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Indomethacin and cognitive function in healthy elderly volunteers

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1 Cognitive function was studied after single and multiple doses of indomethacin (I) and matched placebo (P) in 20 healthy elderly volunteers using a double-blind crossover design.

2 Arousal, attention, integration, coordination, memory and mood were investigated using a battery of psychomotor tests and the Hospital Anxiety and Depression Scale. Assessments were performed before and after the first and last doses of a 7 day course of medication.

3 Critical flicker fusion threshold fell by a mean of 1.96% on indomethacin compared with a 1.13% rise on placebo 5 h after the first dose ($P = 0.029$). A beneficial effect on choice reaction time latency ($P = 0.012$) was seen both after acute and continuing administration of indomethacin. Performance at the most discriminating level (level 3) of the paired word association test was significantly better following 8 days of treatment with indomethacin in the younger (55–65 year-old) age group ($P = 0.001$).

4 There was no significant difference in performance on the symbol-digit substitution test and the continuous attention task. No change was seen in hospital anxiety and depression scale scores.

5 These results suggest that performance on tests of sensorimotor coordination and short term memory may improve in healthy volunteers following indomethacin administration, whereas tests of attention and psychomotor speed remain unaffected. However, further controlled studies in rheumatic patients are needed to evaluate fully the psychomotor effects of indomethacin and other NSAIDs in clinical practice.

Keywords indomethacin cognitive function

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently associated with adverse effects in several body systems. Neurological effects, most commonly headache and dizziness, are well recognised and confusion and psychotic symptoms may occur after overdose of some agents [1, 2]. There have also been anecdotal reports of adverse cognitive effects [3, 4]. Such effects may have particular significance for the elderly in whom cognitive impairment is common.

Previous prospective studies have shown minor effects after acute dosage, mostly in healthy volunteers [5–11]. However, the studies have been of short duration [5–10], have used only small numbers of subjects [5, 8, 11], have not studied the elderly specifically, have been inadequately controlled [8, 12], or have been confounded by the simultaneous use of other psychoactive agents [8]. The present study was undertaken to determine whether indomethacin, the NSAID most frequently reported to affect CNS function, produces measurable cognitive effects in the elderly under appropriate experimental conditions, and to assess the role of age in vulnerability to such effects.

Methods

Subjects

Twenty subjects, ten each from the age groups 55–65 years and over-65 years, were recruited from a panel

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of healthy elderly research volunteers. Subjects were free of arthritis or chronic pain, psychiatric illness, peptic ulceration or dyspepsia and had no history of adverse reactions or contraindications to NSAIDs. None had been taking NSAIDs in the previous 2 weeks, anticoagulants or medications known to affect cognitive function. A Hodkinson Abbreviated Mental Test was performed at screening to exclude pre-existing cognitive dysfunction (score < 7/10).

Study design

The study followed a placebo-controlled, double-blind cross-over design. Two 7 day study periods were separated by an interval of 7 days. Stratified randomisation ensured that equal numbers took active medication and placebo first within each age group.

Measures of psychomotor function

A battery of five automated psychomotor tests together assessing arousal, attention, coordination, memory, and central integration was administered at each occasion [13]. The tests were administered in varying order by a single observer under low-level artificial lighting and in silence. The test battery took approximately 30 min to administer and included the following:

Choice reaction time (CRT) [14] This test assesses attention and sensorimotor coordination. The mean latency (CRT-P) and total reaction time (CRT-T) in seconds over 30 responses were recorded and the movement time (CRT-M) taken as the difference between these. Only CRT-P and CRT-M results were analysed.

Critical flicker fusion threshold (CFFT) (modified from [15]). This measures arousal and central integration. The mean of five observations in each direction (alternating) was recorded.

Continuous attention task (CAT) [16] A test comprising 240 patterns including 40 repetitions was used. Correct (CAT-C) and incorrect (CAT-I) responses were recorded and an Error Index calculated by the formula: Error Index = (1 − CAT-C/40) + (CAT-I/100) [17].

