Journal of Pharmacology and Toxicology

ISSN 1816-496X

Academic Journals Inc.

www.academicjournals.com

Journal of Pharmacology and Toxicology 3 (3): 203-212, 2008
ISSN 1816-496X

Histomorphological Assessments of the Female Reproductive Organs of Rats under Indomethacin and Aspirin Treatments

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Abstract: The effect of Aspirin (ASA) and indomethacin (Indocin) on the histomorphology of the female reproductive organs was investigated. A total of 60 female albino rats of the Wister Strain were randomly divided into 12 groups of 5 rats each (group's 1-12). Groups 1 and 2 served as the control groups and were administered normal saline and dimethylsulfoxide (DMSO 5 mg kg^{-1} body weight), respectively for 14 days. Groups 3-7 were administered 10, 25, 50, 75 and 100 mg kg^{-1} body weight of aspirin respectively for 14 days while groups 8-12 received 2.0, 2.5, 3.0, 3.5 and 4.0 mg kg^{-1} body weight of indomethacin respectively for 14 days. At the end of the 14 day, the animals were sacrificed and the ovary, uterine tubes and uterus obtained for routine histological processing and subsequent histopathological assessment. Results from this study showed normal histological profiles of all organs obtained from the rats in the control groups while the experimental groups treated with aspirin and indomethacin presented with vasoconstriction in the ovary and atrophy of smooth muscles of the uterine tubes and uterus. This study has establish to some extent, the vasoconstrictive potency of aspirin and indomethacin and thus providing an experimental basis for the use of these drugs to reduce and if possible stop ovarian and uterine hemorrhage but further investigation to elucidate the vasoconstrictory effect, smooth muscle atrophy and the reversibility of some of the toxic effect of these drugs on the female reproductive organs and the mechanism involved is recommended in further studies.

Key words: Vasoconstricton, atrophy, NSAIDs, ASA, Indocin

INTRODUCTION

The use of medicinal substances to relieve pain and fever dates back to ancient Egypt when quinine and extracts obtained from the bark of the Willow tree were used as remedies to relieve the pain of child-birth and fever (Rang *et al*., 1999). But with the advent of modem pharmaceutical products, Non Steroidal Anti-Inflammatory Drugs (NSAIDs) such as aspirin and indomethacin are now used extensively as analgesics and anti-inflammatory agents and these agents produce their therapeutic effects through the inhibition of prostaglandin synthesis (Gilman *et al*., 1990; Klaassen, 2001). As a group non-steroidal and anti-inflammatory drugs are non-narcotic relievers of mild to moderate pain of many causes, including injury, menstrual cramps, osteoarthritis, rheumatoid arthritis, gout and musculoskeletal conditions (Bjarnason and Macpherson, 1989). Their role of inhibiting the formation of colon cancer and colorectal cancer in experimental animals and humans respectively has also been reported (Gupta and DuBois, 1999).

Aspirin was the first-discovered member of the class of the non-steroidal anti-inflammatory drugs, not all of which are salicylates, though they all have similar effects and a similar mechanism of

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action Aspirin a drug in the family of salicylates is often used as an analgesic, antipyretic and as an anti-inflammatory. It also has an antiplatelet effect which in long-term and low dose can prevent heart attacks and thrombus formation in hypercoaguable states (e.g., cancer). Low-dose and long-term aspirin use irreversibly blocks the formation of thromboxane A_2 in platelets, producing an inhibitory effect on platelet aggregation. This anticoagulant property makes it useful for reducing the incidence of heart attacks. High doses of aspirin are also given immediately after an acute heart attack, these doses may also inhibit the synthesis of prothrombin and may, therefore, produce a second and different anticoagulant effect, but the mechanism is not well understood. Its primary undesirable side-effects, especially in higher doses, are gastrointestinal distress (including ulcers and stomach bleeding) and tinnitus. Another side-effect, due to its anticoagulant properties, is increased bleeding in menstruating women. Because there appears to be a correlation between aspirin and Reyes syndrome in children under the age of about 12, aspirin is no longer used to control flu-like symptoms or the symptoms of chickenpox in minors (Macdonald, 2002).

