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Effect of YM934, a Novel Potassium-Channel Opener, in Various Experimental Asthma Models in Guinea-pigs

JUN ISHIKAWA, CHIKASHI SAITOH*, KATSUHIRO MASAKI† AND MASAHARU ASANO*

*Infectious Disease & Immunology Research Laboratory, Institute for Drug Discovery Research, *Pharmacology Department, Clinical Pharmacology Research Laboratory, and †Pharmaceutical Department, Pharmaceutical Research Laboratory, Institute for Drug Development Research, Yamanouchi Pharmaceutical Co. Ltd, 21 Miyukigaoka, Tsukuba-shi, Ibaraki 305, Japan*

Abstract

YM934 is a novel synthetic potassium-channel opener. We have investigated its anti-asthma effect after intravenous (i.v.) and oral (p.o.) administration in various experimental asthma models in the guinea-pig, and compared the results with those for lemakalim, theophylline and salbutamol.

In an ovalbumin-active sensitization anaphylaxis asthma model, YM934, lemakalim, theophylline and salbutamol dose-dependently prolonged the time before the occurrence of asthma attacks and reduced the mortality rate. The respective ED50 values (dose required to prolong by 50% the time before the occurrence of attacks) of the anti-asthma effects of YM934, lemakalim, theophylline and salbutamol were 6, 340, 30 000, and 45 $\mu g\ kg^{-1}$ (i.v.); the efficacy ratios were YM934 (1) > salbutamol (1/9) > lemakalim (1/57) > > theophylline (1/5000). YM934 also prolonged the period before the occurrence of attacks in the anti-BSA (bovine serum albumin) serum-passive sensitization anaphylaxis, histamine-induced and methacholine-induced asthma models, with respective ED50 values for these models of 15, 22 and 20 $\mu g\ kg^{-1}$ (i.v.). Among these models a reduction in mortality rate was seen in the histamine- and methacholine-induced asthma models. After oral administration, YM934 showed an anti-asthma effect in the ovalbumin-active sensitization anaphylaxis, histamine-induced and methacholine-induced asthma models, with respective ED50 values of 38, 44 and 193 $\mu g\ kg^{-1}$. YM934 was 5–6 times more potent than salbutamol. These results indicate that YM934 has potent anti-asthma activity, and that this activity is mainly attributable to bronchodilation, most likely mediated through its potassium-channel opening activity.

The potassium channel, present in all cell membranes, is known to play a role in the physiological regulation of various cellular functions such as cell-membrane potential. Its role in the mechanism of relaxation of smooth muscle has been shown to be particularly important (Cook 1988; Cavero et al 1989; Buckingham et al 1986). The recent development of potassium-channel openers, which activate this potassium channel, has focussed attention on the effect of these compounds on relaxation of smooth muscle, particularly the smooth muscle of the trachea (Allen et al 1986; Black & Barnes 1990). It has, moreover, recently been reported that potassium-channel openers not only directly relax smooth muscle, but also inhibit the release from the sensory nerve endings of tachykinins, which induce bronchial constriction (Ichinose & Barnes 1990; Burka et al 1991; Good et al 1992). These drugs therefore have promise as anti-asthma agents. YM934 (Fig. 1) is a benzoxazine derivative which, unlike cromakalim and its optical isomer lemakalim, does not have an asymmetric centre. This compound is reported to have potent potassium-channel opening activity (Yamada et al 1993; Uchida et al 1994). In this study, we have evaluated the possible use of YM934 as an anti-asthma drug in various immediate-type asthma models created by exposing conscious guinea-pigs to antigens and spasmogens.

Correspondence: J. Ishikawa, Infectious Disease & Immunology Research Laboratory, Institute for Drug Discovery Research, Yamanouchi Pharmaceutical Co. Ltd, 21 Miyukigaoka, Tsukuba-shi, Ibaraki 305, Japan.

Materials and Methods

Animals

Male Hartley guinea-pigs (Charles River Japan, Tokyo), 290–690 g, age 6–7 weeks, were used in the anti-BSA (bovine serum albumin) serum-passive sensitization anaphylaxis, histamine-induced, methacholine-induced and ovalbumin-active sensitization anaphylaxis asthma models. In the ovalbumin-active sensitization anaphylaxis model the study was conducted approximately 3 weeks after ovalbumin sensitization.

