Short communications

Correlation of the cardiac sensitizing potential of halogenated hydrocarbons with their physicochemical properties

D. G. CLARK AND D. J. TINSTON

Imperial Chemical Industries Limited, Industrial Hygiene Research Laboratories, Alderley Park, Nr. Macclesfield, Cheshire SK10 4TJ

The cardiac sensitizing potencies of a range of 14 halogenated hydrocarbons were assessed in conscious dogs by comparing the partial pressures (Pcs) needed to sensitize the heart to adrenaline. These were found to be directly related to their saturated vapour pressures (Ps) and the ratio Pcs/Ps was approximately constant although the values of partial pressures differed nearly 700-fold. It is suggested that cardiac sensitization is probably a structurally non-specific action and may be regarded as another example of physical toxicity.

Cardiac sensitization is an increased susceptibility of the heart to catecholamines, resulting in arrhythmias such as ventricular fibrillation or ventricular tachycardia. It has been shown to occur after the inhalation of a wide range of unsubstituted or halogenated hydrocarbons (Reinhardt, Azar, Maxfield, Smith & Mullins, 1971) and is a well known phenomenon in the field of anaesthetics. It has recently been the subject of detailed toxicological investigations following the suggestion that it was responsible for the sudden deaths of asthmatics using isoprenaline and a halogenated hydrocarbon pressurizing agent as an aerosol spray (Silverglade, 1972).

Although many chemicals have been studied in attempts to correlate cardiac sensitizing activity with chemical structure, no general pattern has emerged. Suggestions have been made that the degree of saturation (Carr, Burgison, Vitcha & Krantz, 1949), the molecular size and shape (Burgison, O'Malley, Heisse, Forest & Krantz, 1955), the degree and type of halogenation (Reinhardt *et al.*, 1971), or the carbon-halogen interatomic distance (Hopkins & Krantz, 1968) may be important.

In a recent series of experiments on the toxicity of the fluorinated hydrocarbons used as aerosol propellants, fire extinguishants and solvents (Clark & Tinston, 1972; Beck, Clark & Tinston, 1973) we observed that whereas cardiac sensitization could not be related to chemical structure, it did seem to be related to the physicochemical properties of the molecule. The present paper, therefore, describes the results of a more detailed investigation of this observation, using a range of chemical types, varying widely in their boiling points.

Methods.—Conscious beagle dogs (10–13 kg body weight) were exposed to atmospheres of the chemicals by means of a face mask. Oxygen was added when high concentrations of chemicals were used. During the last 10 s of the 5 min exposure period a bolus injection of adrenaline (5 μg/kg) was given via a cephalic vein, and the E.C.G. (lead II) changes were recorded. A further injection of adrenaline was also given 10 min after the end of exposure. As a control injection of adrenaline given during air exposure often produced some unifocal ventricular ectopic beats, only the appearance of more serious arrhythmias such as multifocal ventricular ectopic beats or ventricular fibrillation was taken as evidence of cardiac sensitization. Several dose levels of the chemical being tested were used, each differing by a factor of two, and the concentration at which 50% of the animals could be sensitized (EC_{50} cardiac sensitization) calculated by the moving average interpolation technique of Thompson (1947). Separate groups of 4 to 7 dogs were used at each dose level.

Results.—None of the chemicals produced cardiac arrhythmias on inhalation without an injection of adrenaline, but all were able to cause cardiac sensitization when the adrenaline was injected during exposure to a sufficiently high concentration. The post exposure injection of adrenaline, however, never resulted in arrhythmias even when it followed a challenge injection that had caused ar-

TABLE 1. *Concentrations of the chemicals causing cardiac sensitization and their physiochemical properties*

Chemical		EC_{50} cardiac sensitization and 95% confidence intervals (volume %)	Molecular weight	Boiling point (°C)	Vapour pressure at 37°C Ps (mmHg)	Partial pressure at EC_{50} Pcs (mmHg)	Relative saturation for cardiac sensitization Pcs/Ps
Tetrachlorodifluoromethane	$CFCl_2CFCl_2$	0·12 (0·10–0·14)	206	93	99	2	0·02
Carbon tetrachloride	CCl_4	0·5 (0·3–0·6)	156	77	190	4	0·02
Trichloroethane	CH_3CCl_3	0·75 (0·4–1·1)	135	74	210	6	0·03
Halothane	CF_3CHCl Br	2·0 (1·2–2·7)	198	50	480	15	0·03
Trichlorotrifluoroethane	$CFCl_2CF_2Cl$	1·0 (0·5–1·4)	189	48	524	8	0·02
Methylene chloride	CH_2Cl_2	2·4 (1·9–3·4)	86	40	661	18	0·03
Trichlorofluoromethane	$CFCl_3$	1·25 (0·5–1·6)	139	24	1186	10	0·01
Dichlorofluoromethane	$CHFCl_2$	2·5 (1·1–3·6)	104	9	2052	19	0·01
Dichlorotetrafluoroethane	CF_2ClCF_2Cl	10 (5·1–13)	172	4	2310	76	0·03
Vinylchloride	CH_2:$CHCl$	5 (3·7–6·8)	63	−14	4218	38	0·01
Dichlorodifluoromethane	CF_2Cl_2	8 (7·0–8·5)	122	−30	6764	61	0·01
Propane	$CH_3CH_2CH_3$	20 (12–26)	44	−42	9538	153	0·02
Bromotrifluoromethane	CF_3Br	20 (15–27)	149	−58	15276	153	0·01
Chlorotrifluoromethane	CF_3Cl	80*	105	−81	40698**	610	0·02

