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Differences in the Effects in the Newborn Piglet of Various Nonsteroidal Antiinflammatory Drugs on Cerebral Blood Flow but Not on Cerebrovascular Prostaglandins

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ABSTRACT. To characterize the role of prostaglandins (PG) in the regulation of basal cerebral blood flow (CBF) in the newborn, we determined the effects of four nonsteroidal antiinflammatory drugs, indomethacin (3 mg/kg, *n* = 8 and 10 mg/kg, *n* = 5), aspirin (65 mg/kg, *n* = 6), ibuprofen (30 mg/kg, *n* = 8), and naproxen (15 mg/kg, *n* = 6), on CBF, cerebral metabolism, and cerebrovascular PG in conscious 1- to 3-d-old piglets. Drugs and vehicle (*n* = 8) were injected i.v., and measurements were made 5 min before and 20 and 60 min after injections. Neither the vehicle nor any of the nonsteroidal antiinflammatory drugs exerted significant effects on mean arterial blood pressure and on blood gases and pH. All four drugs, with the exception of indomethacin at the lower dose (3 mg/kg), decreased PG to nearly undetectable levels within 20 min; the low dose of indomethacin caused a small decrease (18–32%) in PG at 60 min. However, the effects of these agents on CBF were diverse. CBF increased after the administration of aspirin, decreased to almost the same extent after both low and high doses of indomethacin, and did not change after the administration of ibuprofen and naproxen. Cerebral metabolic rate for oxygen was increased by aspirin but was unaltered by the other drugs. The data suggest that PG may not play a critical role in the regulation of basal CBF in the newborn animal and that certain nonsteroidal antiinflammatory drugs may have additional actions unrelated to the inhibition of PG synthesis. (*Pediatr Res* 30: 106–111, 1991)

Abbreviations

PG, prostaglandin
CBF, cerebral blood flow
BP, blood pressure
NSAID, nonsteroidal antiinflammatory drug

The role of PG in the regulation of CBF during various hemodynamic disturbances, such as hypertension, hypotension, hypoxia, and asphyxia, has been reported by various investigators (1–14). However, the significance of PG in the regulation of basal CBF remains controversial (15–19). In most studies examining the role of PG in cerebral hemodynamics, indomethacin has been used as the prototype of nonsteroidal antiinflammatory drugs (NSAID) (20, 21). However, the extremely fast onset of action of indomethacin on the cerebral circulation (15–19, 22) does not coincide with its effects on the cerebral and vascular levels (23, 24) and the disposition (25, 26) of PG.

Therapeutic doses of indomethacin (0.2 mg/kg) have been shown to decrease CBF and CBF velocity in the human infant within 2 min (16–19), long before any decrease in arterial or cerebral PG occurs (23, 24). Our recent data suggest that the effects of indomethacin are not identical to those of other NSAID, such as ibuprofen (12, 13), and may not be produced entirely by an inhibition of cyclooxygenase activity (12, 27–30). Also, the effects of salicylates on cerebral hemodynamics of adults do not correspond with their effects on the synthesis of PG (31). In short, the role of PG in the regulation of basal blood flow to major organs remains controversial (32). We therefore determined the effects of four NSAID, namely, indomethacin, aspirin, ibuprofen, and naproxen, on CBF and cerebrovascular PG, using the conscious newborn piglet as the experimental model. We found that although all NSAID inhibited the synthesis of PG, CBF was increased by aspirin, decreased by indomethacin, and not affected by ibuprofen and naproxen.

MATERIALS AND METHODS

This study was approved by the Animal Care and Ethics Committee of the McGill University-Montreal Children's Hospital Research Institute and the University of Iowa Animal Care and Use Committee.

