0031-3998/95/3701-0081$03.00/0
PEDIATRIC RESEARCH

Vol. 37, No. 1, 1995
Printed in U.S.A.

Alterations in the Electroretinogram of Newborn Piglets by Propionic Acid–Derivative Nonsteroidal Antiinflammatory Drugs but Not by Indomethacin and Diclofenac

NELLY HANNA, PIERRE LACHAPELLE, MARIE-SYLVIE ROY, JACQUELINE ORQUIN, DAYA R. VARMA, AND SYLVAIN CHEMTOB

Departments of Pediatrics, Pharmacology N.H., S.C., and Ophthalmology M.-S.R., J.O., Research Center of Hôpital Ste-Justine, University of Montreal and Departments of Ophthalmology P.L. and Pharmacology and Therapeutics D.R.V., McGill University, Montreal, Quebec, Canada

ABSTRACT

Different nonsteroidal antiinflammatory drugs (NSAID), especially ibuprofen, are being considered as an alternative to indomethacin for use in the newborn and as antipyretics for infants. However, some of these NSAID have been shown to cause visual complications. We therefore studied the effects of different NSAID indomethacin 19.6 μmol/kg (7 mg/kg), diclofenac 15.7 μmol/kg (5 mg/kg), ibuprofen 48 and 194 μmol/kg (10 and 40 mg/kg), naproxen 79 μmol/kg (20 mg/kg), and flurbiprofen 41 μmol/kg (10 mg/kg) on photopic and scotopic electroretinograms (ERG) and retinal prostaglandin E_2, prostaglandin $F_{2\alpha}$, and 6-keto-prostaglandin $F_1\alpha$ levels in piglets 1–5 d old. All NSAID decreased retinal prostaglandin levels, but their effects on the ERG were not identical. Indomethacin and diclofenac did not alter the ERG. In contrast, the propionic acid derivatives ibuprofen (the two doses used), naproxen, and flurbiprofen affected the amplitude as well as the implicit time of the ERG under photopic and scotopic conditions. These changes are suggestive of generalized alterations in the function of rods and cones. Prior inhibition of prostaglandin synthesis by indomethacin did not modify the effects of ibuprofen on the ERG. These findings thus show a dissociation between the effects of NSAID on the ERG and prostaglandin synthesis. Because ERG changes are associated with visual alterations, these effects of propionic acid derivatives should be taken into account before considering their use in infants. (***Pediatr Res* 37: 81–85, 1995**)

Abbreviations
NSAID, nonsteroidal antiinflammatory drug
ERG, electroretinogram
PG, prostaglandin

It is generally agreed that NSAID exert their actions mainly by inhibiting cyclooxygenase activity and in turn PG synthesis (1). NSAID have been found to be of benefit in the treatment of many ocular inflammatory conditions such as uveitis (2), posterior scleritis (3), aphakic cystoid macular edema (4), and allergic conjunctivitis (5). NSAID can also enhance the range of retinal and choroidal blood flow autoregulation (6) and protect retinal function after asphyxia in the newborn (7). However, the effects of different NSAID on retinal function are not identical and do not always correlate with an inhibition of PG synthesis (7, 8). For instance, indomethacin can compromise retinal and choroidal blood flow, and these effects may be unrelated to cyclooxygenase inhibition (8). Ibuprofen can cause ocular complications such as blurring of vision, scotoma, depressed contrast sensitivity (9–11), decreased wave amplitude, and an increase in conduction time of the visual evoked potential (12).

In the course of studies on the effects of NSAID on retinal function, we observed that ibuprofen altered the electrophysiologic function of the retina of newborn pigs. To our knowledge, these effects of ibuprofen have not been reported, and it is not known whether this is a unique property of ibuprofen or is shared by all inhibitors of PG synthesis. Moreover, this issue could be of concern given the fact that NSAID other than indomethacin, in particular ibuprofen, are being considered for use in the newborn (13) and heeded as alternative antipyretics in young infants (14, 15). We therefore studied the effects of three different groups of NSAID (propionic acid derivatives, ibuprofen, naproxen, and flurbiprofen; indole derivative, indomethacin; and phenylacetic acid derivative, diclofenac) on the ERG of piglets in relation to their inhibitory effects on PG synthesis. We are the first to report that propionic acid deriv-

Received April 4, 1994; accepted August 25, 1994.
Correspondence: Dr. Sylvain Chemtob, Research Center of Hôpital Ste-Justine, Department of Pediatrics and Pharmacology, 3175 Côte Ste-Catherine, Montreal, Quebec, H3T-1C5, Canada.
Supported by grants from the Medical Research Council of Canada, the United Cerebral Palsy Foundation, the Fonds de la Recherche en Santé du Québec, the Heart and Stroke Foundation of Québec, and Biopedia.

atives but not other classes of NSAID alter the ERG and that this effect is unrelated to an inhibition of PG synthesis.

