Whatever the role of albumin in these two situations, these studies again question the routine use of heparin in extracorporeal circulation.

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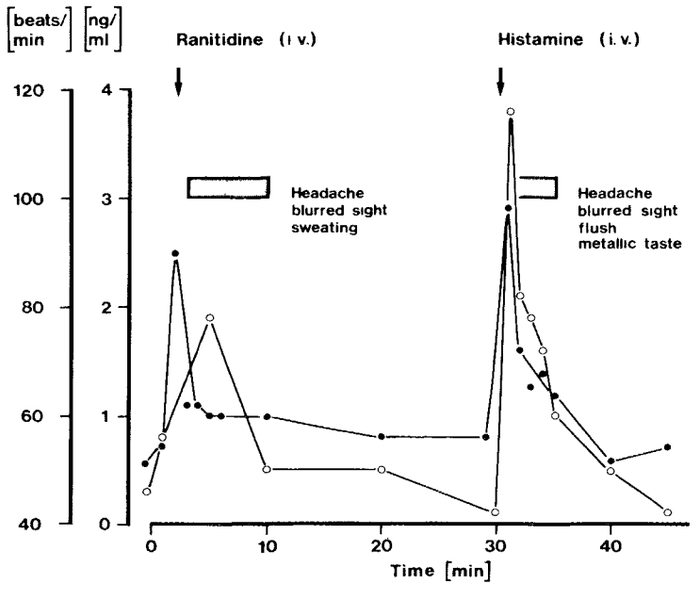
RELEASE OF HISTAMINE BY H_2-RECEPTOR ANTAGONISTS

SIR,—Dr Czerwonka and colleagues (July 25, p 216) report that an intravenous bolus injection of ranitidine and cimetidine did not increase plasma histamine levels, as we had found.[1] They suggest that in the method we used the observed increase in fluorescence extinction might be caused by superprojection of the spectra of two different fluorescing substrates. We do not accept this explanation.

Cimetidine[2] does produce fluorophores with *o*-phthaldialdehyde (OPD) at the conditions that are used for plasma histamine measurement. However, the concentrations that elicit the same fluorescence intensity as histamine at the wavelengths of the histamine-OPD complex differ widely: 1 ng/ml histamine base (a cut-off for clinically relevant histamine release[3]) corresponds to 30, 40, and 150 µg/ml cimetidine, ranitidine, and famotidine, respectively. It is hard to believe that plasma levels as high as this are present 5 min after an intravenous bolus injection of these drugs. The fluorescence intensity of 0·1 ng/ml histamine might have been imitated by that of the H_2-receptor antagonists but such increases in luminescence are not interpreted by us as histamine release.[1] Unfortunately, fig 2 in Czerwonka's letter does not contain data on fluorescence intensity (ordinate) needed to answer this question. The fluorescence of H_2-receptor antagonists can be distinguished from that of histamine by simple chemical tests which must be used in any demonstration of clinically relevant histamine release by drugs. Histamine-OPD fluorescence is destroyed by heating but that of cimetidine and ranitidine is not. Czerwonka should have applied this test, as we do routinely.[2,4]



Plasma histamine levels, heart rate, and duration of clinical symptoms (shaded area) in subject with systemic anaphylactoid response to ranitidine, and comparison with exogenous histamine.

○ = plasma histamine; ● = heart rate.

FREQUENCY OF SYMPTOMS, BLOOD PRESSURE, AND HEART RATE CHANGES, AND HISTAMINE RELEASE

—	Cimetidine (n = 15)	Ranitidine (n = 15)
Burning in trachea	5	0
Metallic taste	7	0
Flush	4	0
Congestion in head, headache	1	4
Narrowness in chest, respiratory distress	1	1
Tachycardia/bradycardia	12/0	7/3
Hypotension/hypertension	8/5	6/5
Histamine release (≥ 1 ng/ml)	6	4

Changes in heart rate > 5 beats/min, changes in systolic BP > 5 mm Hg Tachycardia explained by measured catecholamine increase mediated via adrenal H_2 receptors For the lesser responses to saline see Lorenz et al [5]

Histamine release by drugs must be demonstrated on criteria[4,5] other than simply fluorescence in plasma 5 min after drug injection—eg, the rapid onset of a rise in OPD-complex luminescence and peaks at least 2 SD above baseline, and also by biological effects of histamine release such as flush, metallic taste, and headache (figure).

Histamine release by cimetidine has been confirmed by a radioenzymatic assay[6] based on a different chemical principle from that of the fluorimetric test attacked by Czerwonka et al.

Since rapid injection of H_2-receptor antagonists can lead to life-threatening arrhythmias and hypotensive reactions[7] slow injection or infusion has been recommended by manufacturers. Our randomised study in volunteers given cimetidine or ranitidine confirms the importance of histamine release. 30 healthy volunteers (16 males, 14 females, aged 18–34) who gave written consent were allocated at random to 5 mg/kg cimetidine or 1·25 mg/kg ranitidine given intravenously in 20 s. The two groups were well matched, and 3/15 in the cimetidine group and 2/15 in the ranitidine group had a history of allergy. After 30 min 600 ng/kg histamine was given as a bolus injection (5 s). Reactions were compared by questionnaire[3] and histamine was measured by combined fluorimetry (figure). A histamine-release response of severity grade II[3] was found in 6 volunteers receiving cimetidine and in 4 given ranitidine (table).

The assay described by Czerwonka et al is not yet published. It may turn out to be unique in being able to detect fg/ml plasma histamine (20 pg/ml in our "rough" method[4]) and whether it is more specific than our fluorimetric assay remains to be seen too. Either way, their letter should not be taken as meaning that rapid intravenous injection of H_2-receptor blocking drugs does not result in clinically significant histamine release.

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