Cerebral blood flow and indomethacin drug levels in subjects with and without central nervous side effects

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- 1 Central nervous system (CNS) side effects are observed during treatment with all non-steroidal anti-inflammatory drugs (NSAIDs) but their effects are more common during treatment with indomethacin.
- 2 The aim of the study was to elucidate the mechanism of the CNS related side effects of indomethacin. Two groups were obtained, one with ($n=11$), and one without ($n=7$), CNS symptoms. Cerebral blood flow was measured in these groups with Doppler equipment, indomethacin levels with h.p.l.c. and CNS symptoms graded on a VAS scale.
- 3 Blood flow was reduced by 18–30% and was most marked 60 min after dose and did not differ between the two groups. The maximum CNS effect coincided with indomethacin peak levels 60–70 min after dose. These results could implicate that CNS symptoms may be related to indomethacin levels in sensitive patients.

Keywords indomethacin central nervous system side-effects
blood concentrations cerebral blood flow

Introduction

Side effects from the central nervous system (CNS) can be observed during treatment with all non-steroidal anti-inflammatory drugs (NSAIDs) in about 5% of the patients. This effect is often claimed to be related to inhibition of prostaglandin synthesis. If so, it is surprising to find that CNS side effects are far more common during indomethacin treatment, as all NSAIDs are potent inhibitors of prostaglandin syntheses. Wennmalm *et al.* (1981) studied cerebral blood flow (CBF) in healthy volunteers before and during treatment with indomethacin. In this group of asymptomatic subjects CBF was reduced by 35% without affecting the metabolic rate of oxygen.

To further elucidate the CNS effects of indomethacin we have investigated CBF in two groups of subjects, one with and one without CNS effects. CBF has been related to symptoms from the CNS and indomethacin drug levels in plasma. We postulated different responsiveness in symptomatic compared with asymptomatic subjects.

Methods

Healthy subjects were given a single suppository of indomethacin (100 mg) at daytime in a screening procedure. Two groups were chosen, one (group A), 11

subjects, with side-effects thought to be related to CNS such as headache, vertigo, tinnitus, feeling of faintness etc. and one (group B), seven subjects, free from any side-effects. Subjects that did not fit clearly into either group were excluded from the study.

At least 4 weeks apart from the screening procedure the subjects were given another suppository of indomethacin concentrations were recorded immediately thereafter and followed for 2 h (test I). At 15 min intervals recording of CNS related side-effects, indomethacin concentrations and blood flow measurements were performed. The severity of the CNS symptoms were registered by the subjects on a 100 mm horizontal visual analogue scale (VAS) with 'No symptoms' on the left end of the scale and 'Maximal symptoms' on the right end of the scale.

During the investigation the subjects were placed in a horizontal position. The head was kept in a fixed position with a specially designed pillow. During 5–10 min before indomethacin dosing the carotid arteries on both sides were evaluated by use of a non-invasive ultrasound Doppler equipment (Dopscan 500, Carolina Medical). None of the subjects showed any pathological findings on Doppler examination, all had Doppler shift ≤ 4 kHz. The ultrasound probe was fixed in a position of about 60 degree angle to the corresponding internal artery and was maintained in this position through the 2 h investi-

gation. The blood systolic peak velocity change in the internal carotid artery was monitored continuously (Spencer, 1981). The mean value of systolic peak velocity during a 10 s period was noted at each time point in each individual during the experiment. The blood flow in the internal carotid artery has been shown to be closely correlated to the flow in the middle cerebral artery (Lindegaard *et al.*, 1987). Flow velocity changes in the internal carotid artery are thus directly proportional to corresponding changes in the ipsilateral middle cerebral artery. Furthermore, without significant lumen reduction of the internal carotid artery the velocity changes will be proportional to the corresponding volume flow changes. The blood flow was expressed in percentage of the initial value at each investigation.

Indomethacin serum concentrations were analyzed by a sensitive h.p.l.c. method (Wählin-Boll *et al.*, 1981).

To evaluate the effect on steady state long term treatment, the same procedure was repeated (test II) after 7 days treatment with one suppository of indomethacin (100 mg) before bedtime.

The data were analyzed using a computer program for analysis of variance by a two tailed model (Winer, 1971).

Results

A statistically significant blood flow reduction ($P < 0.05$) in the internal carotid artery was noted both among those with (group A) (23%) and in those without (group B) (18%) central nervous side effects as reported in the previous screening procedure (Figure 1). The flow reduction was most marked at about 60 min after indomethacin dosing (test I). The repeated investigation after 7 days treatment with indomethacin (test II), revealed a similar significant ($P < 0.05$) decrease in blood flow within 60 min (30% in group A and 19% in group B) (Figure 2). There was no statistically significant difference neither between the two groups of subjects

Figure 1 Cerebral blood flow (CBF) change in percentage of initial flow value (0 min) after a single dose of indomethacin (100 mg) in subjects ($n=11$) with CNS related symptoms (-□-) and in subjects ($n=7$) without symptoms (-■-) at screening procedure.

Figure 2 Cerebral blood flow (CBF) change in percentage of initial flow value (0 min) after 7 days treatment with indomethacin (100 mg) in subjects ($n=11$) with CNS related symptoms (-□-) and in subjects ($n=7$) without symptoms (-■-) at screening procedure.

Figure 3 CNS-related symptoms change after (visual analogue scale 0–100 mm) a single dose of indomethacin (100 mg) in subjects ($n=11$) with CNS-related symptoms (-□-) and in subjects ($n=7$) without symptoms (-■-) at screening procedure before the experiment.

