British Journal of Pharmacology (1996) 117, 817-822

Suppression of reperfusion-induced arrhythmias with combined administration of 5-HT_2 and thromboxane A_2 antagonists

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1 The effects of the 5-HT_2 antagonist, ICI 170,809 and the thromboxane A_2 antagonist, ICI 192,605, given alone and in combination ($n = 12$ per group), were examined in anaesthetized rats. Haemodynamics and arrhythmias induced by permanent coronary artery occlusion or by reperfusion after 5 min of ischaemia were monitored.

2 In a study on reperfusion-induced arrhythmias, the only significant effect of ICI 170,809 (1 mg kg^{-1}, i.v.) was a reduction in the number of ventricular premature beats (VPBs). ICI 192,605 (1 mg kg^{-1} min^{-1}, i.v.) did not alter reperfusion-induced arrhythmias. However, in combination, when compared with controls, these drugs caused significant reductions in the incidence of ventricular tachycardia (VT), 100% to 58%; ventricular fibrillation (VF), 92% to 33%; and the mortality due to sustained VF, 67% to 17%. There was also a significant reduction in the number of VPBs following reperfusion.

3 In a second study with lower doses of drugs, ICI 170,809 (0.3 mg kg^{-1}) and ICI 192,605 (0.3 mg kg^{-1} min^{-1}) had no significant effects on reperfusion-induced arrhythmias either alone or in combination.

4 A third study examined the effects of the higher doses of the drugs on ischaemia-induced arrhythmias. Neither drug alone, nor in combination, altered the incidence of ischaemia-induced VT, VF, the mortality, or the number of VPBs.

5 These results indicate that, in contrast to the administration of either drug alone, combined administration of a 5-HT_2 antagonist and a thromboxane A_2 antagonist caused marked suppression of reperfusion-induced but not ischaemia-induced arrhythmias.

Keywords: Arrhythmias; 5-hydroxytryptamine; thromboxane A_2; myocardial ischaemia; reperfusion; coronary artery occlusion; ICI 170,809; ICI 192,605; 5-HT_2 antagonist; TP antagonist

Introduction

Thromboxane A_2 and 5-hydroxytryptamine (5-HT) are two major products of platelet aggregation (Steen & Holmsen, 1987). Both are vasoconstrictors and can either induce or potentiate platelet aggregation (Siess, 1989; De Clerck & Herman, 1983). Platelets have been shown to play a role in coronary vasospasm and sudden cardiac death has been linked to the occurrence of platelet aggregation in the coronary circulation (Haerem, 1972). Sudden cardiac death may be the result of severe arrhythmias occurring as a consequence of either myocardial ischaemia or subsequent abrupt reperfusion. Both 5-HT and thromboxane A_2 have been shown to have possible roles in arrhythmogenesis. Thromboxane A_2 is released during acute myocardial ischaemia in anaesthetized greyhounds (Coker *et al.*, 1981) and thromboxane A_2 antagonists (Coker & Parratt, 1985) and synthetase inhibitors (Coker, 1984) reduced the number and severity of arrhythmias induced by myocardial ischaemia and reperfusion. 5-HT_2 antagonists have been shown to reduce reperfusion-induced but not ischaemia-induced arrhythmias in rats (Coker & Ellis, 1987), an effect which may be linked to their antiplatelet activity (Ellis & Coker, 1992).

There is evidence to suggest that 5-HT and thromboxane A_2 may interact in a synergistic manner. Mullane *et al.* (1992) demonstrated that vasoconstriction in isolated coronary arteries was greater when both 5-HT and thromboxane A_2 were present. Work by Ashton *et al.* (1987) has also shown a co-operative interaction between 5-HT and thromboxane A_2 in the development of cyclic flow variations in a canine model of severe coronary artery stenosis. More recently, Vandeplassche *et al.* (1993) reported that thrombolysis with streptokinase is enhanced by the combination of a 5-HT_2 antagonist and a thromboxane A_2 antagonist in a canine model.

