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The relationship between analgesic activity, acute toxicity and chemical structure in esters of 14-hydroxycodeinone

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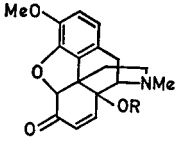
Acylation of 14-hydroxycodeinone with long chain unbranched fatty acids produced compounds of varying analgesic potency, maximal activity being in 14-n-heptoyloxycodeinone. In 14-phenylalkyloxy derivatives maximal analgesic potency was found in 14-cinnamoyloxycodeinone. All codeinone derivatives studied had approximately one-third the duration of morphine in mice. Intravenous and subcutaneous toxicities in mice were generally similar in compounds causing death by convulsions, but differed widely in those causing death by respiratory depression.

IT has recently been shown (Buckett, Farquharson & Haining, 1964) that hydroxylation and subsequent acylation of codeinone at the 14-position produced marked changes in analgesic activity and acute toxicity. Change of the acyl group from acetyl to valeryl gave compounds with increased nalgesic potency and decreased subcutaneous acute toxicity in mice.



It seemed possible that analgesic potency could be enhanced still further in compounds with higher acyl groups at the 14-position. This paper reports on such compounds and on a limited study of the influence of introducing a double bond into the esterifying group.

Methods

Acute toxicity. The LD50 of each compound was determined using albino mice (18–22 g). Water soluble salts were dissolved in 0·9% w/v sodium chloride. Bases were dissolved in either 10% phosphoric acid or 0·1N hydrochloric acid and adjusted to pH 6·0 using 5% w/v sodium bicarbonate solution, then made up to volume with 0·9% w/v sodium chloride. Animals received a dose of 0·2 ml/20 g body weight, either by the intravenous or subcutaneous route. Intermittent observation was continued for 3 hr after injection and mortalities recorded 24 hr later. The LD50 was calculated by the method of Litchfield & Wilcoxon (1949).

Analgesia. Estimates of analgesic potency, peak activity time and duration of action in mice were made using the method of Bianchi &

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Franceschini (1954). Albino mice (18–22 g) were tested for sensitivity to a bulldog artery clip covered with rubber tubing, which was applied to the base of the tail; only those attempting to remove the clip within 15 sec were used. Each compound was administered subcutaneously at three or four dose levels to groups of 10 animals. Animals were tested at 10 min intervals and the proportion in each group which made no attempt to remove the clip within 30 sec was determined. Testing continued until the analgesic effect had terminated, when duration curves could be plotted. The ED50 for analgesia at the time of maximum effect was determined, and the potency relative to morphine calculated by the method of Litchfield & Wilcoxon (1949).

Materials. All compounds were used in the form of bases except 14-cinnamoyloxycodeinone phosphate (R = COCH:CH·Ph) and 14-phenylpropionoxycodeinone hydrochloride (R = $COCH_2CH_2$·Ph); codeine phosphate B.P. and morphine hydrochloride B.P. were used as standards.

Results

Acute toxicity. The LD50 for each compound is given in Table 1. After intravenous administration, death usually occurred rapidly and followed either convulsions or catalepsy and respiratory depression. Death occurred later after subcutaneous injection but the toxic effects were essentially similar. Both intravenous and subcutaneous acute toxicities decreased with the change from codeinone to 14-hydroxycodeinone and through the acetoxy (Krueger, Eddy & Sumwalt, 1943) to the propionoxy compound. The reduced toxicity was particularly marked on converting the 14-hydroxy compound to its acetate (R = COMe). These four compounds produced death by convulsions and the acute toxicities differed little after either subcutaneous or intravenous administration.

Table 1 shows that intravenous toxicity (but not subcutaneous toxicity)

TABLE 1. THE ACUTE TOXICITY OF ESTERS OF 14-HYDROXYCODEINONE IN MICE

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

14-substituent R	Intravenous LD50	Subcutaneous LD50	Toxic effects
None	5·0 (4·2–6·0)	11·0 (9·8–12·3)*	Violent convulsions
–H	11·8 (10·6–13·1)	28 (25–30)*	Convulsions
–COMe	105 (91–121)	127†	Convulsions
–COEt	110 (88–137)	150 (110–190)*	Convulsions
–COPr	66 (58–75)	>500	Respiratory depression
–COBu	38 (28–52)	495 (410–600)*	Respiratory depression
$-COC_5H_{11}$	9·0 (7·8–10·4)	>500	Respiratory depression
$-COC_6H_{13}$	26 (21–32)	>500	Respiratory depression
$-COC_7H_{15}$	40 (32–50)	>500	Respiratory depression
$-COC_9H_{19}$	61 (51–72)	>500	Respiratory depression
$-COC_{11}H_{23}$	120 (112–128)	>500	Respiratory depression
$-COCH_2$·Ph	71 (65–77)	300*	Respiratory depression
$-COCH_2$·CH_2·Ph	45 (39–52)	300	Convulsions
–COCH = CH·Ph	31 (24–39)	200	Respiratory depression
–COCH = CH·Me	41 (36–47)	200	Respiratory depression

* Buckett, Farquharson & Haining (1964).
† Krueger, Eddy & Sumwalt (1943).

increased in the series n-butyrate ($R = COC_3H_7$), n-valerate ($R = COC_4H_9$), and n-hexoate ($R = COC_5H_{11}$). Further increase in the length of the ester group up to n-lauroyloxy ($R = COC_{11}H_{23}$) decreased the intravenous toxicity. In all compounds with an ester group higher than propionate, death followed acute respiratory depression irrespective of the route of administration.

