

# Indomethacin decreases optic nerve oxygen tension by a mechanism other than cyclo-oxygenase inhibition

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## ABSTRACT

**Aims:** We investigated the effect of several Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), on the preoptic nerve oxygen tension (ONPO<sub>2</sub>), as indomethacin previously has demonstrated a strong decreasing effect on ONPO<sub>2</sub>. We tested whether these NSAIDs, like indomethacin, also reduce the increasing effect of dorzolamide on ONPO<sub>2</sub>.

**Methods:** ONPO<sub>2</sub> was measured 0.5 mm above the optic disc in 23 domestic pigs (26–36 kg) with a polarographic oxygen-sensitive electrode. One of the following NSAIDs was administered intravenously as increasing doses or as one large dose: indomethacin, ibuprofen, diclofenac, ketoprofen, parecyclo-oxygenase-2 inhibitor and lornoxicam. Indomethacin was both tested alone and after preceding administration of the other NSAIDs.

Dorzolamide was also tested after preceding administration of NSAIDs different from indomethacin.

**Results:** Indomethacin decreased ONPO<sub>2</sub> significantly in a dose-dependent manner. None of the other NSAIDs produced any effect on the ONPO<sub>2</sub> ( $p > 0.05$ ;  $n = 17$ ). No difference was found between the effect of indomethacin injected alone, and after preceding administration of the other NSAIDs. Intravenous dorzolamide (500 mg) increased ONPO<sub>2</sub> by 32 (7)% ( $n = 7$ ;  $p < 0.001$ ) after preceding administration of several NSAIDs different from indomethacin.

**Conclusions:** Indomethacin decreased ONPO<sub>2</sub>, while the other NSAIDs showed no effect on ONPO<sub>2</sub>, and they did not affect the effect of indomethacin. The hypoxic effect of indomethacin must be due to another mechanism than cyclo-oxygenase inhibition. The effect of dorzolamide on ONPO<sub>2</sub> is not related to prostaglandin production.

Optic nerve head hypoxia and retinal ischaemia are believed to play an important role in the pathogenesis of glaucoma,<sup>1,2</sup> and diabetic retinopathy.<sup>3</sup> We have previously reported that a large dose of indomethacin decreases preoptic nerve oxygen tension, ONPO<sub>2</sub>, by 41% and almost abolishes the augmenting effect of dorzolamide, a carbonic anhydrase inhibitor, and hypercapnia on the porcine ONPO<sub>2</sub>.<sup>4</sup> It is not known whether these effects of indomethacin persist with smaller, more clinically relevant, doses of the drug.

Indomethacin is a non-steroidal anti-inflammatory drug (NSAID) which, along with all other drugs of this class, inhibits the cyclo-oxygenase, or COX, enzyme.<sup>5</sup> However, it is clear from previous studies that indomethacin possesses additional effects that are not dependent on the COX enzyme when compared with other NSAIDs.<sup>6–10</sup> It is not known whether the decreasing effect of

indomethacin on ONPO<sub>2</sub> is dependent on the COX enzyme, or whether it is caused by another mechanism.

In the present study, we investigated the dose-response curve for the effects of indomethacin on the porcine ONPO<sub>2</sub>. We also tested whether other NSAIDs than indomethacin might have a similar decreasing effect on the ONPO<sub>2</sub>. We further tested whether the effect of indomethacin on ONPO<sub>2</sub> could be inhibited with preceding COX inhibition by other NSAIDs. Finally, we investigated the mechanism of dorzolamide on the ONPO<sub>2</sub>, by testing the effects of the drug after COX inhibition with other NSAIDs than indomethacin.

## METHODS

We used 23 pigs of Danish Landrace/Duroc/Hampshire/Yorkshire breed (age, 3–4 months; weight, 28–38 kg). The Danish Animal Experiments Inspectorate granted the permission for the use of the animals, and the experiments were conducted in compliance with the ARVO statement for the use of animals in ophthalmological and vision research.

