Brit. J. Pharmacol. (1965), **25**, 534–544.

PHARMACOLOGY OF *N*-[2-(2,6-XYLYLOXY)ETHYL]-GUANIDINE SULPHATE; AN ADRENERGIC NEURONE BLOCKING AGENT

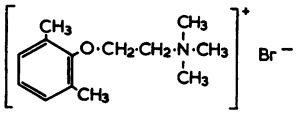
BY

D. I. BARRON*, I. L. NATOFF AND D. K. VALLANCE*

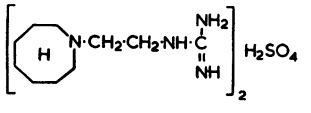
From the Department of Pharmacology, Smith Kline & French Laboratories, Welwyn Garden City, Herts

(*Received May* 10, 1965)

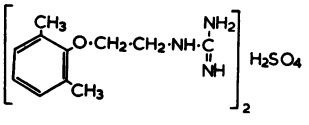
The observation that xylocholine (choline 2,6-xylyl ether bromide; TM10) has an inhibitory effect on the conduction of nervous impulses in the postganglionic fibres of the sympathetic nervous system (Hey & Willey, 1954) led to its clinical examination as an antihypertensive agent. Its marked parasympathomimetic activity, however, prevented its further use. Maxwell, Plummer, Schneider, Povalski & Daniel (1960) have demonstrated that guanethidine sulphate also has marked adrenergic neurone blocking activity, and this compound is widely used clinically. The adrenergic neurone blocking activity of xylocholine is rapid in onset and of a relatively short duration, whereas that of guanethidine is slow in onset and of long duration. In an attempt to prepare compounds having a specific adrenergic neurone blocking activity with a rapid onset and a short duration of action while being devoid of parasympathomimetic activity, the xylyloxyethyl chain of xylocholine was combined with the guanidino-group of guanethidine. The resulting compound, *N*-[2-(2,6-xylyloxy)ethyl]guanidine sulphate (SK&F 70418), showed marked adrenergic neurone blocking activity (Boura, Copp, Green, Hodson, Ruffell, Sim, Walton & Grivsky, 1961; Barron, Bavin, Durant, Natoff, Spickett & Vallance, 1963). The pharmacology of this compound is reported below.



Xylocholine
(Choline 2,6-xylyl ether bromide)



Guanethidine sulphate
(*N*-[2-(Octahydroazocin-1-yl)ethyl]-guanidine sulphate)



SK&F 70418
(*N*-[2-(2,6-Xylyloxy)ethyl]guanidine sulphate)

* Present address: Biological Research Department, British Drug Houses Limited, Godalming, Surrey.

METHODS

Effect on the nictitating membrane of the conscious cat. SK&F 70418 and guanethidine sulphate were administered orally in hard gelatine capsules at various dose levels to groups of eight or twelve fasted male cats. At 24 hr after dosing, the animals were photographed and the proportion of each eye covered by the nictitating membrane was measured. The median effective dose and its confidence limits ($P=0.95$) for each compound were estimated by the method of Litchfield & Wilcoxon (1949) from the number of animals in each group having 15% or more of each eye covered.

Effect on the blood pressure, heart and nictitating membrane of the anaesthetized or spinal cat. Female cats were anaesthetized by the intravenous injection of chloralose (80 mg/kg) following induction with ether, or were made spinal in the usual manner. Mean arterial blood pressure was recorded from the left carotid artery with a mercury manometer, and contractions of the right nictitating membrane were recorded with a frontal-writing lever. In some experiments the adrenal glands were excluded from the circulation by ligature of the adrenal veins. In others, the amplitude of cardiac contractions and heart rate were recorded with a Cushny myocardiograph. All drug solutions were injected through a cannula in the right femoral vein.

Effect on the blood pressure of the anaesthetized dog. Anaesthesia was induced in male mongrel dogs by the intravenous injection of sodium pentobarbitone (30 mg/kg) and was maintained by the intravenous infusion of sodium pentobarbitone (0.1 mg/kg/min) throughout the experiment. Mean arterial blood pressure was recorded from the left femoral artery with a mercury manometer, and Lead II electrocardiograms were recorded using a Phillips Cardioluxe electrocardiograph. All subsequent drug solutions were injected through a cannula in the right femoral vein.

Effect on the blood pressure of the anaesthetized rat. Male albino Wistar rats were anaesthetized by the intraperitoneal injection of sodium pentobarbitone (60 mg/kg). Mean arterial pressure was recorded from the left carotid artery with a Condon manometer. All drug solutions were injected through a cannula in the right external jugular vein.