Surgical preparation. Experiments were conducted on 41 newborn piglets (1.2–2 kg), 1 to 3 d old. The catheterization of the blood vessels was done under halothane anesthesia, as previously described (12–14). A polyethylene catheter was placed into the left ventricle via the right subclavian artery for the injection of radiolabeled microspheres. The left subclavian artery was catheterized for continuous recording of BP by means of a pressure transducer (Statham, Glen Burnie, MD) connected to a multichannel recorder (DR-8; Electronics for Medicine, White Plains, NY). The femoral artery was cannulated for the withdrawal of blood samples including reference samples. A polyethylene catheter (Intramedic, PE-50; Becton Dickinson, Parsippany, NJ) was placed into the inferior vena cava via the femoral vein for drug injection, and the sagittal vein was cannulated through a burr hole in the skull for blood sampling.

After catheterization, the animals were allowed to recover from anesthesia under an overhead lamp for approximately 3 to 4 h. For the purposes of experimentation, the awake and sponta-

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neously breathing animals were placed comfortably on a cloth sling, which did not interfere with breathing movements. Body temperature was maintained at 38°C by an infant radiant warmer.

Experimental protocol. Animals were divided randomly to receive i.v. either aspirin (65 mg/kg, $n = 6$), ibuprofen (30 mg/kg, $n = 8$), naproxen (15 mg/kg, $n = 6$), indomethacin (3 mg/kg, $n = 8$ or 10 mg/kg, $n = 5$), or vehicle ($n = 8$) in a total volume of approximately 1 to 2 mL. These doses of NSAID were selected because they have been previously shown to inhibit cyclooxygenase activity in the brain and/or alter cerebral hemodynamics (6, 12, 13, 15, 22, 23, 31, 33–38).

CBF measurements were made 5 min before and 20 and 60 min after the administration of the drug or the vehicle. Immediately after each injection of microspheres and after the withdrawal of the reference blood sample, blood was withdrawn from the sagittal vein and left subclavian artery for the determination of blood gases and oxygen saturation of Hb (Instrumentation Laboratory, Inc., Lexington, MA), concentration of Hb, and assays of plasma PGE, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$ (the stable metabolite of PGI_2). Withdrawn blood was promptly replaced with blood from a donor piglet. After the experiment, the animal was killed with an administration of pentobarbital. An autopsy was performed to verify the location of catheters and to remove the brain for the counting of microspheres.

Measurement of CBF. CBF was measured using the radiolabeled microsphere technique (39), as previously used (12–14). Approximately 300 000 microspheres of 15-μm diameter labeled with [^{141}Ce], [^{51}Cr], and [^{46}Sc] were injected in a random order into the left ventricle, and the catheter was flushed with 2 mL of saline. Reference blood samples were withdrawn from the left subclavian catheter, beginning 10 s before microsphere injection, and were continued for 70 s at a rate of 2 mL/min, using a Harvard infusion/withdrawal pump (Harvard Apparatus Co., Inc., S. Natick, MA). The brain was weighed and divided into four major regions: cortex, periventricular area, brainstem, and cerebellum. Radioactivity in the tissues and reference blood samples was counted by a gamma counter (Biogamma II; Beckman Instruments, Inc., Fullerton, CA), with appropriate provision for interference between nuclides. Microspheres were equally distributed to both cerebral hemispheres. In all of the brain regions and reference blood samples, the number of microspheres exceeded 1200, indicating reliable blood-flow measurements (39).

Regional CBF (mL/min/100 g) was calculated using the following formula: CBF = cpm/100 g of tissue × withdrawal rate of reference sample per cpm in the reference sample. Cerebral metabolic rate for oxygen was calculated as CBF × (arterial − sagittal venous O_2 content) and expressed in mL/min/100 g.

Assay of PG. Arterial and sagittal venous blood samples (1.5 mL) were collected in ice-cold polypropylene tubes containing 28 mg/mL EDTA and 40 μg/mL indomethacin. The blood was immediately centrifuged at 2450 × g for 15 min at 4°C, and the plasma was stored at −70°C until it was assayed. PG were measured using RIA (40) kits that were previously tested for reproducibility (12). Plasma proteins were precipitated with acetone at −20°C. Neutral lipids were removed with petroleum ether. The aqueous phase was acidified to pH 3 to 4. PG were extracted with ethyl acetate, which was subsequently evaporated to dryness. The residue was dissolved in a 0.01 M phosphate buffer (pH 7) containing 0.1% bovine gamma globulin and 0.1% sodium azide.

