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The effect of a selective 5-HT_2 antagonist, ketanserin, on the pulmonary responses to *Escherichia coli* endotoxin

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1 5-Hydroxytryptamine (5-HT, 5–160 $\mu g\,kg^{-1}$) injected intravenously in pentobarbitone-anaesthetized, open-chest cats caused dose-dependent increases in pulmonary arterial and intratracheal pressures. There was also a marked systemic hypotension and bradycardia. The pulmonary effects were completely prevented by ketanserin (0.2 $mg\,kg^{-1}$), a selective 5-HT_2 blocking drug.

2 Ketanserin (0.2 $mg\,kg^{-1}$) itself lowered arterial pressure (by 30–40 mmHg) but this systemic hypotension was relatively transient.

3 Endotoxin (*E. coli*) administration resulted in pulmonary hypertension, increases in intratracheal pressure and airways resistance and reductions in lung compliance and in arterial P_{O_2}. Only the airways resistance response was modified by ketanserin (0.2 $mg\,kg^{-1}$), suggesting a relatively unimportant role for 5-HT in mediating the acute, pulmonary effects of endotoxin in this species.

4 The reductions in arterial (mixed venous) pH and in P_{O_2} that resulted from endotoxin administration were not affected by pretreatment with ketanserin.

Introduction

Although there is good evidence that 5-hydroxytryptamine (5-HT) is released by endotoxin (recently reviewed by Parratt, 1983) the role played by this amine in the pathophysiology of shock is unclear. An earlier study from this laboratory led to the conclusion that 5-HT played little part in the acute (pulmonary) effects of *Escherichia coli* endotoxin in anaesthetized cats, since administration of methysergide (in a dose that markedly reduced the effects of 5-HT) did not influence the cardiovascular effects of endotoxin (Parratt & Sturgess, 1977). Furthermore, the pulmonary effects of endotoxin in this species (increased airways resistance, reduced pulmonary compliance, pulmonary hypertension) are completely prevented by a variety of cyclo-oxygenase inhibitors, suggesting an important role for substances (e.g. thromboxane, prostaglandin $F_{2\alpha}$) derived from arachidonic acid (Parratt, Coker, Hughes, Macdonald, Ledingham, Rodger & Zeitlin, 1982). However, one practical problem associated with the use of methysergide as a 5-HT antagonist was its depressant effects on the cardiovascular system (Parratt & Sturgess, 1977) with prolonged and pronounced reductions in systemic arterial pressure and in heart rate, effects which are rather like those of large doses of 5-HT itself.

There has been a recent report regarding attenuation of the pulmonary effects of *E. coli* endotoxin in dogs (Makabali, Mandal, Morris, Brown, Chang, Bankhead & Reeves, 1982) by ketanserin (3-[2-(4-[4-fluorobenzoyl]-l-piperidinyl) ethyl]-2,4-(1H, 3H)-quinazolinedione; R41468), a selective antagonist of 5-HT at certain peripheral (5-HT_2) receptors (Van Neuten, Janssen, Van Beek, Xhonneux, Verbeuren & Vanhoutte, 1981; Awouters, Leysen, De Clerk & Van Neuten, 1982). We have therefore re-investigated a possible role of 5-HT as one of the mediators of the acute pulmonary effects of endotoxin by using this more selective 5-HT_2 receptor blocking drug which, unlike methysergide, has less pronounced direct depressant cardiovascular effects.

Methods

The methods were similar to those already described (Parratt, 1973; Parratt & Sturgess, 1976; Parratt *et al.*, 1982). Cats of either sex (1.6–4.2 kg) were dep-

rived of food for 18 h before use and were anaesthetized with sodium pentobarbitone (42 mg kg^{-1}) by intraperitoneal injection; additional intravenous doses (6–12 mg in 0.5 ml saline) were given as required. The right jugular vein was cannulated and used for the administration of drugs and a catheter, introduced into the thoracic aorta by way of the right femoral artery, was used for pressure measurement and blood sampling. The trachea was cannulated and, after a left thoracotomy, the lungs ventilated with room air (20 ml kg^{-1}, 27 strokes min^{-1}) using a respiration pump (Ideal, model 16/24, C.F. Palmer). A needle-tipped catheter, inserted (downstream) through the wall of the main pulmonary artery, was used for pressure measurement and blood sampling. Heparin (500 iu kg^{-1}) was administered intravenously and all catheters filled with heparinized (100 iu ml^{-1}) normal saline.