Indomethacin, a Prostaglandin (PG) and Thromboxane (Tx) synthetase inhibitor, was first introduced in 1963 (Shen *et al*., 1963). Indomethacin inhibits COX (COX-1 and COX-2) enzymes and prevents the formation of prostaglandin PGE_2, $PGF_{2\alpha}$, PGD_2, prostacyclin (PGI_2) and TxA_2 from arachidonic acid (Smith and Dewitt, 1996). Toxicological review of the effects of indomethacin treatment on various body systems showed it causes acute renal failure within hours of ingesting large doses (Bach, 1997; Tarloff, 1997; Whelton and Watson, 1998), analgesic nephropathy following chronic consumption (Elsevier and DeBroe, 1998) and interstitial nephritis which is characterized by a diffuse interstitial edema with infiltration of inflammatory cells (Whelton and Waston, 1998).

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), widely used due to their analgesic and anti-inflammatory properties, consistently inhibit ovulation in all mammalian species investigated so far, likely due to the inhibition of cyclooxygenase 2 (COX-2) because COX-2 inhibition has major effects on ovulation, fertilization and implantation and NSAID therapy is likely implicated in human infertility and could be an important, frequently overlooked, cause of ovulatory dysfunction in women. (Gaytan *et al*., 2006) Studies have also implicated Non Steroidal Anti-Inflammatory Drugs (NSAIDs) and selective cyclooxygenase-2 inhibitors in interfering with ovulation and the rupture of follicle, causing reversible infertility (Skomsvoll *et al*., 2005) and the induction of delayed follicular rupture or LUF in previously ovulating women, a link can therefore be identified between NSAID use and reversible female infertility and NSAID withdrawal should be considered prior to or concurrent with fertility investigations (Sophia *et al*., 2002).

The Non Steroidal Anti-Inflammatory Drugs (NSAIDs) to which aspirin and indomethacin belongs to, are one of the most abused groups of drugs by virtue of combining the pharmacological actions of anti-inflammatory and analgesia and because they can easily be bought over the counter. This study was therefore designed to assess the histomorphology of the rats ovary, uterine tube and the uterus under aspirin and indomethacin treatment.

MATERIALS AND METHODS

Drugs and Chemicals

Acetylsalicylic acid (ASA)(Sigma chemical company, USA); indomethacin (Indocin) (Sigma chemical company, USA); Dimethylsulfoxide (DMSO) (BDH chemical limited,England); Xylene (May and Baker, England); Paraffin (BDH chemical limited, England); Haematoxylin (Harris, England) and Eosin (SOH chemicals, England).

Animal and Husbandry

This study was carried out in the Department of Human Anatomy, University of Maiduguri, Nigeria between October 2006 and January 2007. A total of sixty matured female albino rats of the

Wister strain weighing between 150 and 210 g were used in this study. They were purchased from the animal facility centre of the National Veterinary Research Institute Vom, Plateau State, Nigeria. Following an acclimation period of 2 weeks, the rats were individually identified by colour tattoo and weighed. The rats were kept in plastic cages at room temperature of 32±4°C and <30% relative humidity with a 12 h light/dark cycle. They had access to drinking water and standard laboratory diet (Sanders SEEPC feed PLC, Jos, Nigeria) *ad libitum*. After 1-2 weeks of acclimatization the animals were monitored daily for vaginal cytology and only animals showing at least 3 consecutive estrous cycle were used.

Preparation of Drugs

Aspirin (500 mg) was weighed and dissolved in 10 mL DMSO to give the stock solution of aspirin while 500 mg of Indocin was also weighed and dissolved in 50 mL DMSO to give the Indocin stock solution. Both stock solutions were thoroughly stirred to allow for proper dissolution and then stored in a refrigerator.

