THE EFFECT OF INDOMETHACIN ON GLUCOSE SERUM

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ABSTRACT

Indomethacin is used to treat moderate to severe osteoarthritis, rheumatoid arthritis, acute gouty arthritis, ankylosing spondylitis, bursitis, tendinitis, diabetes insipidus and for closing of patent ductus arteriosus (PDA).

Indomethacin is unique among NSAIDs in that it is the drug of choice for management of gouty arthritis, indomethacin is a very ulcerogenic medication that can cause fatal ulcer bleeding, it causes more fluid retention compared to ibuprofen, frequent frontal headache, pancreatitis, heart attack and stroke are specific unwanted effects of indomethacin, it shouldn’t be used as other NSAIDs if one have had recently or will be having bypass heart surgery, as well as pregnant women more than 29 weeks of gestation.

Indomethacin is not recommended for pediatric patients 14 years of age and under, because there have been cases of hepatotoxicity reported in pediatric patients with juvenile rheumatoid arthritis, including fatalities.

Indomethacin is provided in much trade formulation namely indocin and indolin, it is available in multiple dose variations, depending on pathologic conditions, to reduce the possibility of peptic ulcers, indomethacin should be prescribed at the lowest dosage needed to achieve a therapeutic effect, usually between 50–200 mg/day. It should always be taken with food, for osteoarthritis and rheumatoid arthritis typically as indomethacin 25, 50 mg orally b.i.d. or t.i.d., its dosage for gouty arthritis is 50 mg orally or rectally 3 times a day, the dose may be increased (2-4 days).

The aim of recent study is to evaluate the effect of indomethacin on carbohydrate metabolism, as most of NSAIDs are all thought to increase risk of hypoglycemia, about 35 patients with gouty arthritis, (GA), osteoarthritis (OA) and rheumatoid arthritis (RA) were investigated for about 2 weeks, patients were treated by indomethacin, WBCs count, C-reactive protein (CRP), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR) and blood glucose levels are examined before during and after treatment.

The main finding of this research study is that indomethacin produces a strong anti-inflammatory effect which may be similar to diclofenac and methotrexate in treating early stages of OA and GA respectively; in addition indomethacin causes evident reversible hypoglycemia in elderly patients older than 50 years of age, in all 3 investigated groups.

KEYWORDS: Indomethacin, NSAIDs, Ibuprofen, Pancreatitis, Peptic Ulcer, Gestation, Gouty Arthritis, Osteoarthritis, Rheumatoid Arthritis, Hypoglycemia, Ibuprofen, Methotrexate
INTRODUCTION

Non-steroidal anti-inflammatory drug (NSAIDs), are the second most popular medications, following antibiotics in medical and dental uses over the world.

NSAIDs exert their pharmacologic effects by blocking cyclooxygenase (COX) enzymes, the key proteins that act on arachidonate to yield prostaglandins (PGs)- the main mediators of inflammation, that can cause set-effects on blood vessels, nerve endings and cells, including vasodilation, chemotaxis, increased sensitivity of pain receptors to mediators, (inflammatory pain is mainly due to bradykinin), increased production of interleukin-1, free radicals, as well as PGs act on hypothalamus to increase body temperature all of which are manifested clinically by hyperemia, edema, pain and pyrexia.

COX enzyme is present in 2 forms, COX-1 is known as housekeeping enzyme which is essential for endothelial integrity, vascular patency, gastric cytoprotection, bronchodilation, renal glomerular filtration as well as platelet aggregation, on the other hand COX-2 is recognized to be pathologic enzyme and expressed mainly in the state of inflammation or cell injury, but low concentrations of COX-2 are required for normal functioning of CNS, renal and osseous tissues.

NSAIDs are chemically dissimilar agents that differ in their antipyretic, analgesic and anti-inflammatory properties, the prototype is aspirin, other commonly prescribed NSAIDs include nonselective COX inhibitors such as diclofenac K- Na, paracetamol, ibuprofen, naproxen, indomethacin and piroxicam, on the other hand selective COX-2 inhibitors are available for clinical uses including celecoxib, etoricoxib and rofecoxib.

NSAIDs are mainly prescribed to reduce pain arising from integumental structures rather than from viscera, they are ineffective in reducing pain associated with ischemia, necrosis, cancer or spasms, sometimes are combined with narcotic analgesics to decrease pain tumor. NSAIDs compared to opioids don’t cause addiction, but they are inferior to opioids in that NSADs have no effect of emotional aspect of pain.

NSADs are particularly employed to treat rheumatoid arthritis, ankylosing spondylitis, gouty arthritis, osteoarthritis, bursitis, synovitis, diabetes insipidus, gingivitis, closure of patent ductus arteriosus (PDA) and postoperative pain.

