Mucosal delivery systems of antihypertensive drugs: A practical approach in general practice

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Patients who are unable to receive oral medication (p.o.) are a major problem in outpatient settings, especially in home health care systems. Mucosal administration of drugs offers an alternative to the oral route, especially when the parenteral mode cannot be used. There are three main pathways of mucosal administration: sublingual/buccal, intranasal and rectal. We discuss the possibility of mucosal delivery of antihypertensive drugs. Perindopril arginine and Amlodipine besylate are registered in the EU as orodispersible tablets for oromucosal delivery, however, they are not available in all countries. For this reason, we describe other drugs suitable for mucosal delivery: Captopril and Nitrendipine in the sublingual system and Metoprolol tartrate, Propranolol and Furosemide by the transrectal route.

Based on the published data and common clinical practice we discuss the use of mucosal delivery systems of all these antihypertensive drugs with special attention to their pharmacokinetics. We illustrate this mini-review with a case report of the prolonged-term use of mucosal delivery of sublingual Captopril and Nitrendipine combined with rectal Metoprolol tartrate and Furosemide in a patient with severe hypertension unable to receive medication p.o. This is also a report on the first human use of Furosemide-containing suppositories as well as prolonged-term transmucosal administration of these four drugs, describing a practical approach leading to successful control of severe hypertension with four antihypertensive drugs delivered via the mucosal route. The treatment was effective and without side effects; however, the long-term safety and efficacy of such therapy must be confirmed by randomized clinical trials.

Key words: antihypertensive drugs, mucosal drug delivery, metoprolol, furosemide, suppositories

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CLINICAL PROBLEM

Patients who are unable to tolerate oral medications (a.k.a. p.o.) create a major problem in general practice, esp. in home health care system. Parenteral therapy is problematic for General Practitioners and home health nurses. It is normally not available for long-term home therapy in Poland. In some countries, parenteral administration of drugs is part of the Hospital in the Home (HiTH) programs coordinated by inpatient centers, but not by outpatient general practice, esp. in Outpatient Parenteral Antimicrobial Therapy (OPAT) programs, which focus on short-term administration of antibiotics\textsuperscript{1}. Mucosal administration systems offer an alternative to p.o. or parenteral (i.v. or i.m.) routes. They can be easily used for self-administration of drugs\textsuperscript{2}. Another alternative is the transdermal system. Clonidine patches are commonly used in the US, but they are not available in the EU.

MUCOSAL ADMINISTRATION ROUTE

There are three main pathways of mucosal administration: sublingual/buccal (a.k.a. s.l.), rectal (a.k.a. p.r.) and nasal. The mucosal route is commonly used if rapid action of a drug is required and the parenteral administration cannot be used or is not acceptable\textsuperscript{3,4}. The substances absorbed from oral, nasal or rectal mucosa bypass liver first-pass metabolism. Therefore, ideal drugs for mucosal route should be given in their active form (not pro-drugs). In the case of drugs undergoing extensive hepatic inactivation, their action is more potent in comparison to p.o. administration\textsuperscript{5}. The mucin present in saliva increases drug absorption from the oral cavity\textsuperscript{6}.

