PHARMACODYNAMIC ACTIONS OF DIETHYLCARBAMAZINE IN THE DOG WITH PARTICULAR REFERENCE TO NICOTINE - LIKE PROPERTIES

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INTRODUCTION

Diethylcarbamazine, a derivative of piperazine, was introduced in 1947 as a filaricidal agent in man and its outstanding anthelmintic action is against filarial worms, notably *Wuchereria bancrofti*, *Brugia malayi*, *Loa-loa* of man (Rollo, 1965) and *Dirofilaria immitis* of the dog. At the present time, the most important use is for mass treatment of human communities in endemic areas. The aim of the therapy is to reduce the reservoir of microfilariae in the population to a level at which infection of mosquitos is prevented and transmission to fresh individuals ceases (Wilson, 1968). This method of control is reported to be showing considerable promise of success (Sasa, 1968).

In addition, the drug has been suggested for treatment of cutaneous larva migrans and dracunculosis in man and has proved a useful remedy for various lungworm infections - notably *Dictyocaulus viviparous* in cattle, *D. filaria* in sheep, *Metastrongylus* in pigs, *D. arnfieldi* in horses and *Aleurostrongylus abstrusus* in cats.

Comprehensive pharmacodynamic studies, with several species of animals, were carried out by Harned *et al.*,(1948) and more recently, the action of the drug on levels of circulating eosinophils has been reported by Thevathasan (1970).

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The dog is regarded very suitable for drug studies preliminary to use in man and the purpose of this short communication is to report observations made during studies of pharmacology of diethylcarbamazine, which are significant because of the continuing chemotherapeutic role of the drug in filariasis control.

MATERIALS AND METHODS

Young dogs of mixed breeding were used. Anaesthesia was induced with thiamylal sodium (Surital, Parke Davis) and maintained by infusion with chloralose. Blood pressure was recorded with a mercury manometer connected to a common carotid artery and respiration from a tambour attached to the side-arm of a T-shaped tracheal cannula. Injections of drugs were made through a cannula in the femoral vein and tracings were recorded on smoked kymograph paper (Forbes, 1964).

Diethylcarbamazine citrate (Boots) was used in the form of a 40% solution prepared for subcutaneous injection in cattle; hexamethonium bromide as Vegolysen (May and Baker) phentolamine mesylate B.P., as Rogitine (Ciba) and adrenaline hydrochloride as adrenaline injection, B.P.

RESULTS

A. Effects of Diethylcarbamazine citrate and Adrenaline hydrochloride

Intravenous dosages of diethylcarbamazine citrate of from 2.5 to 10 mg/kg caused a pre-

cipitous rise in blood pressure and a well-defined increase in rate and depth of respiration (Fig. 1). Respiration was sometimes inhibited, slightly at the peak of the pressor response, particularly when the highest dose was given—probably as a result of reflex inhibition of respiration arising from the effects of hypertension on the baroreceptors of the carotid and aortic bodies. These responses, are identical to those given by nicotine and are attributable to: excitation of sympathetic ganglia giving vasoconstriction, stimulation of the adrenal medullae releasing catecholamines and stimulation of the respiratory chemoreceptors affecting respiration.

The vasomotor effects of adrenaline (Forbes, 1971a) are identical to those of diethylcarbamazine, but respiration is often inhibited, because adrenaline has no stimulatory effects on the chemoreceptors and reflex inhibition predominates.