Symbol-digit substitution test (SDST) [18] This test involves attention, coordination, and response speed. A test duration of 90 s was used. Total responses (SDST-T) and the proportion incorrect (SDST-I) were analysed.

Paired word association test (PWAT) (modified from [19]). This is a test of verbal memory. Different sets of words were used on each occasion. Only the results for the pairs of unassociated words (level 3) were analysed (score/9) because almost all responses at other levels were correct.

The CRT and CFFT were administered using the Leeds Psychomotor Tester, and the CAT, SDST and PWAT via a BBC microcomputer.

Mood assessment

The hospital anxiety and depression scale (HADS) [20] was administered with each set of psychomotor tests in order to assess whether any effects seen might have been due to mood changes.

Study procedure

Before commencing the study subjects were introduced to the psychomotor tests and practised them until their performance reached a plateau. In each subject this was achieved during a single visit at the end of which variability between performances was less than 10%. Alcohol and caffeine-containing beverages were proscribed from midnight on each test day, and subjects fasted until after dosing.

In each study period subjects took 25 mg indomethacin or matched placebo three times daily for 7 days with a final (22nd) dose on the last day. Psychomotor tests and the HADS were administered on the first and last days of each period, before, 2 h and 5 h after dosing. Pre-dose testing commenced at 08.30–09.00 h and doses were given at 09.00–09.30 h.

Compliance with medication was assessed by inspection of empty tablet containers and by a venous blood sample for indomethacin assay taken approximately 5.5 h after dosing on the final day of each period.

Each subject gave their written consent to participation after receiving a full explanation of the study. The study was approved by the Ethics Committee of Bromley Health Authority.

Statistical analysis

For CRT and CFFT the proportional changes from baseline scores on indomethacin were compared with those on placebo at each subsequent test occasion by paired-difference *t*-tests. The analysis of SDST-T and level 3 PWAT results was similar but used the absolute change from baseline. For the HADs results indomethacin-placebo differences in change from baseline at each time point were analysed by the one-sample Wilcoxon signed-rank test.

In order to look for age group and treatment order effects the results from all the tests of psychomotor function were also analysed by multiple regression using the change (absolute for SDST, PWAT and HADS; proportional for CRT and CFFT) from baseline score as the dependent variable and treatment, age group, test occasion, treatment order and a treatment-treatment order interaction term as independent variables.

The CAT-C has a strong 'ceiling' effect and the CAT-EI and SDST-I have strong 'floor' effects. Therefore for these tests, absolute changes from baseline were analysed solely by multiple regression with the baseline score as an additional independent variable.

Results

Subjects

Eight men and 12 women aged 59–73 years (mean 66) were recruited. The 55–65 year-old group comprised nine women and one man aged 59–65 years (mean 62.2) and the over-65 group three women and seven men aged 66–73 years (mean 69.1). Only one subject, in the over-65 group, was taking any prior medication (nifedipine SR 10 mg twice daily). All subjects had AMT scores of 8/10 or more (14 scored 10/10). Empty tablet containers were returned at the appropriate visit by all the subjects. Indomethacin was undetectable in samples from three subjects at the end of the indomethacin phase; levels in other subjects were 0.15–1.24 mg l^{-1}. Since the immediately preceding dose was taken under supervision and the plasma half-life of indomethacin is very variable between individuals, the negative assays do not necessarily imply non-compliance.

Psychomotor performance

Mean (s.d.) scores for each test are given in the tables, and the figures display mean ± s.e. mean changes from baseline scores on indomethacin and placebo for CRT, CFFT and PWAT.

Choice reaction time Latency (CRT-P) was reduced on indomethacin to a maximum of 6.62% below baseline before dosing on day 8 (Figure 1). The indomethacin-placebo difference was significant overall (P = 0.012) although not at individual time points taken separately. There was no significant difference in movement time (CRT-M) (P = 0.652) (Table 1).

Critical flicker fusion threshold There was a significant increase in CFFT on placebo overall (P < 0.001) and also at each time point (Figure 2). After the first dose there was a mean fall of 1.96% on indomethacin at 5 h compared with a rise of 1.13% on placebo (P = 0.029). CFFT had risen by 4.59% prior to dosing on day 8 on placebo but only by 0.35% on indomethacin (P = 0.0041).