Blood pressure was monitored from the aortic and pulmonary artery catheters using Statham P23 ID transducers and intratracheal pressure was monitored by means of a similar transducer connected to a side arm of the tracheal cannula. Zero pressure was adjusted to the level of the right atrium. Pressures, together with a lead III electrocardiogram, were displayed on a Mingograph 82 ink-jet recorder (Seimens-Elema).

In some cats, a more detailed analysis of the responses of the airways were obtained. Transpulmonary pressure (Ptp) was measured with a Statham differential pressure transducer (model PM15) with one inlet port connected to a side arm of the tracheal cannula and the other left open to the atmosphere. Airflow ($\dot{V}$) was measured with a mesh screen pneumotachograph (Mercury Electronics, model F2–12 mm) connected to a second Statham differential transducer. Electrical integration of the resulting signal (using a Grass 7P10 integrator) gave a measure of tidal volume (Vt). All three parameters (Ptp, $\dot{V}$ and Vt) were recorded on a Grass 4 channel curvilinear polygraph (model 7). Airways resistance (Ptp/$\dot{V}$) was calculated from transpulmonary pressure and airflow records at isovolumic points on the tidal volume trace; lung compliance (Vt/Ptp) was calculated from the tidal volume and transpulmonary pressure records at points of zero airflow (i.e. at the beginning and end of inspiration). Details are given in the paper by Houston & Rodger (1974).

Rectal temperature was monitored with a copper-constantan thermocouple (Ellab) and body temperature was maintained at approximately 37°C by means of heaters placed below the table. Arterial and mixed venous blood samples were taken at regular intervals and analysed for oxygen and carbon dioxide tensions (P_{O_2} and P_{CO_2}) and pH using an IL 213 blood gas analyser.

Experimental protocol

The volume of ventilation was first adjusted to give a systemic arterial P_{O_2} of 70–90 mmHg; the volume required to achieve this resulted in a slight degree of alkalosis. At least 15 min were then allowed to elapse before proceeding.

Four groups of cats were studied: *Group A* (4 cats). In order to establish the effect and duration of action of ketanserin, varying doses of 5-HT (2.5 $\mu g\,kg^{-1}$–160 $\mu g\,kg^{-1}$ as base) were administered in random order; 5–7 min were allowed between doses. Ketanserin (0.2 mg kg^{-1} intravenously over $\frac{1}{2}$ min) was then administered and the effects of different doses of 5-HT were examined commencing 20 min after ketanserin administration. The direct cardiovascular effects of a larger dose of ketanserin (0.75 mg kg^{-1}) were also examined. *Group B* (12 cats): These cats were given saline and then, 30 min later, *E. coli* endotoxin (purified lipopolysaccharide B; 055:B5; 3923–23 Difco Laboratories) was infused intravenously, over a period of 30 s in a dose of 2 mg kg^{-1}. *Groups C and D* (8 and 5 cats) received ketanserin 0.2 or 0.05 mg kg^{-1} respectively, administered intravenously (over a period of 1 min) 30 min before endotoxin.

Airway parameters and systemic and pulmonary haemodynamics were recorded continuously and blood samples (0.3 ml) taken from the aorta and pulmonary artery 35 and 5 min before endotoxin administration and again 7,15,30,60 and 120 min afterwards. Blood removed for pH and blood gas analysis was replaced with an equal volume of saline.

To reverse any progressive atelectasis, the lungs were 're-inflated' (sighed) 35 min after endotoxin by occluding the tube from the tracheal cannula for the duration of one respiratory cycle.