Effect on postganglionic sympathetic nerve transmission. Short segments of rabbit ileum, with mesentery attached, were suspended in an 80-ml. organ-bath according to the method of Finkleman (1930). Inhibition of pendular movements was elicited by postganglionic sympathetic nerve stimulation (40 V intensity, 0.5 msec duration, 50 shocks/sec frequency) for constant periods of 15 to 30 sec at intervals of 10 min. Compounds were added to the bath fluid as solutions in 0.9% saline.

Local anaesthetic activity. The guinea-pig intradermal wheal test of Bülbring & Wajda (1945) was used. The concentration of each agent preventing 50% of the applied stimuli from eliciting a response (PC50) was estimated graphically.

Effect on neuromuscular transmission. Male albino Wistar rats were anaesthetized by the intraperitoneal injection of sodium pentobarbitone (60 mg/kg). Rectangular pulses (30 V intensity, 80 μsec duration, 3 shocks/min frequency) were applied to the distal portion of the cut left sciatic nerve and contractions of the left gastrocnemius muscle were recorded with an isometric lever.

Parasympathomimetic activity. Short segments of guinea-pig ileum were suspended in a 20-ml. organ-bath containing oxygenated Tyrode solution at 32° C. Contractions were recorded using a frontal-writing lever. Compounds dissolved in 0.9% saline were added directly to the bath fluid.

Effect on monoamine oxidase activity. Groups of three female Wistar rats were given either SK&F 70418, tranylcypromine sulphate or saline by stomach tube, and were killed 3 or 24 hr after dosing. The livers and brains were rapidly removed from each animal, rinsed in chilled saline, blotted and weighed. The bulked tissue from each group was then homogenized in nineteen volumes of 0.067 M-phosphate buffer (*p*H 7.4) and the monoamine oxidase activity was determined by the method of Green & Haughton (1961).

RESULTS

Effect on the nictitating membrane of the conscious cat

The oral administration of either SK&F 70418 or guanethidine sulphate to conscious cats resulted in marked relaxation of the nictitating membranes. The median effective

doses with confidence limits (P=0.95) were 8.5 mg/kg (6.0 to 12.0) and 9.5 mg/kg (5.9 to 15.2) respectively. The effect of each compound developed within 5 to 6 hr and persisted for more than 3 days.

Effect on the blood pressure, heart and nictitating membranes of the anaesthetized or spinal cat

SK&F 70418 (5 or 10 mg/kg, intravenously) caused an initial prolonged rise in blood pressure, followed by a fall to or below the control level within 5 hr. The pressor phase was generally preceded by a transient fall in blood pressure, a phenomenon which has been reported for both bretylium and guanethidine sulphate (Gokhale, Gulati & Kelkar, 1963). A contraction of the nictitating membrane occurred simultaneously with the rise in blood pressure and was sustained for the remainder of the experiment. Observations using the Cushny myocardiograph showed the rise in blood pressure to be associated also with a positive chronotropic and inotropic action on the heart, the heart rate being increased from a control value of 276 beats/min to 336 beats/min within 20 min of injection of SK&F 70418.

