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Non-Steroidal Anti-Inflammatory Drug (NSAID)-Induced Small Intestinal Injury

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Abstract

Non-steroidal anti-inflammatory drug (NSAID), including aspirin, induced small intestinal injuries are frequently seen in clinical field. Capsule endoscopy and double balloon endoscopy are major diagnostic methods. Small intestinal injury includes bleeding, erosion, and ulceration. Unfortunately, accurate mechanism(s) of NSAID-induced small intestinal injuries are remained to be determined so far. In terms of therapy, there are currently no therapies specifically designed or approved for the prevention of NSAID-induced enteropathy, although many medications are prescribed. Further clinical and basic researches are waiting.

Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs), including low-dose aspirin, are among the most widely prescribed medications, with approximately 30 million patients worldwide ingesting NSAID [1]. NSAID could cause small intestinal injury. It became clear from the studies of post-mortem samplesby Bjarnason and colleagues (1993) that NSAID use is alsoassociated with significant damage to the more distal regionsof the small intestine (i.e. distal to the ligament of Treitz) [2]. Small intestinal injury includes bleeding, erosion, and ulceration [3,4]. Serious complications can includemassive bleeding, perforation and strictures, sometimes leading to death [5]. PubMed with key words "NSAID and enteropathy" was used in 1994 through 2013 for selecting articles. The aim of this short review is to summarize out current understanding of NSAID induced small intestinal injury.

Diagnosis of Non-Steroidal Anti-Inflammatory Drug (NSAID)-Induced Small Intestinal Injury (Table 1)

NSAID can affect the jejunum and ileum [6]. Capsule endoscopy (CE) and double-balloon endoscopy (DBE) are diagnostic methods for visualizing small intestinal lesions [4]. In the DBE group, out of 61 patients, ulcers or erosions were observed in the ileum in six patients and in the jejunum in one patient, respectively [4]. In the cases indicated for enteroscopy, NSAIDs enteropathy occurred in half of the patients taking NSAIDs [7]. Sixteen patients used NSAID showed ulcerative lesions, and the remaining 2 patients showed diaphragm diseases. For localized lesions, 12 patients evidenced lesions in the ileum, 5 patients had lesions in the duodenum and/or jejunum, and 1 had lesions in both intestines [8]. Using CE, several studies have been reported. Post- low-dose aspirin CE detected 10 cases (50%) with mucosal damage not apparent in baseline studies (6 cases had petechiae, 3 had erosions, and 1 had bleeding stigmata in 2 ulcers) [9]. After 2 weeks of low-dose aspirin, the percentages of subjects with small bowel pathology were 80% in the aspirin group compared with 20% in the control group ($p=0.023$) [10]. CE demonstrates evidence of macroscopic injury to the small intestine, in up to 68% of volunteers, resulting from 2 weeks ingestion of slow-release diclofenac [11]. CE found intestinal lesions in 75% (12/16) of patients in the chronic therapy with NSAIDs and in 11.76% (2/17) of controls ($p<0.01$) [6]. Small bowel injury compatible with NSAID-induced enteropathy was observed in 7/8 animals [12]. 80% patients who took aspirin or NSAID had positive results, including the presence of erosions (n=5), ulceration (n=2), and ulcers with early stricturing (n=1, diagnosed with Crohn's disease). 13.6% took NSAIDs or aspirin, but most did not declare using these medications. Medical history would be important for the diagnosis of NSAID induced small intestinal injury [13]. Post-treatment CE identified 636 lesions in 32 of 53 subjects (60%); including 115 denuded areas in 16 subjects, 498 erosions in 22 subjects and 23 ulcers in 8 subjects [14]. Capsule