Indomethacin-placebo differences were also significant (P < 0.001) for each age group when these were analysed separately.

One subject (number 17, over-65 group) had changes from baseline opposing and much greater than those in other subjects, both on indomethacin and placebo, largely due to a very high baseline in the placebo phase, and was eliminated from the analysis. However, whilst inclusion of this subject erased any significant differences between indomethacin and placebo at individual time points, the overall difference shown by multiple regression remained (P = 0.001).

Paired word association test Overall, level 3 scores were significantly higher on indomethacin (P = 0.014) (Figure 3, Table 2). Analysis of each age group separately showed this to be due to an increase in correct responses, particularly after chronic dosing, in the younger (55–65 year-old) group (P = 0.001). The maximum difference in scores was 2.4 points more than placebo 5 h after dosing on day 8 (P = 0.022). There was no significant drug effect in the

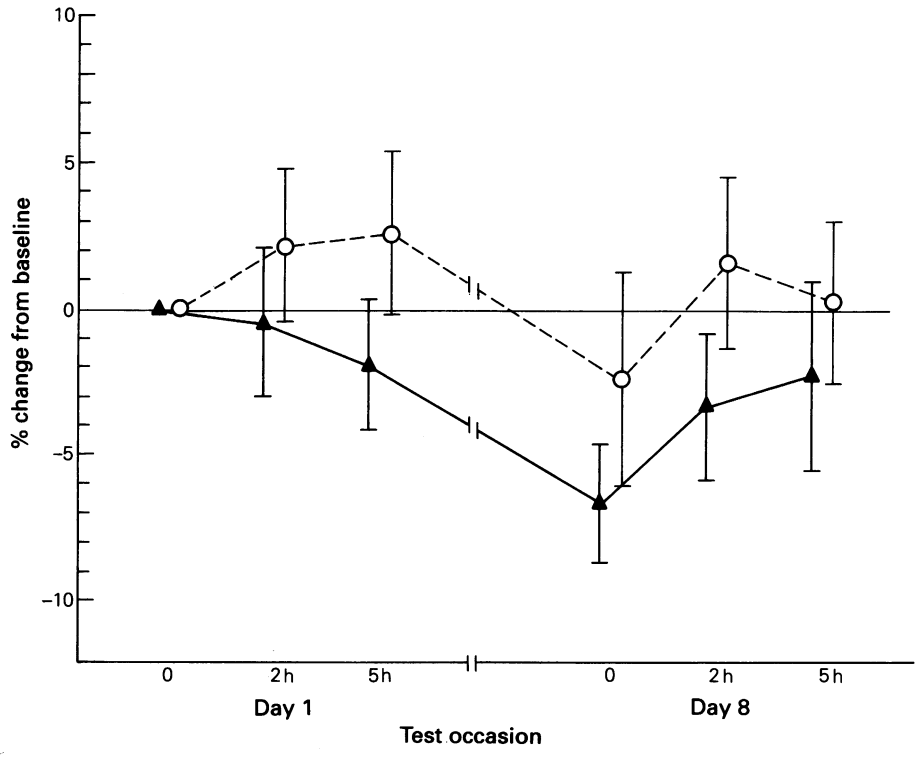

Figure 1 Mean (± s.e. mean) proportional change in Choice Reaction Time latency (CRT-P) in 20 healthy elderly subjects receiving indomethacin and placebo over 1 week in a double-blind crossover study (P = 0.012). (Solid line indomethacin, dotted line placebo.)