All the 14-phenylalkoxy derivatives tested were more toxic intravenously than subcutaneously. Death was due to acute respiratory depression except with the 14-β-phenylpropionate ($R = COCH_2 \cdot CH_2 \cdot Ph$) which produced convulsions. Replacing the single bond between the methylene groups in the side-chain with a double bond ($R = COCH : CH \cdot Ph$), increased the acute toxicity and changed the mode of death. With the crotonate ($R = CO \cdot CH : CH \cdot Me$) rather than the cinnamate ($R = CO \cdot CH : CH \cdot Ph$) the toxicity did not alter significantly and the manner of death was similar.

Analgesia. Esterification of 14-hydroxycodeinone produced derivatives with enhanced analgesic potency (Table 2). Esterification to give 14-

TABLE 2. THE ANALGESIC ACTIVITY OF ESTERS OF 14-HYDROXYCODEINONE IN MICE AFTER SUBCUTANEOUS ADMINISTRATION

[All results are expressed in terms of base. Limits of error (P = 0·95) are given in parentheses].

14-substituent R	Relative analgesic potency (morphine = 1·0)	Onset of peak activity (min)	Duration of analgesic ED50 (min)
None	Not determined due to toxic excitation		
-H			
-COMe	4·0 (2·27–7·05)	10	30
-COEt	18·8 (12·6–28·3)	10	30
-COPr	28·7 (16·0–51·5)	10	30
-COBu	38·8 (22·1–68·4)	10	30
$-COC_5H_{11}$	47·2 (26·5–84·6)	10	30
$-COC_6H_{13}$	60·1 (39·0–92·3)	10	30
$-COC_7H_{15}$	5·1 (2·9–8·9)	10	50
$-COC_9H_{19}$	1·12 (0·56–2·21)	10	30
$-COC_{11}H_{23}$	0·034 (0·023–0·051)	10	30
$-COCH_2Ph$	52 (33–82)	10	30
$-COCH_2CH_2Ph$	115 (78–168)	10	30
$-COCH = CH \cdot Ph$	177 (101–310)	10	30
$-COCH = CH \cdot CH_3$	31 (19–48)	10	30
Standard drugs			
Morphine	1·0	20	90
Codeine	0·49 (0·35–0·7)	10–20	40

acetoxycodeinone produced a compound with four times the potency of morphine. Further increases in the length of the acylating group at position 14 gradually increased the analgesic potency. The maximum potency (sixty times that of morphine) was obtained with 14-heptoyloxycodeinone ($R = COC_6H_{13}$). Still further increases reduced the analgesic activity until with 14-lauroyloxycodeinone ($R = COC_{11}H_{23}$) a compound having only one-thirtieth the potency of morphine was obtained.

Buckett & others (1964) have previously shown that benzoylation at the 14-position reduced analgesic potency but the introduction of a single methylene group between the ester carbonyl and terminal phenyl gives a compound ($R = CO \cdot CH_2 \cdot Ph$) of high analgesic potency. A further

methylene group (R = CO·CH_2·CH_2·Ph) increased the activity still more to give a compound having over one hundred times the potency of morphine and the introduction of a double bond (R = CO·CH:CH·Ph) did not diminish this activity. With the crotonate (R = CO·CH:CH·Me) the potency was equivalent to that of the corresponding saturated straight chain compound (R = COPr). In these two pairs of compounds a double bond in the 14-substituent has no effect on analgesic potency or duration of action. Both the onset and duration of analgesia of all these compounds in mice are shorter than either morphine or codeine (Table 2).

Discussion

Beckett, Casy, Harper & Phillips (1956) postulated an analgesic receptor surface consisting of a charged anionic site separated from a flat surface by a cavity. The flat surface accommodates the aromatic position of the analgesic molecule on the basis of Van der Waals forces and the cavity allows close contact between drug and receptor in a third dimension.

The compounds in this series would appear to fit such a receptor at the anionic site, the flat surface and possibly at the cavity. Since the 14-substituent consists of a flexible acyl grouping, its position relative to the codeinone nucleus is a matter for conjecture at the present time.

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The paper was presented by THE AUTHOR.