



Case Report

The Management of Delayed Onset Cramps Related to Irinotecan during Oncological Treatment

Jaques van Heerden^{1,2*}, Nicolette Moes^{3*}, Katleen Balliauw⁴, Elien Romaen⁴, Joris Verlooy¹, Machiel van den Akker¹, Koen Norga^{1,2}

¹Paediatric Haematology and Oncology, Department of Paediatrics, Antwerp University Hospital, Antwerp, Belgium

²Department of Medicine, Molecular imaging, Pathology, Radiotherapy and Oncology, University of Antwerp, Antwerp, Belgium

³Department of Paediatric Gastro-enterology and Paediatrics, Antwerp University Hospital, Antwerp, Belgium

⁴Pharmacy Department, Antwerp University Hospital, Antwerp, Belgium

***Corresponding Authors:** Jaques van Heerden, Department of Paediatric Haematology and Oncology, Antwerp University Hospital, Drie Eiken Street 655, Edegem, 2650, Belgium

Nicolette Moes, Department of Paediatric Gastro-enterology, Antwerp University Hospital, Drie Eiken Street 655, Edegem, 2650, Belgium

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Abstract

Background: Irinotecan-induced gastro-intestinal side effects are well described in the literature. The

pathophysiology and treatment of diarrhea, especially acute onset, is the most understood. Yet delayed onset cramps and management have not been sufficiently documented.

Materials: A case report of a nine-year-old girl diagnosed with rhabdomyosarcoma who was treated with irinotecan in the relapse setting, is presented. A limited literature review was done based on the challenges experienced during the management of a patient with delayed onset irinotecan-induced cramps. The pathophysiology of delayed onset irinotecan induced cramps is based on cholinergic, inflammatory and enzymatic factors as well as neural damage. Treatment was based on the etiology described in the literature with a positive result.

Conclusion: Delayed onset irinotecan related cramps are part of a multifactorial etiology that should be approached systematically, especially when first line treatment does not yield an adequate response.

Keywords: Irinotecan; Delayed onset; Cramps; Treatment; Side effects

List of abbreviations: ADR: Adverse Drug Reaction; CD: Crohn's disease; IT-P: Irinotecan-Temozolomide-Palbociclib; S/C: Subcutaneous; UC: Ulcerative colitis; VIT: Vincristine-Irinotecan-Temozolomide

1. Introduction

Irinotecan, a topoisomerase I inhibitor, has become an effective chemotherapeutic in the first line treatment of colon cancer in adults and relapsed and resistant solid tumours in children [1, 2]. Gastro-intestinal side effects and neutropenia are the most commonly reported toxicities in both adults and children [1, 2]. Early and late onset diarrhea are well described in the literature [1, 3]. Early diarrhea may be accompanied by cholinergic symptoms such as cramps [3]. Concomitant administration of atropine before

irinotecan administration may ameliorate the short-term cholinergic symptoms [3]. Yet atropine has an elimination half-life of 2-5 hours [4]. The hepatic metabolism of atropine is incomplete and is then mainly excreted via the urine. Approximately 50% of the dose is excreted within 4-5 hours with 90% excreted within 24 hours [4]. Late diarrhea is defined as diarrhea starting more than 24 hours after administration of irinotecan [5]. Fluid and electrolyte monitoring and treatment with loperamide are effective in the management [5]. Studies have shown that neuropathic changes in especially the colon may manifest as delayed-onset diarrhea even after the irinotecan therapy has been completed [6]. What is not clear is whether this also causes late onset of cramps. Although early onset cramping may ease with atropine, the management of late onset cramps due to irinotecan has not been discussed in the literature.

2. Methods and Materials

This case report describes the clinical course of abdominal cramps after irinotecan administration, defining the causality and then presents a solution to improve the quality of life in a patient receiving chemotherapy in a tumour relapse setting. A Pubmed- and Google Scholar search was conducted in the English-language literature using the keywords 'irinotecan', 'cramps', 'late onset', 'delayed onset' and/or 'treatment'.