The pigs were prepared for the experiments as previously described.<sup>11</sup> In brief, sedation was induced by intramuscular injection of a mixture of tranquilisers (midazolam, zolazepam, tiletamin, zylazine, ketamine and methadone). Anaesthesia was followed with pentobarbital (Mebumal®) into the ear vein. After intubation, the animals were artificially ventilated and catheterised into the femoral artery and vein, and the superficial epigastric vein. During the experiments, anaesthesia was maintained by continuous administration of pentobarbital (Mebumal®) into one vein and fentanyl (Haldid®) and pancuronium bromide (Pavulon®) into the other vein. A pressure transducer was connected to the arterial catheter for continuous measurements of arterial blood pressure (MAP). Heart rate (HR) was recorded from ECG electrodes. The signals from the arterial pressure transducer, the rectal temperature probe and the ECG were sampled continuously. The pig was placed in a sling, and the head was secured with a stereotactic headholder to avoid eye movements. A speculum was placed between the eyelids.

The animals were ventilated at approximately 4 l/min, using a continuous flow of 21% O<sub>2</sub>, 79% N<sub>2</sub>O, using a variable-volume respirator. Blood pressure was monitored via the femoral artery, and arterial blood gas samples were analysed for arterial



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**Table 1** Effects of accumulated doses of indomethacin on ONPO<sub>2</sub> under baseline conditions and after COX inhibition with NSAIDs other than indomethacin

Indomethacin dose (mg)	Baseline	After COX inhibition
	ONPO <sub>2</sub> change (kPa)	ONPO <sub>2</sub> change (kPa)
3	0.2 (0.1), 3	0.4 (0.1), 4
5	0.5 (0.1), 3	0.4 (0.2), 5
10	0.6 (0.2), 6	0.8 (0.5), 5
25	0.6 (0.2), 5	0.6 (0.2), 6
50	0.8 (0.3), 6	0.9 (0.6), 8
100	0.8 (0.3), 5	1.7 (1.4), 2
150	1.1 (0.4), 5	0.3), 1

Results are presented as the average (SD), followed by the number of experiments.

oxygen tension (PaO<sub>2</sub>), arterial CO<sub>2</sub> tension (PaCO<sub>2</sub>) and arterial pH (apH) (ABL 605 blood gas analyser Radiometer, Copenhagen, Denmark). Prior to the administration of the drugs, PaO<sub>2</sub>, PaCO<sub>2</sub> and apH were kept within normal values by adjusting the rate of ventilation.

The pupil was dilated and anaesthetised with topical 1% tropicamid (Mydracyl®), 2.5% methaoxedrine (Metaoxedrin®) and 0.4% oxybuprocaine (Oxybuprokain®) as eye-drops. A sclerotomy was placed 2.0 mm behind the corneal limbus in the superior nasal quadrant, and a plastic canula (16 Gauge) was placed in the sclerotomy.

The following drugs were used and either purchased at the local pharmacy or at Sigma Chemicals or provided by Merck, Sharp & Dohme (MSD, Glostrup, Denmark): Indomethacin (Confortid®, Actavis, Gentofte, Denmark), diclofenac (Voltaren®, Novartis Healthcare, Copenhagen, Denmark), ibuprofen (Sigma-Aldrich Chemicals, Broendby, Denmark), ketoprofen (Orudis®, Aventis Pharma, Hoersholm, Denmark), parecyclo-oxygenase-2 inhibitor (Dynastat®, Pfizer, Ballerup, Denmark), lornoxicam (Xefo®, Nycomed, Roskilde, Denmark), dorzolamide (MSD). All NSAIDs were administered in accordance with the enclosed instruction that came with the drug except from ibuprofen, which was dissolved in saline water. Dorzolamide hydrochloride was dissolved as a 3% solution in 100 mM citrate buffer, pH 5.6.

