

# Upper Gastrointestinal Complications associated with NSAIDs in Children

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**Abstract – Objective:** To analyse serious upper gastrointestinal (UGI) complications associated with non-salicylate non-steroidal anti-inflammatory drugs (NSAIDs) in children.

**Methods:** All serious UGI complications associated with non-salicylate NSAIDs approved in France to treat moderate pain or fever in children, spontaneously reported to the French Pharmacovigilance system or to the companies, between the launching of each study drug in France to December 31, 2000.

**Results:** Serious UGI complications were reported in 61 children aged from 11 months to 15 years during treatment with niflumic acid (27), ibuprofen (23) and tiaprofenic acid (11). No case was reported with ketoprofen. UGI manifestations were UGI bleeding (15) and 46 gastrointestinal symptoms with endoscopic lesions i.e. gastritis (18), gastric ulcer (13), duodenal ulcer (7), duodenitis (4) and oesophageal ulcer (4). NSAID was combined with a salicylate in 36% of cases, given by the parents in self medication in 6.6% of cases and used outside its product licence in 33.8% of cases.

**Conclusion:** NSAIDs used in children for fever or moderate pain are associated with a risk of serious UGI complications which increases with length, dose and association with a salicylate.

**Mots clés :**  
complication  
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**Résumé – Complications gastro-intestinales associées aux AINS chez l'enfant. Objectif :** Analyser les manifestations gastro-intestinales graves associées aux anti-inflammatoires non stéroïdiens (AINS) chez l'enfant.

**Méthode :** Ont été retenues, toutes les manifestations gastro-intestinales graves associées à un AINS non salicylé ayant l'AMM chez l'enfant pour le traitement des douleurs modérées ou de la fièvre, spontanément rapportées au système français de pharmacovigilance ou aux firmes, entre la date de commercialisation de chaque produit et le 31 décembre 2000.

**Résultats :** Des manifestations gastro-intestinales graves ont été rapportées chez 61 enfants âgés de 11 mois à 15 ans. Il s'agissait de 15 hémorragies digestives hautes et de 46 manifestations avec, à l'endoscopie, une gastrite (18), un ulcère gastrique (13) ou duodénal (7), une duodénite (4) et un ulcère de l'oesophage (4). L'AINS concerné était l'acide niflumique (27), l'ibuprofène (23), l'acide tiaprofénique (11). Aucun cas n'a été rapporté avec le kétoprofène. Les AINS étaient associés à un salicylé dans 36 % des cas, étaient donnés en automédication parentale dans 6,6 % des cas, et étaient utilisés en dehors des conditions de l'AMM dans 33,8 % des cas.

**Conclusion :** Les AINS utilisés dans la fièvre ou la douleur modérée sont associés à un risque accru de complications gastro-intestinales hautes qui augmente avec la durée, la dose et l'association à un salicylé.

## 1. Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs)-related adverse events include 3 different types of complications : simple heart-burn, dyspepsia, nausea and abdominal pain, mucosal lesions such as ulcers seen on endoscopy and serious gastroin-

testinal complications, such as perforated ulcers and bleedings. Bleeding/perforation risk is well documented in adults. It is higher during the first week of treatment and increases with the NSAID dose,<sup>[1,2]</sup> by combination with another NSAID including aspirin<sup>[3]</sup> and in patients who experienced a previous history of bleeding/perforation.<sup>[2,4]</sup> Ibuprofen appears to carry the

lowest risk of gastrointestinal bleeding followed by diclofenac, indomethacin, naproxen, piroxicam and ketoprofen.<sup>[1,3,5]</sup>

Four NSAIDs are approved in France in children for fever or moderate pain, at ages that depend on the pharmaceutical form. Niflumic acid (Nifluril<sup>®</sup>) and tiaprofenic acid (Surgam<sup>®</sup> and generics) are indicated for inflammatory ear-nose-throat (ENT) pain (sore throat and otitis) and for dental pain. Ibuprofen (Nureflex<sup>®</sup>, Advil<sup>®</sup>, Antarene<sup>®</sup>) is indicated for moderate pain and fever, and ketoprofen (Toprec<sup>®</sup>) is indicated solely for fever. Three of them (tiaprofenic acid, niflumic acid, and ibuprofen) are also approved for paediatric rheumatic disorders.

Because they are used in lower doses and for shorter periods than in rheumatic disorders, NSAIDs used in fever or moderate pain management seem to be better tolerated. However, despite NSAIDs are more and more used to treat fever and moderate pain, few paediatric data about serious upper gastrointestinal complications of NSAIDs in this indication are available.

## 2. Objective

The aim of the study was to analyse French spontaneous reported cases of serious upper gastrointestinal (UGI) complications associated with non-salicylate NSAIDs used in children to treat fever or moderate pain.