METHODS

Animals and Surgical Preparation

Piglets (1–5 d old, 1.2–2.2 kg) were used in this study according to a protocol approved by the Animal Care Committee of the Research Center of Hôpital Ste. Justine. The pig was used because its retina shares similarities with that of the human, such as the absence of tapetum, the ratio of rods to cones, an holangiotic vascularization, and a paracentral fovea (16, 17).

Animals were anesthetized with halothane (2.5%). A small polyethylene catheter (Intramedic PE-50, Becton Dickinson & Co., Parsippany, NJ) was introduced in the femoral vein for drug administration and to sample blood for measurement of pH, Pco_2, and Po_2. Tracheostomy was performed, and the animals were ventilated with air by means of a Harvard small-animal respirator (Ealing Scientific Limited, Quebec, Canada). After surgery, halothane was discontinued and the animals were sedated with acepromazine (0.02 μmol/kg i.v.) and paralyzed with pancuronium (0.14 μmol/kg i.v.). Animals were allowed to stabilize for approximately 1 h, and their body temperature was maintained at 38°C by means of a heating pad.

Experimental Protocol

Treatments. Thirty-one animals were randomly assigned to receive an i.v. injection of indomethacin (19.6 μmol/kg, 7 mg/kg), diclofenac (15.7 μmol/kg, 5 mg/kg), ibuprofen (48 μmol/kg, 10 mg/kg), ibuprofen (194 μmol/kg, 40 mg/kg), naproxen (79 μmol/kg, 20 mg/kg), flurbiprofen (41 μmol/kg, 10 mg/kg), or saline; these doses have previously been shown to reduce PG levels (8, 18, 19). Naproxen and the lower dose of ibuprofen were within therapeutic limits for young children (13, 14, 20); doses for children have not been determined for the other drugs with the exception of indomethacin, hence adult doses were used.

Electroretinograms. Pupils were maximally dilated with cyclopentolate hydrochloride (1%) (Alcon Canada, Inc., Mississauga, Canada) eye drops. ERG were recorded (7, 21) before and 1 h after drug administration using corneal contact lens electrodes (ERG Jet, Universo, SA-La-Chaux-De-Fonds, Switzerland) filled with hydroxypropyl-methylcellulose (2%). Reference and ground electrodes were placed on the forehead and the scalp, respectively. The head of the animal was adjusted in the center of a Ganzfeld stimulator (LKC Technologies Inc., Gaithersburg, MD), the flash stimulus (Grass Instrument Co., Quincy, MA) was set at 3.65 $cd{\cdot}s/m^2$. ERG signals were amplified using the EPIC 2000 electrodiagnostic instrument (LKC Technologies Inc.) with a bandwidth of 0.3 to 500 Hz. After a 40-min period of dark adaptation, scotopic (combined rod and cone) responses were obtained; 10 min after light adaptation, photopic (cone) responses were measured. Measurements were based on the average response to 10 flash stimulations and stored on computer disks for subsequent analysis (7, 21). The amplitude of the a-wave was calculated as the difference in voltage from baseline to the maximum negative deflection of the ERG; the b-wave amplitude was calculated from the most negative deflection (peak of a-wave) of the ERG to the maximum positive one. The implicit time for each wave was calculated as the time from the flash onset to the peak of the wave.

