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Regular Article

Absence of Excretion of the Active Moiety of Bisacodyl and Sodium Picosulfate into Human Breast Milk: an Open-label, Parallel-group, Multiple-dose Study in Healthy Lactating Women

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Summary: The aim of this study was to determine whether administration of the prodrugs bisacodyl (Bisa) and sodium picosulfate (SPS) leads to excretion of their common active metabolite, bis-(*p*-hydroxyphenyl)-pyridyl-2-methane (BHPM), in breast milk. Two groups of 8 healthy lactating women who had stopped breast feeding received multiple doses of Bisa or SPS. Plasma, urine, and breast milk were collected and concentrations of free and total BHPM were determined using validated liquid chromatography/mass spectrometry methods. BHPM remained below the limits of detection in breast milk following single- and multiple-dose administration of Bisa and SPS. First, BHPM plasma concentrations were observed after a lag time of about 3 to 4 h and 4 to 5 h following Bisa and SPS administration, respectively. C_{max} was attained approximately 5 h after dosing of Bisa and 9 h after dosing of SPS. BHPM did not accumulate after multiple administrations of Bisa and only slightly accumulated following multiple doses of SPS. About 12% and 13% of Bisa and SPS was excreted as BHPM into urine at steady state. BHPM, the active moiety of Bisa and SPS, was not excreted into human breast milk. Hence, use of Bisa or SPS to treat constipation of breast-feeding women is considered well tolerated with regard to exposing infants to BHPM *via* breast milk.

Keywords: bisacodyl; sodium picosulfate; pharmacokinetics; lactating women; breast milk; constipation; laxative

Introduction

Constipation is one of the most commonly occurring disorders and has an incidence of up to 27% in otherwise healthy individuals.[1–7] In a multinational survey, the incidence of self-reported constipation ranged from 5% in Germany to 18% in the US.[8] Epidemiology studies have also reported that constipation occurs in all age groups and has generally a higher incidence among women than men.[2,4,7,9–11] Constipation has multiple symptoms, including infrequent bowel movements, passing hard stool, straining, sensing that bowel movements are incomplete or unsatisfactory, and having the need for manual maneuvers to facilitate bowel movements.[1]

Possibly due to its common occurrence, its episodic symptom pattern, and generally understood symptoms, most individuals who suffer from constipation self-diagnose and self-manage the condition.[6–8] Hence, treatment consists primarily of life-style changes (mainly improving diet and increasing intake of liquids) and use of non-prescription

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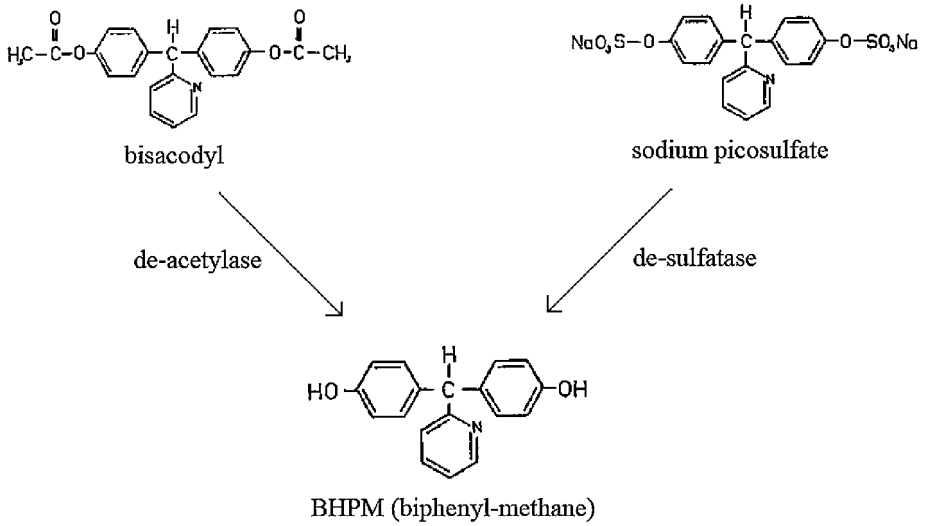