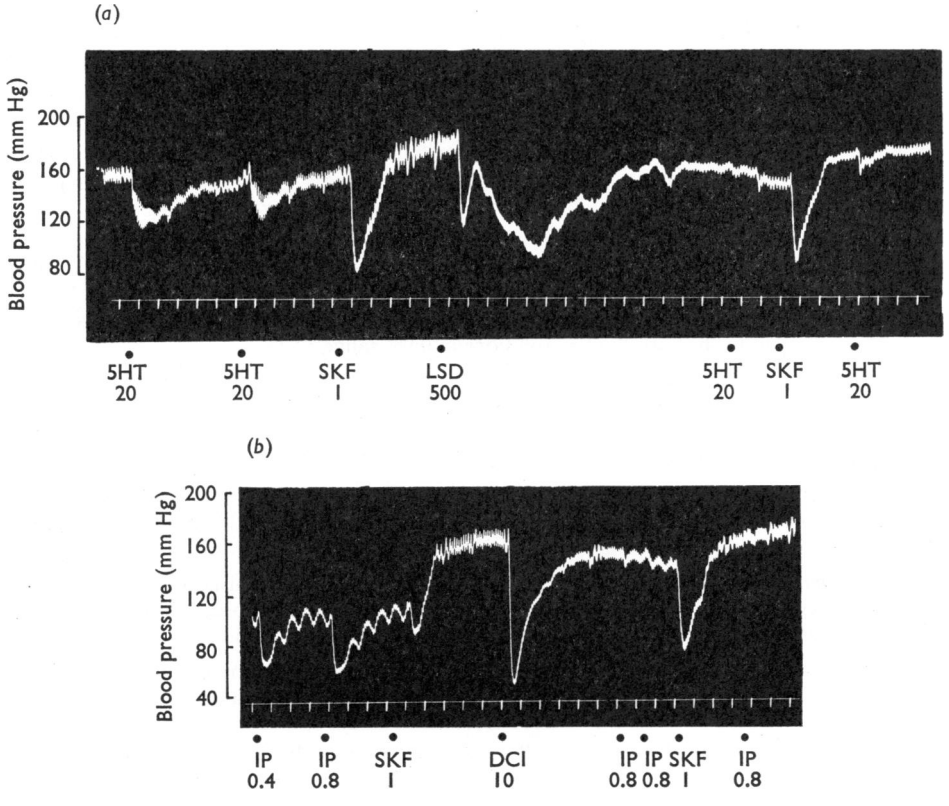


Fig. 1. Record of the arterial blood pressure of a cat, anaesthetized with chloralose, during continuous intravenous infusion of (−)-noradrenaline (2.5 μg of base/kg/min). In (*a*), intravenous injections of 5-hydroxytryptamine (5HT, 20 μg/kg) and SK&F 70418 (SKF, 1 mg/kg) before and after intravenous injection of lysergide (LSD, 500 μg/kg). In (*b*), intravenous injections of isoprenaline (IP, 0.4 and 0.8 μg/kg) and SK&F 70418 (1 mg/kg) before and after dichloroisoprenaline (DCI, 10 mg/kg). Time marks, 30 sec.

The mechanism involved in the initial depressor response was investigated using anaesthetized animals in which the mean arterial pressure was elevated by the continuous intravenous infusion of (−)-noradrenaline (2.5 μg of base/kg/min). Repeated intravenous doses of SK&F 70418 (1 mg/kg) during this infusion resulted in reproducible depressor responses of short duration. These responses were not affected by the prior intravenous administration of promethazine hydrochloride (2 mg/kg), lysergic acid diethylamide (lysergide, 0.5 mg/kg), dichloroisoprenaline (10 mg/kg) or atropine sulphate (2 mg/kg) (Fig. 1,*a* and *b*). The doses of these antagonists did, however, inhibit the depressor responses to intravenously injected histamine acid phosphate (5 μg/kg), 5-hydroxytryptamine creatinine sulphate (20 μg/kg), isoprenaline sulphate (0.8 μg/kg) and acetylcholine bromide (2 μg/kg) respectively.

Wylie (1961) showed that potentiation of the pressor responses to small doses of guanethidine in the spinal cat is produced by the catechol-*O*-methyl transferase inhibitor, pyrogallol. Similar small intravenous doses of SK&F 70418 (0.1 and 0.2 mg/kg) also elicited pressor responses in the spinal cat and these, too, were augmented both in magnitude and duration by prior injection of pyrogallol (4 mg/kg, intravenously). They were completely abolished by tolazoline (4 mg/kg, intravenously). The pressor effect to SK&F 70418 was prevented by treatment of the animals with reserpine (5 mg/kg, intraperitoneally on each of the two preceding days) but acute adrenalectomy had no effect.

TABLE 1

EFFECT OF SYMPATHETIC STIMULI ON THE MEAN ARTERIAL PRESSURE OF AN ANAESTHETIZED CAT BEFORE AND AFTER INJECTION OF SK&F 70418

Values are rises in blood pressure, except for the "no stimulus" values (top row) which are absolute. All drugs were injected intravenously. The second column gives values 5 hr after 5 mg/kg of SK&F 70418

Stimulus	Blood pressure (mm Hg)	
	Control phase	After SK&F 70418
None	68	34
Bilateral carotid arterial occlusion (60 sec)	+10	+6
(±)-Amphetamine sulphate (0·5 mg/kg)	+84	+10
(−)-Adrenaline bitartrate (6·0 μg/kg)	+50	+58
(−)-Noradrenaline (3·0 μg/kg)	+68	+110

In some experiments, responses to bilateral carotid arterial occlusion for 1 min, and to intravenous injection of (±)-amphetamine sulphate (0.25 and 0.5 mg/kg), (−)-adrenaline bitartrate (6.0 μg/kg) and (−)-noradrenaline (3.0 μg of base/kg) were obtained before and 5 hr after the intravenous injection of SK&F 70418 (5 or 10 mg/kg). Table 1 shows that SK&F 70418 reduced the responses to bilateral carotid arterial occlusion and amphetamine, but potentiated those to adrenaline and noradrenaline.

Effect on the blood pressure of the anaesthetized dog

Intravenous injection of SK&F 70418 (5 mg/kg) into the anaesthetized dog produced effects on blood pressure similar to those seen in the cat. No changes in the electrocardiogram were observed which could be attributed to the administration of SK&F 70418.

