Treatment of elevated intracranial pressure with indomethacin: Friend or foe?

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Indomethacin has been suggested as a therapeutic tool to manage elevated intracranial pressure in patients with severe head injury and patients undergoing craniotomy for brain tumors. Indomethacin is a non-selective cyclooxygenase inhibitor. Compared to other cyclooxygenase inhibitors indomethacin has unique effects on cerebral blood flow. Administration of indomethacin causes cerebral vasoconstriction and decreases cerebral blood flow, which elicits a decrease in intracranial pressure. The mechanism of indomethacin-induced cerebral vasoconstriction is not completely understood and controversies exist whether indomethacin causes cerebral ischemia. The primary aims of this article were to review the existing knowledge of indomethacin’s influence upon cerebral hemodynamics and elevated ICP in patients with brain pathology. Furthermore, indomethacin’s mechanism of action and whether it causes cerebral ischemia are discussed.

Accepted for publication 27 October 2004

Key words: Indomethacin; intracranial pressure; review; blood flow, regional; cerebrum; brain neoplasm; head injury, closed; prostaglandins.

The traditional approach for treating elevated intracranial pressure (ICP) in patients with severe head injury and during craniotomy consists of reducing either cerebral arterial blood volume (hyperventilation, bolus injection of barbiturate or other hypnotics), brain tissue volume (osmotic therapy) or cerebral venous volume (head elevation) and cerebrospinal fluid (CSF) (1-7). Decompressive craniectomy, which can also increase edema formation (8), is a final option (9). However, these treatments are not always effective. Controlled hyperventilation is often of limited value: patients with cerebral pathology may have an impaired or abolished cerebrovascular reactivity to changes in PaCO₂; the effects of hyperventilation upon cerebral blood flow (CBF) and ICP are subject to adaptation (10), and adverse effects have been reported (11, 12). The efficacy of osmotherapy, which aims to reduce cerebral water content, has also been questioned (13). Barbiturates may induce cardiovascular depression with reduction of cerebral perfusion pressure (CPP), and cerebrospinal fluid drainage may be impossible due to difficult access to the ventricular system. Thus, alternative methods to reduce ICP seem justified.

Recently, other strategies focusing on different aspects of brain injury have been suggested in treating patients with severe head injury. These approaches focus on the management of cerebral perfusion pressure (14) and minimizing edema formation in the brain (15). None of these approaches, however, convincingly improves outcomes in head-injured patients compared to traditional ICP management strategies (16).

Experimental and clinical studies suggest that indomethacin may be useful in the treatment of high intracranial pressure (17-20). Indomethacin is a cerebral vasoconstrictor but until now the clinical use of indomethacin in managing elevated ICP has been limited due to the risk of causing cerebral ischemia (21). However, recent studies suggest that this may not be the case. This article reviews the existing knowledge of indomethacin’s influence on cerebral hemodynamics and elevated ICP in patients with brain pathology. Additionally, indomethacin’s mechanism of action and whether indomethacin causes cerebral ischemia are discussed.

Effects on cerebral blood flow

The cerebrovascular effects of indomethacin were first reported by Pickard and Mackenzie, who
demonstrated that indomethacin (10 mg kg\(^{-1}\) i.v.) reduced basal CBF in anesthetized baboons by 40% and attenuated the response of the cerebral circulation to hypercapnia (22). Subsequent experimental investigations confirmed that indomethacin (10 mg kg\(^{-1}\) i.v.) markedly reduced CBF (23) and nearly abolished the increase in CBF to hypercapnia in rats (24, 25) without influencing the cerebrovascular response to arterial hypoxia or affecting the cerebral metabolic rate of oxygen (CMRO\(_2\)) (26). These results have been confirmed in a number of different animal models (27–29). Recently, a pig model was used where indomethacin (0.05 mg kg\(^{-1}\)-min\(^{-1}\)) caused a 31% decrease in CBF without any impact on CMRO\(_2\), measured with positron emission tomography (30). However, a few studies reported no influence of indomethacin on CBF (31) or hypercapnia-induced cerebral vasodilation (32). The contradictory results are explained by differences concerning species and methodology.

