Treatment of Hypertension with KK-25-S, a New Potent Ganglionic Blocking Agent

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Antihypertensive effect of KK-25-S, a new potent ganglionic blocking agent, was evaluated in patients with moderate to severe essential hypertension. In 7 subjects, hypotensive responses after single oral dose were tested. Significant blood pressure reduction occurred within one or 2 hours after the administration of the drug and persisted for 4 hours or more. Thirty-two patients were treated with KK-25-S for periods of 2 to 29 weeks. Seven of 9 patients treated with KK-25-S alone failed to maintain significant hypotensive effect, whereas in 20 of 26 patients who received KK-25-S combined with other hypotensive drugs, significant blood pressure reduction was maintained throughout the treatment. Side-effects of the drug due to parasympathetic blockade were seen but readily controlled. Postural hypotension was relatively infrequent and slight in degree. Comparative studies on hypotensive potencies were made among different ganglionic blocking agents. It is concluded that KK-25-S is a potent hypotensive drug and is useful for the treatment of hypertension.

SINCE the introduction of hexamethonium¹⁾ and pentolinium²⁾ into the clinical use for the treatment of hypertension, various potent antihypertensive drugs, including several ganglionic blocking agents, have been developed and their therapeutic values have been widely recognized.

A new ganglionic blocking agent, provisionally named KK-25-S, which is one of the bis-quaternary salts containing a bicyclo-(2, 2, 2)-octane ring, was synthesized in Japan, and experimental data on its excellent pharmacologic properties have been published recently.³⁾ The chemical structure of the drug is, as shown below, 2-(3-dimethylaminopropyl)-3a, 4, 7, 7a-tetrahydro-4, 7-ethanoisindoline dimethiodide.

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The present study concerns our clinical trials of KK-25-S for the treatment of hypertensive cardiovascular disease. Hypotensive responses after single oral dose to 7 hypertensive subjects were estimated, and effectiveness of the drug in continuous treatment was evaluated in 32 patients with moderate to severe essential hypertension. In some of these patients, the hypotensive potency of the drug was compared quantitatively with those of other ganglioplegic agents.

MATERIALS AND METHODS

Single oral dose of KK-25-S was administered to 7 hypertensive subjects. Before starting the test, patients were kept in bed for at least half an hour until appropriately stable conditions were attained. Blood pressure readings were made both in recumbent and sitting position every 10 to 60 minutes after ingestion of the drug. In 3 of the 7 patients, the tests were repeated with sufficient intervals so that observations were made 11 times in total. Dosage given ranged from 5 mg. to 40 mg. Patients were regarded as having shown significant hypotensive responses when their blood pressure reduction exceeded 20/10 mm. Hg.

Thirty-two patients, 14 males and 18 females, with moderate to severe essential hypertension were treated with KK-25-S continuously for periods of 2 to 29 weeks; duration of the treatment averaged 7.9 weeks. Their ages varied from 22 to 72 years old, with a mean of 52.4. Their initial blood pressures were greater than 180/100 mm.Hg except in one juvenile hypertensive case. In 6 patients, treatment was started during hospitalization, and 26 were out-patients in our hypertensive clinic.

Control blood pressure was determined when a patient had achieved a stable blood pressure level with low salt diet and full sedation.

Initial dosage was started with 15 to 20 mg. of KK-25-S daily, which was gradually increased at weekly intervals according to patient's responses. The drug was given in 3 or 4 divided doses in most patients.

In 9 patients, treatment was begun with KK-25-S alone; in 3 of them other hypotensive drugs were combined later. In 23 patients who had been under treatment with various antihypertensive drugs, KK-25-S was added to the regimen. Rauwolfia alkaloids were used in all of these 26 patients with combined therapy. Fourteen patients were given hydralazine. Chlorothiazide was given in 2 cases, flumethiazide in one, hydrochlorothiazide in one, and benzydoflumethiazide in 6 patients. Four patients received Rauwolfia, hydralazine and one of those benzo-thiadiazine derivatives simultaneously combined with KK-25-S.

Twelve patients had been receiving other ganglionic blocking agents which were withdrawn and replaced by KK-25-S; in 14 patients KK-25-S was later replaced by other ganglionic blocking agents. Clinical potencies of different drugs were thereby compared with each other according to the daily requirements necessary to achieve similar degree of hypotensive effect in the same patient.