Fig. 1. Metabolism of bisacodyl (left) and sodium picosulfate (right) to yield the active drug

laxatives which are widely available. These agents, when indicated for short-term use, are generally effective, and for most individuals provide symptomatic relief within hours or a few days of treatment. Common non-prescription laxatives include bulk fiber, osmotic agents, surfactant agents, and stimulant laxatives. The latter increase propulsive motility in the colon to promote defecation and thereby reduce residence time of stool in the colon.[12)]

Since constipation can affect people of all ages, it is also common among women during pregnancy and lactation. Hence, it is important to understand the pharmacokinetics of laxatives in women when breast feeding and the potential for excretion of the drug into breast milk.

Bisacodyl (Dulcolax) and sodium picosulfate (Laxoberal) are commonly used stimulant laxatives. Both compounds are prodrugs, and as such have no intrinsic laxative activity themselves. However, as shown in **Figure 1**, both are converted within the gut into the same active metabolite, bis-(*p*-hydroxyphenyl)-pyridyl-2-methane (BHPM), which causes the desired laxative effect.[13,14)] As shown in the figure, conversion of bisacodyl is mediated by the action of endogenous deacetylase enzymes found on the mucosa of the small intestine and colon, whereas picosulfate is converted by the action of desulfatase enzymes localized on colonic microflora. Following conversion, BHPM partly reaches the systemic circulation and undergoes enterohepatic clearance as its glucuronide salt;[13,15,16)] neither sodium picosulfate nor bisacodyl is absorbed from the gut to a significant degree.[16,18,19,20)] To ensure that bisacodyl is activated to BHPM in the colon and to limit the absorption of bisacodyl, the substance, if administered orally, is taken as an enteric coated tablet that does not disintegrate until it enters the colon.

This study evaluated the single-dose and steady-state pharmacokinetics of BHPM following multiple oral dosing of bisacodyl and sodium picosulfate (10 mg once daily) and its potential for excretion into breast milk. Bisacodyl and sodium picosulfate are widely available as non-prescription laxatives. Labeling allows dosing of 5 to 10 mg daily. Hence the selection of a 10-mg dose is consistent with label usage recommendations, reflecting the highest approved dose.

Methods

This open-label, parallel-group treatment study was conducted at a single site, Xendo Drug Development, BV, Groningen, The Netherlands. Sixteen healthy, postpartum lactating women aged 23–38 years were included. Eight women received enteric coated bisacodyl tablets (as Dulcolax) and 8 received sodium picosulfate (Laxoberal) as a liquid preparation. Inclusion criteria required women aged 18 to 50 years who had been breast feeding their infant for at least 14 days, had stopped breast feeding prior to starting the study, produced at least 200 mL of breast milk per day (verified during screening), had a BMI $\leq 35\,kg/m^2$, had a negative pregnancy test, and were using an acceptable method of contraception. All subjects gave informed consent. Exclusion criteria included clinically relevant findings observed during the screening visit or a medical history that could interfere with the participation or safety of subjects. Use of other medications, with the exception of acetaminophen and hormonal therapy, was contraindicated. Smoking was limited to no more than 10 cigarettes/day.

The primary objective of the study was to determine whether multiple oral administration of bisacodyl or sodium picosulfate at a dose of 10 mg/day leads to significant excretion of their common active metabolite, BHPM, into breast milk. As a secondary objective, the pharmacokinetics of BHPM in plasma, urine, and milk were investigated. The pharmacokinetic parameters of BHPM were calculated after the first and after the seventh dose (day 8) of bisacodyl and

sodium picosulfate using WinNonlin 5.2. Safety was assessed by the reporting of any adverse events during the whole study as well as by the vital signs and the 12-lead ECG and laboratory test results recorded at screening and on the last visit day.

