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NSAID-Containing Drug Combinations and Risk of Upper GI Bleeding

Nonsteroidal antiinflammatory drug (NSAID) use is among the most common causes of upper gastrointestinal bleeding (UGIB). According to recent American College of Gastroenterology practice guidelines, risk factors for NSAID-related UGIB include age >65, a previous NSAID-induced ulceration (particularly if complicated), concomitant use of anticoagulants, corticosteroids, or other NSAIDS, including low-dose aspirin, high-dose NSAID treatment, and chronic medical conditions, particularly cardiovascular disease. Measures to prevent NSAID-induced ulceration and bleeding include co-administration of proton pump inhibitors and use of cyclooxygenase 2 selective (COX2) inhibitors. However, the risk of UGIB from concurrent use of NSAIDs and other drugs, such as corticosteroids, anticoagulants, selective serotonin reuptake inhibitors, and antiplatelet agents has not been widely studied. In this issue of *Gastroenterology* (accompanied by an editorial), Masclee et al perform a case series analysis of data from >114,000 patients with UGIB associated with drug exposure to nonselective NSAIDs (nsNSAIDs), COX2 inhibitors, and low-dose aspirin, alone and in combination with other drugs that affect risk for UGIB. Monotherapy with nsNSAIDs increased the risk for the diagnosis of UGIB to a greater extent than monotherapy with COX2 inhibitors or low-dose aspirin, with an incidence rate ratio (IRR) of 4.3, 2.9, and 3.1, respectively. The risk of diagnosed UGIB for other drugs ranged from a low IRR of 1.6 for calcium channel blockers to 4.1 for corticosteroids, similar in magnitude to the risk of nsNSAID monotherapy; selective serotonin reuptake inhibitors as a class had an IRR of 2.1. Concomitant nsNSAID use with other drugs had a higher risk for diagnosed UGIB compared with combination with COX2 inhibitors and low-dose aspirin, with the highest risk (IRR 12.8) observed with the combination of nsNSAIDs and corticosteroids. Use of aldosterone antagonists with nsNSAIDs also was associated with a high IRR (11.0). Selective serotonin reuptake inhibitors demonstrated significant interaction with nsNSAIDs and COX2 inhibitors, but not with low-dose aspirin (Table 1). Excess risk owing to concomitant drug use, measured by the additive interaction of nsNSAIDs/COX2 inhibitors/low-dose aspirin use with other drugs was highest with the combination of nsNSAIDs and corticosteroids. Corticosteroids also had a significant interaction with low-dose aspirin, but not with COX2 inhibitors. The risk of diagnosed UGIB with monotherapy from the drugs studied was lower for individuals below the age of 60 compared with older individuals, and individuals >70 had an excess risk from the combination of COX2 inhibitors and corticosteroids. The results of this study may allow clinicians to tailor therapy to minimize the risk of UGIB for their patients, particularly their elderly patients who may be on multiple drugs concurrently.

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Table 1. Relative Risk of Diagnosed UGIB During Exposure to Specific Drug Groups (With Corresponding 95% CIs) in Monotherapy and in Combination With Other Drugs

			Combination with					
	Monotherapy		nsNSAIDs		COX-2 inhibitors		Low-dose aspirin	
Drug groups	n	IRR (95% CI)	n	IRR (95% CI)	n	IRR (95% CI)	n	IRR (95% CI)
No drug[a]	69,664	1.00 (reference)		NA		NA		NA
nsNSAIDs	3327	4.27 (4.11–4.44)		NA		NA	416	6.77 (6.09–7.53)
COX-2 inhibitors	635	2.90 (2.67–3.15)		NA		NA	131	7.49 (6.22–9.02)
Low-dose aspirin	4733	3.05 (2.94–3.17)	416	6.77 (6.09–7.53)	131	7.49 (6.22–9.02)		NA
Corticosteroids	1378	4.07 (3.83–4.32)	244	12.82 (11.17–14.72)	40	5.95 (4.25–8.33)	190	8.37 (7.14–9.81)
SSRIs	1793	2.06 (1.94–2.18)	210	6.95 (5.97–8.08)	65	5.82 (4.45–7.62)	401	4.60 (4.09–5.17)
GPAs	5279	1.61 (1.56–1.66)	678	3.90 (3.59–4.24)	95	2.37 (1.92–2.93)	607	2.54 (2.32–2.78)
Aldosterone antagonists	1211	3.27 (3.06–3.50)	76	11.00 (8.63–14.03)	10	4.02 (2.07–7.81)	131	5.01 (4.13–6.08)
Calcium channel blockers	3546	1.57 (1.51–1.63)	363	4.45 (3.98–4.98)	77	3.11 (2.46–3.93)	1123	3.07 (2.86–3.29)
Anticoagulants	1760	3.01 (2.85–3.19)	143	8.69 (7.3–10.35)	21	5.01 (3.21–7.82)	168	6.94 (5.86–8.22)
Antiplatelets (excluding low-dose aspirin)	994	1.74 (1.61–1.87)	87	6.50 (5.19–8.15)	9	1.73 (0.87–3.44)	246	5.49 (4.71–6.41)
Nitrates	2572	2.55 (2.43–2.68)	172	5.82 (4.97–6.82)	49	5.09 (3.79–6.82)	859	3.79 (3.51–4.10)

NOTE. n refers to the number of UGIB events during exposure to specific drug groups (the total number does not add up to 114,835 because of diagnoses of UGIB in "other drug category").
NA, not applicable.
[a]No use of the predefined drugs of interest.