In further experiments, groups of dogs were treated with SK&F 70418 (10 mg/kg, intravenously) at various times before induction of anaesthesia and recording the blood pressure. The resting arterial pressure (means and standard errors) for control dogs was 144.0±4.8 mm Hg (thirteen dogs), while 3 hr after SK&F 70418 it was 153.0±6.2 mm Hg (four dogs); at 24 hr it was 93.88±14.4 mm Hg (four dogs) (significantly less than the control group value, $P<0.001$) and at 48 hr it was 95.7±3.6 mm Hg (twenty-two dogs) (significantly less than the control group value, $P<0.001$). The pressor responses to intravenous tyramine hydrochloride (0.2 mg/kg) and (±)-amphetamine sulphate (0.5 mg/kg) were also significantly reduced throughout this period, but were restored by the intravenous infusion of (−)-noradrenaline (50 μg of base/min for 20 min) (Table 2). Burn & Rand (1958) originally demonstrated that the pressor response to tyramine in the reserpinized cat may be restored by intravenous infusion of noradrenaline.

TABLE 2

EFFECT OF TREATMENT WITH SK&F 70418 (10 MG/KG, INTRAVENOUSLY) ON THE PRESSOR RESPONSE TO (±)-AMPHETAMINE SULPHATE OR TYRAMINE HYDROCHLORIDE IN THE ANAESTHETIZED DOG

Increases in blood pressure are means and standard errors, with numbers of animals in parentheses. The noradrenaline infusion was 1 mg during 20 min. (±)-Amphetamine sulphate was given intravenously in a dose of 0·5 mg/kg, and tyramine hydrochloride intravenously in a dose of 0·2 mg/kg. * Significantly different from controls ($P<0.01$)

Group	Increase in blood pressure (mm Hg) after	
	Amphetamine sulphate	Tyramine hydrochloride
Control	121·6±8·5 (5)	101·6±11·4 (5)
SK&F 70418		
3 hr previously	33·5±7·9* (4)	
24 hr previously	56·0±8·5* (4)	
48 hr previously	51·2±9·1* (5)	58·8±4·5* (5)
48 hr previously plus infusion of noradrenaline	114·4±10·6 (5)	96·6±3·5 (5)

Effect on the blood pressure of the anaesthetized rat

SK&F 70418 had depressor activity at doses (0.25 to 2.0 mg/kg, intravenously) which were normally pressor in anaesthetized cats and dogs (Fig. 2). Guanethidine also exerted a depressor effect, the responses being much more prolonged.

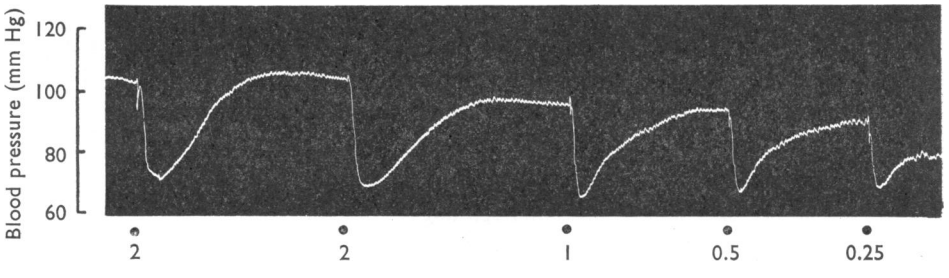


Fig. 2. Record of the arterial blood pressure of a rat anaesthetized with sodium pentobarbitone. Intravenous injections of SK&F 70418 (2, 1, 0.5 and 0.25 mg/kg) produced depressor responses.

Effect on postganglionic sympathetic nerve transmission

After a latent period of up to 40 min, SK&F 70418 (0.05 and 0.5 μg/ml.) blocked the inhibition of pendular movements of the rabbit ileum resulting from sympathetic nerve stimulation. This latent period decreased as the concentration of the compound was increased. Blockade persisted for more than 4 hr at the lowest concentrations studied despite repeated washings. It was reversed by the addition of 3,4-dihydroxyphenylethylamine (dopamine; 5 μg/ml.) within 30 min (Fig. 3), but not by 3,4-dihydroxyphenylalanine (dopa; 5 μg/ml.) or noradrenaline (0.05 μg of base/ml.) even after 1 hr. Qualitatively similar results were obtained with guanethidine sulphate although it was twenty-times less potent than SK&F 70418 in inhibiting the effect of sympathetic neurone stimulation.

