ITEM 3: MCNEIL'S RESPONSE TO FDA'S PROPOSED LABELING FOR OTC NON-STEROIDAL ANTI-INFLAMMATORY DRUG (NSAID) PRODUCTS

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1. INTRODUCTION

McNeil markets a comprehensive line of Motrin® (ibuprofen) brand products for adults, children, and infants as well as St. Joseph® aspirin (81 mg) for use by adults only. As a major manufacturer of OTC internal analgesic products, McNeil is committed to encouraging scientifically appropriate and adequate labeling, which includes consistent, clear and appropriate language for consumer use.

2. BACKGROUND TO FDA'S PROPOSED RULE

At the September 2002 Nonprescription Drugs Advisory Committee (NDAC) meeting, the potential for gastrointestinal (GI) bleeding and renal toxicity related to the use of OTC non-steroidal anti-inflammatory drugs (NSAIDs) was discussed. In February 2005, a joint meeting of the Arthritis and Drug Safety and Risk Management Advisory Committees was held to discuss the overall benefit to risk considerations (including cardiovascular (CV) and GI safety concerns) of COX-2 selective and non-selective NSAIDs and related agents. Consistent with recommendations made by the joint committee and NDAC, on June 14, 2005, FDA issued a supplemental labeling request letter and labeling template to NDA holders of current OTC NSAIDs.

The labeling changes requested by FDA in the supplemental labeling request letter provide more specific information for consumers and caregivers about the potential risks of CV and GI adverse effects associated with the use of OTC NSAIDs (excluding aspirin).

Based on a review of comments from industry regarding the June 14th supplemental labeling request letter and labeling template, on July 15, 2005, FDA issued revised templates for OTC adult and pediatric ibuprofen, ketoprofen, and naproxen products. The supplemental labeling request letters requested that sponsors make the required labeling changes to their products within six months.

3. MCNEIL'S GENERAL COMMENTS AND PREVIOUS ACTIONS

McNeil agrees with FDA's statements [71 FR 77315] that ibuprofen and other OTC analgesics:

- are generally recognized as safe and effective when labeled appropriately and used as directed,
- benefit millions of consumers every year for the intermittent treatment of minor aches and pains and fever, and
- should continue to be accessible to consumers in the OTC setting.

McNeil is committed to adopting labeling that has a sound scientific basis. McNeil agrees with FDA's comments in the proposed rule [71 FR 77326] that the majority of healthy people who are exposed to therapeutic doses of NSAIDs for a limited time tolerate these drugs without untoward renal effects, however that some subsets of the population are more susceptible to potentially life-threatening nephrotoxicity including people with underlying kidney disease, congestive heart failure, or liver dysfunction with ascites, and the elderly.

3.1 Ibuprofen

McNeil agreed with FDA's recommendations as stated in the June/July 2005 OTC NSAID supplemental labeling request letters and fully implemented all labeling changes for its OTC ibuprofen products by January 2006. The labeling changes FDA proposes for OTC NSAIDs in its 2006 proposed rule are consistent with the 2005 supplemental labeling request letters. As such, all currently marketed McNeil OTC ibuprofen products are in compliance with the December 2006 proposed rule.

3.2 Aspirin

McNeil agrees with FDA's labeling comments as stated in the proposed rule for OTC NSAID products including aspirin and is committed to adopting labeling for its St. Joseph® aspirin (81 mg) OTC product that is consistent with sound science and is provided as clear consistent language for consumer use.

As FDA is aware, McNeil previously submitted a Citizen Petition on January 31, 2005 [Docket No. 2005P-0048] requesting that the agency change the professional labeling for aspirin dosing under 21 CFR 343.80 to 75-150 mg/day for secondary cardiovascular prevention, and 50-150 mg/day for secondary cerebrovascular prevention based on the better safety profile of lower doses. FDA acknowledged receipt of the Petition on February 1, 2005. On July 28, 2005, FDA notified McNeil that due to the existence of other priorities, it could not provide a response to the Petition at that time. McNeil subsequently submitted a Supplement under 21 CFR 10.30(g) on August 3, 2005 to the above referenced Citizen Petition. No final action has been taken as of the date of this response.

