Research Article

Hepatotoxicity associated with piroxicam therapy

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ABSTRACT

Background: The purpose of this study is to estimate the hepatic risk associated with the use of piroxicam, in patients suffering from primary form of osteoarthritis (OA). **Materials and Methods:** We investigated 32 patients with primary form of OA, and the patients were divided into 2 categories according to stages of OA (II and III stages) and medicated orally by 10 and 20 mg/d piroxicam, respectively, in a period of 2 months and patients' follow-up for 6 months. Complete blood count and hepatic tests including bilirubin, alanine aminotransferase, and aspartate transaminase were done before, during, and after treatment, in both categories to determine the onset of possible hepatotoxic effect of piroxicam. Ultrasonography and liver biopsy were also provided only for certain patients of II category, in whom hepatotoxicity has occurred due to piroxicam management. **Results:** Orally prescribed piroxicam, 10 and 20 mg/d in both categories, is a good medicament for the management of OA with a small average percentage of ulcerogenicity (19%). Piroxicam was expected to decrease nocturnal pain and spasticity of OA in the II category. Piroxicam 10 mg/d produces no hepatotoxic effect in the first category but on the other hand (piroxicam 20 m/d) causes a mixed hepatocellular-cholestatic reversible injury in about 75% of OA patients in the second category, predominantly in female gender, at the end of the 8th week of treatment. The hepatic injury is unknown but strongly believed to be idiosyncratic. **Conclusion:** Piroxicam therapy should be evaluated clinically and laboratory in the first 3–12 weeks to decrease its possible hepatotoxic effect.

KEY WORDS: Cholestasis, Liver biopsy, Non-steroidal anti-inflammatory drugs, Osteoarthritis, Piroxicam, Ultrasonography

INTRODUCTION

The liver plays an astonishing array of vital functions in the maintenance, performance, and regulating homeostasis of the body, and its major functions are immunity, carbohydrate, protein and fat metabolism, exogenous (drug) and endogenous substances detoxification, secretion of bile, and storage of vitamins.

More than 900 drugs have been implicated in causing liver injury, and it is the most common reason for a drug to be withdrawn from the market.[1,2] Drug-induced liver injury (DILI) is progressively increased, general pathophysiologic mechanisms involved in DILI include (1) direct injury of hepatocytes with their membrane rupture, (2) interruption of bile flow through blocking of transport proteins at the canalicular membrane, (3) apoptosis of hepatocytes, (4) immunologic when a drug acts an immunogen and can affect the P450 system, and (5) bile duct injury, and the most commonly DILI are antibiotics, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetic agents, antihyperlipidemics, antirheumatic drugs, TNF inhibitors, antiepileptics, antipsychotic drugs, acetylcholinesterase inhibitors, tricyclic antidepressants, and antihypertensive agents.[3-5]

NSAIDs are consumed massively worldwide, and along with antimicrobial agents, are the most frequent causes of drug-induced liver injury.[6] The pharmacology of NSAIDs is broad and diverse, their principle effects are analgesic, antipyretic, and anti-inflammatory, and these effects are highly advantages in the clinical settings, so many patients are afflicted by one or more of these symptoms. For this reason, NSAIDs are utilized for relieving pain, associated with toothache, arthralgia, myalgia, headache, and migraine, as well as to decrease inflammatory reactions in arthritic diseases such as rheumatoid arthritis (RA), osteoarthritis (OA) and gout.[4,7]

More than 20 different NSAIDs are available commercially, and these agents are used worldwide, for their three above-mentioned therapeutic effects in patients with multiple medical conditions.[8] The prototype is aspirin, commonly prescribed NSAIDs

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are diclofenac K or Na, ibuprofen, indomethacin, piroxicam, naproxen, meloxicam, and etoricoxib, and they share a common mode of action which involves blocking cyclooxygenase (COX) enzymes. Different NSAIDs inhibit COX isoenzymes COX-1 and COX-2 to different extents, and this differential mechanism of action explains their differing wanted therapeutic effects and unwanted adverse actions.[5,9] Acetaminophen (paracetamol) is not considered as NSAIDs as it has negligible anti-inflammatory powers even at high doses, (compared to aspirin), and its analgesic and antipyretic effects are due to central inhibition of COX-1.[10]