The aliquots of plasma were assayed in duplicate for total PGE, $PGF_{2\alpha}$, and 6-keto-$PGF_{1\alpha}$. [^{3}H]PG were used for the assays. After an incubation period of 2 h at 25°C, the bound analyte was separated from the free analyte, using dextran-coated charcoal. Biofluor was used as the emulsifier-scintillation cocktail. Radioactivity was counted in an automated β-scintillation counter (Beckman). All antibodies exhibited <1.6% cross-reactivity to other PG, with the exception of antibodies to PGE that displayed 100% cross-reactivity for PGE_1 and PGE_2. Recovery was determined, using aliquots of plasma with known concentrations of PG, and was >80%. The normalized percentage of bound tracer on standard curves varied <5% between assays. The standards used to determine these curves allowed measurements of PG in the concentration range of 20 to 20 000 pg/mL.

Chemicals and reagents. Indomethacin, aspirin, ibuprofen, and naproxen were purchased from Sigma Chemical Co. (St. Louis, MO), dissolved in NaCl 150 mM and NaOH 0.3 N, and titrated to pH 7.4. PG RIA kits were purchased from Advanced Magnetics (Boston, MA), radionuclide-labeled microspheres from 3-M (Newbrighton, MN), and Biofluor from New England Nuclear (Boston, MA). All other chemicals were purchased from Fisher Laboratories (Montreal, Quebec and Springfield, NJ).

Statistical analysis. Data were analyzed using analysis of variance for different groups and repeated measures and comparison among means tests; for regression analysis, the Pearson's product-moment correlation coefficient was determined. A p of less than 0.05 was assumed to denote significant differences. Data were expressed as means ± SEM and as ranges.

RESULTS

Stability of experimental preparations. Mean BP and arterial pH, P_{CO_2}, and P_{O_2} remained stable after treatment with the vehicle or any of the NSAID (Table 1; results with the low dose of indomethacin are not shown).

Effects of NSAID on CBF and metabolism. The effects of the various NSAID on total and regional CBF are shown in Figure 1. In the vehicle-, ibuprofen-, and naproxen-treated animals, CBF remained constant throughout the experimental period. In contrast, indomethacin (3 and 10 mg/kg) decreased total and regional CBF by 31 to 42% at 20 and at 60 min after drug injection ($p < 0.01$ compared with basal values). The changes in CBF observed 20 and 60 min after indomethacin was administered were similar to each other, and there were no differences in these CBF changes when comparing the two doses of indomethacin. Aspirin produced a significant increase ($p < 0.05$ compared with basal values) in CBF at 20 min (16–22%) and a similar rise in CBF at 60 min (20–32%) after its administration. The cerebral metabolic rate for oxygen was increased by 23 ± 2% and 26 ± 3% 20 and 60 min, respectively, after the administration of aspirin ($p < 0.05$ compared with basal value) but was not affected by any other treatment (Table 2).

Effects of NSAID on PG concentrations. The administration of the vehicle did not change the PG concentrations in the sagittal sinus and arterial plasma (Figs. 2*a* and 3*a*). The 3-mg/kg dose of indomethacin produced no significant changes in PG concentrations at 20 min but decreased their concentrations by 18 to 32% ($p < 0.05$) at 60 min after the injection (Figs. 2*e* and 3*e*). On the other hand, the higher dose of indomethacin (10 mg/kg) as well as aspirin (65 mg/kg), ibuprofen (30 mg/kg), and naproxen (15 mg/kg) markedly decreased the concentrations of PG to nearly undetectable levels of $PGF_{2\alpha}$ and 6-keto-$PGF_{1\alpha}$ ($p < 0.001$) at 20 and 60 min after their injections; the levels of PG 20 and 60 min after the administration of these drugs were similar (Figs. 2*b–d* and *f* and 3*b–d* and *f*).