4. MCNEIL'S SPECIFIC COMMENTS ON FDA'S PROPOSED LABELING FOR OTC NSAID PRODUCTS

McNeil is committed to adopting labeling that has a sound scientific basis and provides consistent, clear and appropriate language for consumer use.

McNeil agrees with FDA's comments in FDA's proposed rule [71 FR 77326] that some subsets of the population are more susceptible to potentially life-threatening nephrotoxicity with NSAIDs including the elderly and individuals with underlying kidney disease, congestive heart failure, or liver dysfunction with ascites. As such, McNeil provides specific comments and scientific perspective on why consumers with existing liver disease may benefit from explicit labeling language that encourages them to seek advice from a doctor prior to taking OTC NSAID products.

The proposed OTC labeling for NSAIDs directs certain subsets of the population (those with high blood pressure, heart disease, kidney disease, or are age 60 or older) to seek advice from their doctor before using OTC NSAIDs. Additionally, all individuals who are under a doctor's care for any serious condition are directed to seek advice from their doctor or pharmacist before using an OTC NSAID. Thus, individuals with pre-existing liver disease, a serious condition, while not explicitly referenced in the proposed labeling, are implicitly directed to seek out health professional guidance prior to initiating OTC NSAID use.

As previously stated, McNeil implemented these proposed label changes in January 2006. Figure 1 provides these specific OTC NSAID label warnings.

Figure 1. Current Labeling Text for NSAID OTC Products

Ask a doctor before use if you have

- problems or serious side effects from taking pain relievers or fever reducers
- stomach problems that last or come back, such as heartburn, upset stomach, or stomach pain
- ulcers
- bleeding problems
- high blood pressure
- heart or kidney disease
- taken a diuretic
- reached age 60 or older

Ask a doctor or pharmacist before use if you are

- taking any other drug containing an NSAID (prescription or nonprescription)
- taking a blood thinning (anticoagulant) or steroid drug
- under a doctor's care for any serious condition
- taking any other drug

As noted throughout the NSAID sections of the proposed rule, serious renal events following NSAID therapy almost always occur in patients with pre-existing renal dysfunction, congestive heart failure, or compromised hepatic function [71 FR 77327, 71 FR 77330-77331]. McNeil asserts that individuals in this latter subset population may also benefit from explicit label language similar to current language for those with heart or kidney disease. The addition of liver disease under the “Ask a doctor before use if you have” warning so that the bullet reads, “heart, kidney, or liver disease” provides additional instruction for a consumer with liver disease.

In the following sections, McNeil provides a review of clinical and metabolism data regarding NSAID use in adults with liver disease in support of this recommendation.

5 METABOLISM DATA REVIEW OF NSAIDS IN ADULTS WITH LIVER DISEASE

Drug metabolism may be altered in cirrhosis of the liver due to a range of pathophysiologic changes: parenchymal damage with loss of enzyme activity, impaired hepatic blood flow, and reduced protein binding of drugs in the blood [1]. These factors may affect the concentrations of free drug in blood, and the distribution and clearance of drugs. Normally pharmacological response, including adverse effects, results from the free drug concentration in the blood. In cirrhosis, a reduced concentration in serum albumin results in an increased free, unbound fraction of drug compared with healthy individuals [1]. NSAIDs, including aspirin, ibuprofen, naproxen, and ketoprofen have high protein binding (> 85%).

In decompensated cirrhotics, renal function is usually impaired due to reduced renal perfusion and increased sodium reabsorption [1]. In fact, NSAIDs exacerbate renal disease associated with cirrhosis, and patients frequently retain fluids (because of vasodilation) resulting in decreased arterial and renal blood flow and subsequent renin-angiotensin system activation [1]. Clinical data from published metabolism studies show that NSAIDs have altered pharmacokinetics in adults with liver disease, and a summary of studies are provided herein.

Ibuprofen is normally eliminated by glucuronidation, hydroxylation, and carboxylation. Furthermore, there are two enantiomers of ibuprofen: the inactive R-form and active S-form. In humans, the R-enantiomer is metabolically converted to the S-enantiomer, probably in the liver. The inversion from R- to S-enantiomer might be delayed in adults with liver disease.

