ANTI-ARTHRITIC AND ANTI-ANAPHYLACTIC EFFECTS OF DIETHYL-CARBAMAZINE

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ABSTRACT

The anti-inflammatory potential of diethylcarbamazine has been studied in three laboratory models of inflammation namely, carrageenin oedema, adjuvant arthritis and mouse pinnal anaphylaxis. Two standard anti-inflammatory drugs, hydrocortisone and indomethacin were used as reference drugs.

This study was prompted by the fact that during therapy with the antifilarial drug, diethylcarbamazine, severe inflammation occurs even though diethylcarbamazine is reported to be an inhibitor of the release of mediators of inflammation.

The results of the study revealed that diethylcarbamazine, like indomethacin and hydrocortisone dose-dependently inhibited the experimentally induced inflammation in all the three models used. Hydrocortisone, the indirectly acting phospholipase A_2 inhibitor, was the most potent in all three models. Indomethacin, a cyclo-oxygenase inhibitor, was found to be more potent than diethylcarbamazine in carrageenin oedema and adjuvant arthritis but less potent than diethylcarbamazine in the mouse pinnal anaphylaxis model.

It was concluded that diethylcarbamazine with its leukotriene C_4 synthetase inhibitory properties would be a suitable anti-inflammatory agent in inflammations mediated most prominently by the cysteinyl leukotrienes and PAF. Asthma is one such inflammation.

Keywrds: Diethylcarbamazine, anaphylaxis, inflammation, indomethacin, hydrocortisone, arthritis

INTRODUCTION

Diethylcarbamazine is a potent filaricidal drug used in the treatment of onchocerciasis (river blindness). During treatment with this drug patients experience severe itching of the skin and eyes, tender lymph node enlargement, arthralgia and fever. There is evidence that this reaction has an immunological basis involving the antigenicity of the killed mirofilariae and subsequent release of the mediators of anaphylaxis [7]. In contrast however, diethylcarbamazine has been shown to inhibit anaphylactic release of endogenous substances which are mediators of inflammation, such as histamine, leukotrienes and prostaglandins [9, 13, 12]. Furthermore, diethylcarbamazine is reported to attenuate coronary vasoconstriction induced by Platelet Activating Factor (PAF) [12].

These reported actions of diethylcarbamazine make unclear what precise therapeutic role the drug could play in inflammation. The present investigation was undertaken to determine whether diethylcarbamazine would behave as a pro - or anti-inflammatory agent in three laboratory models of inflammation and to compare its activity with the standard anti-inflammatory drugs indomethacin and hydrocortisone.

METHODS

Carrageenin Oedema in Rats:

Fifty female albino rats, derived from a Wistar strain, weighing 190-220g were randomly distributed into four groups and treated as follows: Group A (5 rats - saline, 0.2ml orally), Group B (15 rats - indomethacin, 1.25-5mg/kg orally), Group C (15 rats - hydrocortisone, 2.5-10.0mg/kg intraperitoneally) and Group D (15 rats - diethylcarbamazine, 2.5-10mg/kg orally). One hour after this treatment, carrageenin oedema was induced in the rats according to the method of Winter Risley and Nuss [14] by injecting 0.05ml of a 1% suspension of carrageenin in normal saline into the planter aponeurosis of both hind paws. Immediately after this injection (within 30 seconds) the diameter of each hind paw was measured using a micrometer screw guage. Three

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hours later the paw diameters were again measured. From the mean increases in paw diameter in the saline and drug treated rats, the percentage inhibition of the carrageenin oedema produced with the drugs was expressed as 100 (1-Dt/Dc) where Dt is mean paw diameter in drug treated rats and Dc is mean paw diameter in saline treated rats.

Adjuvant Arthritis in Rats:

Fifty albino rats derived from a Wistar strain (180-200g body weight) were randomly distributed into four groups: A (5 rats), B (15 rats), C (15 rats) and D (15 rats). Adjuvant arthritis was induced in the rats according to the method of Newbould [11] by an intradermal injection of 0.05ml of a (5mg/ml) fine suspension of dead tubercule bacilli in liquid paraffin into the plantar surface of the right hind paw. The volume of each hind paw was measured plethysmometrically [6] for 56 consecutive days commencing on day 1 (i.e. the day of injection of adjuvant). For 14 consecutive days only, commencing on day 1, all the rats were treated as follows: Group A rats - 0.2ml saline orally; Group B rats - indomethacin 1.25-5mg/kg orally; Group C rats - hydrocortizone 2.5-10mg/kg intraperitoneally and Group D rats - diethylcarbamazine 2.5-10mg/kg orally. For every rat the paw volume on day 1 was taken as the base line value for determining increases in paw volume on subsequent days. In the drug treated rats, percentage inhibition of adjuvant arthritis on any particular day was calculated as 100(1 - Vt/Vc) where Vc is the mean increase in paw volume in saline-treated group and Vt is mean increase in drug-treated groups.

