity*

1) *Acute toxicity*

The values for LD_{50} of QB-1 and sparteine sulfate are compared in Table 1. As indicated, the acute toxicity of QB-1 in subcutaneous route in male mice was about one

TABLE 1. LD₅₀ expressed in mg per kg of QB-1 and sparteine sulfate in mice and rats.

	Mouse			Rat	
	Male	Female		Male	Female
Route of administration	s.c.	i.v.	i.v.	i.v.	i.v.
QB-1	430	33.9	31.8	45.0	56.2
Sparteine sulfate	117	23.7	15.0	30.4	50.7

third of that of sparteine sulfate. In intravenous injection, however, there was no remarkable difference in their acute toxicity regardless of the animal species used and sexes.

2) *Subacute toxicity*

i) *Mice*

Those mice even in the higher dose levels, 25 and 12.5 mg/kg groups, did not show a retarded weight increase but there were no obvious symptom and death at any time. Hematological findings of few mice in group received 12.5 mg/kg showed slightly normoblast, but red and white cell counts remained within normal limits. At autopsy the animals were examined for gross and microscopic pathologic changes, and no abnormalities were observed.

ii) *Rats*

There was no significant difference in weight gains after 30 days. Behavior and appearance of animals throughout the experiment was normal, but local ulceration and necrosis were observed at the injected site of all animals except 7.5 mg/kg and control group. The hematological examinations of control and test animals revealed insignificant differences between the control and test groups. Gross and microscopic examination on the liver, kidneys, stomach, spleen, brain, pancreas, adrenals, thymus and heart did not reveal any cellular changes in the test animals except suppurative inflammation and necrosis of injected site of QB-1.

2. *Behavioral change*

In small animals (mice and rats), many symptoms were commonly observed in both drugs (QB-1 and sparteine sulfate), which might indicate the stimulation of central nervous system especially the spinal cord, such as Straub's tail erection, increased knee jerk reflex and various convulsive movements. Opisthotonus was a characteristic symptom in QB-1 and observed in all the animals tested. Tremor was common to both drugs in mice but not in rats, rabbits and dogs. Convulsive movement was produced by the intravenous injection of 5 mg/kg of QB-1 in rabbits and 4 mg/kg in dogs. In a dose of 10 mg/kg only one female rabbit was dead and the other two male rabbits survived. A dog received 10 mg/kg of QB-1 intravenously showed serious convulsive movements but survived. But when injected again 20 mg/kg of QB-1, 1 hour after the first dose of 10 mg/kg, the dog was dead with weaker convulsive movements than before. In the case of sparteine sulfate, rabbits and dogs were generally dead without remarkable convulsion.

Stimulation of respiration and salivation were also common to both drugs. Vomiting that was characteristic to sparteine sulfate, was not observed in QB-1. It was considered that the death caused by both drugs was due to the respiratory paralysis.

TABLE 2. Log-concentration response relationship of uterine contraction, *in vitro*, between QB-1 and sparteine sulfate.

Concentration Log (Conc.)	Sparteine sulfate		QB-1	
	66.8 γ /ml 1.8248	29.8 γ /ml 1.4742	5.48 γ /ml 0.7388	2.44 γ /ml 0.3874
1	21.5	1.5	14.5	2.0
2	30.0	16.0	27.0	14.0
3	17.5	7.5	21.0	9.0
4	10.5	1.0	11.5	4.0
Mean	19.9	6.5	18.5	6.8

Values were expressed as uterine contraction in mm on the kymograms.

FIG. 1. Volume change of rabbit uterus *in vivo* following intravenous injection of various doses of QB-1, sparteine sulfate and ergometrine maleate. Doses were expressed per kg of body weight; time scale, minute; experimental No. 2 and No. 5, the same animal. Mature virgine rabbits were used except a rabbit used in experiment No. 4, that having given birth one week before.

3. Effects on uterus

1) *In vitro* experiment

The results obtained from 4 rats are summarized in Table 2. Since the deviation from parallelism was not significant at 5% level in the concentration range tested, the calculation for the true relative potency according to the parallel line assay is valid, and gave the value of 12.0 (9.62 to 14.9, 95% confidential limit) for QB-1, where the potency of sparteine sulfate was expressed as 1.0.

2) *In vivo* experiment

In Fig. 1, it is shown the examples of contraction induced by several doses of QB-1 and sparteine sulfate, and 0.2 mg/kg ergometrine maleate. As can be seen in this figure, these drugs produce the augmentation of uterine movement and rise in tonus.