COX-1 isoenzyme is constrictively expressed because it is involved in many physiological processes, for instance, GIT mucosa protection, platelets aggregation, and potency of blood vessels. COX-2 in contrast to COX-1 is facultatively expressed mainly during inflammatory states, but this does not exclude its physiologic role in CNS, macula densa of renal tissues as well as ovaries and uterus.[1,11]

Most NSAIDs competitively inhibit both isoenzymes to some degree, though aspirin - as an exception irreversibly blocks its target. COX inhibition is vital, as its COX enzymes are responsible for the generation of prostanoids - substances which include prostaglandins "PGs" (implicated in inflammation and anaphylaxis), prostocyclins (active in resolution phase of inflammation), and thromboxanes (mediators of vasoconstriction).[7,9,12]

Non-selective COX-1/COX-2 inhibitors, e.g., aspirin, piroxicam, and naproxen- target COX-1 and as a result gastric PG levels are reduced, and for this reason, GIT symptoms are considerably more common, ranging from mild erosions to severe bleeding, about 15% of patients experience dyspepsia on NSAIDs, and the use of misoprostol (PG analogue) with naproxen, diclofenac, or aspirin protects GIT mucosa from ulcerogenic effects of NSAID.[4,5,10]

Their antipyretic effect is due to inhibition of PGE-2 synthesis form the thermoregulatory center, the hypothalamus, but not hyperthermia in which the set point is not altered. Selective COX-2 inhibitors such as celecoxib, valdecoxib, and meloxicam in low doses are superior to non-selective in that they have less GIT distress, without affecting the bleeding time, and therefore preferred for patients suffering from GIT and bleeding disorders; on the other hand, selective COX-2 inhibitors should not be used in CNS and renal diseases.[10,13]

NSAIDs (non-narcotic analgesics) exert their pain-killing effect at the peripheral nervous system (PNS) level, by minimizing sensitization of receptors to bradykinin and PGs, in contrast to narcotic analgesics that act at the central nervous system (CNS), by inhibiting opioids receptors. NSAIDs compared to opioids are ineffective to diminish ischemic, necrotic, spastic, visceral and neoplastic pains, in addition NSAIDs don't affect the affective aspect of pain, which is ameliorated by opioids. Sometimes, they are combined with opioids to decrease pain arising from non-integumental structures, and finally, addiction and tolerance are specific for opioids rather than NSAIDs.[4,6,10]

Pharmacokinetically, NSAIDs are well absorbed from the gastrointestinal tract, with the exception of aspirin (and possibly diclofenac) which undergoes pre-systemic hydrolysis to form salicylic acid. Concomitant administration of NSAIDs with food or antacids may in some cases lead to delayed or even reduced absorption, and they are highly bound to plasma proteins (mainly albumin), which limit their body distribution to the extracellular spaces, and undergo hepatic transformations variously by CYP2C8, 2C9, 2C19, and/or glucuronidation. Half-lives of the NSAIDs vary but in general can be divided into "short-acting" (<6 h, including ibuprofen, diclofenac, and indomethacin) and "long-acting" (more than 6 h, including naproxen, celecoxib, meloxicam, and piroxicam). The elimination of these drugs depends largely on hepatic biotransformation; renal excretion of unchanged drugs is usually small (<5% of the dose).[3,9,14] NSAIDs differ in potency, duration of action, side-effect profile, and potential for drug interactions, The selection of NSAID should be based on clinical experience, patient convenience (e.g., once or twice daily dosage schedule), side effects, and cost. Despite the increasing number of NSAIDs available, there are few data comparing the old and new agents for efficacy and safety, and there are few guidelines governing choices of NSAIDs for particular patients.[8]

Many studies for the management of OA reveal that indomethacin, naproxen, isoxicam (chemical analog of piroxicam), and ketoprofen are equal in efficacy, but the latter three had fewer side effects than indomethacin.[15,16] Naproxen and aspirin are preferred for the treatment of muscle contraction headache, whereas indomethacin should be avoided, and in contrast, indomethacin is the drug of choice for chronic paroxysmal hemicrania and hemicrania continua.[17]

Studies show that piroxicam (20 mg/day) compared to other NSAIDs is more potent and less frequently employed daily, because of its long half-life, notably piroxicam in RA is equal to ibuprofen (400 mg 3–4 times a day), but better than indomethacin (25 mg administered 3 times daily). In OA, piroxicam is slightly superior to naproxen (500 mg B.I.D).[13]