The major side effects of NSAIDs are linked to blocking of COX-1 enzyme, manifested clinically by mild, moderate to severe GIT effects, hypersensitivity reactions, mainly urticaria, bronchospasm (due to shifting of arachidonic acid metabolism toward lipoxygenase pathway with the formation of leukotriines) and even anaphylaxis, inhibition of platelet aggregation, (the effect is restricted to aspirin and manifested laboratory by prolongation of bleeding time), so NSAIDs are absolutely contraindicated in cardiovascular diseases, gastritis, peptic ulcers, bronchial asthma, hemorrhagic disorders and renal diseases. Most of these problems could be dissolved by prescribing selective COX-2 inhibitors with an exception for bronchial asthma and renal diseases.

The most important NSAIDs drug-drug interactions are with caffeine which amplifies the effects of NSAIDs and for this reason; pharmacists prepare pills that contain both an NSAID and caffeine.

Other significant drug interactions of NSAIDs is with warfarin with increased risk of bleeding. Hypotension is also a severe drug- drug interaction of NSADs with antihypertensive agents excluding Ca channel blockers, angiotensin
The Effect of Indomethacin on Glucose Serum

Converting enzymes inhibitors (ACEIs) and diuretics.

NSAIDs potentiate toxicity of methotrexate, phenytoin, bisphosphonates, lithium and selective serotonin reuptake inhibitors (SSRIs) (No concern with short-term use 5-7 days).

Ibuprofen decreases antiaggregant effect of aspirin, which in its turn reduces the total anti-inflammatory effect of ibuprofen.

In conclusion the choice of any member of NSAIDs must be done on the basis of a presenting pathologic condition, associated diseases, as well as medications that have been used by the patient, to reduce possibility of unwanted drug-drug interactions.

**METHODOLOGY**

About 35 patients were examined for possibility of hypoglycemic effect of indomethacin, 20 of them are men and the others are women, the ages of all patients were between 25 and 60 years, cardiovascular, GIT and endocrine disorders were excluded, according to patient's pathologic conditions; they are divided into the following groups:

The first group includes 11 patients, 7 of them are men, suffering from GA and treated by indomethacin orally at a dose of 100 mg tid. For 2-4 days.

The second group contains 15 patients with OA, 8 of them are men, this group was medicated by indomethacin per os. 50 mg 3 times /d, for 2 weeks.

The third group includes 9 patients, 5 of them are men, it was treated from RA by indomethacin at a dosage of 50 orally mg 3 times /d, for 2 weeks.

WBCs count, RF, CRP, ESR as well as serum of glucose are taken from all groups before, during and upon completion of therapy, a fasting glucose serum was measured, during the period of treatment, and on time of measurement of fasting glycemia, the patients were examined for signs of hypoglycemia to determine the possibility of hypoglycemic effect of indomethacin after excluding disorders that can cause hypoglycemia, as well as to ensure reversibility of expected hypoglycemic effect of indomethacin.

**METHODS OF INVESTIGATION & DISCUSSION**

Investigations show that the signs of acute inflammatory process are significantly decreased after treatment by indomethacin in all examined groups, the patients note after completion of therapy that swelling of articulations, pain, pyrexia are diminished as well as motion in affected joints becomes more freely, hematologically this relieve is reflected by returning of WBCs, CRP and ESR to their normal values. RF was reduced markedly in patients with RA.

Although indomethacin is not the drug of choice for treatment of either OA or RA, but it shows similar effects to diclofenac that is the most effective medication in the state of OA and to methotrexate which is very effective in the treatment of RA.

The strong pharmacologic action of indomethacin that shows nearby the same efficacy to diclofenac and methotrexate in treating OA and GA respectively could be explained by one of two phenomena, firstly the early stages of OA and RA and secondary may be associated with persistent continuous therapy of indomethacin for 2 weeks, which is confirmed by
evident improvement of patients as well as hematologic tests. (Table -1)

**Table- 1: Hematologic Profile of Patients Groups Medicated by Indomethacin**

<table>
<thead>
<tr>
<th>Hematologic Tests</th>
<th>Normal Values</th>
<th>I Group B/T</th>
<th>I Group A/T</th>
<th>II Group B/T</th>
<th>II Group A/T</th>
<th>III Group B/T</th>
<th>III Group A/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBCs</td>
<td>4.1-10.9 K/uL</td>
<td>15-18</td>
<td>5-10</td>
<td>14-19</td>
<td>4-8</td>
<td>18-22</td>
<td>6-11</td>
</tr>
<tr>
<td>CRP</td>
<td>5-10 mg/L</td>
<td>12-16</td>
<td>6-9</td>
<td>14-16</td>
<td>5-9</td>
<td>13-16</td>
<td>6-9</td>
</tr>
<tr>
<td>RF</td>
<td>less than 15 IU/mL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>22-25</td>
<td>10-14</td>
</tr>
</tbody>
</table>

**N.B**

B/T= Before Treatment. A/T= After Treatment.

K/uL= one ul is equal to mm (3) and K means a thousand (1000 cells/ul).

