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Relaxant and β_2-adrenoceptor blocking activities of labetalol, dilevalol, amosulalol and KF-4317 on the rat isolated aorta

SHEILA A. DOGGRELL, *Department of Pharmacology, School of Medicine, University of Auckland, Private Bag, Auckland, New Zealand*

Abstract—The KCl-contracted rat aorta is relaxed by labetalol, dilevalol, amosulalol and KF-4317. These relaxations are not reversed by ICI 118,551 at 10^{-6} M and, therefore, are not due to β-adrenoceptor agonism. At 10^{-7} M, labetalol, dilevalol, amosulalol and KF-4317 were β_2-adrenoceptor antagonists as they inhibited the relaxant responses of rat aorta to procaterol.

Combined α- and β-adrenoceptor antagonists have the potential to cause both vasodilation and vasoconstriction by acting as antagonists at α- and β_2-adrenoceptors, respectively. However, labetalol which is a potent β_2-adrenoceptor antagonist ($pA_2 = 7{\cdot}40$, guinea-pig trachea) and a mild α_1-adrenoceptor antagonist ($pA_2 = 6{\cdot}99$, rabbit aorta, Brittain et al 1982) is used in the treatment of hypertension. Other combined α- and β-adrenoceptor antagonists, including dilevalol (the R_1R isomer of labetalol: Baum & Sybertz 1983), amosulalol (Nakashima et al 1984) and KF-4317 (Kubo et al 1985) are being developed for clinical use in hypertension. Dilevalol is a potent β_2-adrenoceptor antagonist ($pA_2 = 8{\cdot}52$, guinea-pig trachea) but only a weak α_1-adrenoceptor antagonist ($pA_2 = 5{\cdot}87$, rabbit aorta, Brittain et al 1982). Amosulalol is a potent α_1- and β_2-adrenoceptor antagonist (pA_2 at α_1 of rabbit aorta = 7·97, pA_2 at β_2- of guinea-pig trachea = 7·04, Honda et al 1986) and KF-4317 has a similar mild inhibitory effect at α_1- and β_2-adrenoceptors (pA_2 at α_1 of rabbit aorta = 6·25, pA_2 at β_2 of guinea-pig trachea = 5 : 99, Kubo et al 1983).

In addition to in-vivo and in-vitro studies showing the ability of these combined α- and β-adrenoceptor antagonists to cause vasodilation by α_1-adrenoceptor blockade, labetalol and dilevalol have been reported to cause vasodilation by a mechanism independent of α_1-adrenoceptor blockade in-vivo (e.g. Baum et al 1981). There have been no in-vitro studies of this ability of labetalol and dilevalol to cause α_1-adrenoceptor independent vasodilation. Also, there have been no studies of the effects of labetalol, dilevalol or KF-4317 at the β_2-adrenoceptors of isolated blood vessels. The present study has examined the effects of labetalol, dilevalol, amosulalol and KF-4317 on the rat isolated aorta and I report their ability to cause a small relaxation of the KCl-contracted preparation. I then studied the effect of ICI 118,551 (a β-adrenoceptor antagonist) on these relaxations. Finally, I investigated the effects of labetalol, dilevalol, amosulalol and KF-4317 on the relaxant responses of the rat aorta to procaterol (a potent and selective β_2-adrenoceptor agonist, O'Donnell & Wanstall 1985).

Materials and methods

Male Wistar rats (250–350 g) were stunned and exsanguinated. The thoracic aorta was rapidly removed and placed in Krebs solution that was saturated with 5% CO_2 in oxygen. All experiments were performed in the presence of a modified Krebs solution [composition (mM): NaCl, 116; KCl, 5·4; $CaCl_2$, 2·5; $MgCl_2$, 1·2; $NaHPO_4$, 1·2; $NaHCO_3$, 22·0; D-glucose, 11·2; Na_2EDTA, 0·04], at 37°C which was being vigorously bubbled with 5% CO_2 in oxygen. Contractile responses were measured isometrically with force displacement transducers (Grass model FTO3. C) and displayed on a polygraph (Grass Model 79B). In each series of experiments, the individual values obtained were compared by Student's paired t-test and were considered to be significantly different when $P < 0{\cdot}05$. Mean values ± s.e.m. were also obtained.