Drugs

Ketanserin base (R41468, a gift from Janssen Pharmaceuticals) supplied as 2 ml ampoules (5 mg ml^{-1}) was diluted with saline to a concentration of 0.5 mg ml^{-1}, 15 min before use. Serotonin creatinine sulphate (5-HT; BDH Chemicals) was dissolved in saline to give a stock solution of 230 $\mu g\,ml^{-1}$ (i.e. equivalent to 100 $\mu g\,ml^{-1}$ base) and appropriate dilutions in saline were made as required. All drug solutions were kept at 4°C and protected from light.

Statistical analysis and calculation

The Wilcoxon matched-pairs signed-rank test (two-tailed) was used to analyse for differences within the control (saline-treated) group of cats (group B). The Mann-Whitney U-test (two-tailed) was used to anal-

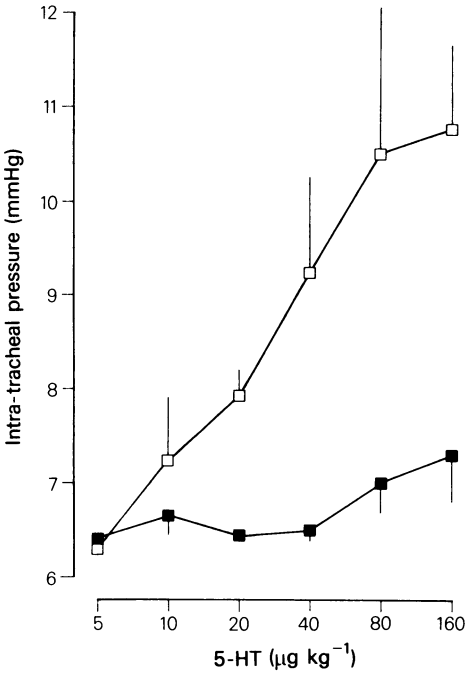

Figure 1 The effect of 5-hydroxytryptamine (5-HT, $\mu g\,kg^{-1}$) on intra-tracheal pressure in anaesthetized cats before (□) and after (■) the intravenous administration of ketanserin ($0.2\,mg\,kg^{-1}$).

yse for differences between the control and the drug-treated groups (C and D) at each particular time; a level of $P<0.05$ was considered to be significant. Data are expressed as mean ± 1 s.e.mean.

Results

Haemodynamic effects of 5-hydroxytryptamine and ketanserin

Intravenous injections of 5-HT ($5-160\,\mu g\,kg^{-1}$) resulted in increases in pulmonary artery pressure (mean increases in diastolic pressure of +1, +2, +5, +7 +11 and +10 mmHg after doses of 5,10,20,40,80 and $160\,\mu g\,kg^{-1}$ respectively) and in intratracheal pressure. These were usually dose-related (Figure 1). There was also a pronounced initial bradycardia. There was no evidence, with the protocol described above, of tachyphylaxis with these doses of 5-HT. The systemic vascular response to 5-HT varied but almost always included a hypotensive component, sometimes (especially with the higher doses) preceded by an initial hypertension. For example, the mean reduction in diastolic arterial pressure at the peak of the response was 28 mmHg (after $40\,\mu g\,kg^{-1}$) and 37 mmHg (after $80\,\mu g\,kg^{-1}$). These results are rather similar to those described in our earlier study (Parratt & Sturgess, 1977) and are illustrated in Figure 2.

The haemodynamic effects of three different doses of ketanserin were examined (i.e. 0.05, 0.2 and $0.75\,mg\,kg^{-1}$). The lower dose (administered to five cats) had no significant effect on pulmonary or systemic arterial pressures or on intratracheal pressure. In a dose of $0.2\,mg\,kg^{-1}$, ketanserin lowered (mean) systemic arterial pressure (e.g. from 124 ± 4 mmHg to 81 ± 6 mmHg ($P<0.05$) at 4 min, 95 ± 4 mmHg at 15 min and 107 ± 4 mmHg at the time (30 min) endotoxin was administered). There was also a slight (but not statistically significant) reduction in mean pulmonary artery pressure at 3 and 5 min (from