Drugs and chemicals

The YM934 and lemakalim used in this study were synthesized by Yamanouchi. The other drugs used were: histamine dihydrochloride (Ishizu Seiyaku, Osaka, Japan), methacholine chloride (Tokyo Kasei, Tokyo, Japan), indomethacin (Sigma, St Louis, USA), mepyramine (Sigma), propranolol hydrochloride (Sigma), theophylline (Sigma), salbutamol (Sigma), bovine serum albumin (BSA fraction V; Sigma) and ovalbumin (Funakoshi, Tokyo, Japan). The YM934 was dissolved in a mixture of physiological saline solution with ethanol (Wako Pure Chemical Industries, Tokyo, Japan), polyethyleneglycol 400 (PEG 400, Nakalai Tesque, Kyoto, Japan), or dimethylsulphoxide (DMSO; Wako). The solvent content (v/v) in 1 mg mL^{-1} YM934 solution was adjusted to 20% for ethanol, 10% for PEG 400 and 10% for DMSO; serial dilution was then performed with physiological saline solution. In the same manner, the solvent content (v/v) in 1 mg mL^{-1} lemakalim solution was adjusted to 20% for ethanol and 10% for PEG 400, serial dilution again being performed with physiological

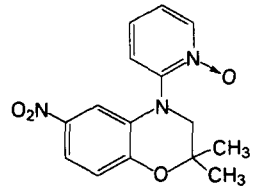

FIG. 1. The chemical structure of YM934.

saline solution. The indomethacin used was dissolved in distilled water with adjustment to pH 6 by addition of 0·1 M hydrochloric acid and 0·1 M sodium hydroxide solution. All other drugs were dissolved in physiological saline solution before use.

Intravenous administration study

Anti-BSA serum-passive sensitization anaphylaxis asthma model. Using guinea-pigs which had been injected with rabbit anti-BSA serum (1 mL kg^{-1}) on the day before the study (approximately 24 h previously), the study was conducted under treatment with indomethacin (2 mg kg^{-1}, i.v.), mepyramine (2 mg kg^{-1}, i.v.) and propranolol (0·3 mg kg^{-1}, i.v.). Indomethacin, mepyramine and propranolol were administered 30, 10 and 10 min, respectively, before BSA exposure. The animals were placed in a sealed chamber having a side opening (capacity 11 L), and an anaphylactic asthma reaction was induced by inhalation exposure to 1% BSA using a glass nebulizer (KG-20, Kinoshita, Tokyo). The BSA exposure time was 2 min, including 30 s of exposure to 1% BSA inhalation. The treatment drug was given by intravenous administration 5 min before inhalation.

Ovalbumin-active sensitization anaphylaxis asthma model. Guinea-pigs subjected to 3-week sensitization by intramuscular administration (0·1 mL on each leg) of ovalbumin-Freund's complete adjuvant (1 : 1) were placed in a sealed chamber (capacity 11 L) having a side opening, and an anaphylactic asthma reaction was induced by 30 s inhalation exposure to 5% ovalbumin using a nebulizer.

Evaluation of drug effect was conducted with the animals under constant exposure to ovalbumin while the chamber was kept airtight. The drugs were given by intravenous administration 5 min before ovalbumin exposure.

Spasmogen-induced asthma models. The animals were placed in a sealed chamber having a side opening, and an asthmatic reaction was induced by 10 s inhalation exposure to 0·1% histamine or 0·1% methacholine using a glass nebulizer. Evaluation of drug effect was performed with the animals under constant exposure to spasmogens while the chamber was kept airtight. The drugs were given by intravenous administration 5 min before exposure to spasmogens.

Oral administration study

Studies were conducted according to the method used for intravenous administration. The drugs were suspended in 0·5% methylcellulose and given by oral administration using a metal gastric probe 30 min before evaluation.