In the present experiments, the main aim was to examine whether interactions between 5-HT and thromboxane A_2 are important in the genesis of reperfusion-induced arrhythmias. The effects of a selective 5-HT_2 antagonist, ICI 170,809 (2-2[dimethylamino-2-methylpropylthio]-3-phenylquinoline hydrochloride) (Blackburn *et al.*, 1988; Millson *et al.*, 1992) and a thromboxane A_2 antagonist, ICI 192,605 (4(Z)-6-(2,4,5 *cis*)[2-chlorophenyl)-4-(2-hydroxy phenyl) 1,3-dioxan-5-yl]hexenoic acid) (Jessup *et al.*, 1988) were examined alone and in combination against reperfusion-induced arrhythmias in anaesthetized rats. Since previous studies (Coker & Ellis, 1987; Ellis & Coker, 1992) had indicated that 5-HT_2 antagonists were effective only against reperfusion-induced arrhythmias and not against ischaemia-induced arrhythmias, a further study was performed to examine the effects of ICI 170,809 and ICI 192,605 alone and in combination on arrhythmias induced by acute myocardial ischaemia. Part of this work has been presented to the British Pharmacological Society (Shaw & Coker, 1992).

Methods

Animal preparation

Male Wistar rats (weight range 240 to 430g) were obtained from the departmental animal unit. The rats were anaes-

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thetized with sodium pentobarbitone (60 mg kg^{-1}, i.p.) and prepared for coronary artery occlusion by surgical techniques which have been described in detail recently (Barnes & Coker, 1995). Briefly, a femoral vein was cannulated to allow administration of further anaesthetic and drugs, a tracheotomy was performed to permit artificial ventilation when required, and a carotid artery was cannulated for blood pressure measurement. A left thoracotomy was performed and the pericardium removed to expose the heart. The heart was exteriorized briefly and a fine silk ligature (Mersilk W812; Ethicon) was placed around the left coronary artery close to its origin.

After the chest was opened, the rats were ventilated artificially (Searle Bioscience Ventilation Pump) with room air at a rate of 54 strokes min^{-1}, a stroke volume of 1.0 to 1.5 ml 100 g^{-1} and a positive end expiratory pressure of 0.5 to 1.0 cmH_2O. The carotid arterial cannula was connected to a Bell and Howell type 4-422 transducer linked to a Grass 7P122 or 7P1/7DA amplifier system to allow the recording of blood pressure on a Grass model 79D polygraph. A lead 1 ECG was monitored from subcutaneous stainless steel needle electrodes connected to a Grass 7P4 or 7P6 amplifier and also recorded with the Grass 79D polygraph. In addition, both blood pressure and ECG were displayed continuously on an oscilloscope (Telequipment DM63). A rectal thermometer was inserted and the rats were kept at a body temperature of 37–38°C by means of a heated table.

A 10 min stabilization period was allowed, during which an arterial blood sample (0.1 ml) was taken and PO_2, PCO_2 and pH were measured with a Corning 158 gas analyser. If necessary, the stroke volume of the ventilation pump was adjusted to maintain an arterial PO_2 above 70 mmHg. After completion of the stabilization period, drug or vehicle administration commenced 10 min before coronary artery occlusion.

Reperfusion-induced arrhythmias

In rats used for studies on reperfusion-induced arrhythmias, both ends of the ligature around the coronary artery were threaded through a small polythene button which was placed in contact with the heart. Coronary artery occlusion was achieved by applying tension to and clamping the ligature against the button with a small, light weight, rubber-sheathed artery clip. After 5 min of myocardial ischaemia the clip was removed thus releasing the tension on the ligature and allowing reperfusion. Reperfusion-induced arrhythmias were monitored for 10 min.

Ischaemia-induced arrhythmias

Separate groups of rats were used to study ischaemia-induced arrhythmias. In these rats the ligature around the coronary artery was tied securely to induce permanent regional myocardial ischaemia. The arrhythmias induced by permanent coronary artery occlusion were monitored for 25 min.

Exclusion criteria

Experiments were terminated and excluded from the final data analysis if any of the following occurred: arrhythmias prior to coronary artery occlusion; mean arterial blood pressure less than 60 mmHg prior to drug or vehicle administration; heart failure during the first 5 min of ischaemia (i.e. a progressive reduction in arterial blood pressure towards zero, which is probably due to the ligature being placed too deeply such that the septal branch of the left coronary artery is also occluded). In reperfusion experiments two additional exclusion criteria were: reperfusion not evident (i.e. maintenance and/or progression of ECG changes typical of those occurring during sustained ischaemia); severe arrhythmias at 5 min post-occlusion thus preventing reperfusion. Any rats that were excluded were replaced immediately.