A ring of rat aorta was suspended between stainless steel hooks under 1 g tension in 5 mL organ baths containing Krebs solution. Tissues were equilibrated for 30–60 min before exposure to phenoxybenzamine at 5×10^{-5} M for 30 min to block α-adrenoceptors and extraneuronal uptake. Tissues were washed for 20 min and then contracted by $\geqslant 200$ mg by the addition of KCl to the organ bath to give a final concentration of $2\text{–}3 \times 10^{-2}$ M. When the contraction was constant, four series of experiments were performed.

(i) *The effects of drugs alone were compared to those of procaterol.* A cumulative challenge to procaterol, labetalol, dilevalol, amosulalol or KF-4317 at $10^{-9}/10^{-8}$–10^{-4} M was made on a 4 min cycle.

(ii) *The effects of ICI 118,551 on the relaxant responses to labetalol, dilevalol, amosulalol and KF-4317 was examined.* A 10 min challenge to a single concentration of a drug was made. Tissues were then washed for 90 min in the absence or presence of ICI 118,551 at 10^{-6} M before recontracting the aorta with KCl to a constant level and repeating the challenge to the drug.

(iii) *The reproducibility of the relaxant response curves to procaterol was determined.* A cumulative challenge to procaterol, 10^{-9}, 3×10^{-9}, 10^{-8} M, etc. was made to each aorta on a 4 min cycle. Tissues were then washed for 45 min before recontracting the aorta with KCl and repeating the challenge to procaterol. Tissues were then washed for a further 45 min before a third contraction with KCl and challenge with procaterol.

(iv) *The effects of drugs (labetalol, dilevalol, amosulalol or KF-4317) on the responses to procaterol were determined.* An initial cumulative challenge to procaterol was made to each aorta on a 4 min cycle in the absence of drugs. Tissues were then equilibrated for 45 min in the presence of a drug before recontracting the aorta and repeating the challenge to procaterol. Tissues were then equilibrated for a further 45 min, in the presence of a higher concentration of the drug being tested, before a third contraction with KCl and challenge with procaterol.

Assessment of data. The maximal decrease in contractile response to each concentration of procaterol, labetalol, dilevalol, amosulalol or KF-4317 was measured. These relaxant responses were calculated as a percentage of the KCl contraction. When successive relaxant response curves to procaterol were obtained, if the maximal relaxant responses to procaterol expressed as a percentage of the KCl contraction were not significantly different between curves, all the relaxant responses were calculated as a percentage of the maximal relaxant response to procaterol, i.e. normalized. For normalized data slopes, pD_2 and pA_2 values were determined. The slope of the agonist concentration-response curve (difference in percentage maximum of the response/unit of logarithm molar concentration of agonist) and pD_2 value (the negative logarithm of the molar concentration of agonist producing 50% of the maximum response) were computed by regression line analysis. This was performed on the steepest part of the concentration-response curve, which was

usually over the range 20–80% of the maximum response. For each tissue, the ability of a drug to alter responses was expressed as the concentration ratio (the antilogarithm of the difference between the pD_2 value in the presence and in the absence of the drug). When the effects of a drug were compatible with competitive antagonism (i.e. there was no effect on the slope of the concentration-response curve and a reduction in pD_2 value) pA_2 values were determined. pA_2 values (the negative logarithm of the molar concentration which causes a twofold shift of the concentration response curve for agonist) were calculated for each tissue pair from the formula $pA_2 = pA_x + \log(x-1)$, where pA_x is the negative logarithm of the molar concentration of drug and x is the agonist concentration-ratio.

Drugs used. The drugs used were labetalol hydrochloride* (Allen and Hanbury's Research Ltd.), KF-4317* (4-(2-hydroxy-3-[(1-methyl-3-phenylpropyl)amino]propoxy)-benzeneacetamide hydrochloride, Kyowa Hakko Kogyo Co. Ltd), dilevalol hydrochloride* (SCH 19930, Schering Corporation), phenoxybenzamine hydrochloride (Smith Kline and French) made up in absolute ethanol containing 10 mM HCl, procaterol hydrochloride* (Warner-Lambert) and amosulalol hydrochloride* (5-[1-hydroxy-2-[[2-(O-methoxyphenoxy) ethyl]-amino]ethyl]-2-methylbenzenesulfonamide hydrochloride (YM-09538, Yamanouchi Pharmaceuticals). Compounds marked with an asterisk were donated.