Ref number	Authors Year published	Methods	NSAID	Controls
4	Hayashi Y (2005)	DBE	11.5% (ileum/85.7%, jejunum/14.3%)	-
7	Matsumoto T (2008)	DBE	51%	5%
8	Hayashi Y (2009)	DBE	100% (ileum/55.6%, duodenum and/ or jejunum/27.8%, both/5.6%)	-
9	Smecuol E (2009)	CE	50%	-
10	Endo H (2009)	CE	80%	20%
11	Maiden L (2009)	CE	68%	-
6	Caunedo-Alvarez A (2010)	CE	75%	11.76%
12	Tachecí I (2010)	CE	87.50%	-
13	Sidhu R (2010)	CE	80%	-
14	Fujimori S, 2010	CE	60% denuded areas were predominantly located in the proximal part erosions throughout the small intestine and all ulcers in the distal part	-
3	Lim YJ, 2012	CE	55-70%	-

Abbreviations
CE: capsule endoscopy
DBE: double-balloon endoscopy

Table 1: Diagnosis of Non-steroidal anti-inflammatory drug (NSAID)-induced small intestinal injury.

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endoscopy studies have demonstrated that NSAIDs use in healthy volunteers raised the incidence (55% to 75%) of intestinal damage [3]. When we prescribe NSAID, we have to speculate the small intestinal lesions. Because the incidence ratio of the lesions are high (11.5-87.5%).

Probable Mechanisms of Non-Steroidal Anti-Inflammatory Drug (NSAID)-Induced Small Intestinal Injury (Table 2)

In the stomach, inhibition of COX-1 activity leads to a rapid, compensatory increase in expression of COX-2, and suppression of both enzymes leads to exacerbation of tissue injury [2]. However, the mechanisms of NSAID-induced injury in small intestine remains to be determined so far. Many possible mechanisms have been reported. Enterobacterial translocation in the mucosa is the first step required for activation of various factors such as iNOS/NO and neutrophils, all involved in the pathogenesis of indomethacin-induced intestinal lesions [2,15]. PPI can significantly worsen NSAID-induced damage in the small intestine [5,16]. Intestinal damage occurs when both COX-1 and COX-2 are inhibited, especially COX-2 [17,18]. Nitric oxide derived by iNOS plays a key pathogenic role in the ulcerogenic process [19-21]. Oxidative metabolites that induce severe endoplasmic reticulum stress or mitochondrial stress and lead to cell death [22,23]. NSAIDs that were absorbed into the enterocytes inhibit the mitochondrial oxidative phosphorylation [24]. Insoluble dietary fibre, intestinal hypermotility, leukotrienes and cholinergic pathways are implicated in the pathogenesis of small intestinal ulcers induced by NSAIDs [25]. TNF-alpha plays an early pro-inflammatory role in indomethacin-induced jejunoileitis [26]. Combination of low-dose aspirin therapy and thienopyridine may exacerbate small bowel injury [27]. Other candidate mediators of NSAID-induced small intestinal injury are JNK pathway [28], Reg I (Regenerating gene I) [29], MMP-9 (matrix metalloproteinase-9) [30], urocortin 1(a nonselective CRF receptor agonist)[31], IL-17A [32], enhanced platelets-bearing neutrophil migration [33], HMGB1(High mobility group box 1) [34], serotonin (5-HT) 3 receptors [35], and hemopexin [36]. If the contribution of any of these candidates to NSAID-induced injury of are enough high, they would be also candidates for treatment.

Ref number	Authors Year published	Responsible candidates	Study style
15	Konaka A (1999)	Enterobacterial translocation	A
2	Wallace JL (2012)	enteropathy of enteric bacteria, and bile	A
16	Wallace JL (2011)	PPIs exacerbate NSAID-induced intestinal damage	A
5	Wallace JL (2013)	PPI can significantly worsen NSAID-induced damage in the small intestine	A
17	Takeuchi K (2010)	COX-1 and CO X-2	A
18	Hotz-Behofsits C (2010)	COX-2	A
19	Tanaka A (1999)	Nitric oxide derived by iNOS	A
20	Parasher G (2001)	Nitric oxide	A
21	Xue B (2009)	iNOS-dependent nitric oxide	A
22	Boelsterli UA (2013)	Oxidative metabolites	A
23	Omatsu T (2009)	Reactive oxygen species	CL
24	Matsui H (2011)	mitochondrial oxidative phosphorylation	A
25	Satoh H (2009)	Insoluble dietary fibre, intestinal hypermotility, leukotrienes and cholinergic pathways	A
26	Nandi J (2010)	TNF-alpha	A
27	Shiotani A (2011)	Combination of low-dose aspirin therapy and thienopyridine	C
28	Ramirez-Alcantara V (2009)	JNK	A
29	Imaoka H (2010)	Reg I	A
30	Kakimoto K (2010)	MMP-9	A
31	Kubo Y (2010)	Urocortin 1(a nonselective CRF receptor agonist)	A
32	Yamada S (2011)	IL-17A	A
33	Higashiyama M (2012)	Enhanced platelets-bearing neutrophil migration	A
34	Nadatani Y (2012)	HMGB1	A
35	Kato S (2012)	serotonin (5-HT) 3 receptors	A
36	Takagi T (2012)	Hemopexin	A