The experiments for a quantitative comparison were performed on mature virgin rabbits. Sparteine sulfate as well as ergometrine maleate was used as a referential compound. Tables 3 and 4 are the summaries of the results both of which were obtained in urethan anesthetized rabbits. Since the statistical analysis

TABLE 3. Dose-response relationship of uterine contraction, *in vivo*, between QB-1 and sparteine sulfate.

	Sparteine sulfate		QB-1	
Dose mg/kg	7.2	3.2	3.24	1.44
Log (Dose)	0.8573	0.5052	0.5105	0.1584
1	59.0	15.0	67.0	22.0
2	20.0	5.0	28.0	10.0
3	10.0	6.8	23.5	9.3
4	10.7	6.3	15.2	6.5
Mean	24.9	8.3	33.4	12.0

Values were expressed as the area under the uterine contraction curve in 1.0 cm² on the kymograms.

TABLE 4. Dose-response relationship of uterine contraction, *in vivo*, between QB-1 and ergometrine maleate.

	Ergometrine maleate		QB-1	
Dose mg/kg	0.2	0.1	2.0	1.0
Log (Dose)	1.3010	1.0000	0.3010	0.0000
1	30.0	19.5	22.0	14.5
2	29.0	19.5	31.5	22.5
3	55.0	32.5	37.5	24.5
4	49.5	26.0	48.0	30.0
5	45.0	31.0	46.0	27.0
6	97.0	70.0	74.0	49.5
7	84.0	60.0	107.5	72.0
Mean	55.6	36.9	52.4	34.3

Values were expressed as the area under the uterine contraction curve in 1/7.5 cm² on the kymograms.

FIG. 2. Plot of maximum per cent of a decrease in heart rate and in amplitude of contraction against various concentration (g/ml) of QB-1, sparteine sulfate (Sp) and quinidine sulfate in the isolated toad heart.

proved that the deviation from parallelism and linearity were not significant in both cases ($P > 0.05$) in the range of tested doses. The parallel line assay was properly employed. The calculated relative potency was found to be 2.9 (1.7 to 6.6, 95% confidential limit) for QB-1, where the potency of sparteine sulfate was expressed as 1.0, and 0.09 (0.07 to 0.12, 95% confidential limit), where the potency of ergometrine maleate was expressed as 1.0.

4. Effects on small intestine

Both QB-1 and sparteine sulfate produced two inverse effects (contraction and relaxation) on the excised guinea pig jejunum in the higher concentrations over 2.5×10^{-5} g/ml according to the nature of preparation used. In some preparations which were frequently obtained after the repeated treatment with acetylcholine, followed by washing with Ringer's solution, relaxation of the tonus was observed with both drugs, otherwise contraction was usual response. In the lower concentrations below 10^{-6} g/ml, neither QB-1 nor sparteine sulfate showed any effect on the excised jejunum.

An intravenous injection of 1 mg/kg of QB-1 caused a weak increase in the tonus and a slight enhancement of a spontaneous movement of *in vivo* small intestine of rabbits. The duration of these responses was so short that it disappeared 10 minutes after the dosing. The magnitude and duration of the responses produced by QB-1 were almost equal to those by the same doses of sparteine sulfate.

FIG. 3. Changes in the blood pressure following the intravenous injection of 10 mg/kg of QB-1 or sparteine sulfate (Sp) to a male rat anesthetized with 80 mg/kg intraperitoneal injection of pentobarbital.

Resp. : Respiration, B.P. : Blood pressure.

5. *Effects on cardiovascular system and respiration*1) *Effects on isolated toad heart*

The depressive effects of QB-1, sparteine and quinidine sulfate are illustrated in Fig. 2. All the tested drugs showed a decrease in the heart rate and the amplitude of contraction. QB-1 showed the same degree of bradycardia as quinidine sulfate did, while QB-1 was the most potent in producing the diminution of the amplitude.

2) *Effects on the blood vessels*

Neither vasoconstricting nor vasodilating action was noted on the toad blood vessels after the perfusion with 0.1 ml (0.1 to 0.4 mg) of QB-1 solution (concentration, 10^{-3} to 4×10^{-3} g/ml).

FIG. 4. Changes in the respiratory movement and blood pressure of cat following the intravenous injection of QB-1 (5 mg/kg), quinidine sulfate (2.5 mg/kg) and sparteine sulfate (10 mg/kg).

B.P. : Blood pressure, Resp. : Respiration (Cat anesthetized with pentobarbital, 48 mg/kg i.p.).

