Acta Poloniae Pharmaceutica – Drug Research, Vol. 77 No. 3 pp. 417–421, 2020
DOI: 10.32383/appdr/123017
Received 5 April 2020, Received in revised form 5 May 2020, Accepted 28 May 2020.

ISSN 2353-5288
Polish Pharmaceutical Society

REVIEW

BIOAVAILABILITY OF DRUGS FROM SUPPOSITORIES IN CLINICAL PRACTICE AFTER 1995

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Abstract: A review has been supposed to be arranged on the literature published between 1996 and 2019 concerning applications of suppositories in clinical practice. The rectal route of drug administration has been in use for centuries particularly in children, elderly and comatose patients as well as in palliative care and preterm infants undergoing painful procedures. Morphine, salbutamol, methadone, lidocaine, propranolol, theophylline, and mianserin, which allow avoiding the hepatic first-pass effect, are examples of preference of rectal route over oral one. Only two main classes of antibiotics (â-lactams and macrolides) have been studied recently after the rectal route of their administration. With the help of modern pharmaceutics and novel RDDS, higher bioavailability and controlled release of the drug have become possible. A number of antiepileptic drugs can be given rectally either for acute seizure control or in maintenance therapy. UC can be effectively treated with topical formulations and is superior to rectal corticosteroids. To suppositories most often used in Europe and the United States for their local treatments belong: bisacodyl, glycerol, mesalazine, diclofenac, glyceryl trinitrate, budesonide, prednisolone, and hydrocortisone. Suppositories applied for the treatment of systemic conditions are more numerous.

Keywords: morphine, paracetamol, methadone, mesalazine, diazepam, rectal vs oral

Abbreviations: IBD: inflammatory bowel disease, RDDS: rectal drug delivery systems, HT: hollow-type, SR-HT: sustained-release hollow-type, Alg-Na: sodium alginate, PANa: sodium poly-acrylate, PA-PANa: poly-acrylate PANa co-polymer, AEDs: antiepileptic drugs, DZP: diazepam, UC: ulcerative colitis, 5-ASA: 5-aminosalicylic acid, SE: status epilepticus, GI: gastro-intestinal

25 years ago an article on the bioavailability of drugs from suppositories has been published (1). Now, it is time to update the review and to concentrate on publications regarding suppositories bioavailability in humans in the period from 1996 up to 2019. An answer should be given to the questions, why and when suppositories are a more advantageous formulation of drug administration. A term suppository comes from a Latin word *suppositorium* which means to substitute because this formulation was supposed to substitute another rectal formulation – enema (2). The rectal route is already used clinically to provide several therapies to treat both local (constipation, IBD, hemorrhoids) and systemic conditions (pain, fever, nausea and vomiting, migraine, allergy, seizure, sedation) (3) as well as asthma and malaria. The rectal route of administration has also been in use for centuries particularly in children (4), elderly and comatose patients (2, 5) as well as in palliative care (6). The rectal drug administration is more advantageous over the oral route when swallowing may be difficult, to save enzymatically unstable drugs like insulin, to reduce the hepatic first-past metabolism, to prevent the gastric mucosa from irritant drugs and to improve topical treatments in the rectum (5).

Anatomical and physiological features

The rectum is the inferior segment of the large intestine that begins at the recto-sigmoid junction, and it ends at the anorectal junction (Fig. 1). The epithelia in the rectum and the upper GI tract are his-

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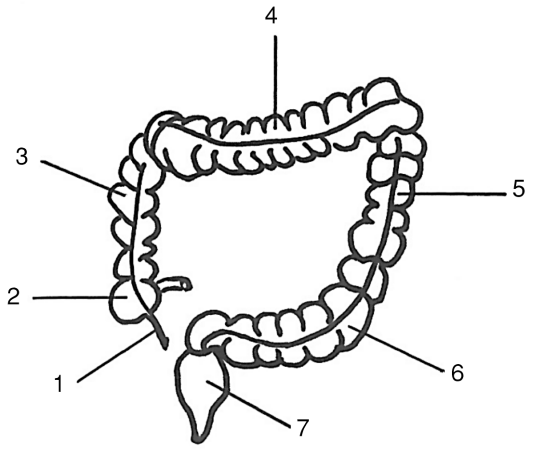

Figure 1. Anatomy of the large intestine: 1 – appendix, 2 – caecum, 3 – ascending colon, 4 – transverse colon, 5 – descending colon, 6 – sigmoid colon, 7 – rectum.

