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Signal Detection Study Focusing on Differences in the Drug Delivery System of Oral 5-Aminosalicylate for Inflammatory Bowel Disease Using the Japanese Pharmacovigilance Database

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Abstract: Although 5-Aminosalicylate (5-ASA) has been shown to act on the local mucosa, when 5-ASA is orally administered, most of it is absorbed in the upper gastrointestinal tract and does not reach the large intestine, where lesions are present. Therefore, different drug delivery systems have been developed for each oral 5-ASA formulation. Currently, the oral 5-ASA formulation approved in Japan is salazosulfapyridine (SALAZOPYRIN®; Pfizer Japan Inc.: Tokyo, Japan), in which 5-ASA and sulfapyridine are azo-bonded. In addition, there are several 5-ASA release formulations, including ASACOL®; ZERIA Pharmaceutical Co., Ltd.: Tokyo, Japan (delayed release formulation dependent on pH), PENTASA®; KYORIN Pharmaceutical Co., Ltd.: Tokyo, Japan (delayed release formulation dependent on time), and LIALDA®; MOCHIDA Pharmaceutical Co., Ltd.: Tokyo, Japan (delayed release formulation dependent on pH and time). Adverse events may occur because of differences in the drug delivery systems of these products. In this study, we focused on the adverse events of different 5-ASA formulations and investigated differences in the detection of safety signals for each 5-ASA formulation using disproportionality analysis. There were 15 adverse events detected only with SALAZOPYRIN®. On the other hand, ASACOL®, PENTASA®, and LIALDA® have different drug delivery systems. Although the detected signal intensities varied, the detected adverse events were not significantly different. These findings provide important insights, which should be considered by physicians during treatment selection and drug manufacturers during drug development.

Keywords: 5-Aminosalicylate; drug delivery systems; safety signal; disproportionality analysis; Japanese Ad-verse Drug Event Report database (JADER)

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1. Introduction

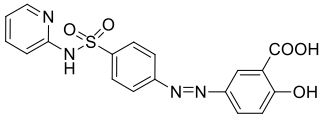
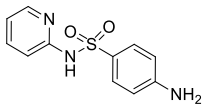
Ulcerative colitis and Crohn's disease are chronic, relapsing inflammatory bowel diseases of unknown etiology [1]. According to data from the United States of America, the national annual direct and indirect costs related to ulcerative colitis are estimated to be $8.1–14.9 billion, and the prevalence of this disease is approximately 238 in every 10,000 individuals [2].

Treatments for ulcerative colitis have not been established, and because remission is typically followed by recurrence, long-term drug therapy is often required. 5-Aminosalicylate (5-ASA) is a first-line therapy for treating mild-to-moderate ulcerative colitis and is widely prescribed. Additionally, within 1 year of initial diagnosis, 88–97% of patients with ulcerative colitis receive mesalamine therapy, and 60–87% of these patients continue to receive mesalamine after 10 years [3].

In clinical practice, multiple oral 5-ASA formulations are available, with each having a unique efficacy profile. Although 5-ASA has been shown to act on the local mucosa [4],

when 5-ASA is orally administered, most is absorbed in the upper gastrointestinal tract and does not reach the large intestine, where lesions are present. Therefore, different drug delivery systems have been developed for each oral 5-ASA formulation. Currently, the oral 5-ASA formulation approved in Japan is salazosulfapyridine (SALAZOPYRIN®; Pfizer Japan Inc.: Tokyo, Japan), in which 5-ASA and sulfapyridine are azo-bonded [5]. In addition, there are several 5-ASA release formulations, including ASACOL®; ZERIA Pharmaceutical Co., Ltd.: Tokyo, Japan (delayed release formulation dependent on pH) [6], PENTASA®; KYORIN Pharmaceutical Co., Ltd.: Tokyo, Japan (delayed release formulation dependent on time) [7], and LIALDA®; MOCHIDA Pharmaceutical Co., Ltd.: Tokyo, Japan (delayed release formulation dependent on pH and time) [8] (Table 1).

Table 1. The properties of each oral 5-aminosalicylate.

Drug	Structural Formula	Property
SALAZOPYRIN®		5-ASA and sulfapyridine are azo-bonded.
ASACOL®		Delayed release formulation dependent on pH.
PENTASA®		Delayed release formulation dependent on time.
LIALDA®		Delayed release formulation dependent on pH and time.

5-ASA: 5-Aminosalicylate.