Preoptic nerve oxygen tension (ONPO<sub>2</sub>) was measured with a polarographic oxygen-sensitive electrode with an internal Ag/AgCl reference electrode, as described previously.<sup>11</sup> Briefly, the platinum electrode was mounted with an internal Ag/AgCl reference electrode inside a 20-gauge needle (model 768 R20, Diamond General, Ann Arbor, MI). The tip of the needle was sharpened at the end to an area of 0.15 mm<sup>2</sup> in a crescent shape. The signal from the electrode was measured continuously with a chemical micro sensor (model 1231, Diamond General). The electrode was advanced by a micromanipulator through a Teflon cannula inserted in the sclerotomy. The electrode was guided by indirect ophthalmoscopy, and the tip of the electrode was placed 0.5 mm above the optic disc in an area without retinal vessels. The entry site of the sclerotomy was watertight, and all eyes maintained their normal shape throughout the experiments. The intraocular pressure was not measured. The oxygen electrode was calibrated before and after each experiment in 100% N<sub>2</sub> and 5% O<sub>2</sub>/95% N<sub>2</sub> in a calibration cell (model 1251, Diamond General Development). The drift of the oxygen electrode was less than 0.1 kPa/h.

Initially, a baseline oxygen recording was obtained. Next, the pig was provided with 100% oxygen in the inspiratory air to verify that the oxygen-sensitive electrode measured and recorded sufficiently. Finally, the pig was ventilated with normal air until a baseline recording was obtained again, before

the administration of drugs. Three types of experiments were performed.

First, the dose-response relationship of indomethacin was investigated by injection of increasing, accumulated amounts of indomethacin (n = 6). Each injection was separated by approximately 20 min until a new baseline ONPO<sub>2</sub> was reached.

Second, each of five NSAIDs different from indomethacin was tested in a large, saturating dose (1000 mg of ibuprofen, 150 mg of diclofenac, 100 mg of ketoprofen, 40 mg of parecyclo-oxygenase-2 inhibitor or 16 mg of lornoxicam) (n = 17). Approximately 20 min later, when a new baseline ONPO<sub>2</sub> was reached, the dose-response relationship of indomethacin was investigated with intravenous injections of increasing, accumulated amounts of indomethacin.

Third, the other NSAIDs different from indomethacin were administered in large doses, with the administration of each drug separated by approximately 10–20 min. After a new baseline ONPO<sub>2</sub> was reached, the effects of 500 mg of intravenous dorzolamide on the ONPO<sub>2</sub> were examined (n = 7). The result of the first NSAID that was injected in these experiments was also included when the results of the single NSAIDs were analysed.

Some experiments did not follow the full experimental course due to complications with anaesthesia or the oxygen-recording system.

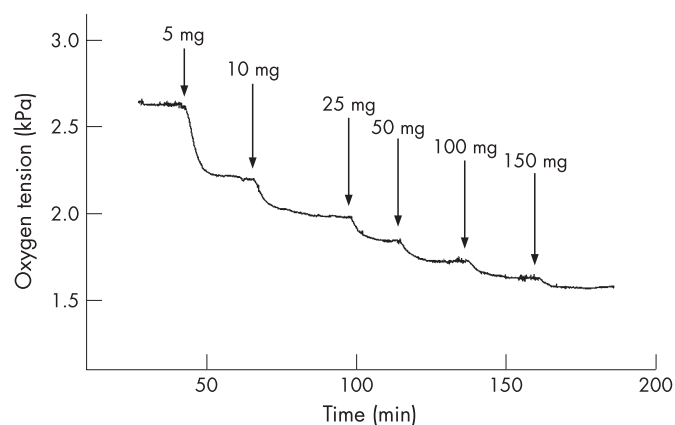
All results are presented as oxygen changes in kPa as the mean (SD) of the initial baseline. The statistical tests used are indicated in the Results section, and a one-way ANOVA was supplemented with multiple-comparison t tests corrected with the Holm-Sidak method. Throughout the study, we used a significance level of 5%. Statistical computations were made with Sigmastat software (Systat Software, San Jose, CA).