## 3. Materials and methods

The study was based on spontaneous reports of adverse drug reactions (ADRs) reported to the French Pharmacovigilance system or to companies. Reporting "serious" or "unexpected" ADRs to the 31 Regional Pharmacovigilance Centres is mandatory for any prescriber, pharmacist, dentist or midwife in France. Reports were selected according to the presence of specific ADR terms including endoscopic lesions as "gastritis" "oesophagitis" "gastric ulcer" "duodenal ulcer" or "oesophageal ulcer" and clinical symptoms as "upper gastrointestinal bleeding" associated with non-salicylate NSAIDs approved in France to manage moderate pain or fever in children (age  $\leq 15$  years), namely ibuprofen, ketoprofen, niflumic acid and tiaprofenic acid. Only UGI symptoms confirmed by endoscopic lesions and UGI bleeding were retained. All spontaneous reports submitted to each company marketing a target drug were also identified. Our study period was between the launching of each study drug in France to December 31, 2000 *i.e.* 9, 6, 2 years respectively for Advil<sup>®</sup>, Nureflex<sup>®</sup>, and Toprec<sup>®</sup> and more than 15 years for the others. UGI ADRs associated with the two NSAIDs (diclofenac, naproxen) only indicated for paediatric rheumatic disorders were not studied.

For each ADR we noted information about the patient (age, gender, medical history), the drug exposure (suspected and concomitantly used drugs) and the characteristics of the ADR (time of onset, seriousness and outcome). All files were analysed by the Regional Pharmacovigilance Centre of Tours. A paediatric gastroenterologist examined all cases in which the diagnosis was equivocal. ADRs were considered as serious according to the WHO definition *i.e.* "A serious adverse event or reaction is any untoward medical occurrence that at any dose: results in death, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, is life-threatening".

## 4. Results

### 4.1. Global analysis

We collected 61 spontaneous reports of UGI complications, with a non-salicylate NSAID used in children. Patients were aged from 11 months to 15 years (median 4 years), and 31 (53.4%) were girls. Twenty-nine of these UGI complications were reported to the French Pharmacovigilance System, 53 to the companies and 21 to both systems. For 15 UGI bleeding we don't know if an endoscopy was performed. The 46 other cases were gastrointestinal symptoms with endoscopic lesions which were gastritis (n = 18), gastric ulcer (n = 13), duodenal ulcer (n = 7), duodenitis (n = 4) and oesophageal ulcer (n = 4), complicated by UGI bleeding for 37 of them and by perforation for 1 of them. The mean time to symptom onset after treatment was  $5 \pm 5.8$  days (median 3 days, range 1-30 days). Surgery was necessary in 3 (10.7%) cases of UGI complications, transfusion in 5 (17.9%), and drug therapy in 22 (78.6%) cases. One UGI complication resulted in death and one in persistent disability (antral stenosis). Niflumic acid was involved in 27 (44%) cases, ibuprofen in 23 (38%), and tiaprofenic acid in 11 (18%). The NSAID was used for pain or fever (42%), ENT indications (42%) or acute muscular or ligament pain (14.8%). The NSAID was the only gastrotoxic drug in 37 cases (61%). In the 24 other cases (39%), the NSAID was combined with a salicylate (22 cases) or a corticosteroid (2 cases). The NSAID was given by the parents in self-medication in 4 cases (6.6%). The NSAID was not used according to its product licence characteristics in 21 cases (33.8%): with a too long treatment duration (6 cases), with a too high dose (6 cases), at a lower age (5 cases), for an off-license indication (3 cases) or despite a contraindication (1 case). Thus, 52% of children had at least one other risk factor for NSAID induced UGI complications consisting of co-administration with a salicylate (36%) or a corticosteroid (3%), a higher-than-recommended dose regimen (23%),

**Table I.** Characteristics of the spontaneous reports of upper gastrointestinal bleeding and ulceration according to the NSAID.

Drug	Number of case	Age median [range] (years)	Time to onset median [range] (day)	Combination with a salicylate n (%)	Self-medication n (%)	Off-license use n (%)
Ibuprofen	23	2.8 [1-12]	2 [1-19]	6 (25%)	3 (13%)	3 (12.5%)
Niflumic acid	27	3 [1-15]	4 [1-25]	12 (44%)	1 (3.7%)	13 (45 %)
Tiaprofenic acid	11	10 [1-14]	2 [1-30]	4 (40%)	0	4 (30%)
Ketoprofen	0					

**NSAID** = non steroidal anti inflammatory drugs.

or longer-than-recommended treatment (12%). We have no data about infection with *Helicobacter Pylori* in this study.