Measurement of blood pressure and heart rate in anaesthetized guinea-pigs

Guinea-pigs were anaesthetized with pentobarbital sodium (30 mg kg^{-1}, i.p.) and blood pressure and heart rate were measured under artificial respiration using a respirator (SN-480-7, Shinano Seizakujo, Tokyo) via a tracheal cannula. Blood pressure was measured using a pressure transducer (TP-200T; Nihon Kohden Corp., Tokyo) via a polyethylene cannula (PE-50) inserted in the left carotid artery. Heart rate was measured with a heart-rate monitor (AT-601G; Nihon Kohden Corp.) triggered by the blood pressure pulse waves. The drugs were administered via a polyethylene cannula (PE-50) inserted in the left femoral vein.

Method of evaluation and statistical analysis

Asthma symptoms were evaluated on the basis of the time taken for the occurrence of attacks and mortality rate; time until the occurrence of attacks was expressed as the time elapsed (s) until an attack occurred (coughing, convulsions, dyspnoea). Cases in which no attack had occurred after 10 min

Table 1. ED50 values (μg kg^{-1})* for effects of intravenous administration of YM934, lemakalim, theophylline and salbutamol on the time before the occurrence of attacks in various experimental asthma models in guinea-pigs.

Drug	Anaphylaxis asthma		Histamine-induced asthma	Methacholine-induced asthma
	Passive sensitization	Active sensitization		
YM934	15 (1)†	6 (1)	22 (1)	20 (1)
Lemakalim	117 (1/8)	340 (1/57)	60 (1/3)	70 (1/4)
Theophylline	8000 (1/533)	30 000 (1/5000)	> 30 000	> 30 000
Salbutamol	Evaluation not possible‡	45 (1/8)	39 (1/2)	88 (1/4)

Drugs were given 5 min before inhalation exposure to the asthma-inducing stimulants. *Dose of drug (μg kg^{-1}, i.v.) resulting in a 50% prolongation of the time before the occurrence of attacks. †Numbers in parentheses indicate efficacy ratios, assuming the ED50 of YM934 to be unity. ‡Previous pre-treatment with propranolol in this model.

evaluation were evaluated as 600 s. The rate of change compared with the control group (solvent administration group) was expressed as mean ± s.e. Results were statistically analysed by one-way analysis of variance. Mortality rate was evaluated by comparing the number of animals which died of dyspnoea during evaluation with the number of animals used in the study (number of cases).

Results

Intravenous administration study

Effects in the anti-BSA serum-passive sensitization anaphylaxis asthma model. In the anti-BSA serum-passive anaphylaxis asthma model in conscious guinea-pigs, asthma attacks in the control group (vehicle administration group) occurred 309 ± 14 s (n = 5) after exposure to BSA. In contrast, administration of YM934 (3–100 $\mu g\ kg^{-1}$, i.v.), lemakalim (10–300 $\mu g\ kg^{-1}$, i.v.) and theophylline (1–30 $mg\ kg^{-1}$, i.v.) prolonged the time until the occurrence of attacks in a dose-dependent manner (Fig. 2), with respective ED50 values (dose required to prolong by 50% the time until attacks occurred) of 15, 117 and 8000 $\mu g\ kg^{-1}$ (i.v.). Potency ranking, on the basis of these ED50 values was: YM934 (1) > lemakalim (1/5) > theophylline > > (1/533), with YM934 showing the most powerful anti-asthma effect (Table 1). Lemakalim (100 and 300 $\mu g\ kg^{-1}$, i.v.) reduced mortality rate and theophylline (10 $mg\ kg^{-1}$, i.v.) completely eliminated mortality (Table 2). Because in this model pre-treatment was performed with indomethacin, mepyramine and propranolol, it was not possible to evaluate the effect of the β-stimulant salbutamol.

Effects in the ovalbumin-active sensitization anaphylaxis asthma model. In the ovalbumin-active sensitization anaphylaxis asthma model, asthma attacks in the control group occurred at 212 ± 11 s (n = 5) after inhalation exposure to ovalbumin. Administration of YM934 (1–10 $\mu g\ kg^{-1}$, i.v.), lemakalim (100–1000 $\mu g\ kg^{-1}$, i.v.), theophylline (3–30 $mg\ kg^{-1}$, i.v.) and salbutamol (30–300 $\mu g\ kg^{-1}$, i.v.) resulted in dose-dependent prolongation of time before the occurrence of attacks (Fig. 2), with respective ED50 values of 6, 340, 30 000 and 45 $\mu g\ kg^{-1}$ (i.v.). The potency ranking on the basis of these ED50 values was: YM934 (1) > salbutamol (1/8) > lemakalim (1/57) > theophylline (1/5000), with YM934 showing the most powerful effect (Table 1). YM934, lemakalim, theophylline and salbutamol also resulted in a dose-dependent reduction in mortality rate (Table 2).

