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Bioavailability of rectal acetaminophen in children following anorectal surgery

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ABSTRACT

Background: Acetaminophen is widely used as an analgesic and antipyretic agent in pediatrics.
Although bioavailability of rectal acetaminophen is unpredictable, rectal route is a usual and acceptable method of prescription. Major anorectal surgery may alter the normal structure of the surgical site, especially the vascular elements and the normal connections between port and systemic vessels. As a result the pharmacokinetics of rectal medications might also be altered.
Based on this hypothesis, we decided to study acetaminophen plasma concentration among children who underwent these types of surgeries to determine the pharmacokinetic of absorption, plasma concentration, safety, and efficacy of rectal acetaminophen.
Materials and methods: The study included 20 cases with previous history of pull-through procedure owing to Hirschsprung's disease (HD), 20 cases with imperforate anus (IA) reconstructive surgeries who were admitted for colostomy closure, and 20 otherwise healthy cases of inguinal herniotomy. Venus blood sampling was done 4, 8 and 12 hrs after a single loading dose of rectal acetaminophen (40 mg/kg), and plasma acetaminophen concentration was compared between groups.
Results: Mean serum acetaminophen levels of the HD group were significantly higher than those of the herniotomy group (36.3 ± 6.79, 27.4 ± 8.42, 16.8 ± 7.62 versus 25.9 ± 9.12, 16.7 ± 6.74, 8.1 ± 5.79 (μg/ml) at 4, 8 and 12 hrs after drug administration and $P < 0.05$). The IA group had higher concentrations of plasma acetaminophen compared to the herniotomy group; however, the p values were not statistically significant. (31.4 ± 10.39, 21.5 ± 9.12, 13.3 ± 6.79 versus 25.9 ± 9.12, 16.7 ± 6.74, 8.1 ± 5.79 (μg/ml) at 4, 8 and 12 hrs after drug administration). Serum concentrations of acetaminophen in IA and HD patients were above the therapeutic range four hours after administering the loading dose (31.4 ± 10.39 and 36.3 ± 6.79 versus 5–20 μg/ml).
Conclusion: Bioavailability of rectal acetaminophen might get altered after major anorectal surgery in children. Rectal acetaminophen should be administered with special caution among infants with history of anorectal operations. Repeated dose of rectal acetaminophen may cause the drug blood concentration to reach toxic levels in these patients.
Type of study: Prospective comparative study.
Level of evidence: Level II.

Acetaminophen is the most commonly used antipyretic agent in pediatrics that may be administered orally, per rectum or intravenously [1–3].

It is one of the most common over the counter medications that is used for control of fever and pain in children [3]. Recommended dose of acetaminophen is 10–20 mg/kg/dose every 4 h, although some authors have suggested a single high dose of rectal acetaminophen as a simple and effective strategy for pain relief [4]. Transrectal administration of acetaminophen is commonly used for postoperative pain relief or fever control in pediatrics [1]. Advantages of rectal administration include easier application, especially in postoperative cases that cannot ingest the medication, and a more persistent action that allows longer intervals between medication doses [5].

Pharmacokinetic studies on bioavailability of rectal acetaminophen have shown variations in the plasma level of acetaminophen following a single loading dose among different patients. These variations may be because of difference in the volume and mucosal contact of rectum

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with the medication, and differences in rectal venous drainage among individuals [1,4]. We hypothesize that owing to alterations in rectal vasculature after major anorectal surgeries, there may be changes in the bioavailability of transrectal medications.

Unpredictable bioavailability of rectal acetaminophen raises concerns about high drug plasma levels and hepatotoxicity by administration of multiple doses in small children [4]. On the other hand, some articles recommend higher doses of rectal acetaminophen to achieve therapeutic levels [1,5].

Observing neovascularization and varicose vein formation around the ostomy sites, similar to what is observed in portosystemic shunt in portal hypertension cases, gave us the inspiration for this study.

Since a similar phenomenon might happen after major anorectal surgeries, the absorption of transrectal drugs might get altered. To test this hypothesis, we designed this study to determine the bioavailability, safety and efficacy of rectal administration of acetaminophen in children with a history of previous major anorectal surgery.