3) Effects on blood pressure and respiration

Typical effects of QB-1 and sparteine sulfate on the blood pressure in rats are shown in Fig. 3. An intravenous injection of QB-1 of 5 mg/kg or 10 mg/kg produced a temporary fall of the blood pressure, which was then replaced by a rise, and this was characterized by a gradual return of the blood pressure to almost original or slightly below the original value, while sparteine sulfate produced a pronounced fall of the blood pressure after a slight transient rise. The change in the respiratory movement produced by QB-1 was shown associated with that in the blood pressure. Thus, a transient depression in the respiratory movement with a short fall of the blood pressure was followed by an increase in the frequency and amplitude of respiration which preceded the rise of the blood pressure. Duration of these changes in the respiratory movement produced by QB-1 was rather short, and recovery was attained within 1 or 2 minutes. On the other hand, sparteine sulfate produced a gradual increase in the frequency and amplitude of respiration, and is lasted much longer (usually 5 or 10 minutes) than QB-1.

The changes of the blood pressure observed in rabbits anesthetized with urethan or pentobarbital were essentially well in accord with those in rats; by QB-1 a rise after a transient fall, and by sparteine sulfate, often a fall only.

In cats, a slight rise of the blood pressure was observed after an intravenous injection of lower dose of QB-1 (1 mg/kg), while a marked fall without rise was produced following

FIG. 5. Changes in the respiratory movement (upper), blood pressure (middle) and carotid arterial blood flow (lower) following the intravenous administration of QB-1 to a male dog, 10 kg of body weight, anesthetized with 75 mg/kg intravenous injection of amobarbital. Time scale, 1 minute.

Resp. : Respiration, B.P. : Blood pressure, C.B.F. : Carotid blood flow.

FIG. 6. Blood pressure changes in various animals. Indicated doses were administered intravenously. Each downward arrow represents the initial fall and upward arrow the reversed rise of blood pressure which were observed following the injection of QB-1. Data from the rat, cat and dog were taken from each one animal.

FIG. 7. Alterations in electrocardiograms in cats following the intravenous injection of 5 mg/kg of QB-1 (A, Cat 1; B, Cat 2; C, Cat 3), 10 mg/kg of sparteine sulfate (D, Cat 1) and 2.5 mg/kg of quinidine sulfate (E, Cat 1). Cat 1, 1 mm=0.04 sec., 10 mm=1.5 mV; Cat 2 and Cat 3, 1 mm=0.02 sec., 10 mm=1.0 mV. Cats were anesthetized with 40 to 50 mg/kg intraperitoneal injection of pentobarbital.

the doses of more than 2.5 mg/kg. QB-1 produced three stages of changes in the respiratory movement which were similar to those in rabbits: firstly, a very transient depression or dyspnea, secondly, a marked increase in the frequency and amplitude, and thirdly, a gradual decrease in amplitude. Quinidine sulfate was administered to the same cat and substantially, the same changes were observed in both the blood pressure and respiratory movement as with QB-1 (Fig. 4).

The changes of the blood pressure and respiratory movement observed in dogs were similar to those observed in the other animals described above. Fig. 5 shows representative cases. Simultaneous recording for carotid arterial blood flow rate (C.B.F.) reflected exactly the changes in the blood pressure; thus, a fall of the blood pressure with the decreased blood flow rate, and then the reversed rise of the blood pressure with the increased blood flow rate. An enhancement in the respiratory movement was also shown.

FIG. 8. Alterations in electrocardiographic intervals at various times following the intravenous injection of QB-1, sparteine sulfate and quinidine sulfate to the cat anesthetized with 50 mg/kg intraperitoneal injection of pentobarbital. Each interval is expressed as per cent of the respective interval at 0 time.

Key : —○—, P-R ; —▲—, QRS ; —□—, Q-T ; —●—, R-R.

The changes of the blood pressure observed in various animals are summarized in Fig. 6.

4) Effects on electrocardiogram

Electrocardiograms were recorded in rabbits and cats. The results were consistent in both animals. As illustrated in Fig. 7, the very prompt alterations in the electrocardiograms were observed after the intravenous administration of 5 mg/kg of QB-1 to the cats. However, neither cardiac block nor arrhythmia was observed. During the period of 15 to 30 seconds after the injection of QB-1, there was a lowering of QRS complex which was followed by a rise, and then recovered to the original height in 1.5 minutes. The change in QRS complex produced by QB-1 was compared with those observed in quinidine sulfate, but it lasted considerably longer than in 5 mg/kg of QB-1, i.v., almost 5 minutes. There were also various alterations of T wave produced by both QB-1 and quinidine sulfate.