3. Case Presentation

A nine-year-old girl was diagnosed with metastatic alveolar rhabdomyosarcoma, involving a mass originating from the muscles of the right hand with metastatic disease involved her lungs, liver, T12 – L3 vertebrae, abdominal and thoracic lymph nodes. She was managed according to the very high risk (VHR) arm of the European Paediatric Soft

Tissue Sarcoma Study Group (EpSSG) RMS2005 protocol [first line treatment (Ifosfamide, Vincristine, Actinomycin D and Doxorubicin (IVADo), three cycles, followed by second line treatment (one cycle IVADo, surgery, radiotherapy combined with five cycles IV(A)]. After the intensive treatment, maintenance therapy, consisting of 12 cycles (daily oral cyclophosphamide and, on day 1, 8 and 15 IV vinorelbine of 28-day cycles), was given. Four months after the last cycle, the patient relapsed at the right epitrochlear lymph node and at further sites outside the radiation field in the abdomen and lungs. She started relapse therapy based on the VIT protocol (vincristine 1.5 mg/m² on days 1 and 8 and irinotecan 50 mg/m² and temozolomide 150 mg/m² on days 1 to 5 of 21-day cycles) [7]. The patient received ciprofloxacin and successfully prevented diarrhea, but she did develop delayed abdominal cramps on day seven of each cycle for seven days (Table 1). Initially, the cramps were present throughout the day, but later limited to the night. At the beginning, the cramps responded to paracetamol. From the third cycle it was necessary to administer tramadol to gain pain relief.

After six cycles of the VIT protocol, metabolic remission of the disease was confirmed by PET/CT and consolidation radiotherapy of the lesions started. Unfortunately, during treatment tumor progression in the lungs was observed. From next-generation diagnostics from the Individualized therapy for relapsed malignancies in childhood (INFORM) study a CDK4 gain amplification target was identified. Based on this information and the previous positive response on irinotecan and temozolomide, a combination palbociclib (CDK4/6 inhibitor) and irinotecan/temozolomide (IT-P) was started (oral palbociclib 75 mg/m² on days 1 and 8 and irinotecan 50 mg/m² and temozolomide 150 mg/m² on days 1 to 5 of 21-day cycles).

The abdominal cramps reemerged as previously on day seven lasting for seven days (Table 2). Following the IT-P regimens diarrhea was present from and the analgesics were less effective than in the VIT regimen. The duration of pain relief decreased and the frequency of analgesic administration increased. Additional anti-spasmodic therapy with hyoscine butylbromide (Buscopan®) had no effect.

3.1 Establishing irinotecan as the causative agent

3.1.1 Isolating irinotecan as causative agent: The patient received two independent courses that included irinotecan. During the first relapse vincristine, irinotecan, temozolomide (VIT) and during progression of disease irinotecan, temozolomide and palbociclib (IT-P). Vincristine can cause abdominal cramps in 1-10% of cases and may be independent or caused by constipation [8]. The cramps were present in both courses, but vincristine was only present in the first course. Abdominal cramps are not a reported side effect of palbociclib and temozolomide [9, 10].

3.1.2 The Naranjo scores and pharmaceutical

interactions: The Naranjo scores, a causality assessment method for determining the likelihood of whether an adverse drug reaction is actually due to the drug [10], of the irinotecan, vincristine, temozolomide and palbociclib were respectively 9, 6, 6, 6 (Table 3), showing that irinotecan had a definite causality, whilst vincristine, temozolomide and palbociclib only had a probable causality. Since neither vincristine nor palbociclib were present in both courses and abdominal cramps are not a reported side effect of temozolomide, all three drugs were excluded as causative agents. No pharmaceutical interactions have been described between the chemotherapy products used in either the VIT-

regimen or IT-P regimen that could contribute to the abdominal cramps [8, 9, 11]. We cannot confirm whether this has been as specific study question in a clinical trial.

