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Comparative Study Of Two Non-Selective Cyclooxygenase Inhibitors Paracetamol And Ibuprofen On Maternal And Neonatal Growth

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ABSTRACT

The comparative study of the effects of two non- selective cyclooxygenase inhibitors ibuprofen and paracetamol on maternal and neonatal growth was conducted using 15 Sprague dawley rats, with mean body weight ranging between 165 and 179g. The rats were separated at random into three groups (A, B, and C). Identification of each animal was done by the number of strokes marked on their tail. The first test group (A) was given 7.3mg/kg/day of paracetamol, while the second test group (B) was given 3.5mg/kg/day of ibuprofen. The third group (C) was used as the primary control group and as such was given normal saline. Each rat was weighed at an interval of three days before and after pregnancy. Drug administration was done by gavage and commenced from the 10^{th} day of gestation till the 13^{th} day after parturition. On the 13^{th} day after parturition the maternal weight, neonatal weights, tail lengths, crown rump lengths and the kidney weight was measured, in other to determine their effects on growth. The ibuprofen treated animals with a percentage weight loss (16.10%) and a mean weight difference (26.64g) were significantly affected ($P < 0.001$) when compared to the control animals with a mean weight difference (3.66g) and a percentage weight loss (2.19%) while paracetamol with a maternal percentage weight loss (9.6%) and maternal mean weight difference (17.24g) were significantly affected ($P < 0.05$) when compared to control animals. On the other hand only ibuprofen fed animals showed effects on the neonatal growth; with a mean neonatal weight (12.18g), mean tail length (2.11g), mean crown rump length (5.8cm), and mean weight of neonatal kidney (0.058g). All these parameters were statistically significant ($P<0.05$) when compared to control; with a mean neonatal weight (16.98g), mean tail length (4.02cm), mean crown rump length (7.3cm) and mean weight of neonatal kidney (0.17g). The paracetamol fed animals showed approximately the same values as stated above for the control animals. Our result shows that ibuprofen convey a greater effect than paracetamol on maternal and neonatal growth when used in pregnancy. This could be due to a compromised nutritional status of the maternal rat consequent on gastrointestinal, liver and kidney derangement by these drugs. Hence the abuse of these drugs in pregnancy should be avoided.

Keywords: Comparism, cyclooxygenase inhibitors, gestation, growth.

In the past and present times several workers had cited the effects of analgesics/painkillers on the gastro-intestinal tract, liver and kidney, but nothing has been reported as to their effects on neonatal growth and the maternal weight after parturition.

Cyclooxygenase enzymes are said to play a role in the biosynthesis of prostanglandins required for several activities in the body (Komhoff et al, 2000, Zhang et al, 1997). In the biosynthesis of prostaglandins, two isoforms of cyclooxygenase enzymes are recognized, the cyclooxygenase-1 and cyclooxygenase-2, the former is considered a house keeping enzyme expressed constitutively in most tissues of the body, while cyclooxygenase-2 is the inducible form expressed in response to proinflammatory cytokines and growth factors, indicating a role in inflammation and growth (Vane, 1998; Wang et al, 1998; Williams and Dubois, 1999). The cyclooxygenase-1 is involved in the biosynthesis of prostaglandin's, in organs where these eicosanoids play certain protective role as in the gastrointestinal tract (GIT) and the kidney. The cyclooxygenase-2 maintains haemodynamics, while the cyclooxygenase-1 enhance mucus secretion. Non-selective cyclooxygenase inhibitors - paracetamol and ibuprofen are substances that have the ability to inhibit both cyclooxygenase-1 and cyclooxygenase-2 isoforms, which are commonly used in pregnancy for the management of some clinical conditions such as pains, fever and rheumatism (Woodbury et al, 1999).

MacConnachie et al (1997) reported the derangement of gastrointestinal tract following paracetamol administration, Encarta Encyclopeadia (2002), Mesembe et al (2004) reported kidney and liver toxication following paracetamol and caffinated panadol extra administration. In the past, the reason

for retarded neonatal growth (RNG) was attributed to premature delivery but in 1961, the World Health Organization (WHO) recommended that RNG no longer be used as an official definition of prematurity (Mac Dorman et al 2001). In recent times, Mac Dorman et al (2001) introduced Intrauterine Growth Retardation or " small for Gestational Age for babies born at term with weight less than 2.5kg.The identifiable causes of "Retarded Neonatal Growth" are nutritional status of the mother, low socio-economic status, high maternal age and organ malformations. This study is therefore aimed at determining the effects of two non-selective cyclooxygenase inhibitors ibuprofen and paracetamol on maternal weight and neonatal growth when used in pregnancy. This is against the background that it was documented safe when used in pregnancy. Secondly, it has been observed to induce gastrointestinal tract derangement, kidney and liver toxicity when used indiscriminately, or even below the sub-threshold level in highly sensitive individuals

MATERIALS AND METHOD

Animals

Fifteen Sprague - Dawley rats were procured from the Animal House University of Nigeria, Enugu Campus and kept in the Animal House of Physiology Department, College of Medicine, Enugu Campus for 2 weeks for acclimatization. They were housed in cages measuring 11 by 7cm and were allowed free access to food and water ad libitum. Individual identification of the animals were done by the number of stokes marked on their tails.