Representative changes in P-R, QRS, Q-T and R-R intervals at various times after the administration of QB-1 (5 mg/kg), sparteine sulfate (10 mg/kg) or quinidine sulfate (2.5 mg/kg) to the same cat are illustrated in Fig. 8. R-R interval was indicative of the reciprocal of heart rate. QB-1 produced prolongation of P-R and Q-T intervals which resulted in the lowering of heart rate, while the interval of QRS complex remained unchanged. On the other hand, both sparteine sulfate and quinidine sulfate produced the prolongation of QRS interval.

Fig. 9 illustrates the per cent of the maximum lowering of the heart rate after intravenous administration of various doses of QB-1 or sparteine sulfate to rats. Maximum lowering was recorded 30 seconds after the injection of QB-1 and 1 to 3 minutes after with sparteine sulfate. Although the magnitude of decrease in the heart rate was larger in QB-1 than in sparteine sulfate over the dose of 2 mg/kg, it should be noted that the lowering of the heart rate in a dose of 1 mg/kg did not differ, and that below 1 mg/kg a smaller extent of the lowering may be expected with QB-1 than with sparteine sulfate. Fig. 10 illustrates the case of cat.

FIG. 9. Dose response relationship of per cent maximum lowering of the heart rate in female rats anesthetized with 60 mg/kg intraperitoneal injection of pentobarbital. Each value for the dose of 1 mg/kg represents the average of 3 rats, and for the doses of 2 mg/kg and 4 mg/kg, the average of 2 rats.

Key: —▲—, QB-1; —●—, sparteine sulfate.

FIG. 10. Dose response relationship of per cent maximum lowering of the heart rate in a female cat anesthetized with 50 mg/kg intraperitoneal injection of pentobarbital.

Key: —▲—, QB-1; —●—, sparteine sulfate.

The results were in good agreement with in rats; below 1 mg/kg there was no appreciable lowering of the heart rate with both drugs. Maximum lowering was recorded a half to 2 minutes after the dose of 1 mg/kg of QB-1, and 3 minutes after with 5 mg/kg: a half minute after in a case of 2 mg/kg of sparteine sulfate, 1 minute with 5 mg/kg, and 5 minutes with 10 mg/kg.

6. *Effects on central nervous system*

1) *Effects of pentobarbital on the acute toxicity of QB-1*

Table 5 shows its result. This result shows that pentobarbital reduces the toxicity (central nervous system stimulant action) of these compounds.

2) *Effects of QB-1 on the EEG*

QB-1, 1 mg/kg, caused no remarkable changes in the EEG of the rabbit and cat, although administration of large doses (4 mg/kg) of QB-1 revealed the desynchronization pattern in the neocortex and regular slow waves in the hippocampus.

Effects of sparteine sulfate was similar as that of QB-1.

TABLE 5. Effects of pentobarbital on the mortality due to QB-1 or sparteine sulfate.

Dose mg/kg	Mortality due to QB-1		Mortality due to sparteine sulfate	
	without pentobarbital	with pentobarbital	without pentobarbital	with pentobarbital
36.0	4/5	1/5	—	—
30.0	3/5	1/5	5/5	3/5
25.0	2/5	0/5	5/5	1/5
20.8	—	—	5/5	2/5
17.4	—	—	4/5	1/5
14.5	—	—	2/5	—

DISCUSSION

There lies a great difficulty in quantifying the magnitude of uterine contraction *in situ* produced by an oxytocic agent. One may take the frequency of contraction, but it does not show the intensity of contraction. In addition, the movement of uterus *in situ* is so irregular and so complexed that one might make an erroneous estimation if judged only from either frequency or amplitude of contraction by eye. The intensity of each contraction is not constant. Tonic contraction are also observed as well as rhythmic contractions. The authors chose the way, which may be accepted by intuition, to express the magnitude of overall contractions may be the integration of the contraction curve on the kymograms. This involves a factor for time. In this experiment, the area under the contraction curves was measured for the calculation of the relative potencies of the drugs.

As shown in the results, the activity of QB-1 to produce uterine contraction *in vitro* is calculated to be 12 times as that sparteine sulfate in rats uteri. However, the relative potency *in vivo* was decreased to about 2.9 times in the rabbit uteri. This difference in

the relative potency might be illustrated by the affinity of the compound to uterus.