3.1.3 The pathophysiology of irinotecan abdominal cramps:

Where the pathophysiology of acute symptoms has been documented, the aetiology of late onset symptoms is more complex [3]. Early-onset diarrhoea is caused by irinotecan-induced cholinergic syndrome. This acute cholinergic reaction is associated with both acute and delayed diarrhoea, reduced capacity of the intestinal mucosa for absorption and intestinal hyper-peristalsis leading to abdominal cramps [3, 12]. Although acute irinotecan-induced diarrhoea may be prevented by blocking anticholinergic receptors with atropine, no prophylactic treatment for delayed irinotecan-induced diarrhoea has been described [3].

A number of contributing factors have been described with late onset irinotecan-induced diarrhoea [3, 13]. The pathophysiology has a neural, inflammatory and enzymatic component that leads to intestinal dysfunction and contributes to late onset cramps [3, 5, 6, 12, 13]. This set of etiological factors contributes to long-term gastrointestinal dysfunction and symptoms. Irinotecan is converted in the liver into an active metabolite SN-38 by enzymatic de-esterification. This active substance is excreted via bile into the intestine [3, 5]. A second parallel process occurs when the SN-38 glucuronide is converted by beta-glucuronidase from gut bacteria from a noncytotoxic metabolite to active SN-38 [3, 5]. The cytotoxicity causes mucositis and the epithelial damage [13, 14].

Studies evaluating beta-glucuronidase activity in intestinal fluids concluded that the highest activity was in the caecum and low in the duodenal and jejunum [15]. Thus, direct cytotoxicity to the caecum and colon leads to mucosal damage. The duodenum and jejunum are sites where carboxylesterase activity converts irinotecan to SN-38 and are thus spared from mucosal damage [15]. The mucosal damage is observed further down the intestinal tract [15]. The main process of damage is inflammation or intestinal mucositis [14, 15]. The result is morphological and physiological damage within the small intestinal mucosa and loss of normal tissue architecture in the ileum and caecum. Histopathologically the SN-38 toxicity causes epithelial vacuolation and apoptosis of the absorptive cells in the ileum [15, 16]. In the caecum goblet-cell hyperplasia occurs with excessive production of sulfomucin. The abnormal intestinal mucosa is therefore the site of abnormal ion transport, malabsorption and eventually increased electrolyte and water secretion [15, 16]. Simultaneously the irinotecan-induced neuronal loss was associated with changes in colonic motility and gastrointestinal transit [6]. TLR4 signalling may be a contributing factor of both delayed diarrhoea and cramps [12]. The aetiology of irinotecan-induced mucositis is mediated through the interleukin-1/Toll-like receptor [3]. Mucosal damage and inflammation can be present following short and long-term treatment with irinotecan [13, 14]. Therefore, irinotecan toxicity is not just dependent on dose but also on the duration of exposure as well.

VIT regimen 5/6/2020 – 8/10/2020						
Vincristine 1.5 mg/m ² D1 and D7 Intravenous						
Irinotecan 50 mg/m ² D1-D5 Intravenous						
Temozolomide 150 mg/m ² D1-D5 Oral						
Date of cycle	5/6/2020	26/6/2020	10/8/2020	28/8/2020	18/9/2020	1/10/2020
Cycle number	1	2	3	4	5	6
Prophylaxis	Ciprofloxacin	Ciprofloxacin	Ciprofloxacin	Ciprofloxacin	Ciprofloxacin	Ciprofloxacin
Diarrhea	None	None	None	None	None	None
Cramps	Day and night	Day and night	Day and night	Night	Night	Night
Pain score	7	7	10	10	7	7
Duration	7 days	7 days	7 days	7 days	7 days	7 days
Day cramps start	D7	D7	D7	D7	D7	D7
Action	Paracetamol	Paracetamol	Paracetamol and Tramadol	Paracetamol and Tramadol	Paracetamol and Tramadol	Paracetamol and Tramadol
Outcome	Pain free	Pain score 1 - 2	Pain score 1 - 2	Pain score 1 - 2	Pain score 1 - 2	Pain score 1 - 2

Abbreviations: VIT – Vincristine, Irinotecan and Temozolomide; Pain score: 0 – no pain; 10 – need for in hospital pain management

Table 1: The Vincristine – Irinotecan – Temozolomide regimen, side effects and severity scales.