Experimental Design

Fifteen female Sprague dawley rats weighing between 165g 179g were randomly divided into three groups (A, B, and C) of five rats each. Animals in group A received distilled water orally and served as control. The ibuprofen treated rats (group B) received doses of 3.5mg/ kg/day while paracetamol treated rats (group C) received doses of 7.3mg/kg/day respectively by gavage. The animals were allowed feed and water liberally. The treatment commenced from 10^{th} day of gestation to 13^{th} day after parturition.

Experimental Procedure

The reproductive status and estrous period of the animals were determined by obtaining their virginal smears. After two complete regular cycles, timed mating of female animals was done on the night of the pro-estrous (N) phase of the cycle. In the morning following mating, vaginal smears were taken again. The presence of spermatozoa and squamous cells in the smear confirmed mating and fertilization of ovulated spermatozoa. The sperm positive morning was thus designated day 0 of pregnancy. Each rat was weighed at an interval of three days, before the experiment, up to thirteen days after the experiment. On the 13th day after parturition, the neonatal weights, kidney weights, tail lengths and crown rump lengths was measured the thirteen day old neonatal rats in the two experimental and control groups were exposed to chloroform and opened up, in other to obtain their kidneys for weight measurement and determine the drug effects on growth. The mean weight of the animal before pregnancy was taken and designated as (a). The weight on the 10th day of pregnancy at the unset of drug administration was taken and the mean weight for each group at the 13th day after parturition was taken and designated as (b), after which the mean weight at 13th day after parturition was subtracted from the mean weight before pregnancy for each animal group (ab), in other to determine the mean weight difference for each group, and the percentage weight loss. The paracetamol treated group and the ibuprofen group was then tested statistically from that of control using Students T test to compare the differences, (Paracetamol vs. control and ibuprofen vs. control). An Anova was used to test the variance in the three groups.

RESULTS

Effects of Paracetamol and Ibuprofen On Maternal Weight

The difference in maternal weight between paracetamol fed rats with a mean weight difference (17.24g) compared to the control group with a mean weight difference (3.66g) was statistically ($p < 0.05$) significant, as shown in Table 1. This group also had a percentage weight loss of 9.60% compared to the control, which showed a percentage weight loss of 2.19% (Table 1).

The ibuprofen group had a mean weight difference (26.64g) this showed a great statistical significant difference of ($P < 0.001$) when compared to control. However ibuprofen maternal rats also had a percentage weight loss of 16.10% compared to the control group, which had a percentage weight loss of 2.19% (Table 1).

Effects of Paracetamol and Ibuprofen On Neonatal Growth

The mean neonatal weight was 16.96g for paracetamol group, 12.18g for Ibuprofen group and 16.98g for the control group. Ibuprofen had a mean weight difference much lesser compared to Paracetamol and the Control group which was approximately of the same value, but the statistical significance difference was ($P < 0.05$) when compared to the control group, as shown in Table 2.

The neonatal mean tail length was 3.9cm for the Paracetamol group, 2.11cm for Ibuprofen group and 4.02cm for Control group. The T test for Paracetamol group had no significance difference from the value of control, but Ibuprofen group was statistically significant from the Control ($P < 0.05$), Table 2.

The neonatal mean crown rump length was 7.12cm for Paracetamol, 5.8cm for ibuprofen and 7.3cm for the control group. Here the paracetamol group had approximately the same value when compared to the control while the ibuprofen had a lesser value of 5.8cm, when compared to the control that had a value of 7.3cm. However this was observed to be statistically significant ($P < 0.05$), as shown in Table 2.

The mean weight for neonatal kidneys was 0.15g for the Paracetamol group, 0.058g for the ibuprofen group and 0.17g for the Control group.The Paracetamol group when compared to the control had approximately the same value, while the ibuprofen had a lesser value of 0.058g compare to control, which weighed 0.17g,and this difference was statistically significant ($P < 0.05$), as shown in Table 2.

DISCUSSION

The current investigations reveals that ibuprofen has greater negative effect on maternal rat compared to paracetamol following its indiscriminate administration in pregnancy, as evident in the statistical analysis with ibuprofen showing a statistical significant value of $P < 0.001$ and paracetamol with a statistical significant value ($P < 0.05$). The drastic reduction in weight two weeks after parturition suggest the extent of reduction in glomeruli size in agreement to the stated law that there is a relation between total glomerular volume and kidney weight expressed in a straight line on a logarithmic scale, (Junqueira et al, 1995). Secondly it could probably be due to greater impairment of the kidney and liver in ibuprofen treated maternal rats than the paracetamol treated maternal rats. Thirdly, it could probably be attributed to ulceration and erosive effect of these drugs on the gastrointestinal tract and organs (Johnston and Fox, 1997, Vane and Botting, 1998; Smith, 1998; Williams and Dubois, 1999). Ibuprofen, however; led to retarded growth in the neonates as evidenced by the low mean neonatal weight, tail length, mean crown- rump length and kidney weight, which all showed statistical significant ($P < 0.05$), but paracetamol showed no significant effect on neonatal growth.

