action resulting from its highly lipophilic nature (e.g. retention of croton oil on the surface of the ear skin), a control experiment was run in which paraffin oil (Paraffinum liquidum Ph. H.V) was incorporated in the irritant and tested simultaneously with benzyl glucofuranoside. From the data presented in Table II it is evident that paraffin oil is slightly inhibitory at concentrations starting from 30 mg/ml. A statistically significant reduction of the ear oedema, however, is only obtained with the oil at a concentration of 300 mg/ml, its effect then being roughly equal to that of benzyl glucofuranoside at a concentration 10 times lower. The anti-inflammatory effect of benzyl glucofuranoside at concentrations of 100 and 300 mg/ml is highly different from that of paraffin oil at the same concentrations ($P < 0.001$). It can therefore safely be concluded that the inhibitory actions of benzyl glucofuranoside at concentrations of 30 and 100 mg/ml are entirely due to the compound, and that some non-specific effect contributes only minimally to the decrease in the inflammatory reaction observed with benzyl glucofuranoside at a concentration of 300 mg/ml.

Table II.

Preparation	No.	Concentration (mg/ml)	Weight increase of the ear mg ± S.E.[a]		P[a]	Inhibitory effect (%) I[b]	II[c]
Controls	5	–	37.8	2.3	–	–	–
Paraffinum liquidum Ph. H.V.	5	30	33.7	2.0	0.1	11	–
	5	100	32.7	3.4	0.1	14	–
	5	300	26.1	4.3	0.05	31	–
Benzyl glucofuranoside	5	100	13.8	1.8	0.001	64	58
	5	300	4.4	1.8	0.001	89	83

[a] Mean ± S.E., and P calculated according to LORD. [b] As compared with control ears treated with irritant in vehicle described by TONELLI et al.[5]. [c] As compared with ears treated with irritant as above containing identical amounts of paraffin oil instead of benzyl glucofuranoside.

Hydrocortisone, on the other hand, exerts an inhibitory action at concentrations starting from 0.3 mg/ml. At concentrations of 1 and 3 mg/ml hydrocortisone is roughly comparable with benzyl glucofuranoside at concentrations of 30 and 100 mg/ml respectively. Graphical determination of the ED_{50} for hydrocortisone yields a figure of 2 mg/ml, i.e. the corticosteroid is some 30–35 times more active than benzyl glucofuranoside. This quantitative inferiority of benzyl glucofuranoside is largely offset by qualitative advantages, i.e. a complete absence of undesirable effects on the thymus and adrenals even following prolonged administration at very high daily doses[3]. On the other hand, it seems worth noting that the anti-inflammatory action of hydrocortisone as determined by the mouse ear assay outlined here compares favourably with that established for the same corticosteroid in the rat by TONELLI et al.[6], i.e. the mouse ear assay would seem equally suitable as a means of assessing the activity of anti-inflammatory agents applied topically.

Zusammenfassung. Es wird gezeigt, dass Äthyl-3,5,6-tri-*O*-benzyl-D-glucofuranosid (CIBA 21401-Ba, Glyvenol®) eine am Mausohr erzeugte Entzündung bei topikaler (epikutaner) Applikation zu hemmen vermag.

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A Pharmacological Investigation of the Influence of Suxamethonium on Cardiac Function in the Horse

A number of investigators have reported on the use of suxamethonium as a casting agent in large animals, particularly in the horse[1–9]. The events following i.v. injection of the drug consist of the onset of muscular fasciculations within 10–40 sec, rapidly followed by muscular paralysis, the animal gently falling to the ground. This phase is associated with a period of apnoea of 0.5–3 min duration. The horse is usually able to stand again within 4–7 min of administration of the drug. Other untoward effects observed when suxamethonium is administered for this purpose, consist of changes in cardiac rate and rhythm. HOFMEYR[3], NEAL and WRIGHT[5] and TAVERNOR[8,9] observed a marked acceleration of heart rate, with values exceeding 150 beats/min in many cases. Since the average normal heart rate in horses at rest is of the order of 30–40 beats/min, these responses involve a three- to six-fold increase in rate. Moreover, serious disturbances of cardiac rhythm have been reported and some investigators[3,8,9] have recorded deaths from primary cardiac arrest.

In the present experiments we have attempted to analyse further the changes in cardiac function that occur

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following the administration of suxamethonium to the horse, and to assess the efficacy of the β-adrenergic blocking agent, propranolol, in preventing such changes. For this purpose suxamethonium chloride was given i.v. to the conscious horse at a dose rate of 0.2 mg/kg, and during the subsequent 10–15 min period maximum and minimum heart rates were recorded electrocardiographically. In further experiments the same animals were cast with suxamethonium 5 min after the i.v. injection of 0.1 mg/kg of propranolol hydrochloride. The order of performance of these 2 experimental procedures was varied from animal to animal and at least 2 days was allowed to elapse between castings.