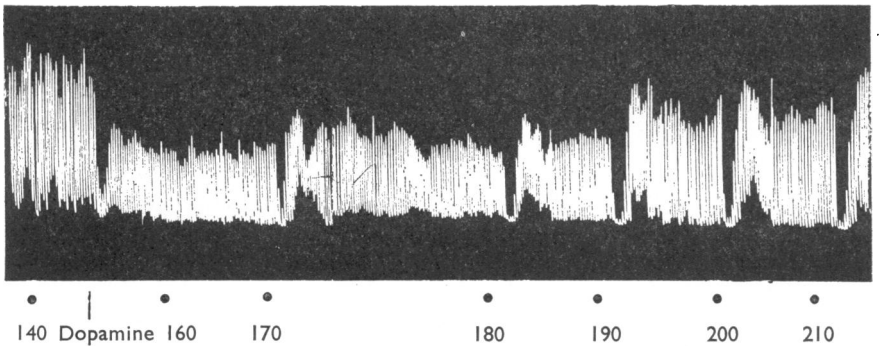


Fig. 3. Rabbit ileum isolated-sympathetic nerve preparation treated with SK&F 70418 (0.5 μg/ml.) 140 min previously. At the black dots, the periarterial nerves were stimulated for 20 sec with 0.5-msec, 40-V pulses at 50 shocks/sec. The addition of dopamine (5 μg/ml.) to the bath fluid in the presence of SK&F 70418 reversed the inhibition of the response to nerve stimulation. At the bottom are times (in min) after the injection of SK&F 70418.

Day (1962) showed that the effect of guanethidine on the Finkleman preparation could be reversed by certain inhibitors of monoamine oxidase which possess inherent sympathomimetic properties. Tranylcypromine sulphate (6.25 μg/ml.), phenelzine (12.5 μg/ml.) and pheniprazine (12.5 μg/ml.) have also been shown to reverse the blockade due to SK&F 70418 (Fig. 4).

Local anaesthetic activity

SK&F 70418 was twice as potent as xylocholine and ten-times as potent as guanethidine sulphate as a local anaesthetic. The PC50 values (w/v) were 0.2% for SK&F 70418, 0.4% for xylocholine and 2.1% for guanethidine sulphate. The local anaesthetic effect of each of these compounds persisted for more than 24 hr.

Effect on neuromuscular transmission

SK&F 70418, in doses exerting a marked effect on the blood pressure, did not affect the responses of the gastrocnemius muscle to sciatic nerve stimulation in the anaesthetized rat.