Different drug delivery systems have been simulated to have different distributions of 5-ASA in the colon (Figure 1) [9]. Therefore, adverse events may occur because of differences in the drug delivery systems of these products.

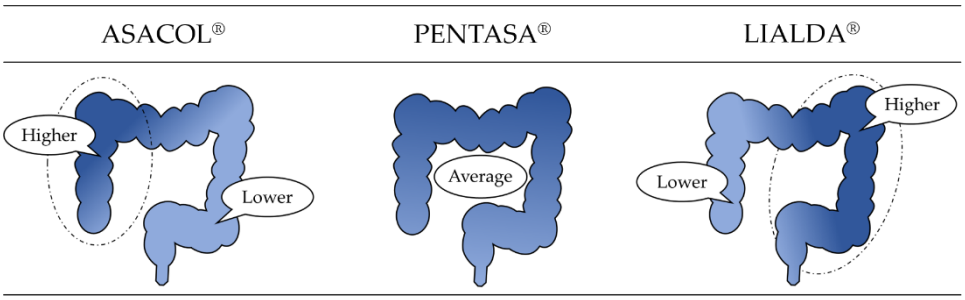


Figure 1. Differences in distributions of oral 5-aminosalicylate formulations by Drug Delivery System in the colon: the blue regions show distributions of oral 5-aminosalicylate formulations. The deeper the contrast, the higher the concentration.

Clinical trials may not detect serious adverse events associated with the tested drug until they are sold during post-marketing because various conditions, such as age and disease severity, are applied as inclusion criteria for patient enrollment. Therefore, post-marketing surveillance is a critical activity in pharmacovigilance [10,11]. Spontaneous reporting systems are an important source of post-marketing drug safety monitoring, and reports of adverse events centered on post-marketing can be made to the World Health Organization (WHO) and in various countries (e.g., the United States of America, the US Food and Drug Administration Adverse Event Reporting System [FAERS]; Japan, the Japanese Adverse Drug Event Report database [JADER]). Moreover, several detection algorithms for adverse events detected using the spontaneous reporting system have been reported [12–18].

In this study, we focused on adverse events due to differences in the drug delivery systems of oral 5-ASA formulations and investigated differences in the detection of safety signals for each oral 5-ASA formulation using the JADER.

2. Results

The adverse events in which signals were detected in any of the various 5-ASA products investigated in this study were classified by SOC (System Organ Class) as "Gastrointestinal disorders (7 High Level Terms [HLTs])", "General disorders and administration site conditions (4 HLTs)", "Infections and infestations (2 HLTs)", "Hepatobiliary disorders (1 HLT)", "Musculoskeletal and connective tissue disorders (2 HLTs)", "Blood and lymphatic system disorders (5 HLTs)", "Vascular disorders (1 HLT)", "Respiratory, thoracic and mediastinal disorders (4 HLTs)", "Injury, poisoning and procedural complications (1 HLT)", "Cardiac disorders (2 HLTs)", "Nervous system disorders (1 HLT)", "Renal and urinary disorders (2 HLTs)", "Metabolism and nutrition disorders (1 HLT)", "Skin and subcutaneous tissue disorders (6 HLTs)", "Immune system disorders (3 HLTs)", and "Investigations (1 HLT)" (Figure 2).

Adverse events with an IC_{025} value greater than 0 are indicated by a red marker; the higher the IC_{025} value, the darker the red, indicating a stronger signal. If the IC_{975} value is less than 0, it indicates a reverse signal. In Figure 1, the inverse signal is indicated by the blue marker. The smaller the IC_{975} value, the darker the blue, indicating a stronger inverse signal.

The detected signals and their IC_{025} values are as follows. There were 15 adverse events detected only with SALAZOPYRIN® (salazosulfapyridine), i.e., mucosal findings abnormal (IC: 2.44, 95% credible interval [CI]: 1.82–3.06); Epstein–Barr virus infection (IC: 1.98, 95%CI: 0.78–3.17); inflammatory disorders following infection (IC: 1.93, 95%CI: 1.24–2.62); lymphatic system disorders (IC: 1.49, 95%CI: 0.03–2.95); anemia deficiencies (IC: 2.15, 95%CI: 0.84–3.47); marrow depression and hypoplastic anemia (IC: 1.01, 95%CI: 0.12–1.90); leukocytoses NEC (IC: 2.67, 95%CI: 1.55–3.79); poisoning and toxicity (IC: 1.37, 95%CI: 0.78–1.97); water soluble vitamin deficiencies (IC: 2.73, 95%CI: 1.59–3.86); erythemas (IC: 1.58, 95%CI: 0.54–2.62); bullous conditions (IC: 1.84, 95%CI: 1.25–2.43); dermatitis ascribed to a specific agent (IC: 3.51, 95%CI: 3.14–3.89); pustular conditions (IC: 1.62, 95%CI: 0.16–3.08); rashes, eruptions and exanthems NEC (IC: 2.05, 95%CI: 1.38–2.72); allergies to foods, food additives, drugs, and other chemicals (IC: 3.25, 95%CI: 2.88–3.62).

