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Intra-hepatic vascular response to sodium nitrite

AIDA GEUMEI, I. ISSA AND M. MAHFOUZ

Departments of Pharmacology and Medicine, Faculty of Medicine, Alexandria University, Alexandria, U.A.R.

1. In the perfused liver of the dog, sodium nitrite produced vasoconstriction in the hepatic arterial bed and, particularly, in the portal venous vascular bed.

2. These effects on the hepatic vasculature may account in part for the reduction of venous return and diminution in cardiac output recorded by other workers, and may therefore be a factor in the clinical efficacy of the nitrites in angina pectoris.

Nitrites are the oldest and still the most important drugs used for the relief of angina pectoris, but the mechanism by which these drugs relieve the pain of coronary ischaemia is still debated. The liver plays an important part in systemic adjustments in both physiological and pathological conditions ; because the hepatic venous flow contributes 30–40% of the total venous return, the liver is one of the principal determinants of the venous return to the heart (Coleridge & Hemingway, 1958 ; Greenway & Lawson, 1966 ; Chien, Chang, Dellenback, Usami & Gregersen, 1966).

In view of these findings the present investigation was designed to study the effect of sodium nitrite on the hepatic vasculature.

Methods

The dog isolated liver was perfused with Tyrode solution gassed with 95% oxygen and 5% carbon dioxide (Geumei, 1964 ; Geumei & Mahfouz, 1968). The pH was 7.35 ± 0.15 and the temperature $37.5° \pm 0.5°$ C. The pressure in the hepatic artery was 130 mm Hg, and in the portal vein 10 mm Hg. The portal vein was cannulated and perfusion begun before final isolation of the liver in order to avoid hypoxia. The hepatic artery and the portal vein were perfused simultaneously and the perfusate was collected from the hepatic veins by means of a cannula inserted in the inferior vena cava. Hepatic arterial portal venous and total hepatic flows (ml./min) were measured for 1 hr before (control period) and 1–2 hr after the addition of sodium nitrite. Although the structure and function of the liver can be maintained for prolonged periods by this method (Geumei, 1964 ; Mahfouz & Geumei, 1965, 1967 ; Geumei & Mahfouz, 1968) the duration of the perfusion never exceeded 3 hr. Freshly prepared sodium nitrite solution (50 μg/ml. Tyrode solution) was used. In twenty dog liver preparations sodium nitrite solution was infused in the hepatic artery, in the portal vein or simultaneously in the hepatic artery and the portal vein.

Results

The results are presented in Table 1. In ten liver preparations (Expts. 1–10), perfusion of the hepatic artery with nitrite-containing Tyrode solution, and of the portal vein with Tyrode solution, produced a decrease in the flow in the hepatic artery by 15% and in the portal vein by 12%. In another series of ten experiments (Expts. 11–20), perfusion of the portal vein alone with nitrite-containing Tyrode solution did not affect the hepatic arterial flow whereas the flow in the portal vein diminished by 67%. When the hepatic artery and the portal vein were perfused simultaneously with nitrite-containing Tyrode solution (Expts. 11–20), the hepatic arterial, portal venous and total hepatic flows decreased by 15, 70, and 56% respectively.

In all twenty preparations there was a transient initial increase in the hepatic venous outflow which lasted 1 min. This was followed by a maintained decrease in the hepatic outflow equal to the decrease in hepatic inflow. During perfusion, the liver diminished in size and its edges remained fine and sharp; there was no indication of engorgement.

Discussion

In spite of the widespread use of the nitrite group of drugs for the relief of the pain of angina pectoris, considerable controversy still surrounds the mechanism of action of these drugs. Some investigators state that nitrites improve the relationship between coronary blood flow and the oxygen requirement of the heart by a direct dilating action on the coronary arteries (Honig, Tenney & Gabel, 1960; Muller & Rorvik, 1958; Wegria, Nickerson, Case & Holland, 1951; Goodman & Gillman, 1965). Others found that nitrites diminish the oxygen requirement of the myocardium by diminishing the work of the heart (Sharpey-Schafer & Ginsburg, 1962; Perloff, Roman & Leon, 1965; Williams, Glick & Braunwald, 1965; Najmi, Griggs, Kasparian & Novack, 1967; Arborelius, Lecerof, Malm & Malmborg, 1968; Robinson, 1968).

From the present experiments it would appear that sodium nitrite increases the resistance in both the hepatic arterial and the portal venous vascular beds. Perfusion of the hepatic artery alone with a nitrite-containing Tyrode solution diminishes both hepatic arterial and portal venous flows, whereas perfusion of the portal vein with the same solution produces an effect on the portal vein only. The data are compatible with the existence of unidirectional hepatic arterio-portal venous shunts (Geumei, Mahfouz & Aboul-Enein, 1968).

TABLE 1. *Effects of sodium nitrite on hepatic flow*

Blood vessels perfused with nitrite-containing Tyrode solution	Mean decrease in flow (% of control flow ± S.E. of the mean)		
	Hepatic artery	Portal vein	Total hepatic
Hepatic artery (Expts. 1–10)	15·0±1·6	12·3±1·0	—
Portal vein (Expts. 11–20)	0	67·2±2·6	—
Hepatic artery and portal vein simultaneously (Expts. 11–20)	15·3±1·0	70·0±1·9	55·8±0·8

The values were the means of ten observations; all changes were significant ($P<0·01$).

The initial transient increase in hepatic venous outflow which was followed by a steady decrease was most probably due to the constrictive action of nitrite on both hepatic vascular beds expelling their contents by a squeezing action. These findings are in accordance with the observation of Honig *et al.* (1960), who found that nitroglycerine causes a transient increase in cardiac output followed by a fall. Later, Kot, Croke & Pinkerson (1967) found that amyl nitrite inhalation in dogs leads to a transient increase in venous return followed by a sustained decrease.

More recently, a decrease in cardiac output has been noted after nitrites and ascribed to reduction in venous return due to peripheral venous pooling (Najmi *et al.*, 1967). It has been suggested that the splanchnic vascular bed is a likely site for this pooling (Goodman & Gillman, 1965), but this has not been confirmed by Ferrer, Bradley, Wheeler, Enson, Preisig, Brickner, Conroy & Harvey (1966), who found that nitrites cause an overall vasoconstriction in the splanchnic circulation.

The control of the outflow from the livers of human beings is a major factor in the control of cardiac output (Knisely, Harding & Debacker, 1957; Chien *et al.*, 1966). It has been shown by Chasis, Ranges, Goldring & Smith (1938) that nitrites cause renal ischaemia with a decline in renal blood flow and glomerular filtration rate. Thus the combined hepatic, splanchnic and renal circulations, which together receive a large amount of the cardiac output, seem to react differently from other peripheral local vascular areas, such as lung, skin, eye, forearm and brain (Ferrer *et al.*, 1966; Goodman & Gillman, 1965).

Preliminary experiments on perfused human livers carried out by us have given results similar to those found in the dog.

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