The study design required subjects to visit the test site only for the initial screening and end-of-study visits. Supervised daily drug administrations and the pharmacokinetic procedures could be conducted at the subjects' homes. Screening to determine eligibility was conducted between 22 and 2 days prior to initiating treatment. Two days before initiating treatment, subjects were instructed on how to complete their daily diaries, use the pump to collect breast milk, and on the collection and storage of urine and milk samples. During the 24-h period prior to initiating treatment (day −1), subjects collected at least 200 mL of breast milk, which served as a baseline sample; subjects who did not produce this volume were not eligible to enter the treatment phase of the trial. Subjects received either 10 mg of bisacodyl (two 5-mg Dulcolax enteric coated tablets) or 10 mg of sodium picosulfate (20 drops of Laxoberal liquid) in the morning of day 1 and days 3–8 of the study (no drug was administered on day 2). A standardized breakfast was consumed 1 h after dosing.

Blood samples (5 mL) were obtained from a forearm vein 5 min prior to and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 24, 28, 32, and 48 h after dosing on days 1 and 8. In addition, a single 5-mL blood sample was obtained prior to dosing in the morning of days 3, 4, 5, 6, and 7. Blood was collected, centrifuged (10 min at 2000–4000 *g*) within 30 min, and stored on ice. Two 1-mL aliquots of plasma were transferred into cryogenic vials, stored at −70°C at the research facility and shipped on dry ice to the analytical laboratory.

A single baseline urine sample was obtained at least 2 h prior to dosing on day 1. Subsequently, all voided urine was collected for the following time intervals after the first dose (day 1) and the last dose (day 8): 0–4, 4–8, 8–12, 12–24, and 24–48 h. Urine was collected in pre-weighed containers and stored by subjects until transfer to the research center. Urine samples were homogenized, and two 3-mL aliquots were transferred into cryogenic vials and stored at −70°C until shipment on dry ice to the analytical laboratory.

All breast milk (minimal volume 10 mL each collection; collection time recorded) was collected from day −1 until day 9; samples were stored under refrigeration until transfer to the study center. Following homogenization, two 3.0-mL aliquots were transferred to cryogenic vials and stored at −70°C until shipment on dry ice to the analytical laboratory.

Concentrations of free and total (free + glucuronidated) bis-(*p*-hydroxyphenyl)-pyridyl-2-methane (BHPM) in plasma, urine, and breast milk were determined using validated high performance liquid chromatographic methods coupled to tandem mass spectrometry (HPLC-MS/MS) with a lower limit of detection of 1 ng/mL in all matrices at AAIPharma Deutschland GmbH & Co. KG, Neu-Ulm, Germany. In the following, free BHPM describes unconjugated BHPM, whereas total BHPM refers to the sum of glucuronidated and nonglucuronidated BHPM.

Table 1. Demographics of treated subjects

	Bisacodyl group	Picosulfate group	All subjects
Number of subjects	8	8	16
Age [years] (mean ± SD)	30.6 ± 2.5	31.8 ± 4.3	31.2 ± 3.5
Height [cm] (mean ± SD)	170.9 ± 5.1	170.4 ± 7.2	170.6 ± 6.0
Weight [kg] (mean ± SD)	72.4 ± 6.6	71.5 ± 18.9	71.9 ± 13.7
BMI [kg/m^2] (mean ± SD)	24.8 ± 1.7	24.4 ± 4.8	24.6 ± 3.5
Smoking status (*n*):			
Never	5	2	7
Ex-smoker	1	4	5
Current	2	2	4

Results

Sixteen lactating women, mean (± SD) age 31.2 ± 3.5 years (range 23 to 38 years), were included; 8 subjects received bisacodyl and 8 received sodium picosulfate. All subjects were Caucasian and all completed the trial. The demographics of the subjects are shown in **Table 1**. Body weight ranged from 52 to 84 kg, with the exception of one subject who had a body weight of 111 kg.

Free and total BHPM in breast milk after oral administration of 10 mg bisacodyl or 10 mg sodium picosulfate: Levels of both free and total BHPM excreted into breast milk remained below the limits of detection (1 ng/mL) in all subjects after administration of either bisacodyl or sodium picosulfate once daily (10 mg/day) on all study days. Thus no pharmacokinetic parameters were calculated for breast milk.