The relationship between total CBF and sagittal sinus PG concentrations was also examined (Fig. 4). There was no correlation between CBF and any of the PG measured for each of the individual treatment groups or for the combination of these groups ($r = -0.31$–0.25, $p > 0.24$).

DISCUSSION

To find out whether or not an inhibition of PG synthesis by different NSAID produced similar effects on CBF, we administered indomethacin, aspirin, ibuprofen, and naproxen at doses expected to completely inhibit the synthesis of PG in the cerebral spinal fluid or brain (23, 31, 33, 37, 38) as well as a lower dose

Table 1. *Effects of vehicle and different nonsteroidal antiinflammatory drugs on blood pressure and gases of conscious newborn piglets**

Agent	Dose (mg/kg)	Parameters	Basal	Time after injection of agent: 20 min	Time after injection of agent: 60 min
Vehicle		MBP	8.02 ± 0.62	8.69 ± 0.40	7.63 ± 0.39
		pH	7.42 ± 0.02	7.46 ± 0.03	7.47 ± 0.03
		P_{O_2}	9.86 ± 0.83	9.63 ± 0.67	9.04 ± 0.99
		P_{CO_2}	5.04 ± 0.29	4.54 ± 0.28	4.65 ± 0.36
Aspirin	65	MBP	8.55 ± 0.77	8.16 ± 0.92	8.29 ± 0.97
		pH	7.37 ± 0.05	7.36 ± 0.04	7.36 ± 0.05
		P_{O_2}	12.15 ± 0.77	12.59 ± 1.00	13.00 ± 0.85
		P_{CO_2}	4.99 ± 0.55	4.75 ± 0.71	4.49 ± 0.90
Ibuprofen	30	MBP	9.61 ± 0.52	10.26 ± 0.55	9.61 ± 0.53
		pH	7.41 ± 0.02	7.39 ± 0.02	7.37 ± 0.02
		P_{O_2}	11.66 ± 1.11	11.49 ± 1.67	10.92 ± 1.29
		P_{CO_2}	5.21 ± 0.37	5.71 ± 0.60	5.63 ± 0.77
Naproxen	15	MBP	9.21 ± 0.66	9.48 ± 0.78	9.08 ± 0.65
		pH	7.40 ± 0.04	7.41 ± 0.03	7.39 ± 0.03
		P_{O_2}	10.90 ± 1.16	10.50 ± 1.25	11.20 ± 1.09
		P_{CO_2}	4.84 ± 0.58	5.08 ± 0.67	5.33 ± 0.61
Indomethacin	10	MBP	8.03 ± 0.52	7.77 ± 1.03	8.95 ± 0.51
		pH	7.36 ± 0.03	7.36 ± 0.04	7.38 ± 0.03
		P_{O_2}	12.53 ± 0.60	11.70 ± 0.93	11.86 ± 0.43
		P_{CO_2}	5.08 ± 0.40	4.86 ± 0.65	4.78 ± 0.53

* Values are mean ± SEM, expressed in kPa (1 mm Hg = 0.13 kPa), except for pH. Analysis of variance for repeated measures was performed to test for statistical significance. MBP, mean arterial blood pressure.