Measurement of PG. The effect of different NSAID on PGE_2, $PGF_{2\alpha}$, and 6-keto-$PGF_1\alpha$ (a stable metabolite of PGI_2) was measured in separate groups of animals (n = 3–4 in each treatment group) 1 h after the drug or saline treatments described for the ERG. Animals were killed by an injection of pentobarbital (483 μmol/kg i.v.). Eyes were immediately enucleated and placed on ice; the retina was dissected and suspended in ice-cold buffer (pH 7.4) containing 5 mM Tris-HCl, 0.67 mM acetylsalicylic acid, and 0.5 mM sodium edetate. Retinas were homogenized, and an aliquot was used to measure proteins (22). The homogenate was centrifuged at 1000 × g for 10 min to remove undisrupted cells. The supernatant was recentrifuged at 50 000 × g for 30 min at 4°C to remove membranes and enhance the extraction of PG on octadecylsilyl

Table 1. *Changes in a- and b-wave amplitude and implicit times during photopic and scotopic conditions 1 h after treatment with saline and different nonsteroidal antiinflammatory drugs in newborn pigs*

		a-Wave				b-Wave			
		Amplitude		Implicit time		Amplitude		Implicit time	
Treatment	Dose (μmol/kg)	Photopic	Scotopic	Photopic	Scotopic	Photopic	Scotopic	Photopic	Scotopic
Saline		0.2 ± 2	9.2 ± 6	0.6 ± 0.7	0.9 ± 0.5	3.8 ± 5.9	15.7 ± 20.5	0.1 ± 0.7	0.8 ± 1.3
Indomethacin	19.6	−1 ± 1	−1.7 ± 8.7	0.3 ± 0.7	0.5 ± 0.6	−11 ± 9.3	0 ± 9.3	1.8 ± 1.1	1 ± 0.8
Diclofenac	15.7	−2 ± 3	4.3 ± 5	0.3 ± 0.2	0.5 ± 0.8	2.5 ± 3.9	13 ± 13	1.2 ± 1.4	1.7 ± 0.9
Naproxen	79	−3 ± 1	2.3 ± 8	1.2 ± 0.2*	2.2 ± 0.3*	11.3 ± 12.4	0.3 ± 28.6	2.8 ± 0.7*	2.2 ± 0.3*
Flurbiprofen	41	5 ± 3	1.6 ± 4.2	0.8 ± 0.1	1.3 ± 0.1*	−2.5 ± 17.5	−3.5 ± 15	2.3 ± .3*	3.5 ± 1.5*
Ibuprofen	48	3 ± 1.4	28.4 ± 3.8*	0.2 ± 0.3	0 ± 0.1	21.5 ± 6.5*	55.2 ± 12*	0 ± 0.1	1.5 ± 0.2*
Ibuprofen	194	1.5 ± 1.2	−1.8 ± 1	2.7 ± 0.5*	1.9 ± 0.4*	−33.1 ± 5.4*	−43 ± 8.3*	5.3 ± 1.4*	3.6 ± 0.9*
Ibuprofen +Indomethacin	194 19.6	−0.3 ± 2	0.5 ± 2	1.5 ± 0.4*	1.7 ± 0.2*	−30 ± 7.4*	−35 ± 4.2*	2.0 ± 4*	2.8 ± 0.7*

Values are mean ± SEM of the difference in the amplitude (μV) and implicit time (ms) of the a- and b-wave from pre- to 1 h posttreatment; hence a negative value refers to reduction and a positive one to an increase in the parameters. n = 3–6 for each treatment.

* $p < 0.05$ compared with value of 0.