Mouse pinnal anaphylaxis:

Fifty male albino mice (20-35g body weight) were randomly distributed into 4 groups and treated orally (p.o) or subcutaneously (s.c.) as follows: Group A (5 mice - saline, 0.1ml s.c.) Group B (15 mice - diethylcarbamazine, 2.5 - 10mg/kg p.o.), Group C (15 mice - indomethacin, 5-20mg/kg p.o) and Group D (15 mice - hydrocortisone, 2.5 - 10mg/kg s.c.). Prior to the treatment with saline and the drugs, the mice were sensitized to bovine serum albumin (BSA). Each mouse was injected twice with BSA s.c. The first dose was 0.1ml of a solution of BSA (0.05mg/ml). Fourteen days later the second dose, 0.1ml of a solution of BSA (0.02mg/ml) was given. The mice were kept for a further period of seven days before challenge with BSA (0.1mg/ml) by innoculation into the pinna. The mice treated orally with diethylcarbamazine and indomethacin received treatment 1 hour before challenge and those treated subcutaneously with saline and hydrocortisone received treatment 30 min before challenge.

Antigenic challenge of the sensitized mice was preceded by an intravenous injection of Evans Blue dye. The mice were lightly anaesthetized with ether and 0.2ml of a 1% solution of Evans Blue dye was injected into the tail vein. Promptly after this, and while still under anaesthesia, the mice were laid supine and each pinna was spread out and innoculated with BSA (0.1mg/ml) using a 21 guage hypodermic needle. Each pinna was pierced in the centre through a drop of BSA solution. Thirty minutes after this operation the mice were killed and their ears cut off, spread out and the area of extravasation of the blue dye was measured by matching it with the best fit of standard circles. The area of the reaction was taken as the square of the diameter (mm) of the circle of best fit. Percentage inhibition of the inflammatory reaction was expressed as: 100(1 - At/Ao) where Ao is the area of extravasation of the blue dye of the pinna in the saline control mice and At is the area of extravasation of the blue dye of the pinna in the drug treated mice. the pinnal inflammation model used in this study was based upon the method of Church, James and Miller. [4]

Materials

Carrageenin (Batch Rex 6993), Mycobacterium tuberculosis (Heat-killed strain C, DT and PN mixed and freeze dried)were donated by ICI PLC, Pharmaceuticals Division, Alderley Park, England. Indomethacin was obtained from Merck Sharp & Dohme and liquid paraffin BP (batch 6E 6730) from Evans Medical, England. Hydrocortisone was obtained from Boots Company (Nottingham, UK) and Diethylcarbamazine and Bovine serum albumin were from Sigma Chemical Co. (St. Louis, USA).

Statistical Analysis:

Data were analysed by Student's t-test and the results are expressed as mean ± standard error of means.

RESULTS

Carrageenin Oedema

All the three drugs used in this study produced dose-dependent inhibition of the carrageenin oedema in the rat. The results presented in Table 1 show that on a weight basis hydrocortisone was the most potent and diethylcabamazine was the least potent. ID_{50} values for the three drugs were, hydrocortisone, 1.0mg/kg, indomethacin, 4.2mg/kg and diethylcarbamazine, 8.5mg/kg. Thus, in this test model, diethylcarbamazine has been shown to be anti-inflammatory but at half and one-eight the potencies of indomethacin and hydrocortisone respectively.

Adjuvant Arthritis

The arthritic syndrome induced with tubercule bacilli in the rat, as described by Newbould [10], is characterised by two inflamed lesions separated by two to three days. The primary lesion which occurred

Table I
Effects of Diethylcarbamazine, Hydrocortisone and Indomethacin on Carrageenin-induced oedema in the rat