Results

(i) *The effects of drugs alone.* When the rat aorta has been contracted by the addition of KCl, it is relaxed by procaterol, $\geqslant 10^{-9}$ M (Fig. 1). Labetalol and dilevalol, 10^{-8}–10^{-4} M, have a similar relaxant effect to procaterol on the rat aorta (Fig. 1). Amosulalol, $\leqslant 10^{-6}$ M, and KF-4317, $\leqslant 10^{-7}$ M, did not relax the rat aorta (Fig. 1). Higher concentrations of amosulalol ($\geqslant 10^{-5}$ M and KF-4317 ($\geqslant 10^{-6}$ M) caused a small but significant relaxation of the KCl contracted rat aorta (Fig. 1).

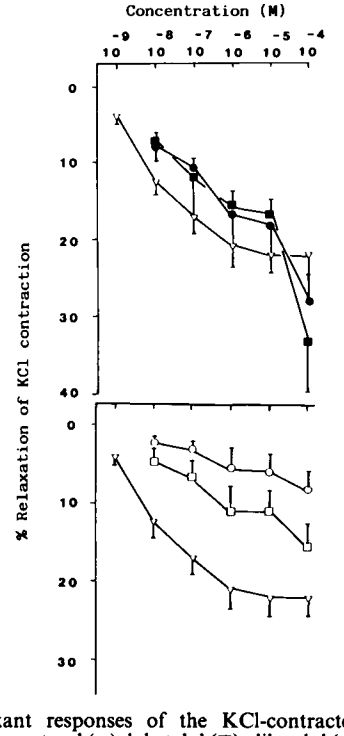

FIG. 1. Relaxant responses of the KCl-contracted rat aorta. Responses to procaterol (▽), labetalol (■), dilevalol (●), amosulalol (○) and KF-4317 (□). All relaxations are calculated as a percentage of the KCl contraction. Each value is the mean ± s.e.m. from 8–10 animals.

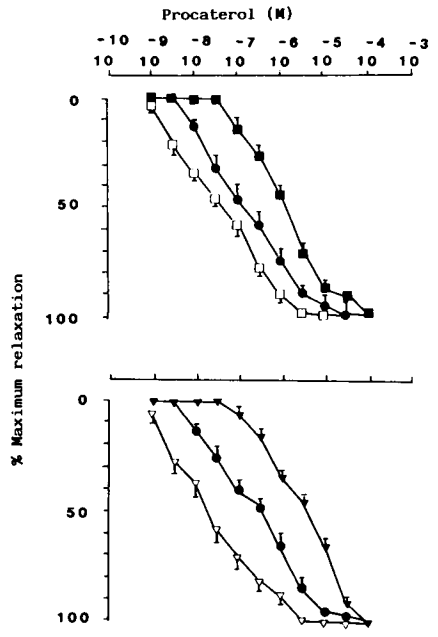

FIG. 2. Effect of labetalol (top) and dilevalol (bottom) on procaterol response curves. Responses in the absence (□) and presence of labetalol at 10^{-7} (●) and 10^{-6} M (■) and, from other animals, in the absence (▽) and presence of dilevalol at 10^{-7} (●) and 10^{-6} M (▽). Responses are calculated as a percentage of the maximum relaxation and plotted against the log of the molar concentration of procaterol. Each value is the mean ± s.e.m. from 8 or 9 animals.

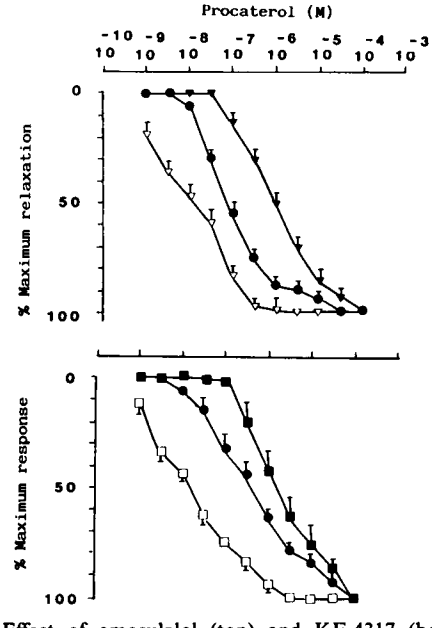

FIG. 3. Effect of amosulalol (top) and KF-4317 (bottom) on procaterol response curves. Responses in the absence (▽) and presence of amosulalol at 10^{-7} (●) and 10^{-6} M (▼) and, from other animals, in the absence (□) and presence of KF-4317 at 10^{-7} (●) and 10^{-6} M (■). Responses are calculated as a percentage of the maximum relaxation and plotted against the log of the molar concentration of procaterol. Each value is the mean ± s.e.m. from 0 preparations.