M= Male. F= Female.

Concerning glycemia, generally the glucose level that defines hypoglycemia is variable. In people with diabetes levels below 70 mg/dL is diagnostic. In non-diabetics adults, levels below 55 mg/dL, symptoms are related to hypoglycemia; at the time of symptoms, and improvement when blood sugar is restored to normal confirm the diagnosis.

A fasting blood glucose test is taken from all groups, before, during and after treatment with indomethacin, the result of investigation are shown on (table- 2), in which a fasting blood glucose levels are below 55 mg in patients aged above 50 years of all 3 groups, at the time of glucose testing, these patients experience anxiety, palpitations, hunger, trembling, blurred vision and sweating, the patients are asked to take glucose, after which the level of glucose is raised to normal and symptoms begin to disappear.

According to whipple's triad, after excluding insulinoma, renal, hepatic and endocrine diseases., these patients were suffering from indomethacin –induced hypoglycemia, which may be explained by many factors including, decreased at all metabolic rate in these patients as well as the ability of indomethacin to increase insulin secretion, or decreased its clearance, increased glucose utilization in the periphery, and reduced gluconeogenesis due to decreased levels of glucagon, all appear to contribute to the hypoglycemic effect of indomethacin.

These facts oppose normal mechanisms by which glucose levels are regulated, during periods of fasting, glucose levels are regulated by glycogenolysis and gluconeogenesis. Glycogenolysis impacts serum glucose levels in the first 8 to 12 hours of fasting, while gluconeogenesis contributes more to glucose levels after longer periods of fasting, all these process are regulated by glucoregulatory hormones. Insulin and glucagon play large roles in the overall regulation of blood glucose (Figure -1).
Hyperglycemia stimulates insulin release from the pancreas. Insulin is not released until blood glucose levels reach 59.4 mg/dl. Insulin binds to receptors on fat, muscle, and liver cells to stimulate glucose uptake. Additional serum glucose is converted to glycogen, insulin decreases gluconeogenesis and glycogenolysis by inhibiting glucagon release from the pancreas. The combination of these actions contribute to hypoglycemic effect of insulin.

Glucagon controls fasting levels by stimulating gluconeogenesis and glycogenolysis in the liver, resulting in hyperglycemia. Release of glucagon from the pancreas occurs when serum glucose levels fall below approximately 90 mg/dl.

A fasting blood glucose was taken from all patients who have had hypoglycemia on indomethacin therapy, blood sugar is obtained a week after completion of therapy, the main finding is that the level of glucose in these patients was around normal ranges indicating that indomethacin has reversible hypoglycemic effect. (Table -2).

Table- 2: A Fasting Glycemia Profile of Patients Groups Treated by Indomethacin

<table>
<thead>
<tr>
<th>Patient's Group</th>
<th>Normal Values of Glycemia</th>
<th>B/T</th>
<th>D/T 2 day</th>
<th>D/T 4 day</th>
<th>D/T 7 day</th>
<th>D/T 10 day</th>
<th>D/T 14 day</th>
<th>A Week A/T</th>
</tr>
</thead>
<tbody>
<tr>
<td>First (GA)</td>
<td>70-100 mg/dl</td>
<td>72-94</td>
<td>42-44</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>75-91</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5 M 2 F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second (OA)</td>
<td>70-100 mg/dl</td>
<td>71-98</td>
<td>45-48</td>
<td>46-49</td>
<td>44-48</td>
<td>41-48</td>
<td>42-48</td>
<td>71-100</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 M 5 F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Third (RA)</td>
<td>70-100 mg/dl</td>
<td>78-89</td>
<td>40-44</td>
<td>42-46</td>
<td>45-49</td>
<td>43-47</td>
<td>43-48</td>
<td>80-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3 M 3 F</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

N.B B/T= Before Treatment A/T= After Treatment D/T= During Treatment M= Male F= Female.

Figure -1
CONCLUSIONS

- Indomethacin shows effective anti-inflammatory effect in treating early stages of OA and RA, instead of using front-line therapy, including diclofenac and methotrexate respectively.
- Indomethacin doesn’t cause hypoglycemic effect in all investigated patients under 50 years with OA, RA treated for 2 weeks and GA managed for 4 days,
- Indomethacin has evident reversible hypoglycemic effect in all examined patients above 50 years, medicated for 2 weeks.
- Indomethacin- induced hypoglycemia mechanism may be associated with increased insulin secretion, decreased its clearance, increased glucose utilization in the periphery and decreased levels of glucagon.
- It is recommended to check glycemia in patients over 50 years of age medicated by indomethacin for possibility of hypoglycemia.

REFERENCES


11. Fasting hypoglycemia. // Taber's Cyclopedic Medical Dictionary (2009);2009, Issue 21, p850


16. Lanas Advances in the adverse effects of NSAIDs in the gastrointestinal tract Gastroenterol Hepatol, 29 (2006), pp. 16-22