Pharmacokinetics of BHPM after oral administration of 10 mg bisacodyl: Free BHPM could not be measured in plasma; it was measured only at low concentrations in the urine of a very few subjects. Therefore pharmacokinetic parameters were calculated based on total BHPM concentrations (sum of free BHPM and BHPM glucuronides) only. Consequently, the parameters presented for total BHPM can be seen as surrogates for the pharmacokinetic characteristics of BHPM glucuronide.

Single-dose and steady-state pharmacokinetic parameters are summarized in **Tables 2** and **3**, and plasma concentration profiles (mean ± SD) for total BHPM (free + glucuronidated BHPM) over the 8 days of the study are shown in **Figure 2**. Following dosing of bisacodyl on day 1, total BHPM in plasma increased rapidly after a lag time of about 4 h; a similar effect was observed at steady state with a lag time of about 3 h. C_{max} ranged from 20.5 to 195 ng/mL (geometric mean, 64.6 ng/mL) and 19.7 to 118 ng/mL (geometric mean, 60.7 ng/mL) on day 1 and day 8 respectively, and was attained about 4–5 h after dosing (median t_{max}). Geometric mean AUC after single dosing

Table 2. Noncompartmental pharmacokinetic parameters for total BHPM following a single oral 10-mg dose of bisacodyl or sodium picosulfate

	Bisacodyl, 10 mg ($n = 8$)		Sodium picosulfate, 10 mg ($n = 8$)	
	gMean	gCV (%)	gMean	gCV (%)
AUC_{∞} [ng-h/mL]	471	54.1	209	49.7
C_{max} [ng/mL]	64.6	93.3	18.1	41.2
t_{max} [h][a]	5.0	3.0–24.0	9.0	6.0–10.0
$t_{1/2}$ [h]	7.7	41.1	7.3	38.6
MRT_{po} [h]	13.8	44.0	15.7	19.7
CL/F [mL/min]	272	54.1	459	49.7
V_z/F [L]	181	78.0	291	43.7
$CL_{R,0-24}$ [mL/min]	47.8	12.9	52.6	28.1

Results are presented as geometric means (gMean) and geometric coefficients of variation (gCV).
[a]t_{max} is reported as median and range.
MRT_{po}, mean residence time after oral administration. V_z/F, apparent volume of distribution.

Table 3. Noncompartmental pharmacokinetic parameters for total BHPM after multiple 10 mg doses of bisacodyl or sodium picosulfate

	Bisacodyl, 10 mg ($n = 8$)		Sodium picosulfate, 10 mg ($n = 8$)	
	gMean	gCV (%)	gMean	gCV (%)
$AUC_{\tau,ss}$ [ng·h/mL]	311	75.3	275	25.1
$C_{max,ss}$ [ng/mL]	60.7	64.4	21.3	24.8
$t_{max,ss}$ [h][a]	4.0	3.0–8.0	9.0	0.0–24.0
$t_{1/2,ss}$ [h]	8.1	63.7	10.0	37.3
$R_{Ac(AUC)}$	0.80	35.5	1.59	50.5
$R_{Ac(Cmax)}$	0.94	65.7	1.18	44.7
$MRT_{po,ss}$ [h]	11.9	31.4	22.3	36.3
CL/F_{ss} [mL/min]	412	75.3	349	25.1
V_z/F_{ss} [L]	289	85.2	300	50.1
$CL_{R,ss}$ [mL/min]	50.0	15.6	46.2	26.9

Results are presented as geometric means (gMean) and geometric coefficients of variation (gCV).
[a]$t_{max,ss}$ is reported as median and range.

(AUC_{∞}) and at steady state ($AUC_{\tau,ss}$) were 471 and 311 ng·h/mL, respectively. BHPM did not accumulate in plasma following daily administration of 10 mg bisacodyl. Geometric mean accumulation ratios (R_{Ac}) based on C_{max} and AUC were 0.94 and 0.80, respectively.

