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Evidence for a pharmacokinetic interaction between ibuprofen and meptazinol in the mouse

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Of a variety of non-steroidal anti-inflammatory drugs administered concurrently with meptazinol (p.o.), only ibuprofen potentiated the antinociceptive response (mouse, hot-plate test) to the opioid. In addition, the brain tritium concentration of mice given [^{3}H]meptazinol (p.o. or i.v.) was significantly raised by the oral administration of ibuprofen. It is argued that the interaction between these drugs is pharmacokinetic in nature, due probably to an action of ibuprofen on the biotransformation of meptazinol.

Introduction

Some formulations containing centrally active opioid analgesics and non-steroidal anti-inflammatory agents have been prescribed for the control of mild-to-moderate pain. The theoretical advantages of this approach are that: (a) with idiopathic pain there is a greater likelihood of effective analgesia if two drugs are used which modify different parts of the mechanisms involved in pain induction and perception than if a single treatment is used, and (b) if the analgesic effects are additive or supra-additive, lower doses of the two components (hence less severe side effects) should be required to achieve a particular degree of analgesia than would be necessary if either drug were used alone. There is little published evidence to support these contentions but Woodbury & Fingl (1975) have reported that aspirin and opioid analgesics produce additive analgesic effects in man.

During routine pre-clinical investigations, results were obtained from a writhing procedure which suggested a supra-additive antinociceptive interaction in the mouse between the new opioid analgesic agent, meptazinol, and ibuprofen – but not other non-steroidal anti-inflammatory drugs. Both individual drugs were active in this test but subsequent studies, the results of which form the basis of the report, utilized a hot-plate procedure. As anti-inflammatory drugs do not affect responses to thermal noxious stimuli, it was considered that any potential effect of ibuprofen on meptazinol might be easier to demonstrate by this means.

Methods

Antinociception experiments. In all experiments, the reaction latencies of mice placed on a hot-plate (Woolfe & MacDonald 1944) maintained at 55 °C were measured immediately before dosing and at 30, 60 and 90 min thereafter. In pilot experiments various doses of meptazinol (p.o.) were used to estimate the dose required to induce a doubling of the control reaction latency and the time of peak antinociceptive activity. In the first interaction experiment, the following treatment groups (n = 10) were examined (mg kg^{-1}): meptazinol 40; meptazinol 80; meptazinol 40 in combination with ibuprofen 240; ibuprofen 240 and vehicle p.o. The same treatments were used in subsequent experiments except that ibuprofen was replaced by each of the anti-inflammatory agents at the doses shown in Table 1, in turn. In each experiment, mice from the five treatment groups were tested in a balanced order to militate against any temporal influence on the results. Also, the observer was unaware of the treatments each mouse had received.

The reaction latency of each mouse before treatment was subtracted from that obtained at each time after treatment. The mean changes in latency so obtained for each single drug treatment group were compared with the appropriate change of the vehicle control group using Student's *t*-test. The same test was used to compare the effects of meptazinol alone (40 mg kg^{-1}) with those obtained when meptazinol was given in combination with the anti-inflammatory agents.

Brain concentration of meptazinol. Groups of 50 mice were treated orally with 40 mg kg^{-1} [^{3}H]meptazinol (50 μCi/mouse) alone or in combination with 240 mg kg^{-1} ibuprofen. Thirty minutes later the animals were killed by cervical dislocation, their brains (minus cerebellum, pons and medulla) homogenized in 10 ml ice-cold Tris buffer and centrifuged at 20 000 rev min^{-1} for 5 min. Aliquots of the supernatant from each brain

preparation were removed and the concentration of tritium was measured. Similar experiments (n = 10–20) were performed using [^{3}H]meptazinol alone and in combination with several of the other listed anti-inflammatory agents.

In a subsequent study, mice were given 240 mg kg^{-1} ibuprofen or vehicle p.o. 30 min before 5 mg kg^{-1} [^{3}H]meptazinol i.v. Half the animals from each group were killed 5 min after the administration of meptazinol and the remainder 25 min later. Brain levels of tritium were obtained as described above.