Table 1 Critical flicker fusion threshold and choice reaction time. Mean (s.d.) values in healthy elderly volunteers receiving indomethacin (I) and placebo (P) for 1 week in a double-blind crossover study

	CFFT (Hz) (n = 19)		*CRT-P (s)* (n = 20)		*CRT-M (s)* (n = 20)	
Time	*I*	*P*	*I*	*P*	*I*	*P*
Day 1						
Pre-dose	28.2 (2.8)	27.7 (2.9)	0.426 (0.060)	0.413 (0.057)	0.278 (0.051)	0.284 (0.061)
+ 2 h	27.7 (2.5)	28.1 (2.7)	0.425 (0.091)	0.420 (0.059)	0.296 (0.068)	0.280 (0.066)
+ 5 h	27.6 (2.7)	28.0 (2.9)	0.415 (0.048)	0.420 (0.049)	0.288 (0.066)	0.275 (0.067)
Day 8						
Pre-dose	28.2 (2.6)	28.9 (2.9)	0.395 (0.049)	0.401 (0.071)	0.255 (0.049)	0.277 (0.066)
+ 2 h	28.2 (2.4)	28.6 (2.5)	0.409 (0.053)	0.419 (0.078)	0.266 (0.057)	0.277 (0.061)
+ 5 h	28.1 (2.8)	28.5 (2.8)	0.413 (0.067)	0.412 (0.059)	0.270 (0.061)	0.270 (0.059)

CFFT = critical flicker fusion threshold, CRT-P = choice reaction time latency, CRT-M = choice reaction movement time.

Table 2 Paired word association test. Mean (s.d.) scores (at level of no association between words) in healthy elderly volunteers receiving indomethacin (I) and placebo (P) for 1 week in a double-blind cross-over study

	All subjects (n = 19)		*55–65 Group* (n = 10)		*Over-65s* (n = 9)	
Time	*I*	*P*	*I*	*P*	*I*	*P*
Day 1						
Pre-dose	6.3 (2.0)	6.8 (2.2)	5.6 (2.3)	7.4 (1.9)	7.1 (1.5)	6.3 (2.4)
+ 2 h	5.7 (1.8)	6.2 (1.9)	5.7 (1.8)	6.8 (2.0)	5.7 (2.0)	5.7 (1.8)
+ 5 h	5.8 (1.9)	6.8 (1.5)	6.2 (2.0)	6.7 (1.8)	5.4 (1.9)	7.0 (1.1)
Day 8						
Pre-dose	6.4 (2.1)	5.9 (1.8)	6.6 (2.4)	6.4 (1.9)	6.3 (1.9)	5.5 (1.6)
+ 2 h	6.5 (1.5)	6.5 (2.1)*	7.0 (1.3)	7.2 (1.6)	6.1 (1.6)	5.7 (2.3)*
+ 5 h	6.7 (1.6)	6.1 (1.6)	6.6 (1.8)	6.0 (1.7)	6.8 (1.4)	6.2 (1.5)

*Placebo phase data missing for one subject.

over 65s (see Figure 3c). The age groups did not have significantly different baseline scores (by ANOVA).

One subject (number 11, over-65s) was found to have consistently outlying results and was eliminated from the analysis. However, this subject was not in the group displaying an indomethacin/placebo difference and when they were included only the difference for the study group as a whole was abolished and the principal findings were unaffected.

No significant changes were seen in either the SDST or CAT (Table 3). No effects of treatment order were found for any of the psychomotor function tests and there were no differences between the age groups except in the PWAT as described.

Hospital anxiety and depression scale There was no significant difference between indomethacin and placebo for either the anxiety or the depression scores.

Clinical effects

Symptoms were reported by seven subjects during the indomethacin phase, three others on placebo (none reported symptoms in both phases), and one between phases. On indomethacin, headaches were reported by four subjects, one a known migraine victim, giddiness by one and 'fuzziness' 'wooziness' (during sport) or a 'cotton wool' sensation after capsule ingestion by one each. The headaches lasted from 10 min to 4.5 h and all were of mild intensity except in the migraine victim. Transient constipation and diarrhoea were also reported by one subject each on indomethacin. On placebo, one subject had a mild headache lasting for a day and one experienced dyspepsia. Another subject had low back pain in the placebo phase but this was after strenuous physical activity (gardening). One subject reported transient non-specific abdominal discomfort, salivation and drowsiness beginning 3 days after finishing indomethacin but before commencing placebo. All the subjects completed the study.

