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The analgesic and related properties of 6-deoxy-6,6-ethylenedioxy-7,8-dihydro-14-hydroxycodeine hydrochloride

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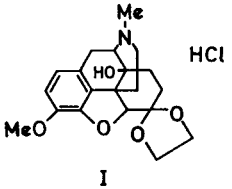
The compound 6-deoxy-6,6-ethylenedioxy-7,8-dihydro-14-hydroxycodeine hydrochloride possesses analgesic potency greater than either morphine or codeine when examined by a variety of methods in mice and rats. Compared with these two analgesics the compound showed greater separation between effective analgesic doses and doses producing inhibition of gastrointestinal motility or death, but not for mydriasis or respiratory depression. Some evidence for a lower addictive liability than morphine is discussed.

A NUMBER of cyclic ketals derived from 14-hydroxydihydrocodeinone have been synthesised as potential analgesic drugs by Lester, Petrow & Stephenson (1965). Routine biological screening indicated that the most active of these was the 6-ethylene ketal. The pharmacology of this compound (I; 6-deoxy-6,6-ethylenedioxy-7,8-dihydro-14-hydroxycodeine hydrochloride, BDH 5499) is now reported.



I

Methods

General. Female albino mice, about 20 g, from the BDH colony, male Sprague-Dawley rats, about 160 g, from Animal Supplies Ltd., cats of either sex, 2·6–4·3 kg, and adult male rabbits, 2·4–3·4 kg, of various breeds, were used. Unless otherwise stated, the compounds were administered at varying dose levels with a dose ratio of 2·0 to groups of twenty animals. Drugs were administered in 5% (w/v) acacia or physiological saline; dose volumes were 25 ml/kg orally or subcutaneously and 10 ml/kg intravenously or intraperitoneally for mice and rats, and 5 ml/kg orally for rabbits. ED50 or LD50 values and their confidence limits ($P = 0.95$) were estimated by the method of Litchfield & Wilcoxon (1949) where appropriate.

Acute toxicity. The acute oral and subcutaneous toxicities of BDH 5499, morphine hydrochloride and codeine phosphate were compared in mice using a dose ratio of 1·5. The number of animals dying within seven days was recorded.

Analgesic activity. The oral and subcutaneous analgesic potencies of BDH 5499 and morphine hydrochloride and the oral potency of codeine

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phosphate were compared using the tail pinch, hot plate and phenylquinone-induced writhing methods in mice. Oral potencies were also assessed by a radiant heat method in rats.

The criterion of analgesia in the tail pinch method (Bianchi & Franceschini, 1954) was the absence of any attempt to remove an artery clip applied for 30 sec 1 cm from the base of the tail 30 min after administration of the compound. Only animals which previously made repeated attempts to remove the clip within 15 sec were used.

The criterion of analgesia in the hot plate method of Eddy & Leimbach (1953) was the absence of any sign of discomfort within 30 sec when the animal was placed 30 min after dosing on a hot plate maintained at 55–56°.

The writhing test was essentially as described by Siegmund, Cadmus & Lu (1957). The criterion of analgesia was the total absence of writhing during the 15 min after an intraperitoneal injection of phenylquinone (2 mg/kg) given 30 min after the drug.

The radiant heat method was based on that described by D'Amour & Smith (1941). Ten rats were used at each dose level. The criterion of analgesia was the absence of the typical tail flick response within 10 sec of the application of radiant heat from a 6 V, 45 W lamp 1 hr after dosing.

The development of tolerance was assessed by giving a single oral dose on five consecutive days in each week for three weeks. The presence of analgesia was determined daily by the hot plate method 30 min after dosing.

The possibility of antagonism by nalorphine was examined by adminstering varying doses of nalorphine hydrobromide subcutaneously to groups of 10 mice. BDH 5499, morphine hydrochloride or codeine phosphate were given at the same time at dose levels producing a near-maximal effect in animals not treated with nalorphine. Analgesia was determined by the hot plate method.

Straub index. The method was essentially as described by Shemano & Wendel (1964). The numbers of mice with the tail raised through at least 90° (Straub effect) within 2 min of intravenous administration of the drugs were determined as also were the numbers dying within 24 hr. The Straub index is given by the ratio LD50 : ED50.