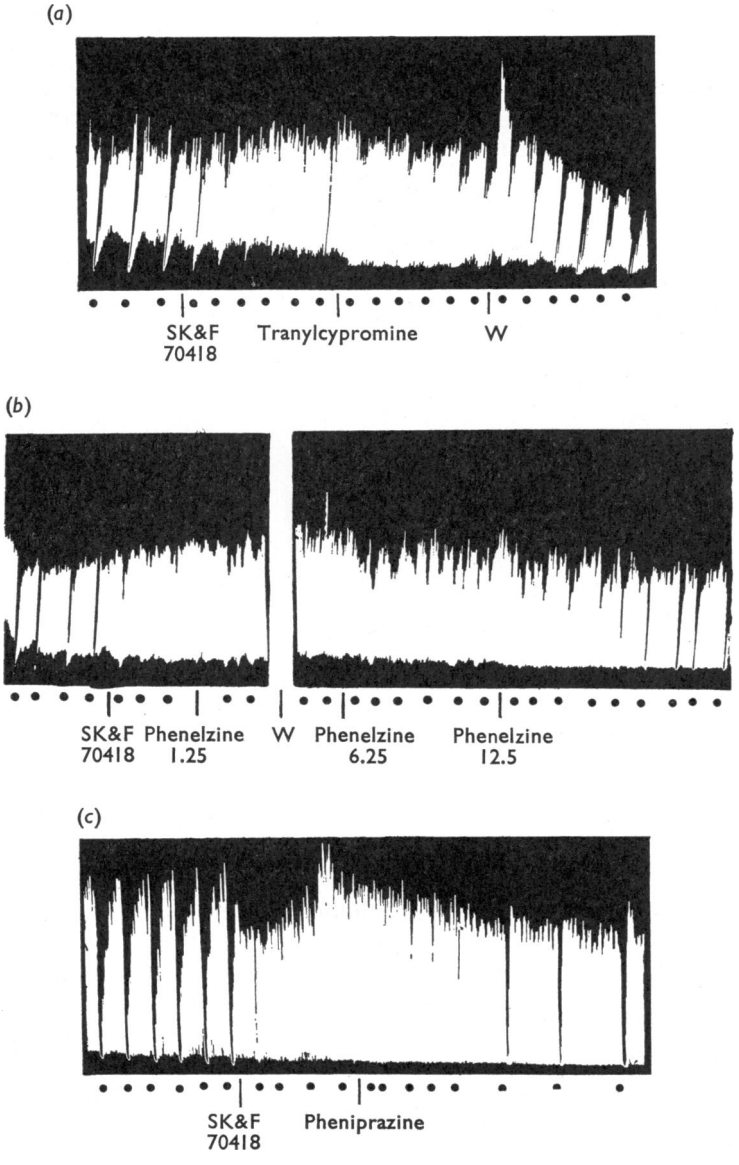


Fig. 4. Rabbit ileum isolated-sympathetic nerve preparation. At the black dots, the periarterial nerves were stimulated for 15 sec with 0.5-msec, 40-V pulses at 50 shocks/sec and at 10-min intervals. In (*a*), inhibition of pendular movements due to periarterial nerve stimulation was prevented by the addition to the bath of SK&F 70418 (0.2 μg/ml.). The response to nerve stimulation was recovered by the addition of tranylcypromine (6.25 μg/ml.) to the bath. In (*b*), the prevention by SK&F 70418 (0.2 μg/ml.) of the inhibitory response to periarterial nerve stimulation was reversed by the addition of phenelzine (1.25, 6.25 and 12.5 μg/ml.) to the bath. There was an interval of 1 hr between records. No substantial antagonism was apparent until the cumulative concentration amounted to 20 μg/ml. In (*c*), the prevention by SK&F 70418 (0.2 μg/ml.) of the inhibitory response to periarterial nerve stimulation was reversed by the addition of pheniprazine (12.5 μg/ml.) to the bath. The drum speed was doubled in (*c*). At W, the bath fluid was changed.

TABLE 3

EFFECT OF SK&F 70418 AND TRANYLCYPROMINE SULPHATE ON THE MONOAMINE OXIDASE ACTIVITIES OF THE BRAIN AND LIVERS OF RATS *IN VIVO*

Results are expressed in optical density (means and ranges) at 450 mμ which are directly related to monoamine oxidase activity

Group	Monoamine oxidase activity in	
	Brain	Liver
Control	0·451 (0·383–0·530)	0·556 (0·497–0·630)
Tranylcypromine sulphate (5 mg/kg, 3 hr previously)	0·095 (0·051–0·150)	0·064 (0·054–0·070)
SK&F 70418 (250 mg/kg, 3 hr previously)	0·336 (0·210–0·462)	0·478 (0·464–0·489)
SK&F 70418 (250 mg/kg, 24 hr previously)	0·291 (0·200–0·242)	0·487 (0·384–0·561)

Parasympathomimetic activity

SK&F 70418 (1 to 20 μg/ml.) produced irregular contractions of the isolated ileum of the guinea-pig which were not related to the dose. These contractions were prevented by methanthelinium bromide, a specific muscarinic blocking agent, at a concentration of 5 μg/ml., whereas 0.01 μg/ml. was sufficient to abolish the response to acetylcholine (0.1 μg/ml.).

Effect on monoamine oxidase activity

Rats receiving SK&F 70418 (250 mg/kg), 3 and 24 hr before removal of tissues, appeared depressed and lethargic. Those receiving tranylcypromine sulphate (5 mg/kg) or saline showed no apparent symptoms 3 hr after dosing. Table 3 shows that SK&F 70418 produced only a slight decrease in the monoamine oxidase activity of the brain and liver of the rat, the effect being most pronounced in the brain 24 hr after dosing.

DISCUSSION

The pharmacological properties of SK&F 70418 are similar to those of guanethidine sulphate.

After oral administration of SK&F 70418 to the conscious cat there is an initial period of sympathetic activity evidenced by piloerection, tachypnoea, exophthalmos and mydriasis. Relaxation of the nictitating membranes occurs approximately 5 hr after dosing. This corresponds to the time necessary for complete loss of sympathetic tone in the cardiovascular system following intravenous injection into the anaesthetized animal. The duration of relaxation of the nictitating membrane indicates that SK&F 70418 has a very persistent action. This is also shown by experiments in which the blood pressure of the dog was recorded at various intervals after intravenous injection of the compound, there being no sign of a return to the control level even after 48 hr.

Both SK&F 70418 and guanethidine produce a triphasic effect on the blood pressure of the anaesthetized cat and dog after intravenous administration. First there is a transient fall in blood pressure, followed by a prolonged hypertension and subsequently a persistent hypotension. The initial fall in blood pressure does not appear to involve the release of histamine, 5-hydroxytryptamine, acetylcholine or an action on β-receptors in the sym-

pathetic nervous system. A depressant action on the heart may also be excluded since SK&F 70418 produced positive chronotropic and inotropic effects on the heart of the anaesthetized cat and did not affect the electrocardiogram of the anaesthetized dog.