1. Materials and method

In this prospective nonrandomized clinical comparative study from 2014 to 2018 that was performed in pediatric surgery department of Dr. Sheikh and Akbar pediatric children's hospitals with collaboration of toxicology department of Emam Reza hospital, Mashhad University of Medical Sciences, Iran, patients who met the inclusion criteria were allocated to 3 different groups. General inclusion criteria consisted of children between five and fifteen months admitted for elective surgery whose parents gave informed consent for the trial protocol.

The first group included 20 patients with history of pull-through operation for Hirschsprung's disease (HD) who were admitted again for elective interventions such as anorectal examination under anesthesia, fecal disimpaction or other minor surgeries.

The second group consisted of 20 patients with history of anorectal reconstructive surgery for anorectal malformations (Imperforate anus) who were admitted for closure of colostomy during the study timeline.

The third group included 20 otherwise healthy infants and toddlers who were admitted for elective inguinal herniotomy without any previous anomaly or surgical intervention in anorectal region.

Exclusion criteria were: hepatic disease or dysfunction, renal failure, vascular diseases such as portal hypertension, history of umbilical catheterization, anorectal trauma or other anorectal regional problems (e.g. perianal abscess), use of acetaminophen during the week before admission, history of acetaminophen allergy or intolerance, failure to thrive (under 50% percentile of normal weight for age) and known cases of enzyme deficiency. Also patients with hemoglobin less than 10 mg/dl in the preoperative complete blood count or those with significant intraoperative bleeding were excluded from the trial owing to blood sampling restrictions dictated by the ethics committee.

The purpose of study, the benefits of determining medication bioavailability, and the need for three times blood sampling were explained to all parents. Those guardians who accepted to enter the trial signed an informed consent.

To avoid the risk of anesthesia related hepatotoxicity, general anesthesia was induced with remifentanil and propofol in all patients. Digital rectal examination was performed at the end of the surgical procedure to make sure there was no bulky fecal material that could interfere with acceptance and absorption of suppositories. All patients were given a single loading dose of 40 mg/kg of transrectal acetaminophen at the end of operation in the form of 125 mg, 250 mg and 500 mg Paracetamol® suppositories (Hexal, Germany).To apply the calculated dose with the available suppositories we used the lower closer available dose of suppository.

In case of notable pain in the postoperative period, 1 mg/kg/dose of meperidine was given for pain control [6,7].

One milliliter of venous blood sample was taken 4, 8 and 12 hrs after administration of acetaminophen suppository. Plasma acetaminophen concentration was measured by spectrophotometry using Perkin Elmer 550SE (UV–Visible, USA), with the accuracy of 0.01 mg/dl or 0.1 μM/ml. Plasma acetaminophen level was finally compared among the three groups of patients and the results were analyzed by SPSS Ver. 25 (IBM Inc. Armonk, NY) using analysis of variance (ANOVA) with Tukey post hoc test. P-value less than 0.05 was considered significant.

Those patients who left the study during the trial (incomplete blood sampling) were excluded and substituted with new patients.

2. Results

Patients' age, gender, weight, past medical history, indication of operation and other general data are shown in Table 1. Patients in HD group were older than the other two groups so the mean weight and acetaminophen loading dose were also larger in this group. Gender distribution was almost the same among all groups.

Loading dose deviation was measured as the difference between the applied suppository dosage and the calculated loading dose. Applied acetaminophen dose was less than calculated dose in most cases but these variations were small and negligible compared to the total dose and the difference between groups was not significant.

The need for opioid administration was higher in herniotomy group but the difference was not significant. Operation time was significantly longer in patients who underwent colostomy closure in the ARM group compared to other patients.

Plasma acetaminophen concentration at 4, 8 and 12 h after the suppository insertion is summarized and compared between the groups in Table 2.

Plasma acetaminophen levels showed significant difference between the groups in all 3 samples at 4, 8 and 12 h after application of the suppository. We used Tukey post hoc test to search for differences between the groups.