## RESULTS

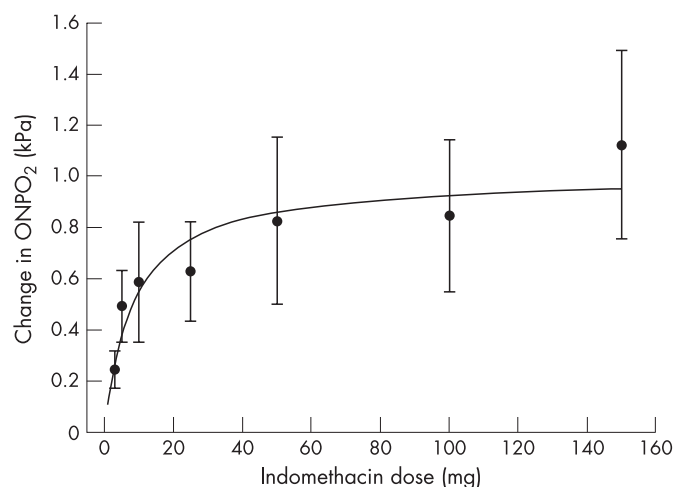
Administration of increasing, accumulated doses of indomethacin decreased the optic nerve oxygen tension (ONPO<sub>2</sub>) in a dose-dependent manner with a full effect 4–7 min after the administration of each dose (table 1; figs 1 and 2). As can be seen from fig 2, the effect of indomethacin saturates around the 50 mg dose. The fit of Michaelis-Menten kinetics yielded a K<sub>m</sub> of 8.4 (3.5) mg, corresponding to 0.28 (0.12) mg/kg.

Figure 3 shows recordings from experiments in which we tested the five NSAIDs different from indomethacin. We found that these NSAIDs did not have any systematic effect on the ONPO<sub>2</sub>.

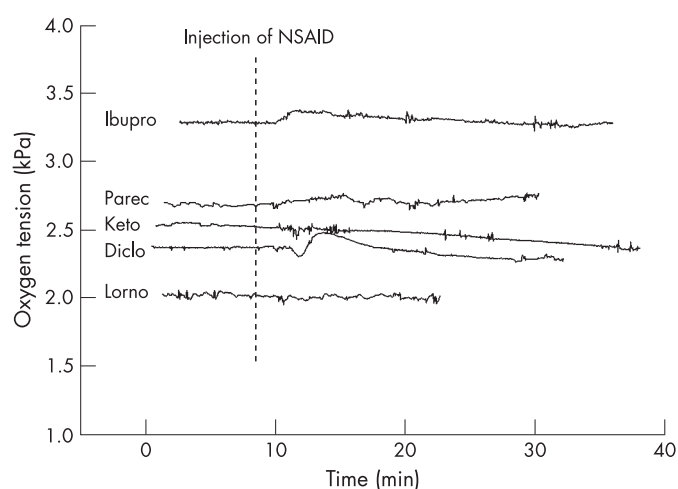
Table 2 compiles the results of the tested NSAIDs, including indomethacin. The effect of indomethacin on the ONPO<sub>2</sub> was significantly different from that of the other NSAIDs (F test, and post hoc multiple comparisons with the Holm-Sidak method, p < 0.005). There was no significant difference between



**Figure 1** Typical recording of the effect of increasing amounts (accumulated mg) of indomethacin on the preoptic nerve oxygen tension.



**Figure 2** Effect of increasing accumulated doses of indomethacin on the ONPO<sub>2</sub> in kPa: mean (SD).



**Figure 3** Typical recordings of the effects of the five NSAIDs different from indomethacin on ONPO<sub>2</sub>. The recordings are derived from five different experiments. The dashed line marks the time for injection of each of the NSAID. Ibu, 1000 mg ibuprofen; Diclo, 75 mg diclofenac; Parec, parecyclo-oxygenase-2 inhibitor; Keto, ketoprofen; Diclo, diclofenac; Lorno, lornoxicam.

**Table 2** Effects of six different NSAIDs on ONPO<sub>2</sub>

NSAID	Change in ONPO <sub>2</sub> (kPa)
Ibuprofen (1000 mg)	0.007 (0.1), 7
Diclofenac (150 mg)	-0.2 (0.2), 4
Ketoprofen (100 mg)	-0.04 (0.1), 3
Parecyclo-oxygenase-2 inhibitor (40 mg)	0.1 (0.01), 2
Lornoxicam (16 mg)	-0.03, 1
Indomethacin (50 mg)	0.8* (0.3), 6

Results are presented as the average (SD), followed by the number of experiments. \*Statistical difference ( $p < 0.05$ ) between baseline and after the NSAID.

the effects of any of the other NSAIDs (F test,  $p > 0.1$ ), and the change in ONPO<sub>2</sub> after their individual administration was not significantly different from zero (paired t test,  $p > 0.2$ ).

