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Inhibition by Lysergic Acid Derivatives of Bronchospasm Induced in Guinea Pigs by Serotonin Aerosol

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A new compound l-methyl-lysergic acid butanolamide (UML-491)[1] has been recently recommended and successfully tried in the prophylaxis of migraine attacks (*Sicuteri*, 1959; *Heyck*, 1960), in view of its antiserotonin properties: UML-491 inhibits the serotonin-induced contraction of the smooth fibres of the isolated rat uterus and the serotonin oedema of the rat paw (*Cerletti and Doepfner*, 1958; *Doepfner and Cerletti*, 1958). Whereas UML-491 has not been shown to exert anti-histamine effects in man, it definitely antagonises the effect of the histamine-releasing substance 48/80 (*Sicuteri, Michelacci and Franchi*, 1959).

The aim of the studies reported here was to confirm the antiserotonin action of UML-491 by testing it against the bronchospasm and related asphyctic phenomena which unanesthetized guinea pigs undergo when exposed to 5-hydroxy-tryptamine (serotonin) aerosol inhalation (*Herxheimer*, 1953).

Parallel studies were made of d-lysergic acid diethylamide (LSD-25)[1], 2-bromo-lysergic acid diethylamide (BOL-148)[1] ergotamine tartrate[1] and two antihistamine compounds: mepyramine and trimeprazine.

These drugs were also tested against bronchospasm induced in pigs by histamine aerosol inhalation.

[1] UML-491, LSD-25, BOL-148 and ergotamine tartrate were kindly supplied by Sandoz Ltd., Basle, Switzerland.

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TABLE I

Aerosol with serotonin solution

Drug	Dose (in μg./kg.)	Pre-coma time (in sec.)	Controls Pre-coma time (in sec.)	Drug	Dose (in μg./kg.)	Pre-coma time (in sec.)	Controls Pre-coma time (in sec.)
UML-491	2.5	110	170	LSD-25			
	2.5	130	150				
	2.5	150	100				
	2.5	120	100				
	2.5	120	75				
	2.5	p *	70				
	5	p	100		5	140	120
	5	p	100		5	130	120
	5	p	90		5	120	120
	5	p	80		5	120	110
	5	p	120		5	100	90
	5	100	130		5	100	90
	10	P **	110		10	p	110
	10	P	110		10	p	100
	10	P	100		10	p	100
	10	P	80		10	p	90
	10	P	120		10	p	80
	10	P	p		10	p	60
	20	P	110		20	P	120
	20	P	100		20	P	120
	20	P	80		20	P	130
	20	P	80		20	p	90
	20	P	60		20	p	90
	20	P	60		20	p	60
	50	P	130		50	P	180
	50	P	120		50	P	170
	50	P	110		50	P	85
	50	P	90		50	P	70
	50	P	90		50	P	60
	50	P	80		50	P	p
	100	P	140		100	P	120
	100	P	130		100	P	120
	100	P	100		100	P	100
	100	P	100		100	P	100
	100	P	60		100	P	80
	100	P	60		100	P	70

Pre-coma time is the time elapsing before the animal falls into a coma.

* p = partial protection (animal not in coma but in respiratory distress for 10 minutes).

** P = complete protection for 10 minutes.

All controls, except two exhibiting partial protection, fell into coma within 1 to 3 minutes.

TABLE 1 (continued)

Aerosol with serotonin solution

Drug	Dose (in µg./kg.)	Pre-coma time (in sec.)	Controls Pre-coma time (in sec.)	Drug	Dose (in µg./kg.)	Pre-coma time (in sec.)	Controls Pre-coma time (in sec.)
BOL-148	40	80	100	Ergotamine	100	90	100
	40	80	100	tartrate	100	90	90
	40	70	100		100	80	90
	40	60	90		100	60	70
	40	60	75		100	60	60
	40	60	75		100	60	60
	100	100	120		200	100	80
	100	90	120		200	95	80
	100	p	120		200	80	75
	100	p	90		200	70	70
	100	p	90		200	70	70
	100	p	60		200	60	60
	200	120	160		300	90	110
	200	p	80		300	90	110
	200	p	70		300	80	90
	200	P	140		300	80	80
	200	p	140		300	70	60
	200	p	120		300	60	60
	400	P	110		600	90	180
	400	P	120		600	120	120
	400	P	70		600	60	120
	400	P	90		600	120	110
	400	P	130		600	90	80
	400	P	60		600	70	60
Mepyramine	100	90	100	Trimeprazine	500	120	130
	100	90	80		500	120	130
	100	90	80		500	90	110
	100	80	70		500	p	110
	100	60	60		500	p	110
	100	60	60		500	p	60
	500	90	100		1.5 mg./kg.	p	140
	500	90	100		1.5 mg./kg.	p	140
	500	70	75		1.5 mg./kg.	p	120
	500	70	75		1.5 mg./kg.	p	120
	500	60	75		1.5 mg./kg.	p	80
	500	p	60		1.5 mg./kg.	p	75

Methods

The guinea pigs were exposed to a 1% solution of 5-hydroxytryptamine creatinine sulphate and to a 2‰ solution of histamine hydrochloride given by aerosol inhalation.