Arrhythmia definitions and analysis

Arrhythmia definitions were based on those detailed in the Lambeth Conventions (Walker *et al.*, 1988). Ectopic activity was categorized as single ventricular premature beats (VPBs), bigeminy (alternating normal and premature beats), salvos (doublets and triplets), ventricular tachycardia (VT, 4 or more consecutive VPBs) or ventricular fibrillation (VF, inability to distinguish individual QRS complexes or measure a rate). Reference was also made to the blood pressure signal to confirm which type of ectopic activity was occurring, particularly to distinguish between polymorphic VT and VF. When the former occurs the pressure trace is usually still pulsatile whereas with VF the blood pressure falls rapidly towards zero and is no longer pulsatile. VF may be sustained or may revert spontaneously to normal sinus rhythm. In all experiments the incidence of VT, VF and the mortality (due to terminal VF sustained for 3 min or more) were noted. In survivors, the total number of VPBs (including those occurring as VT) that occurred during the first 25 min of permanent coronary artery occlusion or the first 10 min of reperfusion was counted.

Experimental protocols

Three separate arrhythmia studies were carried out. There were four different groups in each study with $n=12$ in each group. In each study, rats were allocated in a random manner to one of four groups: control; 5-HT_2 antagonist, ICI 170,809; thromboxane antagonist, ICI 192,605, or both drugs. Each rat received a bolus dose of ICI 170,809 (or its vehicle, acidified water) followed immediately by a continuous infusion of ICI 192,605 (or its vehicle, alkaline saline). Thus, rats in the control group received both vehicles, those in the 5-HT_2 antagonist group received ICI 170,809 plus the vehicle for ICI 192,605, those in the thromboxane A_2 antagonist group received ICI 192,605 plus the vehicle for ICI 170,809 and the final group received both the drugs. In the first study on reperfusion-induced arrhythmias the 5-HT_2 antagonist was administered as a 1 mg kg^{-1} bolus and the thromboxane A_2 antagonist was infused at 1 mg kg^{-1} min^{-1}. In the second reperfusion study the 5-HT_2 antagonist was administered as a 0.3 mg kg^{-1} bolus and the thromboxane A_2 antagonist infused at 0.3 mg kg^{-1} min^{-1}. The doses of the 5-HT_2 antagonist were chosen on the basis of previous work in our laboratory, which indicated that the higher dose of 1 mg kg^{-1}, but not the lower dose of 0.3 mg kg^{-1} had some antiarrhythmic and antiplatelet activity (Ellis & Coker, 1992). Since we were advised that ICI 192,605 had a short half life in the rat (personal communication; R. Jessup, Zeneca Pharmaceuticals) this drug was administered as a continuous infusion. In the third study, ischaemia-induced arrhythmias were examined and the drugs were given at the higher doses used in the first study.

Drugs

ICI 170,809 and ICI 192,605 were gifts from Zeneca Pharmaceuticals, Macclesfield. ICI 170,809 was dissolved in distilled water with 1M HCl added dropwise until a clear solution was obtained. ICI 192,605 was dissolved in saline with 1M NaOH added dropwise until a clear solution was obtained. Control vehicle solutions also contained equivalent concentrations of HCl or NaOH. Sodium pentobarbitone (Sagatal) was obtained from RMB Animal Health Ltd; Dagenham.

Statistics

Where appropriate, values are expressed as mean ± s.e.mean of n experiments. Between group differences in haemodynamics and blood gas values were compared by one way analysis of variance with subsequent modified t tests (with Bonferroni corrections). Mann-Whitney U-tests were used to compare the durations of VT and the numbers of VPBs. Fisher's Exact tests

were used to compare the incidence of events. A probability of $P<0.05$ was considered to be significant.

