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Case Study

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CASE REPORT: ADVERSE DRUG REACTION CAUSED BY IBUPROFEN

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Ibuprofen is a drug largely available as over the counter and on prescription as well, it is mainly indicated for headache, joint pain, inflammatory disease and fever. It is available in combination with various other drugs and paracetamol. Related side effects with non-steroidal anti- inflammatory drugs and aspirin are gastrointestinal ulcers, rash, Steven Johnson syndrome, hepatic toxicity, acute exacerbation of asthma, respiratory skin rashes and anaphylaxis.[1] Ibuprofen is (2RS)-1[4-(2-methyl propyl) phenyl] propionic acid (BP. 2004). Ibuprofen was the first member of propionic acid derivatives to be introduced in 1969 as a better alternative to Aspirin. It inhibits synthesis of prostaglandins in body tissues by inhibiting at least 2 cyclooxygenase (COX) isoenzymes, inhibitor of cyclo-oxygenase-1 (COX-1) and Cyclooxygenase-2 (COX-2). Prostaglandins have an important role in the production of pain, inflammation and fever.[2] It may inhibit chemotaxis, alter lymphocyte activity, decreased proinflammatory cytokine activity, and inhibit neutrophils aggregation; these effects may contribute to anti-inflammatory activity. Ibuprofen is supplied as tablets with a potency of 200 to 800 mg. The usual dose is 400 to 800 mg three times a day.

CASE REPORT

Here was a female patient of age 28yrs old admitted to the hospital on 23rd of June 2019 with complaints of amenorrhea since 4 months, abdominal pain since 12 days and generalized weakness since 1 week. Based on her subjective and objective findings the patient was diagnosed with ENDOMETRIAL HYPERPLASIA.

The patient had normal bp of 120/90 and pulse rate was 88. Lab investigations were in the normal ranges with total count-7500/cumm, RBC- 3.5m/cmm.

Patient was being treated with the following drugs:
T.C-TRI (CEFTRIAXONE) 1GM BD
T.METROGYL (METRONIDAZOLE) 400MG BD
INJ RANTAC (RANITIDINE) 50MG OD
INJ. ZOFER (ONDANSETRON) 8MG SOS
TAB.VOVERAN (DICLOFENAC) 75MG TID
T.MAHACEF (CEFIXIME 200MG + ORNIDAZOLE 500MG) (1-0-1)
TAB. PANTOP (PANTOPRAZOLE) 40MG (1-0-1)
TAB. BRUFEN (IBUPROFEN) 400MG TID

On the first day that was 23rd the patient was given tablet c-tri which is ceftriaxone at the dose of 1gm (1-0-1) as prophylaxis to bacterial infections the same dose was given on the 2nd day as well. On the 2nd day injection metrogyl was started at the dose of 100ml (1-0-1) it was indicated for bacterial and parasitic infections the same dose was continued on the 3rd day as well. On the 2nd day along with metronidazole and tablet ceftriaxone, injection rantac was gives at the dose of 50 mg once in the morning as it helps in reducing gastrointestinal secretions, injection voveran which is diclofenac was given at the dose of 75 mg (1-0-1) it was given for pain, patient complained of vomiting so injection zofer which is ondansetron was given at the dose of 8mg (sos). On the 3rd day inject metrogyl, injection rantac and injection zofer was administered. On the 4th day patient was given injection zofer, tab.pantoprazole at the dose of 40mg (1-0-1) as it reduces the GI secretions this tablet replaced injection rantac, and tablet mahacef oz (1-0-1) which contains cefixime 200mg and ornidazole 500mg was given for bacterial infections. On the 5th day patient was given tab pantoprazole, tab mahacef oz and tablet brufen was added at the dose of 400mg (1-1-1) which was given for her pain.

Patient did not have any fresh complaints and had a stable BP and pulse rate.

ON 27TH after consumption of brufen in the afternoon before food, after 2 hrs patient went into respiratory distress showing signs of bronchospasm(wheezing, breathlessness, chest tightness, dry cough), swollen lip and a high bp of 160/90, capsule depin 10mg was given immediately to reduce her bp.

Patient was then treated with parenteral avil, hydrocortisone and deriphylline, the patient condition was not completely stable.

However the patient took immediate discharge after the event thus we couldn't follow up the case.

DISSCUSION

Minor aches and pains can be managed by non-prescription ibuprofen. Dysmenorrhea is frequent menstrual complain, its symptoms can be reduced by OTC ibuprofen. Ibuprofen was superior to placebo for pain relief and menstrual fluid PGF2 alpha suppression. Cyclooxygenase inhibitors reduce the amount of menstrual prostanoids release, with concomitant reduction in uterine hyper contractility. Over-the-counter (OTC) ibuprofen preparations are mainly used for acute indications, such as fever or headaches, especially tension type headache.

It was sure that the reaction was due to ibuprofen since that was the only medication she took in the afternoon and the reaction was seen approximately after 2 hrs and we have referred other case reports in which ibuprofen has caused similar adverse reactions. Whereas pantoprazole and ceftriaxone were also consumed in the morning but these drug do not tend to have such adverse effects in human body, and no appropriate literature evidences are available to support that these drugs can cause bronchospasm.