Indomethacin’s vasoconstrictive effect is mainly confined to small resistance vessels, and the reduction in CBF appears to be homogeneous throughout the brain (33–36). Indomethacin does not affect normal autoregulation and it appears that the decrease in CBF after indomethacin is not secondary to a decrease in cerebral glucose metabolism (33, 34).

Animal study results have to a large extent been confirmed in humans. With the exception of one study (37), subsequent studies have shown that indomethacin administered i.v. (bolus of 0.1–0.4 mg kg\(^{-1}\) followed by infusion of 0.1–0.4 mg kg\(^{-1}\)-h\(^{-1}\); 38, 39), orally (100 mg; 40), or as a 100-mg suppository (41, 42) decreases CBF at normocapnia ranging from 18 to 40%, and attenuates the cerebrovascular reaction to hypercapnia (41, 43, 44) without influencing CMRO\(_2\) (Fig. 1). In two studies, however, no change in CO\(_2\) reactivity was observed (38, 45). The observed difference in CBF reduction and CO\(_2\) reactivity among these studies may to a large extent be explained by different methods of measuring CBF, different patient material, different dosage regimens and different ways of administering indomethacin.

**Conclusion**

A considerable body of evidence in both animals and humans has demonstrated that indomethacin markedly reduces CBF and decreases cerebrovascular response to hypercapnia without affecting CMRO\(_2\). Indomethacin does not appear to influence normal cerebral autoregulation or cerebral glucose metabolism.

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**Effect on elevated intracranial pressure**

Jensen et al. were the first to report the use of indomethacin in head-injured patients with high ICP refractory to standard treatment modalities (20). In their study indomethacin (bolus of 30 mg i.v., followed by infusion of 30 mg h\(^{-1}\)) elicited a significant decrease in ICP within 5–10 s after administration, and ICP reached a minimum within 1–5 min. The reduction in ICP was accompanied by a non-significant increase in CPP and an average decrease in CBF from 34 to 29 ml 100 g\(^{-1}\)-min\(^{-1}\), measured 15 min after initiation of treatment. The cerebral metabolic rate of oxygen remained unchanged (20). The effect on ICP was later confirmed in an uncontrolled study by Biestro et al. who treated 10 patients with severe head injury and elevated ICP refractory to treatment with mannitol, hyperventilation and barbiturates (17). In their study indomethacin was administered as a bolus dose of 50 mg followed by continuous infusion of 21.5 ± 11 mg h\(^{-1}\) over 30 ± 9 h. The bolus dose of indomethacin significantly reduced ICP with a significant improvement in CPP. Continuous indomethacin infusion elicited a further decrease in ICP, however, without changes in CPP. Subsequent discontinuation of the indomethacin treatment resulted in a significant return of ICP to pretreatment levels. The authors did not measure CBF or CMRO\(_2\) (17).

In another study of patients with severe head injury and elevated ICP, the decrease in ICP following an indomethacin bolus dose of 30 mg kg\(^{-1}\) was comparable to the ICP decrease observed during a 0.88-kPa decrease in PaCO\(_2\) (19). However, compared to hyperventilation the authors reported that indomethacin
administration was accompanied by a more pronounced decrease in CBF and a significant increase in both mean arterial blood pressure (MABP) and CPP. This observation reflects the fact that indomethacin elicits both cerebral and peripheral vasoconstriction. No correlation between relative reactivities to indomethacin and CO₂ (evaluated from changes in CBF and AVDO₂) were found. Interestingly, some patients reacted to indomethacin but not to hyperventilation or vice versa, and the authors suggested that indomethacin and hyperventilation may act via different mechanisms (19). Additionally, a recent study demonstrated that indomethacin significantly reduced ICP and improved CPP in patients with fulminant hepatic failure (46). Furthermore, several case reports have demonstrated that indomethacin is effective in lowering ICP in patients with cerebral arterio-venous malformation associated with intracerebral hematoma (47), acute liver failure (48), idiopathic intracranial hypertension (49), and brain edema following stroke (50).

