

Rectal Suppositories in Children: 'Up' may be the Way to Go!

PEEYUSH JAIN

Department of Pediatrics, Hindu Rao Hospital and Associated NDMC Medical College, Delhi, India. peeyushjain@gmail.com

The June 1969 issue of *Indian Pediatrics* reported a double blinded study on antipyretic effects of indomethacin suppositories. The authors saw a scope for assessing indomethacin in suppository form, which had earlier mostly been used in oral form. Even though the rectal route had been used earlier for drug delivery in adults, it was never the preferred route in children – not merely because of social taboos attached with this route but also because of lack of well-planned studies on the utilization of this route in children.

In this write-up, the reader is taken down the memory lane from ancient ages to present regarding drug delivery through rectal route in children.

THE PAST

The Study: Kerawalla, *et al.* [1] from St. George's Hospital, Mumbai (then Bombay) decided to try indomethacin suppositories in children requiring antipyretic therapy. In this randomized double blind placebo controlled trial, 90 febrile children (age 4 months to 12 years having a groin temperature of at least 101°F) were administered a single dose of either indomethacin suppository (12.5 mg for children weighing <40 lbs and 25 mg for those weighing ≥40 lbs) or a placebo. The temperature was then noted at half-hour intervals for 5 hours. The median age (3 years in both groups) and morbidity profile was comparable between indomethacin and placebo groups. The mean reduction in temperature from baseline was significantly higher at all observation times ($P < 0.01$ till 1.5 hours, and $P < 0.001$ from 1.5 hours to 5 hours) in the indomethacin group in comparison with placebo group. Indomethacin suppositories were found to be well tolerated, convenient to administer, and had no side effects. The authors suggested that indomethacin suppositories should offer a useful alternative in form of medication, whenever antipyretic therapy is indicated in children in whom oral medication is not feasible. The

authors stated that they were not aware of any other published study on the use of indomethacin administered rectally in a large number of patients, and recognized the scope for indomethacin use in suppository form in febrile children where oral medication is not feasible.



Historic background and past knowledge: Enemas (or clysters) have been administered since before recorded history. Administration of drugs via the rectal route is an ancient method with evidence available in the Old Testament, and even of Hippocrates having used this route. The instruments ranging from cow horns and hollowed-out bamboo shoots to metal syringes have been used to inject laxatives, herbs, opium, turpentine, tobacco, and sometimes even oxygen or noxious chemicals. The word 'enema' is said to have originated from a Greek word meaning "I throw it in", but in fact until very late, the

preferred term was not 'enema' but 'clysters.' Legend has it that Ibis, the sacred bird of Egypt, used to take up water in its beak and then insert it into anus to clean it out. Use of clysters was thought to be so important that in Mesopotamia, a senior physician held the position of 'Keeper of Royal Rectum.' Enema were also used in ancient India as has been mentioned in ancient medical and surgical literature – Chakra-Samhita and Sushruta-Samhita. The first use of rectal route for giving nutrition was possibly by Mongols in Asia. In Greek texts also, there are references to 'Latroklysteres' meaning 'The Enema Doctor' working in Alexandria, possibly ancestors of today's Gastroenterologists [2].

With rectal route being used mainly for laxative enemas, it was realized that medicinal substances impregnated on solid bases can also be effectively given via this route. These ancient suppositories, 'magerarta', as they were called, used a silver compound as base. Subsequently, other solid supports like acorns were used as a solid base. By late 18th century, they were substituted

by cocoa butter base with opium being the substance added [2]. The word 'suppository' was first used in 1763 in the Universal Pharmacopeia of Lemery, with the word originating from Latin word 'Supponere' that means 'substitute', as it was used as a substitute to enema [3]. Rectal dosage forms presented many advantages, due to their low cost and ease of administration by untrained personnel, even in emergencies that too in unconscious and vomiting patients.

Paracetamol was the most commonly used antipyretic in suppository form. Though used mostly for adults, indomethacin was of considerable use in treating pyrexia even in 60's and 70's, albeit only in oral forms. The first literature reference on the use of pediatric rectal dosage form of indomethacin was in 1936, but the first market formulation for its pediatric suppository in France was only granted in 1981 – 12 years after publication of this study [1].

THE PRESENT

Children with emesis, those who are unable to accept oral medication or in whom oral treatment is contraindicated, are considered as problematic cases both in hospital and home-based settings. 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. The rectal route is most feasible amongst these routes [4].

The rectal route can be used for both local anorectal diseases and for systemic drug delivery. This route is useful for drugs that possess limited absorption in the upper gastrointestinal tract; are unstable to proteolytic enzymes; exhibit a high hepatic first pass effect; tend to cause gastric irritation; or are not available in oral dosage forms. The rate of rectal transmucosal absorption is affected by formulation, volume of the product, drug concentration used, site of delivery (high or low), presence of stools in rectum, pH of the rectum, and time available till absorption [4]. The drugs absorbed from lower rectum also bypass the portal venous system, and hence are free from the hepatic first pass effect, thus allowing the drug to reach the systemic circulation. However, there is great variability in the upper and lower rectal venous system thus leading to significant variation in the peak drug levels attained, and also in the time taken to achieve the same [4,5].