Effects in the histamine-induced asthma model. In the histamine-induced asthma model asthma attacks in the control group occurred 109 ± 8 s (n = 5) after inhalation exposure to histamine. Administration of YM934 (10–100 $\mu g\ kg^{-1}$, i.v.), lemakalim (30–1000 $\mu g\ kg^{-1}$, i.v.) and salbutamol (3–100 $\mu g\ kg^{-1}$, i.v.) resulted in dose-dependent prolongation of the time for the occurrence of attacks (Fig. 3), with respective ED50 values of 22, 60 and 39 $\mu g\ kg^{-1}$ (i.v.). The potency ranking on the basis of these ED50 values was: YM934 (1) > salbutamol (1/2) > lemakalim (1/3), with YM934 showing the most powerful effect (Table 1). Theophylline (1–30 $mg\ kg^{-1}$, i.v.) had no significant effect on the time before the occurrence of attacks (Fig. 3). YM934, lemakalim, theophylline and salbutamol also resulted in a dose-dependent reduction in mortality rate (Table 2).

Table 2. Effect of intravenous administration of YM934, lemakalim, theophylline and salbutamol on mortality rates (%) in various experimental asthma models in guinea-pigs.

Drug	Anaphylaxis asthma				Histamine induced asthma		Methacholine-induced asthma	
	Passive sensitization		Active sensitization					
	Dose ($\mu g\ kg^{-1}$)	Mortality (%)	Dose ($\mu g\ kg^{-1}$)	Mortality (%)	Dose ($\mu g\ kg^{-1}$)	Mortality (%)	Dose ($\mu g\ kg^{-1}$)	Mortality (%)
YM934	0	66·7	0	66·7	0	66·7	0	100·0
	3	60·0	1	60	10	100·6	10	100·0
	30	66·7	3	16·7	30	66·7	30	66·7
	100	60·7	10	33·3	100	0·0	100	33·3
Lemakalim	0	66·7	0	50·0	0	83·3	0	100·0
	10	60·0	100	50·0	3·0	100·0	30	100·0
	30	83·3	300	16·7	100	66·7	100	83·7
	100	33·3	1000	16·7	300	16·7	300	50·0
	300	33·3			1000	0·0		
Theophylline	0	66·7	0	66·7	0	83·3	0	100·0
	1000	66·7	3000	33·3	3000	100·0	3	100·0
	3000	66·7	10000	16·7	10000	83·3	10	100·0
	10000	0·0	30000	0·0	30000	33·3	30	100·0
Salbutamol	Evaluation not possible*		0	100·0	0	100·0	0	100·0
			30	50·0	3	83·3	100	83·3
			100	0·0	10	50·0	300	50·0
			300	0·0	30	0·0	1000	66·7
			1000	0·0				

Drugs were given 5 min before inhalation exposure to the asthma-inducing stimulants. *Previous treatment with propranolol in this model.