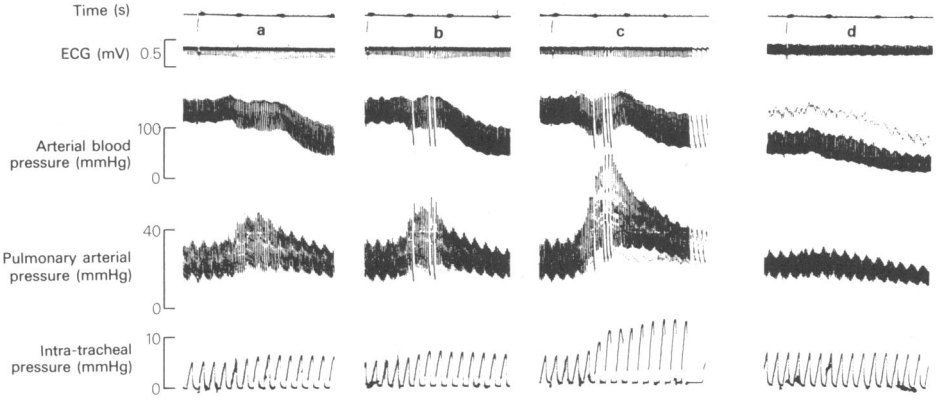

Figure 2 The effect of 5-hydroxytryptamine ($20\,\mu g\,kg^{-1}$ at (a), $40\,\mu g\,kg^{-1}$ at (b), $80\,\mu g\,kg^{-1}$ at (c) and at (d) on (from above) the electrocardiogram, arterial blood pressure (mmHg), pulmonary arterial pressure (mmHg) and intra-tracheal pressure (mmHg). Ketanserin ($0.2\,mg\,kg^{-1}$) was given between (c) and (d).

20 ± 2 to 15 ± 1 mmHg); intratracheal pressure was unaffected by this dose of ketanserin (e.g. 6.3 ± 0.5 mmHg to 6.5 ± 0.6 mmHg at 5 min). In one cat a larger dose of ketanserin (1.0 mg kg^{-1}) caused a pronounced, long-lasting reduction in systemic arterial pressure (e.g. 136/84 mmHg to 58/40 mmHg at 5 min and 75/48 mmHg at 1 h).

Modification of 5-hydroxytryptamine responses by ketanserin

There was a considerable inter-animal variation in the haemodynamic responses to 5-HT, especially in the time-course of the effects on systemic arterial pressure and this made difficult a detailed analysis of the effects of ketanserin on these responses. However, it was clear that whereas the 5-HT-induced pulmonary responses were abolished, the effects of 5-HT on systemic arterial pressure and heart rate were unaffected by ketanserin. For example, the mean increase in pulmonary artery pressure (PAP) was + 15 (systolic) and + 7 mmHg (diastolic) after a dose of 40 μg kg^{-1} 5-HT; the increases after ketanserin (0.2 mg kg^{-1}) were only + 3 and + 1 mmHg respectively. The corresponding values after a dose of 160 μg kg^{-1} 5-HT were + 21/+ 10 mmHg before ketanserin and + 5/0 mmHg afterwards; in no animal did the increase in diastolic PAP exceed 1 mmHg with any dose of 5-HT after this dose of ketanserin. The effect of 5-HT on intratracheal pressure was also completely abolished by this dose of ketanserin (Figure 2). Bradycardia induced by 5-HT (e.g. mean decrease in heart rate of 19 and 55 beats min^{-1} after 20 and 40 μg kg^{-1} 5-HT respectively) was unaffected by ketanserin (mean decrease in heart rate after ketanserin of 33 and 38 beats min^{-1} respectively); neither was systemic hypotension modified (e.g. a mean reduction of 23 mmHg after 5-HT (40 μg kg^{-1}) and of 31 mmHg in the presence of ketanserin.