During craniotomy for cerebral tumors a high ICP may result in cerebral swelling after opening of the dura (51). This condition can seriously jeopardize surgical access and may increase the risk of cerebral ischemia with a poor outcome. Bundgaard et al. evaluated the effect of indomethacin on ICP, CBF and CMRO₂ in isoflurane-anesthetized patients subjected to craniotomy for supratentorial brain tumors (18). The patients were randomized to receive either indomethacin (bolus 50 mg, i.v.) or placebo, administered after exposure of the dura. A significant decrease in ICP from 6.5 mmHg to 1.5 mmHg (median) and increase in CPP from 63 to 80 mmHg (median) were observed (Fig. 2). The reduction in ICP was associated with a significant decrease in CBF from 39 to 20 ml.100 g⁻¹.min⁻¹ (median) without influencing CMRO₂. The authors did not report whether indomethacin affected the degree of brain swelling through the craniotomy.

A recent study compared the effects of indomethacin (bolus 0.2 mg kg⁻³, followed by infusion of 0.2 mg kg⁻¹.h⁻¹) on ICP, cerebral hemodynamics, and the degree of brain swelling in 30 patients undergoing craniotomy for supratentorial brain tumors in propofol/fentanyl anesthesia (52). Indomethacin was administered before induction of anesthesia and the infusion was terminated after opening the dura. Cerebral blood flow velocity was measured before and after induction of anesthesia. Indomethacin elicited a significant decrease in cerebral blood flow velocity measured before induction of anesthesia. However, after induction of anesthesia cerebral blood flow velocity decreased significantly in both groups without intergroup difference. Subdural ICP measured through the first burr-hole was 9 mmHg in each group without a difference in CPP and the degree of brain swelling. The authors suggested that these findings are partly caused by the propofol-induced cerebral vasoconstriction and suppression of CBF. Thus, this is the first study demonstrating that prophylactic indomethacin administration does not further reduce ICP in propofol/fentanyl anesthetized patients with cerebral tumors (52).

**Conclusion**

Studies of patients with severe head injury, patients with cerebral tumors anesthetized with isoflurane and finally patients with hepatic failure have demonstrated that indomethacin effectively reduces ICP and improves CPP. A recent study, however, could not demonstrate an effect of prophylactic indomethacin administration on ICP in propofol/fentanyl anesthetized patients with cerebral tumors. Case reports have shown that indomethacin reduces ICP in patients with liver failure, brain edema, intracerebral hematoma and idiopathic intracranial hypertension.

**Mechanism of action**

The mechanism behind indomethacin-induced cerebral vasoconstriction is not completely understood. Clearly, indomethacin inhibits cyclooxygenase (COX) and the vasoactive properties of the cyclooxygenase pathway products including prostaglandins, prostacyclin and tromboxanes are well documented (53).
Pathways for the metabolism of arachidonic acid are shown in Fig. 3. Cyclooxygenase exists as two distinct isoforms, COX-1 and COX-2. Cyclooxygenase-1 is constitutively expressed by most human cells and tissues, whereas COX-2 is induced by inflammatory agents and mitogens (54). Indomethacin is a non-selective COX-1 and COX-2 inhibitor, and whether indomethacin primarily inhibits COX-1 or COX-2 has not yet been determined (54).

Cerebral arteries generate both tromboxanes (which aggregate platelets and are vasoconstrictor) and prostacyclin (which inhibits platelet aggregation and is vasodilator) with the prostaglandin biosynthesis preferentially oriented towards the generation of prostacyclin (53, 55, 56). This observation has led some authors to postulate that prostaglandins have an active role in controlling the cerebrovascular tone (22, 34). One hypothesis is that by blocking cyclooxygenase, indomethacin preferentially inhibits generation of prostacyclin, thereby changing the balance of prostaglandins in the cerebral vessels towards vasoconstrictive prostaglandins (57).

In addition to inhibiting prostanoid synthesis, it has been demonstrated that indomethacin blocks dilator prostanoid-mediated cellular responses by inhibiting dilator prostanoid binding to prostacyclin receptors. This dual inhibition may explain why indomethacin, compared to other cyclooxygenase inhibitors, is the most effective inhibitor of dilator prostanoid-mediated physiological responses in the cerebral vasculature (58, 59).