B. Effects of Hexamethonium bromide and Diethylcarbamazine citrate

This ganglionic blocking agent, antagonizes the action of acetylcholine, nicotine and nicotine-like drugs; at the autonomic ganglia, the adrenal medullae and the respiratory chemoreceptors. In a dosage of 1 mg/kg, it causes a moderate fall in blood pressure,

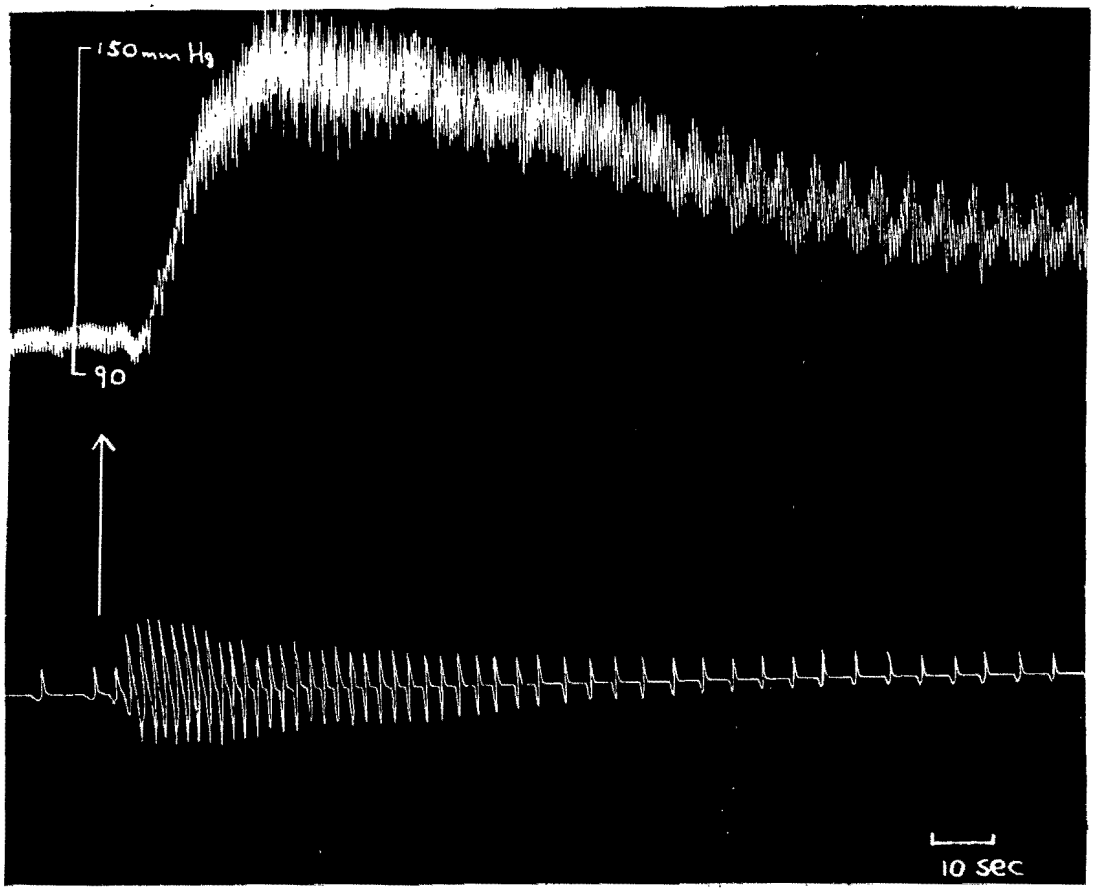

Fig. 1—Showing the effects of diethylcarbamazine citrate at a dosage of 5 mg/kg on the blood pressure (upper tracing) and respiration (lower tracing). Dog anaesthetized with chloralose.

as a result of blockade of sympathetic ganglia and consequent removal of normal vasoconstrictor tone (Forbes, 1971a). However, with simultaneous administration of hexamethonium, the actions of diethylcarbamazine are virtually abolished (Fig. 2).

C. Effects of Phentolamine mesylate and Diethylcarbamazine citrate

The adrenergic blocking agent, phentolamine, specifically antagonizes the alpha effects of sympathomimetic amines and when given at a dosage of 1 mg/kg, causes a small fall in blood pressure (Fig. 3) probably as a result of blockade of alpha receptors in peripheral vessels and consequent removal of normal vasoconstrictor tone. The vasomotor effects of diethylcarbamazine are considerably reduced when given after phentolamine, but the respiratory effects are not altered (Fig. 3).

