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Case Report

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IBUPROFEN INDUCED HEMOGLOBINURIA- CASE REPORT

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ABSTRACT

Ibuprofen is the most commonly used NSAIDS for analgesic, anti inflammatory and antipyeritic effect. The major adverse reactions include the effects on the gastrointestinal tract (GIT), the kidney and the coagulation system. rarely NSAIDS can cause drug induced haemolytic anemia. We noted a case of hemoglobinuria in 5 yr old male child postoperatively after administration of ibuprofen. Diagnosis was made on the basis of exclusion of other drug, and review of literature. Suspected drug was stopped, following which urine colour changed to normal and hemoglobinurea subsided.The causality assessment as per the Naranjo algorithim established a 'probable' association between the hemoglobinurea and Ibuprofen (Naranjo Score 6).

KEYWORDS- drug induced haemolytic anemia, hemoglobinuria, ibuprofen.

INTRODUCTION

Ibuprofen is the most commonly used and most frequently prescribed NSAID. It is a non-selective inhibitor of cyclooxygenase- 1 (COX-1) and Cyclooxygenase-2 (COX-2). It is widely used as an analgesic, an anti inflammatory and a antipyretic agent.[1,2] Recemic ibuprofen and S(+) enantiomer are mainly used in the treatment of mild to moderate pain related to dysmenorrhea, headache, migraine, postoperative dental pain, management of spondylitis, osteoarthritis, rheumatoid arthritis and soft tissue disorder.[3] The major adverse reactions include the effects on the gastrointestinal tract (GIT), the kidney and the coagulation system.[4] Ibuprofen was a potential cause of GI bleeding[5], increasing the risk of gastric ulcers and damage, renal failure, epistaxis[6], apoptosis[7], heart failure, hyperkalaemia[8], confusion and bronchospasm.[9] Other less frequent adverse effect include thrombocytopenia, rashes, headache, dizziness, blurred vision and in few cases toxic amblyopia, fluid retention and oedema. Effects on kidney include acute renal failure, interstitial nephritis, and nephritic syndrome but these adverse effects are very rare.[10] NSAIDS rarely can cause drug induced haemolytic anemia.[11] There is no explicit data exist regarding the incidence of ibuprofen induced hemolysis, various case series have found that NSAIDS compromise less than 15% of cases.[12] Most of the cases of drug induced haemolytic anemia are caused by β lactamase antibiotics (penicillin and cephalosporins). Here we have noticed drug induced hemoglobinuria and suspected drug is ibuprofen.

CASE REPORT

our patient was a 5 yr old male child admitted with complains of difficulty in walking and speaking since 3yr, repeated episode of of seizure since 6month for which syrup valporate and syrup piracetam was given. Patient ophthalmic examination reveals bilateral cataract. So cataract surgery was planned. But after few days of admission he complains of fever and burning micturation. So Injection Taxim, Inj. Amikacin and Tab Norfloxacin were started. After 7 days patient become afebrile and urine routine and microscopic examination become normal and patient was found fit for cataract surgery. IV fluids were started from night. During surgery he recived inj ketamine, inj propofol, inj scoline, inj hydrocortisone, inj aciloc, inj deriphylline, inj neostigmine. Intraoperative period was normal. In postoperative period syrup ibugesic was added for relief from post operative pain. Within 24 hr of surgery patient has passed dark coloured urine. Urine routine and microscopic examination was done which showed presence of haemoglobin. The glucose-6-phosphate Dehydrogenase (G6PD) deficiency status was normal. We did not check the haemoglobin status of the patient as there was no features suggestive of anaemia. Biochemical test showed serum creatinine-0.4 mg/dl,

sodium-135 mmol/l and potassium-3.8 mmol/l and urine analysis found that colour-cola coloured, PH - acidic, transparency – clear, albumin – 1+, pus cell – 2-4 / HPF, epithelial cell –nil, crystal – negative and in special test it was found that hemoglobin '3+' in urine. So we withhold the drugs except syrup valporate. Glucose infusion was given and urine becomes clear after 48 hr(as shown in fig.). Thereafter injection Taxim and inj. Amikacin were again started. Here the suspicious drugs were cefotaxim, Fluoroquinolones and ibugesic as there are literature reports of hemoglobinuria due to these drugs. Chance of hemoglobinuria with Fluoroquinolones is less as there was long gap between the appearance of hemoglobinuria and norfloxacin therapy. Injection cefotaxim was again started after 48 hr and did not result in reaapearence of hemoglobinuria. So next suspected drug left is ibugesic. There are few case reports available which has reported immune haemolytic anemia with ibuprofen.[12] In rewiev of literature we found that Suprofen[13] a drug very similar to ibuprofen has caused hemoglobinuria. We carried out the causality assessments as per the naranjo[14] algorithm and preventability and severity assessments as per the hartwig[15] scale. The causality assessment revealed a "probable" association (naranjo score 6) between the ADR and Ibugesic. The severity was found to be moderate (level 3). The preventability analysis revealed the ADR to be "not preventable.