IT-P regimen 27/11/2020 – 13/3/2021						
Irinotecan 50 mg/m ² D1-D5 Intravenous Temozolomide 150 mg/m ² D1-D5 Oral Palbociclib 70 mg/m ² D1-D14 Oral						
Date of cycle	27/11/2020	19/12/2020	26/1/2021	16/2/2021	18/9/2021	9/3/2021
Cycle number	1	2	3	4	5	6
Prophylaxis	Ciprofloxacin	Ciprofloxacin	Ciprofloxacin	Ciprofloxacin	Ciprofloxacin	Ciprofloxacin
			Atropine S/C 30 min before starting Irinotecan	Atropine S/C 30 min before starting Irinotecan	Atropine S/C 30 min before starting Irinotecan	
			Enterocort D6	Enterocort D2		
			Peppermint oil D6	Peppermint oil D2		
Diarrhea	At night 2-3x	At night 2-3x	At night 2-3x	None	None	None
Quality of diarrhea	Watery	Watery	Watery	None	None	None
Cramps	Night	Night	Night	Night	Night	Night
Pain score	6	6	9	2	2	2
Duration	7 days	7 days	7 days	2 days	2 days	2 days
Day cramps start	D7	D7	D7	D7	D7	D7
Action	Paracetamol and Tramadol	Paracetamol and Tramadol	Paracetamol, Tramadol and Buscopan	Paracetamol	Paracetamol	
Outcome	Pain score 1 – 2 (short acting)	Pain score 3 - 5 (short acting)	Pain score 1 - 2	Pain score 0 - 1	Pain score 0 - 1	Pain score 0 - 1

Abbreviations: ITP – Irinotecan, Temozolomide, Palbociclib; S/C – subcutaneous; Pain score: 0 – no pain; 10 – need for in hospital pain management

Table 2: The Irinotecan – Temozolomide – Palbociclib (IT-P) regimen, side effects and severity scales.

Question	Answer	Score
1. Are there previous conclusive reports on this reaction?	Yes	1
2. Did the adverse events appear after the suspected drug was given?	Yes	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	Yes	1
4. Did the adverse reaction appear when the drug was readministered?	Yes	2
5. Are there alternative causes that could have caused the reaction?	No	2
6. Did the reaction reappear when a placebo was given?	Not done	0
7. Was the drug detected in any body fluid in toxic concentrations?	Not done	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	Not done	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	Yes	1
10. Was the adverse event confirmed by any objective evidence?	Not done	0
	Total	9 Definite ADR

Abbreviations: ADR – adverse drug reaction

Table 3: The Naranjo score of Irinotecan.

	Cholinergic pathology	Inflammation	Neuronal loss	Enzyme related pathology
Side affect	Acute	Late	Acute and Late	Late
Causative	Acute setting	Acute	-	-
Treatment	Atropine	Budesonide Peppermint (menthol)	Peppermint (menthol)	Ciprofloxacin Cefexime
Diarrhoea	Loperamide Morphine	-	-	-

Table 4: Summary of the pathophysiology and treatment.

4. Discussion

The pathology of delayed onset cramps is a multifactorial process involving mucosal inflammation and damage, neuronal dysfunction as well as enzymatic and electrolyte imbalances (Table 4) [3]. Since escalation of analgesia,

which included opioid-based therapy, produced no effect, we postulated that various aetiological pathways of the cramps had to be addressed. Irinotecan-induced diarrhoea may be caused by intestinal bacterial deglucuronidation of SN-38G by beta-glucuronidase-producing flora [15]. Daily

ciprofloxacin 15 mg/kg/day (maximum of 500 mg) prophylaxis two days prior till the last day of irinotecan-therapy was already in place during both the VIT and IT-P regimens and insufficiently treated the cramps and diarrhoea in our patient.