In general, moderate to high inter-individual variability was observed for drug plasma concentrations measured at all sampling time points. Geometric mean trough concentrations of total BHPM before administrations on days 4 to 8 ranged from 3.0 to 3.6 ng/mL. These data suggest that the steady state for bisacodyl was achieved on the fifth day of the study at the latest. As shown in **Tables 2** and **3**, geometric mean terminal half lives following single (day 1)

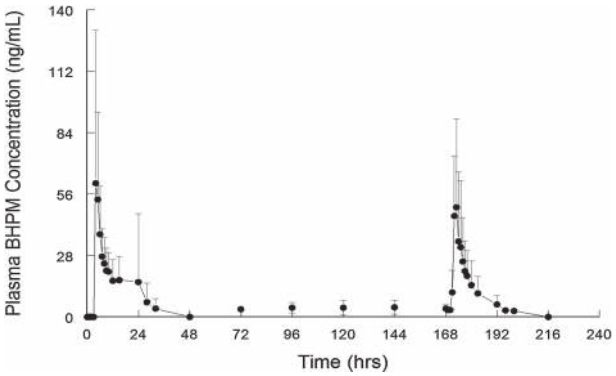

Fig. 2. Mean (± SD) plasma concentration-time profile of total BHPM following multiple oral doses (day 1 and day 3 to 8) of 10 mg bisacodyl

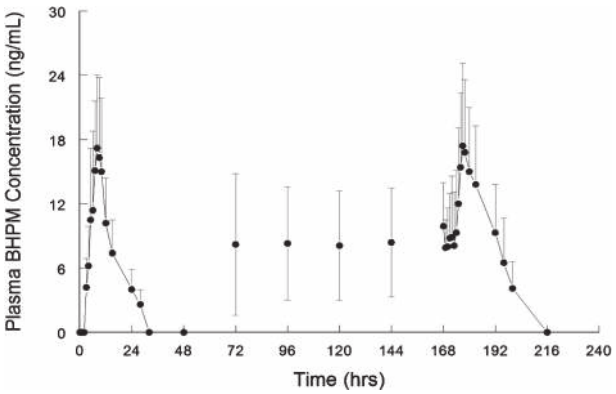

Fig. 3. Mean (± SD) plasma concentration-time profile of total BHPM following multiple oral doses (day 1 and day 3 to 8) of 10 mg sodium picosulfate

($t_{1/2}$) and steady-state dosing (day 8, $t_{1/2,ss}$) were similar. The apparent plasma clearance (CL/F, CL/F_{ss}) was low: 272 and 412 mL/min after a single dose and at steady state, respectively. The volume of distribution was high, *i.e.*, 181 L after a single dose and 289 L at steady state.

Pharmacokinetics of BHPM after oral administration of 10 mg sodium picosulfate: Single-dose and steady-state pharmacokinetic parameters are summarized in **Tables 2** and **3**, and plasma concentration profiles (mean ± SD) for total BHPM (free + glucuronidated BHPM) over the 8 days of the study are shown in **Figure 3**. Just as for bisacodyl, there was a lag time of 3 to 4 h before observing a detectable level of plasma BHPM following oral administration of sodium picosulfate. Median t_{max} after single and multiple administrations of sodium picosulfate was 9.0 h, considerably longer than that observed with bisacodyl. C_{max} for sodium picosulfate ranged from 9.2 to 29.7 ng/mL (geometric mean, 18.1 ng/mL) and 13.0 to 27.1 ng/mL (geometric mean, 21.3 ng/mL) after single and multiple dosing, respectively. Geometric mean AUCs after single dosing (AUC_{∞}) and at steady state ($AUC_{\tau,ss}$) were 209 and 275 ng·h/mL, respectively. There may be slight accumu-