Abbreviations
COX-1: Cyclooxygenase 1
COX-2: Cyclooxygenase 2
iNOS: Inducible nitric oxide synthase
JNK: c-Jun-N-terminal kinase
Reg I: Regenerating gene I
MMP-9: Matrix metalloproteinase-9
HMGB1: High mobility group box 1
A: Animal study
CL: Cell line
C: Clinical study

Table 2: Probable mechanisms of Non-steroidal anti-inflammatory drug (NSAID)-induced small intestinal injury.

Prevention and Therapy of Non-Steroidal Anti-Inflammatory Drug (NSAID)-Induced Small Intestinal Injury (Table 3)

There are currently no therapies specifically designed or approved for the prevention of NSAID-induced enteropathy [2]. Many candidates medications are summarized in Table 3. Rebamipide has not only the healing effect for NSAIDs-induced enteropathy compared with placebo [37-40]. Misoprostol have a preventive effect forNSAID-induced small intestinal mucosal injuries [40,41]. Endogenous PGE (2) promotes the healing of small intestinal lesions [42,43]. Lansoprazole prevents indomethacin-induced small intestinal ulceration [44,45]. However opposite results have been reported later on. Omeprazole and pantoprazole cannot protect the small intestine from the damage induced by diclofenac [46,47]. Lafutidine (histamine H(2) receptor antagonist with a mucosal protective action) protects the small intestine against loxoprofen-induced lesions [48,49]. Satoh et al. [50] reported inhibition of acid secretion by antisecretory drugs may exacerbate NSAID-induced intestinal lesions. In terms of PPI and H2 receptor antagonist, the efficacy might be still controversial. Agents such as probiotics, able to modify the gut ecology, might theoretically be useful in preventing small intestinal damage induced by NSAIDs [51]. Soluble dietary fibers protect the small intestine against NSAID-induced damage [52,53]. Zinc was effective in protecting against indomethacin-induced small intestinal damage [54,55]. Since endogenous NO plays a role in healing of intestinal lesions [56], NO-releasing NSAID may represent a novel class of drugs with markedly reduced intestinal toxicity [57]. Selective COX-2 inhibitors showed controversial results for small intestinal injury [3,58]. TNF-α could become a new therapeutic target for NSAID-induced small intestinal damage [59]. Highly selective pharmacologic targeting of luminal bacterial β-D-glucuronidase by a novel class of small-molecule inhibitors protects against diclofenac-induced enteropathy [60]. Mitochondrial cyclophilin D plays a key role in NSAID-induced enteropathy, lending itself as a potentially new therapeutic target for cytoprotective intervention [61]. Activation of α7 nicotinic acetylcholine receptors ameliorates indomethacin-induced small intestinal ulceration [62]. Other possible medications are geranylgeranylacetone [63,64], cilostazol (specific phosphodiesterase (PDE)-3 inhibitor) [33], sildenafil (inhibitor of phosphodiesterase

