Responses of systolic blood pressure (SBP), diastolic blood pressure (DBP) and heart rate (HR) after hydrallazine, before and after practolol

Hydrallazine dose		Responses before practolol	Responses after practolol	P value
0.1 mg/kg	SBP	-5.8 ± 3.7	-2.4 ± 1.8	>0.5
	DBP	-4.3 ± 0.9	-4.6 ± 2.9	>0.5
	HR	$+15.9 \pm 4.0$	$+1.3 \pm 0.5$	$0.005 > p > 0.001$
0.3 mg/kg	SBP	-5.2 ± 1.7	-1.2 ± 1.3	$0.2 > p > 0.1$
	DBP	-8.6 ± 2.2	-3.0 ± 3.5	$0.025 > P > 0.01$
	HR	$+14.4 \pm 3.4$	$+0.3 \pm 0.3$	$0.025 > p > 0.01$
0.6 mg/kg	SBP	-10.7 ± 2.5	-5.8 ± 1.9	$0.2 > p > 0.1$
	DBP	-10.8 ± 1.8	-5.2 ± 1.6	$0.025 > p > 0.01$
	HR	$+2.8 \pm 1.4$	$+1.8 \pm 0.5$	>0.5
1.0 mg/kg	SBP	-27.0 ± 9.8	-24.3 ± 8.9	$0.2 > p > 0.1$
	DBP	-33.0 ± 8.6	-21.6 ± 8.9	$0.1 > p > 0.05$
	HR	$+7.8 \pm 2.7$	$+1.9 \pm 0.6$	$0.2 > p > 0.1$

Values present means $\pm$ S.E.M. in 9 experiments.

electrocardiogram R-waves. Hydrallazine hydrochloride (Apresoline hydrochloride, Ciba) was given i.v. in the following order: 0.1, 0.3, 0.6 and 1.0 mg/kg. Each dosage was flushed in by injecting 3 ml of heparinized normal saline. The peak hypotensive effect was observed within 10–20 min. The blood pressure was allowed to return to its baseline value, which took an additional 5–10 min before the following injection was made. The heart rate increase lasted longer than 30 min, and it was usually higher than its baseline value when the following injection was made. Priority was given to the hypotensive effect because it was the primary purpose of the study. Practolol (Eraldin, ICI) 2 mg/kg i.v. was given over 5 min. 30 min after practolol administration, the hydrallazine dose-effect study was repeated.

The paired changes in systolic blood pressure, diastolic blood pressure and heart rate observed after hydrallazine administration before and after practolol administration were compared by t-test, and P values less than 0.05 are taken as significant[6].

Results. The Table shows that i.v. hydrallazine lowered systolic and diastolic blood pressure. Practolol lessened hydrallazine effects of lowering systolic and diastolic blood pressure which were significant for the changes in diastolic blood pressure observed after hydrallazine in doses of 0.3 and 0.6 mg/kg. The increase in heart rate was highest after the first hydrallazine injection and did not return to baseline for the second and subsequent injections. The absolute values for heart rates per min before and after hydrallazine injections, in order, were: 136.6 rising to 152.7; 152.7 rising to 167.1; 159.8 rising to 162.8 and 155.4 rising to 163.2. The comparable values were, after practolol, 138.7 rising to 140.0; 135.7 rising to 136.0; 134.9 rising to 136.7 and 134.6 rising to 136.5 following injections of hydrallazine. Practolol effectively blocked the increase in heart rate.

Discussion. These experiments have shown that after practolol administration hydrallazine caused minimal or no tachycardia. Despite this practolol did not enhance the acute hypotensive effect of hydrallazine in normotensive dogs. Rather, it lessened it. A similar observation was made by BRUNNER et al.[4] when propranolol was tested in combination with hydrallazine. The peripheral β-adrenergic blocking action of propranolol was suspected as a possible explanation. However, practolol, a selective cardiac β-adrenergic blocking agent did not enhance the hypotensive effect of hydrallazine. This would suggest that the increase in cardiac output after hydrallazine is not of importance in modifying the hypotensive effect of hydrallazine. Hence blockade of the increase in cardiac output does not bring about further lowering of blood pressure by hydrallazine. It is conceivable but unlikely that blockade of the cardiac component of the increased sympathetic stimulation has intensified its peripheral component manifested by peripheral vasoconstriction.

Zusammenfassung. Es wird gezeigt, dass Verabreichung von Hydrallazin einen Blutdruckabfall und eine reflektorische Tachykardie zur Folge hat. Nach Praktololgabe wird eine Hemmung der reflektorischen Tachykardie erreicht, während die blutdrucksenkende Wirkung erheblich vermindert wird.

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[6] A. GOLDSTEIN, *Biostatistics*, 1st edn (The MacMillan Company, New York 1964), p. 59.

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On the Anti-Inflammatory Properties of the Schistosomicide Niridazole (Ambilhar®)

In patients suffering from a guinea-worm infestation (*Dracunculus medinensis*) who were treated with niridazole it was noted that tenderness and swelling of the leg tended to disappear and that the worm could be easily extracted from its location[1–4].

From experiments carried out in monkeys (*Macacca mulatta, Cercopithecus aethiops*) artificially infected with *Dracunculus medinensis* no evidence could be obtained that niridazole impairs motility or viability of the worm[5].

Likewise, histological examination of clinical material obtained from patients treated with niridazole did not reveal any noticeable damage of the worm[6].