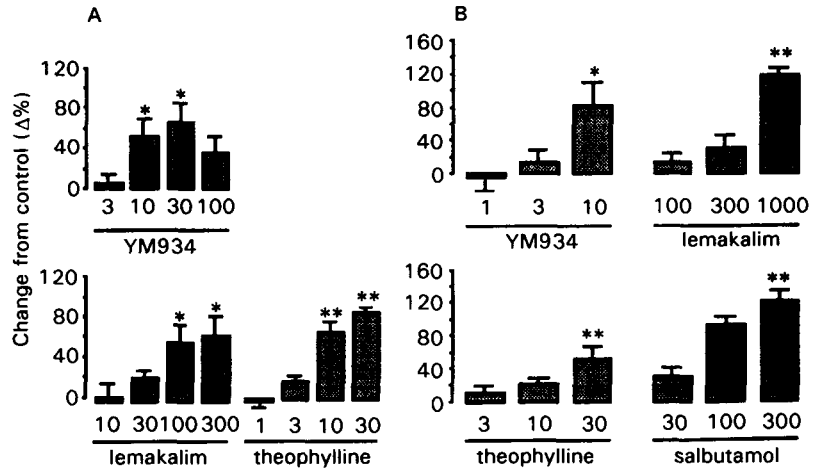

FIG. 2. The effect of YM934, lemakalim, theophylline and salbutamol on the time before the occurrence of attacks in anaphylaxis asthma models in guinea-pigs (intravenous administration study). A, anti-BSA serum-passive sensitization anaphylaxis asthma model; B, ovalbumin-active sensitization anaphylaxis asthma model. The columns show the mean value ± s.e. of the rate of change (Δ%) compared with the time before the occurrence of attacks in the control group. Asterisks indicate a significant difference compared with the control group (*$P < 0.05$, **$P < 0.01$, one-way analysis of variance, n = 5 or 6).

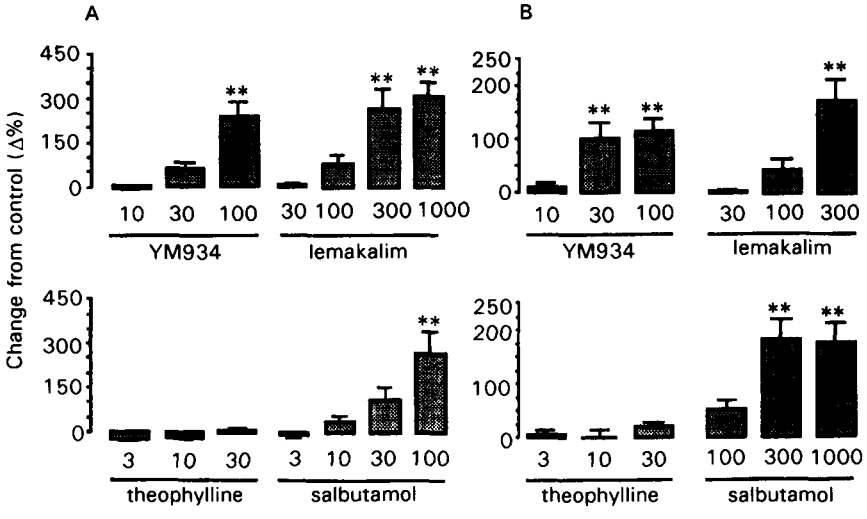

FIG. 3. The effect of YM934, lemakalim, theophylline and salbutamol on the time before the occurrence of attacks in spasmogen-induced asthma models in guinea-pigs (intravenous administration study). A, histamine-induced asthma model; B, methacholine-induced asthma model. The columns show the mean value ± s.e. of the rate of change (Δ%) compared with the time before the occurrence of attacks in the control group. Asterisks indicate a significant difference compared with the control group (**$P < 0.01$, one-way analysis of variance, n = 5 or 6).

Effects in the methacholine-induced asthma model. In the methacholine-induced asthma model, asthma attacks in the control group occurred 92 ± 11 s (n = 5) after inhalation exposure to methacholine. Administration of YM934 (10–100 $\mu g\ kg^{-1}$, i.v.), lemakalim (30–300 $\mu g\ kg^{-1}$, i.v.) and salbutamol (100–1000 $\mu g\ kg^{-1}$, i.v.) resulted in dose-dependent prolongation of the time before the occurrence of attacks (Fig. 3), with respective ED50 values of 20, 70 and 88 $\mu g\ kg^{-1}$ (i.v.). Potency ranking on the basis of these ED50 values was YM934 (1) > lemakalim = salbutamol (1/4), with YM934 showing the most powerful effect (Table 1). YM934, lemakalim and salbutamol also resulted in a dose-dependent reduction of mortality rate (Table 2). Theophylline (3–30 mg kg^{-1}, i.v.) did not prolong the time before the occurrence of attacks and had no inhibitory effect on mortality rate (Fig. 3, Table 2).