Discussion

We have shown a shortening of choice reaction time latency without a change in movement time, and, in the younger age group, an improvement in level 3 paired word association test scores on indomethacin. Also, CFFT was significantly lower on indomethacin than on placebo, although there was only a small and transient fall from baseline. These effects occurred without any change in mood.

These results agree in part with previous work but

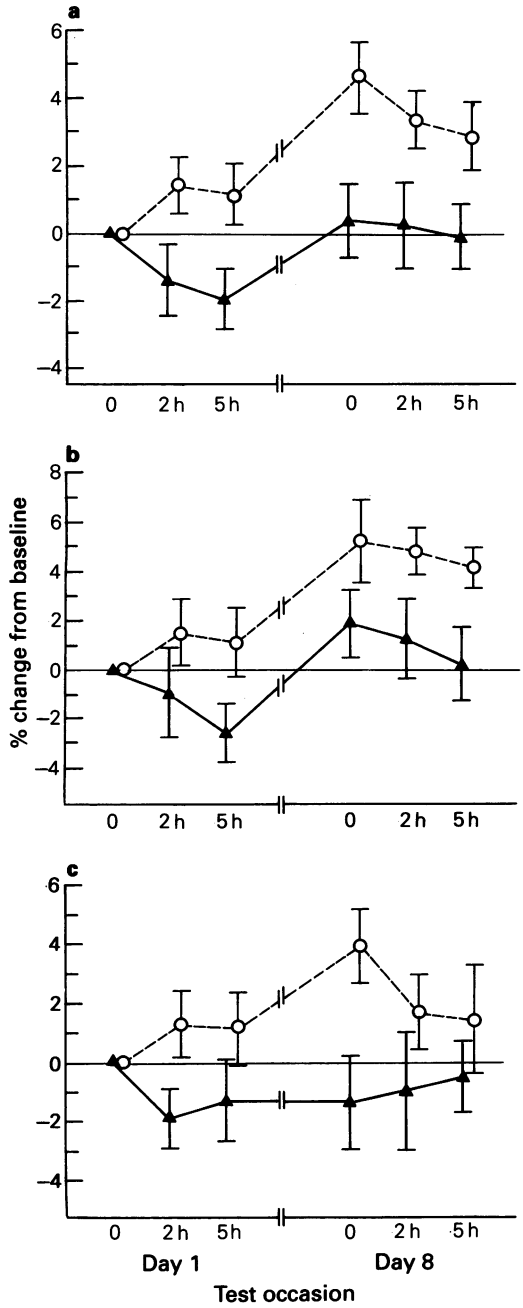

Figure 2 Mean (± s.e. mean) proportional change in Critical Flicker Fusion Threshold (CFFT) in healthy elderly subjects receiving indomethacin and placebo over 1 week in a double-blind crossover study; (a) whole study group, $n = 19$ ($P < 0.001$); (b) 55–65 year-old group, $n = 10$; (c) over-65 year-old group, $n = 9$. (Solid line indomethacin, dotted line placebo.)