At 4 h after the loading dose, mean acetaminophen level in the HD group was significantly higher than the herniotomy group (36.3 ± 6.79 versus 25.9 ± 9.12 μg/ml, $P = 0.002$). Although acetaminophen blood concentration was higher in the ARM group compared to the hernia group (31.4 ± 10.39 versus 25.9 ± 9.12), the P value was not statistically significant ($P = 0.137$). Acetaminophen levels were not different between the ARM and HD groups at 4 h ($p = 0.192$).

At the second blood sampling (8 h after the loading dose) mean acetaminophen level in the HD group was significantly higher than the herniotomy cases (27.4 ± 8.42 versus 16.7 ± 6.74 μg/ml) ($P < 0.001$), while the difference between the herniotomy group and the ARM patients was not statistically significant. ($P = 0.159$) (Table 2). Comparing the ARM and the HD groups, Tukey post hoc p value was 0.069.

The third blood sampling (12 h after the loading dose) also revealed significantly higher mean acetaminophen level in the HD group compared to the herniotomy cases ($P < 0.001$) (Table 2). The difference between the herniotomy and the ARM groups was not statistically significant ($P = 0.051$). Comparing the ARM and the HD groups, Tukey post hoc p value was 0.240.

We compared patients with anorectal surgery (HD or ARM) to those without history of anorectal surgery (hernia). Serum acetaminophen levels, 4 h after the loading dose were 33.9 ± 9.02 μg/ml and 25.9 ± 9.12 μg/ml in the two groups respectively. (independent samples t test; p value = 0.002).

Plasma concentrations after 8 and 12 h were 24.4 ± 9.16 μg/ml and 15.0 ± 7.34 μg/ml in patients with history of major reconstructive surgeries, compared with 16.7 ± 6.74 μg/ml and 8.1 ± 5.79 μg/ml in the hernia group (independent samples t test; p values = 0.001 and 0.001 respectively).

3. Discussion

Rectal acetaminophen in the form of suppository is considered a useful route for administration of acetaminophen when oral route is

Table 1
Comparison of general variables among three study groups.

General variables	Herniotomy group ($N = 20$)	ARM group ($N = 20$)	Hirschsprung group ($N = 20$)	P value
Sex (male/female)	13/7	9/11	11/9	0.446
Age (months)	7.9 ± 6.7	6.0 ± 3.43	16.1 ± 14.14	0.002
Weight (g)	6146 ± 3951	5470 ± 2298	9175 ± 4104	0.004
Duration of operation (min)	16.5 ± 6.64	54.2 ± 15.7	25.7 ± 15.15	0.001
Acetaminophen loading dose (mg)[a]	245.8 ± 158.1	218.8 ± 91.9	367.1 ± 164.2	0.004
Mean dose deviation (mg)	−3.1 ± 17.4	−9.3 ± 16.5	−4.7 ± 12.3	0.427
Need for opioid	6 (30%)	2 (10%)	3 (15%)	0.235

[a] The dose was calculated based on 40 mg/kg. The actual dose differs between groups owing to difference in patients' weight.

impractical such as in the early postoperative period when the patient is not fully conscious or eating is not allowed [2]. Transrectal administration of medications in infants is a common practice and is well accepted by parents [2,8].

Bioavailability of rectal acetaminophen is supposed to be 80% of the oral dose and the clinical effects are often delayed but more prolonged [9].

Several authors have suggested using higher doses of rectal acetaminophen compared to the oral dose considering variations in bioavailability of acetaminophen through the rectal route [1,5]. Unpredictable bioavailability of rectal acetaminophen might be because of variations in the absorptive capacity of mucosa of both rectum and anal canal, rectal condition (emptiness, PH), and the different roles of the upper or lower rectum in drug absorption [1]. Regional venous drainage plays an important role since lower rectum is considered as one of the physiological portocaval shunts [10]. The venous plexus of anal canal and lower rectum is drained directly into systemic veins while the venous return of upper rectum drains into the portal system, so medications which are absorbed through the latter will be affected by the hepatic first pass [10,11]. In this light, there is a possibility that the altered vascular anatomy of the colorectal region in infants with history of ARM or HD reconstructive surgeries could affect the bioavailability of transrectal medications. This hypothesis was the basis for performing the current study to evaluate the efficacy and safety of rectal acetaminophen in children with previous anorectal operations.