Oral administration study

Effects in the ovalbumin-active sensitization anaphylaxis asthma model. In the ovalbumin-active sensitization anaphylaxis model, administration of YM934 (10–100 $\mu g\ kg^{-1}$, p.o.) and salbutamol (100–1000 $\mu g\ kg^{-1}$, p.o.) resulted in dose-dependent prolongation of the time before the occurrence of attacks (Fig. 4), as was observed for intravenous administration, and also dose-dependent inhibition of mortality rate (Table 3). The respective ED50 values for YM934 and salbutamol were 38 and 180 $\mu g\ kg^{-1}$ (p.o.), with YM934

Table 3. Effect of oral administration of YM934 and salbutamol on mortality rates (%) in various experimental asthma models in guinea-pigs.

Drug	Active sensitization anaphylaxis asthma		Histamine-induced asthma		Methacholine-induced asthma	
	Dose ($\mu g\ kg^{-1}$)	Mortality (%)	Dose ($\mu g\ kg^{-1}$)	Mortality (%)	Dose ($\mu g\ kg^{-1}$)	Mortality (%)
YM934	0	50·0	0	83·3	0	91·7
	10	40·0	30	33·3	30	50·0
	30	16·7	100	33·3	100	66·7
	100	0·0	300	16·7	300	75·0
					1000	50·0
Salbutamol	0	50·0	0	83·3	0	100·0
	100	0·0	100	83·3	300	33·3
	300	0·0	300	50·0	1000	41·7
	1000	0·0	1000	16·7	3000	41·7

Drugs were given 30 min before inhalation exposure to the asthma-inducing stimulants.

showing an anti-asthma effect five times stronger than that of salbutamol (Table 4).

Effects in the histamine-induced asthma model. In the histamine-induced asthma model, administration of YM934 (30–300 $\mu g\ kg^{-1}$, p.o.) and salbutamol (100–1000 $\mu g\ kg^{-1}$, p.o.) resulted in dose-dependent prolongation of the time before the occurrence of attacks (Fig. 5) and dose-dependent inhibition of mortality rate (Table 3). The respective ED50 values for YM934 and salbutamol were 44 and 203 $\mu g\ kg^{-1}$ (p.o.), with YM934 showing an anti-asthma effect five times stronger than that of salbutamol, as was observed for the ovalbumin-active sensitization anaphylaxis asthma model (Table 4).

Effects in the methacholine-induced asthma model. In the methacholine-induced asthma model, administration of YM934 (30–1000 $\mu g\ kg^{-1}$, p.o.) and salbutamol (300–3000 $\mu g\ kg^{-1}$, p.o.) resulted in dose-dependent prolongation of the time before the occurrence of attacks (Fig. 5) and a reduction in the mortality rate (Table 3). The respective ED50 values for YM934 and salbutamol were 193 and 1100 $\mu g\ kg^{-1}$ (p.o.), with YM934 showing an anti-asthmatic effect six times stronger than that of salbutamol (Table 4).

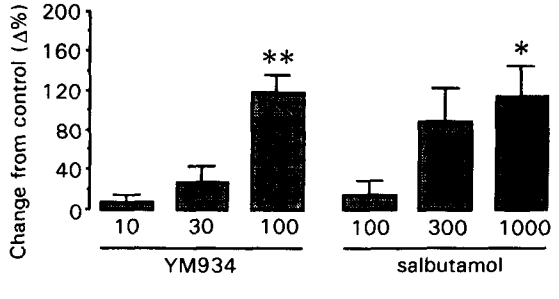

FIG. 4. The effect of YM934 and salbutamol on the time before the occurrence of attacks in the ovalbumin-active sensitization anaphylaxis asthma model in guinea-pigs (oral administration study). The columns show the mean value ± s.e. of the rate of change (Δ%) compared with the time before the occurrence of attacks in the control group. Asterisks indicate a significant difference compared with the control group (*$P < 0.05$, **$P < 0.01$, one-way analysis of variance, n = 6).

Effect on blood pressure and heart rate in anaesthetized guinea-pigs

In guinea-pigs under pentobarbital anaesthesia, administration of both YM934 (0·03–100 $\mu g\ kg^{-1}$, i.v.) and lemakalim (0·03–100 $\mu g\ kg^{-1}$, i.v.) induced a reduction in blood pressure at a dose of 3 $\mu g\ kg^{-1}$ (i.v.) or more, and a slight decrease in heart rate at a dose of 100 $\mu g\ kg^{-1}$, (i.v.) (Fig. 6). Theophylline (0·3–30 $mg\ kg^{-1}$, i.v.) also induced a decrease in blood pressure and an increase in heart rate at a dose of 3 $mg\ kg^{-1}$ (i.v.) or more (Fig. 6).