Materials. The animals were Tuck albino T/O strain mice (21–25 g). The drugs were: aspirin Na (Monsanto), diclofenac Na (Geigy), fenoprofen Ca (Lilly), fentiazac Na (Wyeth), flurbiprofen (Boots), ibuprofen (Boots), ketoprofen (Bayer), meptazinol HCl (Wyeth) and paracetamol (Winthrop). For oral administration they were suspended in 0·5% hydroxypropylmethylcellulose in distilled water at concentrations such that 10 ml kg^{-1} supplied the required doses. For i.v. administration meptazinol was dissolved in 0·9% NaCl solution (dose volume: 5 ml kg^{-1}); [^{3}H]meptazinol (50·2 Ci nM^{-1}) was supplied by Amersham International.

Results

Antinociception. Meptazinol induced a dose-dependent increase in the reaction latency of mice placed on the hot-plate. The estimated dose to induce a doubling of the pre-treatment latency (usually 5–6 s) was 40 mg kg^{-1} p.o. With the exception of paracetamol at one recording time (60 min after dosing), none of the anti-inflammatory agents alone modified the reaction latency (cf. vehicle controls) significantly.

In the studies involving the concurrent administration of meptazinol and anti-inflammatory drugs, a significant interaction was observed only with ibuprofen. Thus, the increase in latency induced by 40 mg kg^{-1} meptazinol plus 240 mg kg^{-1} ibuprofen was approximately double that evoked by 40 mg kg^{-1} meptazinol alone at 30, 60 and 90 min after treatment and approximately equal to that evoked by 80 mg kg^{-1} meptazinol (Table 1). Although in some experiments a smaller yet significant interaction was recorded with 120 mg kg^{-1} ibuprofen, the lowest dose at which a consistent interaction was observed was 240 mg kg^{-1}.

The only other mixture to induce an increase in reaction latency significantly larger than that to meptazinol alone, was that containing 400 mg kg^{-1} paracetamol – 60 min after treatment. The difference between the mean latencies (4·2 s and 7·8 s with and without paracetamol respectively) at this time, however, was approximately equal to the increase in latency evoked by paracetamol alone (3·4 s). Thus, the effects of meptazinol and paracetamol were additive.

Brain concentration of meptazinol. The mean brain concentration of tritium of mice given [^{3}H]meptazinol plus ibuprofen orally was significantly larger (43%) than that of mice given [^{3}H]meptazinol alone (Table 2). The distribution of the values of both groups (n = 50) did not differ significantly from normal and the coefficients of variation were 34 and 31 respectively for the data from the groups with and without coadministered ibuprofen. The concurrent oral administration of diclofenac, flurbiprofen or paracetamol with [^{3}H]meptazinol failed to modify the brain concentration of tritium.

Pretreatment with 240 mg kg^{-1} ibuprofen p.o. evoked a 49% increase in brain tritium concentration 30 min after the i.v. injection of [^{3}H]meptazinol com-

Table 1. Antinociceptive effect of meptazinol alone and in combination with various anti-inflammatory agents (NSAI) in the mouse hot-plate test.

Drugs (dose, mg kg^{-1} p.o.)	Increase in response latency (sec ± s.e.m.) 30 min after following treatments				
Meptazinol plus:	Vehicle	NSAI	NSAI + Mept (40)	Mept (40)	Mept (80)
Aspirin (400)	0·5 ± 0·7	1·5 ± 1·0	3·0 ± 1·3	5·5 ± 1·4	10·7 ± 2·2
Diclofenac (30)	1·1 ± 1·0	−0·5 ± 0·7	5·4 ± 1·3	5·0 ± 1·3	11·7 ± 1·6
Fenoprofen (300)	1·0 ± 0·6	0·2 ± 0·4	6·5 ± 1·6	4·4 ± 0·8	9·0 ± 1·2
Fentiazac (12)	−0·5 ± 0·6	0·8 ± 0·7	6·4 ± 1·6	4·1 ± 1·1	10·5 ± 2·6
Flurbiprofen (40)	1·0 ± 1·0	1·0 ± 1·0	3·1 ± 0·9	5·0 ± 1·3	11·7 ± 1·6
Ibuprofen (240)	1·3 ± 0·7	0·6 ± 0·4	12·2 ± 2·6*	6·0 ± 0·6	12·2 ± 1·5
Ibuprofen (120)	0·7 ± 0·6	1·1 ± 1·3	7·6 ± 1·0	6·1 ± 1·0	13·0 ± 3·0
Ketoprofen (20)	1·2 ± 0·8	1·2 ± 0·7	7·0 ± 1·6	5·6 ± 0·9	13·4 ± 3·1
Paracetamol (400)	0·0 ± 0·3	1·3 ± 0·6	7·6 ± 1·0	5·0 ± 1·0	9·4 ± 1·7

Reaction latency of mice before treatment was approx 6 s. Each line represents a single, balanced, blind experiment. In all experiments increases in latency following meptazinol (40 and 80 mg kg^{-1}) were significantly greater ($P < 0·05$) than vehicle controls.