It was therefore felt that the niridazole treatment might affect the inflammatory reaction of the host and

Table I. Inhibitory activity of niridazole on turpentine-induced pleurisy

Dose (mg/kg p.o.)	Volume of exudate (ml + S.D.[a]) at n hours					
	3 h			24 h		
	ml	Change (%)	P[a]	ml	Change (%)	P[a]
Controls	0.49 ± 0.04	–	–	1.21 ± 0.12	–	–
30	0.43 ± 0.04	−12	> 0.1	1.02 ± 0.04	−16	> 0.1
100	0.35 ± 0.05	−23	< 0.05	0.70 ± 0.04	−42	0.002
300	0.28 ± 0.01	−43	< 0.001	0.77 ± 0.09	−36	0.01

[a] P and S.D. calculated according to Lord. $n = 5$ per group.

Table II. Inhibition of kaolin-induced paw oedema by niridazole

Dose (mg/kg p.o.)	Oedema volume (µl + S.D.[a]) at n hours								
	4 h			24 h			48 h		
	µl	Change (%)	P[a]	µl	Change (%)	P[a]	µl	Change (%)	P[a]
Controls	440 ± 49	–	–	520 ± 30	–	–	280 ± 26	–	–
30	420 ± 62	− 5	> 0.1	430 ± 50	−17	> 0.1	230 ± 36	−18	> 0.1
100	210 ± 29	−52	< 0.001	350 ± 33	−33	< 0.002	200 ± 29	−29	< 0.05
300	140 ± 26	−78	< 0.001	290 ± 33	−44	< 0.001	160 ± 18	−43	0.001

[a] S.D. and P calculated according to Lord. $n = 10$ per group.

Table III. Anti-arthritic action (reduction of size of secondary lesion) and normalization of serum albumin-globulin ratio

Dose (mg/kg/p.o./day)	Reduction of the paw volume (%) after 4 days' treatment	Normalization (%) of A/G ratio
30	−42	34
100	−69	71
300[a]	(−93)[a]	(83)[a]

[a] 4 out of 6 animals died on days 3 or 4 of the treatment. $n = 6$ per group.

thus render extraction of the worm possible. As a consequence, the possible anti-inflammatory activity of niridazole was examined on 3 different rat models of an experimental inflammatory reaction: a) turpentine pleurisy[6], b) kaolin-elicited paw oedema[7] and c) adjuvant-induced polyarthritis[8]. The experimental procedures were identical with those described in previous papers[7–10], niridazole being applied in suspension by the oral route (stomach tubing).

The results obtained are summarized in Tables 1–3. It can be seen from these tables that niridazole is capable of reducing the exudation caused by turpentine in the pleural cavity and the paw oedema resulting from subplantar injection of kaolin at a dose of 100 mg/kg or more.

The anti-inflammatory effect of a single dose (administered 1 h pre-irritant) was found to last 24 h in the pleurisy test and 48 h in the paw test. Besides exerting an inhibitory action when administered prophylactically, niridazole was also active when administered to rats suffering from full-blown adjuvant-arthritis. Thus, as small a dose as 30 mg/kg/day given on 4 consecutive days (18–21 post-adjuvant) exerted a beneficial effect in that the swelling of the contralateral non-injected hind paw was reduced by 42% and the disturbed serum albumin-globulin ratio normalized by 34%. The next higher dose (100 mg/kg) produced a drastic reduction of the arthritic lesions and a similar improvement of the serum pattern, whereas 300 mg/kg given daily on 4 consecutive days were not tolerated by the arthritic rats.

In connection with the anti-inflammatory effect of niridazole it is worth noting that the above-mentioned active dosage in the different inflammatory models is roughly the same as that which exerts a schistosomicidal action in the experimentally infected animal[11–13].

From these results we conclude that niridazole may owe its efficacy in the treatment of guinea-worm infestation to an indirect action, i.e. a rather pronounced anti-inflammatory activity.

Zusammenfassung. Es wurde gezeigt, dass das Schistosomizid Niridazol (Ambilhar®) in verschiedenen Entzündungsmodellen an der Ratte (Terpentinpleuritis, Kaolin-Pfotenoedem, Adjuvans-Arthritis) eine deutlich anti-inflammatorische Aktivität besitzt.

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[1] A. Bühler, R. Geigy, A. Gigon and F. Meier, Acta trop. *22*, 350 (1965).
[2] M. L. Kothari, D. S. Pardinani and M. P. Anand, Am. J. trop. Med. Hyg. *17*, 864 (1968).
[3] G. Raffier, Ann. N.Y. Acad. Sci. *160*, 720 (1969).
[4] C. R. R. M. Reddy, M. Madduleti Reddy and M. D. Sivaprasad, Am. J. trop. Med. Hgyg. *18*, 516 (1969).
[5] R. Müller, personal communication.
[6] H. Striebel, personal communication.
[7] L. Riesterer and R. Jaques, Helv. physiol. Acta *25*, 156 (1967).
[8] R. Jaques, H. Majer, L. Riesterer and M. Rüegg, Pharmacology, *5*, 81 (1971).
[9] L. Riesterer and R. Jaques, Helv. physiol. Acta *26*, 287 (1969).
[10] L. Riesterer and R. Jaques, Pharmacology *2*, 288 (1969).
[11] C. R. Lambert, M. Wilhelm, H. Striebel, F. Kradolfer and P. Schmidt, Experientia *20*, 452 (1964).
[12] C. R. Lambert, Acta trop. *23*, 1 (1966).
[13] H. Striebel, Ann. N.Y. Acad. Sci. *160*, 491 (1969).
[14] E. C. Faust and P. F. Russel, *Craig and Faust's Clinical Parasitology* (Lea + Febiger, Philadelphia 1964).