Drugs for transmucosal absorption in the oral cavity can be given in the form of tablets, lozenges, films, sprays, gels, patches etc. Orally disintegrating tablets (a.k.a. ODT) also called orodispersible tablets are specially designed for drug delivery through the oral mucosa. ODT are mouth dissolvable, rapidly disintegrating tablets. These are prepared by addition of super-disintegrants i.e. crosspovidone, crosscarmellose sodium, sodium alginate, acrylic acid derivatives\textsuperscript{7,8}. The European Pharmacopoeia has used the term orodispersible tablet for tablets that disperse readily within 3 minutes in the mouth before swallowing\textsuperscript{7}. In the US, the FDA has defined ODT as “A solid dosage form containing a medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue” (ref.\textsuperscript{9}). The disintegration time for ODTs generally ranges from several seconds to about a minute\textsuperscript{9}. 
Perindopril arginine and Amlodipine besylate are registered in the EU in the form of orodispensible tablets for oromucosal delivery. However, they are not available in all EU countries. Sublingual clonidine sublingual tablets are available in the US. Currently there are no special oral mucosal forms of any hypertensive drug available in Poland. In the case of the ACE inhibitor Captopril, one of most widely used hypertensive drugs, normal p.o. tablets are used for sublingual administration in hypertensive urgencies. Such administration guarantees faster drug action. However, 1 h after administration the antihypertensive activity of sublingual Captopril is comparable to that for tablets which have been swallowed immediately. The intra nasal route has been used for the delivery of several drugs. However, there is only one report on the possibility of antihypertensive drug (timolol) administration via this route. The rectal route does not require significant patient cooperation creating a big advantage in special cases, e.g. if patients are unconscious or vomiting, as well as in the elderly, delirious or pediatric patients, when they refuse to receive p.o. drugs. Suppositories are the most common form of trans-rectal drug delivery. There are three main types of bases used to make suppositories: hydrophobic (e.g. Cacao Butter, Adeps Solidus [Witepsol]); amphipatic (e.g. Suppocire AP), or water soluble/emulsions (e.g. PEG-s/glycerol) (ref.17). In compounding pharmacies, Cacao Butter is most often used to prepare suppositories. Drugs administered per rectum also avoid liver first-passage effect but they absorption from commonly used suppositories is longer than from special sublingual tablets. Moreover, vagina can be considered also as a potential route for systemic drug delivery in women.

SELECTED ANTI-HYPERTENSIVE DRUGS FOR MUCOSAL ADMINISTRATION

According to ESC/EHC guidelines several drug categories are recommended for antihypertensive therapy including angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, calcium channel-blockers, beta-blockers, diuretics, renin-antagonists, alpha-adrenergic agonists and other central acting drugs. Here we will discuss selected drugs from the main groups of antihypertensive agents in the context of their mucosal (s.l. and p.r.) delivery.

Perindopril

Perindopril is a nonsulphydryl prodrug ester of perindoprilat. There are two types of esters available: Perindopril erbumine and Perindopril arginine. Perindopril arginine is ∼30% more stable in tablets than erbumine ester resulting in increased experience time for use of tablets to 2-3 years. Both of them require liver metabolism for activation and display first pass effect (62%) and systemic hydrolysis (38%) to perindoprilat after administration p.o. (ref.24). The half time of Perindopril is 1.2 h, however, its active metabolite perindoprilat has a much more longer reaching 30-120 h thus the antihypertonic effect of Perindopril is more then 24 h (ref.25). Use of Perindopril is well established in the treatment of patients with hypertension or heart failure and it has been used in clinical practice from several years.

Perindopril arginine is registered in some EU countries in the form of orodispensible tablets. However it is not commercially available in Poland. Pharmacological properties of ODT Perindopril arginine are the same as conventional tablets. However, Perindopril is a prodrug and needs liver metabolism for its activation to perindoprilat the peak plasma concentration of perindoprilat is achieved within 3 to 4 after s.l. administration of the ODT (ref.25). The antihypertensive effect of Perindopril arginine in after ODT delivery is exactly the same as the classic arginine Perindopril tablet, hence they can be administered once a day.

The effectiveness and compliance of Perindopril arginine ODT was assessed in the OPTIMUM program. In this post-marketing open observational study the patients with 1st and 2nd degree hypertension were included and observed for 6 months. The mean duration of disease was 7.0+/−6.2 years (median 5 years). During the observation 91.4% of patients reached target BP (<140/90 mm Hg) after 3 months of treatment. Adherence to the treatment improved significantly and patients declared that ODT form dissolves quickly and is easy to use at home or traveling.

Captopril

Captopril is a sulphydryl inhibitor of angiotensin-converting enzyme (ACE-I). It is an active compound (not a pro-drug) and in contrast to almost all ACE-I (with exception of Lisinopril) it does not require liver metabolism for its activation. Thus it is active directly after sublingual mucosal absorption. It is a short-lived drug (half-life of approximately 2 h) therefore requires TID administration. In hypertensive urgencies oral tablets Captopril are most widely used sublingually, enabling faster antihypertensive effect.