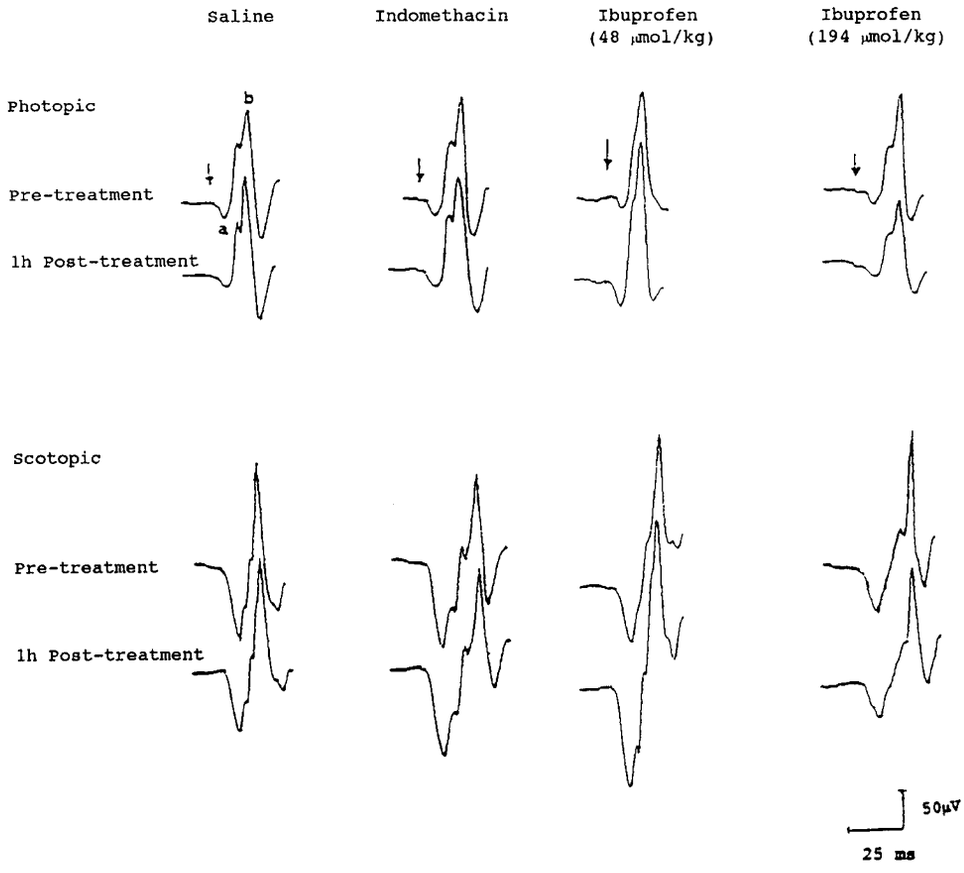

Figure 1. Photopic and scotopic ERG before and 1 h after saline, indomethacin 19.6 μmol/kg (7 mg/kg), ibuprofen 48 μmol/kg (10 mg/kg), and ibuprofen 194 μmol/kg (40 mg/kg) in newborn pigs. The *arrows* represent the flash stimulus. *a* and *b* shown on the presaline photopic ERG refer to the a- and b-waves.

silica columns (7, 8). The supernatant was dissolved in 15% ethanol and acidified to pH 3 with glacial acetic acid. The samples were applied to octadecylsilyl silica columns that were then washed with 15% aqueous ethanol followed by petroleum ether. PG were subsequently eluted with methyl formate. The efficiency of recovery after extraction for all PG was 96%. PG were measured using RIA kits, as we have previously described (7, 8). The interassay variability was ≤5%.

Drugs and chemicals. Diclofenac, indomethacin, ibuprofen, naproxen, and flurbiprofen were purchased from Sigma Chemical Co. (St. Louis, MO). RIA kits for PGE_2, $PGF_{2\alpha}$, and 6-keto-$PGF_1\alpha$ were obtained from Advanced Magnetics (Boston, MA). All other chemicals were obtained from Fisher Scientific (Montreal, Quebec).

Statistical analysis. ERG and PG were analyzed by two- and one-way analysis of variance, respectively, factoring for time and treatment group, as well as by comparison among means tests. Statistical significance was set at $p < 0.05$.

RESULTS

Stability of the preparation. As indicated by pH, Po_2, and Pco_2, all animals were stable throughout the duration of the experiments. In the saline-treated group of animals, venous pH was 7.33 ± 0.03, Pco_2 5.97 ± 0.6 kPa, and Po_2 6.03 ± 0.3 kPa; these values remained stable and were not altered by NSAID.

ERG patterns. Saline, indomethacin, and diclofenac did not exert significant effects on the a- and b-waves of the ERG (Fig. 1 and Table 1). In contrast, naproxen, flurbiprofen, and the higher dose of ibuprofen (194 μmol/kg) produced a significant prolongation of the implicit time of both a- and b-waves during photopic and scotopic conditions (Fig. 1 and Table 1); in addition, ibuprofen (194 μmol/kg) produced a marked depression of the b-wave amplitude by 22–31% under photopic and scotopic conditions. The lower dose of ibuprofen (48 μmol/kg) also affected the ERG by significantly increasing the a- and b-wave amplitudes and by prolonging (albeit to a lesser extent) the b-wave implicit time during scotopic recordings. Prior inhibition of PG synthesis by indomethacin in a separate group of animals ($n = 3$) did not significantly modify the effects of ibuprofen (194 μmol/kg) on the ERG.

PG concentrations. Indomethacin, diclofenac, naproxen, flurbiprofen, and ibuprofen (194 μmol/kg) significantly decreased retinal levels of $PGF_{2\alpha}$, PGE_2, and 6-keto-$PGF_1\alpha$ (Table 2); ibuprofen (48 μmol/kg) decreased 6-keto-$PGF_1\alpha$ levels. Injection of saline had no effect on retinal PG concentrations.