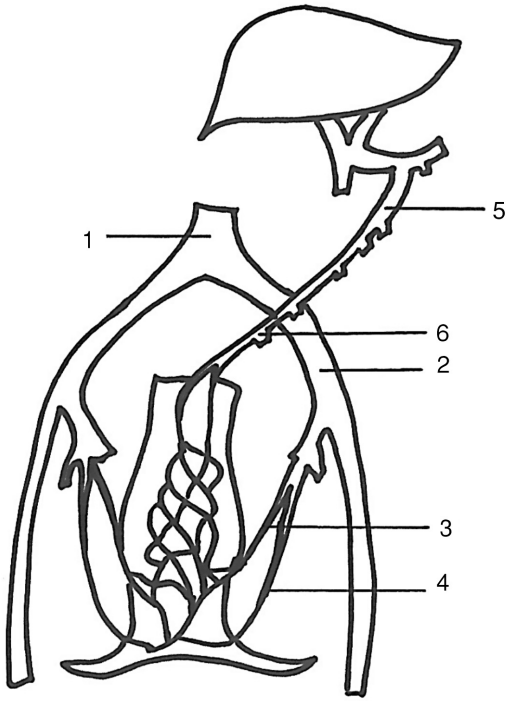

Figure 2. Systemic and portal venous drainage of the rectum: 1 – vena cava inferior (*Systemic drainage*), 2 – internal iliac vein, 3 – middle rectal vein, 4 – inferior rectal vein, 5 – inferior mesenteric vein (*Portal drainage*), 6 – superior rectal vein.

tologically similar, giving them comparable abilities to absorb drugs (7).

The venous drainage of the rectum is into the superior, middle, and inferior rectal (hemorrhoidal) veins. The superior rectal vein drains into the portal vein, which passes the blood through the liver prior to reaching the systemic circulation. In contrast, the inferior and middle rectal veins drain into the inferior vena cava and therefore directly into the systemic circulation at least partly (about 50%) avoiding the liver-first-pass effect (Fig. 2). If the formulation reaches the end of the colon, the drug can get lost in the portal circulation. To avoid it a suppository should be inserted into the lower part of the rectum, just over the anorectal junction (5).

In turn, the influence of the lymphatic vessels may contribute to the systemic absorption of highly lipophilic drugs (3). The environment in the rectum is relatively constant and static if compared to the other parts of the GI tract. The average fluid volume in the rectum is 1-3 mL of a neutral pH (7-8) (5). Pharmaceutical factors affecting bioavailability of drugs from suppositories have been published previously (1).

Avoidance of the hepatic first-pass effect in clinical practice

Morphine (1, 6, 8), 6-mercaptopurine (1), salbutamol (1, 9), methadone (10), lidocaine, and propranolol (11, 12) are examples of drugs, among others, which are used in clinics with the aim of avoiding hepatic and/or alimentary tract first-pass effects and the results are relatively positive without any use of absorption promoters. The oral availability of peptide and protein drugs is generally poor since they are poorly absorbed and easily degraded by proteolytic enzymes in the GI tract. Information was provided (1) on pharmacokinetic studies which had indicated that rectal salbutamol was more effective than the oral one. Nevertheless, oral opioids are frequently used in the chronic, palliative cancer therapy, rectal methadone absorption was faster than after the oral route (Table 1).

It can be learned from Table 1 that the pharmacological effect of methadone should come significantly earlier after its rectal administration (t_{max} = 1.3h) if compared to the oral route (t_{max} = 2.8h).