There is a high degree of "cross-sensitivity" between aspirin and other NSAIDs in patients who have symptoms of rhinitis or asthma, and the Genesis is pharmacologic rather than immunologic, compared to urticaria (on exposure to aspirin) in which mechanism is probably immunologic (salicylate metabolite), that does not correlate with other NSAIDs.[11,18,19]

There is no proved advantage to use more than one NSAID at a time unless a rapid onset of action is needed. If one drug does not prove efficacious after 1–3 weeks at the maximally tolerated dose, another agent should be substituted.[4,7,14] For patients with gastric intolerance to one NSAID, alternative therapy from another class should be considered.[10] If unsuccessful, therapy with choline salicylate, salsalate, or enteric-coated aspirin may prove useful.[20] When adverse effects of NSAIDs on platelets are of concern, sulindac or ibuprofen should be considered, with non-acetylated salicylates as alternatives.[2,8,21] In fact, NSAIDs inhibit PGE2 and PGI2, resulting in decreased renal blood flow and therefore retention of Na and water, edema and interstitial nephritis, which can occur with all NSAIDs, especially fenoprofen, aspirin is the only NSAID that does not cause nephrotoxicity. Sulindac is perhaps the least offensive agent, but close monitoring should be instituted.[22,23] When central nervous system side effects such as headache occur, aspirin or naproxen may be used. In hypertension, the pressor effect of NSAIDs could be minimized by prescribing sulindac and avoiding indomethacin. Paracetamol is still the only analgesic choice for asthmatic patients. Hence, the choice of any member of NSAIDs should be done carefully, assuming to the above-mentioned factors.[16,23]

MATERIALS AND METHODS

The consent from patients for this study has been taken. 32 primary knee joint OA patients aged from 30 to 60 years were investigated for the possibility of piroxicam-induced hepatitis in the period of 6 months, Among arthritic patients, are 16 males, the patients were categorized in two categories, (II and III stages) according to the Kellgren and Lawrence system, oral piroxicam therapy was indicated for 2 months, because its therapeutic effects become evident, only after the 1st 8th –12 weeks of treatment:[6]

The first category includes 16 patients with the II stage, mild of OA, and 9 of them are women, medicated orally by piroxicam, 10 mg/day. The second category contains 16 patients with the III stage, moderate of OA, 10 of them are women, and they were given piroxicam 20 mg/d. per.os.

Complete blood count (CBC), the rheumatoid factor, (RF), hepatic test functions including bilirubin, alanine aminotransferase (ALT), and alkaline phosphatase (ALP) were done before, during, and on completion of treatment in all patients.

All patients were investigated for the possibility of liver injury effect of piroxicam at the 1st 3–4 weeks following treatment.[24]

At the end of treatment, iron, ferritin, ultrasonography (US), serologic reactions, and liver biopsy were indicated only to 12 jaundiced patients of the second category.[24-26]

RESULTS

- Nocturnal acute pain of OA present in most (75%) of the patients (above 55 years) of second group, and mainly dominant in women.
- Piroxicam, 10–20 mg/d for 2 months' duration therapy, is a good medicament for the treatment of OA (II and III stages), with an ulcerogenic effect (12.5%–25%) in the first and second categories, respectively.
- Piroxicam, 10 mg/d given for 8 weeks, causes no hepatic injury.
- Piroxicam, 20 mg/d, decreases the incidence of nocturnal pain and may be muscle spasticity, which suggests it as one of most effective drugs against pain at the night.
- Piroxicam, 20 mg/d, is thought to cause hepatic injury at the end of 8th week of treatment in about 75% of patients belonging to the second category.
- Piroxicam, 20 mg/d, causes a mixed hepatocellular-cholestatic pattern of injury, based on R values of ALT and ALP enzymes.
- The hepatic injury induced by piroxicam is reversible as jaundiced patients completely recovered, and laboratory values returned to their normal limits, by the end of the 4th month of piroxicam withdrawal therapy.
- The mechanism of piroxicam-induced hepatotoxicity is unknown but strongly believed to be idiosyncratic character, rather than dose-related mechanism.
- It is recommended to control CBC indices as well as hepatic enzymes in patients on piroxicam therap in the 1st 3–12 weeks to minimize its possible hepatotoxic effect.