DISCUSSION

The actions of endogenous acetylcholine at autonomic ganglia, adrenal medullae and the neuromuscular junction, are described as nicotine-like, because they are mimicked by nicotine. Moreover, nicotine-like drugs, stimulate the chemoreceptors of the carotid and aortic bodies to bring about an increase in the rate and depth of respiration.

The experiments show clearly, that diethylcarbamazine possesses certain pharmacological actions which are identical to those of nicotine and the finding that these actions are

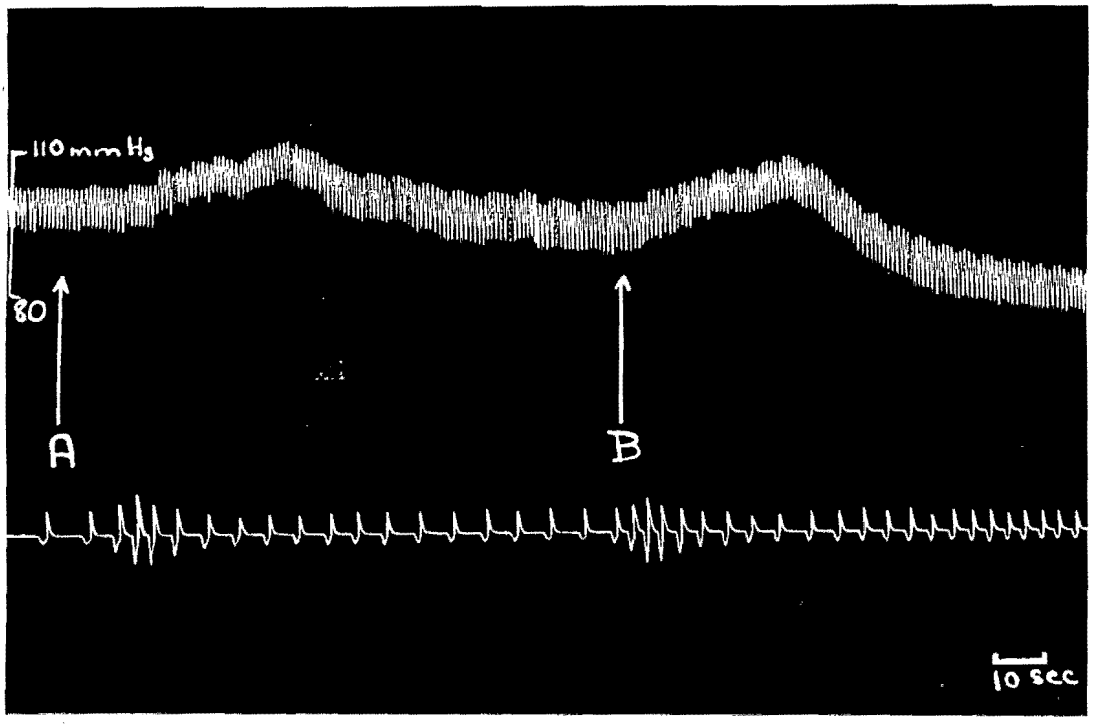

Fig. 2—Showing the effects of diethylcarbamazine citrate on the blood pressure (upper tracing) and respiration (lower tracing) when given simultaneously with hexamethonium bromide at a dosage of 1 mg/kg. Dosages of diethylcarbamazine citrate at A, 10 mg/kg and at B, 20 mg/kg. Dog anaesthetized with choralose.