Results

Reperfusion studies – arrhythmias

In anaesthetized rats, ischaemia-induced arrhythmias normally commenced 4 to 6 min after coronary artery occlusion. At this time arrhythmias consist mainly of single VPBs. Abrupt reperfusion after 5 min of acute myocardial ischaemia caused severe arrhythmias which were rapid in onset but of short duration. Arrhythmias started within a few seconds of release of the ligature around the coronary artery and then either progressed to terminal VF or reverted to normal sinus rhythm within 5 min. In the high dose study, combined administration of both drugs reduced the incidence of reperfusion-induced VT, VF and the mortality (Figure 1). The duration of reperfusion-induced VT was 95 ± 19 s in controls, 39 ± 15 s in rats receiving ICI 170,809, 48 ± 24 s in rats receiving ICI 192,605 and $27\pm10^*$ s in rats receiving both drugs ($^*P<0.05$ compared with controls, Mann-Whitney U test). Thus combined drug administration not only reduced the incidence of VT but also its duration when it did occur. Although administration of the 5-HT_2 antagonist ICI 170,809 at a dose of 1 mg kg^{-1} appeared to reduce VF and mortality (Figure 1) these apparent changes failed to reach statistical significance.

In the second study on reperfusion-induced arrhythmias, when lower doses of both drugs were administered there were no significant alterations in the incidence of VT, VF or the mortality with either drug alone or in combination (Figure 2). Similarly, there were no significant alterations in the durations of reperfusion-induced VT in the rats that survived the 10 min reperfusion period.

Reperfusion studies – haemodynamics and blood gases

Combined administration of both drugs at the higher doses caused significant decreases in heart rate and systolic blood pressure (Table 1). There was also a significant decrease in heart rate in rats receiving the 5-HT_2 antagonist alone at the higher dose (1 mg kg^{-1}). In the lower dose study, combined administration of both drugs caused a significant decrease in heart rate and both systolic and diastolic blood pressure. Again, in rats receiving the lower dose of the 5-HT_2 antagonist alone, a significant bradycardia was observed (Table 2). There were no significant differences among the pre-drug haemodynamic values in either study (analysis of variance). The magnitude of the changes in haemodynamics induced by either ICI 170,809 alone or by both drugs, did not appear to increase when the doses of the drugs were increased.

The values for blood gases in the control group in the high dose study were as follows: $pH=7.47\pm0.01$, $P_{CO_2}=29\pm1$ mmHg and $P_{O_2}=84\pm3$ mmHg. There were no statistically significant differences between these control measurements and those for any of the other groups in the reperfusion experiments.

Ischaemia study – arrhythmias

In separate groups of rats subject to permanent coronary artery occlusion, ICI 170,809 (1 mg kg^{-1}) and ICI 192,605 (1 mg kg^{-1} min^{-1}) given alone or in combination did not alter the incidence of ischaemia-induced VT, VF or mortality (Figure 3). There were also no significant differences in the total number of VPBs that occurred during the first 25 min of myocardial ischaemia in the survivors in each group (Figure 4). The values for the duration of ischaemia-induced VT were 84 ± 30 s in controls, $25\pm11^*$ s in rats receiving ICI 170,809, 110 ± 34 s in rats receiving ICI 192,605 and 44 ± 16 s in rats receiving both drugs ($^*P<0.05$ compared with controls, Mann-Whitney U test). Thus the only significant alteration in ischaemia-induced arrhythmias was observed with the 5-HT_2 antagonist administered alone.

Ischaemia study – haemodynamics and blood gases

The effects of the drugs on heart rate and blood pressure prior to coronary artery occlusion were similar in this study to those observed in the high dose reperfusion study. When the 5-HT_2 antagonist, ICI 170,809 was administered, either alone or in combination with the thromboxane antagonist, ICI 192,605, there were significant reductions in heart rate and blood pressure. For example, the values for heart rate measured 10 min after drug administration were 382 ± 12, $319\pm14^*$, 357 ± 14 and $333\pm16^*$ beats min^{-1} in the control group, the ICI 170,809 group, the ICI 192,605 group and the group receiving both drugs, respectively. Diastolic blood pressure values were 70 ± 5, $44\pm1^{**}$, 56 ± 5 and $47\pm6^*$ mmHg, respectively ($^*P<0.05$, $^{**}P<0.01$ compared with corresponding value in the control group, one way analysis of variance and modified t test with Bonferroni correction). The arterial blood gas and pH values in the group of control rats subject to permanent coronary artery occlusion were: $pH=7.41\pm0.01$ units, $P_{CO_2}=30\pm1$ mmHg and $P_{O_2}=80\pm3$ mmHg. Again, there were no significant differences between these values and those measured in the