Recent studies support this observation where indomethacin reduces or abolishes the vascular response to functional brain activation during somatosensory stimulation (60–62). During cerebral activation, vaso-dilator arachidonic acid metabolites like prostacyclin, prostaglandin E2 and epoxyeicosatrienoic acids are released by astrocytes and play a key role in the coupling between neuronal activity and increased cerebral blood flow (63–65). Thus, indomethacin may inhibit the action of vasodilator arachidonic acid metabolites by reducing synthesis and direct receptor blockade. The inhibiting action of indomethacin on these mediators of functional hyperaemia may

Fig. 3. Pathways for the metabolism of arachidonic acid. Arachidonic acid is metabolized via the cyclooxygenase, lipoxygenase and cytochrome P-450 enzymes to prostaglandins, prostacyclin (PGI2), thromboxane (TxA2), leukotrienes or a series of hydroxyeicosatetraenoic acids (HETEs) and epoxyeicosatrienoic acids (EETs).
also explain previous observations where indomethacin elicits an uncoupling of the relationship between cerebral blood flow and metabolism (23, 26, 30, 41).

However, other cyclooxygenase inhibitors have no effect on CBF and cerebrovascular tone, suggesting an alternative contribution to indomethacin-induced cerebral vasoconstriction than inhibition of cyclooxygenase and blockade of prostacyclin receptors (43, 44, 67). The cerebral vasoconstrictive effect observed after administration of indomethacin may involve the vasoconstrictive effect of endothelins. Therkelsen et al. demonstrated that indomethacin administration elicited an increase in plasma concentration of endothelins together with a marked decrease in CBF (68, 69). Recently, it was tested whether the mixed endothelin receptor antagonist bosentan modifies or prevents indomethacin-induced reduction of CBF in a pig model (30). The pigs were randomized to receive either indomethacin and bosentan or indomethacin and placebo (saline). Indomethacin elicited a significant and comparable decrease in CBF in both groups (30). This finding indicates that endothelin-receptor stimulation is not involved in indomethacin-induced cerebral vasoconstriction.

In addition to the cyclooxygenase pathway, arachidonic acid can be metabolized by lipoxygenase and cytochrome P-450 enzymes, thus producing several vasoactive metabolites sensitive to cyclooxygenase inhibition (70). One hypothesis is that blockade of cyclooxygenase by indomethacin shifts the metabolism of arachidonic acid down the lipoxygenase pathway, thereby enhancing synthesis of vasoactive leukotrienes (57). Leukotrienes are produced in the central nervous system (71) and some are vasoconstrictive (72).

Brain tissue and cerebral arterioles synthesize vasoactive cytochrome p-450 metabolites, including epoxygenosatrienoic acids (EETs) and hydroxyeicosatetraenoic acids (HETEs) (70, 73, 74). Studies have demonstrated that indomethacin attenuates pial arteriolar vasodilation produced by 5,6-epoxyeicosatrienoic acid (5,6-EET) in-vivo (75, 76). Conversely, other studies have demonstrated that the contraction of aortic rings elicited by 20-hydroxyeicosatetraenoic (20-HETE) was completely inhibited by indomethacin (77, 78). Thus, indomethacin inhibits the action of metabolites synthesized by cytochrome p-450 enzymes, thereby producing either vasodilation or vasoconstriction.

Indomethacin’s mechanism of action may involve mechanisms other than inhibition of cyclooxygenase enzymes. Wang et al. showed that indomethacin abolishes the cerebral blood flow increase in response to acetazolamide-induced extracellular acidosis. The authors suggested that the effect of indomethacin in reducing CO₂ reactivity is caused by a non-prostaglandin-mediated mechanism that directly interferes with the regulation of cerebrovascular tone mediated by extracellular pH (79).

Conclusion
Indomethacin’s mechanism of action on the cerebral vessels is not clearly understood. There is sufficient evidence to conclude that the action of indomethacin is partially mediated by inhibition of vasodilator arachidonic acid metabolites. Further studies are needed to clarify the mechanisms involved.

Does indomethacin cause cerebral ischemia?