DISCUSSION

In the course of studies on the effects of NSAID on retinal functions, we found some evidence of adverse effects of ibuprofen on the ERG. Inconclusive evidence of such an adverse effect of ibuprofen on the ERG was found in an earlier study (7). Because ibuprofen is being considered as a substitute for indomethacin in the newborn (13) and as an antipyretic in

infants (14, 15), we compared the effects of three chemically different classes of NSAID on the ERG and PG synthesis. These studies revealed that propionic acid derivatives, ibuprofen including doses used in the human newborn and infant (13, 14), naproxen, and flurbiprofen, altered the ERG, whereas relatively high doses of the indole derivative indomethacin and the phenylacetic acid derivative diclofenac did not, although all these agents inhibited synthesis of PG.

The propionic acid–derivative NSAID produced effects on the a-wave (generated from the photoreceptors) and the b-wave (generated mainly from the Müller cells) during photopic and scotopic conditions (Fig. 1 and Table 1); this would suggest a generalized effect on the function of rods and cones as well as of the inner retina. The lower dose of ibuprofen caused an increase in the a- and b-wave amplitudes, and the higher dose caused a decrease in the b-wave amplitude as well as a slightly greater prolongation of the implicit time; thus, the effects of ibuprofen on the ERG are dose dependent. Delayed implicit time as seen in our study after ibuprofen, naproxen, and flurbiprofen and, in certain conditions, an increase in the ERG wave amplitudes are often observed as a first sign of widespread damage to rods and cones; as injury progresses, the ERG amplitudes begin to diminish (23–25).

ERG changes are known to be associated with significant visual disturbances (26). Interestingly, propionic acid derivatives such as ibuprofen have been reported to cause several ocular complications including blurring of vision and scotoma (9–11) as well as electrophysiologic changes of the visual evoked potential (12). Data of this study are also in accordance with reports of fewer ocular complications with other NSAID that are not propionic acid derivatives (5, 27).

The mechanisms responsible for the ERG changes caused by ibuprofen, naproxen, and flurbiprofen are not known. PGE_2 and PGI_2 have cytoprotective functions (28, 29) such that inhibition of their synthesis may conceivably result in alterations of retinal function; this, however, is unlikely because indomethacin and diclofenac also inhibited PG synthesis but did not alter the ERG (Table 2). Furthermore, ibuprofen produced ERG changes even after prior inhibition of PG synthesis by indomethacin. A role for deleterious free radicals in the observed ERG changes after the administration of propionic acid derivatives is also unlikely, because these agents may in fact act as effective free radical scavengers (30). A decrease in ocular circulation can cause changes in the ERG (31, 32); however, ibuprofen and naproxen do not affect basal retinal and choroidal blood flow (8) but rather improve ocular blood flow autoregulation (6). Effects of propionic acid derivatives on the ERG cannot also be attributed to an uncoupling of oxidative phosphorylation (26) because all NSAID can produce these effects, which are usually seen at high doses (33–36). However, propionic acid–derivative NSAID such as ibuprofen are more potent inhibitors of calcium channels than other NSAID (37). A greater inhibition of ocular calcium channels by ibuprofen, naproxen, and flurbiprofen than by indomethacin and diclofenac may be responsible for their adverse effects on the ERG. This, however, remains to be determined.

Table 2. *Retinal PG concentrations before and 1 h after saline and different NSAID*

Treatment	Dose (μmol/kg)	$PGF_{2\alpha}$ (pmol/g protein)	PGE_2 (pmol/g protein)	6-keto-$PGF_{1\alpha}$ (pmol/g protein)
None		88.5 ± 7.7	73.4 ± 12.4	56.6 ± 18.6
Saline		92.3 ± 8.6	82.5 ± 23.8	64.7 ± 12.9
Indomethacin	19.6	22.4 ± 7.1*	28.9 ± 6.8*	20.2 ± 4*
Diclofenac	15.7	9.4 ± 2.9*	51.6 ± 8.2*	11.3 ± 1.8*
Naproxen	79	22.9 ± 5.6*	25.5 ± 9.3*	24.2 ± 0.8*
Flurbiprofen	41	9.2 ± 4.6*	60.9 ± 21.2	12.1 ± 3.7*
Ibuprofen	48	90.4 ± 9.6	78 ± 12.7	16.5 ± 1.6*
Ibuprofen	194	19.1 ± 5.6*	18.7 ± 4.3*	15.3 ± 5.6*

Values are mean ± SEM; n = 3–4 for each treatment modality.
* $p < 0.05$ compared with saline and before treatment (none).