Treatment 1 hr. before Carrageenin injection	Mean increase in paw volume (ml) 3hr. after carrageenin injection	Percentage Inhibition of oedema	ID_{50} mg/kg
Saline 0.2ml p.o.	1.57 ± 0.06		
Indomethacin mg/kg p.o.			
1.25	1.49 ± 0.05 (ns)	5.1	
2.50	1.23 ± 0.04*	21.7	
5.00	0.65 ± 0.02*	58.6	4.2
Hydrocortisone mg/kg i.p			
2.50	0.68 ± 0.02*	56.7	
5.00	0.58 ± 0.03*	63.1	
10.00	0.49 ± 0.02*	68.8	1.0
Diethylcarbamazine mg/kg p.o.			
2.50	0.90 ± 0.03*	42.7	
5.00	0.85 ± 0.06*	45.9	
10.00	0.75 ± 0.03*	52.3	8.5

Figures represent means of 10 paws ± s.e.m. Student's t-test significant differences between saline control and treated groups are denoted by (*) p<0.05 (ns) denotes no significant difference from saline control.

only in the injected paw reached peak intensity on day 3 or 4 after adjuvant injection. Thereafter the paw swelling waned. The secondary lesion was more generalised and affected not only the injected paw but all four paws, the ears and tail. In this study, diethylcarbamazine (2.5-10mg/kg) inhibited the primary lesion by a magnitude of 22.5-70.6% and abolished the secondary lesion. Similar results were obtained with indomethacin (1.25-5.0mg/kg) and hydrocortisone (2.5-10mg/kg) Table II. Comparison of the ID_{50} values indicated a ratio of 1:1.45: 4.33 (hydrocortisone: indomethacin: diethylcarbamazine).

Table II
Effects of diethylcarbamazine, hydrocortisone and indomethacin on Adjuvant arthritis in the rat (Evaluated on day 14 after injection of adjuvant)

Treatment	No of rats	Mean increase in volume (ml) of injected paw at day 14	Percentage Inhibition of Arthritis	Evidence of secondary Lesions	ID_{50} mg/kg
Saline 0.2ml p.o.	5	2.15 ± 0.05	-	++++	-
Diethylcarbamazine mg/kg p.o.					
2.50	5	1.95 ± 0.03	22.5	+	
5.00	5	1.70 ± 0.04*	52.9	0	
10.00	5	1.55 ± 0.02*	70.6	0	5.20
Hydrocortisone mg/kg i.p					
2.50	5	1.55 ± 0.04*	66.7	0	
5.00	5	1.43 ± 0.03*	98.0	0	
10.00	5	1.28 ± 0.03*	96.7	0	1.20
Indomethacin mg/kg p.o					
1.25	5	1.80 ± 0.02*	38.9	0	
2.50	5	1.58 ± 0.03*	70.0	0	
5.00	5	1.63 ± 0.05*	80.0	0	1.74

++++ denotes severe generalised swelling of all four paws, tail and ears.
O denotes no swelling in the un-injected parts of the body. Figures represent means ± s.e.m. Student's t-test significant differences between saline group and treated groups are denoted by (*) P < 1.001

Mouse pinnal anaphylaxis

In this model, diethylcabamazine (2.5-10mg/kg) produced inhibition of the magnitude of 5.76 - 60.63%. Similar degrees of inhibition were produced with indomethacin (5-20mg/kg) 24.75-70.47% and hydrocortisone (2.5-10mg/kg) 43.9 - 71.75% Comparison of the ID_{50} values however revealed that diehtylcarbamazine was more potent than indomethacin (Table III).

Table III
Effects of diethylcarbamazine, hydrocortisone and indomethacin on mouse pinnal anaphylaxis

Treatment	No of mice	Extravasation of Blue dye (nm²)	Percentage Inhibition	ID_{50} mg/kg
Saline 0.1ml p.o	5	20.32 ± 4.23	-	-
Diethylcarbamazine mg/kg p.o				
2.50	5	19.15 ± 2.00 (ns)	5.76	
5.00	5	11.77 ± 2.03*	42.08	
10.00	5	8.00 ± 1.67*	60.63	7.08
Hydrocortisone mg/kg i.p				
2.50	5	11.40 ± 2.12*	42.90	
5.00	5	9.47 ± 1.59*	53.40	
10.00	5	5.74 ± 1.12*	71.75	3.98
Indomethacin mg/kg p.o				
5.00	5	15.29 ± 1.72 (ns)	24.73	
10.00	5	9.96 ± 1.84*	50.08	
20.00	5	6.20 ± 1.37*	70.47	10.47

Figures represent means of 10 ears ± s.e.m. Student's t-test significant differences between saline group and treated groups are denoted by (*) p< 0.05 (ns) denotes no significant difference from saline control.

