Short communications

The effects of a new α- and β-adrenoceptor antagonist (AH5158) upon the general and coronary haemodynamics of intact dogs

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AH5158, a salicylamide derivative, said to be a blocker of α- and β-adrenoceptors, has been studied in intact anaesthetized dogs. At a dose of 2·5 mg/kg intravenously, the drug increased cardiac output and caused a late fall in mean systemic and pulmonary arterial pressure. Coronary sinus flow increased, as did cardiac oxygen extraction. External cardiac efficiency decreased. Blood glucose and non-esterified fatty acid values increased, but cardiac extraction of these did not change.

AH5158, 5-1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino] ethyl salicylamide is said to block both α- and β-adrenoceptors (Farmer, Kennedy, Levy & Marshall, 1972). These authors also reported a fall in aortic flow, systolic pressure, and heart rate, and suggested that the drug might be of value in various cardiac disorders. The present study was made in order further to explore the general and coronary haemodynamics effects of the drug.

Methods.—The study was made in 22 intact, anaesthetized dogs by methods previously described (Maxwell, 1968), including pressure measurement by strain-gauge, measurement of cardiac output by dye-curve, and measurement of coronary sinus flow by a thermodilution flow-meter (Afonso, 1966). Blood samples were analysed for O_2 and CO_2 in a Van Slyke apparatus, and haemoglobin, glucose, and non-esterified fatty acid by accepted methods.

After control measurements were made, AH5158 (2·5 mg/kg, dissolved in 0·9% w/v NaCl solution) was injected intravenously, and the measurements repeated over the following 60 minutes. Comparison of the control and experimental results was made by Student's *t* test, significance being accepted at the 5% level.

Results.—These are shown in Table 1; the heart-rate increase was immediate and cardiac output increased consistently during the study-time. Mean pulmonary arterial pressure decreased after 30 min, and systemic pressure one hour after the injection. The derivatives of these primary observations are increased ventricular work, both right and left, and a significant decrease in calculated resistance, both pulmonary and systemic. These changes were rapid in onset, and continued for at least an hour after the injection.

The results for coronary flow and myocardial O_2 and CO_2 metabolism were obtained in 2 separate groups of 11 dogs,

TABLE 1. *Effects of AH5158 on general and coronary haemodynamics*

Factor	Control	Minutes after injection of AH5158 5	10	15	20	30	40	60
Heart rate	83± 21	105± 12*	107± 14*	—	110± 14*	110± 14*	111± 15*	108± 18*
Cardiac output (1 minute)	2·77± 0·98	3·86± 1·39*	4·02± 1·24*	—	4·05± 1·23*	4·15± 1·29*	4·06± 1·75*	3·43± 1·13*
Femoral pressure (mean, mmHg)	103± 13	99± 14	102± 16	—	104± 16	103± 14	102± 12	96± 15*
Pulmonary arterial pressure (mean, mmHg)	11± 3	11± 3	10± 2	—	10± 3	9± 2	9± 2*	9± 2*
Coronary sinus flow (ml/min)	46± 13	62± 20*	62± 21*	63± 21*	62± 19*	79± 36*	80± 30*	78± 37
Δ Arterial coronary sinus O_2 (vols %)	7·5± 2·4	8·3± 2·5	9·5± 1·4	10± 1·5*	10± 1·4*	10·3± 1·4	10·2± 1·2	10·1± 1·6
Δ Coronary sinus–arterial CO_2 (vols %)	6·8± 2·3	7·5± 3	8·8± 3·5	8·6± 3*	7·9± 2·5	8·6± 2	9·2± 2·3	9·7± 2·5

Values are group means with S.E. *=statistically significant changes.

although the general haemodynamic changes described above occurred in all. Coronary flow increase occurred within 30 s of completing the injection, and persisted for an hour. Cardiac O_2 extraction and CO_2 production had increased by 10 min after the injection, and remained so until the end of the study period.

The following factors were measured before and 20 min after the drug: haemoglobin (13·8±0·6 to 14·4±0·5 g%), glucose in the artery (93·6±7 to 107±6 mg%) and in the coronary sinus (85±6 to 96±5 mg%). Non-esterified fatty acid values increased both in the artery (0·51±0·08 to 0·76±0·08 mEq/litre) and coronary sinus (0·41±0·07 to 0·59±0·07 mEq/litre). Each of these changes was statistically significant.

Discussion.—The results suggest that AH5158 is a vasodilator in that cardiac output increased, and resistance decreased both in the lesser and greater circuits. These findings do not agree with the observations of Farmer *et al.*, (1972) who described a decrease in aortic flow, together with a fall in systolic systemic pressure and heart-rate. The measurements cited were made in only 3 'open-chest' animals, the response being most consistent with a dose of 3 mg/kg. The results of the present study were found consistently in 22 dogs. As far as systemic pressure is concerned, minor changes in systolic levels were found, which were however offset by diastolic pressure increases so that mean pressure showed little change until the end of the study.

Since the drug also increased coronary sinus flow without substantially changing perfusion-pressure, it is clear that its vasodilator properties also extend to the coronary vascular bed. The increase in coronary flow is reasonably coincident with the same trends in cardiac output and heart-rate, and appropriate correlation coefficients could be calculated for each, i.e. for coronary flow and cardiac output, $r=·5648$; for coronary flow and heart-rate, $r=·8035$.

The table shows the coincidence of the increased coronary flow with enhanced cardiac O_2 extraction (Δ arterial-coronary sinus O_2); the product of these two is cardiac O_2 consumption which clearly must increase under the influence of the drug, especially in the latter half of the study. Thus, control cardiac O_2 consumption would be 345 arbitrary units, becoming 814 units 30 min after the drug. The ratio of left ventricular work to cardiac oxygen consumption decreased from 0·8 (control) to 0·4 thirty min after the injection. This suggests that AH158 reduces external cardiac efficiency.

It has been stated (Collier, Dawnay, Nachev & Robinson, 1972), that the β-adrenoceptor blocking properties of AH5158 exceed the α-blocking effects. Overall then, the drug might in its haemodynamic effects, resemble a β-blocker. This appears to be so for its general effects which are similar to those of pronethalol or oxprenolol (Maxwell, Robertson & Elliott, 1963; Maxwell, 1968). The main difference is that AH5158 stimulates coronary flow, unlike the β-blockers which consistently decrease this parameter (e.g. Bergamaschi, Shanks, Caravaggi & Mandelli, 1971). On the other hand, α-blockers can increase coronary flow (Nickerson, 1949) and it is conceivable that the α-blocking properties of AH5158 are not negligible, at least as far as coronary sinus flow is concerned.

The drug may have, as predicted, some therapeutic value, but this may not reside in its alleged ability to reduce cardiac work (Farmer *et al.*, 1972), since this did not occur in our dogs. Unlike the usual β-adrenoceptor blockers, AH5158 has a mild coronary vasodilator effect, which may render it more acceptable in some cardiac disorders.

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