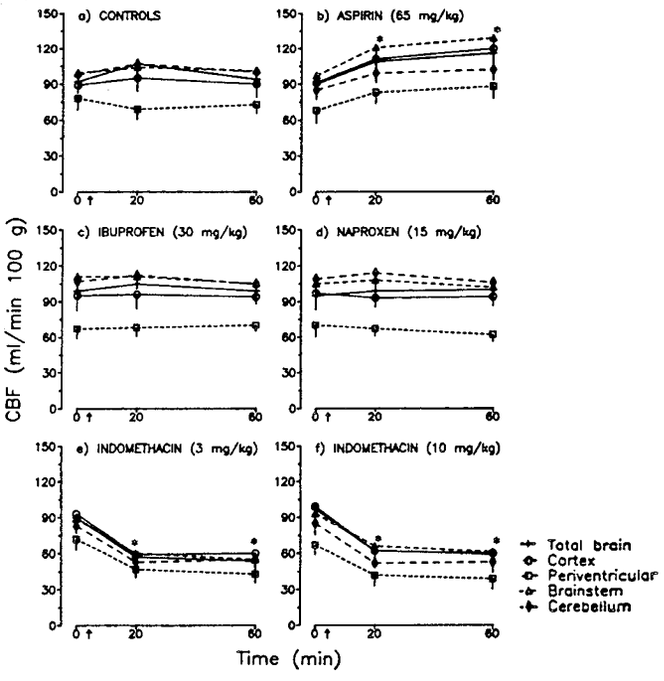

Fig. 1. Effects of aspirin, ibuprofen, naproxen, indomethacin, and vehicle on CBF of 1- to 3-d-old conscious piglets. The 0 time refers to preinjection values. Aspirin (n = 6), ibuprofen (n = 8), naproxen (n = 6), indomethacin (n = 8 for 3 mg/kg and n = 5 for 10 mg/kg), and vehicle (n = 8) were injected 5 min later, as indicated by the *arrows*. Values are mean ± SEM. *, $p < 0.05$ compared with preinjection values (by analysis of variance for repeated measures and comparison among means tests).

(3 mg/kg) of indomethacin expected to minimally change PG concentrations up to 1 h (12, 23). As discussed below and illustrated in Figure 4, our data show that the effects of different NSAID on cerebral hemodynamics do not correlate with those of PG.

The mean arterial BP and blood pH, P_{CO_2}, and P_{O_2} of piglets

Table 2. *Effects of vehicle and different nonsteroidal antiinflammatory drugs on cerebral metabolic rate for oxygen of conscious newborn piglets**

Agent	Dose (mg/kg)	Basal	Time after injection of agent: 20 min	Time after injection of agent: 60 min
Vehicle		4.0 ± 0.7	3.8 ± 0.5	3.8 ± 0.6
Aspirin	65	3.7 ± 0.5	4.5 ± 0.5†	4.8 ± 0.6†
Ibuprofen	30	3.2 ± 0.7	3.0 ± 1.0	3.4 ± 0.8
Naproxen	15	3.4 ± 0.6	3.7 ± 0.8	3.6 ± 0.7
Indomethacin	3	4.2 ± 1.1	4.2 ± 0.9	4.0 ± 0.7
Indomethacin	10	3.9 ± 0.9	3.5 ± 1.0	4.1 ± 0.9

* Values are mean ± SEM, expressed in mL/min/100 g.

† $p < 0.05$ compared to basal value (by analysis of variance for repeated measures and comparison among means tests).

used in this study did not change after the administration of the vehicle or any of the four NSAID; these variables were similar in all of the six groups of experiments and at all three periods of observation (Table 1). Moreover, blood gases, PG concentrations, and hemodynamic parameters remained stable throughout the duration of the experiment in vehicle-treated animals, and these as well as the other measurements taken before administration of the drugs (basal values) were comparable with data in the literature (Tables 1 and 2; Figs. 1*a*, 2*a*, and 3*a*) (1, 2, 5–8, 12–14, 34, 37). This would suggest that the experimental conditions were suitable for purposes of our study. Nevertheless, the stressful experimental conditions may be a limitation of these studies.