Considerable evidence has been obtained in support of the hypothesis that the prolonged hypertension and subsequent hypotension produced by large doses of SK&F 70418 may be due to a massive release of sympathetic neurohormones and their ultimate depletion at postganglionic storage sites. Thus the pressor effects of small doses of SK&F 70418 in the spinal cat were potentiated by pyrogallol and abolished by tolazoline. Moreover, these pressor responses were prevented by treatment of the animal with reserpine. During the persistent hypotensive phase, the effects of tyramine, amphetamine and bilateral carotid arterial occlusion were reduced or abolished, indicating that depletion of catechol amines or blockade of sympathetic α-receptors had occurred. The responses to tyramine and amphetamine were restored by the intravenous infusion of noradrenaline into animals previously treated with SK&F 70418, as was originally demonstrated in the reserpine-treated animal by Burn & Rand (1958). Sympathetic α-receptor blockade may be excluded since it was observed that the responses to injected adrenaline and noradrenaline were, in fact, potentiated. The possibility that this potentiation was due to an inhibition of monoamine oxidase was excluded by the demonstration of the compound's very weak inhibitory effect on the enzyme *in vivo*. Similar potentiation of the responses to adrenaline and noradrenaline has been demonstrated after sympathetic denervation (Bülbring & Burn, 1938) and also after treatment with guanethidine (Maxwell *et al.*, 1960) and bretylium tosylate (Boura & Green, 1959). The lack of contribution of the adrenal medullae to the pressor effect of SK&F 70418 was demonstrated by the failure of ligation of the adrenal veins to prevent the hypertensive effects of this compound in the spinal cat.

Experiments involving stimulation of the periarterial sympathetic nerve fibres supplying the intestine of the rabbit reveal a further similarity in the modes of action of SK&F 70418 and guanethidine. Impairment of sympathetic transmission to the ileum treated with SK&F 70418 or guanethidine is abolished after incubation of the tissue with dopamine, but not with dopa or noradrenaline. Schümann (1960) reported that, of the total catechol amine content of the intestine, more than 95% consists of dopamine. As this amine has an apparently greater affinity than dopa or noradrenaline for sympathetic nerve endings inhibited by either SK&F 70418 or guanethidine, one may speculate that the actual transmitter in the rabbit ileum may be dopamine itself (Bain, 1960; Schümann, 1960). A further similarity between SK&F 70418 and guanethidine arises from the observation of the reversal of SK&F 70418-induced blockade of the Finkleman preparation by certain monoamine oxidase inhibitors (Fig. 4).

Willey (1957) demonstrated that the depressor effect of small doses of xylocholine in the anaesthetized cat may be attributed to a muscarinic action. Boura *et al.* (1961) have also attributed muscarinic properties to the guanidino congener of xylocholine, that is SK&F 70418. Examination of this compound *in vitro* did, in fact, reveal some stimulation of the isolated ileum of the guinea-pig, but this was inhibited by methanthelinium bromide only at concentrations far in excess of those required to antagonize the specific muscarinic effects of acetylcholine. Moreover, the lack of effect of atropine sulphate in antagonizing the acute depressor effect of SK&F 70418 in the anaesthetized cat indicates that parasympathetic stimulation is not a significant feature of this compound.

Boura, Copp, Duncombe, Green & McCoubrey (1960) found that bretylium tosylate possesses appreciable local anaesthetic activity, and is also selectively accumulated in the postganglionic sympathetic fibres. They suggested that the adrenergic blocking action of this compound may therefore be due to inhibition of conduction in the nerve fibre. SK&F 70418, guanethidine (Bein, 1960) and xylocholine (Hey & Willey, 1954) similarly have local anaesthetic activities of long duration, but there is no evidence that this property contributes to their sympathetic blocking action.

It may be concluded, therefore, that SK&F 70418 has qualitatively similar effects to those of guanethidine sulphate. Replacement of the trimethylammonium head of xylocholine with the guanidino moitey removes the muscarinic properties of this compound while retaining its adrenergic neurone blocking effects. These effects are slow in onset and of a prolonged duration equivalent to those of guanethidine, indicating that they may be attributed principally to the guanidino moiety. Structure activity relationships have been discussed elsewhere (Barron *et al.*, 1963). Because clinical evaluation has shown SK&F 70418 to be quantitatively and qualitatively similar to guanethidine with no advantages over this compound (I. Schrire; Director of Medical Services, Smith Kline & French Laboratories, personal communication, 1962), no further work has been carried out for its development as a therapeutic agent.

SUMMARY

1. *N*-[2-(2,6-Xylyloxy)ethyl]guanidine sulphate (SK&F 70418) possesses marked adrenergic neurone blocking activity.

2. In the conscious cat, oral administration results in prolonged relaxation of the nictitating membranes.

3. Intravenous injection into dogs causes a fall in the mean arterial pressure which is maintained for more than 48 hr.

4. Intravenous injection into anaesthetized cats and dogs produces sympathomimetic effects. When these effects have abated, responses to agents causing the release of endogenous catechol amines are reduced or abolished, while responses to exogenous catechol amines are potentiated.

