Interaction of Δ^9-tetrahydrocannabinol and cannabidiol on intestinal motility in mice

There are few data that describe the effects of cannabis on gastrointestinal motility *in vivo*. Masur, Märtz & Carlini (1971) and Drew, Miller & Wikler (1972) have reported that Δ^9-tetrahydrocannabinol (THC) produces a depression of defaecation in rats which had previously been found to have a high index of defaecation. Drew & others (1972) were also able to show a dose-dependent effect for Δ^9-THC on this parameter.

The effect of cannabinoids on the rate of passage of a charcoal meal in mice was first reported by Dewey, Harris & Kennedy (1972) who found that Δ^9-THC was at least ten times less potent than morphine, although a dose-dependent effect to the cannabinoids was not shown. Recently, Chesher, Jackson & others (1973) demonstrated dose-dependent depressive effects on the passage of a charcoal meal in mice with Δ^9-THC, Δ^8-THC, and three cannabis extracts. Δ^9-THC was equipotent with Δ^8-THC and was six times less potent than morphine. Cannabidiol was inactive. We now report on the effects of cannabinoids on intestinal motility in mice and describe an interaction between cannabidiol and Δ^9-THC.

Cannabidiol, cannabinol and Δ^9-THC were suspended in a solution of lissapol-dispersol (ICI) (Whittle, 1964) and propylene glycol so that the final concentration of propylene glycol was 5%. Female mice (SW strain, 17–30 g) were starved overnight (17–21 h) and allowed free access to water up to the time of the experiment. The cannabinoids were administered by gavage (0·2 ml dose volume/20 g body weight) 1 h before death, whilst a constant dose of 0·2 ml charcoal meal (Chesher & others, 1973) was administered to each mouse 15 min before death, and the distance travelled by the charcoal meal was expressed as a percentage of the total length of the intestine as measured for each mouse, from pylorus to ileo-caecal junction. The mean of this estimation for the control group was taken as 1 and the values for each in the dosed groups expressed as a percentage of the control value. The dose-response curves were analysed by the method of Litchfield & Wilcoxon (1949) and comparisons made by Student's *t*-test.

Cannabinol and Δ^9-THC both exhibited a parallel dose-dependent depression of intestinal motility (Table 1). Δ^9-THC was 8 times more potent than cannabinol in this test and cannabidiol was inactive in doses up to 50 mg kg^{-1}. The effects of various combinations of the cannabinoids are shown in Table 2. Of particular interest is the combination of Δ^9-THC and cannabidiol which had a greater depressant effect than Δ^9-THC alone. Since cannabidiol at the dose used (10 mg kg^{-1}) was itself inactive, the interaction with Δ^9-THC appears to be synergistic rather than additive. A further indication of the nature of this interaction is given in the results of experiment 2 (Table 2). In this experiment, the combination of 10 mg each of Δ^9-THC and cannabidiol kg^{-1} produced a greater depression of intestinal motility than did 20 mg Δ^9-THC

Table 1. *Effect of Δ^9-THC, cannabidiol and cannabinol on the passage of a charcoal meal in mice.*

Δ^9-THC mg kg^{-1} (n)*	Distance travelled % of control	Cannabinol mg kg^{-1} (n)	Distance travelled % of control	Cannabidiol mg kg^{-1} (n)	Distance travelled % of control
0 (35)	100·0 ± 3·1	0 (30)	100·0 ± 3·2	0 (50)	100·0 ± 2·9
5 (5)	68·5 ± 2·2†	10 (10)	84·2 ± 2·7†	10 (15)	82·8 ± 2·4†
10 (29)	65·2 ± 2·0†	25 (8)	76·5 ± 2·4†	20 (25)	102·6 ± 3·0
20 (25)	50·7 ± 1·6†	50 (20)	72·3 ± 2·3†	50 (20)	107·4 ± 3·2
40 (5)	35·5 ± 1·1†	70 (20)	61·8 ± 2·0†		

* n = number of animals.
† $P < 0.05$ when compared to the control.

Table 2. *Effect of Δ⁹-THC, cannabinol, cannabidiol and various combinations on the passage of a charcoal meal in mice.*

Drug and dose mg kg^{-1}	Distance travelled by meal: % of control (n)* Experiment 1			Experiment 2		
Control	(10)	100·0 ± 5·1	a	(20)	100·0 ± 3·9	h
Δ⁹-THC, 10	(10)	76·2 ± 3·9	b	(15)	64·9 ± 2·6	i
Δ⁹-THC, 20				(20)	55·0 ± 2·2	j
Cannabinol, 10	(10)	82·7 ± 4·8	c			
Cannabidiol, 10	(10)	93·3 ± 4·7	d	(5)	85·0 ± 3·3	k
Cannabidiol, 20				(25)	99·5 ± 1·0	l
Δ⁹-THC + cannabinol 10 + 10	(10)	77·5 ± 3·9	e			
Δ⁹-THC + cannabidiol 10 + 10	(16)	48·5 ± 2·4	f	(25)	49·7 ± 2·0	m
Δ⁹-THC + cannabidiol 10 + 40				(11)	32·3 ± 1·8	n
Cannabinol + cannabidiol 10 + 10	(10)	98·9 + 5·0	g			

* n = number of animals.

† Some of these results were compared by Students *t*-test: ab, ac, ef, fg, hi, hj, lm, hk, mn, $P < 0{\cdot}05$; jm, ad, hl, $P > 0{\cdot}05$.

kg^{-1}. The combination of 10 mg Δ⁹-THC with 40 mg cannabidiol kg^{-1} produced a depressant effect equal to about 40 mg Δ⁹-THC kg^{-1}.

These findings suggest that the effect of a cannabis extract on intestinal motility is influenced by the ratio of the cannabinoids (Δ⁹-THC, cannabidiol and cannabinol) it contains. An interaction between cannabinoids has also been shown by Krantz, Berger & Welch (1971) who reported an antagonism by cannabinol of the Δ⁹-THC induced prolongation of pentobarbitone anaesthesia in mice. The interaction of Δ⁹-THC and cannabidiol on the duration of pentobarbitone anaesthesia in mice has been reported by Jackson, Chesher & Starmer (1973). In this case, both Δ⁹-THC and cannabidiol were active and the interaction was considered to be additive, rather than synergistic.

This report, whilst demonstrating the potentiating effect of cannabidiol on Δ⁹-THC induced depression of the passage of a charcoal meal in mice, also emphasises the importance of defining the composition of cannabis extracts in terms of all the major cannabinoids rather than of Δ⁹-THC alone.

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