In conclusion, we describe for the first time that ibuprofen and other propionic acid derivatives, unlike other NSAID, significantly alter retinal function in the newborn by an effect that appears to be independent of PG. In an attempt to find NSAID that cause fewer complications than indomethacin in the newborn (38) and that are more effective than other antipyretics in the young infant (14, 15), the use of ibuprofen is being considered (13–15). However, in this context one must take into account the effects of ibuprofen and related drugs on the ERG, and these may also attest to other adverse effects such as those noted on renal function (13).

Acknowledgments. The authors thank Hensy Fernandez for her technical assistance and Les Fermes Ménard Inc. (Ange-Gardien, Québec) for their generosity in supplying us with pigs.

REFERENCES

1. Insel PA 1990 Analgesic-antipyretics and antiinflammatory agents: drugs employed in the treatment of rheumatoid arthritis and gout. In: Gilman AG, Rall TW, Nies AS, Taylor P (eds) The Pharmacological Basis of Therapeutics. Pergamon Press, New York, pp 638–681
2. Fleisher LN 1988 Effects of inhibitors of arachidonic acid metabolism on endotoxin-induced ocular inflammation. Curr Eye Res 7:321–327
3. Wald KJ, Spaide R, Patalano VJ, Sugin S, Yannuzzi LA 1992 Posterior scleritis in children. Am J Ophthalmol 113:281–286
4. Flach AJ 1992 Cyclo-oxygenase inhibitors in ophthalmology. Surv Ophthalmol 36:259–284
5. Miglior M, Scullica L, Secchi AG, Negrini A, Pezzi PP, Brovarone FV, Bonini S, Ruggieri ML, Vargiu G 1993 Nedocromil sodium and astemizole, alone or combined in the treatment of seasonal allergic conjunctivitis. Acta Ophthalmol 71:73–78
6. Chemtob S, Beharry K, Rex J, Chatterjee T, Varma DR, Aranda JV 1991 Ibuprofen enhances retinal and choroidal blood flow autoregulation in newborn piglets. Invest Ophthalmol Vis Sci 32:1799–1807
7. Chemtob S, Roy MS, Abran D, Fernandez H, Varma DR 1993 Prevention of post-asphyxial increase in lipid peroxides and retinal function deterioration in the newborn pig, by inhibition of cyclooxygenase activity and free radical generation. Pediatr Res 33:336–340
8. Parys-Van Ginderdeuren R, Malcolm D, Varma DR, Aranda JV, Chemtob S 1992 Dissociation between prostaglandin levels and blood flow to the retina and choroid in the newborn pig following nonsteroidal antiinflammatory drugs. Invest Ophthalmol Vis Sci 33:3378–3384
9. Nicastro NJ 1989 Visual disturbances associated with over-the-counter ibuprofen in three patients. Ann Ophthalmol 21:447–450
10. Collum LMT, Bowen DI 1971 Ocular side effects of ibuprofen. Br J Ophthalmol 55:472–477
11. Ridder III WH, Tomlinson A 1992 Effect of ibuprofen on contrast sensitivity. Optom Vis Sci 69:652–655
12. Hamburger HA, Beckman H, Thompson R 1984 Visual evoked potentials and ibuprofen. Ann Ophthalmol 16:328–329
13. Aranda JV, Varvarigou N, Beharry K, Modanlou H, Bardin C, Papageorgiou A 1994 The effect of early intravenous (IV) ibuprofen on renal function in premature newborns. Pediatr Res 35:361A(abstr)
14. Kauffman RE, Sawyer LA, Scheinbaum ML 1992 Antipyretic efficacy of ibuprofen vs acetaminophen. Am J Dis Child 146:622–625
15. Wilson JT, Brown RD, Kearns GL, Eichler VF, Johnson VA, Bertrand KM, Lowe BA 1991 Single dose, placebo-controlled comparative study of ibuprofen and acetaminophen antipyresis in children. J Pediatr 119:803–810