To prevent inflammation in the intestines, steroid-based recommendations were sought from immune intestinal pathologies such as ulcerative colitis (UC) and Crohn's disease (CD). The choice was made to administer oral budesonide according to protocols for treating mild Crohn's disease [17]. Budesonide has been proven to be locally effective in mild CD with distal inflammation (mainly in the ileum or caecum) or mild UC [17]. We hypothesised that therefore it could also be effective in stopping ileocecal inflammation caused by irinotecan, causing fewer side-effects than systemic corticosteroids such as prednisone.

During the third cycle budesonide was therefore administrated after completion of the irinotecan cycle on day six. This still resulted in severe (score 8/10) delayed onset cramps, but of a shorter duration (2 days) and responsive to paracetamol monotherapy. During the fourth cycle budesonide was started on the second day of the cycle which resulted in delayed onset cramps of mild intensity. Very limited literature exists on treatment for delayed neuronal dysfunction [6]. In the literature for inflammatory bowel disorders, peppermint oil has been studied for symptomatic management [18, 19]. Through the direct enteric nervous system stimulation and calcium channel blockade, peppermint oil causes smooth muscle relaxation [18,19]. Visceral sensitivity modulation is achieved through transient receptor potential cation channels. This anti-spasmodic effect was present in both the small and large

intestine. Independent from the neuronal effects, peppermint oil has anti-microbial and anti-inflammatory activity [18, 19].

The diarrhoea was a new symptom during the IT-P regimen. The diarrhoea was of late onset which made cholinergic dysfunction less likely and prophylaxis for an enzymatic aetiology was already administered. We postulated that the late onset diarrhoea was due to inflammatory changes in the gut with subsequent neuronal and electrolyte imbalances. Despite not presenting with early onset symptoms, atropine was included before treatment. After the first cycle that included both atropine and steroid therapy the diarrhoea had resolved. In the event that the diarrhoea did not resolve loperamide and/or a peripheral opioid agent could have been introduced to control diarrhoea [3]. Yet these two options do not modulate intestinal mucositis-associated inflammation.

4.1 Alternative treatment options

Although our patient responded well to our management, other treatment options were considered, but never initiated.

4.1.1 Upwards titration of budesonide

The advised dose for children between six years and 18 years is 9 mg/day PO. A short-term increased dose can be given [21].

4.1.2 Anti-inflammatory treatment with an TRPA1 receptor agonist

Anti-inflammatory potential of a TRPA1 agonist in reducing intestinal mucositis is achieved by reducing the production and/or release of pro-inflammatory cytokines

TNF- α , IL-1 β , and KC [14]. Inflammation can be reduced by limiting oxidative stress [14].

4.1.3 Reduction of intestinal motility or water and electrolyte loss

Late onset symptoms have variable etiology and may not adequately respond to standard antispasmodic- and antidiarrheal medication [16]. This is due to mucosal damage of the intestine, loss of abnormal ion transportation and increased electrolyte and water losses [16]. This may be associated with cramps. Although the first line management may include loperamide and antispasmodics, with continued fluid and electrolyte losses other medications should be included in the management [16]. Racecadotril or *acetorphan* is a peripheral acting enkephalinase inhibitor that decreases intestinal secretion and promotes absorption. Racecadotril does however not slow intestinal transit [21]. Octreotide is a peptide that reduces gastro-intestinal motility and secretion of fluids in the intestines and pancreas [22]. Octreotide is indicated in loperamide refractory diarrhea in cancer related diseases [23].

5. Conclusion

Delayed onset irinotecan related cramps are part of a multifactorial etiology that should be approached systematically, especially when first line treatment does not yield an adequate response.

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Competing Interests

The author(s) declare that they have no financial or person-

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Ethical Approval

Informed consent for publication of the clinical case was given by the parents of the patient and assent was given by the patient.

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Conflict of Interest

There is no conflict of interest to disclose.

Data Availability

No data was generated for this case report.

Disclaimer

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