A study was conducted in eight male adults with moderate-to-severe cirrhosis compared with age-matched healthy volunteers to evaluate the effect of cirrhosis on the inversion of the R-to S-enantiomer of ibuprofen [2]. After a single 600-mg dose of racemic ibuprofen, both enantiomers were rapidly absorbed with a Tmax of 1.2 hours in subjects with cirrhosis compared with one-to-three hours for healthy subjects [2]. However, maximum concentrations, Cmax, for S-ibuprofen were statistically significantly lower in patients compared with volunteers (14.2 ± 2.5 vs. 23.3 ± 4.6; $p < 0.001$), suggesting that the inversion from R- to S-ibuprofen might be altered by cirrhosis. In addition, the half-life, t½, for both enantiomers were statistically longer in the hepatic-impaired group compared with healthy subjects (3.1 ± 1.7 vs. 1.7 ± 0.3; $p = 0.045$ for R-enantiomer and 3.4 ± 1.0 vs. 1.8 ± 0.5; $p = 0.001$ for S-enantiomer). Further evidence for the impaired inversion of R- to S-ibuprofen in adults with cirrhosis was demonstrated by a statistically higher ratio of the area under the curve for both enantiomers (AUCR:AUCS) in hepatic-impaired compared with

healthy subjects (1.10 ± 0.28 vs. 0.79 ± 0.18; $p = 0.019$). A substudy was also conducted in which a single dose of the active S-enantiomer (400 mg) was administered to eight adults with cirrhosis and eight volunteers. Results indicated that elimination was slower in patients with liver disease because of the increase in t½ (2.6 ± 0.5 vs. 1.6 ± 0.1; $p < 0.001$) and AUC (144 ± 41 vs. 101 ± 35; $p = 0.041$) values compared with volunteers. The investigators conclude that hepatic elimination of ibuprofen is impaired in liver disease [2].

In a study of 15 subjects with alcoholic liver disease and 29 control subjects, the pharmacokinetics of ibuprofen were similar except for the AUC, which was statistically significantly less in subjects with fair hepatic function (indocyanine green t½ < 10 minutes) compared with controls (79.2 ± 20.8 vs. 103.0 ± 26.1; $p < 0.05$) [3]. Moreover, ibuprofen absorption was somewhat delayed in subjects with poor hepatic function (indocyanine green t½ > 10 minutes) compared with subjects with fair hepatic function and controls. The investigators conclude that liver disease had minimal effect on the pharmacokinetics of ibuprofen, although potential decreases in protein binding with liver disease and with subsequent changes in free ibuprofen were not assessed [3].

The liver is a major source of circulating aspirin esterase (acetylsalicylic acid-acyl-hydrolase), which hydrolyzes aspirin to salicylic acid (SA) plus acetic acid. The beneficial and harmful effects of aspirin are due to the intact compound rather than to its main metabolite. A study was conducted to determine whether the ability to metabolize aspirin was impaired in patients with cirrhosis [4]. Blood was collected and assayed for serum aspirin esterase activity from 22 patients with biopsy-proven portal cirrhosis and 104 control subjects. Results show that patients with cirrhosis had a markedly reduced ability to metabolize aspirin. The mean hydrolytic activity in control subjects was 146.8 and 117.4 (pg of SA/mL of serum/60 min) in men and women, respectively. Mean values for male and female cirrhotics were 47.1 and 56.0, respectively. The differences in hydrolytic activities between groups were statistically significant at $p < 0.001$. The investigators infer from these data that individuals with portal cirrhosis form a population who are more liable to complications (eg, hemorrhagic erosive gastritis) from aspirin ingestion [4].