Patient presented the following after consumption of ibuprofen:

1. Breathlessness
2. Wheezing
3. Chest tightness
4. Dry cough
5. Swollen lips
6. Respiratory distress
7. High BP

The adverse drug reaction she had is due to ibuprofen. Ibuprofen inhibits cyclooxygenase (COX) enzymes leading to increased synthesis of cysteinyl leukotrienes, prostaglandins and thromboxane causing glottal & laryngeal oedema, increased bronchial secretion, and contraction of non-vascular smooth muscle fibres and dilatation of vascular smooth muscle fibres. The bronchi and bronchioles are clogged with mucus. This is anaphylactoid reaction, if not treated promptly, can endanger life. For anaphylaxis/anaphylactoid the treatment of choice is adrenaline and not anti-histamines, steroids & beta-agonists. Because anti-histamines act as competitive antagonists & blocks the action of histamine but does not reverse the changes that have already occurred. Also it does not prevent further release of histamine from mast cells. Moreover time taken for action is long. It takes more than 30 minutes to act whereas patient in anaphylaxis can die in 5 minutes, (2) the steroids act as anti-inflammatory and reduces inflammatory process, it acts indirectly by (a) potentiating alfa 1 adrenergic action on bronchial arterial smooth muscles (b) suppression of genetic transcription of cytokines, and (c) time taken for action is 4-24 hours, (3) bronchodilators no longer work because bronchioles are already stretched by presence of thick mucoid secretions.

Nonsteroidal anti-inflammatory drugs (NSAIDs) can cause bronchospasm and trigger asthma exacerbations, presumably by increasing leukotriene production due to cyclooxygenase-1 isoenzyme inhibition.[3]

Function of kidney can be reduced as ibuprofen can retain fluids in the body. This results in elevation of blood pressure, putting greater stress on heart and kidneys. Higher dose of NSAIDs can increase risk of heart attack and stroke. As it was observed that the patient had elevated blood pressure after consumption of ibuprofen.

Unlike acetaminophen, there is no antidote available for adverse drug reaction (ADR) caused due to ibuprofen hence managing it is big challenge. Therefore it is very important to understanding pathophysiology of ADR to Ibuprofen, to manage the patient. Writing in the field of hypersensitive medication response demonstrates that epinephrine, a physiological adversary of histamine is the primary medication of decision for the treatment of allergic or drug induced angioedema, laryngeal oedema and bronchospasm due to its direct action on target organs. Such reactions should therefore be managed by epinephrine without loss of time. ADR due to ibuprofen could be prevented by (a) avoiding unnecessary intake of drug, (b) educating patients / families and public about adverse drug reactions (c) surveillance and monitoring of drug reactions (d) record keeping (e) drug audit and (f) reporting of ADR to state/central pharmacovigilance agency.

The causality assessment was carried out using Naranjo scale [Table 1]. A total score of 6 was obtained, which indicates that there is a probability that the adverse reaction is caused due to the suspected drug itself. The score of 9 or greater indicates definite, 5 to 8 indicates probable, 1 to 4 indicates possible and 0 indicates doubtful causal relationships.

Naranjo Adverse Drug Reaction Probability Scale	**Yes**	**No**	**Don't know**	**score**
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?a	+1	0	0	0
4. Did the adverse event reappear when the drug was re-administered?	+2	-1	0	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	2

6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1
SCORE				6

**Score: Definite: ≥ 9, Probable: 5-8, Possible: 1-8, Doubtful: 0*
Report: The suspected ADR found to be Probable on Naranjo scale assessment.
Hartwig's Severity Assessment Scale: [Mild=level 1 and 2, moderate=level 3and 4, severe=5, 6 and 7]

Level	Description
1	An ADR occurred but required no change in treatment with the suspended drug.
2	The ADR required that treatment with the suspended drug be held, discontinue or otherwise change. No antidote or other treatment requirement was required. No increase in length of stay (LOS).
3	The ADR required that treatment with the suspended drug be held, discontinue or otherwise change. AND/OR An Antidote or other treatment was required. No increase in length of stay (LOS)
4	Any level 3 ADR which increases length of stay by at least 1 day. OR the ADR was the reason for the admission
5	Any level 4 ADR which requires intensive medical care.
6	The adverse reaction caused permanent harm to the patient.
7	The adverse reaction either directly or indirectly led to the death of the patient.

Report- level 5 which indicates severe adverse reaction.

CONCLUSION

Review of literature and recent studies suggest that epinephrine relieves angioedema with anaphylactoid reaction caused by ibuprofen because of its direct action on bronchial smooth muscles, bronchial mucosa and vasculature. Therefore epinephrine is first line drug in ADR involving respiratory system, angioedema, cardiovascular system. Anti-histamines, steroids and beta agonist can be used as adjuvant. The suspected ADR was found to have "probable" causal relationship between the suspected drug IBUPROFEN and the observed adverse drug reaction through Naranjo causality assessment. According to hartwig's severity assessment scale it shows level 5 which indicates the reaction was "severe".

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