Improvement of absorption by absorption enhancers or adjuvants

A rectal route of administration or sophisticated drug delivery systems has been greatly desired for poorly absorbed drugs such as antibiotics and high molecular weights drugs (1, 2, 7, 9, 12-14). A therapeutic effect of rectally administered ampicillin was similar to that of it when administered orally.

The satisfactory rectal absorption of salbutamol sulfate is a result of avoiding the first-pass effect as well as of lipophilic base application with methylcellulose as an adjuvant. AUC of rectal salbutamol suppositories (F2) is significantly greater than the one of its oral tablets (F4) (Table 2).

The co-administration of adjuvants provides also an advantage of greater bioavailability of rectal delivery of peptide/protein drugs (13). A beneficial effect of HT suppositories is that a drug can be placed in the shell as well as in the hollow cavity, which provides rapid drug release from the core followed by sustained release from the shell (5). Aminophylline suppositories containing poly-acrylate PANa co-polymer provided significantly delayed times: t_{max} and MRT. One can draw also a conclusion that theophylline suppositories with the shell of Witepsol H15 and in addition aminophylline itself in the hollow space should provide an earlier pharmacological effect (t_{max} = 1.4h) if compared to a theophylline suppository with a gelling agent in addition in the shell (t_{max} = 3.0-5.3h) (Table 3) (15).

Suppositories selected on therapeutic indications

Suppositories most often used in Europe and the US for their local treatment include: bisacodyl,

Table 1. Pharmacokinetic and bioavailability (f) parameters (mean 95% Cl) for methadone after IV (5 mg methadone-HCl) and oral as well as rectal (10 mg methadone-HCl) administration in 7 subjects (10).

Route	t_{max} (h)	C_{max} (ng/mL)	$t_{1/2}$ (h)	AUC_{∞} (mg/mL) h	f
IV	0.04 (0.02-0.06)	93 (58-129)	32 (27-37)	587 (388-470)	1.00
Oral	2.8 (1.3-4.3)	30 (25-36)	31 (26-35)	980 (720-1240)	0.86 (0.72-0.99)
Rectal	1.3 (0.8-1.9)	32 (20-43)	32 (27-37)	901 (520-1281)	0.76 (0.69-0.82)

Table 2. Pharmacokinetic parameters of 2% salbutamol sulfate suppositories (F1; F2; F3) and 2% salbutamol commercial oral tablets (F4) in six human volunteers (mean ± SD) (9).

Parameters	F1	F2	F3	F4
AUC (ng h/mL)	40.25 ± 1.88	42.16 ± 1.55	28.00 ± 1.98	32.63 ± 1.44
C_{max} (ng/mL)	12.96 ± 2.11	14.87 ± 2.33	10.92 ± 1.42	11.51 ± 1.22
t_{max} (h)	1.91 ± 0.20	1.83 ± 0.26	2.50 ± 0.00	2.67 ± 0.24
k_a (1/h)	0.89 ± 0.02	0.90 ± 0.11	0.71 ± 0.01	0.71 ± 0.12
$t_{1/2(a)}$ (h)	0.78 ± 0.10	0.77 ± 0.02	0.98 ± 0.01	0.98 ± 0.13
K_e (1/h)	0.55 ± 0.07	0.59 ± 0.05	0.57 ± 0.11	0.55 ± 0.05

F1 - in Suppocire® (Gattefosse, France) hard fat base + 6% Eudispert® gel (EPICO, Egypt); F2 - in Witepsol® H15 (Germany) hard fat base + 3% methylcellulose gel; F3 - in Witepsol® W25 (Germany) hard fat + 3% methylcellulose gel; F4 - commercial 2% salbutamol sulfate tablets.

Table 3. Pharmacokinetic parameters of theophylline (mean ± SEM) following rectal administration of its SR-HT suppositories containing gel agent in 3-4 rabbits (15).

