Evidence Base for some of the more unusual suggestions in the "COVID-management of EoL symptoms chart". March 2020

Morphine via the rectal route.

There appears to be some reasonable evidence that morphine injection, modified and immediate release tablets and suppositories are all absorbed rectally with almost equal (or better) efficacy to morphine pain relief given by the oral route. With regards breathlessness there is no evidence for use of the rectal route, though there seems no reason to think that morphine absorbed into the blood stream will give any regard to the route by which it arrived there. Hence, its actions once in the system should provide the same relief, which many studies have shown, of pain, breathless and to some extent anxiety. Clearly, this ignores many arguments that could be made about different "pharmacokinetics and pharmacodynamics" that may impact upon efficacy.

It seems reasonable to assume however that some morphine in the system at whatever level, via whatever route is better than none in the face of End of Life symptoms.

The best review paper appears to be that by Dr Matt Kestenbaum, who has kindly given his permission for any use of his paper.

Matthew G. Kestenbaum, MD, et al., Alternative Routes to Oral Opioid Administration in Palliative Care: A Review and Clinical Summary, *Pain Medicine*, Volume 15, Issue 7, July 2014, Pages 1129–1153, https://doi.org/10.1111/pme.12464

Leow, 1992	Randomized 48 patients undergoing minor surgery	IV, oral, rectal	Mean elimination half-lives were comparable across all three routes. Rectal administrated demonstrated a longer duration of pharmacological effects after surgery (e.g., analgesia, drowsiness, dizziness) than did oral and intravenous administrations. Authors support the use of rectal administration in patients who cannot tolerate oral administration but warn that patient acceptance may be problematic
Leow, 1995	Randomized 12 inpatients with cancer pain	IV, rectal	Oxycodone Intravenous administration was associated with faster onset of analgesia but shorter duration of pain relief as compared with rectal administration. No difference in side effects reported or observed. Inter-individual variation in rectal bioavailability may reflect differences in rectal absorption rates.
Bruera, 1995	Prospective, open double-blind, crossover 37 patients with cancer	Rectal, oral	Morphine In comparing the efficacy and safety of controlled-release morphine (every 12 hours) with SC morphine (every 4 hours for 4 days) using a 2.5:1 analgesic equivalence ratio, the authors report a small but significant difference in overall ordinal pain-intensity scores favouring the rectal morphine; however, there were no significant differences between the treatments in overall VAS scores for pain intensity, sedation, nausea, or use of rescue analgesia.
[119] Maloney, 1989	Retrospective review 39 patients with terminal illness	Rectal MS Contin®	Twenty-seven of the patients experienced equivalent analgesia with no change in side effects when the route was changed from oral to rectal. In 11 of the patients, the dose was reduced due to increased drowsiness with rectal administration.
[120] Moolenaar, 2000	Randomized, double-blind, two-way, crossover 25 patients with cancer	Rectal, oral MS Contin	In comparing the efficacy of a controlled-release suppository compared with MS Contin tablets, there were no significant differences in pain intensity scores, rescue medication use, sedation, or nausea.
[123] Babul, 1998	Double-blind, crossover 27 patients with cancer	Rectal, oral	Morphine In comparing the safety and efficacy of controlled-release suppositories vs controlled-release tablets when administered every 12 hours for 7 days each using a 1:1 analgesic equivalence ratio, comparable analgesia and side effect profiles were found.

Direct quotes from the paper.

Medications

Commercially available rectal suppositories in the United States include morphine, oxycodone, oxymorphone, and hydromorphone. Rectal suppositories or nonstandard formulations of other opioids also can be custom made by local compounding pharmacies. Tablets used for oral administration can also be administered rectally. Rectal opioids are typically dosed at the same dose as with oral administration. A handful of articles describing the use of rectal administration of hydromorphone [107,108], oxymorphone [109,110], and oxycodone [111,112] were identified. However, due to the paucity of studies, no conclusions supported by literature can be drawn for these opioids (Table 8). Small studies [113,114] and a case report [115] were also identified that evaluated the efficacy of rectal methadone compared with SC hydromorphone. The results of these studies suggested that rectal methadone might be useful for some patients. There are only a few studies that reference the prevalence of rectal administration and are summarized in Table 8.

Indications

This route is useful for patients with stable pain in whom the oral route is problematic or unavailable, such as those with nausea or vomiting or who are restricted to nothing by mouth preoperatively or postoperatively. It may also be useful for patients with dysphagia, GI obstruction, malabsorption [16,116,117], altered consciousness, or impaired neuromuscular function.

