Effect of (3',4'-dichloro-2-(2-imidazolin-2-yl-thio)-acetophenone hydrobromide) (DITA) on pulmonary and systemic arterial blood pressure: a comparison with diethylpropion

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The use of the anorexigenic drug aminorex has been associated with a high incidence of progressive pulmonary hypertension (Gurtner, Gertsch & others, 1968), so too has chlorphentermine (Rau, 1969; Paeprer, 1970). As a result, anorexigenic drugs are suspected of causing pulmonary hypertension. We have compared the effects of the repeated acute administration of the anorexigenic agents DITA (3',4'-dichloro-2-(2-imidazolin-2-yl-thio)-acetophenone hydrobromide, Abdallah & White, 1974) and diethylpropion on the systemic and pulmonary arterial blood pressure of anaesthetized dogs.

Mongrel dogs of either sex, 7 to 24 kg, were anaesthetized with pentobarbitone sodium (32·5 mg kg^{-1}, i.p.). Pulmonary arterial blood pressure was recorded by catheterization of either the femoral or jugular vein. The position of the tip of the catheter was verified by monitoring the changes in blood pressure as the catheter was advanced. The system was filled with a 0·9 % solution of sodium chloride (saline) which contained 10 units ml^{-1} of heparin. Systemic arterial pressure was measured from a femoral artery cannulated with plastic tubing and attached to a pressure transducer. Mean pulmonary and systemic arterial blood pressures were recorded directly. Dogs were heparinized with 500 units kg^{-1} (i.v.). A femoral vein was cannulated for the administration of drugs which were dissolved in saline shortly before use. (No change in blood pressure was observed on injection of vehicle alone). Each dog received one dose (2, 4 or 8 mg kg^{-1}) of the anorexigenic compound every 30 min for 5 doses and 3 dogs were

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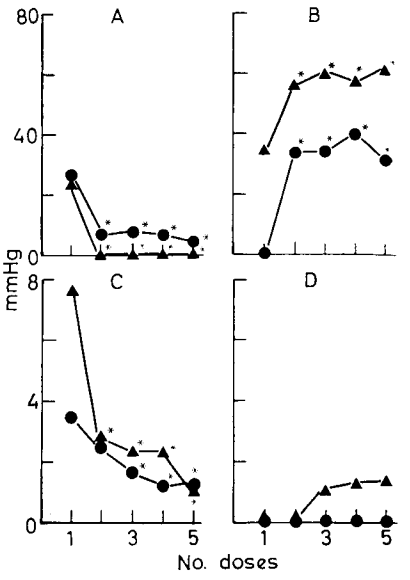

FIG. 1. Effect of repeated administration of DITA and diethylpropion on mean pulmonary arterial and systemic arterial blood pressure in anaesthetized dogs. Abscissa: Number of doses. Ordinate: Average change in mean blood pressure (mmHg). A—Average increase in systemic blood pressure. B—Average decrease in systemic blood pressure. C—Average increase in pulmonary blood pressure. D—Average decrease in pulmonary blood pressure. ●—DITA (8 mg kg^{-1}, i.v.), ▲—diethylpropion (8 mg kg^{-1}, i.v.). *Significantly different ($P<0·05$) from the first dose according to least significant difference test.

Table 1. *Effects of a single intravenous administration of DITA and diethylpropion on systemic arterial and pulmonary arterial blood pressure of anaesthetized dogs* (n = 3 per dose, figures are means ± s.e.).

Dose mg kg^{-1}	Mean systemic arterial b.p. (mmHg) Pretreat.	Δ depress.	Δ press.	Mean pulmonary arterial b.p. (mmHg) Pretreat.	Δ press.
DITA					
2	133 ± 4	0·0	20 ± 8	11 ± 2	0·0 ± 0·0
4	130 ± 3	0·0	15 ± 5	9 ± 1	2 ± 1
8	135 ± 0	0·0	27 ± 9	10 ± 5	4 ± 1*
Diethylpropion					
2	137 ± 9	—12 ± 4	28 ± 15	13 ± 5	6 ± 1**
4	143 ± 15	—12 ± 4	33 ± 16	8 ± 1	6 ± 3
8	140 ± 10	—35 ± 18	25 ± 14	12 ± 3	8 ± 2*