In patients treated with KK-25-S alone, hypotensive effect was regarded as sufficient when blood pressure was lowered continuously more than 20/10 mm. Hg below the control level or when it was maintained at a normotensive level. In patients with combined therapy, treatment was considered as effective when addi-

tional blood pressure reduction was achieved and/or when other drugs could be reduced with satisfactory hypotensive effect maintained successfully.

RESULTS

A) Single Dose of the Oral Administration

Data on single oral dose in 7 patients are listed in Table I. Effective hypotensive responses were obtained in 5 of the 11 observations. In these cases, blood pressure began to decrease apparently within one or 2 hours after the administration of the drug; it remained at a significantly hypotensive

Table I. Blood Pressure Response after Single Oral Dose

Patients	Age	Sex	Doses mg.	Maximal blood pressure reduc- tion supine (sitting)mm. Hg	Onset of signifi- cant blood pres- sure reduction	Duration of blood pressure reduction	Side-effect	Hypotensive response
M. I.	42	F	15	10/5				-
			40	unchanged			weakness	-
M. O.	43	M	5	12/4 (22/2)	(2° 10')	(4° 10')		(±)
N. K.	63	F	15	unchanged				-
			30	unchanged			blurring of vision	-
H. K.	69	F	30	62/24	2° 10'	23°		+
C. N.	73	F	15	32/12 (30/16)	1° 10'	4° 30'		+
			20	36/34		<7°		+
S. E.	22	F	5	32/14 (34/16)	1° 20'	4° 10'		+
			15	28/18 (48/20)	1°	>6°		+
U. T.	67	M	30	30/4 (22/4)	30'	6°		±

level for 4 to 23 hours; maximal blood pressure reduction appeared to occur $1\frac{1}{3}$ to 7 hours after ingestion of KK-25-S. Individual responsiveness to the drug varied considerably from one patient to another. In one patient blood pressure decreased well with 5 mg. of KK-25-S, whereas another patient showed no significant blood pressure change even after as much as 40 mg. Three patients revealed good responsiveness to the drug but others did not show any appreciable responses. There was no significant difference as to the severity of hypertension between ones who responded well and not.

Postural differences of decreased blood pressure were found to be relatively small. One patient who received 30 mg. of KK-25-S complained of blurring of vision, and another patient experienced a feeling of weakness after 40 mg. of the drug, although no blood pressure reduction was recognizable in these 2 patients. In Fig. 1, a case with a good blood pressure response after single oral dose of 15 mg. of KK-25-S is presented. In this case, it was

Fig. 1. Blood pressure reduction after 15 mg. of oral KK-25-S in case C.N.

Table II. Results of the Prolonged Treatment with Oral KK-25-S

	No. of patients			Percentage of effective cases	Dosage mg. per day	Duration of treatment wks.
	Total	Effective	Not effective			
Group I	9	2	7	11	30—150	2—13
Group II	26	20	6	77	15—160 (average in effective cases 62.5)	2—29

demonstrated that postural change in blood pressure was not remarkable.

B) Continuous Treatment with KK-25-S

Results of the prolonged treatment with continuous oral KK-25-S were summarized in Table II.

Effect on Blood Pressure:

When treated with KK-25-S alone (Group I), significant blood pressure reduction could be maintained effectively in only 2 of 9 patients. On the other hand, when KK-25-S was combined with other hypotensive drugs (Group II), 20 of 26 patients showed good hypotensive responses which were maintained well throughout the observed periods. Thus the percentage of cases in which effective blood pressure control was successfully maintained was much greater in the latter group (77 per cent vs. 11 per cent). In Group

I, daily dosage of KK-25-S ranged from 30 to 150 mg.; in 2 cases whose blood pressure was effectively controlled, the drug was given in amount of 30 mg. and 60 mg. per day respectively. In Group II, daily requirements of KK-25-S were in the range of 15 to 160 mg.; an average in effective cases was 62.5 mg. Amounts of drugs given in combination with KK-25-S are listed in Table III.