Advantages

Advantages for using rectal route include its simplicity to administer, non invasiveness, and inexpensiveness. Several studies have documented the efficacy and safety of rectal administration of controlled-release morphine [113,118–123]. For example, a double-blind, double-dummy, crossover study compared the efficacy, tolerability, and time of onset of analgesia after the administration of 10 mg of morphine via the oral and rectal routes in 34 opioid-naïve cancer patients with pain [118]. Rectal administration reduced pain intensity more rapidly than oral (10 vs 60 minutes), and pain relief lasted longer with rectal administration (180 vs 120 minutes). No significant difference was observed in the intensity of sedation, nausea, or number of vomiting episodes between the oral and rectal routes. Further studies are summarized in Table 8.

Cautions and Considerations

Given most people's perception of rectal administration, relative paucity of pharmacologic data, and the availability of multiple other routes, repeated rectal dosing is often unnecessary and should generally not be used. When needed for paediatric patients, this route can work well, especially with gel formulations, and is perhaps more widely acceptable given the use of rectal benzodiazepines for seizures [124] This route is not useful for patients who are physically unable to place the suppository, or if caregivers are unable or unwilling to do so, as some may find this route undesirable. This route should also be avoided in neutropenic and/or thrombocytopenic patients.

Other papers of note, from the Kestenbaum review.			
Yap, 2014	49 caregivers were given a 'Comfort Care Kit' (CCK) for family members entering a care of the dying pathway.	Oral, sublingual, rectal	Packs contained IV morphine sulfate given PR, IV haloperidol give S/L, PO lorazepam given S/L, Atropine eye drops given S/L, Paracetamol suppositories. 33 of the families used the packs, with sublingual use of atropine eye drops the most commonly used. Second most commonly used was morphine parenteral solution PR. 32 of the 33 caregivers found the medication worked successfully to alleviate symptoms. Only 1 caregiver took their family member to hospital for dyspnoea despite rectal morphine use – this patient passed away in hospital, all other patients enrolled passed away at home.
Walsh & Tropiano, 2002	Case study of 72 year old man with advanced prostate cancer with bony metastases.	Rectal SR Oramorph	Switched from s/c morphine to PO MS Contin (due to injection site reactions), to PO SR Oramorph (due to nausea), to use of SR Oramorph tablets PR (due to continued nausea). Dose ratio for PO to PR switch was 1:1. Tablets were placed directly into the rectum with a water-soluble lubricant. Nausea resolved and pain relief remained excellent as per PO dosing. PR administration continued for 6 months.
Kaiko, 1992	14-subject, randomized, single-dose, analytically blinded, crossover study.	Oral, Rectal	Comparison of controlled-release morphine 30-mg tablets administered orally or rectally and immediate-release morphine 30-mg suppositories. Total amounts of drug absorbed systemically were comparable, but peak blood levels from PR dosing were significantly less than PO. Rectal tablets achieved peak levels 5.4 hours after a dose, PO tablets after 2.5 hours. Rectal immediate-release suppositories peaked after just 1.1 hour and had very high peak doses (25.4ng/L vs 6.1ng/L PR tablets & 9.7ng/L PO tablets). Use of MR tablets PR demonstrated less rectal irritation than immediate-release suppositories.
Grauer, 1992	Case report of 8 patients given morphine sulfate MR rectally or vaginally.	Rectal, Vaginal	One study examined the use of 30-mg sustained-release tablets (Oramorph SR) given either rectally or vaginally in eight patients at doses between 60 and 360 mg daily. Pain control and side effects were acceptable and the routes, well tolerated.
Pannuti, 1982	Controlled cohort study of 102 patients	Oral, Rectal, Sublingual	Comparison of morphine sulfate across different routes. All routes were effective, authors state more rapid and significant pain remission for the sublingual route, although rectal was superior in physicians' assessment.

Fentanyl Patches

In short, in a review of the evidence, Simon ST et al. 2013, there appeared to be no evidence that fentanyl patches help breathlessness. There is also very scant evidence that fentanyl in any form helps breathlessness. However the review found only two randomised controlled trials, which were none conclusive. Other studies identified some possible benefit from rapid acting forms of fentanyl.

It seems reasonable in the current COVID pandemic, when supplies of injectable medications start to dwindle, that we should aim for pain relief and hope that the beneficial effects on breathlessness seen with morphine are a group effect, which may also be seen with fentanyl and oxycodone, via whatever route of administration.

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