Some pharmacological studies with 14-cinnamoyloxycodeinone

SIR,—In a recent communication to the British Pharmaceutical Conference (Buckett, 1964), 14-cinnamoyloxycodeinone was shown to be the most potent of a series of esters of 14-hydroxycodeinone. I now report a comparison of its pharmacological properties with those of morphine.

TABLE 1. THE ACUTE TOXICITY OF 14-CINNAMOYLOXYCODEINONE AND MORPHINE IN MICE

Route	Morphine LD50	14-Cinnamoyloxycodeinone LD50	Ratio (Morphine = 1·0)
Intravenous ..	199 (189–210)	31 (24–39)	6·4
Subcutaneous ..	330 (280–390)	530 (44–636)	0·62
Oral	745 (610–895)	1100 (900–1350)	0·68

The LD50 values are expressed in mg/kg in terms of base.
Limits of error (P, 0·95) are given in parentheses.

Table 1 shows the acute toxicity of 14-cinnamoyloxycodeinone in mice. The intravenous and subcutaneous values for morphine are similar to those determined by Randall & Lehmann (1950). There is a wide separation between LD50 values by intravenous and by other routes for 14-cinnamoyloxycodeinone but not for morphine. This may be due in part to the high lipid solubility of the ester facilitating rapid penetration into the central nervous system. In all instances, death was preceded by catalepsy and respiratory depression.

The analgesic potencies of 14-cinnamoyloxycodeinone relative to morphine in different tests are presented in Table 2. The compound is a potent analgesic

TABLE 2. THE ANALGESIC POTENCY OF 14-CINNAMOYLOXYCODEINONE IN RATS AND MICE

Analgesic test	Species	Route	ED50 mg/kg		Potency ratio (Morphine = 1·0)
			Morphine	14-Cinnamoyloxycodeinone	
Tail pressure*	Rat	s.c.	1·45 (1·1–1·9)	0·023 (0·017–0·03)	64 (43–94)
Tail pressure	Rat	Oral	5·76 (4·4–7·6)	0·036 (0·027–0·048)	160 (109–236)
Hot plate†	Mouse	s.c.	4·0 (3·3–4·7)	0·059 (0·048–0·073)	68 (51–87)
Tail clip‡	Mouse	s.c.	6·55 (4·8–8·9)	0·037 (0·024–0·059)	177 (101–310)

All values are based on measurement at times of maximum analgesic effect and are given in terms of base. Limits of error (P, 0·95) are given in parentheses.
* Buckett, Farquharson & Haining (1964); † Eddy & Leimbach (1953); ‡ Bianchi & Franceschini (1954).

and a comparison of subcutaneous and oral ED50 values shows it to be absorbed from the gastrointestinal tract. The onset (10 min) and duration (30 min) of analgesia after 14-cinnamoyloxycodeinone in mice were shorter than after equiactive doses of morphine, where the onset and duration were 20 and 90 min respectively. The compound was similarly potent in mice subjected to either a mechanical (tail clip) or a thermal stimulus (hot plate) and the analgesia produced by 14-cinnamoyloxycodeinone was more intense and depressant than that seen after morphine. This feature is generally associated with molecules in which a ketone group replaces the phenolic hydroxyl (Braenden, Eddy & Halbach, 1955).

At high doses morphine or 14-cinnamoyloxycodeinone increased the spontaneous activity of mice in a photocell box (Dews, 1953), the new compound being 100 times as potent as morphine subcutaneously. A similar ratio of activity was found for rectal hypothermia in mice after subcutaneous administration; but with a test for gastrointestinal motility in mice (Buckett, Farquharson & Haining, 1964), 14-cinnamoyloxycodeinone had 240 times the

potency of morphine. In an adaptation of a clinical method for assessment of respiratory depression (Campbell, Lister & McNicol, 1964) for anaesthetised dogs, 14-cinnamoyloxycodeinone was found to have 106 times the potency of morphine using the reduction of minute volume under 95% oxygen and 5% carbon dioxide and 90 times when the percentage change in pCO_2 under O_2 breathing was measured. The results of other comparative studies are given in Table 3. This evidence shows that 14-cinnamoyloxycodeinone differed from morphine in its ability to produce catalepsy at doses close to analgesic doses.

TABLE 3. THE RELATIVE POTENCY OF 14-CINNAMOYLOXYCODEINONE IN VARIOUS PHARMACOLOGICAL TESTS IN MICE

Test	Route	ED50 mg/kg		Potency ratio (Morphine = 1·0)
		Morphine	14-Cinnamoyl oxycodeinone	
Hind limb catalepsy	i.v.	> 10	0·066 (0·051–0·089)	>150
Grip on 45° plane	i.v.	> 10	<0·02	>500
Pentobarbitone (25 mg/kg i.p.) potentiation	s.c.	12·8 (11·2–14·8)	0·24 (0·20–0·28)	53
Anti-i.v. leptazol infusion	s.c.	>100	0·68 (0·45–1·03)	>147
Chimney*	s.c.	9·5 (5·9–15·2)	0·07 (0·055–0·09)	135
Lenticular opacity†	s.c.	32·6 (27–40)	0·45 (0·31–0·64)	72
		Index		
"Straub index"‡ (LD50/ED50 Straub tail)	i.v.	7·95	500	

All values are expressed in terms of base. Limits of error (P, 0·95) are given in parentheses.
* Boissier, Tardy & Diverres (1960); † Weinstock (1961); ‡ Shemano & Wendel (1964).

In addition the ability of the animals to remain on an inclined plane was lost. Anticonvulsant activity and barbiturate potentiation were exhibited only at high dosage and in common with all narcotic drugs lenticular opacity was observed.

The finding that the "Straub index" far exceeded that for any drug investigated by Shemano & Wendel (1964) suggested that 14-cinnamoyloxycodeinone would have a high capacity to produce physical dependence.

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