At 60 and 90 min post treatment (data not shown), the only NSAI effect significantly different from vehicle control was that to paracetamol at 60 min (see text). Only NSAI + mept (40) effects significantly different from mept (40) were those to ibuprofen (240) + mept (40) at 60 and 90 min.

*$P < 0·5$ cf. mept (40).

Table 2. Brain levels of tritium following [^{3}H]meptazinol alone and in combination with anti-inflammatory agents.

Anti-inflammatory agent (mg kg^{-1} p.o.)	Protocol	Brain tritium concentration (d min^{-1} mg^{-1} ± s.e.m.) [^{3}H]Meptazinol alone	[^{3}H]Meptazinol + anti-inflam.
Ibuprofen (240)	a	69·2 ± 3·0	99·1 ± 4·8***
Ibuprofen (240)	b_1	234 ± 16	238 ± 15
	b_2	89·3 ± 6·3	133 ± 7·7***
Diclofenac (30)	a	68·9 ± 5·9	73·4 ± 3·5
Flurbiprofen (40)	a		71·0 ± 6·5
Fentiazac (12)	a	62·8 ± 4·1	74·7 ± 6·1
Paracetamol (400)	a	75·8 ± 6·3	76·6 ± 3·5

Protocol a: Mice given 40 mg kg^{-1} meptazinol p.o. alone and in combination with anti-inflammatory agent p.o. 30 min before mice were killed and brain excised.

Protocol b: Mice given 5 mg kg^{-1} meptazinol i.v. 30 min after 240 mg kg^{-1} ibuprofen p.o. Mice killed 5 (b_1) or 30 min (b_2) after injection of meptazinol.

***$P < 0.001$ cf meptazinol alone.

pared with that observed in vehicle pretreated controls. Measurements taken 5 min after the i.v. injection, however, were virtually identical for the two groups (Table 2).

Discussion

The results of these experiments confirmed that non-steroidal anti-inflammatory drugs are not effective antinociceptive agents in procedures involving heat as the noxious stimulus. Also, as the antinociceptive response to meptazinol was enhanced by the oral coadministration of ibuprofen, it was considered that the supra-additive interaction recorded between these drugs in preliminary experiments involving a writhing test may have been due to a potentiating action of ibuprofen on meptazinol. It is pertinent to note, however, that the effective dose of ibuprofen in the present study was approximately an order larger than the lowest to affect the incidence of writhing significantly.

Meptazinol is extensively metabolized in man and other species to the glucuronide conjugate (Franklin et al 1976). This metabolite, however, unlike the parent compound, is not found in appreciable quantities in the brain. Thus, it is likely that the substantial amount of tritium present in the brains of mice given [^{3}H]meptazinol in the present study was associated with the parent drug. As both the brain concentration of tritium and the antinociceptive response to meptazinol were enhanced by the oral administration of ibuprofen, it was assumed that the interaction was probably pharmacokinetic, rather than pharmacodynamic, in nature. In addition, it was deduced that the anti-inflammatory agent affected the metabolism or excretion of meptazinol, rather than its absorption from the gastrointestinal tract, because an elevation of brain tritium levels was induced after the i.v. as well as after the p.o. administration of [^{3}H]meptazinol in mice given ibuprofen p.o. A modification by ibuprofen of the distribution of meptazinol to the brain was discounted because the brain levels of tritium 5 min after the i.v. injection of [^{3}H]metpazinol, unlike those recorded 25 min later, were not affected by the prior administration of ibuprofen.

Less than 5% of meptazinol is excreted unchanged (see review Stephens et al 1978). In consequence it was thought improbable that the observed results could have been due predominantly to an inhibitory effect of ibuprofen on the excretion of meptazinol. It was concluded, therefore, that the most probable cause of the interaction between ibuprofen and meptazinol was a subtle effect of ibuprofen on the biotransformation of meptazinol.

The doses of the other anti-inflammatory agents used in this study were in proportion to their maximum recommended daily clinical doses, relative to ibuprofen at 240 mg kg^{-1} p.o. As all the 2-arylpropionic acids, including ibuprofen, are subject to similar metabolic processes (hydroxylation and conjugation), it is not clear why ibuprofen was the only one to modify responses to meptazinol.

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