Therefore, retarded growth in maternal and neonatal rats compared to the control could be attributed to a compromised nutritional status of the

Table 1: Showing Effects Of Paracetamol And Ibuprofen On The Maternal Body weight.

Animal Group	Drugs Administered	Weight before Pregnancy (a)	Weight at 10th Day of Pregnancy	Weight at 13th Day after Parturition (b)	Mean weight Difference (a – b)	% Weight Loss
A	Paracetamol	178.64	191.2	161.4	**17.24	**9.60%
B	Ibuprofen	165.44	172.8	138.8	***26.64	***16.10%
C	Control	166.76	175	163.1	3.66	2.19%

**Significantly different from the value of control $P < 0.05$
*** " " " " " " $P < 0.001$

Table 2: Showing Effects Of Paracetamol and Ibuprofen On Neonatal Growth.

Anima Group	Mean neonatal Weight (g)	Mean tail length (Cm)	Mean crown Rump length (Cm)	Mean Weight Of neonatal Kidney (g)
A	16.96	3.9	7.12	0.15
B	**12.18	*2.11	**5.8	***0.058
C	16.98	4.02	7.3	0.17

*Statistically different from the value of control
(* < 0.05; ** P < 0.05 *** P < 0.05)

maternal rat consequent on gastrointestinal derangement by the drugs.

This study has revealed that both ibuprofen and paracetamol have effect on growth when used in pregnancy, though ibuprofen has a greater effect. Therefore, pregnant mothers should be wary of their indiscriminate use in pregnancy.

REFERENCES

Junqueira I. C., Carneiro J., Contropoulos A. (1975): Basic Histology: Lange Medical Publications. Pp 355 365.

Komhoff M; Grone J: Klein T; Seyberth H.H; Nursing R. M. (1997): Localization of Cox 1 and 2 in adult and foetal human kidneys: implication for renal function. Am. Physiol. **272**:F460-8.

Komhoff M; Jun-ling, W;Langenbach. R; Mckanna, J. A., (2000); Cyclooxygenase 2 selective inhibitors impair glomerulogenesis and renal cortical development kidney international. **57**:414-422.

MacConnachie A. M. (1997): (1997): Paracetamol poisoning. Intens. Crit. Care. Nurs. **13**:238-9.

Mesembe, O. E., Igiri, A. O, Naikot, I., Ekam, V. S., Odukana, J. F., and Fischer, V. A. (2004): Liver and Kidney Morphologies Following Vitamine E SupplementationDuring Caffeinated and Non Caffeinatsd Paracetamol Administration in Rats. J. Exp. & Clin. Anat. **3** (1) 35 -38.

Sakari, Y; Jacobson, H. R.; Nolad, T. D.; Breyer M. D. (1995): Luminal prostaglandin E. receptors regulate salt and water transport in rabbit cortical collecting ducts. Am. J. Physiol **269**:F257-65.

Sanchez, P.L.; Salgado, L.M.; Ferreri, N. R.; Escalante B. (1999): Effects of Cox 2 inhibitor on renal function after ablation. Hypertension. **34**:848-53.

Smith T. J. (1998): Cyclooxgenase as the principal targets for the action of non-steroidal anti-inflammatory drugs. Rheum Dis. Clin. North. Am. **24**:501-23.

Smith, T. J. (1998): Cyclooxygenase as the principal targets for the action of non steroidal anti inflammatory drugs. Rheum Dis. Clin. North. Am. **24**: 501 23.

Smith, W. L.; Dewitt, D. L. (1995): Biochemistry of prostaglandin endoperoxide H syntheses 1 and syntheses-2 and their differential susceptibility to non-steroidal anti-inflammatory drugs. Semin. Nephrol. **15**: 179:94.

Vane J. R.; Booting R. M. (1998): Anti-inflammatory drugs and their mechanism of action. Inflammatory Research. 47 Suppl. 2:578-87.

Williams, C. S.; Mann M.; Dubbois, R. N. (1999): The role of cyclooxygenase in inflammation, cancer and development. Oncogene. **18**:7908-16.

Woodbury, D. M. (1971) The Para-amino phenol Derivatives: Phenacetin, Acetaminophen and Acetanilinid. In: Gilman a. AND Goodman L. S., Editors. The Pharmacological Basis of Therapeutic. The MacMillan Co. 392.

Zhang M. Z.; Harris, R. C.; McKanna, J. A. (1999): regulation of cyclooxygenase 2 in rat renal cortex by adrenal glcocorticoids and mineralocorticoids. Proc. Natl. Acid. Sci. USA. **96**: 15280-5.