Mydriatic activity. Pupil diameters of mice were determined under constant illumination and magnification with a binocular dissecting microscope before, and 30 min after giving BDH 5499, morphine hydrochloride or codeine phosphate orally. An increase in pupil diameter of 50% was recorded as a positive response.

Antitussive activity (Domenjoz, 1952). Square wave stimuli (width 10 msec, frequency 5/sec, intensity 2–6 V) were applied at 5 min intervals to the cut central end of the superior laryngeal nerve of cats anaesthetised with pentobarbitone sodium (37–58 mg/kg intraperitoneally). Movements of the diaphragm were recorded with an isometric lever attached by a thread to the abdominal wall. BDH 5499 was given by way of the femoral vein.

Respiratory depression. Thirty min after oral dosing, groups of 10

mice immobilised individually in paper cones were placed inside a desiccator containing self-indicating soda lime ("Carbosorb," BDH). The desiccator was connected to a float recorder writing on a smoked drum and then allowed to equilibrate to a constant temperature by complete immersion in a water-bath at 27°. The time required by each group to take up a constant amount of oxygen was determined, an increase in time being a measure of the degree of respiratory depression. Five groups of ten mice were used at each dose of BDH 5499 or morphine; five groups were given the vehicle only. The dose of each drug producing a 20% increase compared with the control in the time taken to consume the given volume of oxygen was estimated graphically.

The effect of BDH 5499, morphine hydrochloride and codeine phosphate on the respiratory minute volume of restrained conscious rabbits was determined using Gaddum's (1941) apparatus. Ten animals were used at each dose. When the animals had become accustomed to the apparatus, measurements were made before and 60 min after the drugs were given orally. The dose of drug producing a 30% decrease in respiratory volume compared with a group of animals given the vehicle alone was estimated graphically.

Effects on the gastrointestinal tract. The effect of BDH 5499, morphine hydrochloride and codeine phosphate on defaecation by mice was examined using a method based on that of Lou (1949). The number of faecal pellets eliminated by each group of mice during the 24 hr following oral administration was determined and compared with that of a group receiving the vehicle alone. The dose of each compound required to produce a 50% decrease in the number of faecal pellets was estimated graphically.

The effect on gastrointestinal propulsion was also determined using the method described by Macht & Barba-Gose (1931). Twenty-five min after oral administration of the above compounds or the vehicle alone, 0·5 ml of a 10% w/v suspension of charcoal in 5% w/v acacia was administered by stomach tube. Ten min later the animals were killed, the gastrointestinal tract dissected out and the distance which had been traversed by the charcoal measured. Ten animals were used for each dose with a dose ratio of 3·0. The amount of each compound producing a 50% decrease in the distance travelled was estimated graphically.

The effects of the three compounds on smooth muscle *in vitro* were examined using rabbit duodenum and guinea-pig ileum preparations. Short segments of rabbit duodenum were suspended in oxygenated Tyrode solution at 37° and the contractions recorded with a frontal writing lever. The compounds were added to the bath in saline, and were washed out after 90 sec contact. Short segments of guinea-pig ileum were suspended in oxygenated Tyrode solution at 32°. The compounds were given 30 sec before the various agonists. In some experiments, the peristaltic reflex was recorded (Trendelenburg, 1917) and the compounds were introduced 150 sec before eliciting the reflex.

Cardiovascular effects. Cats were anaesthetised with chloralose (80 mg/kg intravenously) following induction with ether. Mean arterial

pressure was recorded from the carotid artery with a mercury manometer. BDH 5499 was administered via the femoral vein.

Isolated rabbit hearts were perfused with Ringer-Locke solution at 37°, the amplitude and rate of ventricular beat being recorded on a smoked drum. BDH 5499 was dissolved in saline and added to the perfusing fluid just before its entry into the coronary vessels.

Results

Acute toxicity. There is little difference in acute toxicity between BDH 5499 and morphine hydrochloride after oral or subcutaneous administration. Codeine phosphate is 2·5 times as toxic as BDH 5499 by both routes (Table 1).