Experimental Procedure

The rats were randomly divided into 12 groups (1-12) of 5 rats each.

Control Groups

Group 1 and 2 served as the control groups and were administered normal saline and 5 mL kg^{-1} body weight of Dimethylsulfoxide (DMSO), respectively for 14 days.

Treatment Groups

Groups 3-7 received (10, 25, 50, 75 and 100 mg kg^{-1} body weight) of aspirin respectively for 14 days.

Groups 8-12 received (2.0, 2.5, 3.0, 3.5 and 4.0 mg kg^{-1} body weight) of indomethacin also for 14 days.

Route of Administration

The drugs were administered intraperitonealy between 9.00 and 10.00 am daily for 14 days.

Histological Analysis

At the end of the experimental period of 14 days, the rats were anaesthetized using chloroform and midline incision carried out to obtain the ovaries, uterine tubes and uterus. The organs obtained were then fixed in Bouins fluid and processed for paraffin sections. Sections were stained with Haematoxylin and Eosin and mounted in Canada balsam. Light microscopic examination of the sections was then carried out.

RESULTS

Behavioural Observations

Initial administration of indomethacin and aspirin to the rats caused lethargy, slight loss of appetite and slight abdominal distension. However, the rats subsequently adjusted slightly in the course of the experiment, with the animals becoming more tolerant and exhibiting shorter recovery periods.

Gross Anatomical Observations

Gross anatomical observation of organs obtained after sacrifice showed normal ovaries, uterine tubes and uterus in the control animals. The treatment groups also showed apparently normal ovaries, uterine tubes and uterus with no significant pathological changes.

Histopathologic Findings

Histological sections obtained from the ovary, uterine tubes and uterus from rats in the control group showed normal features. The medulla of the ovary showed connective tissue stroma in which was stromal cells with scattered blood vessels. The cortex presented follicles at different stages of development, embedded in dense cellular stroma which was composed of mesenchymal or stromal cells (Fig. 1). Tubal mucosa was seen to be covered by simple ciliated secretory epithelium which was thrown into folds. The folds were more pronounced at the region of the fimbria. The mucosa was also richly supplied with blood vessels and lymphatics (Fig. 2). The uterine endometrium had a layer of endometrial stroma lined by simple columnar epithelium, which was continuous with large numbers of uterine glands. The endometrial stroma also presented with blood vessels and lymphatics between the glands while the myometrium was composed of largely smooth muscle fasciculi mingled with loose connective tissue, blood vessels, lymphatics and nerves (Fig. 3).

The histological changes observed in all the indomethacin treated groups were the same. Sections of the ovary presented with marked vasoconstriction which was evident by clear occlusion of blood vessels (Fig. 4). The uterus and uterine tubes of the indomethacin treated group presented with vasoconstriction and atrophy of smooth muscles (Fig. 5 and 6). Treatment with varying doses of Aspirin also presented with marked vasoconstriction in the ovary (Fig. 7) and vasoconstriction and atrophy of smooth muscles of the uterus and uterine tubes (Fig. 8 and 9).

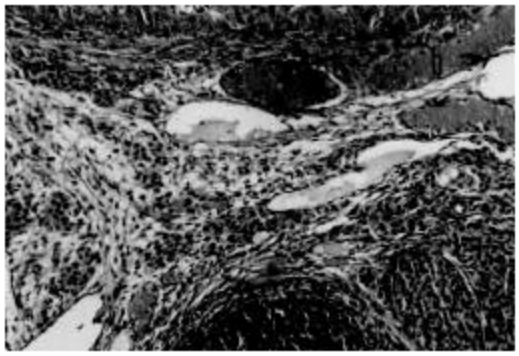

Fig. 1: Micrograph of the ovary of control rat showing normal blood vessels (b) and follicles (g). H and E stain. Mag. x400