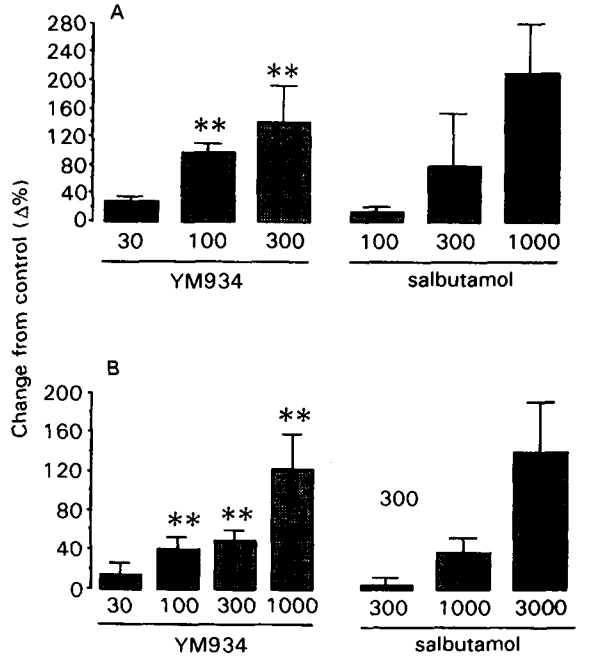

FIG. 5. The effect of YM934 and salbutamol on the time before the occurrence of attacks in spasmogen-induced asthma models in guinea-pigs (oral administration study). A, histamine-induced asthma model (n = 6); B, methacholine-induced asthma model (n = 12). The columns show the mean value ± s.e. of the rate of change (Δ%) compared with the time before the occurrence of attacks in the control group. Asterisks indicate a significant difference compared with the control group (**$P < 0.01$, one-way analysis of variance).

Table 4. ED50 values ($\mu g\ kg^{-1}$)* for effects of oral administration of YM934 and salbutamol on time before the occurrence of attacks in various experimental asthma models in guinea-pigs.

Drug	Active sensitization anaphylaxis asthma	Histamine-induced asthma	Methacholine-induced asthma
YM934	38 (1)†	44 (1)	193 (1)
Salbutamol	180 (1/5)	203 (1/5)	1100 (1/6)

Drugs were given 30 min before inhalation exposure to the asthma-inducing stimulants. *Dose of drug ($\mu g\ kg^{-1}$, p.o.) resulting in a 50% prolongation of the time before the occurrence of attacks. †Numbers in parentheses indicate efficacy ratios, assuming the ED50 of YM934 to be unity.

Discussion

Potassium-channel openers first attracted attention because of the potent vasodilating effect which results from their relaxant activity on vascular smooth muscle (Buckingham et al 1986; Cook 1988; Cavero et al 1989), and they have been studied for possible use as new cardiovascular agents. In recent years, however, the bronchodilating effect of these compounds (Black & Barnes 1990; Ichinose & Barnes 1990) has been recognized, and their potential use in the treatment of asthma has been widely examined (Edward & Weston 1990).

In this study we have determined the anti-asthma effect of the novel potassium-channel opener YM934 (Yamada et al 1993; Uchida et al 1994), a benzoxazine derivative which, unlike cromakalim and its optical isomer lemakalim, has no chiral centre in its chemical structure. The results of the study clearly demonstrate the anti-asthma effect of YM934. Intravenous administration of YM934 resulted in dose-dependent prolongation of the time before the occurrence of attacks in anti-BSA serum-passive sensitization and ovalbumin-active sensitization asthma models, as well as in histamine-induced and methacholine-induced asthma models. The anti-asthmatic effect of YM934 administered orally in the ovalbumin-sensitization asthma model and the histamine-induced and methacholine-induced asthma models clearly shows that it is adequately absorbed by this route. The anti-asthma effects of YM934 were compared with those of various control drugs. On the basis of ED50 values, YM934 showed potencies which were 8–57 greater than those of lemakalim and 8 times greater than those of salbutamol, in the antigen-induced asthma model, and 2–4 times greater than those of lemakalim and salbutamol in the spasmogen-induced model. In the oral administration study, moreover, YM934 showed an anti-asthma effect which