DISCUSSION

Drug-induced hematologic disorders are generally rare adverse effects associated with drug therapy. The most common drug-induced hematologic disorders include aplastic anemia, agranulocytosis, megaloblastic anemia, hemolytic anemia, and thrombocytopenia.[11] The Berlin Case-Control Surveillance Study was conducted from 2000 to 2009 to assess the incidence and risks of drug-induced hematologic disorders. This evaluation found that almost 30% of all cases of blood dyscrasias were "possibly" attributable to drug therapy.[16] Drug induced immune haemolytic anemia is a rare condition affecting approximately 1 per million of population.[12] In immune hemolytic anemia, IgG or immunoglobulin M (IgM) (or both) binds to antigens on the surface of RBCs and initiates their destruction through the complement and mononuclear phagocytic systems.[17] Drug-induced immune hemolytic anemias involve the formation of antibodies directed against RBCs. Antibodies associated with drug-induced immune hemolytic anemia are of two main types. Drug-independent antibodies are those that are found even in the absence of the drug. Drug-dependent antibodies are those that will only react in the presence of drug, and are the more common form of antibodies causing drug-induced immune hemolytic anemia.[18] A laboratory test called the direct Coombs test (or direct antiglobulin test [DAT]), which identifies foreign immunoglobulins either in the patient's serum or on the RBCs themselves, is the best means to diagnose drug-induced immune hemolytic anemia. Four mechanisms have been proposed to explain drugs can induce immune hemolytic anemia. The first mechanism is the "hapten mechanism" or "drug adsorption" mechanism. In this mechanism, patients make an antibody against a stable complex of the drug with some soluble noncellular molecule or protein. When the drug is administered again, an immune complex of drug - antidrug forms and attaches non-specifically to RBCs, activating complement and leading to cell destruction.[19, 20] The anemia usually develops gradually over 7 to 10 days and reverses over a couple of weeks after the offending drug is discontinued. The second mechanism is the immune complex or "innocent bystander" mechanism. In this mechanism, drugs bind to an antibody, usually IgM, to form an immune complex. This immune complex then attaches to the RBC membrane, activating complement and leading to intravascular hemolysis[19]. This type of mechanism is associated with acute intravascular hemolysis that can be severe, sometimes leading to hemoglobinuria and renal failure. The third mechanism involves the production of true RBC autoantibodies. The first drug associated with this type of reaction was methyldopa.[20, 21, 22] The mechanism by which methyldopa induces antibody production is not completely known, but two hypotheses have been proposed.[21] The first suggests that methyldopa or its metabolites act on the immune system and impair immune tolerance. An alternative hypothesis is that the offending drug may bind to immature RBCs, altering the membrane antigens and inducing autoantibodies. The fourth mechanism of drug-induce immune hemolytic anemia is through nonimmunologic protein adsorption (NIPA) to RBC membranes.[19,23] In this "membrane modification mechanism," drugs can change the RBC membrane so that proteins attach to the cell, leading to a positive antiglobulin test result. Our patient shows hemoglobinuria in which free hemoglobin is found in urine which is characterized by cola- or tea-colored urine. Hematuria differ from hemoglobineuria showing abundant red cells in microscopical examination. The common causes of hemoglobineuria are infectious diseases, neoplasms, exposure to the cold etc.[24] Drug induced hemoglobinuria is very rare. The most common drugs causing hemoglobineuria are Chloroquine, Rifampicin, Primaquine etc.[24] The treatment of drug-induced immune hemolytic anemia includes the immediate removal of the offending agent and supportive care. In severe cases, glucocorticoids can be helpful, but their use outside of autoimmune hemolytic anemia is not supported by strong evidence.[25] Other agents such as the chimeric anti-CD20 monoclonal antibody rituximab and IgG treatments have been used, but their role is yet to be clearly defined.[26,27]

CONCLUSION

Ibuprofen is widely prescribed by physician as well as also a popular OTC drug. Physician must know and suspect if such reaction occurs during therapy involving ibuprofen and should carefully evaluate drug-associated reaction. If such reactions timely recognised and offending drug are timely discontinued, fatal complications can be avoided. It is important that such

reactions are identified and documented in the patient record and patient should be explained properly about sign and symptoms associated with reaction and instructed not to use that drug so that their recurrence can be avoided in future.

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