* Significantly different ($P < 0·05$) from pretreatment according to one tailed paired *t*-test.
** Significantly different ($P < 0·01$) from pretreatment according to one tailed paired *t*-test.

used at each dose level. The effect of first doses were analysed by paired Students's *t*-test. Blood pressure responses to each anorexigenic agent administered repeatedly at the same dose level were subjected to analysis of variance. The compounds were: DITA (3′,4′-dichloro-2-(2-imidazolin-2-yl-thio)-acetophenone hydrobromide, The Dow Chem. Co., Midland, Mich.) and diethylpropion hydrochloride (Tenuate, compliments of the WM. S. Merrel Co. Division of Richardson-Merrel Inc., Cincinnati, Ohio).

Table 1 summarizes the effects of the drugs on pulmonary and systemic arterial blood pressure. It is apparent that the DITA and diethylpropion data do not support linear dose-response relations at the doses used. The pressor response to DITA and diethylpropion were similar in the systemic arterial system. Diethylpropion caused a pressor effect on the pulmonary system a few mm higher than that caused by DITA.

The intravenous administration of diethylpropion caused a transient depressor effect followed by a pressor effect. At 8 mg kg^{-1} it produced an average depressor and pressor response systemically of − 35 and 25 mmHg respectively with a half life duration of 1 and 22 min, respectively (Table 1). With DITA, the first injection of 8 mg kg^{-1} produced only a systemic arterial pressor effect averaging 27 mmHg with a half life duration of 3 min. Subsequent doses of DITA produced biphasic responses similar to diethylpropion.

Tachyphylaxis developed to the systemic and pulmonary arterial pressor effects of the 8 mg kg^{-1} dose of both DITA and diethylpropion (Fig. 1, A and C). Their depressor effects on the systemic arterial blood pressure became more pronounced upon repeated administration (Fig. 1B) but did not cause a significant depressor effect in the pulmonary arterial system (Fig. 1D).

As with (+)-amphetamine, (Abdallah, 1974), tachyphylaxis developed to the pressor effects of DITA and diethylpropion on systemic and pulmonary arterial blood pressure. With aminorex, tachyphylaxis develops only to its pressor effect on systemic arterial pressure but not to its pressor effect on pulmonary arterial pressure (Abdallah, 1974).

The pressor effect of diethylpropion on pulmonary arterial blood pressure was greater overall than that of DITA. This holds true when the compounds are compared to a mg kg^{-1} or μmol kg^{-1} basis. For example, the 2 mg kg^{-1} (10 μ mol kg^{-1}) dose of diethylpropion produced a greater pressor response than the 4 mg kg^{-1} (130 μmol kg^{-1}) dose of DITA.

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Adsorption as a possible limitation in solubility determination

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Filtration is an essential step in the determination of solubility. Recently, the most commonly used filters have been cellulosic type membranes. The adsorption of organic compounds by commercial cellulosic (MF–Millipore Filters) filter membranes has been previously reported (Chiou & Smith, 1970; Batra, 1975; Chiou, 1975). The purpose of this study was to determine means to minimize the possible error due to adsorption during solubility determination.

Studies in our laboratory compared adsorption onto two commercial cellulosic filter membranes, I (MF–Millipore) and II (Gelman GA-8) with that onto commercial polycarbonate membrane, III (Nuclepore) or a commercial silver membrane, IV (Flotronics FM 13).

Aqueous suspensions or clear unsaturated solution of drugs had their pH values adjusted with 0·1 N hydrochloric acid or sodium hydroxide. Adsorption onto the filters was assessed after passing successive 5 ml portions of sample through filter membranes held in Pyrex filter holders (Pyrex Microanalysis Filter Holder, Millipore Corp.) or in syringe filter holders (Swinney Filter Holder No. 4310, Gelman Inst.). Filtration time was always kept within 1 min. The percentage adsorption was calcu-

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