After COX inhibition with one or more of the five NSAIDs different from indomethacin, we investigated the effects of increasing, accumulated amounts of indomethacin. There was no significant difference between the effects of indomethacin on the ONPO<sub>2</sub> in baseline conditions and after COX inhibition (two-way ANOVA, F test,  $p > 0.6$ ).

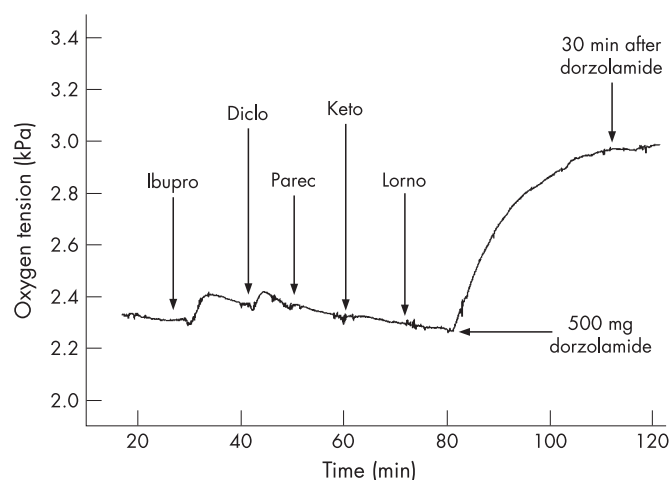
After preceding COX inhibition with one or more of the five NSAIDs different from indomethacin, intravenous administration of 500 mg dorzolamide increased ONPO<sub>2</sub> by  $0.7 \pm 0.3$  kPa (32 (7)%;  $n = 7$ ) (fig 4). This change is statistically significant (paired t test,  $p < 0.001$ ).

No other parameter (arterial PCO<sub>2</sub>, PO<sub>2</sub>, pH, BP, temperature) changed significantly within 30 minutes after the administration of any of the NSAIDs, including indomethacin (table 3). 500 mg of intravenous dorzolamide, though, increased PaCO<sub>2</sub> and decreased apH significantly, but did not affect any of the other parameters (table 3).

## DISCUSSION

This study shows that indomethacin in clinically relevant doses decreases ONPO<sub>2</sub> in pigs. This extends our previous findings where a very large dose of 10 mg/kg was used.<sup>4</sup>

In patients with glaucoma and ocular hypertension, a decreased blood flow in the midperipheral retinal microcirculation has been observed after administration of intravenous



**Figure 4** Typical recording after the five NSAIDs different from indomethacin, and of the effect of 500 mg dorzolamide administered after the five NSAIDs. Each injection of NSAIDs was separated by 10 min. Ibu, 1000 mg ibuprofen; diclo, 75 mg diclofenac; parec, 40 mg parecyclo-oxygenase-2 inhibitor; keto, 100 mg ketoprofen; lornox, 8 mg lornoxicam.



**Table 3** Effect of NSAIDs and indomethacin on arterial  $\text{PaO}_2$ ,  $\text{Paco}_2$  and pH

	$\text{PaO}_2$	$\text{Paco}_2$	pH
Before indomethacin	10.7 (0.6)	7.6 (0.5)	7.43 (0.02)
After indomethacin	10.1 (1.1)	7.3 (0.6)	7.41 (0.03)
Before NSAIDs	11.3 (1.3)	7.2 (1.0)	7.42 (0.03)
After NSAIDs	10.8 (1.2)	7.4 (1.0)	7.42 (0.03)
Before NSAIDs and indomethacin	11.2 (1.8)	6.6 (0.6)	7.42 (0.04)
After NSAIDs and indomethacin	10.2 (1.1)	7.0 (0.7)	7.41 (0.06)
Before dorzolamide	11.1 (0.5)	7.2 (0.5)	7.42 (0.03)
After dorzolamide	11.4 (0.3)	8.6* (0.4)	7.34* (0.02)

No parameter showed any significant change after administration of any of the NSAIDs. Results are presented as the average (SD).