Nitrendipine

Nitrendipine is a dihydropyridine calcium channel blocker with a terminal half-life time of 8h. Usually it is administered BID (ref.25). It is inactivated in liver displaying “first pass” effect after p.o. administration. Sublingual mucosal administration of both Captopril and Nitrendipine is a well-accepted strategy in the treatment of hypertensive urgencies. In these case, the most common is sublingual Captopril administration. Sublingual Captopril acts faster within first 30 min, however, there are no differences in blood pressure reduction 1 h after drug delivery in comparison to the conventional p.o. route.

The sublingual mucosal route of Nitrendipine administration enables also fast and effective blood pressure reduction during first 45 min and lasting at least 8 h (ref.29,30). This route of Nitrendipine administration is safe and does not cause hypotension even combined with PDE-V inhibitor tildenafil. However, when Nitrendipine is administered s.l. in the form of normal oral tablets
(available in Poland) it displays slower anti-hypertensive activity than the same tablets taken p.o. (ref.42).

**Amlodipine**

Amlodipine is a third-generation dihydropyridine calcium channel blocker with very slow rate of elimination (half-life time of 40-60 h) thus it is administered once a day43. It is slowly but almost completely absorbed from the gastrointestinal tract with oral bioavailability ~60-90% (ref.53). The peak plasma concentrations are reached 4-8 h following p.o. administration. It is inactivated in liver displaying slow but extensive (90%) hepatic biodegradation to inactive metabolites after p.o. administration44.

The position of Amlodipine in the treatment of hypertension and coronary heart disease is well established by several clinical trials and meta-analyses27,45-49)

Amlodipine can also be produced in the form of various orodispersible tablets50-52. In this form Amlodipine is registered in some EU countries for transmucosal administration53. However it is not commercially available in Poland. The ODT form of Amlodipine besylate is comparatively bioequivalent to conventional tablets54,55. ODT Amlodipine was successfully tested in geriatric patients56. The main drawback of using ODT Amlodipine is its bitter taste57.

**Metoprolol**

Metoprolol is a selective β1 receptor blocker without intrinsic sympathomimetic activity that is administered BID in the form of tartrate due to its short half-life 3-4 h (ref.24). In contrast, Metoprolol succinate has a much longer half-life allowing for once daily administration58. Metoprolol is lipophilic and undergoes enzymatic inactivation in the liver displaying an extensive first-pass metabolism reducing its bioavailability ~40% after p.o. administration54,59. Rectal administration of Metoprolol tartrate has been tested both in animal models60-64. In healthy volunteers, rectal bioavailability of Metoprolol tartrate of Adeps Solidus (Witepsol)-based suppositories was comparable to that for p.o. route. Metoprolol was absorbed quickly from rectum with AUC higher than those after p.o. administration; however, this difference was not statistically significant65. In animal model the use of emulsion suppository base significantly increased the AUC (1.88-fold) as compared to the oral tablets66. The same authors reported the highest in vitro Metoprolol release for emulsion suppository bases (40-80% after 120 min) and the lower for amphipathic Suppocire AM (45% after 120 min) and lipid-based (15-30% after 120 min). Among all lipid bases the lowest drug release was observed from Cacao Butter (about 5% after 120 min). The emulsion based Metoprolol tartrate suppositories reduced BP significantly faster while the effect of lipid-based suppositories was delayed (1.5-4 h after single dose p.r. dose). However, all types of Metoprolol tartrate suppositories strongly decreased heart rate in this model67. Moreover, Adeps soludus-based suppositories containing 25 mg of Metoprolol tartrate reduced effectively heart rate (19%), systolic BP (14%) and diastolic BP (15%) also in humans 8 h after medication68. Thus, due to the liver by-pass after p.r. administration and higher bioavailability of Metoprolol tartrate, it is administered in slower-releasing suppository bases for obtaining heart rate and BP reduction without severe side effects.