Accepted serum concentration of acetaminophen as an antipyretic is 5–20 μg/ml and seems to be higher for analgesic effects [5], although the clinical effects of acetaminophen correlate more with the cerebrospinal concentration of the medication than its blood level [10].

Slow drug clearance [12] and lower level of hepatic enzymatic activity, for instance the lower levels of cytochrome p-450 in infants, have raised concerns about the possibility of drug toxicity induced by repeated doses of acetaminophen in this group of patients [4,9,11]. Liver is the main organ damaged by acetaminophen overdose, since it metabolizes the medication [13]. Acetaminophen blood concentration greater than 120 μg/ml is defined as drug overdose and is close to toxic levels [4]. Acetaminophen toxicity is the leading cause of acute liver failure in the United States and is the second cause of liver failure requiring transplantation. Acetaminophen plasma level greater than 140–150 μg/mL four hours after administration is considered an indication for starting treatment with N acetyl cysteine to prevent hepatic damage [13].

In this study, we observed significantly higher than therapeutic range levels of acetaminophen in blood samples obtained from ARM and HD patients four hours after rectal administration. Acetaminophen blood levels remained in the therapeutic range even eight hours after administration. Since these patients usually receive repeated doses of rectal acetaminophen, there may be an increased risk of drug overdose. Higher and persistent levels of serum acetaminophen concentration in the ARM and HD groups may have caused a more effective and durable analgesia that resulted in less opioid injections in these patients compared to the herniotomy group.

The exact mechanism of increase in the bioavailability of acetaminophen in these patients is not clear. We propose that anorectal operations, and reconstruction of perineum and pelvic floor might alter the regional vascular anatomy that could result in a new venous drainage pattern. This regional new vascular pattern may increase the bioavailability and durability of rectal acetaminophen, such that it necessitates special caution in calculating the loading dose and intervals of drug administration via the rectal route among these infants. Although the focus of this study was on the bioavailability of acetaminophen after major anorectal surgeries, findings of this study may also apply to other transrectally administered medications in these children, such as benzodiazepines, barbiturates or NSAIDS. Further studies are needed in this regard.

Transcolostomy route is also used for administration of suppository laxatives, opioid analgesics, and nonopioid analgesics such as acetaminophen. The pharmacokinetics of drugs in this method is variable and not reported in detail [14].

This work has been a pilot study, and its results need to be approved in a larger multicenter study.

4. Conclusion

Major anorectal reconstructive surgeries such as anorectoplasty in imperforate anus or pull-through operation in HD can alter the bioavailability of transrectal acetaminophen. The higher blood concentration of the drug after rectal administration should be kept in mind, as repeated doses may reach toxic levels, especially among infants. Based on the results of this study, we suggest lower doses of rectal acetaminophen in infants and children with history of major anorectal reconstructive surgeries and encourage other routes of administration in these patients.

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Table 2
Serum acetaminophen concentration in serial blood samplings after acetaminophen suppository insertion (40 mg/kg) among three study groups.

Serum paracetamol level (μg/ml)	Herniotomy group ($N = 20$)	ARM group ($N = 20$)	Hirschsprung group ($N = 20$)	ANOVA P value HD/herniotomy	(HD/ARM) group ($N = 40$)	T test P value (ARM, HD/hernia)
At 4 h after loading	25.9 ± 9.12	31.4 ± 10.39	36.3 ± 6.79	0.002	33.9 ± 9.02	0.002
At 8 h after loading	16.7 ± 6.74	21.5 ± 9.12	27.4 ± 8.42	0.001	24.4 ± 9.16	0.001
At 12 h after loading	8.1 ± 5.79	13.3 ± 6.79	16.8 ± 7.62	0.001	15.0 ± 7.34	0.001

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