\*Significant difference after the injection of 500 mg dorzolamide, which significantly increased  $\text{Pco}_2$  and decreased pH.

indomethacin and topical latanoprost.<sup>12</sup> No information is available on the effects of solitary indomethacin on the blood flow in the human retina or optic nerve.

Through its effect on the COX enzyme, indomethacin is a powerful inhibitor of the synthesis of prostanoids, and the drug is widely used experimentally as a typical COX inhibitor.<sup>5 13 14</sup> Prostanoids, among them 6-ketoprostaglandin  $\text{F}_{1\alpha}$ , are important vasodilators that have been implicated in the cerebral and ocular vascular response to  $\text{CO}_2$  and carbonic anhydrase inhibition. We therefore speculated that the decreasing effect of indomethacin on the  $\text{ONPO}_2$  might be caused by COX inhibition and the consequently diminished synthesis of vasodilating prostanoids.<sup>4</sup> However, the results from the present study clearly show that a mechanism, other than COX inhibition, must be responsible for the decrease in  $\text{ONPO}_2$ . First, COX inhibitors other than indomethacin, among them ibuprofen, given in very large doses had no effect on the  $\text{ONPO}_2$ . Second, the effect of indomethacin on the  $\text{ONPO}_2$  was unabated by prior inhibition of COX that was induced by large doses of the other COX inhibitors.

The other five COX inhibitors used in the present study have different COX1/COX2 characteristics.<sup>15</sup> Ketoprofen is regarded to have a COX1/COX2 selectivity that is similar to indomethacin, and these are considered to be among the most COX1-selective NSAIDs. Ibuprofen and diclofenac were studied because of their widespread use, and because ibuprofen has been shown to cause complete inhibition of the prostanoid synthesis in a porcine system when used in approximately the same dose as in the present study (30–40 mg/kg).<sup>7 10</sup> Ibuprofen is rather COX1-selective, while diclofenac is quite COX2-selective and fairly similar to celecoxib (Celebra®). Lornoxicam is rather COX2-selective, while parecyclo-oxygenase-2 inhibitor is a strong, selective COX-2 inhibitor and the precursor to valdecoxib, which has been withdrawn from the market. Considering the variety of tested NSAIDs different from indomethacin, it is unlikely that the lack of effect is due to different COX1/COX2 selectivity or lack of inhibition of the prostanoid synthesis in the porcine system.

Indomethacin, but not other COX inhibitors, has previously been found to inhibit blood flow in the retina, choroid and brain of experimental animals, albeit with different methods than used in the present study.<sup>7–9 16–18</sup> It has been reported that indomethacin stimulates carbonic anhydrase, which might be an explanation for the non-COX dependent effect of indomethacin on the blood flow in the brain and the eye.<sup>19 20</sup>

Carbonic anhydrase inhibition with dorzolamide has repeatedly been shown to increase blood flow and oxygen tension in the porcine optic nerve head and retina,<sup>4 11 21 22</sup> and indomethacin has shown to reduce this effect by 69%.<sup>4</sup> After COX

inhibition with other NSAIDs than indomethacin, the present study found that the effect of dorzolamide on the  $\text{ONPO}_2$  was similar to what we previously have found under baseline conditions (without preceding COX inhibition) in the same experimental setup as that used in the present study.<sup>4</sup>

In conclusion, we found that the decreasing effect of indomethacin on the  $\text{ONPO}_2$  was dose-dependent, and the effect had a saturation point. Furthermore, the effect on the  $\text{ONPO}_2$  was independent of cyclo-oxygenase inhibition. No other NSAID than indomethacin affected the  $\text{ONPO}_2$ . The effect of dorzolamide on the  $\text{ONPO}_2$  is also independent of COX inhibition as it was unaffected by NSAIDs different from indomethacin. Hence, indomethacin seems to be particularly unsuited for experimental studies of the effects of COX inhibition on the optic nerve blood flow, and probably also in other vascular systems.

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**Competing interests:** None.

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