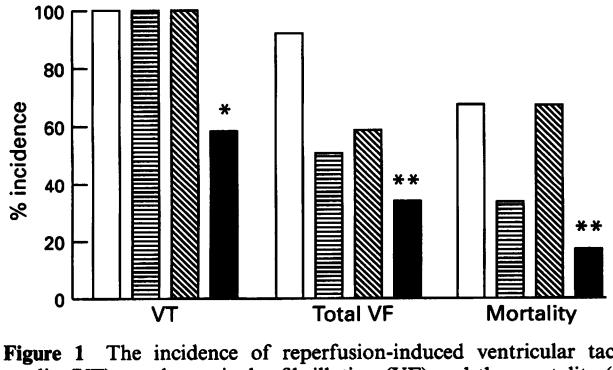

Figure 1 The incidence of reperfusion-induced ventricular tachycardia (VT), total ventricular fibrillation (VF) and the mortality (due to sustained VF) in the control group (open columns), and in rats which received the 5-HT_2 antagonist ICI 170,809 (1 mg kg^{-1}) alone (horizontally hatched columns), the thromboxane A_2 antagonist ICI 192,605 (1 mg kg^{-1} min^{-1}) alone (diagonally hatched columns) and the combination of both drugs (solid columns). $n=12$ per group. $^*P<0.05$ $^{**}P<0.01$ compared with control group, Fisher's Exact test.

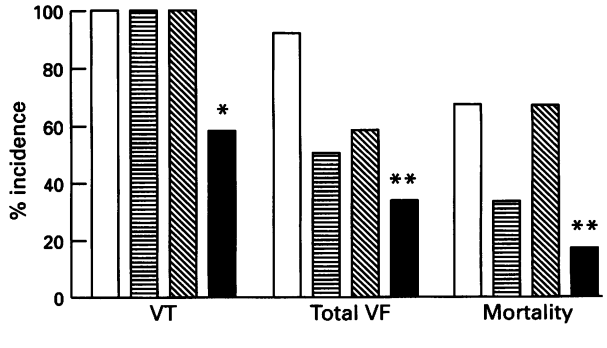

Figure 2 The incidence of reperfusion-induced ventricular tachycardia (VT), total ventricular fibrillation (VF) and the mortality (due to sustained VF) in the control group (open columns), and in rats which received the 5-HT_2 antagonist ICI 170,809 (0.3 mg kg^{-1}) alone (horizontally hatched columns), the thromboxane A_2 antagonist ICI 192,605 (0.3 mg kg^{-1} min^{-1}) alone (diagonally hatched columns) and the combination of both drugs (solid columns). $n=12$ per group.

Table 2 Haemodynamics in the low dose reperfusion study: heart rate, systolic blood pressure (BP) and diastolic BP 1 min before and 10 min after drug or vehicle administration, i.e. immediately prior to coronary artery occlusion

	Heart rate (beats min^{-1})		*Systolic BP* (mmHg)		*Diastolic BP* (mmHg)	
	Pre	Post	Pre	Post	Pre	Post
Control	416±10	388±12	112±7	108±6	86±7	84±6
ICI 170,809 0.3 mg kg^{-1}	394±16	345±6*	100±5	92±4*	77±4	68±5
ICI 192,605 0.3 mg kg^{-1} min^{-1}	419±11	394±10	108±4	110±3	77±3	79±3
Both drugs	398±17	347±12*	101±6	85±4*	77±5	58±4*

Values are the mean ± s.e.mean, $n=12$. *$P<0.05$ compared with corresponding value in the control group, one way analysis of variance and modified t test (Bonferroni correction).

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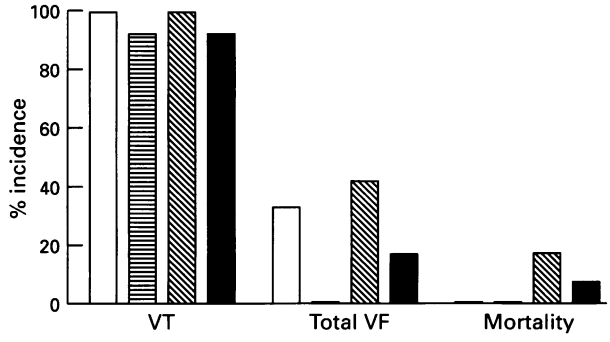

Figure 3 The incidence of ischaemia-induced ventricular tachycardia (VT), total ventricular fibrillation (VF) and the mortality (due to sustained VF) in the control group (open columns), and in rats which received the 5-HT_2 antagonist ICI 170,809 (1 mg kg^{-1}) alone (horizontally hatched columns), the thromboxane A_2 antagonist ICI 192,605 (1 mg kg^{-1} min^{-1}) alone (diagonally hatched columns) and the combination of both drugs (solid columns). $n=12$ per group.