Zinc and Bacterial Clearance in Intestinal Macrophages

NOD2 belongs to a class of pattern recognition receptors that are able to recognize microbial components and initiate an immune response. Activation of NOD2 results in the release of cytokines that recruit inflammatory cells such as monocytes. Chronic exposure of NOD2 results in attenuation of cytokine secretion by myeloid cells, but is also associated with microbial clearance. The attenuation of cytokine secretion is proposed to minimize tissue injury, but what was not known were the mechanisms responsible for microbial clearance in the setting of waning cytokine levels.

In this issue of *Gastroenterology*, Lahiri and Abraham report on their results that explore cytokine independent mechanisms that support microbial clearance during chronic stimulation of NOD2. Their work is based on previous studies in which gene expression profiling revealed the induction of metallothionein genes with chronic exposure of monocytes to lipopolysaccharides. Metallothioneins are cysteine-rich proteins that bind a variety of metals, but in particular zinc. The authors found that metallothionein expression was induced in myeloid-derived macrophages in which NOD2 was chronically stimulated with muramyl dipeptide. Consistent with increase metallothionein expression, chronic NOD2 stimulation resulted in higher intracellular zinc levels.

The authors used several approaches to study the effects of metallothioneins and zinc. Myeloid-derived macrophages were stimulated with muramyl dipeptide and then exposed to *Salmonella*, followed by incubation with the antibiotic gentamycin. Salmonella that is engulfed by the macrophages would be protected from the effects of the gentamycin, which were subsequently quantified by culturing the cell contents on bacterial plates and counting the resultant colonies. Viable colonies represent the bacteria that were engulfed but not killed within the macrophage. When the assay was performed in the presence of a chelator that lowered intracellular zinc levels, the number of viable macrophage-associated bacteria increased, which supported an important role for zinc in bacterial killing in the setting of chronic NOD2 stimulation. An alternative approach taken by the authors reduced metallothionein expression by targeting the metal-regulatory transcription factor. Metal-regulatory transcription factor-1 induces the expression of multiple metallothionein isoforms, whose expression can be reduced with RNA interference. Similar to previous results, reduced metallothionein expression also reduced bacterial clearance by chronically stimulated macrophages (Figure 1). It should be noted that the results were applicable only to chronically induced macrophages as bacterial clearance was not affected when the cells were not prestimulated with muramyl dipeptide.

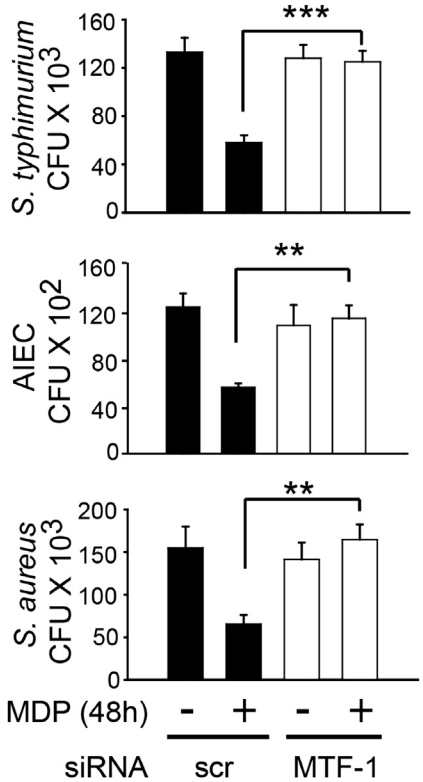

Figure 1. Viability of 3 different bacteria in macrophages after chronic NOD2 stimulation with muramyl dipeptide (MDP). Increased viable bacteria in the presence of MDP were observed if metallothionein expression was reduced with metal-regulatory transcription factor-1 small interfering RNA.

Additional studies determined that the induced metallothionein and intracellular zinc levels after chronic stimulation were dependent on nuclear factor-κB and caspase-1 induction of interleukin-1 secretion. Once induced, the increase metallothionein and zinc levels supported the induction of autophagy and increased bacterial clearance.

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Protective Immunity in HCV Reinfection

Although there have been major and rapid advances in the development of direct-acting antivirals to treat chronic infection with hepatitis C virus (HCV) that hold the promise of cure for most patients, development of a vaccine against HCV has been comparatively slow. HCV infection spontaneously clears in $\leq$25% of acutely infected individuals and intravenous drug users who have already cleared 1 HCV infection have been shown to be resistant to reinfection. However, the HCV-specific T-cell response during reinfection has not been well characterized, limiting vaccine development. In this issue of *Gastroenterology*, Abdel-Hakeem et al have analyzed blood samples from 9 patients reinfected with HCV after spontaneous clearance of their first infection, 5 of whom spontaneously resolved their second infection (SR/SR group) and 4 who developed chronic infection (SR/CI group). Using an interferon-γ enzyme-linked immunospot assay against overlapping peptide pools representing a HCV genotype 1a polyprotein, the magnitude of the HCV-specific T-cell response during reinfection, the response to pools representing the structural and nonstructural regions of HCV, and the breadth of the immune response, measured by the number of peptide pools targeted by the immune response, were all higher in the SR/SR group compared with the SR/CI group, consistent with generation of de novo T-cell response in the SR/SR group. Expansion of the HCV-specific memory T cells and enhanced proliferation of HCV-specific CD4 and CD8 T cells was also associated with