Short communications

Effects of a new tetrahydroisoquinoline (NC-7197) in experimental cardiogenic shock

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Intravenous administration of 1·0 mg/kg of NC-7197 to open and closed-chest anaesthetized dogs immediately after induction of cardiogenic shock by miliary coronary embolization resulted in significant haemodynamic improvement and prolonged survival. These results suggest that NC-7197 may prove to be valuable in the initial management of myocardial infarction complicated by hypotension and shock.

NC-7197 (2-[3-ethylsulphinylpropyl]-1,2,3,4-tetrahydroisoquinoline hydrochloride) has been previously shown to produce α-adrenoceptor blocking effects in animals (Privitera, Blickenstaff, Gaffney & Mohammed, 1971) as well as positive inotropic and chronotropic effects in both animals and man (Kim, Nassos & Shoemaker, 1971). More recently, Sriussadaporn & Cohn (1973) have reported that patients with chronic congestive heart failure, acute myocardial infarction, and shock responded favourably to intravenous treatment with NC-7197. Because of these reported pharmacological actions, it became of interest specifically to determine the effects of this agent in experimental cardiogenic shock.

Methods.—A total of 30 adult mongrel dogs of either sex and ranging in weight from 11·0 to 24·6 kg were used. All animals were anaesthetized with sodium pentobarbitone, 30–35 mg/kg intravenously, and maintained on positive pressure, room air respiration via a cuffed endotracheal tube.

Open chest preparations. In twelve dogs, cardiogenic shock was induced by miliary coronary embolism superimposed upon hearts with aortic insufficiency and left ventricular hypertrophy accomplished in the following manner. Approximately one month prior to the experiments, a transcarotid aortic valve cuspectomy was performed under aseptic conditions with small laryngeal biopsy forceps. Evulsion of one valve cusp immediately resulted in aortic regurgitation as evidenced by an aortic diastolic murmur, waterhammer pulse, and arterial pistol shot sounds. The animals recovered without incident. On the day of the experiment a median sternotomy was performed and catheters were placed in the ascending aorta at the level of the coronary ostea, in the aortic arch, and in the right ventricle. In this manner, it was possible to measure aortic pressure (1 mmHg≡1·333 mbar), cardiac output by the dye-dilution technique using indocyanine green (Cardiogreen; Hynson, Westcott & Dunning, Baltimore, Maryland), and produce the coronary embolization required to induce cardiogenic shock. The latter was accomplished by injection of 100–200 mg of polyethylene microspheres (230–350 μm diameter) through the ascending aortic catheter during a momentary manual occlusion of the ascending aorta distal to the catheter tip. In some cases, this procedure had to be repeated at 5 to 15 min intervals until systolic aortic pressure had diminished to below 80 mmHg.

Five dogs served as untreated controls while the remaining seven received a single intravenous injection of NC-7197, 1·0 mg/kg, immediately following the onset of shock. Aortic pressure was continuously recorded on a Sanborn Recorder while cardiac output determinations were made prior to embolization, immediately after onset of shock, and approximately 30 min afterwards in surviving animals.

Closed-chest preparations. Similar experiments were performed in 18 closed-chest dogs. Right heart and aortic arch catheters were placed as in the former experiments; however, the embolization catheter was a specially bent Judkins catheter passed into the left main coronary artery under fluoroscopic control. Its position was confirmed by injection of 2–3 ml of Renografin-76 (E. R. Squibb & Sons, New York, New York) or Vascoray (Mallinckrodt Chemical Works, St. Louis, Missouri). Two forms of embolic material were used: (1) lycopodium spores (30 μm diameter) and (2) polyethylene microspheres (as in the for-

mer experiments), or combinations of both. Usually 5–50 mg of spores, given in divided doses, was sufficient to induce shock but occasionally up to 250 mg of microspheres was also required. Cardiovascular parameters and times of measurement were the same as before. Twelve animals were treated with a 1·0 mg/kg intravenous dose of NC-7197 after the onset of shock, seven of which were allowed to recover from anaesthesia. The remaining six animals were untreated controls.