(A and B) nor between the two treatment regimens (test I and II).

At test I subjects in group A reported increasing symptoms with a peak at about 60 min (Figure 3). Only minor symptoms were reported in group B. The symptoms were almost completely abolished within 2 h after indomethacin dosing.

At test II no significant CNS symptoms were noted in any of the two groups (Figure 4).

Serum concentrations of indomethacin (test I) showed a gradual increase with a maximum of $2.5 \mu\text{g l}^{-1}$ at 60–70 min after a single dose of indomethacin (100 mg) had been given (Figure 5). Indomethacin concentrations were fairly stable during the last hour of the experiment. After treatment with indomethacin 100 mg daily during 1 week (test II) serum concentrations were similar in both groups of subjects (Figure 5).

Figure 4 CNS-related symptoms change (visual analogue scale 0–100 mm) after 7 days treatment with indomethacin (100 mg) in subjects ($n=11$) with CNS-related symptoms ($-\square-$) and in subjects ($n=7$) without symptoms ($-\blacksquare-$) at screening procedure before the experiment.

Figure 5 a) Serum concentration of indomethacin after a single dose of indomethacin (100 mg) in subjects ($n=11$) with CNS-related symptoms ($-\square-$) and in subjects ($n=7$) without symptoms ($-\blacksquare-$) at screening procedure before the experiment. b) Serum concentrations after 7 days treatment with indomethacin (100 mg) in subjects ($n=11$) with CNS-related symptoms ($-\square-$) and in subjects ($n=7$) without symptoms ($-\blacksquare-$) at screening procedure before the experiment.

Discussion

The effect of indomethacin on cerebral circulation has been investigated before and a reduction in cerebral blood flow was demonstrated in adult humans of 35 to 50% (Siesjö & Nilsson, 1982; Wennmalm *et al.*, 1981), in the newborn of 12 to 40% (Pryds *et al.*, 1988) and in animal studies of 18 to 28% (Bill, 1979; Crockard *et al.*, 1982; Saeed Abdel-Halim *et al.*, 1980; Leffler *et al.*, 1985). These reports of indomethacin effect on cerebral blood flow are similar to the results obtained in our study with flow reductions of 21 to 30%. Earlier reports have suggested the indomethacin effect on cerebral blood flow is by inhibition of prostaglandin biotransformation, since cerebral blood vessels can produce prostacyclin from exogenous precursors (Boullin *et al.*, 1979; Saeed Abdel-Halim *et al.*, 1980) and dilate all types of cerebral blood vessels (Boullin, 1980). However, all NSAIDs are potent inhibitors of prostaglandin syntheses and if measured in platelets a 90% suppression of prostaglandin can be observed at very low doses (Rane *et al.*, 1978). Furthermore no release of free fatty acids, arachidonic acid or prostacyclin metabolites could be measured in arterial and jugular vein blood performed during invasive studies (Wennmalm *et al.*, 1981). It is also surprising to note that no change in CBF was observed during diclofenac, naproxen or aspirin treatment (Saeed Abdel-Halim *et al.*, 1980; Wennmalm *et al.*, 1981).

Some recent studies contest the hypothesis that PGI_2 acts as a physiological vasodilator involved in the homeostasis of normal cerebral blood flow (Cook *et al.*, 1983). It has been suggested that indomethacin has a rapid constricting activity on vessels, not related to prostacyclin (Wennmalm *et al.*, 1981). These results oppose the hypothesis that the cerebral vascular circuit is outstanding concerning sensitivity to indomethacin and unique with regard to its dependence on vascular prostaglandin for maintenance of basal flow. Other theories, e.g. that indomethacin chemically resemble serotonin also have to be considered.

To get more insight into the mechanism of the CNS effect of indomethacin we investigated its effect on blood flow in two different groups of subjects both with and without CNS symptoms and related the effect to indomethacin serum concentrations and cerebral blood flow. We found a decrease in blood flow by about 30% with its peak effect 45–60 min after indomethacin dosing. Reduction in blood flow measured by Doppler sonography was very similar to the results obtained with other methods (Siesjö *et al.*, 1982; Wennmalm *et al.*, 1981). Our results indicate that non-invasive methods might be an alternative to measurements of cerebral blood flow by nitrous oxide or $^{133}\text{-xenon}$ clearance technique (Wennmalm *et al.*, 1981). The utility of the Doppler technique in cerebral blood flow measurements is further supported by studies after closure of the ductus arteriosus in the newborn (Perlman *et al.*, 1981).

We have earlier investigated the spontaneous change of flow in nine control healthy subjects without treatment. Our results showed that 90% of the flow reduction occurred within 5 min after horizontal recumbent position. In the study reported in this paper the subjects were in the horizontal recumbent position for about 15 min

before the flow signal was recorded and the test measurements started. Thus the reduced CBF is not likely to be explained by spontaneous flow reduction.

The maximum CNS effect in our study was seen 60–75 min after the indomethacin dose had been given, which coincides with peak levels of indomethacin in serum. These results may indicate that CNS symptoms during indomethacin treatment is concentration dependent (Melsom & Laake, 1979). Furthermore, it seems as if the sensitivity of CNS to indomethacin may vary between

patients and may be reduced after chronic treatment. This finding is supported by Pullar *et al.* (1988), who found psychomotor disturbances only in patients who had no recent history of NSAID treatment. In their study the psychomotor impairment was reduced after multiple doses of indomethacin. Finally the CNS effect does not seem to be directly related to blood flow as no difference between subjects with and without side-effects could be demonstrated.

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