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Drug use in patients with short bowel syndrome and intestinal failure

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ABSTRACT

Introduction. In patients with short bowel syndrome (SBS), severe malabsorption may cause a need for parenteral support and, by definition, these patients suffer from SBS intestinal failure. Absorption of oral medications is likely diminished in patients with SBS intestinal failure and higher than normal doses may be required to achieve sufficient pharmacologic effect. We investigated the prescription patterns and oral dosages in a well-defined population of patients with non-malignant SBS intestinal failure.

Methods. This was a cross-sectional analysis based on a cohort of adult patients with SBS intestinal failure treated with home parenteral support and registered in 2016 at the Department of Gastroenterology at the Copenhagen University Hospital – Rigshospitalet. The patients' clinical data and prescription patterns were extracted from electronic medical and medications records.

Results. The patients in our cohort (n = 74) were primarily females (58%), the median age was 63 years (interquartile range (IQR): 52-72 years) and the median BMI was 22 kg/m^2 (IQR: 19-26 kg/m^2). Each patient was treated with a median of eight drugs (range: 1-20). Most (75%) of the medications were administered orally. Only codeine, levothyroxine and loperamide were prescribed in higher dosages than recommended in their product labelling. All medication-treated patients were prescribed between one and four different analgesics.

Conclusion. In our single-centre cohort of patients with SBS intestinal failure, orally administered medications were generally prescribed in recommended dosages.

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Trial registration. Approved by the Danish Data Protection Agency (BFH-2016-058, I-Suite no.: 04906) and the Danish Patient Safety Authority (3-3013-1884/1/).

Short bowel syndrome (SBS) can derive from extensive surgical resection of the small intestine due to malignant and non-malignant causes and is anatomically defined by a remnant small bowel length below 200 cm [1]. Some patients with SBS also fulfil the definition of intestinal failure as they have impaired intestinal absorption requiring intravenous home parenteral nutrition with water, nutrients and/or electrolytes to maintain health [2].

SBS intestinal failure is rare. Thus, in a recent retrospective study from the Capital Region of Denmark, 331 patients had been registered discharged with non-malignant SBS intestinal failure from 1970 to 2016 [3].

Because of the limited nutritional absorption in patients with SBS intestinal failure, it is natural to assume that medication absorption might also be critically impaired. The European Society for Clinical Nutrition and Metabolism (ESPEN) guideline on intestinal failure in adults recommends that medications should be prescribed to patients on an individual basis where one should evaluate the absorptive capacity of the remnant bowel in relation to the pharmacokinetics of the medications [1]. However, valid data on pharmacokinetics in patients missing specific parts of the intestine are generally lacking [4]. In addition, whereas the majority of orally administered medications are believed to be absorbed primarily in the duodenum and the upper jejunum, the absorption may be affected by other factors than the missing intestinal type and length, including the physicochemical quality of the medications and gastrointestinal transit time [5, 6].

To our knowledge, overall medication use in patients with intestinal failure due to SBS has not been described before. Here, we investigated medication utilisation, including dosages and administration routes, in a cohort of patients from a single tertiary centre (Department of Intestinal Failure and Liver Diseases, Rigshospitalet, Copenhagen) mainly covering referrals from the eastern part of Denmark.

METHODS

Study design

This is a cross-sectional analysis based on data from all patients with SBS intestinal failure who received home parenteral support registered with the Department of Intestinal Failure and Liver Diseases at Copenhagen University Hospital – Rigshospitalet on 1 January 2016. Individual data recorded in the Electronic Patient Record (EPJ), the Electronic Patient Medication Module (EPM) [7] and the Shared Medication Record (FMK) were crosslinked by use of social security numbers.

Patients

Patients were included if they were diagnosed with SBS due to non-cancer, had received home parenteral support and had been hospitalised at least once at the Department of Gastroenterology during 2015. Cancer patients were excluded to avoid patients with comorbid intestinal radiation injury, which may affect medication absorption, and to avoid chemotherapy and medications related to cancer. The following clinical parameters were gathered for all patients: age, sex, BMI, length of the remnant intestine, stoma or not, days since surgery, commencement date and amount of home parenteral support. The patients were divided into three categories by disease aetiology: mesenteric vascular, inflammatory bowel disease (IBD) and complication to non-IBD surgery.

Prescribed medications

Each patient's prescribed medication was categorised by the Anatomical Therapeutic Chemical (ATC) classification system. Both medications for long-term and temporary use were included in the analyses. The items of information included were: ATC code, medication name, strength, indication for treatment, route of administration and actual dosage and recommended dose according to the summary of product characteristics.

Data analysis

Demographics were described with medians and interquartile ranges, except for the number of medications where the full range was used. Medication dosages were described with means and full range. Microsoft Office Excel 2016 and SAS/STAT (Statistical Analysis Software) version 9.4 were used for the data analysis.

Ethics

The study was approved by the Danish Data Protection Agency (BFH-2016-058, I-Suite no.: 04906) and the Danish Patient Safety Authority (3-3013-1884/1/). Data were pseudo-anonymised and stored in an encrypted database.