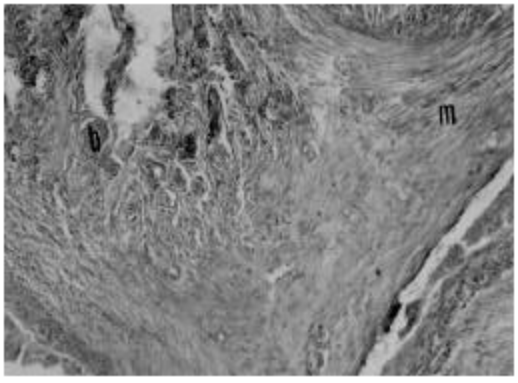

Fig. 2: Micrograph of the uterine tube of control rat showing smooth muscles (m) and blood vessels (b). H and E stain. Mag. x400

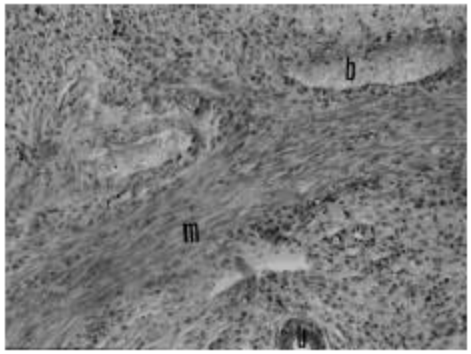

Fig. 3: Micrograph of the uterus of control rat showing normal blood vessels (b), smooth muscles (m) and uterine glands (u). H and E stain. Mag. x400

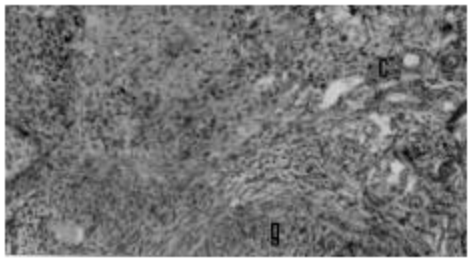

Fig. 4: Micrograph of the ovary of rat treated with Indomethacin (3.5 mg kg^{-1}) showing areas of vasoconstriction (c) and follicles (g). H and E stain. Mag. x400

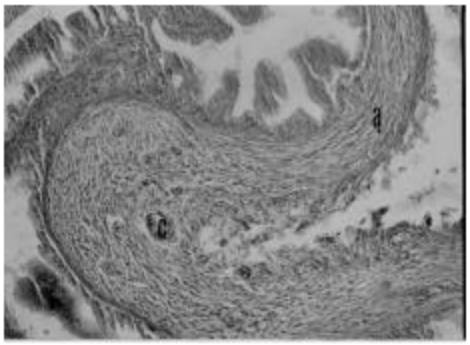

Fig. 5: Micrograph of the uterine tubes of rat treated with Indomethacin (2.5 mg kg^{-1}) showing areas of vasoconstriction (c) and smooth muscle atrophy (a). H and E stain. Mag. x400

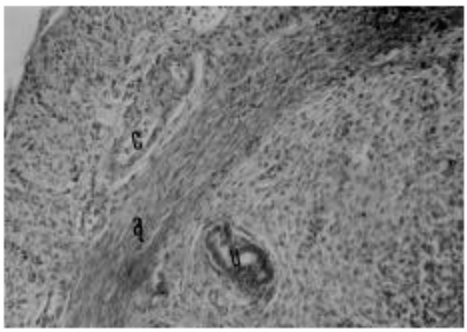

Fig. 6:Micrograph of the uterus of rat treated with Indomethacin (2 mg kg^{-1}) showing areas of vasoconstriction (c) and smooth muscle atrophy (a) and uterine glands (u). H and E stain. Mag. x400