Table III. Drugs Given in Combination with KK-25-S

Drugs combined with KK-25-S	No. of patients	Dosage mg. per day
Rauwolfia alkaloids		
Reserpine	21	0.5—1.0
Alseroxylon	5	4—8
Benzothiadiazine compounds		
Chlorothiazide	2	250—500
Flumethiazide	1	500
Hydrochlorothiazide	1	75
Benzydrolumethiazide	6	2.5—10
Hydralazine	14	50—250

Side-Effects:

Side-effects seen during prolonged treatment with KK-25-S are listed in Table IV. Most of them seemed to be due to parasympathetic blockade. Constipation was encountered in 6 patients (3 in Group I and 3 in Group II), which was most frequent but was readily relieved with the aid of laxatives. Blurring of vision due to impaired accommodation and mydriasis was seen in

Table IV. Side-Effects in Patients Treated with KK-25-S

		No. of patients	Dosage of KK-25-S mg. per day
Group I	Constipation	3	60—150
Group II	Constipation	3	30—90
	Blurring of vision	2	45—90
	Diarrhea	2	90—120
	Dryness of the mouth	1	75
	Postural hypotension	2	75—90
	Dizziness	1	90
	Headache	1	45
	Transient disturbance of consciousness	1	30

2 patients, diarrhea in 2, dryness of the mouth in one, and headache in one. Marked postural hypotension was seen in only 2 patients, one of whom complained of dizziness at the same time. One patient had an episode of transient disturbance of consciousness while taking the drug at home. Whether this should be attributed to the drug or not was unknown. Side-effects disappeared rapidly when the drug was withdrawn or dosage was decreased.

Development of Drug Tolerance:

The development of tolerance was observed in 3 cases of Group I and in 3 of Group II. In these patients blood pressure which had once come down with KK-25-S was again elevated and requirement of the drug increased. The tolerance appeared to develop within 2 to 4 weeks after initiation of the treatment.

Severity of the Disease and Efficacy of the Drug:

As shown in Table V, effectiveness appeared to be greater in cases with retinal findings of Grade 1 and smaller in cases of Grade 3 according to the classification of Keith and Wagener.⁴⁾

Table V. Retinal Findings and Efficacy of KK-25-S

Retinal findings	No. of patients		
	Effective	Not effective	Total
Grade 1	3	0	3
Grade 2	12	6	18
Grade 3	3	5	8
Total	18	11	29

Table VI. Renal Function and Efficacy of KK-25-S

		No. of patients		
		Effective	Not effective	Total
RBF	Normal (>600 ml./min.)	6	6	12
	Subnormal (<600 ml./min.)	4	4	8
GFR	Normal (>60 ml./min.)	5	5	10
	Subnormal (<60 ml./min.)	5	5	10

In 20 patients in whom renal function tests were performed by means of PAH clearance and endogenous creatinine clearance methods, no difference was observed with regard to efficacies among the patients with normal and subnormal renal function (Table VI).

Comparison with Other Ganglionic Blocking Agents:

Hypotensive potencies of different ganglionic blocking agents were compared with that of KK-25-S in regard to daily dosage required to maintain comparable blood pressure reduction. For this purpose, patients were treated with KK-25-S and other drugs alternatively. Results were summarized in Table VII.

Table VII. Comparison of Daily Requirements of Different Ganglionic Blocking Agents

Ganglionic blocking agents compared with KK-25-S	No. of patients	Dosage of KK-25-S mg. per day	Dosage required for same degree of hypotensive effect mg. per day	KK-25-S equivalent to 1 mg. of the drug mg. (average)
Hexamethonium	4	30—75	200—1,000	0.03—0.23 (0.12)
Pentolinium	8	45—120	50—200	0.4 —1.0 (0.76)
Trimethidinium methosulfate	3	15—75	30—60	0.5 —1.5 (1.0)
Pempidine	8	15—140	2.5—10	6. —20. (12.1)
Mecamylamine	2	75—90	5—10	9. —15. (12.0)

Daily requirements of KK-25-S were compared with those of hexamethonium in 4 patients. Amounts of KK-25-S equivalent to 1,000 mg. of hexamethonium were observed to be within a range of 30 to 230 mg., with an average of 120 mg. Amounts of KK-25-S equivalent to 10 mg. of pentolinium estimated in 8 patients were found to be ranged from 4 to 10 mg., averaging 7.6 mg. Amounts of KK-25-S necessary for maintaining approximately the same degree of blood pressure reduction with 10 mg. of trimethidinium were 5 to 15 mg. in 3 patients, and the mean was 10 mg. Equivalency of KK-25-S to pempidine was attempted to determine in 11 patients, and in 8 of them comparable blood pressure reduction was achieved. In these comparable cases, it was estimated that 6 to 20 mg. of KK-25-S, averaging 12.1 mg., was equivalent to 1 mg. of pempidine. In this manner, amounts of KK-25-S equivalent to 1 mg. of mecamylamine in 2 patients were found to be 9 and 15 mg. with a mean of 12 mg.