**Propranolol**

Propranolol is a highly lipophilic drug nonselective beta-blocker without intrinsic sympathomimetic activity. It is administered BID or TID due to its short half-life (3-4 h) time, however the main metabolite 4-hydroxy-propranolol has a longer half-life (5.2-7.5 h) (ref.24,62,63). Propranolol displays extensive and unpredictable first-pass liver metabolism (75-85%) when administered p.o. reducing its bioavailability to 26% because it is metabolized by the liver before it can reach the circulation when taken orally64. Propranolol is almost completely absorbed from the GI tract; however, plasma concentrations attained are quite variable among individuals65. It was reported to be appropriate for buccal mucosal tablets66. Rectal administration of Propranolol has been tested both in animals66,67 and in humans70-72. In healthy volunteers, rectal bioavailability of Propranolol is better than for administration p.o. An approximately two-fold higher plasma Propranolol concentration was observed after rectal administration as compared with oral dosing due to omitting liver by pass effect. AUC indicate a significantly higher bioavailability of Propranolol administered by the rectal route73. In clinical use, rectal Propranolol was reported to be effective in a case report of paroxysmal sympathetic hyperactivity in critically ill 15-year-old Caucasian male with altered gastrointestinal tract. Because oral intake was contraindicated he was successfully administered Propranolol 40 mg per rectum every 6 h for symptomatic control74. Rectal suppositories based on highly hydrophobic bases i.e. stearic acid or bees wax are slow releasing but relative bioavailability of Propranolol from these bases is good about 83 to 87% and beta-blockade lasts during 1-9 h post administration up to about 40-50% in rabbits67. The tempo of absorption form suppositories can be increased by addition of disintegrants i.e. microcrystalline cellulose thus rapidly reaching high serum concentration corresponding to more than 95% β-blockade, while absorption and bioavailability are more than 3 fold increased in comparison to p.o. administration68. Moreover addition of cremophores i.e. lauric acid increases Propranolol absorption rate from Witepsol base69, hence dispersion of Propranolol in microspheres within suppositories results in sustained release of the drug70.

**Furosemide**

Furosemide is a commonly used loop diuretic inhibiting the Na+/K+2Cl- cotransporter in the thick ascending limb of the loop of Henle with short terminal half-life of approximately 2 h (ref.24). As it is a weak acid soluble in organic solvents Furosemide is not absorbed completely from the GI tract after p.o. administration74.75. Moreover, Furosemide displays a first pass effect by undergoing enzymatic deactivation in liver76,77. Thus, its p.o. bioavailability is 50% lower than after parenteral administration24.
The sublingual route of Furosemide has been tested in humans for pharmacokinetic studies and sublingual administration offers higher bioavailability and a stronger initial diuretic response than oral\textsuperscript{79}. However, in the published literature there are no reports of p.r. Furosemide administration in humans. However, it has been reported that Furosemide can be administered in the form of p.r. suppositories in rats\textsuperscript{79-81}. After p.r. administration the highest Furosemide release was observed from amphipatic suppository bases (i.e. Suppocire) or after addition of non-ionic surfactants (i.e. Solutol HS 15, Cremophor RH 60, Montanox 60 DF) to lipophilic bases. However a diuretic effect of Furosemide released from Lipophilic base (Witepsol H 15) was comparable to that after oral administration\textsuperscript{79}.

### PRACTICAL APPROACH

To illustrate the use of mucosal route for the delivery of multiple antihypertensive drugs in general practice settings, we describe a case of a 60-y old hypertensive woman complaining of postprandial emesis. Her past history is significant for partial gastrectomy \textit{modo Billroth II} several years ago due to peptic ulcer disease, complicated by severe gastric stenosis with debris retention within gastric stump confirmed by EGD, malabsorption syndrome (BMI 17.4 kg/m\textsuperscript{2}), and microcytic anemia. At the first visit to a new Family Physician (GP/FP) she complained of severe vomiting lasting since 3 days, making p.o. drug administration ineffective. Her blood pressure was 220/120 mmHg and heart rate was 110/min. ECG revealed sinus tachycardia with features of left ventricle hypertrophy (Sv1+Rv5/6 >>35 mm). She denied chest pain or shortness of breath. Patient refused the recommendation to be transported to regional hospital emergency unit.

Sublingual administration of Captopril 25 mg in the outpatient clinic reduced BP to 200/105 mmHg within 45 min. No further BP reduction was observed within next 30 min. After s.l. administration of a second dose of Captopril (25 mg) with Nitrendipine (10 mg) BP fell to 185/100 within next 60 min. BP reduction to 160/80 was achieved 60 min after administration of a second dose of s.l. Nitrendipine (10 mg) combined with 20 mg of Furosemide l.m. At that point patient was released home.