Sagittal sinus blood concentrations of PG were assayed because these have been suggested to reflect levels in specific organ vasculature and may better disclose their role as chemical mediators in organ blood-flow regulation (41–43). Also, no change in sagittal sinus and arterial blood PG concentrations was observed after three (Figs. 2*a* and 3*a*) or four (12) injections of microspheres in vehicle-treated animals, indicating that this number of microsphere injections does not alter cerebrovascular PG concentrations. In support of these inferences, the levels of PG we observed in the sagittal sinus were similar to those previously reported at the same site (13, 34) as well as in the cerebral spinal

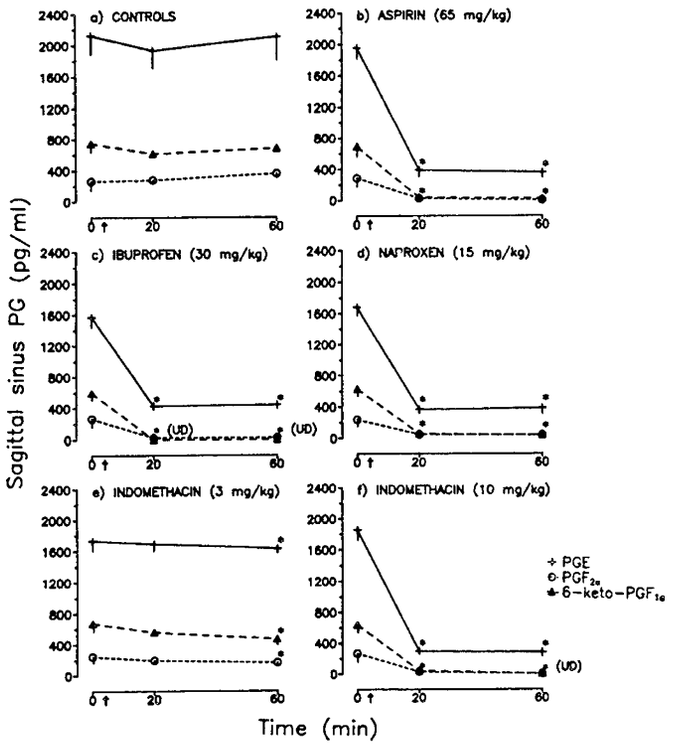

Fig. 2. Effects of aspirin, ibuprofen, naproxen, indomethacin, and vehicle on sagittal sinus concentrations of PG of 1- to 3-d-old conscious piglets. The 0 time refers to preinjection values. Aspirin ($n = 6$), ibuprofen ($n = 8$), naproxen ($n = 6$), indomethacin ($n = 8$ for 3 mg/kg and $n = 5$ for 10 mg/kg), and vehicle ($n = 8$) were injected 5 min later, as indicated by the *arrows*. Values are mean ± SEM. *UD*, undetectable levels (<20 pg/mL). *, $p < 0.05$ compared with preinjection values (by analysis of variance for repeated measures and comparison among means tests).