Trial registration: not relevant.

RESULTS

We identified 76 patients who were eligible for inclusion. Two patients were excluded; one did not have a Danish social security number and one did not receive home parenteral support at the time of inclusion. Thus, the final cohort comprised 74 patients. Patient characteristics are presented in **Table 1**. Seventy-one patients (96%) were treated with two or more medications.

TABLE 1 Patient characteristics.

Gender, n (%)	
Male	31 (42)
Female	43 (58)
Total	74
Age, yrs, median (IQR)	63 (52-72)
Male	56 (42-70)
Female	63 (57-73)
Body weight, kg, median (IQR)	65 (56-75)
BMI, kg/m^2, median (IQR)	22 (19-26)
Medications, n, median (range)	8 (1-20)
Cause of bowel resection, n (%)	
IBD:	
Crohn's disease	27 (36)
Ulcerative colitis	3 (4)
Mesenteric vascular disease	24 (32)
Non-IBD surgery	20 (27)
Home parenteral supplement, n (%)	
Cernevit, 5 ml	59 (80)
Soluvit, 10 ml	5 (7)
Unspecified	10 (14)

IBD = inflammatory bowel disease; IQR = interquartile range.

We identified the 25 most frequently prescribed medications (**Table 2**) and compared the number of medications administered by oral route with te number of medications administered intravenously. The majority (75%) of the medications were prescribed for oral administration. The only medications that were prescribed in higher dosages than recommended in their product labelling were codeine (n = 3, 23% of the users), levothyroxine (n = 1, 20% of the users) and loperamide (n = 1, 8% of the users). The other medications were prescribed in dosages falling within the recommended range (**Table 3**). Only vitamins (D and B_{12}), proton pump inhibitors, paracetamol, zoledronic acid (once yearly), morphine and loperamide were prescribed for parenteral administration in a subset of patients.

TABLE 2 The 25 most frequently used medications classified by the Anatomical Therapeutic Chemical Classification System (ATC) level 4[a] in our cohort (N = 74) sorted by total frequency and furthermore divided by administration route.

ATC code	Group: medication	Treated with medication, n (% of total)	Administration, n (% of group)	
			oral	parenteral
		56 (76)	19 (34)	37 (66)
N02BE	Anilides: paracetamol	42 (57)	40 (95)	2 (5)
A11CC	Vitamin D and analogues	30 (41)	8 (27)	22 (73)
A07DA	Antipropulsives: loperamide	17 (23)	16 (94)	1 (6)
N05CF	Benzodiazepine related drugs: zolpidem, zopiclone	16 (22)	16 (100)	-
N02AA	Natural opium alkaloids: morphine	15 (20)	13 (87)	2 (13)
R05DA	Opium alkaloids and derivatives: codeine	15 (20)	15 (100)	-
B03BA	Vitamin B_{12}: cyanocobalamin and analogues	14 (19)	-	14 (100)
N02AX	Other opioids: tramadol	12 (16)	12 (100)	-
B01AA	Vitamin K antagonists: warfarin	12 (16)	12 (100)	-
A12AX	Calcium, combinations with vitamin D and/or other drugs	11 (15)	11 (100)	-
B01AC	Platelet aggregation inhibitors excl. heparin: acetylsalicylic acid, clopidogrel	10 (13)	10 (100)	-
C07AB	Selective beta blocking agents: metoprolol	8 (11)	8 (100)	-
A04AA	Serotonin (5-HT3) antagonists: ondansetron	8 (11)	8 (100)	-
C03BA	Plain sulfonamides: furosemide	8 (11)	8 (100)	-
N05BA	Benzodiazepine derivatives: oxazepam, diazepam	7 (9)	7 (100)	-
M05BA	Bisphosphonates: zoledronic acid	7 (9)	-	7 (100)
P01BC	Methanolquinolines: quinine	7 (9)	7 (100)	-
M01AE	Propionic acid derivatives: ibuprofen	7 (9)	7 (100)	-
N03AX	Other antiepileptics: gabapentin, lamotrigine	6 (8)	6 (100)	-
C08CA	Dihydropyridine derivatives: amlodipine	6 (8)	6 (100)	-

a) ATC groups unavailable as oral administration have been excluded.

TABLE 3 Daily doses of orally administered medications listed alphabetically.

Generic name	Observations, n	Dose, mg, mean (range)	Recommended dose, mg
Acetylsalicylic acid	8	75	75
Amlodipine	5	5 (5-10)	5-10
Codeine	13	265 (40-480)	240a
Furosemide	8	70 (40-500)	20-2,000[a]
Levothyroxine	5	0.23 (0.05-0.60)	0.10-0.20
Loperamide	13	12 (4-32)	2-16
Metoprolol	8	137.5 (50-200)	50-200
Pantoprazole	10	80 (40-80)	20-80
Paracetamol	15	4,000 (1,000-4,000)	500-4,000
Prednisolone	6	5 (5-25)	5-60
Zopiclone	5	7.5 (3.8-7.5)	3.75-7.5

a) Max. daily dosage recommended in the summary of product characteristics.