DISCUSSION

In both categories, signs of inflammation are reflected on CBC by increased white blood cell (WBC) count and erythrocyte sedimentation rate (ESR) values. The first category of patients experiences minor knee pain after walking and running, joint stiffness, and tenderness; they were medicated by piroxicam, 10 mg/d for 2 months, and the usual dose of piroxicam for OA arthritis is 20 mg/d, but many studies show that giving piroxicam; 10 mg/d was successful in a small

number of arthritic patients; the other purpose why we gave these patients this dose was to determine if piroxicam is dose-related toxicant or not.[3,6,17]

Patients of the second category clinically complain of more intense symptoms compared to the first one, they manifest acute knee joint pain with swelling, the pain is exacerbated by motion and relieved by rest, night pain is said to be present in almost patients, especially patients above 55 years (8 females and 3 males), joint pain is typically accompanied by morning stiffness and generally lasts less than an hour, and they also experience a decreased range of motion and muscle spasm.

On examination, patients of II category demonstrate localized tenderness along the joint; osteophytes is palpable around the affected knee joint, before treatment, by piroxicam; all patients of I and II groups were investigated for possibility of the presence of cardiovascular, endocrine, hepatic, skin, and renal diseases, all of which were excluded, and a detailed medical history including thorough questioning about medical factors, risk factors, use of prescription drugs, self-medication, and use of unconventional substances such as alternative and herbal medicine was provided with negative answers.[13,27,28] RF was negative in both categories.

Investigations show that treatment by piroxicam in both categories equally and markedly decreases the signs of acute inflammatory process of knee joint. Patients of I group after the treatment demonstrate improvement of motility, ability to flex or extend their knees, as well as decreased tenderness and joint stiffness. Along a period of 2 months' treatment, only 2 of 16 patients demonstrate mild dyspepsia and abdominal pain, reflecting the ulcerogenic effect of piroxicam on GIT mucosa, and any change in the skin or eye pigmentations are not noted in all patients of this category.

Piroxicam given to this group for 2 months at a dose 10 mg/d markedly decreases inflammatory reactions of OA that was reflected on CBC, in which leukocytosis and ESR are normalized, indicating the efficacy of piroxicam, against OA, without any side effect on GIT mucosa (except only in 12,5% of patients dyspepsia appears, as mentioned above), because hepatic tests (bilirubin, ALP and ALT levels) before, during, and after treatment have no any significant deviation; therefore, piroxicam, 10 mg/d for 2 months produces a strong effect against OA and has no hepatotoxic effect in these patients [Table 1].

Concerning the second category, piroxicam, 20 mg/d exerts a strong analgesic and anti-inflammatory effects in all patients, confirmed by decreasing WBCs count as well as normalization of ESR; most of the patients demonstrate that motion becomes more better than before treatment, swelling, morning stiffness, night pain, and muscle spasm are significantly diminished. Only 4 patients of this group demonstrate nausea and vomiting, other complaints are not observed, and their hematologic analysis and biochemistry show no any significant deviation, before, during, and after treatment. 12 patients of this category (9 females and 3 males) at the end of 8 weeks of course treatment complained of abdominal tenderness, fatigue, nausea, vomiting, generalized pruritus, jaundice, dark urine, and pale stool. At this period, piroxicam therapy was stopped.

The mean average of biochemical analysis was taken from the 12 jaundiced patients of the II category showed increased total concentration of bilirubin, (5.9 mg/dl), increased serum of bilirubin accounts for conjugated form, and ALT and ALP levels are also increased (694 and 575 U/L, respectively), with normal CBC. US (ultrasound) showed a normal liver, gallbladder, and biliary tree. Liver biopsy reveals intrahepatic cholestasis with only mild inflammation and hepatocellular necrosis as shown in Table 2.