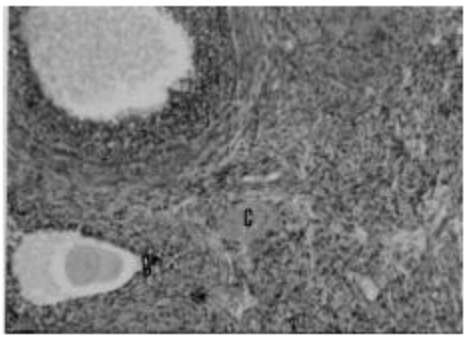

Fig. 7: Micrograph of the ovary of rat treated with Aspirin (75 mg kg^{-1}) showing areas of vasoconstriction (c) and follicles (g). H and E stain. Mag. x400

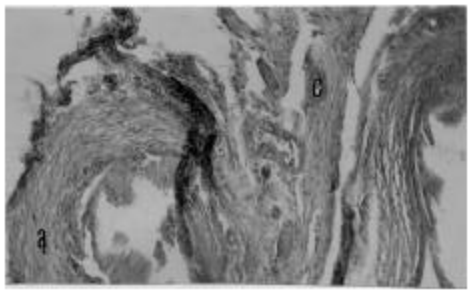

Fig. 8: Micrograph of the uterine tubes of rat treated with Aspirin (25 mg kg^{-1}) showing areas of vasoconstriction (c) and smooth muscle atrophy (a). H and E stain. Mag. x400

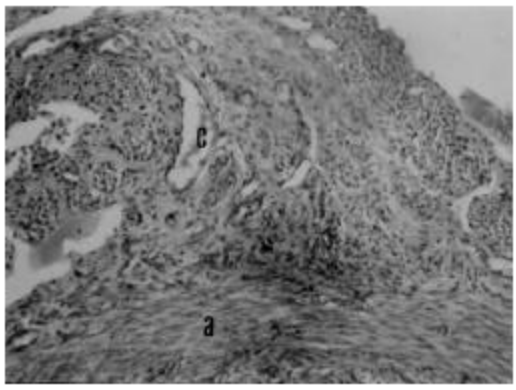

Fig. 9: Micrograph of the uterus of rat treated with Aspirin (10 mg kg^{-1}) showing areas of vasoconstriction (c) and smooth muscle atrophy (a). H and E stain. Mag. x400

DISCUSSION

Despite the various toxicological studies carried out on the toxic effects associated with indomethacin and aspirin ingestion, they still remain one of the most abused drugs in the non steroidal anti-inflammatory group of drugs because of their anti -inflammatory/analgesia properties and their availability over the counter (Abatan *et al*., 2006; Gilman *et al*., 1990). The behavioral observation noted in this study of lethargy, slight loss of appetite and slight abdominal distension are all classical signs of aspirin and indomethacin toxicity that normally ranges from nausea and vomiting, abdominal pain, lethargy, tinnitus and dizziness (Thisted *et al*., 1987).

In the present study, the assessment on the histomorphology of the female reproductive organs under aspirin and indomethacin treatment mainly induced vasoconstriction and smooth muscle atrophy. The vasoconstriction observed in the present study might be attributed to the role aspirin plays in the reduction of platelet function because the formation of the inhibition in the synthesis of PGE_2, PGD_2, PGF_2 and PGI_2 which are potent vasodilators are prevented; this is the basis for aspirin being used as an anti-coagulant but this is in contrast with other studies involving aspirin because it has been shown that low-dose aspirin irreversibly inhibits the enzyme cyclo-oxygenase in platelets, preventing the synthesis of thromboxane (Vane, 1971; Willis, 1974), which is the most potent vasoconstrictive agent in the human body. In contrast by decreasing platelet aggregation and inhibiting vasoconstriction, low-dose aspirin may enhance uterine and ovarian blood flow and tissue perfusion (Wada *et al*., 1994; Rubinstein *et al*., 1999).