(ii) *The effects of ICI 118,551 on the relaxant responses.* Two successive 10 min challenges of the KCl contracted rat aorta to labetalol, dilevalol (both at 10^{-6} M), amosulalol or KF-4317 (both at 10^{-4} M) produced relaxations that were not significantly different. The mean relaxations being 19 and 23% of the KCl contraction during the first and second challenges with labetalol, 13 and 10% with dilevalol, 18 and 16% with amosulalol and 15

and 19% with KF-4317, respectively (n = 4). Pretreatment with ICI 118,551 at 10^{-6} M for 45 min did not alter the relaxations to the second challenge to labetalol, dilevalol, amosulalol or KF-4317 (n = 4, data not shown).

(iii) *The reproducibility of procaterol response curves.* Three successive challenges of the KCl-contracted rat aorta to procaterol produced identical relaxant curves (n = 8, data not shown).

(iv) *The effects of drugs on procaterol response curves.* Labetalol, dilevalol, amosulalol and KF-4317 (all at 10^{-7}–10^{-6} M) produced parallel rightward displacements of the procaterol relaxant curves with no reduction in the maximal response (Figs 2, 3). The submaximal responses to procaterol were inhibited ×7 and ×39 by labetalol at 10^{-7} M and 10^{-6} M, respectively, ×35 and ×248 by dilevalol at 10^{-7} and 10^{-6} M, respectively, ×32 and ×583 by amosulalol at 10^{-7} and 10^{-6} M, respectively, and ×47 and ×332 by KF-4317 at 10^{-7} and 10^{-6} M, respectively (see Table 1 for pD_2 values). As β_2-adrenoceptor antagonists, dilevalol (mean $pA_2 = 8{\cdot}3$), amosulalol ($pA_2 = 7{\cdot}9$) and KF-4317 ($pA_2 = 8{\cdot}4$) had similar high potencies and were significantly more potent than labetalol ($pA_2 = 7{\cdot}4$).

Table 1. Effects on procaterol response curves.

	pD_2[a]	pA_2[a]
Control	7·39 ± 0·16 (9)	
Labetalol, 10^{-7} M	6·73 ± 0·13 (9)*	7·5 ± 0·2 (9)
Labetalol, 10^{-6} M	5·98 ± 0·09 (9)*	7·4 ± 0·2 (9)
Control	7·86 ± 0·08 (8)	
Dilevalol, 10^{-7} M	6·52 ± 0·15 (8)*	8·3 ± 0·2 (8)
Dilevalol, 10^{-6} M	5·52 ± 0·08 (8)*	8·2 ± 0·1 (8)
Control	8·03 ± 0·21 (9)	
Amosulalol, 10^{-7} M	7·08 ± 0·09 (9)*	7·9 ± 0·3 (9)
Amosulalol, 10^{-6} M	6·05 ± 0·09 (9)*	7·9 ± 0·3 (9)
Control	8·01 ± 0·14 (9)	
KF 4317, 10^{-7} M	6·44 ± 0·13 (9)*	8·5 ± 0·1 (9)
KF 4317, 10^{-6} M	5·73 ± 0·20 (9)*	8·2 ± 0·2 (9)

[a] Mean ± s.e.m.
(n) = number of animals.
* $P < 0{\cdot}05$, paired *t*-test with own control.

Discussion

The ability of labetalol and dilevalol to cause vasodilation independent of α-adrenoceptor blockade has been demonstrated in-vivo. Labetalol decreased the blood pressure in adrenalectomized, vagotomized spinal dogs without changing heart rate or cardiac output (Dage & Hsieh 1980) and labetalol and dilevalol increased the blood flow in the denervated limbs of anaesthetized dogs with dilevalol being seven times more potent than labetalol and producing a greater peak vasodilation than labetalol (Baum et al 1981). The present study, using the KCl-contracted rat aorta, confirms the ability of labetalol and dilevalol to cause relaxation but shows labetalol and dilevalol to be equipotent and to produce a similar maximum relaxation of the aorta. The reason for the differences between the in-vivo and in-vitro study is unclear but may reflect the different preparations used.