The drugs being studied for protection were administered intraperitoneally 30 minutes before aerosol inhalation. In some animals the aerosol administration was repeated 60-90 minutes after the injection.

The aerosol was given simultaneously to a guinea pig injected with the trial drug and to a control guinea pig injected with physiological saline.

Each dose of each drug was repeatedly tested in six guinea pigs of either sex with a body weight between 200 and 300 g.

Aerosol treatment was discontinued at the onset of the asphyctic coma or after 10 minutes if coma did not develop. The degree of tolerance to histamine and serotonin aerosol was evaluated on the basis of cough, restlessness and, more particularly, the onset and intensity of dyspnoea.

The range of protection obtained with the drug was measured by the tolerance exhibited by the guinea pigs to serotonin aerosol inhalation. The protection was considered to be complete if no signs of suffering were elicited during 10 minutes of treatment. The protection was considered to be partial if the guinea pigs were resistant for 10 minutes although they exhibited signs of dyspnoea.

The minimal effective dose was considered to be the dose sufficient to offer partial or complete protection in at least 50% of cases.

Results

Tables I and II show the data regarding the doses of the several drugs tested and the degree of tolerance of the guinea pigs to serotonin and histamine aerosol inhalation.

The following conclusions may be drawn with regard to the antagonism exerted by the drugs investigated on the bronchospasm induced in guinea pigs by serotonin aerosol inhalation:

a) Maximum protection is offered by l-methyl-lysergic acid butanolamide (UML-491) and d-lysergic acid diethylamide (LSD-25). As far as the effective minimal doses are concerned, the activity of UML-491 is estimated to be double that of LSD-25.

b) 2-Bromo-d-lysergic acid diethylamide (BOL-148) protects guinea pigs against serotonin-induced bronchospasm but to a lesser degree than the aforementioned drugs (20 times less effective than UML-491).

c) Ergotamine tartrate in high dosage—as much as 120 times the minimal effective dose of UML-491—does not show any antagonism to serotonin.

d) The antihistamine compound mepyramine does not have any inhibiting effect in the test even when given in relatively high dosage, i.e. sufficient at any rate to protect the animal against the effects of inhalation of a 2‰ histamine aerosol.

TABLE II

Aerosol with 2‰ histamine solution

Drug	Dose (in μg./kg.)	Pre-coma time (in sec.)	Controls Pre-coma time (in sec.)	Drug	Dose (in μg./kg.)	Pre-coma time (in sec.)	Controls Pre-coma time (in sec.)
UML-491	100	180	150	LSD-25	100	170	180
	100	180	150		100	160	120
	100	180	130		100	145	160
	100	170	120		100	120	140
	100	80	120		100	120	180
	100	80	80		100	180	140
	200	120	140		200	110	150
	200	140	135		200	110	140
	200	110	180		200	90	140
	200	120	130		200	60	130
	200	135	100		200	170	160
	200	60	90		200	150	120

e) Trimeprazine may have a protective effect against serotonin-induced bronchospasm. However, the minimal effective dose is 100 times higher than that of UML-491.

f) UML-491 and LSD-25 show no antagonism to histamine even if administered in doses 10-20 times higher than those needed to provide good protection against serotonin aerosol.

Summary

By using the bronchospasm test on the guinea-pig from 5-HT aerosol, the antiserotonin power of some of the lysergic acid derivatives (UML-491, LSD-25, BOL-148) is evident. Moreover, some comparative studies with ergotamine tartrate and synthetic antihistamines (mepyranine and trimeprazine) have been made.

The maximum antiserotonin power is shown by UML-491 and LSD-25 whilst the lower power is given by BOL-148 and trimeprazine. No protection has been shown on the part of lysergic acid derivatives on the guinea-pig under histamine aerosol.

Zusammenfassung

Die serotonin-antagonistische Eigenschaft einiger Lysergsäurederivate (UML-491, LSD-25, BOL-148) wurde beim Meerschweinchen an dem durch Serotonin-Aerosol hervorgerufenen Bronchospasmus untersucht. Ferner wurden vergleichende Untersuchungen mit Ergotamintartrat und mit synthetischen Antihistaminen (Neoantergan und Trimeprazin) durchgeführt.

Die stärkste Anti-Serotoninwirkung zeigten UML-491 und LSD-25, während BOL-148 und Trimeprazin schwächer wirksam waren. Gegen das Histamin-Asthma beim Meerschweinchen waren die Lysergsäurederivate wirkungslos.

Résumé

En utilisant le test du bronchospasme chez le cobaye provoqué par inhalation d'aérosols de sérotonine, l'activité antisérotonine de dérivés de l'acide lysergique (UML-491, LSD 25, BOL-148) a pu être démontrée. De plus, des études comparatives avec le tartrate d'ergotamine et des anti-histaminiques de synthèse (néo-antergan et triméprazine) ont pu être faites.

L'activité anti-sérotonine maxima a pu être constatée avec l'UML-491 et le LSD 25, alors que l'activité la plus faible a été notée avec le BOL-148 et la triméprazine.

D'autre part, aucune protection n'a pu être démontrée de la part des dérivés de l'acide lysergique vis-à-vis du bronchospasme du cobaye provoqué par les aérosols d'histamine.

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