The use of indomethacin is controversial because the decrease in CBF may lead to cerebral hypoperfusion and ischemic damage. Nilsson et al. reported in a porcine model of intracranial hypertension that indomethacin elicited progressive changes in AVDO₂, pH and slowing of the EEG, suggesting development of cerebral ischemia (21). However, a number of experimental studies have reported that indomethacin has neuroprotective effects against both global ischemia (80, 81), focal ischemia (82, 83) and delayed neuronal death (84, 85). Several mechanisms may be involved in the neuroprotective effect of indomethacin, including: attenuation of glutamate excitotoxicity (87, 88); attenuation of increased blood brain barrier transport of sodium and albumin (89); attenuation of reactive oxygen species (80, 84—86, 90); inhibition of leukocyte infiltration (91); attenuation of neuroinflammation and restoring of neurogenesis (66); and attenuation of inducible heat-shock protein 70 (92). However, whether indomethacin attenuates the release of glutamate remains controversial. A recent study demonstrated that indomethacin had little effect on glutamate release in-vitro and the authors suggested that glutamate release in severe brain ischemia is mainly caused by reversed uptake by glutamate transporters (93).

In patients with severe head injury and isoflurane-anesthetized patients with cerebral tumors, indomethacin administered as a bolus dose alone or followed by infusion caused an average decrease in CBF to values below 31 ml.100 g min⁻¹ accompanied by elevations in arterio-venous difference of lactate,
AVDO₂ and a decrease in SⱼvO₂ values below 50% (18–20). In addition, an average SⱼO₂ value of 46% was reported in propofol/fentanyl-anesthetized patients with cerebral tumors (52). The reported low CBF, SⱼO₂ and high AVDO₂ values in these studies suggest that the level of CBF under these conditions is critically low, and eventually may fall below the ischemic threshold. To examine whether indomethacin induces severe cerebral ischemic damage, diffusion-weighted magnetic resonance imaging (DWI) was performed in nine patients subjected to craniotomy for cerebral tumors (94). Diffusion-weighted MRI is an established MRI technique that is widely used in the diagnosis of acute stroke due to its extreme sensitivity to acute ischemic damage (95). This technique detects the diffusion of water molecules. Due to the altered hindrance of their Brownian motions caused by cytotoxic edema following ATP depletion, DWI hyperintensities appear within minutes of ischemic tissue damage (96). Diffusion-weighted magnetic resonance imaging sequences were performed: (i) the day before surgery; (ii) before and (iii) 20 min after administration of indomethacin (bolus of 0.2 mg kg⁻¹ followed by infusion of 0.2 mg kg⁻¹ h⁻¹) in the propofol/fentanyl-anesthetized patient; and (iv) 2 days after surgery (94). SⱼO₂ decreased from an average of 51% to 43%, comparable to a previous study in tumor patients (52). However, no ischemic lesions were detected on the DWI images (Fig. 4). It is important to note that DWI is not sensitive to ischemia per se but detects ischemic injury. Moreover, a longer duration of indomethacin infusion or another (longer) time interval between indomethacin administration and DWI acquisition might have produced different DWI results. Thus, this study does not rule out that ischemia actually occurred and whether the patients may have experienced delayed neuronal damage. The results are in accordance with Biestro et al. who reported no evidence of cerebral ischemia or infarctions on follow-up CT scans after indomethacin administration in patients with severe head injury (17). Furthermore, in the studies by Rasmussen et al. all patients recovered without neurological deficits, which could not be explained by the surgical intervention (52, 94). These observations lead to the question of whether the established thresholds of SⱼO₂ for detection of cerebral ischemia apply to tumor patients. In acute head injury SⱼO₂ < 50% suggests hypoperfusion, and values of SⱼO₂ < 40% are supposed to be associated with the development of global cerebral ischemia (97).

A recent study, however, reported that the lower limit of SⱼO₂ was 44.7% in awake subjects (98), a value which is considerably lower than reported in two earlier studies in which the lower limit of SⱼO₂ averaged 54.6% and 55.0%, respectively (99, 100). The findings by Chierogato et al. suggest a redefinition of the lower limit of SⱼO₂ for detecting global cerebral ischemia in anesthetized patients. Both volatile and intravenous anesthetic agents are suggested to have neuroprotective properties (101–104), and comparing absolute levels of SⱼO₂ or AVDO₂ between patients with severe head injury and patients subjected to elective tumor resection in general anesthesia may be misleading. Thus, a SⱼO₂ of 40% may not have the same significance in anesthetized tumor patients compared to sedated head-injured patients with different pathology.