A lower concentration of plasma albumin was identified in alcohol-associated cirrhosis by a study that evaluated six young subjects, seven elderly subjects, and in eight subjects with alcohol-associated liver disease [5]. The hypothesis was that plasma aspirin and salicylate concentration-time profiles might differ between healthy subjects and subjects with liver disease. Results show that Cmax, Tmax, and AUC values were similar between the cirrhotic group and the young plus elderly group combined. Hence, aspirin absorption and disposition

was not affected by alcoholic liver disease. However, two plasma salicylate pharmacokinetic parameters were two-fold higher in the cirrhotic group compared with the combined young plus elderly groups: the average unbound fraction of salicylate (0.186 ± 0.105 vs. 0.085 ± 0.026; $p < 0.005$) and the area under the unbound salicylate concentration-time curve (118.2 ± 117.6 vs. 51.0 ± 18.5; $p < 0.05$). The higher value for the unbound salicylate fraction in the cirrhotic group was a result of lower concentrations of plasma albumin. The pharmacologic effects of salicylate are primarily a function of unbound concentrations, which were higher in the cirrhotics. Thus, individuals with liver disease progressing to cirrhosis who have low concentrations of plasma albumin might be at risk for bleeding adverse effects [5].

Modifications in absorption, distribution, and elimination of naproxen (single capsule, 250 mg) were reported in 11 subjects with hepatic and biliary disorders [6]. For example, a delay in the absorption of the drug was observed in subjects with cholestasis, and in most subjects, naproxen elimination was reduced. The plasma half-life in subjects with liver disorder achieved 20.36 hours compared with an average of 14.14 hours in healthy subjects. Furthermore, a variation in the distribution of the drug in subjects with hepatic failure was attributed to a decrease in the indices of albumin, globulin, and total protein resulting in an increase in the free drug fraction in these subjects [6].

Additional metabolism data suggest that naproxen dosing should be decreased by at least half in individuals with alcoholic cirrhosis and other liver disease, because the unbound concentration of drug is increased [7,8]. The disposition of naproxen was determined in 10 male subjects with alcoholic cirrhosis and 10 male control subjects after a single dose (375 mg) and after repeat dosing at steady state for 13 doses (Day 9). Plasma and serum samples were collected and assayed for concentrations of total and unbound drug. Results show that the decrease in the binding of naproxen was greater in subjects with cirrhosis compared with control subjects. In addition, unbound clearance of naproxen was reduced by > 60% in cirrhotic subjects at steady state [7]. The volume of distribution was significantly greater in patients with cirrhosis compared with controls (16.8 ± 4.79 vs. 12.1 ± 1.73 $p < 0.02$), and protein binding of naproxen was significantly less in cirrhotics, as the free fraction was 0.202 ± 0.082 versus 0.086 ± 0.044 ($p < 0.02$). The terminal elimination rate constant was not different between these two groups [8].

In a study to determine the stereoselective binding of ketoprofen to serum in adults with liver disease, the serum protein binding of racemic ketoprofen was decreased compared with normal volunteers [9], and the stereoselectivity of ketoprofen was increased in the hepatic-impaired population. Furthermore, the ratio of unbound ketoprofen enantiomers (R/S)

resulted in a positive linear correlation with the concentration of albumin. The inhibition of ketoprofen binding to human serum albumin induced by lithocholate, lithocholate sulfate, and bilirubin was also determined. The investigators conclude that the variation of stereoselective ketoprofen binding was primarily the result of a decrease of human serum albumin levels as well as stereoselective inhibition produced by increased concentrations of bile acid [9].

Overall, these metabolic data show altered disposition of OTC NSAIDs in individuals with liver disease, mainly due to a decrease in protein binding and subsequent increase in the free fraction of drug in the blood. These alterations may increase the risk of adverse effects.

6 CLINICAL DATA REVIEW OF NSAIDS IN ADULTS WITH LIVER DISEASE

Despite the wide availability and use of OTC NSAIDs, there is a relatively low risk of adverse drug effects when used at therapeutic doses in healthy individuals. However, as with all drugs, NSAIDs are not risk-free, and certain subpopulations of patients can be susceptible to severe adverse effects of these drugs [10]. The following summary of clinical data regarding the use of NSAIDs (specifically, aspirin, ibuprofen, naproxen, and ketoprofen) and antiplatelet or renal effects in adults with liver disease provides evidence for an increased safety risk. Acetaminophen can be used safely in adults with liver disease and is, in fact, preferred to aspirin and other NSAIDs [11,12,13], because of the absence of inhibitory actions on platelet aggregation or gastrointestinal and renal toxicity.