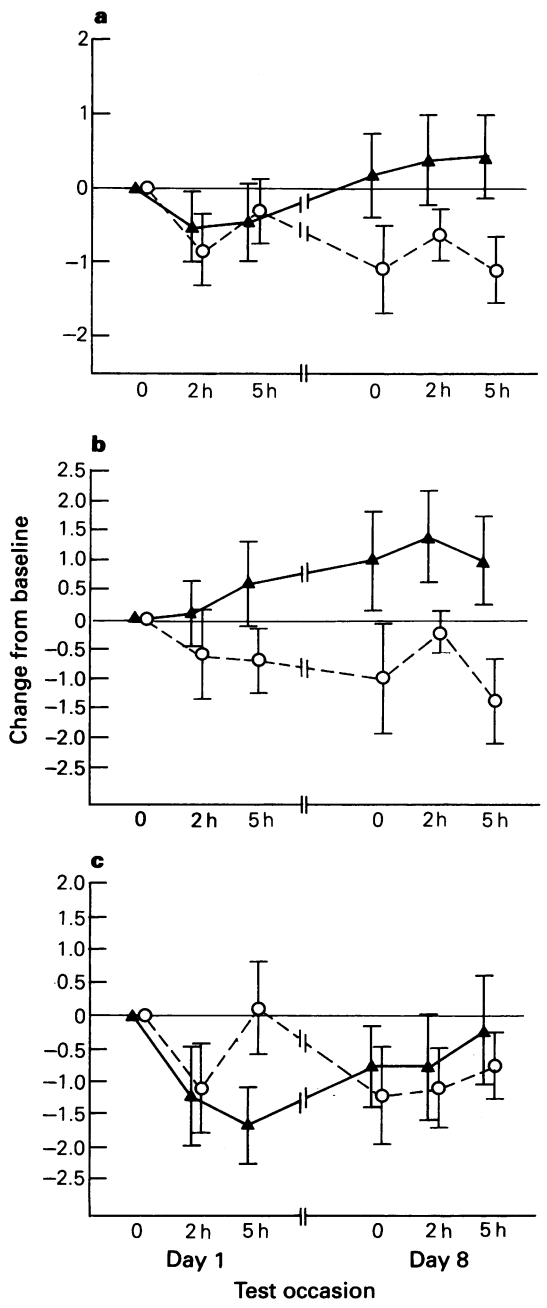

Figure 3 Mean (± s.e. mean) changes in Paired Word Association Test (PWAT) level 3 (no association) scores in healthy elderly subjects receiving indomethacin and placebo over 1 week in a double-blind crossover study; (a) whole study group, $n = 19$ ($P = 0.014$); (b) 55–65 year-old group, $n = 10$ ($P = 0.001$); (c) over-65 year-old group, $n = 9$ (not significant). (Solid line indomethacin, dotted line placebo.)

there are some important differences. In a cross-over study using a small group of patients with rheumatic diseases, Pullar *et al.* [11] found a weak inverse correlation between choice reaction time latency and blood indomethacin concentration after 5 days' dosing, although comparison with placebo showed no significant reduction in this parameter. Neither was any change seen after 2 days' treatment in the rheumatoid arthritis patients studied by Saarialho-Kere *et al.* [10]. Previous studies in volunteers [7, 8] have failed to show any effect on CRT latency, but these studies used respectively only one or two doses of indomethacin and that by Minocha *et al.* [8] was not placebo-controlled. Using a longer dosing period (and a larger subject group than [8]), we have demonstrated a beneficial effect on CRT latency (sensorimotor coordination) both after acute and continuing administration of the drug.

Similarly, our observation of improved performance at the most discriminating level of PWAT (level 3) in the younger study group following continuing administration of indomethacin contrasts with the finding of enhanced impairment of visual memory

Table 3 Symbol-digit substitution test (SDST) and continuous attention task (CAT). Mean (s.d.) scores in 20 healthy elderly volunteers receiving indomethacin (I) and placebo (P) for 1 week in a double-blind cross-over study

Time	*SDST-T* Total responses		*SDST-I* % incorrect	
	I	*P*	*I*	*P*
Day 1				
Pre-dose	41.2 (6.2)	40.1 (6.3)	2.9 (4.3)	2.9 (5.5)
+ 2 h	39.8 (5.3)	39.7 (5.2)	3.8 (5.7)	3.0 (4.5)
+ 5 h	41.2 (5.4)	41.0 (6.8)	4.8 (7.2)	3.7 (7.7)
Day 8				
Pre-dose	41.8 (5.3)	42.5 (6.0)	3.1 (3.2)	2.9 (5.2)
+ 2 h	41.8 (6.3)	41.6 (5.9)*	2.5 (2.7)	2.9 (2.7)*
+ 5 h	41.2 (5.4)	42.6 (7.1)	1.3 (2.8)	1.7 (2.9)
	CAT Correct responses		*CAT* Error index†	
	I	*P*	*I*	*P*
Day 1				
Pre-dose	37.0 (3.0)	37.3 (2.5)	0.100 (0.099)	0.098 (0.086)
+ 2 h	37.3 (3.1)	36.3 (3.6)	0.092 (0.102)	0.113 (0.102)
+ 5 h	36.6 (3.0)	36.4 (2.8)*	0.108 (0.097)	0.108 (0.085)*
Day 8				
Pre-dose	36.8 (3.7)	36.7 (3.0)	0.100 (0.104)	0.098 (0.092)
+ 2 h	36.7 (2.9)	36.6 (3.7)*	0.101 (0.080)	0.099 (0.103)*
+ 5 h	36.5 (3.4)	36.7 (3.6)	0.106 (0.101)	0.095 (0.102)