Indomethacin, aspirin and related anti-inflammatory agents have been reported in delaying the onset and prolongation of the duration of parturition in rat and other animals (Aiken, 1974; Chester *et al*., 1972; Fuchs, 1975; Williams *et al*., 1974). The effects were attributed to the ability of these drugs to inhibit prostaglandin synthetase in the uterus (Aiken, 1974) and thus prompted the suggestion that endogenous Prostaglandins (PGs) play an important role in parturition (Aiken, 1974; Williams *et al*., 1974). However, the mode of action of the PGs in this regard is unclear. Some workers believe endogenous PGs act directly on the myometrium to stimulate contractions (Aiken, 1974; Vane and Williams, 1973; Williams *et al*., 1974), while others (Fuchs *et al*., 1976; Strauss *et al*., 1975) favor the view that PGs act indirectly via the ovaries to cause luteal regression and a decrease in plasma progesterone levels with subsequent enhancement of uterine contractions. Alternatively, indomethacin and aspirin may have some additional depressant effects on the uterus that are unrelated to their ability to inhibit endogenous PG synthesis. For example, Northover (1971, 1977) has shown that indomethacin inhibits calcium uptake in the smooth muscle of the stomach and aorta and suggests

that indomethacin reduces the availability of calcium within the smooth muscle cell and in this manner reduces the contraction and motility of smooth muscles (Northover, 1971, 1977; Anderson and Kohn, 1978). In a study comparing the effects of indomethacin and aspirin, on the longitudinal muscle and circular muscle of the rat uterus during pregnancy it was observed that aspirin and indomethacin delayed parturition by at least 24 h and prevented the evolution of the electrical and mechanical activity in both longitudinal muscle and circular muscle (Anderson *et al*., 1981).

Administration of high doses of NSAIDS such as indomethacin have also been noted to affect the small intestinal smooth muscles leading to marked reduction in small intestinal length (Ettarh and Carr, 1993) and in causing reduction in uterine contraction (Adegoke, 1994). It was also noted that during pregnancy, there is enhanced synthesis of prostaglandins and increased myometrial activity (Speroff *et al*., 1984). If prostaglandins act to cause uterine contraction then one would expect that inhibitors of prostaglandin synthesis such as aspirin and indomethacin would delay or inhibit uterine contraction.

We believe from this study that the vasoconstriction and smooth muscle atrophy observed in after aspirin and indomethacin administration could have led to reduction in the contraction of these smooth muscles. This observation positively correlates with similar observation made that indomethacin causes reduction in uterine contraction (Adegoke, 1994). The vasoconstriction observed in the present study which we are attributing to the inhibition of prostaglandins by the drugs as agreed by Sachin *et al.* (1986) may have led to decrease in blood supply to the uterine tubes and uterus that might have led to the smooth muscle atrophy although, this aspect was not investigated in the present study. The mechanism of action of the NSAIDS had been reported to be mediated through their inhibition of prostaglandin synthetase or arachidonate cyclooxygenase and thus, inhibition of the production of prostaglandins and thromboxane (Vane and Botting, 1998). The smooth muscle atrophy also observed in the present study might be due to ischaemia caused by decreased blood supply to the smooth muscle. The smooth muscle is more vulnerable to ischaemia because it is a very active tissue and requires a high supply of blood to function adequately. However, it is not clear from the present study if the smooth muscle atrophy was a toxic effect of indomethacin and aspirin or if it was due to inhibition of prostaglandin synthesis.

This study has establish to some extent, the vasoconstrictive potency of aspirin and indomethacin and thus providing an experimental basis for the use of these drugs to reduce and if possible stop ovarian and uterine hemorrhage but further investigation to elucidate the vasoconstrictory effect, smooth muscle atrophy and the reversibility of some of the toxic effect of these drugs on the female reproductive organs and the mechanism involved is recommended in further studies.

ACKNOWLEDGMENTS

We are grateful to the technical staff of the Departments of Human Anatomy, Pharmacology and Human Pathology, University of Maiduguri, Nigeria.

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