Meanwhile, there were six common adverse events for ASACOL®, PENTASA® and LIALDA® (5-aminosalicylates); colitis (excl infective) (ASACOL® IC: 2.43, 95%CI: 1.75–3.11, PENTASA® IC: 2.16, 95%CI: 1.55–2.78, LIALDA® IC: 2.38, 95%CI: 1.52–3.24); lower respiratory tract inflammatory and immunologic conditions (ASACOL® IC: 3.21, 95%CI: 2.71–3.70, PENTASA® IC: 3.70, 95%CI: 3.35–4.05, LIALDA® IC: 2.52, 95%CI: 1.75–3.30); pleural infections and inflammations (ASACOL® IC: 3.48, 95%CI: 2.80–4.17, PENTASA® IC: 3.54, 95%CI: 2.95–4.14, LIALDA® IC: 1.56, 95%CI: 0.01–3.01); parenchymal lung disorders NEC (ASACOL® IC: 1.56, 95%CI: 1.16–1.95, PENTASA® IC: 0.53, 95%CI: 0.10–0.96, LIALDA® IC: 1.47, 95%CI: 0.92–2.03); nephritis NEC (ASACOL® IC: 2.44, 95%CI: 1.62–3.26, PENTASA® IC: 3.54, 95%CI: 3.05–4.02, LIALDA® IC: 1.80, 95%CI: 0.61–3.00); immune and associated conditions NEC (ASACOL® IC: 1.58, 95%CI: 1.21–1.95, PENTASA® IC: 0.90, 95%CI: 0.54–1.26, LIALDA® IC: 1.67, 95%CI: 1.18–2.16).

The IC_{975} values of adverse events for which inverse signals were detected were as follows:

SALAZOPYRIN®; parenchymal lung disorders NEC (IC: −1.65, 95%CI: −3.11–−0.20), ASACOL®; poisoning and toxicity (IC: −3.04, 95%CI: −5.09–−0.99), dermatitis ascribed to specific agent (IC: −1.50, 95%CI: −2.95–−0.04), allergic conditions NEC (IC: −2.36, 95%CI: −4.41–−0.32), PENTASA®; inflammatory disorders following infection (IC: −2.59, 95%CI: −4.64–−0.55), poisoning and toxicity (IC: −1.90, 95%CI: −3.00–−0.81), bullous conditions (IC: −2.68, 95%CI: −4.35–−1.01), dermatitis ascribed to specific agent (IC: −0.98, 95%CI: −1.95–−0.01). However, no inverse signal was detected with the LIALDA®. For adverse

events in which inverse signals were detected, the trend of signal detection was the exact opposite for salazosulfapyridine (SALAZOPYRIN®) and 5-aminosalicylates (ASACOL® and PENTASA®) (Figure 2).