It was considered that the toxicity of QB-1 would be mainly attributed to its action on both the central nervous system and the heart, although the death was generally produced from the respiratory paralysis in unanesthetized animals. In rats and mice, comparison of the LD₅₀ by the intravenous route between QB-1 and sparteine sulfate indicated no appreciable difference in their acute toxicities, and both drugs produced approximately the same magnitude of convulsive symptoms. In rabbits and dogs, however, the severe convulsive symptoms were produced by QB-1, whereas larger doses of sparteine sulfate caused the death without a remarkable convulsion. The effects of QB-1 on the EEG were not observed in a dose of 1 mg/kg in rabbits, while those uterine contraction was apparently observed. Since the mortality of mice due to QB-1 was remarkably decreased by the treatment with pentobarbital, it may be said, at least, that if any side effects of QB-1 due to its central nervous stimulant action were seen, patients would be rescued by the administration of barbiturate. And also, clinical use of QB-1 may be recommended to the patients under general anesthesia.

The effect of QB-1 on the heart is quite similar to that of sparteine sulfate. Both agents depress the function of the heart. The reduction in contractility of the myocardium was shown in the experiments on the isolated toad heart. As observed on the isolated toad heart, the heart rate was decreased. The ECG findings on the cat and rabbit also confirmed the prolongation of R-R interval. But it must be noted the fact that the QRS intervals was not affected by QB-1 treatment, while the marked prolongation of QRS intervals was observed in sparteine sulfate and quinidine sulfate treated animal (Fig. 8). The initial fall of the blood pressure is difficult to explain and needs further investigation. No vasoconstricting action of QB-1 was found in the experiment of the toad hind limb blood vessel perfusion.

From another point of view, a quantitative comparison of the effect on the cardiovascular system was made regarding to the blood pressure fall and the heart rate lowering, which were commonly observed in both QB-1 and sparteine sulfate. As summarized in Fig. 6, there appears to be no difference of the blood pressure fall between QB-1 and sparteine sulfate in the rats (5 and 10 mg/kg, i.v.) and rabbits (below 2 mg/kg, i.v.). The results obtained from the cat indicate an almost parallel log-dose response relationship in which the same degree of response was observed by doubling the dose of sparteine sulfate as produced by QB-1. Since, as can be seen in Fig. 9, the log-dose response plot of the heart rate lowering in the rats come close to each other with reducing the dose to the effective range enough to elicit the uterine contraction in the intact rabbits (1 to 2 mg/kg of QB-1), the heart rate lowering action of QB-1 is less than twice of sparteine sulfate. This relationship also holds in the cat (Fig. 10). Thus, the relative intensity of the depressive effect on the heart can be estimated as less than 2 : 1 (QB-1 : sparteine sulfate). When this is compared to the relative potency of the uterine contraction in the rabbits, i.e., 2.9 : 1, it may be concluded that QB-1 possesses some advantage as an oxytocic agent over sparteine sulfate in this respect.

SUMMARY

Pharmacological properties of 3-(*p*-chlorobenzyl)quinolizidine tartarate, a new oxytomic, were examined with following results.

1. *Acute toxicity*

In mice and rats, the acute toxicities of this compound were of almost the same degree or slightly less as those of sparteine sulfate.

In rabbits and dogs, the lethal doses of QB-1 seemed to be lower than those of sparteine sulfate.

2. *Uterus*

QB-1 caused the contraction of uterus. Its activity was evaluated to be 12 times as effective as sparteine sulfate *in vitro* (rat) and 2.9 times *in vivo* (rabbit). In rabbit, 1 mg/kg intravenous injection of QB-1 caused remarkable uterine contraction *in vivo*.

3. *Cardiovascular system*

If low doses of QB-1 (1 to 2 mg/kg i.v.) were administered, they caused at first fall of blood pressure and then mild rise.

In large doses, the effect of QB-1 on blood pressure seemed to be varied with species of animals.

Recording the ECG of rabbits and cats, the following results were obtained : In doses of less than 1 mg/kg, QB-1 caused no change in the heart rate and ECG ; In doses of more than 2 mg/kg, the decrease in heart rate and the increase of ECG change in R-R and Q-T intervals were caused, while no change of P-R interval/R-R interval and QRS interval were observed.

Respiration was generally stimulated by QB-1 injection, although temporal apnea was seen sometimes prior to the stimulation.

4. *Central nervous system*

1) *Effect of pentobarbital on the acute toxicity of QB-1*

In large doses, QB-1 caused convulsion. This central nervous system stimulant action seemed to be antagonized by pentobarbital, that is, the pretreatment with pentobarbital reduced the acute toxicity of QB-1.

2) *Effect on EEG*

At low dose (1 mg/kg), QB-1 caused no remarkable change in the EEG of the rabbit and cat.

Administration of large dose (4 mg/kg) of QB-1 revealed the desynchronization pattern in the neocortex and regular slow wave in the hippocampus in rabbit and cat.

From these results, QB-1 was considered to be superior to sparteine sulfate as an oxytomic.

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