6.1 Hematologic Effects

Nonselective NSAIDs exert an antiplatelet effect by inhibiting platelet COX enzymes and thereby blocking the formation of the metabolite, thromboxane A2. This antiplatelet effect is reversible and only occurs if the drug is present. In contrast, aspirin is unique in that it irreversibly exerts its antiplatelet effect [14]. This effect does not usually lead to clinically important bleeding events, except in individuals who have underlying medical conditions (eg, cirrhosis) that increase their risk for such an event [15,16]. For example, adults with chronic liver disease have an increased risk of experiencing a bleeding event, not only because of the coagulopathy caused by disease itself, but also because of the increase in potential sites for hemorrhage (eg, esophageal varices, ulcers, hemorrhoids) that are the result of portal hypertension [16]. Because the most severe bleeding complications associated with the use of aspirin and NSAIDs are primarily encountered in adults with coexisting coagulation abnormalities, such as those associated with liver disease, a careful history should be

obtained in adults who will undergo long-term therapy with these analgesics [16].

6.2 Gastrointestinal Effects

Case control studies were conducted to investigate the role of NSAIDs and esophageal varices in patients with cirrhosis [17,18,19]. Results of one study indicated that patients with cirrhosis who were admitted for bleeding associated with portal hypertension (esophageal varices) were significantly more likely to have taken NSAIDs compared with cirrhotic patients with esophageal varices who had never bled (controls) ($p = 0.016$). Furthermore, the use of aspirin alone or in combination with other NSAIDs was significantly more prevalent in cirrhotic patients who had bled compared with controls ($p = 0.007$) [17]. Results from a second case study reported that the use of aspirin was significantly more prevalent in patients admitted for bleeding from esophageal or gastric lesions associated with portal hypertension compared with matched controls who did not experience bleeding ($p = 0.004$) [18]. Because aspirin alone, or with other NSAIDs was associated with a first variceal bleed in cirrhotic patients, the authors recommend that the possible benefits of this treatment be considered versus the potential risks, and that patients with portal hypertension should avoid these drugs [17, 18].

Results from a third case-control study [19] also suggest that NSAIDs use can play a significant role in the pathogenesis of bleeding due to peptic ulcer disease in patients with liver cirrhosis and portal hypertension. NSAID consumption was compared among three groups: 35 patients with liver cirrhosis, portal hypertension, and upper gastrointestinal bleeding due to erosions or ulcers; 175 patients with upper gastrointestinal bleeding due to erosions or ulcers but without liver cirrhosis; and 70 patients with liver cirrhosis and portal hypertension, but without upper gastrointestinal bleeding. NSAID consumption was significantly higher in the cirrhotic (42.8%) and noncirrhotic (58.2%) patients with gastrointestinal bleeding than in the cirrhotic patients without gastrointestinal bleeding (8.5%).

6.3 Renal Effects

Prostaglandins play a more important role in the maintenance of renal blood flow and glomerular filtration rate in adults with cirrhosis compared with healthy adults [14,20,21]. Urinary excretion of prostaglandin E2 is increased in cirrhotic patients whose renal perfusion is intact and is reduced in patients who have hepatorenal syndrome [22,23]. The mechanisms by which cirrhosis leads to renal dysfunction are not yet fully understood, but it is believed that portal hypertension triggers vasodilation, and consequently underfilling and

hypotension, within splanchnic arteries. This, in turn, stimulates activation of compensatory vasoconstrictor mechanisms, such as the renin-angiotensin-aldosterone system and the sympathetic nervous system. This stimulation leads to an increase in prostaglandin synthesis within the kidney as a means of maintaining adequate renal blood flow [24,25,26]. Because NSAIDs are potent inhibitors of prostaglandin synthesis, their use by adults with cirrhosis can lead to significant reductions in renal blood flow and glomerular filtration rate, [22,27] resulting in increased sodium retention, edema, and an elevation of serum creatinine [14,20,28,29]. These effects can potentially result in serious adverse events in patients with cirrhosis [30,31].