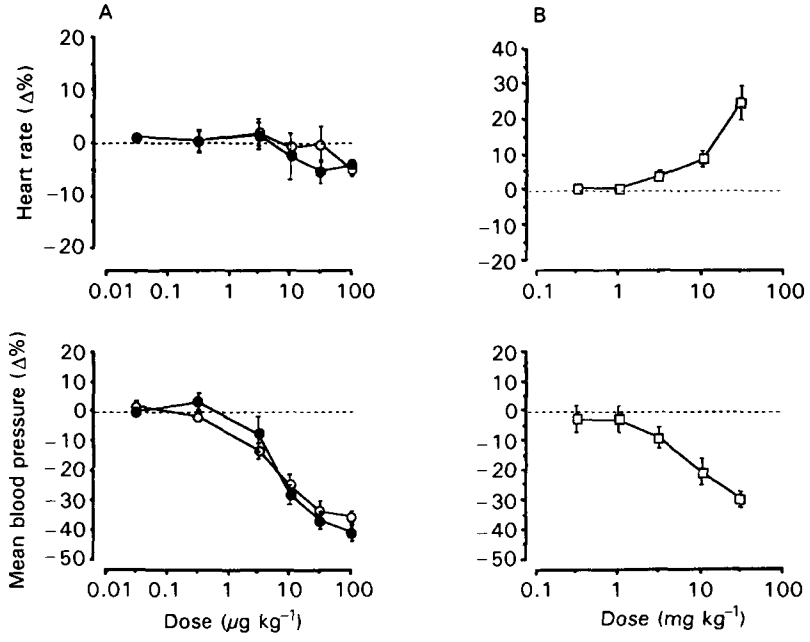

FIG. 6. The effect of YM934 (○), lemakalim (●) and theophylline (□) on heart rate and mean blood pressure in pentobarbital-anaesthetized guinea-pigs. The points indicate mean value ± s.e. of the rate of change (Δ%) compared with values before drug administration (n = 5).

was 5–6 times greater than that of salbutamol. These findings confirm that YM934 has more potent anti-asthma effects against immediate asthma response than either lemakalim or salbutamol.

We also investigated the correlation between the anti-asthma and cardiovascular effects of these drugs by examining their effects on blood pressure in guinea-pigs. Because of technical difficulties in measuring blood pressure in unanaesthetized and unrestrained normal and sensitized guinea-pigs concurrently with evaluation of anti-asthma effect, however, this study was conducted by intravenous administration of YM934, lemakalim and theophylline in pentobarbital-anaesthetized guinea-pigs. The results showed that YM934 produced a dose-dependent reduction in blood pressure at doses of 3 $\mu g\ kg^{-1}$ (i.v.) or above. As the doses which caused a reduction in blood pressure were virtually identical with those at which an anti-asthma effect was manifested in the various guinea-pig asthma models mentioned above, despite the differences between anaesthetized and unanaesthetized and normal and sensitized animals, it was inferred that the anti-asthma and vasodilating effects of YM934 occur in virtually the same dose range. Lemakalim and theophylline also produce a vasodilating effect at virtually the same dose at which they produce their anti-asthmatic effect. This indicated that the occurrence of these effects and in virtually the same dose range is not peculiar to YM934, but is a characteristic shared by all three drugs.

Potassium-channel openers such as cromakalim have, furthermore, been shown to cause relaxation of bronchial smooth muscle in in-vitro studies in isolated trachea from guinea-pig and man (Black et al 1990; Nagai et al 1991), and to inhibit antigen-induced airway contraction in in-vivo studies on animal models (Nagai et al 1991). From reports that administration of YM934 resulted in a bronchodilating action in an in-vitro study in isolated guinea-pig tracheal specimens and in an in-vivo study in anaesthetized guinea-pigs (Takizawa et al 1992), we infer that an important factor in its anti-asthmatic effect is its dilation of bronchial smooth muscle.

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