is also disturbed and the giant cells are now believed to be formed by the fusion of damaged spermatids.

The lowest dose (4 mg/kg) induces tubular dilatation, showing an increase into seminiferous tubule fluid pressure. This dilatation is a clear indication that there is a disruption in the control mechanisms of the bloodtestis barrier. Baradat[9] showed that ochratoxin A increases ions transfer in the rat colon. So we suggest that in the testis ochratoxin A acts in the same way as does the well-known cadmium chloride.

In our study, the introduction of ochratoxin A into the testis shows 2 kinds of damage. 1., The lowest dose used only modifies seminiferous tubules permeability, inducing their dilatation. 2., Higher doses act on the vascular supply causing the degenerating changes observed in the spermatogenic epithelium. Interstitial tissue hyperplasia (4.6 and 5 mg/kg) involving Leydig cells and connective tissue elements has also been described in other intoxications. Its etiology remains unknown; so, we shall only try to define it.

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Attenuation by carbocromen of cardiac metabolism alterations due to ischemia

J.L. Andrieu, M. Ollagnier, M. Lièvre, I. Hugueny, R. Tédone and G. Faucon[1]

Département de Pharmacologie Médicale, Université Claude Bernard, 8, avenue Rockefeller, F-69373 Lyon Cédex 2 (France), 12 October 1978

Summary. Carbocromen prevents to some extent, particularly in subendocardial layer, carbohydrate cardiac metabolism alterations induced by the ischemia obtained by intermittent occlusion of left coronary artery.

Administered i.v. at relatively high doses, carbocromen elicits a considerable and persistent increase of coronary flow[2,3]. This result is more uncertain in presence of obstructive lesions of the coronary bed, especially of the large vessels. However, after reduction in dogs of the circulatory flow in left ventricular wall by 40–70% by narrowing of the coronary artery, the rise of flow was still observed, to a lesser extent than under normal conditions but nevertheless significant, especially if the preliminary reduction had been moderate[4]. The purpose of this study was to verify these data by investigating whether the cardiac metabolism alterations consecutive to ischemia[5,6] were prevented by carbocromen, a compound devoid of any direct effect of its own on cardiac metabolism[7,8].

The investigations were carried out particularly on subendocardial layer in which the modifications of the main substrate concentrations due to ischemia are more marked[6] and the circulatory activation attributable to carbocromen and the other vasodilator drugs of the same category challenged[9,10].

Methods. The experiments were performed under total cardiopulmonary by-pass, so that sampling of the myocardial wall required for cellular metabolism exploration could be achieved several times in the course of an experiment, carbocromen remaining able to act in this way as normally on coronary circulation.

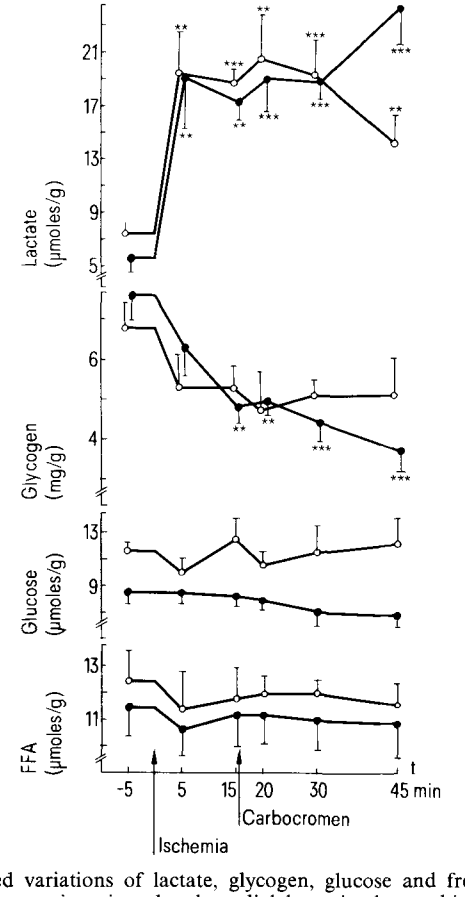
Dogs weighing 20–32 kg, barbiturate anaesthetized, were divided into 2 groups, 6 being subjected only to ischemia for 45 min and 6 being given 4 mg/kg of carbocromen i.v. 15 min after the beginning of ischemia. Considering the difficulty of initiating an ischemia stable at a given degree, the blood flow was alternately completely interrupted for 2 min and left entirely free for an equal period, by means of a thread around left coronary artery. Thus, the mean reduction of flow did not reach 50% because of the reactive vasodilatation raising the flow beyond its reference values

Compared variations of lactate, glycogen, glucose and free fatty acid concentrations in subepicardial layer in dogs subjected to ischemia only and to ischemaia and carbocromen, 4 mg/kg i.v. Mean values±SEM. 1, 2 and 3 asterisks refer to the significance at the 5%, 1% and 0.1% respectively.