Type	t_{max} (h)	C_{max} (µg/mL)	AUC (h µg/mL)	MRT (h)
A-I	1.4 ± 0.4	25.1 ± 3.4	202.2 ± 8.2	6.7 ± 0.2
A-II	2.7 ± 0.7	23.9 ± 2.5	172.3 ± 18.3	6.0 ± 0.2
A-III	2.0 ± 0.0	14.0 ± 1.2	140.7 ± 11.5	7.2 ± 0.5
B-I	3.0 ± 0.6	19.8 ± 1.5	177.9 ± 5.6	6.7 ± 0.2
B-II	5.0 ± 0.0	13.9 ± 0.9	164.0 ± 7.1	7.8 ± 0.3
B-III	5.3 ± 0.5	16.6 ± 3.2	210.2 ± 6.1	8.3 ± 0.3

Type A suppositories with the shell of Witepsol H15 itself and in addition in the hollow space: I - aminophylline itself, II - aminophylline and Alg-Na, III - aminophylline and PANa; Type B suppositories with aminophylline itself in the hollow space and in the shell Witepsol H15 and a gelling agent: I - Alg-Na, II - PANa, III - PA-PANa.

glycerol, mesalazine, diclofenac, glyceryl trinitrate, budesonide, prednisolone, hydrocortisone. Suppositories used for the treatment of systemic conditions are more numerous e.g.: acetaminophen, oxycodone, ondansetron, caffeine + ergotamine tartrate, prochlorperazine, promethazine, ibuprofen, diclofenac, indomethacin, domperidone, DZP (2, 3). The rectal administration of DZP has been reported effective, as an AED, aborting and preventing seizures (16). Diclofenac rectal suppository reduces the post-operative pain e.g. after laparoscopic cholecystectomy as well as the need for opioid consumption (17). The results of some studies suggested that rectal methadone might be useful for some patients superior to opioids (9). Paracetamol has gained wide acceptance as a simple and safe antipyretic and analgesic in children if oral administration is out of consideration (18). After tonsillectomy in children, two studies have reported a relationship between paracetamol concentration and degree of postoperative pain (19, 20). Mild-to-moderate UC can be effectively treated with topical formulations (rectal suppositories, enemas, or foam) of mesalazine or steroids to reduce mucosal inflammation and alleviate symptoms. Oral mesalazine is effective and it can induce remission in active UC; however, delivery of the active agent to the inflamed colon is limited (21). For patients with distal UC, hydrocortisone or budesonide rectal foam can be an efficacious therapeutic choice (21). Rectal budesonide seems to be as effective as conventional rectal corticosteroids but seems to cause less suppression of endogenous cortisol production (22). At present, haloperidol injection is the only option available to treat delirium to patients who have difficulties with oral administration. The first-pass fraction of approximately 32% following oral administration of mianserin hydrochloride was observed in six healthy male subjects and it is maybe promising for its rectal delivery (23). Many drug classes, including antidepressants, have limited non-oral options, which makes it challenging to optimally manage neuropsychiatric conditions in patients without enteral access. There are no available rectal formulations e.g. sertraline, but that administration was successfully tried in the US (24).

CONCLUSIONS

Although the rectal clinical applications of drugs are not numerous (1.2% of the total amount of drug products sold in France in 2012) (2), they are still of importance in quite a few treatments. The rectal route of drug administration is now used clinically to deliver several therapies to treat the first local conditions. Mesalazine and other 5-ASA substances are the first-line choices in the treatment of mild-to-moderate UC. Among systemic ailments can be mentioned first of all pain. The rectal drug administration is more advantageous over the oral route to minimize the first-pass metabolism. The rectal administration is an alternative route for salbutamol, aminophylline, neuroleptics (mianserin), and some opioids (1, 11). SR-HT has offered a controlled release of the drug from the suppository base added by mucoadhesive polymers. Novel RDDS have the potential for outpatients pediatric treatment of some diseases at earlier stages before they progress to severe conditions such as pneumonia or malaria (14, 25). In conclusion, rectal administration is truly explored as a potential drug delivery system particularly for drugs that are either too irritating for the GI tract or more effective when not metabolized by the liver, and not forgetting the anorectal diseases mentioned above to be treated topically (26).

Conflict of interests

The authors declare no conflict of interest.

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