Discussion

In this study two standard anti-inflammatory drugs, hydrocortisome and indomethacin were used as reference drugs. Hydrocortisome is known to promote the synthesis and release of the phospholipase-A_2 inhibitory proteins macrocortin and lipomodulin [2,3,8]. Indomethacin is an established inhibitor of cyclo-oxygenase. Inflammation in the test models used in this study is mediated by the metabolites of arachidonic acid. It is to be expected therefore that inhibitors of arachidomic acid metabolism would effectively inhibit the experimental inflammation produced. The effectiveness of diethylcarbamazine as an inhibitor in the test models used can be explained by the fact that it inhibits the release of metabolites of arachidonic acid such as leukotrienes and prostaglandins [9,13,12]. The order of potency of anti-inflammatory activity of the three drugs used in this study was hydrocortisone > indomethacin >diethylcarbamazine in two of the test models, namely carrageenin oedema and adjuvant arthritis. However, in the mouse pinnal anaphylaxis model, diethylcarbamazine was more potent than indomethacin. This change in the order of potency may be linked with the dominant role that PAF and leukotrienes play in anaphylaxis. Indomethacin is not an inhibitor of the actions of PAF nor does it inhibit leukotriene

synthesis. In contrast however, diethylacarbamazine inhibits PAF actions [12] and also inhibits leukotriene C_4 synthetase [1].

CONCLUSION

On the basis of the results presented in this paper it would be reasonable to conclude that diethylcarbamazine is an anti-inflammatory agent with a preponderance of activity in those inflammations in which PAF and the cysteinyl leukotrienes rather than the prostanoids are the dominant pro-inflammatory madiators. Asthma is one such inflammation and diethylcarbamazine has been reported to be a suitable drug candidate in asthma therapy [5] whereas indomethacin is contra-indicated.

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A SOCIOLOGICAL ANALYSIS OF DRUG ABUSE AND TEENAGE PREGNANCY

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ABSTRACT

The resources of any given society are limited. Consequently individuals have "personal troubles" in coping with their day-to-day activities. Many individuals, although isolated from each other, share similar situational logic and this directs them to adopt the same tactics to ameliorate their personal troubles. When these troubles exceed their tolerable limits they become problems and "public issue". Public issues then are nothing but refractions and reflections of personal troubles of individuals. Two specific areas of major concern with their resultant problems facing Ghanaians currently and in fact the years ahead are the twin evils of so-called drug abuse and teenage pregnancy. It is the modest aim of this paper to demonstrate that what are considered problems are in reality effects of the "structural" sources of "contradictions" between the group that would be defined as the youth and the major institutional structures of society.

Keywords: Personal troubles, public issues, refractions, reflections, structural contradictions.

INTRODUCTION

Societies are normally regarded as "Sui Generis" a la Durkheim, i.e. a fact of existence [1]. This means that the individual is normally born into an already organised and on-going society.

For the smooth running of any society, sociologists are agreed that four problems referred to as functional pre-requisites must be solved [2]. The first of these is the need for survival purpose to meet the physical requirements of its members. Food and shelter are the minimum requirements. Their provision usually involves some system of production and distribution. The term Economy describes this institutional structural arrangement of society. The second requirement for survival is the need to ensure that these requirements reach the society. The term Polity, i.e. Goal Attainment, is used to describe this structural arrangement of society. Goal Attainment is necessary because the resources of society are always scarce or in short supply. It is this term, polity, i.e. goal attainment that brings politics into this picture. Political arrangement are involved because to determine the priorities of scarce resources it is necessary to wield state power. And normally, there are two main ways of attaining this end: one is through the ballot box, the other is through the barrel of the gun. Luckily in Ghana, we have experienced both. The third functional prerequisite is that of kinship i.e. the institution of marriage and family. This important institution is saddled with the problems and responsibilities of procreation and socialisation of the young. The final one consists of community organisations, and these are religious institutions, educational institutions, mass media and communications. In fact community organisations share the functions of integrating the various elements and institutions. Ideally, they can create, demonstrate and reinforce social values. They may however require help from formal agencies of social control such as the Police and the Military, or from the legal institutions of the courts and the judiciary, should they prove inadequate on their own.

CONCEPT OF YOUTH & EMERGENCE OF YOUTH CULTURE

The young are and must be socialised and committed to a special set of values, standard expectations and behaviour patterns. This special set is what is regarded as the mainstream culture or the dominant culture, i.e. the way of doing things or way of life of a people.

Sociologically, the Concept of Youth simply refers to the state or time of being young. In this sense, a young person is someone not far advanced in

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