Antihypertensive activity of a new 3-hydrazinopyridazine derivative: ISF 2123

C. CARPI & L. DORIGOTTI*

Research Laboratories, I.S.F.-Italseber, Trezzano S/N, Milan, Italy

Several hydrazinopyridazine derivatives were shown to display an antihypertensive activity of the same order or even greater than the parent compound hydralazine (Druey & Tripod, 1967; Bellasio, Parravicini & Testa, 1969; Baldoli, Sardi & Bianchi, 1971).

Recently, we demonstrated that among a series of 6-amino-3-hydrazinopyridazines synthetized in our laboratories, some compounds have a higher activity and/or a lower toxicity than hydralazine (Pifferi, Parravicini, Carpi & Dorigotti, 1974). 3-Hydrazino-6-((2-hydroxypropyl) methylamino) pyridazine dihydrochloride (ISF 2123) was selected as the most interesting drug from this series.

Haemodynamic and antihypertensive action of ISF 2123 as well as its toxicity were investigated in various animal species and by means of several tests.

In anaesthetized cats and dogs ISF 2123 0.1 mg/kg i.v. produced a pressure drop of 30-60 mmHg within 8-10 min after administration, it reversed adrenaline effects and inhibited the hypertensive reflex elicited by carotid occlusion. The hypotensive effect lasted 3-5 hours.

ISF 2123 was shown to be inactive on nictitating membrane contractions induced by sympathetic stimulation or by adrenaline injection into the lingual artery. However, at the dose of 0.01 mg/kg i.v., it antagonized the vascular effects of adrenaline, angiotensin and vasopressin in pithed rats and spinal cats.

The haemodynamic changes induced in the anaesthetized dog by ISF 2123 0.1 mg/kg i.v. were the following: decrease in arterial pressure (−31%); increase in femoral (+26%), renal (+33%) and superior mesenteric artery (+11%) flows; slight increase in stroke volume (+10%) and ascending aorta flow (+13%); increase in heart rate (+27%).

Antihypertensive activity of ISF 2123 was evaluated in awake renal hypertensive rats and dogs. Potency of the compound was shown to be from 6 to 10 times greater than that of hydralazine (Table 1) although, from a qualitative point of view, the two drugs act similarly.

Table 1 Antihypertensive activity of ISF 2123 and hydralazine expressed as ED_{30} (dose producing a 30% pressure drop)

	ED_{30} (mg/kg)			
	Rat		Dog	
Drug	i.v.	p.o.	i.v.	p.o.
ISF 2123	0.09	1.7	0.030	0.1
Hydralazine	>0.5	15.0	0.030	2 Approx.

ISF 2123 acute toxicity in mice and rats is low; LD_{50} is 357 mg/kg i.p. and 1170 mg/kg p.o. in mice, 355 mg/kg i.p. and 1230 mg/kg p.o. in rats.

Oral toxicity tests (6 months) at the daily dosages of 10-20-40 mg/kg in Wistar rats and 1-5-10 mg/kg in Beagle dogs did not show any sign of intolerance nor any haematological, haematochemical or histological changes.

References

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