TABLE 1. ACUTE TOXICITY OF BDH 5499, MORPHINE HYDROCHLORIDE AND CODEINE PHOSPHATE IN MICE

Compound	Oral route		Subcutaneous route	
	LD50 and confidence limits (P = 0·95), mg/kg	Relative toxicity	LD50 and confidence limits (P = 0·95), mg/kg	Relative toxicity
BDH 5499	1470 (1246–1734)	1·3	590 (454–767)	1·1
Morphine hydrochloride	1900 (1552–2325)	1·0	620 (504–763)	1·0
Codeine phosphate	580 (491–684)	3·3	260 (218–309)	2·4

Analgesic activity. The results are summarised in Table 2. By mouth BDH 5499 is 10–17 times as potent as codeine phosphate and 3–4 times as active as morphine hydrochloride. It is 0·6–2·3 times as potent as morphine hydrochloride after subcutaneous administration. In contrast to morphine, which is more active by injection, BDH 5499 appears to be

TABLE 2. ANALGESIC ACTIVITY OF BDH 5499, MORPHINE HYDROCHLORIDE AND CODEINE PHOSPHATE

Test	Compound	Oral route		Subcutaneous route	
		ED50 and confidence limits (P = 0·95), mg/kg	Relative activity	ED50 and confidence limits (P = 0·95), mg/kg	Relative activity
Hot plate (mice)	BDH 5499	10·0 (7·0–14·3)	3·4	7·0 (4·5–10·8)	0·6
	Morphine hydrochloride	34·0 (24·3–47·6)	1·0	4·0 (3·0–5·4)	1·0
	Codeine phosphate	100·0 (69·9–143·0)	0·3		
Tail pinch (mice)	BDH 5499	2·9 (2·1–4·1)	4·1	2·6 (2·0–3·4)	2·3
	Morphine hydrochloride	11·8 (8·3–16·8)	1·0	6·1 (4·3–8·6)	1·0
	Codeine phosphate	38·0 (28·1–51·3)	0·3		
Writhing (mice)	BDH 5499	0·34 (0·24–0·49)	3·4	0·52 (0·39–0·69)	0·9
	Morphine hydrochloride	1·15 (0·78–1·70)	1·0	0·58 (0·36–0·65)	1·0
	Codeine phosphate	5·8 (3·9–8·7)	0·2		
Radiant heat (rats)	BDH 5499	6·2 (4·3–9·0)	2·7		
	Morphine hydrochloride	17·0 (11·0–26·3)	1·0		
	Codeine phosphate	82·5 (47·2–144·5)	0·2		

as active orally as subcutaneously. After repeated administration there is essentially no difference between the three compounds either in the extent or rate at which tolerance develops (Fig. 1). The analgesic action of all three compounds is readily prevented by simultaneous administration of nalorphine hydrobromide; 2 mg/kg antagonised the analgesia produced by 30 mg/kg BDH 5499 or 80 mg/kg morphine hydrochloride and 4 mg/kg antagonised 200 mg/kg codeine phosphate.

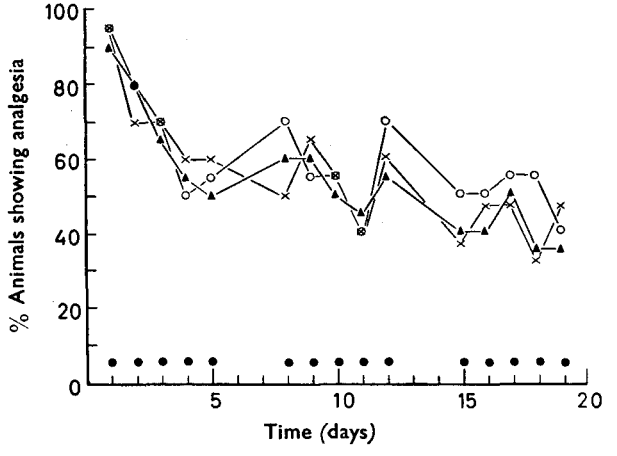

FIG. 1. The development of tolerance to the analgesic action of BDH 5499, 30 mg/kg/day (○—○), morphine hydrochloride, 80 mg/kg/day (▲—▲) and codeine phosphate, 200 mg/kg/day (X—X) administered orally on the days marked ●.

Straub index. The Straub tail effect is only apparent at near-toxic dose levels of BDH 5499, Straub index 2·1, and codeine phosphate, Straub index, 1·2, whereas with morphine hydrochloride the effect is evident at comparatively low dose levels, Straub index 19·6. The indices for codeine and morphine are in reasonable agreement with those obtained by Shemano & Wendel (1964).