lation of BHPM after multiple sodium picosulfate administration; R_{Ac} for sodium picosulfate based on C_{max} and AUC were 1.18 and 1.59, respectively. Geometric mean trough concentrations of total BHPM on days 4–8 ranged from 5.5–9.1 ng/mL with large inter-subject variations (gCV: 47.5% to 141%). As with bisacodyl, the steady state for sodium picosulfate appears to be reached on the fifth day at the latest. Geometric mean terminal half lives following single dose ($t_{1/2}$) and at steady-state ($t_{1/2,ss}$) administration of sodium picosulfate were similar to those observed with bisacodyl, being 7.3 and 10.0 h, respectively. Also similar to bisacodyl, the apparent plasma clearance (CL/F, CL/F_{ss}) was low, *i.e.*, 459 and 349 mL/min after a single dose and at steady state, respectively, and the volume of distribution was high at 291 L after a single dose and 300 L at steady state.

Urinary excretion of BHPM after oral administration of 10 mg bisacodyl or 10 mg sodium picosulfate: Urinary excretion of total BHPM accounted for 13.8% and 17.0% of the bisacodyl dose over the intervals 0–24 h and 0–48 h, respectively. For picosulfate, the fractional urinary excretion of total BHPM over the intervals 0–24 h and 0–48 h was 9.1% and 10.4%, respectively. At steady state, urinary excretion of total BHPM over the dosing interval accounted for 12.0% and 13.3% of the bisacodyl and picosulfate dose, respectively. BHPM renal clearance over the uniform dosing interval following either the first dose ($CL_{R,0-24}$) or at steady state ($CL_{R,SS}$) was similar after both bisacodyl (47.8 *vs.* 50.0 mL/min) and sodium picosulfate (52.6 *vs.* 46.2 mL/min) administration.

Safety: Fifteen of the 16 subjects experienced at least one adverse event (AE) during the course of the study. There were no serious AEs and no AE resulted in premature discontinuation. All but one event (nasopharyngitis ongoing at the end of the trial) resolved during the course of the study. Fifteen subjects, seven receiving bisacodyl and eight receiving sodium picosulfate, reported AEs during the treatment phase. These are summarized in **Table 4**. The most common AEs were diarrhea and abdominal pain, both reported by seven of eight subjects treated with either laxative. These events are known adverse events based on the pharmacological action of the compounds and can be expected when healthy volunteers are treated with laxatives. Four and two subjects treated with bisacodyl and sodium picosulfate, respectively, reported headaches, and two subjects reported nasopharyngitis while on bisacodyl. All but two and one of the AEs reported with use of bisacodyl and sodium picosulfate respectively were of mild intensity and only three required intervention. No subjects discontinued the trial due to an AE, and no clinically relevant changes in laboratory values were observed.

Table 4. Adverse events (AEs) experienced during treatment with multiple 10-mg doses of bisacodyl or sodium picosulfate

	Number of subjects experiencing listed AE	
	Bisacodyl group	Picosulfate group
Abdominal discomfort	0	1
Abdominal distension	2	0
Abdominal pain	7	8
Diarrhea	7	7
Dizziness	1	1
Fatigue	0	1
Flatulence	0	1
Headache	4	2
Migraine	1	0
Myalgia	1	0
Nasopharyngitis	2	0
Nausea	0	2
Scleral hemorrhage	1	0

Discussion

The primary objective of this study was to investigate whether oral administration of bisacodyl (Dulcolax) or sodium picosulfate (Laxoberal) at standard 10-mg doses commonly used for treating constipation leads to excretion of their common active moiety, BHPM, in breast milk of healthy lactating women. In 1972, an early pharmacokinetic study investigated the excretion of sodium picosulfate into breast milk.[21] Neither the parent compound nor its metabolites were identified in the milk of five postpartum women. However, from today's perspective, the bioanalytical method is a major shortcoming of this study. At that time, milk samples were analyzed with thin-layer chromatography and the lower limit of quantification was 0.5 μg/mL.

Therefore, the current study was conducted to confirm the absence of excretion of the active metabolites of sodium picosulfate into breast milk using a bioanalytical method with a considerably lower limit of quantification (1 ng/mL). For bisacodyl, no historical data were available; however, because bisacodyl itself is not systemically available but shares the same active metabolite with sodium picosulfate, it was assumed that also after administration of bisacodyl, no milk excretion of BHPM or BHPM glucuronides will take place.