Acute pulmonary effects of E. coli *endotoxin; modification by ketanserin*

E. coli endotoxin administration resulted in marked increases in pulmonary artery pressure (Figure 3) and in intra-tracheal pressure (Figure 4). Airways resistance increased (with a peak response at 2 min) by 418 ± 100% and dynamic compliance decreased by 57 ± 5%; Table 1). There was also a marked, but transient, systemic hypotension (e.g. a reduction in mean arterial pressure from 110 ± 6 mmHg pre-endotoxin to 63 ± 5 mmHg at 2 min ($P < 0.05$) and to 93 ± 7 mmHg at 7 min).

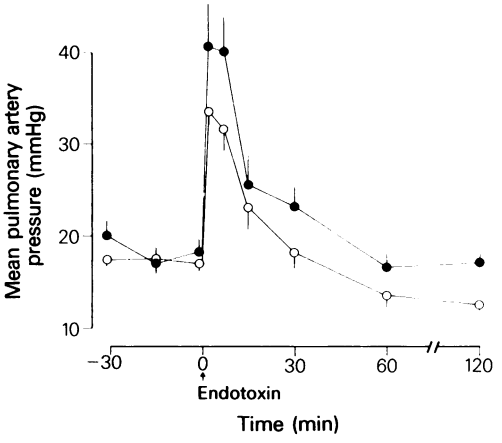

Figure 3 Pulmonary hypertension (mean pulmonary artery pressure, mmHg) induced by endotoxin given (at time zero) in cats pretreated with either saline (○) or ketanserin (●). The pulmonary hypertension was not reduced by a dose of ketanserin (0.2 mg kg^{-1}) which abolished pulmonary responses to exogenous 5-hydroxytryptamine.

The effects of endotoxin were examined in cats pretreated with either 0.2 or 0.05 mg kg^{-1} ketanserin. The pulmonary artery and intra-tracheal pressure responses to endotoxin after the higher dose of ketanserin are also shown in Figures 3 and 4. It is clear that neither response was attenuated by ketanserin; indeed, there was a suggestion that the endotoxin responses were either slightly greater (Figure 3) or more prolonged (Figure 4) in the presence of the 5-HT antagonist. The lower dose of ketanserin (0.05 mg kg^{-1}) likewise failed to modify the pulmo-

Table 1 The effect of *E. coli* endotoxin on airways resistance and lung compliance in cats pretreated 30 min earlier with either saline (control) or ketanserin (0.2 mg kg^{-1})

		Airways resistance (cmH_2O l^{-1} s^{-1})	Lung compliance (ml cmH_2O^{-1})
Control	(a)	9.5 ± 1.5 (6)	12.5 ± 1.0 (6)
	(b)	50.0 ± 12.7* (6) (+418 ± 100%)	5.4 ± 0.8* (6) (−57 ± 5%)
Ketanserin	(a)	9.7 ± 1.1 (5)	11.9 ± 1.8 (5)
	(b)	22.0 ± 4.0†* (5) (+137 ± 49%)	7.0 ± 1.3* (5) (−38 ± 9%)

Values given are those obtained just before endotoxin administration (a) and 2 min after endotoxin (b).
† Endotoxin response after ketanserin statistically different from control endotoxin responses at a level of $P < 0.05$.
* Values at 2 min (b) statistically different from pre-endotoxin values $P < 0.05$.

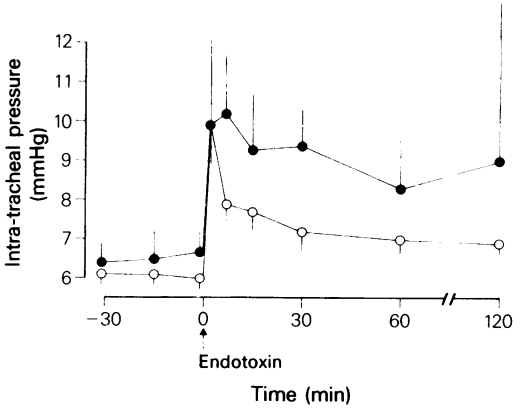

Figure 4 Increases in intra-tracheal pressure (mmHg) in anaesthetized cats induced by endotoxin (at time zero). (○) Controls, pretreated with saline; (●) pretreated with ketanserin (0.2 mg kg^{-1}).

nary responses of endotoxin. Some effect of ketanserin was however observed in the experiments in which airways resistance and lung compliance were measured. This showed that although the change in lung compliance was unaffected by ketanserin, the increase in airways resistance was significantly reduced (Table 1). The initial systemic hypotension induced by endotoxin was unaffected by ketanserin (e.g. 107 ± 5 mmHg to 68 ± 7 mmHg 2 min after endotoxin administration).