Patients presented by acute symptoms of suspected hepatic injury at the end of the 8th week of treatment by piroxicam had no history about hepatic diseases, and they did not take any medication for the past 6 months; serologic reactions to hepatitis A, B, C, cytomegalovirus, herpes simplex, Epstein–Barr virus were negative; values of iron and ferritin are within the reference range, so excluding any infectious or metabolic disorder that could be a cause of hepatic injury. At the onset of symptoms, hepatic tests showed elevated total amount of bilirubin, conjugated hyperbilirubinemia predominates unconjugated variant, normally, the total bilirubin level is <1.2 mg/dL (the reference range of direct bilirubin is 0.1–0.4 mg/dL), and approximately 70% is indirect (unconjugated) bilirubin. Conjugated hyperbilirubinemia (>50% of the total bilirubin is direct) suggests hepatocellular dysfunction or cholestasis, Unconjugated hyperbilirubinemia (>80% of the total bilirubin is indirect) suggests hemolysis or Gilbert's syndrome, when the bilirubin level is above 25–30 mg/d, extrahepatic cholestasis is an unlikely diagnosis; since the predominantly conjugated bilirubin is water soluble, it is easily excreted by the kidney in extrahepatic cholestasis.[18,28,29] Levels of bilirubin in these patients begin gradually to be decreased after discontinuation of piroxicam therapy and normalization had occurred at the end of the 4th month as shown in Table 2.

Regarding ALT and ALP levels, at the onset of symptoms, ALT serum is increased more than ALP,

Table 1: Hematologic and hepatic tests of patients of I Group medicated by piroxicam

Hematologic and hepatic tests ©	Normal values	Before treatment	After treatment
WBCs	4,1–10,9 K/uL	14–18	5–10
ESR	M: 1–20 mm/h	M: 20–24	M: 1–16
	F: 1–30 mm/h	F: 22– 39	F: 4–24
ALT	<40	36	38
ALP	<280	259	270
Bilirubin (mg/dL)	1.2 mg/dL	0.8	1.1

K/uL=1 ul is equal to mm (3) K means a thousand (1000 cells/ul). ©: The symbol refers to mean average of laboratory values among 16 patients. ALT: Alanine aminotransferase, ALP: Alkaline phosphatase, M: Male, F: Female

Table 2: Laboratory values of 12 jaundiced patients of the second category

Time after starting	Time after stopping	©			Others
		ALT (U/L)	ALP (U/L)	Bilirubin (mg/dL)	
0		37	273	0.9	Analysis was taken as "piroxicam" therapy started for OA
55 days					"P" therapy was stopped
57 days	0	694	575	5.9	Itching, jaundice
60 days	7 days	270	736	4.5	Dark urine, pale stool, on the 8th day, liver biopsy was indicated
77 days	14 days	358	1688	3.3	
3th month	20 days	159	1240	2.1	
4th month	1 month	50	630	1.6	
5th months	3 month	61	291	0,7	
6th months	4 months	36	103	0.5	
Normal Values		<40	<280	<1.2	

©The symbol refers to mean average of laboratory values among 12 jaundiced patients ALT: Alanine aminotransferase, ALP: Alkaline phosphatase. OA: Osteoarthritis

a week later, serum ALT is decreased, but the serum of ALP is increased, then at the end of the II week, levels of ALP are significantly elevated, compared to slightly increased ALT levels, and finally, the 20th day of prioxicam withdrawal therapy reveals that levels of both enzymes begin gradually to be decreased, and by the end of 4th month, are within normal limits in all patients. Thus, the R value which is employed to determine the relationship between ALT and ALP is 3.5, at the onset of symptoms, indicating a mixed hepatocellular-cholestatic pattern of injury, further elevations in ALP, and a rapid decrease in ALT (by the 7th day) yielding R values of <2). In general, when ALP is greater than twice the normal upper limit and R ≤ 2, the type of injury is the cholestatic pattern, and in hepatocellular pattern, when ALT is greater than twice the normal upper limit or R ≥ 5 and 2 < R <5, it is the mixed type of injury.[5,12,26,29-31] [Table 2]. Based on the above data, concerning the second group of OA patients, the onset of symptoms, negative serologic tests, biochemical analysis, R values, liver biopsy and taking considerations, that other causes of acute liver injury were effectively ruled out, as well as patients recovered steadily once therapy was stopped, complete recovery has occurred at the end of the 4th month, all suggest that the likelihood that piroxciam at the dose of 20 mg/d for 2 month is the cause of the injury is highly probable. In fact, drug hepatotoxicity mechanisms could be classified into 2 classes: (A) Drugs that directly affect the liver and usually is dose-related, for example, acetaminophen and (B) idiosyncratic drug reactions: are unpredictable reactions occurring with medications that promote hypersensitivity (immune) reactions due to either parent drug or its metabolite, the mechanism of piroxicam induced liver injury is not well known, but may be due to a toxic metabolic intermediate of piroxicam metabolism, which occurs largely in the liver.[2,5,24]

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