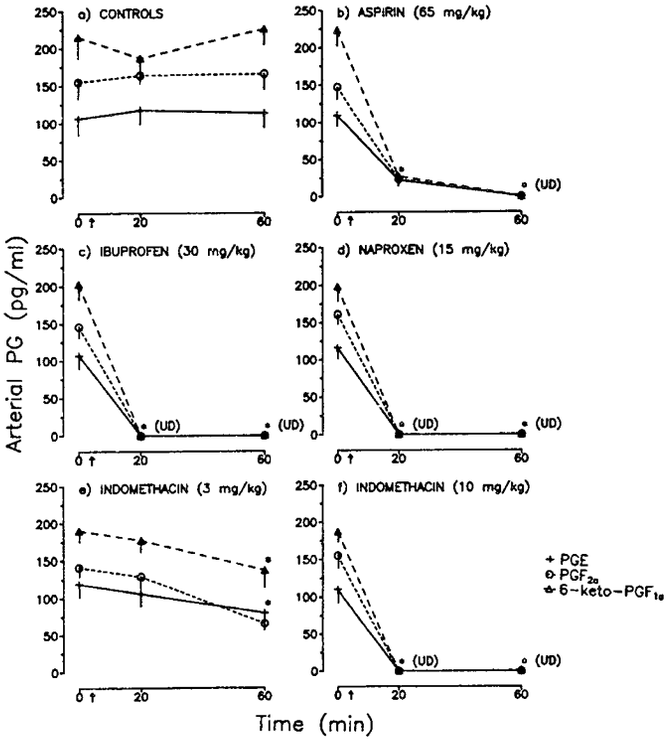

Fig. 3. Effects of aspirin, ibuprofen, naproxen, indomethacin, and vehicle on arterial concentrations of PG of 1- to 3-d-old conscious piglets. The 0 time refers to preinjection values. Aspirin ($n = 6$), ibuprofen ($n = 8$), naproxen ($n = 6$), indomethacin ($n = 8$ for 3 mg/kg and $n = 5$ for 10 mg/kg), and vehicle ($n = 8$) were injected 5 min later, as indicated by the *arrows*. Values are mean ± SEM. *UD*, undetectable levels (<20 pg/mL). *, $p < 0.05$ compared with preinjection values (by analysis of variance for repeated measures and comparison among means tests).

fluid of both acutely instrumented animals and animals that were instrumented on a long-term basis (6, 37, 38). This would suggest that sagittal sinus concentrations reflect cerebral and not arterial PG levels (Figs. 2 and 3). Moreover, the PG with the highest levels in the sagittal sinus was PGE (Fig. 2), as reported for the cerebral spinal fluid (37, 44), in contrast to the arterial blood, where 6-keto-$PGF_{1\alpha}$ exhibited the highest concentrations (Fig. 3) (6, 7). Thus, based on the levels of PG in the sagittal sinus blood, which seems to reflect those in the cerebral spinal fluid, and the doses of NSAID selected, which have been shown to inhibit cerebral PG synthesis (6, 23, 31, 33, 37, 38), we believe that brain and cerebral spinal fluid PG levels were decreased by the NSAID used in this study.

Ibuprofen and naproxen markedly decreased PG concentrations in the sagittal sinus to levels reported in the cerebrospinal fluid and brain (23, 33) but did not change basal CBF (Figs. 1–3). Our findings are in accordance with other studies that have shown that ibuprofen does not reduce basal blood flow to the brain (13, 34) nor to other major organs (renal, cardiac, and mesenteric) (45–48). PGE and PGI_2 are the predominant PG produced by the brain tissue and cerebral vasculature (3, 4, 49, 50). These PG increase CBF in the newborn animal (12). Thus, if PG contributed to basal CBF, one would have expected to see a decrease in CBF after the administration of ibuprofen and naproxen. However, these drugs had no effect on basal CBF.

In contrast to our findings and those of Grice *et al.* (34), Hoffman *et al.* (51) reported that ibuprofen caused a decrease in CBF in the adult goat; Leffler and Busija (21) found that ibuprofen increased CBF in the newborn pig. The reason for the discrepancy is not clear but may be due to differences in the experimental protocols, including the methods of measuring CBF and/or anesthetic agents used. Hoffman *et al.* (51) measured blood flow using electromagnetic probes placed on the internal maxillary artery; it is possible that they measured in part the effect of ibuprofen on extracerebral blood flow. The data of Leffler and Busija (21) are mentioned in a review, and the experimental conditions are not described.

As discussed above, ibuprofen and naproxen did not alter CBF. On the other hand, the reduction in PG levels after aspirin was administered was accompanied by a significant increase in CBF (Figs. 1–3). This increase in CBF is most likely the result of a rise in cerebral metabolic rate for oxygen, which was not observed with the other NSAID (Table 2) and probably results from an uncoupling of oxidative phosphorylation (31). These effects of aspirin reiterate the importance of cerebral metabolism over the role of PG on CBF regulation.