The most prescribed medication in our population was proton pump inhibitors (n = 56, 76%), which were prescribed for oral use in one-third of the patients. All medication-treated patients were prescribed between one and four different analgesics. Paracetamol was the most prescribed analgesic and the second most prescribed medication overall (n = 42, 57%), and it was almost exclusively (95%) prescribed for oral use. Morphine was prescribed to 15 (31%) of the patients, with a majority being prescribed for oral use (93%). Oral tramadol were prescribed to 12 (16%) patients; dermal fentanyl, to 12 (16%) patients. Anti-inflammatory and antirheumatic

products (ATC code M01) were prescribed to nine (12%) patients, most often oral ibuprofen, which was prescribed to seven (9%) patients. Zopiclone was prescribed as oral administration to 16 (22%) patients. The sample size was too small and heterogenous to show any significant association between the remnant length of the intestine and the number of prescribed medications or dosages.

DISCUSSION

This was the first study to investigate the prescription patterns for patients with intestinal failure due to SBS. Surprisingly, despite these patients having severely reduced absorptive capacity for nutrients and vitamins, most of the medications were prescribed for oral administration and in recommended dosages. This finding seems to run somewhat contrary to the ESPEN guideline for intestinal failure, which specifically recommends considering the use of parenteral and transdermal routes and the use of suppositories in SBS patients with limited intestinal absorption [1].

Patients with SBS and intestinal failure often suffer from multiple diseases, which may potentially explain the wide variation in the number of medications per patient. In theory, reduced absorption of individual medications may in itself lead to lower clinical effect and thereby additional medications. For example, most of the patients in our cohort who received paracetamol also received an opioid and occasionally ibuprofen. Thus, considering that a previous study indicated that paracetamol absorption is reduced in patients with SBS due to duodenostomy or jejunostomy [8] and because all patients in our cohort were prescribed oral paracetamol within the recommended dose range – it is conceivable that the patients in our cohort did not experience the intended clinical effect of paracetamol. Alternatively, the need for treatment with multiple analgesics may also simply be the chronic and complex pain from which many of these patients suffer. One way to deal with the uncertainty of absorption of paracetamol and other medications may be to use therapeutic drug concentration monitoring. This means tailoring pharmacotherapy according to plasma concentrations of the medication; however, this requires fairly well-established pharmacokinetics and therapeutic intervals, which are specified for some but far from all medications [9].

Disease-specific medication

Patients with SBS have an increased gastrointestinal luminal volume and diarrhoea, which leads to loss of electrolytes and water [10]. An essential part of their treatment is therefore antidiarrhoeal agents and PPIs, which both reduce these symptoms [11, 12]. This is reflected in our cohort as most patients (76%) received PPIs. The specific absorption site of proton pump inhibitors remains unknown, but the absorption is rapid [13] and the clinical effect is easily monitored by symptoms. Codeine and loperamide are the most used antidiarrhoeal agents in this patient group. In the present study, they were prescribed in higher dosages than recommended according to their product label. Whereas nothing suggests misuse in our cohort, it is noteworthy that the current ESPEN guidelines prefer loperamide over codeine [1] – and both medications may – if significantly absorbed – contribute to opioid addiction [14].

Other medication

According to some case reports, warfarin absorption is not affected in patients with SBS [4, 15]. Unfortunately, the exact warfarin dosages in this study were not registered digitally and we were unable to examine exact dosages of warfarin. Metoprolol, amlodipine, furosemide and zopiclone all have a bioavailability of 60-80% and their clinical effects can readily be monitored by clinical evaluation [13, 16-18]. None of the patients in the study received dosages higher than approved. Of note, a few patients received a combination of antihypertensives (e.g. amlodipine and metoprolol), and there is a possibility that this indicates a low clinical effect due to reduced absorption. Malabsorption of prednisolone has been described from enteric-coated tablets in patients with an

ileostomy [19]. In contrast, one study has shown that patients with at least 30 cm of the small intestine absorb acetylsalicylic acid sufficiently [20], supporting the use in this cohort. Again, sufficient absorption may have been confirmed either by measures of clinical efficacy or by measurement of pharmacodynamic effect or plasma concentrations.

Strengths and limitations

SBS and intestinal failure is a rare condition making 74 patients a relatively large cohort representing most of the patients with SBS and intestinal failure from the eastern part of Denmark. A major limitation is that we only had access to prescription data, leaving us with a risk of misclassification if the patients did not take their medications as prescribed. Our cross-sectional study does not allow us to draw any conclusions about actual absorption, and we regard this paper a primer to further studies of pharmacokinetics in SBS with and without intestinal failure.

CONCLUSION

In a contemporary cohort of Danish patients with SBS, most patients with intestinal failure (requiring parenteral nutrition) were prescribed medications for oral administration in normal doses. As most patients were prescribed several medications and some of these had an uncertain clinical effect, the present study encourages further pharmacokinetic studies in these patients.

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Conflicts of interest Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the article at ugeskriftet.dk/dmj

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