Ref number	Authors Year published	Candidates medications	Report style
38	Fujimori S (2011)	Rebamipide	CS
39	Mizukami K (2011)	Rebamipide	CS
37	Kurokawa S (2013)	Rebamipide	CS
40	Fujimori S (2010)	Rebamipide and misoprostol	CS
41	Watanabe T (2008)	misoprostol	CS
43	Arakawa T (2012)	prostaglandin derivatives, mucoprotective drugs, probiotics, and mitochondrial protective drugs	A
42	Takeuchi K (2010)	Endogenous PGE(2)	A
45	Higuchi K (2009)	Lansoprazole	A
44	Yoda Y (2010)	Lansoprazole	A
47	Lim YJ (2012)	PPIs: no small bowel protective effect	A
46	Zhang S (2013)	Omeprazole and pantoprazole cannot protect the small intestine from the damage induced by diclofenac	A
48	Amagase K (2010)	Lafutidine (histamine H(2) receptor antagonist with a mucosal protective action)	A
49	Umegaki E (2010)	Roxatidine (H(2) receptor antagonist)	A
50	Satoh H (2012)	Inhibition of acid secretion by antisecretory drugs may exacerbate NSAID-induced intestinal lesions	A
51	Guslandi M (2012)	probiotics	CS
52	Satoh H (2010)	Soluble dietary fibers	A
53	Satoh H (2010)	Insoluble dietary fiber and soluble dietary fiber	A
54	Sivalingam N (2011)	Zinc	A
55	Rodríguez de la Serna A (1994)	Zinc acexamate	CS
57	Wallace JL (1994)	NO-releasing NSAID	A
56	Takeuchi K (2007)	Endogenous NO	A
3	Lim YJ (2012)	Selective COX-2 inhibitors (coxibs)	A
58	Maehata Y (2012)	Selective COX-2 inhibitors are not completely safe for the small bowel	CS
59	Fukumoto K (2011)	TNF-α	A
60	LoGuidice A (2012)	bacterial β-D-glucuronidase	A
61	LoGuidice A (2010)	Mitochondrial cyclophilin D	A
62	Kawahara R (2011)	α7 nicotinic acetylcholine receptors	A
63	Shiotani A (2010)	geranylgeranylacetone	CS
64	Iwai T (2011)	Geranylgeranylacetone	A
33	Higashiyama M (2012)	cilostazol (specific phosphodiesterase (PDE)-3 inhibitor)	A
65	Kato N (2009)	Sildenafil (inhibitor of phosphodiesterase subtype 5)	A
66	Yasuda M (2011)	Dopamine D2-receptor antagonists	A
67	Yanaka A (2013)	Sulforaphane	CL
68	Menozzi A (2010)	K(ATP) channel opener diazoxide	A
69	Marchbank T (2008)	Natural bioactive products (nutriceuticals), such as fish hydrolysates	CS
70	Amagase K (2012)	Monosodium glutamate	A
71	Chao G (2012)	Muscovite (natural clay consisting of an insoluble double silicate of aluminum and magnesium) diclofenac	A
72	Davies NM (1997)	tempo (nitroxide stable free radical scavenger) and metronidazole	A

Abbreviations
NO: Nitric oxide
COX-2: Cyclooxygenase-2
CS: Clinical study
CR: Case report
A: Animal study
CL: Cell line

Table 3: Prevention and therapy of Non-steroidal anti-inflammatory drug (NSAID)-induced small intestinal injury.

subtype 5) [64], dopamine D2-receptor antagonists [65], sulforaphane [66], K(ATP) channel opener diazoxide [67], natural bioactive products (nutriceuticals), such as fish hydrolysates [68], monosodium glutamate [69], Muscovite (natural clay consisting of an insoluble double silicate of aluminum and magnesium) [70], and both tempo (nitroxide stable free radical scavenger) and metronidazole [71]. Further studies are necessary for selecting appropriate medication(s) for NSAID-induced small intestinal injury.

Conclusion

NSAID-induced small intestinal injuries are frequently seen in clinical field. CE and DBE are major diagnostic tools. Accurate mechanism(s) of NSAID-induced small intestinal injuries are remained to be determined so far. In terms of therapy, there are currently no therapies specifically designed or approved for the prevention of NSAID-induced enteropathy, although many medications are prescribed. Further clinical and basic researches are waiting.

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