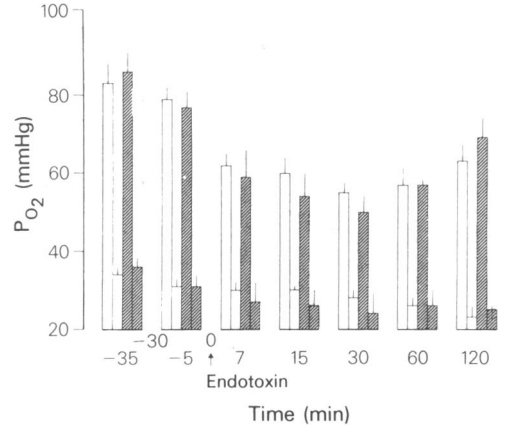

Figure 5 Arterial and mixed venous (pulmonary arterial) P_{O_2} (mmHg, mean with s.e.mean indicated by vertical lines) before, and at different times after the administration of endotoxin. The first open column is the arterial P_{O_2}, the second open column mixed venous P_{O_2}. The first hatched column represents arterial P_{O_2} in cats pretreated with ketanserin, 0.2 mg kg^{-1}; the second hatched column represents the mixed-venous P_{O_2} in these animals. Endotoxin caused an increasing systemic hypoxia in both groups of animals. The animals were 'sighed' at 35 min.

Effects of endotoxin on arterial and mixed venous blood gases and on pH

Endotoxin administration resulted in an early reduction in arterial oxygen tension (Figure 5). For example, at 30 min the arterial P_{O_2} had fallen from 79 ± 3 mmHg, immediately before endotoxin administration, to 55 ± 3 mmHg ($P < 0.01$); the mixed venous (pulmonary arterial) P_{O_2} at this time was only 28 ± 2 mmHg (cf. 34 ± 2 mmHg at the start of the study). Clearly there were problems of pulmonary gas exchange during the acute phase of endotoxin shock with significant increases ($P < 0.05$) in arterial and mixed venous P_{CO_2} (28 ± 3 and 32 ± 3 mmHg at 30 min compared with 20 ± 1 and 23 ± 1 mmHg before endotoxin administration). This accumulation of CO_2 was still apparent 2 h after the start of shock (arterial P_{CO_2} 29 ± 4 mmHg; mixed venous P_{CO_2} 43 ± 3 mmHg; $P < 0.01$) and contributed to the acidosis which developed during shock (Figure 6). Ketanserin pretreatment had no effect on the development of either systemic hypoxia or acidosis (Figures 5 and 6).

Discussion

Pronounced pulmonary hypertension and an increase in airways resistance, with impaired gas-exchange, are characteristic and early consequences of endotoxin administration in cats (Parratt 1973; Parratt *et al.*, 1982; Parratt, Sharma & Zeitlin 1983).

In an earlier study, using a similar model of feline endotoxin shock, Parratt & Sturgess (1977) came to

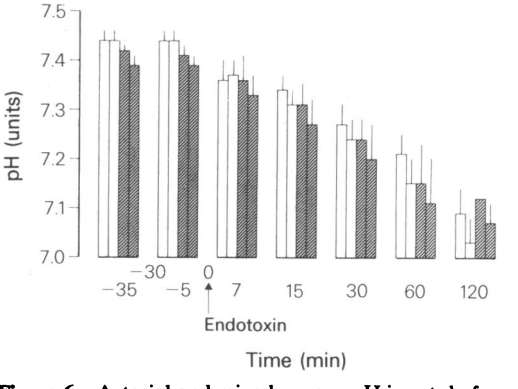

Figure 6 Arterial and mixed venous pH in cats before and after the intravenous administration of endotoxin. Symbols as in Figure 5. Ketanserin did not influence the increasing (mainly metabolic) acidosis induced by endotoxin.