SOC	HLT	SALAZOPYRIN®	ASACOL®	PENTASA®	LIALDA®
Gastrointestinal disorders	Diarrhoea (excl infective)				
	Acute and chronic pancreatitis				
	Colitis (excl infective)				
	Gastrointestinal inflammatory disorders NEC				
	Gastrointestinal and abdominal pains (excl oral and throat)				
	Tongue signs and symptoms				
	Non-site specific gastrointestinal haemorrhages				
General disorders and administration site conditions	Mucosal findings abnormal				
	Inflammations				
	Therapeutic and nontherapeutic responses				
	Pyrexia abnormal				
Infections and infestations	Epstein-Barr viral infections				
	Inflammatory disorders following infection				
Hepatobiliary disorders	Hepatic and hepatobiliary disorders NEC				
Musculoskeletal and connective tissue disorders	Joint related signs and symptoms				
	Muscle pains				
Blood and lymphatic system disorders	Lymphatic system disorders NEC				
	Anaemia deficiencies				
	Eosinophilic disorders				
	Marrow depression and hypoplastic anaemias				
	Leukocytoses NEC				
Vascular disorders	Gastrointestinal haemorrhages				
Respiratory, thoracic and mediastinal disorders	Lower respiratory tract inflammatory and immunologic conditions				
	Respiratory tract disorders NEC				
	Pleural infections and inflammations				
	Parenchymal lung disorders NEC				
Injury, poisoning and procedural complications	Poisoning and toxicity				
Cardiac disorders	Noninfectious myocarditis				
	Noninfectious pericarditis				
Nervous system disorders	Headaches NEC				
Renal and urinary disorders	Glomerulonephritis and nephrotic syndrome				
	Nephritis NEC				
Metabolism and nutrition disorders	Water soluble vitamin deficiencies				
Skin and subcutaneous tissue disorders	Erythemas				
	Bullous conditions				
	Dermatitis ascribed to specific agent				
	Pustular conditions				
	Rashes, eruptions and exanthems NEC				
	Panniculitides				
Immune system disorders	Allergic conditions NEC				
	Allergies to foods, food additives, drugs and other chemicals				
	Immune and associated conditions NEC				
Investigations	Protein analyses NEC				

IC_{025}	NA	0 to 1	1 to 2	2 to 3	3 to 4	4 <
Color						

IC_{975}	< -4	-4 to -3	- 3 to -2	-2 to -1	-1 to 0	NA
Color						

Figure 2. Differences in safety signals of oral 5-aminosalicylate preparations by drug delivery system: *SOC*: System Organ Class, *HLT*: High Level Term, *NEC*: Not Elsewhere Classified, *IC*: information component, *NA*: Not available.

3. Discussion

Traditionally, SALAZOPYRIN® has been used to treat ulcerative colitis. SALAZOPYRIN® is cleaved by enterobacteria to produce 5-ASA, which is the active substance; sulfapyridine produced at the same time is associated with blood concentrations and adverse events [19]. The toxicity of sulfapyridine is reduced by acetylation in the liver. However, the rate of acetylation depends on the genotype of NAT2, and it has been reported that

slow acetylators, which have been identified in about 10% of Japanese patients, cause significantly more adverse reactions than rapid acetylators [20].

The specific 15 adverse events caused by SALAZOPYRIN® shown in this study are likely related to sulfapyridine. The adverse events of "Blood and lymphatic system disorders" and "Skin and subcutaneous tissue disorders" in SOC are characteristic signals of SALAZOPYRIN® compared with ASACOL®, PENTASA® and LIALDA®.

The signals characteristic of SALAZOPYRIN® in "Blood and lymphatic system disorders" were leukocytoses NEC, lymphatic system disorders NEC, anaemia deficiencies and marrow depression and hypoplastic anaemias. However, Eosinophilic disorders was also signaled in all 5-ASA formulations in addition to SALAZOPYRIN®, the signal intensity of eosinophilic disorders was higher in ASACOL®, PENTASA®, and LIALDA® than in SALAZOPYRIN®. Further, even if the signal is detected by 5-ASA, SALAZOPYRIN® may detect the inverse signal (e.g., parenchymal lung disorders NEC).

In "Skin and subcutaneous tissue disorders", SALAZOPYRIN® has detected the signals of dermatitis ascribed to specific agent, rashes, eruptions and exanthems NEC, bullous conditions, and pustular conditions. Of them, "Dermatitis ascribed to specific agent" showed a very strong signal in SALAZOPYRIN®, even though an inverse signal was detected in ASACOL® and PENTASA®.

Since SALAZOPYRIN® becomes 5-ASA and sulfapyridine in the body, it will have to be considered for 5-ASA as well as for sulfapyridine adverse events. Therefore, it may be safer to administer 5-ASA alone for the treatment of ulcerative colitis. However, of them, ASACOL®, PENTASA®, and LIALDA® have detected strong signals of acute and chronic pancreatitis, lower respiratory tract inflammatory and immunologic conditions, noninfectious myocarditis, noninfectious pericarditis, and nephritis NEC. Since these adverse events affect life expectancy and quality of life, appropriate monitoring would be necessary to prevent them.