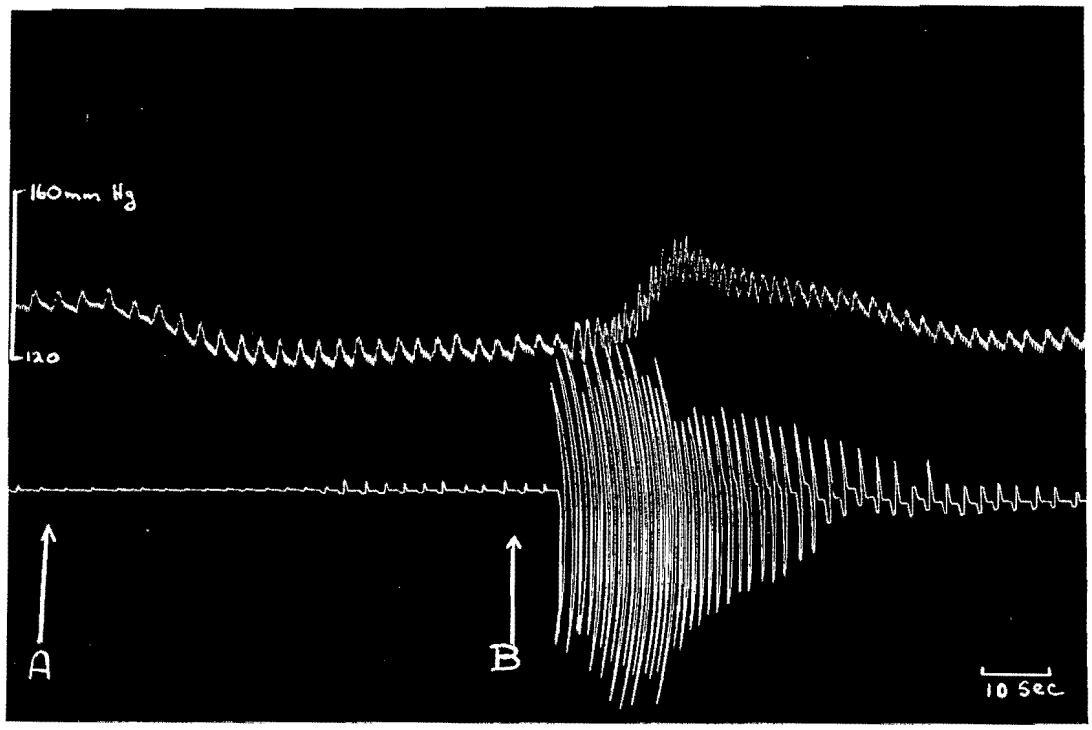

Fig. 3—Showing the effects on blood pressure (upper tracing) and respiration (lower tracing) of: A. phentolamine mesylate at a dosage of 1 mg/kg, followed by: B. diethylcarbamazine citrate at a dosage of 10 mg/kg. Dog anaesthetized with chloralose.

antagonized by hexamethonium, indicates that the sites of actions are the ganglia, the adrenal medullae and the respiratory chemoreceptors. In addition, the observation that the vasomotor effects are substantially inhibited by the alpha adrenergic blocking agent, is confirmatory evidence that these effects are elicited by endogenous amines, that is, catecholamines from adrenergic nerve endings and the adrenal glands.

Thevathasan (1970) reported that diethylcarbamazines produces an eosinophilia in adrenalectomised - splenectomised rats and remarked that this response duplicates that obtained with adrenaline by Thevathasan and Gordon (1954).

The results given above indicate that, in adrenalectomised animals, diethylcarbamazine is capable of evoking endogenous amine release from adrenergic nerves by virtue of its ganglion stimulant properties and the catecholamines could influence the level of circulating eosinophils.

In man, diethylcarbamazine has proved a very safe drug at therapeutic levels. However, it does frequently cause nausea and vomiting and these effects have been reported as the principal cause of the failure of mass treatment control projects in some countries, such as India (Sasa, 1968). These gastrointestinal side effects could arise from local irritant and spasmogenic effects or from stimulation of parasympathetic ganglia and the symptoms might be controlled readily by atropine. A small dose of atropine given by mouth with the anthelminthic could exert

sufficient local action on the gut to alleviate the symptoms without producing systemic effects. This procedure could be of benefit in assisting medication in mass treatment control programmes.

