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Inhibition of cholinesterases by complex derivatives of morphine*

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SEVERAL morphine derivatives prepared by Bentley and Hardy[1] from the adduct of thebaine and methyl vinyl ketone are notable for the very low doses required to produce a pharmacological, for example analgesic, response.[2, 3] When a compound has a much greater potency in one biological system than a substance of similar structure, there is a possibility that there may be a marked increase in potency for other seemingly unrelated biological properties possessed by both compounds. The anti-cholinesterase activity of a series of derivatives of morphine has been compared to the similar activity of morphine, nalorphine and levallorphan within this context.

Human blood provided a serum pseudocholinesterase (E.C. 3.1.1.8; Acylcholine Acyl-hydrolase) and a red cell acetylcholinesterase (E.C.3.1.1.7; Acetylcholine acetyl-hydrolase).[4] The change of pH with time due to hydrolysis of acetylcholine in veronal-phosphate buffer pH 8·0 at 25° was used for assay.[4] Where appropriate 1/V was plotted against 1/S and the apparent inhibitor constant determined.[5] Plots for the acetyl-esterase were non-linear.

Degrees of inhibition, apparent inhibitor constants (K_i) for the pseudo-esterase and ED_{50} doses in rats are given in Table 1. The compounds differed in their substituents at N, 3-O and 7C. They constitute a wide range rather than a graded series.

Of the eighteen compounds, seven has ED_{50} doses in rats either as analgesics by the method of Green and Young[6] or analgesic antagonists by the method of Green, Ruffell and Walton,[7] below 50 μg/kg. Seven compounds partially inhibited the pseudo-esterase at 10^{-4} *M* and exceeded morphine in this respect but only two (140 and 53) were in the highly active group. Both are analgesic drugs. None markedly exceeded nalorphine or levallorphan in inhibitory activity at 10^{-4} *M*.

Nine compounds partially inhibited the acetyl-esterase at 10^{-4} *M* and exceeded morphine but not levallorphan in this respect. Of these, five were in the highly active group (285, 99, 140, 320 and 306), including four analgesics and one analgesic antagonist (285).

Two compounds (277 and 252) were inactive at 10^{-4} *M* against both enzymes. The most potent compounds (99 and 140) were also the best inhibitors of the acetyl-esterase but even without details of the differential distribution of a dose in rat tissues it seems reasonable to conclude that anti-cholinesterase activity plays no part in the morphine-like or nalorphine-like activity of these potent compounds.

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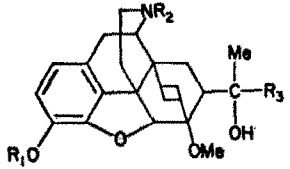
TABLE 1. INHIBITION OF THE CHOLINESTERASES OF HUMAN BLOOD BY MORPHINE DERIVATIVES



Drug	R_1	R_2	R_3	Pseudocholinesterase			Acetylcholin-esterase		ED_{50} s.c. (rats) mg/kg.	
				Inhibition % at		K_i(x10^{-5} M)	Inhibition % at		Analgesic	Analgesic Antagonist
				10^{-3} M	10^{-4} M		10^{-3} M	10^{-4} M		
M99	H	Me	Pr^n	50	0	0·23	—	77, 61*	0·0015	—
M14C	H	Me	$(CH_2)_2{\cdot}CHMe_2$	—	14	—	—	65	0·0076	—
M183	Ac	Me	Pr^n	50, 59	0	0·18	51	0	0·002	—
M53	Me	Me	Pr^n	—	56†	2·8	26	0	0·034	—
M306	H	$CH_2{\cdot}C_3H_5$	C_6H_{11}	0	0	—	26	13	0·042	—
M320	H	$CH_2{\cdot}C_3H_5$	$(CH_2)_2{\cdot}CHMe_2$	0	0	—	47	21	0·055	—
M276	H	$CH_2{\cdot}CH{:}CMe_2$	Pr^n	—	10	3·5	—	41	0·15	—
M288	Me	CH_2-◁ (Me)	C_6H_{11}	—	14	—	—	0	0·62	—
M82	Me	Me	Bu^n	—	0	—	—	10	0·24	—
M285	H	$CH_2{\cdot}C_3H_5$	Me	32	0	0·43	42	20	>100	0·01
M159	H	Allyl	Me	—	0	—	30	12	>100	0·3
M278	Me	$CH_2{\cdot}C_3H_5$	Me	81	0	4·2	26	0	100	0·3
M375	Me	Et	Me	—	15	—	—	0	>100	1·0
M262	Me	Allyl	$CH_2{\cdot}Ph$	—	11	—	—	—	>100	100
M277	Me	Allyl	$CH_2{\cdot}CHMe_2$	—	0	—	—	0	>100	10·5
M252	Me	$CH_2{\cdot}CH{:}CMe_2$	Pr^n	—	0	—	0	0	>100	>20
M294	Me	Allyl	Allyl	—	49	3·7	0	0	—	—
	Morphine			39	19	0·55	82	0	2·1	—
	Nalorphine			—	40	2·0	—	0	—	0·48
	Levallorphan			—	71	2·4	—	80	—	0·30

C_3H_5 = Cyclopropyl.
* 35% at 5×10^{-5}M.
† 62% at 5×10^{-4}M; 14% at 5×10^{-5}M.