Mydriatic activity. BDH 5499 is 9·8 and 2·4 times as active as codeine phosphate and morphine hydrochloride respectively. [ED50 (with confidence limits, P = 0·95) mg/kg: BDH 5499, 7·7 (5·2–11·3); morphine hydrochloride, 18·5 (13·7–25·0); codeine phosphate, 75·0 (52·8–106·4)]. Lenticular opacity was not observed, in contrast to the observations of Weinstock, Stewart & Butterworth (1958).

Antitussive activity. BDH 5499 appeared to have well marked antitussive activity at dose levels of 0·5–1·0 mg/kg intravenously. Although direct comparisons with morphine and codeine were not made, it is likely that BDH 5499 has a similar order of activity to codeine phosphate (David, Leith-Ross & Vallance, 1957).

Respiratory depression. BDH 5499 is approximately four times as potent as morphine hydrochloride in causing respiratory depression in mice (7·5 : 34·0 mg/kg) and rabbits (7·3 : 28·2 mg/kg). In rabbits, it is approximately 36 times as potent as codeine phosphate (7·3 : 263 mg/kg).

Effect on the gastrointestinal tract. BDH 5499 has similar potency to morphine hydrochloride in decreasing the number of faecal pellets by 50% over 24 hr in mice (48 : 52 mg/kg) and is 3·1 times as potent as codeine phosphate (149 mg/kg). In rats, however, BDH 5499 has only 0·4 times the potency of morphine hydrochloride (19·1 : 8·3 mg/kg) and 2·5 times that of codeine phosphate (46·8 mg/kg) in decreasing movement of a charcoal meal by 50%.

BDH 5499 caused a slight decrease in tone of the isolated rabbit duodenum at a concentration of 60 μg/ml. Similar effects were seen with codeine phosphate (6 μg/ml). Morphine hydrochloride (240 μg/ml) was without effect. BDH 5499 (0·05–50 μg/ml) produced varying degrees of inhibition of contractions of the isolated guinea-pig ileum due to histamine (0·05 μg/ml) and barium chloride (30 μg/ml) but never complete suppression. Contractions due to acetylcholine (0·25 μg/ml) were unaffected. When the peristaltic reflex was elicited by an increase in intraluminal pressure, BDH 5499 (1·3 μg/ml) produced almost complete inhibition. A similar degree of inhibition was produced by morphine hydrochloride (0·15 μg/ml) and codeine phosphate (3·3 μg/ml).

Cardiovascular effects. BDH 5499 produced a slight fall (15 mm Hg) in mean arterial pressure of the anaesthetised cat at a dose level of 6 mg/kg i.v. This effect was prevented by prior administration of mepyramine maleate (0·3 mg/kg i.v.). BDH 5499 (8 mg) caused a slight reduction in amplitude of the isolated rabbit heart but no change in rate.

Discussion

The analgesic properties of BDH 5499 have been demonstrated in the mouse and the rat using a variety of stimuli (chemical, mechanical, thermal conduction, and thermal radiation). Although a structural analogue of codeine, it possesses greater potency than morphine. The compound also possesses other properties associated with narcotic analgesics, namely, the Straub tail effect, rapid development of tolerance to its analgesic action, respiratory depression, cough suppression and reduced gastrointestinal motility.

In the evaluation of a narcotic analgesic, particular attention must be paid to the degree of separation between analgesic activity and the associated side-effects since the severity of the latter will be an important factor in determining the clinical utility of the compound. The results indicate that BDH 5499 possesses a greater separation between effective analgesic doses and those inhibiting gastrointestinal function than either codeine or morphine, and the ratio of the lethal to the analgesic dose is also greater. BDH 5499 does not, however, show a markedly greater separation between analgesic and respiratory depressant or mydriatic doses.

The Straub index for BDH 5499 is particularly interesting since Shemano & Wendel have suggested that compounds showing little or no separation between lethal doses and doses producing the Straub effect (i.e. possessing a low Straub index) are likely to be only minimally or mildly addicting.

In contrast, BDH 5499 has been shown to be capable of suppressing withdrawal symptoms in morphine-dependent monkeys and would thus appear to have high physical dependence capacity (personal communication from Dr. G. A. Deneau). Nevertheless, since the dose required to produce suppression of withdrawal symptoms was eleven times that of an equivalent dose of morphine, it seems unlikely that addiction would develop as rapidly as with morphine, particularly in view of the greater analgesic potency of BDH 5499.

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