A pronounced tachycardia was recorded at the time the animal fell to the ground. Hence, this initial cardiac response could not be attributed to the effects of any subsequent period of apnoea. The results presented in Table I indicate that both maximum and minimum heart rates recorded after the administration of suxamethonium were reduced when propranolol had been given previously. Thus, propranolol produced a partial blockade of the positive, chronotropic effects resulting from the administration of suxamethonium and a reduction of the more serious cardiac abnormalities as shown on the electrocardiogram.

Table I. Maximum and minimum heart rates (beats/min) in conscious horses cast with 0.2 mg/kg body weight suxamethonium chloride

Horse	Without propranolol		With propranolol[a]	
	Maximum	Minimum	Maximum	Minimum
1	172	112	152	44
2	104	56	48	28
3	144	48	52	32
4	124	48	78	42
5	208	152	132	48
Mean	150.4 ± 18.3	83.2 ± 19.2	92.4 ± 21.1	38.8 ± 17.3

[a] Suxamethonium administered 5 min after administration of 0.1 mg/kg propranolol.

Table II. Effect of 0.2 mg/kg body weight suxamethonium chloride on heart rate (beats/min) in anaesthetized horses

Experiment	Before propranolol		After propranolol[a]	
	Control	Maximum	Control	Maximum
1	48	68	44	68
1	68	86	56	60
3	46	80	36	40
4	36	60	36	44
5	44	56	32	44
6	40	60	44	64
7	44	48	44	52
8	44	58	40	44
Mean	46.3 ± 3.3	64.5 ± 4.5	41.5 ± 2.6	52.0 ± 3.8

[a] o.1 mg/kg body weight.

Further experiments were performed in anaesthetized horses, anaesthesia being induced by the i.v. administration of thiopentone sodium at a dose level of 10 mg/kg followed by maintenance with a halothane/oxygen mixture in a closed anaesthetic circuit. Intravenous doses of 0.2 mg/kg of suxamethonium chloride caused a reduction in respiratory minute volume for a period of 2–3 min, a rise in mean arterial blood pressure (an average maximal rise of 61 mm Hg in 8 experiments) and a moderate increase in heart rate (Table II). In contrast to the cardiac actions of suxamethonium in conscious horses, however, the drug produced no abnormalities of rhythm, as indicated by the electrocardiogram.

The mild tachycardia produced by suxamethonium during anaesthesia was diminished somewhat by the prior administration of propranolol, but this antagonism was not complete. We found, however, that both the pressor and cardiac actions of suxamethonium in the anaesthetized horse were abolished by the ganglion blocking agent hexamethonium, indicating that these cardiovascular responses were mediated either directly or indirectly via sympathetic ganglionic synapses.

The main finding in the present work has been the demonstration of quantitative and qualitative differences in the action of suxamethonium in conscious as compared with anaesthetized horses. In the conscious animals a three- to six-fold increase in heart rate occurred together with cardiac arrhythmias in most instances, whereas the tachycardia in the anaesthetized horses exceeded the control heart rate by only a factor of 1.4 on average and no arrhythmias were noted. It seems possible that the initial changes in cardiac rate and rhythm in conscious horses result from the fright response which would be expected to accompany the sudden loss of muscular tone in the conscious animal, and not primarily from a stimulant action of suxamethonium on sympathetic ganglia. In addition, the apnoea that follows muscular paralysis in the conscious animal may be expected to subsequently contribute to the tachycardia and arrhythmias. The cardiac effects resulting from activation of the sympathetic nervous system by either of these mechanisms should be partially blocked by β-adrenergic antagonists, and this was found to be the case. A complete antagonism would not be expected for 2 reasons. In the first place, the dose of propranolol employed in these studies is probably less than the amount required to produce complete blockade of cardiac β-receptors. Secondly the cardioaccelerator response will involve not only an increased sympathetic discharge to the heart but also a diminution of the resting vagal tone, this latter component being unaffected by propranolol.

Résumé. Les auteurs étudient les différences quantitatives et qualitatives de l'effet du suxamethonium sur la fonction cardiaque chez des chevaux concients et des chevaux soumis à une anesthésie générale. Ils ont aussi contrôlé l'efficacité du propranolol, agent d'arrêt de transmission β-adrénergique, empêchant tout changement dans les fonctions du cœur.

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