ASACOL®, which is coated with Eudragit-S (Evonik Industries, Essen, Germany), is pH-dependent; therefore, absorption in the upper gastrointestinal tract is completely avoided, and the outer capsule dissolves in the ascending colon and completely disintegrates relatively quickly. The released 5-ASA flows to the anus side but is partially absorbed in the large intestine and is metabolized and acetylated in the mucous membrane. Because of this, 5-ASA concentrations gradually decrease, and the drug travels to the anus side [6]. Therefore, there will be a high concentration in the right colon and a low concentration in the left side colon. PENTASA® is a time-release formulation; 5-ASA eluted in the upper gastrointestinal tract is absorbed, and 5-ASA that has not been absorbed as well as 5-ASA that has not yet been eluted reach the large intestine [7]. Owing to losses due to absorption in the upper gastrointestinal tract, 5-ASA derived from PENTASA® has a slightly lower concentration distribution than ASACOL® and LIALDA® [7]. Finally, because LIALDA® also has a pH-dependent coating, it is assumed that absorption in the upper gastrointestinal tract is similar to that of ASACOL®. However, dissolution of the LIALDA® coating occurs faster than that of the ASACOL® coating [8]. Notably, in LIALDA®, the release of 5-ASA is highly restricted by the multimatrix, and 5-ASA release is therefore low in the ascending colon.

Accordingly, differences in these drug delivery systems affect the drug distribution and usage, and it is necessary to select the most suitable drug for treatment based on these parameters and the results reported [9].

However, the signals of ASACOL®, PENTASA®, and LIALDA® had almost the same detection tendency, albeit with different magnitudes. This indicates that the distribution of 5-ASA formulations in the intestine may be less associated with the adverse events that occur.

In recent years, the studies have focused on adherence as well as lesions as a factor in the use of these drugs [21]. The study indicated that "Often skipping a meal" and "Multiple dose regimen" were factors in decreased adherence (<80%) to oral 5-ASA formulations approved in Japan are ASACOL®, PENTASA®, and LIALDA®. In addition, the authors

report that adopting a once-daily dosing regimen may improve adherence to oral 5-ASA formulations approved in Japan are ASACOL®, PENTASA®, and LIALDA® [21]. If a patient is expected to benefit equally from ASACOL®, PENTASA®, and LIALDA®, it may be possible to tailor the drug selection to the patient's diet, since the side effects to watch for are similar for these drugs.

Meanwhile, this study, like others using spontaneous reporting systems, had some limitations [22]. First, we used the spontaneous reporting system, the JADER. The JADER is a case report database of adverse events, and the total number of patients using this drug is not known, thereby preventing the calculation of incidence and prevalence. Accordingly, the comparisons among the drugs in this study are comparisons of reporting ratios rather than incidence rates.

Second, although differences in reporting ratios are often used to detect signals of adverse events in disproportionality analyses, the detected signals are known to be subject to reporting bias (e.g., the Weber effect [23,24], notoriety effect [25], and ripple effect [25]). Additionally, this study was a signal detection study and was not adjusted for patient background. Therefore, the signals detected in this study should be further validated using a more evidence-based study design.

Third, since the number of adverse events is small, this study used the Bayesian confidence propagation neural network (BCPNN), which can detect a stable signal even with a small number of reports, but even so, statistical power is not sufficient, and the possibility that the difference between 5-ASA formulations is in fact a type 2 error is undeniable.

However, there has been no previous signal detection study using a large database focusing on the differences in drug delivery systems of oral 5-ASA formulations, and physicians and pharmacists who want to use oral 5-ASA formulations appropriately should be aware of the potential for adverse events from this study at this point.

4. Materials and Methods

4.1. Data Sources

This study used the dataset from the first quarter of 2004 to the fourth quarter of 2019 from the JADER; 565,454 cases are registered in this database. The JADER can be accessed directly here: [http://www.info.pmda.go.jp/fukusayoudb/CsvDownload.jsp (accessed on 3 December 2022)] (in Japanese only).

It consists of four comma-separated values (csv) files as data tables: DEMO.csv (DEMO table; patient information), DRUG.csv (DRUG table; drug information), REAC.csv (REAC table; adverse event information), and HIST.csv (HIST table; patient history).

In these files, cases are registered using identification numbers (ID number), and there is no data that can identify individuals. Using the ID number, we combined these files into a database for analysis.

4.2. Drugs and Adverse Events

The drugs evaluated in this study were SALAZOPYRIN®, ASACOL®, PENTASA®, and LIALDA®. All of these drugs contain oral 5-aminosalicylic acid, although they have different drug delivery systems (Table 1).