5. SK&F 70418 appears to exert its adrenergic neurone blockings effects by a depletion of postganglionic sympathetic neurohormones from their storage sites.

6. SK&F 70418 and guanethidine sulphate are qualitatively and quantitatively similar in many laboratory procedures.

The authors wish to express their thanks to Mrs J. Pointer, Mrs M. D. Simpson and Misses H. A. Callear, D. R. J. Goldsmith and V. A. Rees for technical assistance.

REFERENCES

BAIN, W. A. (1960). Interference with the release of transmitter in response to nerve stimulation. In *Ciba Symposium on Adrenergic Mechonisms*, ed. VANE, J. R., WOLSTENHOLME, G. E. W. & O'CONNOR, M., pp. 131–247. London: Churchill.

BARRON, D. I., BAVIN, P. M. G., DURANT, G. J., NATOFF, I. L., SPICKETT, R. G. W. & VALLANCE, D. K. (1963). Potential antihypertensive agents. Some guanidine derivatives. *J. med. Chem.*, **6**, 705–711.

BEIN, H. J. (1960). Some pharmacological properties of guanethidine. In *Ciba Symposium on Adrenergic Mechanisms*, ed. VANE, J. R., WOLSTENHOLME, G. E. W. & O'CONNOR, M., pp. 162–170. London: Churchill.

BOURA, A. L. A., COPP, F. F., DUNCOMBE, W. G., GREEN, A. F. & MCCOUBREY, A. (1960). The selective accumulation of bretylium in sympathetic ganglia and their postganglionic nerves. *Brit. J. Pharmacol.*, **15**, 265–270.

BOURA, A. L. A., COPP, F. F., GREEN, A. F., HODSON, H. D., RUFFELL, G. K., SIM, M. F., WALTON, E. & GRIVSKY, E. M. (1961). Adrenergic neurone-blocking agents related to choline 2,6-xylyl ether bromide (TM10), bretylium and guanethidine. *Nature (Lond.)*, **191**, 1312–1313.

BOURA, A. L. A. & GREEN, A. F. (1959). The actions of bretylium: adrenergic neurone blocking and other effects. *Brit. J. Pharmacol.*, **14**, 536–548.

BÜLBRING, E. & BURN, J. H. (1938). The action of tyramine and adrenaline on the denervated nictitating membrane. *J. Physiol. (Lond.)*, **91**, 459–473.

BÜLBRING, E. & WAJDA, I. (1945). Biological comparison of local anaesthetics. *J. Pharmacol. exp. Ther.*, **85**, 78–84.

BURN, J. H. & RAND, M. J. (1958). The action of sympathetic amines in animals treated with reserpine. *J. Physiol. (Lond.)*, **144**, 314–336.

DAY, M. D. (1962). Effect of sympathomimetic amines on the blocking action of guanethidine, bretylium and xylocholine. *Brit. J. Pharmacol.*, **18**, 421–439.

FINKLEMAN, B. (1930). On the nature of inhibition in the intestine. *J. Physiol. (Lond.)*, **70**, 145–157.

GOKHALE, S. D., GULATI, O. D. & KELKAR, V. V. (1963). Mechanism of the initial adrenergic effects of bretylium and guanethidine. *Brit. J. Pharmacol.*, **20**, 362–377.

GREEN, A. L. & HAUGHTON, T. M. (1961). A colorimetric method for the estimation of monoamine oxidase. *Biochem. J.*, **78**, 172–175.

HEY, P. & WILLEY, G. L. (1954). Choline 2:6-xylyl ether bromide: an active quaternary local anaesthetic. *Brit. J. Pharmacol.*, **9**, 471–475.

LITCHFIELD, J. T. & WILCOXON, F. (1949). A simplified method of evaluating dose-effect experiments. *J. Pharmacol. exp. Ther.*, **96**, 99–113.

MAXWELL, R. A., PLUMMER, A. J., SCHNEIDER, F., POVALSKI, H. & DANIEL, A. I. (1960). Pharmacology of [2-(octahydro-1-azocinyl)-ethyl]-guanidine sulphate (SU-5864). *J. Pharmacol. exp. Ther.*, **128**, 22–29.

SCHÜMANN, H. J. (1960). Formation of adrenergic transmitters. In *Ciba Symposium on Adrenergic Mechanisms*, ed. VANE, J. R., WOLSTENHOLME, G. E. W. & O'CONNOR, M., pp. 6–16. London: Churchill.

WILEY, D. W. (1961). Augmentation of the pressor response to guanethidine by inhibition of catechol-*O*-methyl transferase. *Nature (Lond.)*, **189**, 490–491.

WILLEY, G. L. (1957). Some pharmacological actions of choline 2:6-xylyl ether bromide. *Brit. J. Pharmacol.*, **12**, 128–132.