The two doses of indomethacin produced similar changes in CBF but different effects on PG concentrations. Twenty min after the smaller dose of indomethacin (3 mg/kg) was administered, there was no significant reduction in PG levels, but the cerebral hemodynamic changes were equivalent to those that occurred after the larger dose of indomethacin (10 mg/kg) was administered, which virtually abolished PG synthesis by 20 min (Figs. 2 and 3). Furthermore, there was no correlation between the effects of indomethacin on CBF and sagittal sinus PG levels (Fig. 4). The minimal decrease in PG concentrations 1 h after the lower dose of indomethacin (3 mg/kg) was administered is in agreement with similar reported changes in brain PG levels up to 4 h after the same drug dose (23). The effects of indomethacin we observed are also in accord with previous reports, indicating a very rapid and similar decrease (within 2 min) in CBF in the animal (6, 15, 22) and human neonate (19) as well as a decrease in CBF velocity of the human newborn (16–18) before any changes in arterial or cerebral PG occur (23, 24). Moreover, our findings are consistent with the action of this drug on various other major vascular beds. In contrast to ibuprofen, meclofena-

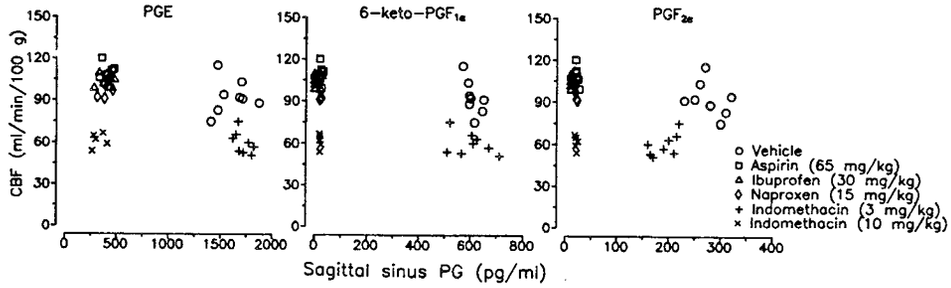

Fig. 4. Relationship between total CBF and sagittal sinus PG levels 20 min after injection of vehicle or NSAID. For all PG, $r = -0.31$ to 0.25, $p > 0.24$, for individual or combined treatment groups. For the undetectable levels of 6-keto-$PGF_{1\alpha}$ and $PGF_{2\alpha}$ (<20 pg/mL) measured in the ibuprofen-treated animals, a value of 10 pg/mL was plotted.

mate, and aspirin, indomethacin has been shown to reduce basal organ (mesenteric, renal, uterine, and cardiac) blood flow (45–48, 52, 53) to the same extent, regardless of its dose (53), and to constrict isolated vessels (29), probably by an action independent of the effects on PG. For instance, indomethacin has been shown to inhibit histamine release (54) and to potentiate the lipoxygenase pathway (28, 55, 56) in contrast to other NSAID (47, 56).

Several factors are involved in the regulation of basal CBF, including K^+, Ca^{2+}, glutamate, ATP, adenosine, endothelium-derived relaxing factor, endothelin, and eicosanoids, and some of them have opposing actions. Consequently, the release of several of these substances during adaptive physiologic conditions may mask specific effects of one or a group of mediators (57). Thus, the possible interactions of vasoactive factors with opposing effects may explain the failure of a single class of agents, such as PG, to exert a predominant contribution on basal CBF (Figs. 1–3).

In conclusion, the effects of NSAID on cerebral hemodynamics of the newborn animal differ markedly among the various agents, and regardless of the drug or dose, they do not correlate with their effects on PG (Fig. 4). Our data indicate that aspirin and indomethacin appear to exert their acute effects on CBF via mechanisms other than through cyclooxygenase inhibition, whereas ibuprofen and naproxen markedly inhibit PG synthesis without altering CBF. These observations suggest that PG may not have a critical role in the regulation of basal cerebral hemodynamics in the newborn animal, as has been suggested for other major organs in the adult (29, 32, 45–47, 52, 53, 58), This, however, does not preclude the important contribution of PG to CBF regulation during adaptive physiologic responses (1–14, 32, 44, 59). Finally, our findings clearly indicate, as previously suggested (20, 60), that it is necessary to compare the cerebrovascular effects of a range of NSAID before attributing a particular role to the PG.

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