Rectal dosage forms as described by the European Pharmacopeia are suppositories, capsules, solutions, suspensions, ointments, creams, gels, foams and tampons. Pediatric suppositories are generally torpedo-

shaped dosage forms weighing only 1 g each to facilitate their insertion. They are generally composed of similar excipients as adult dosage forms; *i.e.*, fatty base or water-soluble bases, based on their ability to melt or dissolve in rectum at a body temperature of 37°C. The volume of the drug administered by rectal route is required to be only 1-3 mL having a neutral (7-8) pH [4,5].

Very few studies are available on use of rectal route in children under 6 years of age. The main usage of rectal dosage forms in children are analgesics, antipyretics, anti-inflammatory, antiemetics and laxatives. Non-steroidal anti-inflammatory drugs are now the most common drugs administered through rectal route, with paracetamol being the most studied drug [6]. Another common indication of rectal route is febrile seizures where diazepam, midazolam or valproate suppositories are used. Paraldehyde has often been used in liquid form when administered rectally for status epilepticus.

Indomethacin use as an antipyretic in children was limited to single dose with dearth of studies regarding its multiple or repeat doses. In 1994, it was shown that rectal indomethacin given for appendectomy reduces the amount of morphine needed to control postoperative pain in children [7]. Later, suppositories went into disrepute due to their potential adverse effects and unpredictable pharmacokinetic and pharmacodynamics. These concerns led the American Academy of Pediatrics (AAP) to discourage the use of paracetamol suppository in 2001[4]. However, a meta-analysis conducted in 2008 concluded that rectal and oral route for paracetamol are comparable with respect to temperature reduction, and the authors suggested that the AAP recommendations should be revised [8]. Recommendations for India for management of febrile children in emergency department also do not comment about rectal use of antipyretics [9].

Despite being one of enteral routes, rectal drug delivery is not as popular as the oral route for obvious socio-cultural reasons. There are many taboos that surround the proctology-related topics and play a role in the reticence of parents in allowing their children to be administered drugs through this route [4,5].

Developments with regards to suppositories are going on regarding their muco-adhesiveness, control of drug release and improvement of stability. Possibility of orodispensible drugs being used as recto-dispensible drugs is also being studied. Administration of antimalarial drugs like Mefloquine and Artesunate by rectal route has also been found to be effective. Recent publications have shown that rectal route can also be efficiently and effectively used in laboratory animals for vaccination against tuberculosis, rotavirus and Herpes. Prophylactic

strategies against HIV infection are also being studied using rectal route [10].

In order to bring about improvement in acceptability, compliance and correct utilization, efforts are needed for production, marketing, education and advocacy of the pharma industry, medical personnel and the caregivers regarding usage and benefits of rectal dosage forms.

REFERENCES

1. Kerawalla FC, Rele V, Mehta A. Antipyretic effects of indomethacin suppositories: A double-blind study. *Indian Pediatr.* 1969;6:422-25.
2. Doyle D. Perirectum: A history of enemata. *J R Coll Physicians Edinb.* 2005;35:367-70
3. Aiache JM, Renoux R, Fistre D. History of the Suppository Form. *In: Glas B, de Blaey CJ (editors), Rectal Therapy: Proceedings of the Symposium on the Advantages and Problems Encountered in Rectal Therapy.* Barcelona: JR Prous Publishers, 1984. p. 5-8.
4. No author listed. Alternative routes of drug administration-advantages and disadvantages. (Subject Review) American Academy of Pediatrics Committee on Drugs. *Pediatrics.* 1997;100:143-52.
5. Janin V, Lemagnen G, Gueroult P, Larrouture D, Tuleu C. Rectal route in 21st century to treat children. *Adv Drug Deliv Rev.* 2014;73:34-49.
6. Vernon S, Christopher B, Weightmann D. Rectal paracetamol in small children with fever. *Archives Dis Childhood.* 1979;5:469-79.
7. Sims C, Johnson CM, Bergesio R, Delfos SJ, Avraamides EA. Rectal indomethacin for analgesia after appendectomy in children. *Anaesth Intens Care.* 1994;22:272-5.
8. Goldstein LH, Berlin M, Berkovitch M, Kozer E. Effectiveness of oral vs rectal acetaminophen: A meta-analysis. *Arch Pediatr Adolesc Med.* 2008;162:1042-6.
9. Mahajan P, Batra P, Thakur N, Patel R, Rai N, Trivedi N, *et al.*; for Academic College of Emergency Experts in India (ACEE-INDIA) – INDO US Emergency and Trauma Collaborative. Consensus Guidelines on Evaluation and Management of the Febrile Child Presenting to the Emergency Department in India. *Indian Pediatr.* 2017;54:652-60.
10. Yu M, Vajdy M. Mucosal HIV transmission and vaccination strategies through oral compared with vaginal and rectal routes. *Expert Opin Biol Ther.* 2010;10:1181-95.