the conclusion that 5-HT played little part in these early (pulmonary) responses. This conclusion was based on the failure of methysergide, in doses that blocked the pulmonary effects of exogenous 5-HT, to modify the early effects of *E. coli* endotoxin. However, there were serious practical problems associated with the use of this antagonist since, in an effective blocking dose, methysergide markedly depressed blood pressure and myocardial function; indeed even 40 min after methysergide administration the diastolic blood pressure was only 60 mmHg. However, the final conclusion from this earlier study is now, in the main, supported by the present experiments with a much more selective 5-HT antagonist which has less pronounced direct effects on cardiovascular function. In a dose that completely prevents the effects of even large doses of 5-HT (up to 160 $\mu g\,kg^{-1}$) on pulmonary arterial pressure and intratracheal pressure (Figure 1), ketanserin failed to modify the pulmonary hypertension induced by endotoxin, or its effects on intratracheal pressure, lung compliance and gas-exchange. Unless one argues that the effects of endogenously released 5-HT are more difficult to prevent than those of intravenously administered 5-HT, the main conclusion from this study is that 5-HT does not participate to an important extent in the early pathophysiology of shock induced by endotoxin. Indeed there is overwhelming evidence (Parratt *et al.*, 1982) that the mediators of these pulmonary effects are derived from arachidonic acid.

The only effect of endotoxin to be significantly modified by ketanserin pretreatment was the effect on airways resistance (Table 1) which is markedly increased within seconds of the intravenous administration of endotoxin (Parratt *et al.*, 1982). This effect is mediated partly through the vagus nerve since bilateral vagotomy markedly reduces this response (e.g. an increase in resistance of $154 \pm 38\%$ in cats with intact vagi and of $59 \pm 18\%$ in cats subjected to bilateral vagotomy; Parratt *et al.*, 1982). There is no evidence that ketanserin interacts with muscarinic receptors (Awouters *et al.*, 1982) so we must conclude that the less pronounced effects of endotoxin on airways resistance in cats pretreated with ketanserin are due to blockade of 5-HT_2 receptors in bronchial smooth muscle or that it interferes in some way with reflex responses originating in the pulmonary vascular bed. However, it should be emphasised that this resistance change is a relatively small component of the endotoxin pulmonary response and that pulmonary gas-exchange was quite unaffected by treatment with ketanserin.

The recent paper by Makabali *et al.* (1982) reported that ketanserin, in a dose of 0.2 $mg\,kg^{-1}$ (i.e. the same as that used in the main part of the present study) markedly suppressed the increase in pulmonary arterial pressure and vascular resistance that resulted from *E. coli* administration. As in the present cat study, it had no effect on the systemic hypotension, the reduced cardiac output or the metabolic acidosis that characterize endotoxin shock. One can only conclude that there appear to be marked species variations in the importance of early mediators of the 'shocked lung', variations which might be due partly to differences in platelet 5-HT levels. In the dog, 5-HT appears to be important and prostaglandins or thromboxane relatively unimportant (since pulmonary hypertension is not attenuated by indomethacin or imidazole; Makabali *et al.*, 1982). On the other hand, arachidonic acid derivations ($prostaglandin_{2\alpha}$, thromboxane A_2) are of crucial importance in mediating pulmonary changes in other species, including cats (Parratt *et al.*, 1982), sheep (Frölich, Ogletree, Peskar & Brigham, 1980), calves (Anderson, Tsagaris, Jaluz & Kuida, 1975) and in primates (Fletcher, Ramwell & Harris, 1981). It is hazardous to transpose data obtained in experimental animals treated with endotoxin to, for example, pulmonary dysfunction in patients in septic shock. Some available evidence (Parratt *et al.*, 1982) suggests an important role for thromboxane in this situation but the possibility that 5-HT might also be involved cannot be excluded; this could have important repercussions for the most effective treatment of shock and trauma patients with pulmonary complications.

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