In the following weeks this patient received an oral combination of more than three hypertensive drugs incl. diuretics and beta-blockers in maximal registered doses without satisfactory control of blood pressure. She was still having nausea and vomiting at least 1 time daily. Her blood pressure measured in outpatient clinic was within the range 180/90 mmHg to 190/100 mmHg.

Finally, she was started on sublingual regimen of Captopril 50 mg TID and Nitrendipine 10 mg BID. On this medication regimen, her BP measured in office ranged from 170/85 to 175/90 mmHg with persistent tachycardia HR 100-120/min.

After analysis of the published literature a specific medical management protocol was developed by the medical team in order to achieve her BP goals. She has been advised to initiate in addition to her sublingual regimen an additional, unorthodox therapy through rectal administration of Metoprolol tartrate and Furosemide suppositories. The patient agreed to such therapy.

Pharmaceutical laws in Poland allow administration of compounded medications made from approved drugs,

### Table 1. Armamentarium of antihypertensive drugs used for mucosal delivery.

<table>
<thead>
<tr>
<th>Name</th>
<th>Group</th>
<th>Mucosal route</th>
<th>Pro-drug liver metabolism</th>
<th>Half-life time (h)</th>
<th>Use in human reported</th>
<th>Registration for mucosal route (EU)\textsuperscript{*}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>ACE-I</td>
<td>s.l.</td>
<td>NO inactivation</td>
<td>2</td>
<td>YES</td>
<td>NO Commonly used off label</td>
</tr>
<tr>
<td>Perindopil arginine</td>
<td>ACE-I</td>
<td>s.l./ODT</td>
<td>YES activation</td>
<td>1.2 (30-120 for Perindoprilat)</td>
<td>YES*</td>
<td></td>
</tr>
<tr>
<td>Nitrendipine</td>
<td>Ca blocker</td>
<td>s.l.</td>
<td>NO inactivation</td>
<td>8</td>
<td>YES</td>
<td>NO Documented use off label</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Ca blocker</td>
<td>s.l./ODT</td>
<td>NO Slow inactivation</td>
<td>40-60</td>
<td>YES</td>
<td>YES*</td>
</tr>
<tr>
<td>Metoprolol tartrate</td>
<td>Beta-blocker</td>
<td>p.r.</td>
<td>NO inactivation</td>
<td>3-4</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Beta-blocker</td>
<td>p.r.</td>
<td>NO inactivation</td>
<td>3-4</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Furosemide</td>
<td>Loop diuretic</td>
<td>p.r.</td>
<td>NO inactivation</td>
<td>2</td>
<td>NO</td>
<td>NO Reported in this mini-Rev</td>
</tr>
</tbody>
</table>

s.l. sublingual; p.o. per os; ODT orodispersible tablets; p.r. per rectum

\textsuperscript{*} registered in some countries in EU, available in few, not commercially available in Poland.

\textsuperscript{*}In UK Ramipril (ACE-I a prodrug converted to its active form ramiprilat with half-life time 9-18 h) available also in Oral Solution. However the low concentration of this solution (2.5 mg/5 mL) makes it not suitable for mucosal delivery\textsuperscript{82}.
even if those drugs have not been approved for a particular route of administration. This type of use of registered and authorized drugs/substances does not require any additional approval in Poland and is not considered as an experimental therapy.

The suppositories were custom-made in a compounding pharmacy from registered and commercially available tablets containing either 50 mg of Metoprolol tartrate (Metocard – Polpharma, PL) or 40 mg of Furosemide (Furosemid - Polpharma, PL). The tablets were powdered in the mortar and suspended in Cacao Butter to form suppositories. Metoprolol suppositories were administered BID while Furosemide QAM. Potassium chloride (20 mEq) was supplemented in oral water-soluble form (Kalium effervescent – Synteza, PL).