DISCUSSION

Experimental investigations on the pharmacologic activities of KK-25-S have shown that the drug possesses a potent ganglionic blocking action with a long duration and less toxicity, and that the drug is relatively well absorbed from the gastrointestinal tract after the oral administration. In the present study, therapeutic usefulness of KK-25-S for the treatment of hypertension is evaluated on the basis of the results obtained in our clinical trials.

Data on the single dose administration suggest that the drug should be given in 3 or 4 divided doses in order to achieve a continuous blood pressure

reduction throughout a day. Individual responsiveness to the drug varied considerably from patient to patient, as is often the case with other anti-hypertensive drugs. Daily dosage therefore should be carefully determined in each case according to the patient's response. Initial dosage of KK-25-S is recommended as much as 15 to 20 mg. per day which is gradually increased until satisfactory blood pressure reduction is achieved.

Treatment with KK-25-S alone failed to maintain sufficient and continuous blood pressure reduction in 7 of 9 patients. In contrast, combination with other drugs such as Rauwolfia, hydralazine and benzothiadiazine compounds resulted in good hypotensive effect in 20 of 26 patients. It may be suggested that hypotensive responses are augmented by additional and synergistic actions of these drugs. It has been also noted that ganglionic blockade is potentiated by saluretic action of benzothiadiazine compounds.⁵⁾ The development of drug tolerance was less frequent in Group II, indicating that combination with other drugs might prevent the development of the tolerance. This evidence may also be contributed for the greater efficacy in combined therapy.

Side-effects of the drug observed in our patients were similar to those seen with other ganglionic blocking agents. Most of these side-effects seemed to be due to parasympathetic blockade. Constipation was most frequent but was readily relieved with laxatives. Side-effects were subsided rapidly when the drug was withdrawn or reduced in dosage.

The observed fact that postural hypotension was relatively infrequent and slight in degree is considered to be of great advantage. It might be likely that the drug should possess certain central action as having been suggested with trimethidinium methosulfate.⁶⁾

Although the use of KK-25-S is indicated for moderately severe or severe hypertension, need for careful precautions should be emphasized when the drug is given to patients with advanced disease. It is especially true when circulatory insufficiencies in vital organs are suspected. One patient had an episode of transitory unconsciousness while taking the drug though it was unknown whether the accident was attributable to cerebral circulatory failure due to excessive hypotension.

Observations on efficacy of the drug and severity of the disease classified according to retinal findings demonstrate that effectiveness of the drug is greater in early cases than in advanced cases. No difference in efficacies was recognizable among patients with normal and subnormal renal function. In this respect, it should be considered that no patient with marked renal failure was included in our study.

Comparative studies on hypotensive potencies were made among different ganglionic blocking agents, and it may be concluded as follows: KK-25-S is approximately 10 times as potent as hexamethonium; it is about one and a half times as potent as pentolinium; almost equivalent to equal dose of trimethidinium methosulfate; and the hypotensive potency of KK-25-S is

about a tenth of those with mecamlamine and pempidine.

SUMMARY

Antihypertensive effect of KK-25-S, a new potent ganglionic blocking agent, was evaluated in patients with moderate to severe essential hypertension.

(1) Hypotensive responses after single oral dose of 5 to 40 mg. of the drug were tested in 7 hypertensive subjects. Significant reduction of blood pressure was observed to occur within one or 2 hours and persisted for 4 hours or more.

(2) Thirty-two patients were treated with KK-25-S for periods of 2 to 29 weeks. Seven of 9 patients treated with KK-25-S alone failed to maintain significant hypotensive effect. But in 20 of 26 patients who received KK-25-S combined with other hypotensive drugs, significant blood pressure reduction was maintained throughout the treatment.

(3) Side-effects of the drug due to parasympathetic blockade were seen but readily controlled. Postural hypotension was relatively infrequent and slight in degree.

(4) The hypotensive potency of KK-25-S was compared with those of different ganglionic blocking agents.

It is concluded that KK-25-S is a potent hypotensive drug and useful for the treatment of hypertension.

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