†Error index = (1 − CAT-C/40) + (CAT-I/100) [17].
*Placebo phase data missing for one subject.

and reduced impairment of auditory-verbal memory by alcohol after pre-treatment with indomethacin in a study which was not double-blind and contained no placebo group [8]. Although the possibility of a Type I error must be acknowledged, it is unlikely that both sensorimotor coordination and short-term memory could have been similarly affected.

Several other workers have found a reduction of CFFT both in volunteers [5, 9] and patients [10, 11]. In the study by Pullar *et al.* [11] this effect was seen only in those subjects who had not taken NSAIDs recently. However, the exact significance of the CFFT result is not clear. Whilst we found CFFT on indomethacin to be lower than on placebo, this is mostly accounted for by a rise on placebo and the only change on indomethacin was a minor fall (much less than 1 s.d.) after initial dosing. Although the initial familiarisation session was designed to minimise any learning effects during the actual study, these cannot be wholly excluded and the rise in CFFT on placebo could represent such an effect. However, no evidence of a learning effect was seen in the other psychomotor tests. Also, this threshold is subject to many influences and this limits its validity [21]. The CFFT has been used primarily as a test of arousal [22] but, in keeping with other studies [9, 10], we found no acute or continuing drug effects on other measures of arousal or attention. These observations suggest that attention, arousal and psychomotor speed are not affected by acute or chronic indomethacin administration.

Age appears to influence at least one of these drug effects, that on verbal memory. There was no difference in baseline PWAT scores between the age groups, so this result is unlikely to be due to a difference in test sensitivity between the groups. Although subject's sex was not controlled for and the age groups did have strong opposing sex biases, when sex was entered into the regression analysis, it was found to have no independent effect, and we therefore conclude that the difference between the study groups was due to their age.

We have made no attempt to correlate the effects seen with measured drug levels. Whilst this would be interesting, the indomethacin assays were intended only to monitor compliance with the medication. Under these circumstances the risk of reaching erroneous conclusions renders further analysis inappropriate.

Side effects were more frequent during the indomethacin phase. That this may have unblinded subjects cannot be ruled out. However, headache, the commonest symptom, is frequent among our volunteer panel when attending the unit and not regarded by them as unusual. Also, the one subject who guessed that he was taking indomethacin in phase one due to dyspepsia was subsequently found to have been on placebo.

Possible mechanisms of action were not the subject of this investigation. They may include direct drug effects such as have been suggested for indomethacin-induced headache and dizziness [23], or indirect effects through, for example, changes in cerebral blood flow.

Studies of the psychomotor effects of indomethacin and other NSAIDs in patients with rheumatic diseases have been more equivocal [10–12, 24]. A lowering of CFFT in rheumatic disease patients has been shown acutely after indomethacin administration [10, 11], but not after multiple dosing [11]. As already discussed, although one study showed an inverse relationship between indomethacin concentration/dose and both CRT latency and total CRT after repeated administration [11], this study and another [10] found no significant difference from placebo, and neither was an effect seen with tenoxicam [24]. A slight impairment in performance in the digit-symbol substitution test has also been observed [9].

Rheumatic diseases themselves and any associated pain and mood disturbances may modify the psychomotor effects of NSAIDs and may account for some of the observed differences between healthy volunteers and patients. It is also possible that NSAIDs may contribute to a feeling of wellbeing by CNS mechanisms, as well as by controlling the arthritic process, as demonstrated by the improvement in some aspects of psychomotor performance seen in this study. However, further controlled studies of rheumatic patients are needed to evaluate fully the psychomotor effects of indomethacin and other NSAIDs in clinical practice.

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