This regimen was well tolerated with no adverse effects observed. It allowed satisfactory BP and HR control. The patient reported increased diuresis after administration of Furosemide-containing suppositories. Her plasma potassium level was within normal range. No episodes of syncope or bradycardia were reported. At four subsequent visits after initiation of this regimen good BP and heart rate control was demonstrated: BP 140/80 mmHg, HR 80/min, BP 140/80 mmHg, HR 80/min; 125/70 mmHg, HR 70/min, BP 130/75 mmHg, HR 72/min. She remained under GP care for 1.5 years, while the combination of the transmucosal antihypertensive drugs was used during a total duration of 9 months, during exacerbations of her GI symptoms.

Due to the chronic progressive malabsorption syndrome with underweight (BW 43 kg, BMI 17 kg/m²) and constant microcytic anemia (RBC 4.0x10⁶/uL (3.9 - 5.2), HGB 9.8 g/dL (12 - 15.5), HCT 33% (36 - 46), MCV 82.3 fL (83 - 103), MCH 24.4 pg (28 - 34), MCHC 29.7 g/dL (32 - 36) patient was referred to a parenteral nutrition center. She finally accepted this decision after long consideration. After the referral she did not follow up with her GP outpatient clinic.

Areas of controversy

In the contrast to the well-established sublingual administration of Captopril and Nitrendipine in hypertensive urgencies, there are no published data of their long-term administration by this route. Metoprolol tartrate suppositories were tested only on very small group of patients and healthy volunteers for duration of 3 days. There are no published data on their long-term administration by this route. Moreover, there are no published reports of rectal administration of Furosemide in humans. It was only tested in animal models. Nevertheless, as we described in our case report, the only feasible alternative for such transmucosal regimen was continuous i.v. drug administration in the hospital, which was refused by our patient. ODT forms of Perindopril and Amlodipine that are registered in EU in are not available in Poland. Moreover, transdermal forms of antihypertensive drugs (such as Clonidine TTS used in the US) are not registered. Therefore, we were forced to use this unorthodox therapy exploiting mucosal delivery of four different antihypertensive drugs.

CONCLUSION

Mucosal administration systems offer a feasible alternative for long-term administration of anti hypertensive drugs. We have described a practical approach leading to a successful control of severe hypertension with four different antihypertensive drugs delivered by the mucosal route (two of them sublingual, other two transrectal). This report illustrates the practicability of such approach in the setting of general medical practice. Three of these four drugs have been used previously in humans by the mucosal route, however, only for short-term treatment of hypertensive urgencies (Captopril s.l. and Nitrendipine s.l.) or in pharmacokinetics studies (Metoprolol tartrate p.r.). They were never used for long-term control of blood pressure. We describe the first case of long-term use of those drugs. Moreover, we report the first successful clinical use of rectal delivery of Furosemide in a human.

Beside these 4 drugs used by us, also Propranolol was reported to be used in humans by mucosal route. Moreover, in the EU Perindopril and Amlodipine are registered in the form of orodispersible tablets for mucosal administration. However, unfortunately, they are not commercially available in all EU countries including Poland.

Thus, mucosal administration systems offer a viable alternative for oral and parenteral routes for administration of antihypertensive drugs in the medical general practice; however, before widespread adoption into clinical practice, randomized clinical trials of drugs administered by the transmucosal route are needed to establish long-term effects and safety of this delivery route for chronic hypertension control. If adapted, such approach can bring substantial savings to the health care systems. It will also be better accepted by patients who are reluctant to the parenteral administration of drugs.

Search strategy and selection criteria

Our research strategy was aimed at evaluating studies for mucosal administration of antihypertensive drugs. The terms “mucosal administration”, “rectal administration”, “sublingual administration”, “orodispersible tablets”, “suppositories” and “hypertension”, “antihypertensive drugs”, as well as “Metoprolol”, “Propranolol”, “Furosemide”, “Captopril”, “Nitrendipine”, “Perindopril”, “Amlodipine” were searched in PubMed (NCBI) and Google Scholar and EMA databases. Scientific articles from 1971 to 2018 were searched. All searches were up to date as of January 2018. The searching results were limited to the drugs reported to be used in humans in mucosal delivery systems at least for pharmacokinetic studies and Furosemide, which we use we first report in a practical approach of this mini-review. All language papers were reviewed. All relevant articles were reviewed. The medical team at the General Medical Practice developed the specific medical management protocol.

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