*Estimate (3/6 showed cardiac sensitization); **extrapolated.

rhythmias. As these hydrocarbons are rapidly eliminated from the body following a brief exposure (Clark & Tinston, 1972; Morgan, Black, Walsh & Belcher, 1972), cardiac sensitization would therefore seem to be only a transient phenomenon dependent on some temporary interaction between the effects of the chemical and the adrenaline, and not to structural damage of the heart cells.

The chemicals varied widely in their ability to cause cardiac sensitization (Table 1), their EC_{50}'s ranging from 0¼12% to 80% in the inspired air. The cardiac sensitizing potency could not be correlated with the molecular structure, the degree of fluorination, the degree of saturation or the molecular weight, but was directly related to the saturated vapour pressure or inversely related to the boiling point.

Discussion.—A direct relationship between vapour pressure and narcotic potency is well known for anaesthetic agents. On the basis of this relationship Ferguson (1939) developed his theory that substances present in a given medium at equal thermodynamic activities have the same degree of biological action. Using the ratio of the partial pressure of the chemical causing cardiac sensitization (Pcs) to the saturated vapour pressure (Ps) as a measure of the thermodynamic activity, it can be seen that despite a 6–700 fold variation in potency when expressed as volumes percent, all the chemicals we tested produced cardiac sensitization at approximately the same relative saturation (Pcs/Ps).

That such a wide range of relatively inert, stable, lipid soluble chemicals producing a rapidly reversible effect, are equipotent when expressed on a thermodynamic scale, would indicate that cardiac sensitization is very likely to be a structurally non-specific action, occurring as soon as the chemical occupies a constant fraction of the critical biophase. Cardiac sensitization may therefore be regarded as another example of 'physical toxicity' (Ferguson, 1939), and may be predictable from the saturated vapour pressure or the boiling point, or any physico-chemical property that is a measure of intermolecular attraction.

REFERENCES

BECK, P. S., CLARK, D. G. & TINSTON, D. J. (1973). The pharmacologic actions of bromochlorodifluoromethane (BCF). *Toxicol. appl. Pharmac.*, **24**, 1–10.

BURGISON, R. M., O'MALLEY, E., HEISSE, C. C., FOREST, J. W. & KRANTZ, J. C. (1955). Anesthesia XLVI. Fluorinated ethylenes and cardiac arrhythmias induced by epinephrine. *J. Pharmac. exp. Ther.*, **114**, 470–472.

CARR, C. J., BURGISON, R. M., VITCHA, J. F. & KRANTZ, J. C. (1949). Anesthesia LXXIV. Chemical constitution of hydrocarbons and cardiac automaticity. *J. Pharmac. exp. Ther.*, **97**, 1–3.

CLARK, D. G. & TINSTON, D. J. (1972). The influence of fluorocarbon propellents on the arrhythmogenic activities of adrenaline and isoprenaline. *Proc. Eur. Soc. Study Drug Toxicity*, **13**, 212–217.

FERGUSON, J. (1939). The use of chemical potentials as indices of toxicity. *Proc. roy. Soc. B.*, **127**, 387–404.

HOPKINS, R. M. & KRANTZ, J. C. (1968). Anesthesia LXXV. Relative effects of haloforms and epinephrine on cardiac automaticity. *Anesth. Analg.*, **47**, 56–67.

MORGAN, A., BLACK, A., WALSH, M. & BELCHER, D. R. (1972). The absorption and retention of inhaled fluorinated hydrocarbon vapours. *Int. J. appl. Radiat. Isotopes*, **23**, 285–291.

REINHARDT, C. F., AZAR, A., MAXFIELD, M. E., SMITH, P. A. & MULLINS, H. S. (1971). Cardiac arrhythmias and aerosol "sniffing". *Arch Environ. Health*, **22**, 265–279.

SILVERGLADE, A. (1972). Cardiac toxicity of aerosol propellants. *J.A.M.A.*, **222**, 827–828.

THOMPSON, W. R. (1947). Use of moving averages and interpolation to estimate median-effective dose. *Bact. Rev.*, **11**, 115–147.

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