A review of published studies on aspirin, ibuprofen, naproxen, and ketoprofen provide data on the untoward renal effects in adults with liver disease. Pertinent data from studies on other NSAIDs are included, as appropriate.

An open-label clinical study in adults with cirrhosis (with and without ascites) found that aspirin produces a reduction in renal blood flow and glomerular filtration rate in cirrhotics with ascites [22]. An intravenous dose of 450 mg lysine acetylsalicylic acid (equivalent to 250 mg aspirin) reduced water diuresis from 8.8 ± 0.9 to 2.7 ± 0.5 ml/min and sodium excretion from 57.1 ± 13.9 to 3.9 ± 1.1 μmol/min in 19 patients with cirrhosis and ascites. It also reduced glomerular filtration rate from 95.4 ± 11.8 to 46.7 ± 9.5 ml/min in 11 patients with cirrhosis and ascites. Renal function was unaltered in five healthy control subjects and in nine patients with cirrhosis but without ascites [22]. A separate study by the same investigators reported that 450 mg lysine acetylsalicylic acid induced statistically significant reductions in renal plasma flow and glomerular filtration rate in 21 patients with cirrhosis and ascites [32]. In addition, the observed effects of the diuretic, furosemide, in increasing renal plasma flow, glomerular filtration rate, urine volume, and sodium excretion were significantly reduced when lysine acetylsalicylic acid was administered 10 minutes before furosemide [32].

Data from a randomized, double-blind, placebo-controlled clinical study suggest that ibuprofen may cause renal dysfunction in decompensated cirrhotics and that co-administration with misoprostol may have some short-lived protective renal effects [33]. Subjects who had decompensated cirrhosis with ascites were given 800 mg ibuprofen in combination with either 400 µg misoprostol (n=9) or placebo (n=10). Ninety minutes after administration of ibuprofen and placebo, the following changes from baseline were measured:

- urinary volume decreased from 4.2 ± 0.8 to 2.0 ± 0.7 ml/min,
- inulin clearance decreased from 86 ± 17 to 56 ± 10 ml/min,

- sodium excretion decreased from 0.012 ± 0.006 to 0.003 ± 0.001 mEq/min,
- osmolar clearance decreased from 1.8 ± 0.2 to 1.2 ± 0.2 ml/min,
- free water clearance decreased from 2.3 ± 0.7 to 0.7 ± 0.6 ml/min, and
- urinary PGE_2 decreased from 995 ± 333 to 364 ± 152 pg/min

All of these changes were statistically significant. The changes in sodium excretion and free water clearance—but not the other changes—were mitigated by the concomitant administration of misoprostol.

A crossover study was conducted to determine effects of ibuprofen 400 mg dosed every eight hours for one day versus sulindac 200 mg dosed twice daily for five days in adults being treated for alcoholic cirrhosis and ascites [34]. Ibuprofen decreased renal clearances of paraaminohippurate and inulin in five subjects with the greatest retention of sodium, but sulindac had no effect. Furthermore, ibuprofen was the more potent inhibitor of urine eicosanoids. The authors conclude that the renal sparing of sulindac may be due to its less potent inhibition of COX systems [34]. However, a separate study suggests the use of caution with the use of sulindac as with other NSAIDs [35].

Untoward renal effects induced by ibuprofen and naproxen were also reported in a small study of four adults with alcoholic cirrhosis who were first given single doses and—if renal effects were modest—multiple doses of sulindac 200 mg [35]. A fifth subject withdrew after sulindac dosing and received neither ibuprofen nor naproxen. Following a single dose of ibuprofen 600 mg, creatinine clearance fell markedly in two subjects, thus precluding subsequent 4-day dosing with ibuprofen. In another subject who did proceed to the 4-day regimen with ibuprofen 600 mg dosed every eight hours, a significant decrease in creatinine clearance was observed. In a fourth patient, a 4-day regimen with naproxen 500 mg dosed every 12 hours led to a significant decrease in creatinine clearance.