In the dog, the drug is extremely well tolerated and the only side effect is a low incidence of vomiting (Link, 1965; Gibson 1965). In cattle, doses twenty times higher than normal caused nervous symptoms, manifest by excitability and muscle twitching, but recovery was rapid and palliative treatment was not required. (Gibson, 1965). However, diethylcarbamazine apparently exacerbates the potential toxicity of methyridine and animals given the two drugs together may show severe purgation, dyspnoea, muscle spasm and may die.

Other experiments (Forbes, 1971b) show that several other modern anthelminthics are capable of evoking nicotinic responses and care should be exercised when prescribing such drugs to patients receiving other drugs or exposed to substances capable of exacerbating toxic propensities. The latter group of chemicals include cholinergics and substances with anticholinesterase properties—such as chloral and phenothiazine derivatives and organophosphorus compounds.

SUMMARY

Diethylcarbamazine citrate, when given intravenously to dogs anaesthetized with chloralose, evoked precipitous hypertension and pronounced increase in rate and depth of respiration. These effects were all abolished by the ganglion blocking agent, hexamethonium, and the hypertension was almost completely antagonized by the alpha adrenergic blocking agent, phentolamine. The results indicate that diethylcarbamazine has nicotine-like properties, in common with several other modern anthelminthics.

Care should be taken when prescribing the anthelminthic to patients exposed to other drugs or substances with nicotine-like propensities, such as cholinergics or anticholinesterases.

REFERENCES

FORBES, L.S., (1964). The relation between method of administration, route of absorption, inhibitory actions and acute toxicity of arecoline hydrobromide in dogs. *Ann. Trop. Med. Parasit., 58*: 119.

FORBES, L.S., (1971a). Some aspects of the pharmacology of pyrantel tartrate in the dog. *New Zeal. Vet. J., (In press).*

FORBES, L.S., (1971b). Toxicological and pharmacological relations between levamisole, pyrantel and diethylcarbamazine and their significance in helminth chemotherapy. *(In press).*

GIBSON, T.E., (1965). "Veterinary Anthelmintic Medication", 2nd ed., Tech. Comm. No. 33 Comm. Bur. Helminth.

HARNED, B.K., CUNNINGHAM, R.W., HALLIDAY, S., VESSEY, R.E., YUDA, N.N., CLARK, M.C., HINE, C.H., COSGROVE, R. and SUBBAROW, Y., (1948). Studies on the chemotherapy of filariasis VI. Some pharmacodynamic properties of 1- diethylcarbamyl-4-methyl piperazine hydrochloride, Hetrazan. *J. Lab. Clin. Med., 33* : 216.

LINK, R.P., (1965). In "Veterinary Pharmacology and Therapeutics". 3rd ed., Ed. L. Meyer Jones. Iowa State University Press, Ames., U.S.A.

ROLLO, I.M., (1965). In "The Pharmacological Basis of Therapeutics" 3rd ed., Eds. Goodman, L.S. and Gilman, A. The Macmillan Company, New York.

SASA, M., (1968). An introduction to epidemiology and control of filariasis. *Proc. of Seminar on Filariasis and Immunology of Parasitic Infections & Labo-*

ratory Meeting. Eds. A.A. Sandosham and V. Zaman. Singapore, p. 89.

THEVATHASAN, O.I. and GORDON, A.S., (1954). Adrenocortical - epinephrine interactions upon the circulating eosinophils in the adrenalectomized rat. *Anat. Rec., 120* : 780.

THEVATHASAN, O.I., (1970). The action of diethylcarbamazine (Hetrazan) on adrenalectomised-splenectomised rats with and without hydrocortisone. *Southeast Asian J. Trop. Med. Pub. Hlth., 1* : 123.

WILSON, T., (1968). The chemotherapy and control of filariasis. *Proc. of Seminar on Filariasis and Immunology of Parasitic Infections & Laboratory Meeting*. Eds. A.A. Sandosham and V. Zaman. Singapore, p. 139.