#### 4.2. Analysis by drug substance

Table I describes characteristics of UGI ADRs (age of the child, time to onset) and of treatments (combination with a salicylate, self medication, off license use) according to each NSAID. Ibuprofen, involved in 23 cases of UGI bleeding (Advil® n = 14; Nureflex® n = 9), was prescribed for fever and/or pain in 17 cases (85%) and for ENT disorders in 3 cases (15%). Niflumic acid was involved in 21 cases of UGI bleeding and in 6 cases of UGI symptoms with endoscopic lesions (Nifluril 400® n = 18; Nifluril 250® n = 8; Nifluril 700® n = 1). Two patients also had another adverse event (renal failure and haematuria), and one patient developed antral stenosis as a sequel. Niflumic acid was prescribed for fever and/or pain in 8 cases (33%), for ENT disorders in 11 cases (45.8%) and for muscular or ligament pain in 5 cases (20.8%). Tiaprofenic acid was involved in 8 cases of bleeding and in 3 cases of UGI symptoms with endoscopic lesions (Surgam 100® n = 10; Surgam 200® n = 1). A 24-month-old girl with psychomotor delay died 12 hours after receiving 50 mg of Surgam®; autopsy showed three perforated gastric ulcers and a peritonitis. Tiaprofenic acid was prescribed for ENT disorders in 5 cases (56%) and for tendinitis in 4 cases (44%). No UGI complication was reported with ketoprofen. Ibuprofen trends to be used off licence less frequently than other NSAIDs but the difference is not statistically significant.

## 5. Discussion

Non-salicylate NSAIDs-associated UGI ADRs (gastritis, oesophagitis, ulcer and bleeding) in children are rare but their incidence is underestimated because of the reporting processes in our study. In fact, although reporting serious or unexpected ADR to Regional Pharmacovigilance Centres is mandatory for any prescriber in France, prescribers do not adhere to this attitude. In fact,

a study showed that only 10% of serious side effects are reported, particularly if the effect is well-known.<sup>[6]</sup> No case reported with ketoprofen does not mean that its UGI ADRs risk is lower. Actually, despite its licensing in France this drug has never been promoted to treat fever in children by the company.

Ibuprofen is rarely used off licence probably because it is authorized from 3 months since niflumic acid and tiaprofenic acid are labelled from respectively 12 and 4 years.

Because ibuprofen has been extensively studied in fever and moderate pain in children, most data concern this NSAID. In efficacy trials of ibuprofen in febrile children, there is a trend for a number of gastrointestinal effects, higher with ibuprofen 20-30 mg/kg/d than with paracetamol or placebo,<sup>[7-10]</sup> but UGI bleedings have not been reported. In clinical trials of NSAIDs in children with pain due to surgery (dental surgery, amygdalotomy or adenolectomy), no cases of UGI bleeding were observed. In contrast, the frequency of surgical wound bleeding and the mean bleeding time were higher in the NSAID arms than in the placebo arms,<sup>[11-13]</sup> probably because of the NSAID's platelet suppressive effect. In two very large trials comparing the tolerance of ibuprofen and paracetamol in painful febrile children, data about UGI bleeding are different. In the unblinded study no case of UGI bleeding was reported in 41 810 children.<sup>[14]</sup> In the double-blind trial involving 84 182 children in which paracetamol (12 mg/kg) was compared with ibuprofen (5 or 10 mg/kg), the four cases of UGI bleeding occurred in the ibuprofen groups within 4 weeks after treatment (2 cases with 5 mg/kg and 2 cases with 10 mg/kg), giving a risk of UGI bleeding of 7.2/100 000 children CI<sub>95%</sub> [2-18]/100 000.<sup>[15]</sup>

This study also showed that UGI complications related to non-salicylate NSAIDs in children are often associated with risk factors identified in adults and possibly preventable. Indeed, 52% of cases involved combination with aspirin, lengthy treatment, or higher-than-recommended doses. Among those risks factors, only high doses during longer-term treatment with ibuprofen,<sup>[16]</sup> naproxen or piroxicam<sup>[17]</sup> used in idiopathic juvenile arthritis have been reported in children. Moreover systematic endoscopic examination of children with UGI symptoms during NSAID therapy

showed a gastric or duodenal ulcer (23%), gastritis or duodenitis (47%) or oesophagitis (12%).<sup>[18]</sup> This high prevalence of endoscopic lesions was not confirmed in a cohort of 702 children treated with NSAIDs, five of whom had a UGI bleeding.<sup>[19]</sup>

## 6. Conclusion

This study suggested that, even at a regular dose, NSAID treatment of children with fever or moderate pain is associated with a risk of serious UGI complications (gastritis, oesophagitis, oesophageal gastric or duodenal ulcer and bleeding). Reminding physicians and pharmacists of the risk of ulcer and UGI bleeding and emphasising on the fact that the risk increases with combination with aspirin, lengthy treatment, or higher-than-recommended doses may prevent many of these adverse effects.

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