Many adults with ascites due to chronic liver disease rely on diuretics to prevent fluid overload. In a study of 56 patients with alcoholic liver disease and ascites and seven healthy control subjects, [36] a decrease in response to two different diuretics was found following the administration of naproxen, aspirin, and indomethacin. Following pretreatment with two doses of naproxen 250 mg, natriuresis after 80 mg of intravenous furosemide was reduced by 52 ± 8% and urine volume was decreased by 22 ± 7%. Natriuresis after 300 mg of spironolactone daily for one week was reduced by 55 ± 9% and urine volume was decreased by 42 ± 10% following naproxen pretreatment. The decrease in natriuresis following pretreatment with two doses of aspirin 900 mg was not significant for furosemide, but for

spironolactone, natriuresis was reduced by 33 ± 8%. Following pretreatment with two doses of indomethacin 50 mg, natriuresis was reduced by 82 ± 4% and urine volume was decreased by 69 ± 7%. Natriuresis after spironolactone was reduced by 82 ± 4% and urine volume was decreased by 67 ± 6% following indomethacin pretreatment. The investigators conclude that their findings reinforced the importance of renal prostaglandins in supporting renal function in patients with sodium retention from liver disease, and that drugs which inhibit prostaglandin synthetase should be avoided during diuretic therapy in these patients [36].

In a randomized, double-blind, placebo-controlled study of adults with cirrhosis and ascites, the effects of naproxen, a nonselective NSAID, were compared with those of celecoxib, a selective COX-2 inhibitor, and placebo on renal function (N=18) and on the diuretic and natriuretic responses to furosemide (N=19) [37]. Naproxen was associated with a significant decrease in urinary excretion of PGE2 (from 3430 ± 430 to 2068 ± 549 pg/min), a significant reduction in glomerular filtration rate (from 113 ± 27 to 84 ± 22 mL/min), and a significant increase in serum creatinine (from 83 ± 4 to 101 ± 10 µmol/L). Such effects were not observed with celecoxib or placebo. Naproxen also significantly reduced both the diuretic and natriuretic responses to furosemide, which was not observed with celecoxib or placebo. The investigators conclude that the prostaglandins responsible for maintaining renal perfusion and the renal response to diuretics in individuals with cirrhosis and ascites are most likely derived from COX-1 rather than COX-2, and that selective COX-2 inhibitors might be safer than nonselective NSAIDs in these patients.

6.4 Hepatic Effects

In addition to gastrointestinal and renal toxicity, the use of NSAIDs at therapeutic doses can cause increases in serum aminotransferase activities (ALT and AST) in adults with chronic liver disease. Riley and Smith reported three cases of NSAID-induced flares of hepatitis in patients with chronic hepatitis C infection [38]. In all three cases, the ingestion of ibuprofen (dose range 1200–1600 mg/d) led to a significant rise in ALT (range 1209–1577 U/L) and AST (range 459–597 U/L), followed by a return to baseline after discontinuation of the drug. In one case, a rechallenge with ibuprofen produced a nearly identical rise in liver aminotransferase activities and subsequent return to baseline, thus confirming the causality. In their conclusion, the authors emphasized that NSAIDs are usually not recommended for use in cirrhotic patients, because of the renal sensitivity and gastrointestinal bleeding risk in these patients.

In a subsequent letter to the editor, Andrade and colleagues reported an additional case of a patient with chronic hepatitis C who experienced increases in ALT (to 1093 IU/L), AST (to 355 IU/L), and SGGT (to 355 IU/L) after receiving ibuprofen 600 mg twice daily [39]. Three months after stopping ibuprofen therapy, ALT, AST, and SGGT had decreased to 119, 52, and 41 IU/L, respectively. A causal role for ibuprofen was found to be highly probable according to the Council for International Organizations of Medical Sciences (CIOMS) Scale. The authors suggested that the increased susceptibility of patients with chronic hepatitis C to NSAID-induced hepatotoxicity seemed to be specific to ibuprofen.