There is controversy as to whether β_2-adrenoceptor agonism is the mechanism underlying the α-adrenoceptor blockade independent vasodilation with labetalol and dilevalol. Baum et al (1981) demonstrated that the vasodilatory action of labetalol and dilevalol in dog denervated limbs was prevented by high doses of propranolol, a nonselective β-adrenoceptor antagonist with membrane-stabilizing activity, and suggested that labetalol and dilevalol caused vasodilation by acting as agonists at β_2-adrenoceptor. However, Dage & Hsieh (1980) were unable to reverse the vasodilator action of labetalol on the isolated perfused gracilis muscle of the dog with propranolol and concluded that the vasodilatory action of labetalol was not related to β_2-adrenoceptor agonism.

ICI 118,551 is a selective β_2-adrenoceptor antagonist having a pA_2 of 8·69 at β_2- (guinea-pig trachea) and 6·96 at β_1-adrenoceptors (guinea-pig atria, O'Donnel & Wanstall 1980). The rat aorta contains both β_1- and β_2-adrenoceptors mediating relaxation with the β_1-adrenoceptors being the minor population (O'Donnell & Wanstall 1984). Procaterol is a highly selective β_2-adrenoceptor agonist which relaxes the KCl-contracted rat aorta (O'Donnell & Wanstall 1985; this study). Recently I have illustrated that ICI 118,551 inhibits the procaterol response curves of the rat aorta with a pA_2 of 8·90 (Doggrell 1987). In the present study the relaxations to labetalol, dilevalol, amosulalol and KF 4317 were not reversed by pretreatment with ICI 118,551 at 10^{-6} M, a concentration that would produce antagonism at β_1- and β_2-adrenoceptors. Consequently it is unlikely that these relaxations are due to either stimulation of the β_1- or β_2-adrenoceptors of the rat aorta.

Adrenaline, and possibly noradrenaline, stimulates vascular β_2-adrenoceptors to produce vasodilation (Fitzgerald 1984). Inhibition of this vasodilation produces an increase in blood pressure (Fitzgerald 1984) and is an unwanted effect in hypertension. Previous studies using the guinea-pig trachea have demonstrated that labetalol, dilevalol and amosulalol are potent β_2-adrenoceptor antagonists. In the present study using the rat aorta, each of these drugs had a similar potency as a β_2-adrenoceptor antagonist as previously reported using the guinea-pig trachea. KF-4317 has previously been reported to be a weak antagonist at the β_2-adrenoceptors of the guinea-pig trachea (Kubo et al 1983). In the present study, KF-4317 was also a potent β_2-adrenoceptor antagonist on the rat aorta. This indicates that there may be some differences between the β_2-adrenoceptors of guinea-pig trachea and rat aorta. In addition the antihypertensive effect of each of the drugs tested may be limited by β_2-adrenoceptor antagonism.

Following the oral administration of labetalol (100–400 mg) and amosulalol (12·5–150 mg) to healthy humans the plasma concentration ranges are 10^{-8}–10^{-6} M (Martin et al 1976) and 10^{-6}–10^{-5} M (Nakashima et al 1984), respectively. In the present study relaxation of the rat aorta independent of α-adrenoceptor blockade and β_2-adrenoceptor antagonism occurred with labetalol and dilevalol $\leqslant 10^{-5}$ M and thus these effects do occur with clinically relevant concentrations.

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The influence of components on the rectal absorption of cefazolin in rats

EWOUD J. VAN HOOGDALEM, JOAN A. M. GEERTS, ALBERTUS G. DE BOER, DOUWE D. BREIMER *Centre for Bio-Pharmaceutical Sciences, Division of Pharmacology, Sylvius Laboratories, State University of Leiden, P.O. Box 9503, 2300 RA Leiden, The Netherlands*

Abstract—A study has been made to identify the component(s) responsible for the absorption-promoting effect of MGK medium chain glyceride preparation commercially available as a mixture of glyceryl-1-monooctanoate, glyceryl-1,3-dioctanoate, glyceryl-1,2-dioctanoate, glyceryl trioctanoate, octanoic acid and glycerol. The action of the individual constituents has been evaluated on the rectal absorption of cefazolin in conscious rats. The results indicate that the action of MGK can be completely explained by the effect of glyceryl-1-monooctanoate, which both enhanced the extent and rate of cefazolin uptake.