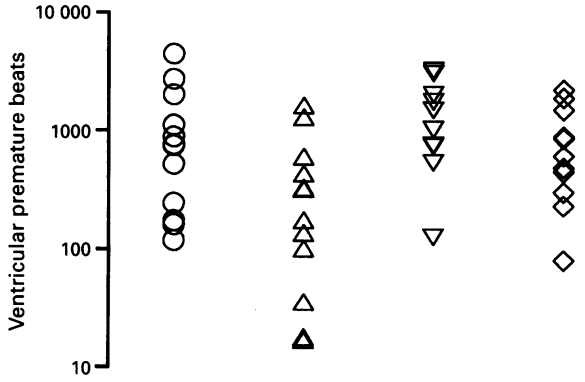

Figure 4 The total number of ischaemia-induced ventricular premature beats in anaesthetized rats which survived 25 minutes of acute myocardial ischaemia in the control group (○), the rats receiving the 5-HT_2 antagonist ICI 170,809 (1 mg kg^{-1}) alone (△), the thromboxane A_2 antagonist ICI 192,605 (1 mg kg^{-1} min^{-1}) alone (▽) and the combination of both drugs (◇). Each symbol represents the value in an individual animal.

other three groups of rats used to study ischaemia-induced arrhythmias.

Discussion

The results detailed above indicate that significant antiarrhythmic activity can be achieved with combined administration of a thromboxane A_2 antagonist and a 5-HT_2 antagonist. It has been reported previously that 5-HT_2 antagonists have some antiarrhythmic activity (Coker & Ellis, 1987; Ellis & Coker, 1992). However, the reductions in arrhythmias observed previously, although significant, were not dramatic. For example, ICI 170,809 did not prevent the initiation of reperfusion-induced VF but it did reduce mortality because the VF was no longer sustained (Ellis & Coker, 1992). In the present study, using the same dose of ICI 170,809, both the total incidence of VF and the mortality tended to be reduced but both these effects failed to reach statistical significance.

Although thromboxane synthetase inhibitors (Coker, 1984) and antagonists (Coker & Parratt, 1985) are particularly effective against both ischaemia-induced and reperfusion-induced arrhythmias in anaesthetized greyhounds they seem to be less effective in rat arrhythmia models. Dazmegrel (UK38,485) reduced the number of VPBs induced by acute myocardial ischaemia but did not alter the incidence of VF in either conscious or anaesthetized rats (Lepran *et al.*, 1985; Wainwright & Parratt, 1985). The thromboxane-mimetic,

U46619, increased the number of VPBs but there was no significant increase in the incidence of ischaemia-induced VF (Wainwright & Parratt, 1985). When given alone, in the present study, the thromboxane A_2 antagonist, ICI 192,605 did not significantly alter ischaemia- or reperfusion-induced arrhythmias. We have not examined the effects of higher doses of ICI 192,605, but the dose used here (1 mg kg^{-1}, min^{-1}) did reduce significantly the ability of the thromboxane-mimetic, U46619, to amplify collagen-induced platelet aggregation and it abolished the effects of U46619 on ADP-induced platelet aggregation (Shaw & Coker, 1994). This suggests that a reasonable degree of thromboxane receptor blockade was achieved with this dose of ICI 192,605 and that at least in the rat, thromboxane A_2 alone is not a major arrhythmogenic factor. However, it is highly unlikely that thromboxane A_2 would be released from platelets without concomitant release of 5-HT, and the present results indicate that in combination, endogenous thromboxane A_2 and 5-HT have considerable arrhythmogenic potential.