Results.—For the most part, all animals responded similarly after the coronary vasculature had been sufficiently embolized. Critical embolism resulted in a precipitous fall in mean arterial pressure averaging 48 mmHg in open-chest dogs and 63 mmHg in closed-chest dogs. There was a concomitant decline in cardiac output, often to unmeasurable levels (see Table 1). The untreated control animals invariably succumbed to this severe myocardial insult within 3–10 minutes. Closed-chest dogs appeared to survive slightly longer than the open-chest preparations.

In the NC-7197 treated dogs, experience indicated that the drug had to be given within minutes of the incurrence of hypotension apparently because of the sudden and profound myocardial compromise. When treated in this manner, both the open and closed-chest animals in cardiogenic shock responded similarly to NC-7197. Within 2–4 min after administration, blood pressure had partially recovered and by 30 min had returned almost to pre-infarct values. Also within 30 min, cardiac output had been restored to acceptable levels. None of the dogs expired during the 1 hour post-drug observation period and, in fact, appeared haemodynamically to have recovered from shock at the time when they were killed. However, it was necessary to maintain respiratory support in the closed-chest dogs during this period or blood pressure and cardiac output would gradually return towards shock levels. Additionally, ventricular tachycardia and fibrillation developed in three closed-chest preparations which required electrical defibrillation without further incident. Of the seven closed-chest dogs that were allowed to recover from anaesthesia, one died 3–4 h later while the remaining six survived longer than 12 h at which time they were necessarily killed.

TABLE 1. *Haemodynamic effects (±S.E.M.) of NC-7197 in anaesthetized dogs with experimentally induced cardiogenic shock*

Preparation	Treatment	No. of animals	Time	Mean arterial pressure (mmHg)	Cardiac output (l/min)
Open chest	Untreated Controls	5	Control	82±7·9	2·07±0·77
			Shock	35±9·2	UM†
			2–4 min	Death	Death
			30 min	Death	Death
	NC-7197 treated*	7	Control	91±7·7	2·08±0·32
			Shock	43±3·5	1·02±0·36
			2–4 min	49±4·0	—
			30 min	74±6·8	2·05±0·33
Closed chest	Untreated Controls	6	Control	110±7·4	2·33±0·22
			Shock	53±5·3	UM†
			2–4 min	4‡	UM†
			30 min	Death	Death
	NC-7197 treated*	12	Control	111±5·1	3·01±0·54
			Shock	43±5·7	0·24±0·11
			2–4 min	66±6·2	—
			30 min	104±5·9	1·93±0·44

* NC-7197, 1·0 mg/kg i.v. immediately after onset of shock.
† UM = Unmeasurable.
‡ Results from 1 animal only.

Discussion.—Cardiogenic shock in dogs engendered by miliary embolism of the coronary arteries is characterized by a marked fall of cardiac output together with pronounced hypotension which usually results in death of the animal (Agress, Rosenberg, Jacobs, Binder, Schneiderman & Clark, 1952; Bynum, Brobman, Jacobson & Su, 1971). Various drugs have been proposed for the treatment of this condition including isoprenaline (Eichna, 1967), phentolamine (Majid, Sharma & Taylor, 1971; Hood, Singh, Abelmann & Polensky, 1971), pressor amines (Kuhn, 1967), and even chlorpromazine (Gullota, 1970). None, however, has been satisfactory and the search continues for a more efficacious agent to treat this morbid disease complex (Goldberg, 1968).

Under the conditions of this study, NC-7197 was demonstrated significantly effective in combating the lethal effects of experimentally-induced cardiogenic shock. Whether or not it is singularly effective is not known since a comparison with other agents was not performed. Nevertheless, NC-7197 improved the blood pressure and cardiac output of all animals to which it was given.

Although not proven in this study, it is suspected that the mechanism by which NC-7197 exerted its effects was that of β-adrenoceptor stimulation in conjunction with moderate α-adrenoceptor blockade. This would result in enhanced myocardial contractile force and cardiac output as well as an improvement in peripheral blood flow which was apparently of sufficient magnitude to carry these dogs through the critical initial phase of the shock syndrome. Thereafter, when the severely acute effects of the myocardial insult have been overcome, the damaged heart again appears to be capable of sustained function, though probably at a lower level of competence. Regardless of the mechanism, the highly significant results of this preliminary investigation indicate that NC-7197 should be more extensively studied as a pharmacological adjunct for the treatment of cardiogenic and other forms of shock.

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