The medium chain glyceride preparation MGK (Nikho, Tokyo, a commercially available mixture of glyceryl-1-monooctanoate, glyceryl-1,2-dioctanoate, glyceryl-1,3-dioctanoate, glyceryl trioctanoate, glycerol and octanoic acid) has been reported to be an effective enhancer of the absorption of cefmetazole sodium from the rat rectum (Sekine et al 1984) and from various intestinal segments in dogs (Sekine et al 1985a). This effect was increased by coadministration of non-ionic surfactants (Sekine et al 1985c). Higaki et al (1987) reported on enhancing effect of the preparation on the intestinal absorption of phenol red in rats. The reported low oral acute toxicity of MGK and the absence of local irritation (Sekine et al 1985b) suggest that a preparation is a potentially useful enhancer of intestinal absorption for poorly absorbed drugs, e.g. peptides, proteins and antibiotics.

To better understand the absorption-enhancing action of MGK and to further develop absorption enhancing compounds, it is necessary to elucidate to what extent each of the components contribute to the effect of the mixture. Using the separated glycerides from the preparation as well as mixtures of several commercial preparations, Sekine et al (1984) observed that the action of MGK could in part be ascribed to glyceryl monooctanoate. It was suggested that a certain component ratio of mono-, di- and trioctanoate was of primary importance for the promoting effect (Sekine et al 1984). However, the results of that study are not unequivocal, because the comparisons were made with mixtures which differed in concentration of more than one component. Furthermore in the study of the effects of the separate glycerides, it was not reported which isomers of mono- and diglycerides had been used. The fact that glyceryl-1,2-dioctanoate could affect membrane permeability by stimulating phosphorylation (Eichberg et al 1986), illustrates the importance of studying the effects of the individual isomers present in MGK.

Our aim was to evaluate the effect of the individual components of the preparation on the rate and extent of rectal absorption of the polar model compound cefazolin sodium in conscious rats and thereby identify the component(s) responsible for the absorption promoting action.

Correspondence to: E. Van Hoogdalem, Centre for Bio-Pharmaceutical Sciences, Division of Pharmacology, Sylvius Laboratories, State University of Leiden, P.O. Box 9503, 2300 RA Leiden, The Netherlands.

Materials and methods

Chemicals. MGK was a gift from Nikko Chemicals Co. Ltd. (Tokyo, Japan) and contained glyceryl-1-monooctanoate 55–57% w/v, glyceryl-1,2-dioctanoate 9% w/v, glyceryl-1,3-dioctanoate 20% w/v, glyceryl trioctanoate 3% w/v, octanoic acid 3% w/v and glycerol 8% w/v (Manufacturer's data). Glyceryl-1-monooctanoate was a gift from Tramedico (Weesp, The Netherlands). Glyceryl-1,2-dioctanoate, glyceryl-1,3-dioctanoate and glyceryl trioctanoate were obtained from Sigma Chemical Co. (St. Louis, USA). Octanoic acid was from Janssen Chimica (Beerse, Belgium), glycerol was purchased from J. T. Baker Chemicals B.V. (Deventer, The Netherlands). Cefazolin sodium (Kefzol) was a gift from Eli Lilly Nederland (Utrecht, The Netherlands), cefoxitin sodium (Mefoxin) was a gift from Merck, Sharp & Dohme (Haarlem, The Netherlands). All chemicals used were of analytical grade. Ethyl acetate was distilled before use.

Animals. Male Wistar rats of laboratory breed, 170–200 g, were used. The rats were fasted for 16 h before the experiments, but water was freely available. Experiments were performed in groups of 5 to 8 animals.

Drug preparations. For i.v. infusion a solution of cefazolin sodium 15 mg mL^{-1} was made isotonic by the addition of sodium chloride.

For rectal administration without enhancer, a solution was used containing cefazolin sodium 15 mg mL^{-1} in 0·067 M phosphate buffer pH 7·4. The preparation with MGK contained cefazolin sodium 15 mg mL^{-1} MGK: water (13:1 w/w). Preparations of the individual components of MGK contained cefazolin sodium 15 mg mL^{-1} and the component, at a percentage corresponding to that in the MGK:water mixture containing MGK, glyceryl-1-monooctanoate, octanoic acid or glycerol were clear which octanoic acid was dissolved by