In the present experiments the incidence of ischaemia-induced VF and mortality was lower than that observed following reperfusion, although almost all of the rats subject to ischaemia-induced arrhythmias had VT. With this relatively low incidence of ischaemia-induced VF in controls and 12 rats per group, it is possible that ICI 170,809 did have some antiarrhythmic activity but that this could not be detected due to the limited power of the study. However, in a previous study, where the incidence of VF and the mortality were higher in controls, ICI 170,809 did not alter these ischaemia-induced arrhythmias (Ellis & Coker, 1992). In addition, other 5-HT_2 antagonists such as ICI 169,369 (Ellis & Coker, 1992) and ketanserin and ritanserin (Coker & Ellis, 1987) also failed to alter ischaemia-induced arrhythmias in anaesthetized rats although the latter two drugs did reduce reperfusion-induced arrhythmias. It is also clear from comparison of Figure 1 with Figure 3 that neither drug alone nor in combination altered the incidence of VT during ischaemia, but the combination caused marked suppression of reperfusion-induced VT.

The profound antiarrhythmic effect of combined 5-HT_2/TP antagonism could theoretically represent an additive, synergistic or a redundancy mechanism between the respective endogenous agonists. When the combined effects of agonists acting together is equal to the sum of their individual effects, then a simple additive mechanism is being observed. However, when the combined effects of agonists acting together is greater than the sum of their individual effects, the phenomenon is called synergy. It is important to stress that the term synergy refers to agonists only and in these present experiments the effects of antagonists were being investigated, thus giving indirect information about the endogenous agonists. Redundancy may occur in a system when the action of one antagonist alone is not sufficient to block the response, as another agonist can compensate. Analysis of the data would suggest that it is not an additive mechanism since neither of the drugs alone produced any significant effect on the incidence of VT, VF or the mortality. If it was true synergy then one antagonist alone would have been sufficient to cause a significant antiarrhythmic effect. This was not the case in the present experiments. These results do support the concept of a redundancy mechanism between the two agonists. Thus if the effects of thromboxane A_2 are blocked then 5-HT can compensate or *vice versa*. Blockade of both 5-HT_2 and TP receptors is necessary for marked suppression of reperfusion-induced arrhythmias.

The present studies do not allow us to draw any firm conclusions about the location of these receptors or the underlying physiological or pathophysiological mechanism(s) although a mechanism dependent on haemodynamic changes can probably be excluded. In both reperfusion studies (high and low dose), combined administration of the 5-HT and thromboxane antagonists reduced heart rate and blood pressure. The bradycardia was probably due to antagonism of endogenous 5-HT because it was also seen with ICI 170,809 alone, as reported previously (Ellis & Coker, 1992), whereas the depressor response was greater when both drugs were given together. In the rat, 5-HT can cause tachycardia which is mediated via direct stimulation of a 5-HT_2 receptor (Docherty, 1988; Saxena & Villalon, 1991). The haemodynamic effects of the drugs, however, seemed to be independent of the doses of drugs used, being similar in magnitude with both higher and lower doses. This suggests that the marked antiarrhythmic activity seen in the high dose study was unlikely to be due to the haemodynamic effects of the drugs.

The results of the present experiments support those of other investigators who have found evidence of interactions between 5-HT and thromboxane A_2 in other models of myocardial ischaemia/reperfusion. Thromboxane A_2 antagonists (Ashton *et al.*, 1986b) and 5-HT_2 antagonists (Ashton *et al.*, 1986a) have been shown to reduce cyclic flow variations caused by platelet aggregation at the site of a coronary artery stenosis in a canine model. However, when used in combination they were even more effective, resulting in the complete abolition of cyclic flow variations (Ashton *et al.*, 1987). Platelet aggregation has also been suggested to contribute to the ability of 5-HT_2 antagonists to reduce reperfusion-induced but not ischaemia-induced arrhythmias (Ellis & Coker, 1992). It is possible that inhibition of platelet aggregation may also be important in the marked suppression of reperfusion-induced arrhythmias observed in the present studies with combined administration of the 5-HT_2 antagonist, ICI 170,809 and the thromboxane A_2 antagonist, ICI 192,605.

In summary, the present experiments have shown that combined administration of a 5-HT_2 antagonist and a TXA_2 antagonist significantly reduced the incidence of reperfusion-induced VT, total VF and the mortality in anaesthetized rats. This antiarrhythmic activity was not evident during ischaemia and was confined to reperfusion-induced arrhythmias. Further experiments are necessary to elucidate the mechanisms underlying this phenomenon.

This work was supported by the award of a British Heart Foundation Studentship (F288) to L.A.S.

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(Received July 24, 1995
Revised September 19, 1995
Accepted October 31, 1995)