In the current study, neither prodrug led to quantifiable recovery of either free or total BHPM from breast milk following single or multiple oral administrations. In all subjects and at all time points, BHPM in breast milk remained below the limit of detection (1 ng/mL). Hence, it appears that following oral administration of bisacodyl or sodium picosulfate, BHPM, the common pre-systemically formed active metabolite, is not excreted into breast milk. This indicates that there is no risk associated with the use of these two laxative drugs by lactating postpartum women with regard to transfer of the active moiety to infants through breast feeding.

The absence of excretion into breast milk of BHPM may not be observed with other laxatives, specifically senna. A study among 20 postpartum lactating women previously

reported excretion of rhein, an active metabolite of sennosides in human breast milk.[17] While rhein was detected in breast milk, its levels varied, and no effects were observed on the stool output of infants. Nonetheless, the appearance of rhein in breast milk indicates a difference in the excretion profile of senna-based laxatives.

The time lag before the initial rise in plasma concentrations of BHPM following oral dosing of both bisacodyl and sodium picosulfate reflects the dosage form of bisacodyl and the mechanism for metabolic conversion of picosulfate, respectively. Bisacodyl is administered as enteric coated tablets, which do not disintegrate until they enter the colon. In contrast, sodium picosulfate, though dosed as a liquid formulation, is not metabolized nor absorbed in the stomach or small intestine, but is converted to BHPM by the enzymes of colonic bacteria.[18] Hence, for both bisacodyl and picosulfate, interindividual variability observed in their lag to onset of absorption reflects inherent physiologic variability in gastric emptying and small intestinal transit time. Mean differences in lag times between the compounds may reflect the kinetics of BHPM formation in the colon, which apparently for bisacodyl tablets (tablet disintegration and deacetylation) is faster than for sodium picosulfate liquid (enzymatic conversion).

In addition, bisacodyl remains intact as its tablet formulation until it enters the colon and then dissolves, while sodium picosulfate, as a liquid formulation, disperses as it transits the small intestine, which in turn could indirectly influence the absorption rate of BHPM in the colon. These differences may explain, at least in part, the threefold higher C_{max} and $C_{max,ss}$ values for bisacodyl. Also, the converted portion might be higher for bisacodyl, which could also explain differences in C_{max} and AUC values.

No plasma accumulation of BHPM was observed following multiple once-daily dosing of 10 mg bisacodyl. In contrast, a low level of accumulation of total BHPM seemed to occur with multiple once-daily doses of 10 mg sodium picosulfate; however, these differences could be chance findings due to the low sample size. It is well established that absorbed BHPM can be eliminated in bile and urine.[16] While this study did not evaluate biliary excretion, about 17.0% and 12.0% of the total bisacodyl dose had been recovered as total BHPM in urine 48 h after a single dose and 24 h after each dose at the steady state, respectively. Corresponding levels of urinary elimination after dosing sodium picosulfate were 10.4% and 13.3%, respectively; both are similar to values reported previously.

The common adverse events observed in this study were those expected with use of laxatives. It needs to be considered that these subjects were healthy and were not suffering from constipation. Adverse events were mostly of mild intensity, and none resulted in the discontinuation of treatment. Overall, both drugs were well tolerated.

In conclusion, neither the active moiety of sodium picosulfate and bisacodyl [bis-(*p*-hydroxyphenyl)-pyridyl-2-methane (BHPM)] nor its glucuronides were excreted into the milk of healthy lactating women following single or repeated dosing of 10 mg bisacodyl or 10 mg sodium picosulfate. The disposition pharmacokinetic profiles of the two agents were similar. Small differences in absorption pharmacokinetics most likely reflect the differences in formulations and the formation mechanism of the active principle. Adverse events observed during the study were mostly the gastrointestinal symptoms expected with use of laxatives, and otherwise, both drugs were well tolerated. Thus, the data indicate that sodium picosulfate and bisacodyl can be safely used during breast feeding.

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