7 ANALGESIC USE RECOMMENDATIONS IN PATIENTS WITH LIVER DISEASE

Hepatologists and gastroenterologists routinely recommend against the use of NSAIDs for their patients with preexisting liver disease due to the adverse effects associated with the use of NSAIDs in this population, and instead, consider acetaminophen the preferred analgesic of choice in this subset population [15,40,41].

At the September 2002 Nonprescription Drug Advisory Committee meeting, Dr. Caroline Riely, a hepatologist from the University of Tennessee College of Medicine, speaking on behalf of the American Liver Foundation, stated that “NSAIDs, but not acetaminophen, are potentially toxic in patients with chronic liver disease, leading to renal failure at modest doses” [42]. Furthermore, the American Academy of Family Physicians recommends the use of acetaminophen as the preferred agent in patients with non-progressing chronic liver disease, but cautions the use of all NSAIDs in this patient population [10].

A survey was conducted to compare the knowledge of risk factors for, and clinical management of, acetaminophen hepatotoxicity between practicing gastroenterologists (N = 333) and primary care physicians (PCPs) (N = 64) [43]. Results indicated that compared to PCPs, gastroenterologists were significantly more likely to recognize that acetaminophen is preferred over NSAIDs in patients with cirrhosis ($p < 0.001$). Furthermore, gastroenterologists were much more likely to indicate that acetaminophen was preferred over NSAIDs in patients with cirrhosis compared with PCPs ($p < 0.001$) [43]. One explanation for this observed difference between the two survey groups might be that gastroenterologists were more aware of the safe metabolism of acetaminophen via glucuronidation and sulfation to nontoxic metabolites compared with PCPs [43].

On behalf of McNeil, in April 2007, TNS™, a market-research company, conducted a survey among 151 office-based gastroenterologists to determine which OTC pain reliever

(acetaminophen, ibuprofen, aspirin, or naproxen) they recommend most often to their patients with liver disease [44]. Fifty-five percent (83/151) of gastroenterologists state they recommend acetaminophen most often to their patients with liver disease, and 30% (25/83) of these physicians only recommend acetaminophen. Nearly 50% (41/83) of these gastroenterologists commented on the potential for GI, renal, hepatic, and hematologic adverse effects of NSAIDs in patients with liver disease and cite avoiding use of an NSAID as one of their reasons for recommending acetaminophen over NSAIDs in this subset population.

8 CONCLUSIONS

McNeil agrees with FDA's statements [71 FR 77315] that ibuprofen and other OTC analgesics:

- are generally recognized as safe and effective OTC when labeled appropriately and used as directed,
- benefit millions of consumers every year for the intermittent treatment of minor aches and pains and fever, and
- should continue to be accessible to consumers in the OTC setting.

All currently marketed McNeil OTC ibuprofen products are in compliance with the December 2006 proposed rule. Although McNeil believes that the current labeling for all OTC NSAID products is adequate for safe consumer use, McNeil recommends that consumers with preexisting liver disease may benefit from more explicit labeling language that encourages them to seek advice from a doctor prior to taking any OTC NSAID products.

As noted throughout the NSAID sections of the proposed rule, serious renal events following NSAID therapy almost always occur in patients with preexisting renal dysfunction, congestive heart failure, or compromised hepatic function. McNeil believes that individuals in this latter subset population may benefit from label language similar to current language for those with heart or kidney disease. The addition of liver disease under the "Ask a doctor before use if you have" warning so that the bullet reads, "heart, kidney, or liver disease" provides additional instruction for a consumer with liver disease.

The scientific data presented in Items 1 and 3 of McNeil's response to the proposed rule indicate that use of NSAIDs in consumers with preexisting liver disease requires caution while use of acetaminophen at therapeutic doses does not. Acetaminophen can be used

safely in adults with liver disease and is preferred to aspirin and other NSAIDs in this subpopulation because of the renal sensitivity and gastrointestinal bleeding risk in this subset population. If consumers with preexisting liver disease are directed on acetaminophen labeling to seek advice from their doctor prior to use but these same consumers are not provided a similar clear, explicit caution on OTC NSAID labeling, the potential for inadvertent consumer use of OTC NSAIDs, without the benefit of consultation with a doctor, may increase in this subset population.

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