		Reference	Ischemia 5 min	15 min	20 min	30 min	45 min
Lactate	Control	6.26±1.46	16.95±3.52(*)	19.83±4.10(*)	20.27±2.55(***)	15.91±1.52(***)	21.81±3.15(***)
	Treated	6.55±0.26	14.60±1.49(***)	20.16±5.27(*)	21.15±4.29(*)	18.80±2.53(***)	17.13±3.63(*)
Glycogen	Control	5.52±0.65	4.91±0.50	3.55±0.71(*)	3.85±0.24(*)	4.41±0.46	3.13±0.61(*)
	Treated	5.38±0.42	4.54±0.81	4.02±1.34	3.82±0.93	4.46±0.65	4.72±0.86
Glucose	Control	8.16±0.97	7.04±0.82	7.00±0.97	7.67±1.21	7.72±1.17	7.21±1.02
	Treated	11.60±0.84	10.35±1.43	9.91±1.68	8.43±1.21	11.01±2.17	10.92±1.22
FFA	Control	12.85±1.17	11.90±1.19	11.94±1.26	12.36±0.99	13.00±1.19	12.53±1.66
	Treated	13.19±1.91	13.56±1.22	13.00±1.08	12.52±1.06	12.80±1.26	11.90±0.95

when the occlusion was suppressed: the ischemia was not sufficient to provoke serious rhythm disorders, as was shown by ECG control. The samples of myocardial tissue, excised from left ventricular wall and kept in liquid nitrogen, were divided into 3 parts, subendocardial, subepicardial and midmyocardial for quantitative determination, in the 2 first parts, of lactate, glycogen, glucose and free fatty acids. Lactate, glycogen and glucose were determined by enzymatic methods, according to Bergmeyer[11], and free fatty acids by the method of Duncombe[12]. Sampling of arterial and coronary venous blood permitted examining simultaneous evolution of lactate, glucose and fatty acid concentration differences. Statistical comparisons were made by Student's t-test.

Results. A. Subendocardial layer (figure). During the first 15 min, therefore prior to carbocromen administration in the treated series, the content of lactate rose to a high degree and that of glycogen was notably lowered, whereas neither glucose nor fatty acid concentrations were affected. Consequently, the carbocromen influence may be effective on the 2 first parameters only. It was not so, however, 5 min after its administration; it began to appear at the 15th min, and became significant at the 30th only. Indeed, while lactate concentration continued to rise ($p < 0.001$) and glycogen concentration to fall ($p < 0.001$) in the control series, the former appeared to be lower at the 30th than at the 15th min and the latter not to be significantly different in the treated series.



Compared variations of lactate, glycogen, glucose and free fatty acid concentrations in subendocardial layer in dogs subjected to ischemia only (●) and to ischemia and carbocromen, 4 mg/kg i.v. (○). Mean values±SEM. 1, 2 and 3 asterisks refer to the significance at the 5%, 1% and 0.1% levels respectively.

B. Subepicardial layer (table). As in the subendocardial layer, the previous evolution persisted beyond 15 min in control animals, while lactate concentration notably decreased and glycogen concentration slightly increased in those treated.

C. Arteriovenous differences. Lactate, glucose and fatty acid concentration arteriovenous differences did not exhibit any variation under the influence of ischemia or of ischemia and carbocromen, the modifications which occurred in the cellular content of lactate not being reflected by the exchange of this metabolite with the blood.

Discussion. Carbocromen elicits in the whole thickness of the myocardium the biochemical modifications which can be expected from the regression of ischemia and, given the absence of any metabolic effect of its own[7,8], these modifications are indeed to be assigned to the partial restoration of blood flow.

However, substrate content is influenced only 15–20 min after its administration, because the increase of blood flow itself is delayed by 5 min at least[2,3] and, chiefly, because the restoration of oxygen supply cannot act on lactate accumulation and glycogen depletion immediately. There is a short wait before one sees the return to normal values of aerobiotic glycolysis terminating the compensatory stimulation of anaerobiotic glycolysis, responsible for excessive glycogenolysis and overproduction of lactate. Moreover, the suppression of the occlusion itself does not result in a clear regression of biochemical alterations before 15–20 min.

But, is the ischemia induced in these experiments similar to the partial permanent ischemia generally observed under clinical conditions? Under these latter conditions, the decrease of vascular tone in proportion to oxygen lack lessens the possibility of action of vasodilator drugs[13] and makes them liable to divert blood flow from the ischemic area to the neighbouring areas remaining intact, in which the vascular relaxing is more marked[14,15]. In fact, the total intermittent obstacle to blood flow is in the same way responsible for vasodilatation, as evidenced by the rise of the flow above its control values when it is abolished.

Consequently, carbocromen must also apparently, in clinical coronary obstructions, correct the circulatory deficiency sufficiently to attenuate the metabolic alterations resulting from it, provided of course that the reduction of flow is not close to complete abolition.

1 Acknowledgments. Financial support from the U.E.R. of Biologie Humaine is gratefully acknowledged.

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