Conclusion
It is still controversial whether indomethacin causes cerebral ischemia. One experimental study demonstrated signs of cerebral ischemia after indomethacin administration. In contrast, other studies suggest that indomethacin has neuroprotective properties. In

![Fig. 4. MR examinations of a 55-year-old man with a gliosarcoma located in the right temporo-parietal region. DWI sequences (upper row) and ADC maps (middle row) were obtained: (1) the day before surgery, (2) before, and (3) 20 min after administration of indomethacin (bolus of 0.2 mg kg⁻¹ followed by infusion of 0.2 mg kg⁻¹ h⁻¹) in the propofol/fentanyl anesthetized patient; and (4) 2 days after surgery. Fluid attenuated inversion recovery (FLAIR) sequences (lower row) were performed: (1) the day before surgery, and (2) 2 days after surgery. Despite the considerable mass effect of the tumor, DWI and FLAIR images revealed no ischaemic tissue damage. The finger-shaped surgical cavity appears black on DWI and white on ADC pictures in the last column (2 days postsurgery). The area in the right frontal operculum just anterior to the surgical cavity, which appears white on DWI and black on ADG images, represents a small cortical lesion during the partial tumor resection. Reprinted with permission (94).](image-url)
humans, only one study has specifically investigated whether indomethacin causes cerebral ischemic damage. Using diffusion-weighted MRI, a very sensitive method for detecting cerebral ischemic injury, the authors provided no evidence that indomethacin causes ischemic damage in patients with brain tumors.

Conclusion and perspectives

Both experimental and clinical studies in patients with head injury and cerebral tumors provide considerable evidence that indomethacin is effective in reducing intracranial pressure. In contrast to hyperventilation, indomethacin improves cerebral perfusion pressure, which is important for securing optimal cerebral oxygenation. Furthermore, indomethacin seems to be effective in situations where standard treatment modalities such as hyperventilation, barbiturate treatment and osmotherapy are not effective. However, the reported clinical studies in patients with head injury were performed on small patient materials using uncontrolled designs. Large-scale randomized studies are urgently needed to conclude whether the use of indomethacin in treating head injury has any benefit on outcome.

The effect of indomethacin on intracranial pressure in patients with brain tumors seems to depend on the choice of anesthesia and mode of administration. Studies are needed to clarify whether the properties of indomethacin are different in patients anesthetized with volatile and intravenous anesthetics.

Cerebral autoregulation is often impaired in patients with brain pathology, but experimental and clinical evidence is lacking on whether indomethacin can restore impaired cerebral autoregulation.

New MRI-techniques offer the advantage of measuring cerebral blood flow by generating flow parameters such as cerebral blood volume and mean transit time with a high spatial resolution. By applying these techniques future studies can reveal detailed information about indomethacin’s effects on regional cerebral hemodynamics in patients with brain trauma and space-occupying lesions.

Several studies in recent years suggest that indomethacin has neuroprotective properties and cerebral ischemia has not been detected in clinical studies. Thus, in addition to being effective in reducing intracranial pressure and improving cerebral perfusion pressure, indomethacin may protect against cerebral ischemia. Further clinical studies, which address this important topic, are needed to further clarify the role of indomethacin in neuroprotection.

Acknowledgements

The author would like to thank Dr Georg E. Cold and Dr Niels Juul, Department of Neuroanesthesia, Aarhus University Hospital, Denmark, for helpful discussions and suggestions concerning the preparation of this manuscript. Language secretary Anita Pachai is thanked for spell-checking the manuscript. This study was supported by grants from: The Western Danish Research Forum; The Alice Brenaa Foundation; The Foundation of the Danish Medical Association; Grosseer CP FrederikSENS Foundation; Oberstinde Jens fra la Cour’s Foundation; and the Institute for Experimental Clinical Research.

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