Adverse events to be investigated were defined as all adverse events caused by the above drugs registered in the JADER. Adverse events were registered in the JADER as preferred terms of the Medical Dictionary for Regulatory Activities/Japanese version (MedDRA/J); version 23.0.

Statistical signal detection is generally conducted at the MedDRA Preferred Term (PT) level, whereas signal evaluation is conducted at the level of the medical concept, such as the MedDRA HLT or Standardized MedDRA Query (SMQ) level [26]. In this study, the target adverse events were defined as HLTs, and the number of reports was based on the number of cases rather than the number of drug/adverse event combinations.

4.3. Statistical Analysis

There are several algorithms for signal detection. In this study, we used the BCPNN, which detects a stable signal even when the number of reports is small. The BCPNN is also used by the WHO-Uppsala Monitoring Centre, which applies the information component (IC) as a signal indicator [27,28].

Table 2 and Equations (1)–(3) were used for calculating lower limits of the 95%CI for IC (=IC_{025}) and the upper limits of approximate 95%CI for IC (=IC_{975}).

Table 2. The 2 × 2 contingency table for signal detection.

	Target AE	Other AEs	Total
Target drug	N_{11}	N_{12}	N_{1+}
Other drugs	N_{21}	N_{22}	N_{2+}
Total	N_{+1}	N_{+2}	N_{++}

AE: adverse event, *N*: the number of reports (e.g., N_{11}: the number of target drug induced AE, N_{++}: the number of all reports).

The BCPNN detection criteria were $IC_{025} > 0$ [27,28]. Furthermore, $IC_{975} < 0$ is often referred to as the inverse signal [14,18].

$$E(IC_{11}) = \frac{(N_{11} + \gamma_{11})(N_{++} + \alpha)(N_{++} + \beta)}{(N_{++} + \gamma)(N_{1+} + \alpha_1)(N_{+1} + \beta_1)} \quad (1)$$

$$Var(IC_{11}) = \left(\frac{1}{log2}\right)^2 \left[\frac{N_{++} - N_{11} + \gamma - \gamma_{11}}{(N_{11} + \gamma_{11})(1 + N_{++} + \gamma)} + \frac{N_{++} - N_{1+} + \alpha - \alpha_1}{(N_{1+} + \alpha_1)(1 + N_{++} + \alpha)} + \frac{N_{++} - N_{+1} + \beta - \beta_1}{(N_{+1} + \beta_1)(1 + N_{++} + \beta)}\right] \quad (2)$$

$$IC\ (95\%\ \text{credible interval}) \approx E(IC_{11}) \pm 2\sqrt{Var(IC_{11})} \quad (3)$$

However, each parameter; γ_{11}, γ, α_1, β_1, α, β is shown in Equation (4).

$$\gamma = \gamma_{11}\frac{(N_{++} + \alpha)(N_{++} + \beta)}{(N_{1+} + \alpha_1)(N_{+1} + \beta_1)},\ \gamma_{11} = 1,\ \alpha_1 = \beta_1 = 1,\ \alpha = \beta = 2 \quad (4)$$

4.4. Analysis Software

The analysis software in this study used Visual Mining Studio (NTT DATA Mathematical Systems Inc., Shinjuku, Tokyo, Japan) version 8.4 and Microsoft Excel 2019 (Microsoft Corp., Redmond, WA, USA).

5. Conclusions

Ulcerative colitis and Crohn's disease are chronic inflammatory bowel diseases that are typically treated with various drugs, including 5-ASA. Therefore, formulation development that makes full use of advanced drug delivery systems has been carried out in order to improve the deliverability of 5-ASA to lesions. In this study, we comprehensively investigated the adverse events associated with four 5-ASA formulations with different drug delivery systems, i.e., SALAZOPYRIN®, ASACOL®, PENTASA®, and LIALDA®. With the exception of SALAZOPYRIN®, which is a combination of 5-ASA and sulfapyridine, the 5-ASA preparations ASACOL®, PENTASA®, and LIALDA® showed similar tendencies to induce adverse events, regardless of the location of the drug in the intestinal tract. These findings provide important insights which should be considered by physicians during treatment selection and drug manufacturers during drug development.

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H.T. (Hitomi Teramachi); writing—review and editing, all authors.; visualization, Y.N.; supervision, Y.N.; project administration, Y.N. and H.T. (Hitomi Teramachi); funding acquisition, Y.N. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: All authors declare no conflict of interest.

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