16. Beauchemin ML, Babel J 1973 Proceedings: a preliminary study on the ultrastructure of the pig retina. Exp Eye Res 17:400
17. Bloodworth Jr JM, Gutgesall HP J, Engerman RL 1965 Retinal vasculature of the pig. Light and electron microscope studies. Exp Eye Res 4:174–178
18. Naito K, Osama H, Ueno R, Hayaishi O, Honda K, Inoue S 1988 Suppression of sleep by prostaglandin synthesis inhibitors in unrestrained rats. Brain Res 453:329–336
19. Jamali F, Berry BW, Tehrani MR, Russel AS 1988 Stereoselective pharmacokinetics of flurbiprofen in humans and rats. J Pharm Sci 77:666–669
20. Mäkelä AL 1977 Naproxen in the treatment of juvenile rheumatoid arthritis. Scand J Rheumatol 6:193–205
21. Lachapelle P, Roy MS, Little JM 1990 The electroretinogram in Stargardt's disease and fundus flavimaculatus. Doc Ophthalmol 73:395–404
22. Bradford MM 1976 A rapid and sensitive method for the quantitation of microgram quantities of protein utilizing the principle of protein-dye binding. Anal Biochem 72:248–254
23. Berson EL, Gouras P, Gunkel RD 1969 Dominant retinitis pigmentosa and reduced penetrance. Arch Ophthalmol 81:226–234
24. Bresnick GH 1987 Electroretinography and color vision in diabetes mellitus. In: Crepaldi G, Cunha-Vaz JG, Fedele D (eds) Microvascular and Neurological Complications of Diabetes. Livina Press, Padova, Italy, pp 17–33
25. Yonemura D, Kawasaki K 1977 Electrophysiological study on activities of neuronal and non-neuronal retinal elements in man with reference to its clinical application. Jpn J Ophthalmol 22:195–213
26. Beson EL 1992 Electrical phenomenon in the retina. In: Hart Jr WM (ed) Adler's Physiology of the Eye. Mosby-Year Book, St Louis, MO, pp 641–708
27. Kulkarni P, Srinivasan BD 1986 Diclofanc and enolicarn as ocular anti-inflammatory drugs in rabbit corneal wound model. J Ocular Pharmacol 2:171–175
28. Robert A, Nezamis JE, Lancaster C, Hancher AJ 1979 Cytoprotection by prostaglandins in the rats. Gastroenterology 77:433–443
29. Miller TA 1983 Protective effects of prostaglandins against gastric mucosal damage: current knowledge and proposed mechanisms. Am J Physiol 245:G601–G623
30. Kennedy TP, Rao NV, Noah W, Micheal JR, Jafri Jr MH, Gurtener GH, Hoidal JR 1990 Ibuprofen prevents oxidant lung injury and *in vitro* lipid peroxidation by chelating iron. J Clin Invest 86:1565–1573
31. Bresnick GH, Korth K, Groo A, Palta M 1984 Electroretinographic oscillatory potentials predict progression of diabetic retinopathy: preliminary report. Arch Ophthalmol 102:1307–1311
32. Sabates R, Hirose T, McMeel JW 1983 Electroretinography in the prognosis and classification of central retinal vein occlusion. Arch Ophthalmol 101:232–235
33. Masumoto S, Masuda C 1976 Mechanism of anti-inflammatory action of 2-(2-fluoro-4-biphenyl) propionic acid (flurbiprofen). Folia Pharmacol Jpn 72:753–762
34. Tomov T, Velchkova-Markova S 1983 Effect of Feloran (diclofenac sodium) on the oxidative phosphorylation of rat liver mitochondria. Acta Physiol Pharmacol Bulg 9:66–72
35. Cox PG, Van OS CH, Russel FG 1993 Accumulation of salycilic acid and indomethacin in isolated proximal tubular cells of the rat kidney. Pharmacol Res 27:241–252
36. Knights KM, Drewrew R 1992 The effect of ibuprofen enantimors on hepatocyte intermediary metabolism and mitochondrial respiration. Biochem Pharmacol 44:1291–1296
37. Drews G, Garrino MG, Henquin JC 1975 Ionic, electrical, and secretory effects of inhibitors of arachidonic acid metabolism in mouse pancreatic beta-cells. Diabetes 41:620–626
38. Gelman CR, Rumack BH 1990 Metabolism and toxicity of antiprostaglandin agents. In: Kacew S (ed) Drug Toxicity and Metabolism in Pediatrics. CRC Press, Boca Raton, FL, pp 241–250