ELSEVIER

International Journal of Pharmaceutics 196 (2000) 11–20

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Is bisacodyl absorbed at all from suppositories in man?

E. Flig [a], T.W. Hermann [a,*], M. Zabel [b]

[a] *Department of Physical Chemistry, K. Marcinkowski University of Medical Sciences, 6 Święcickiego Street, 60 781 Poznań, Poland*

[b] *Department of Histology and Embryology, University of Medical Sciences, 6 Chałubińskiego Street, 50368 Wrocław, Poland*

Received 21 April 1999; received in revised form 8 October 1999; accepted 2 November 1999

Abstract

A HPLC procedure was developed to determine free BHPM in human plasma and urine after prior deconjugation of its glucuronides with glucuronidase. A single dose administration of a 10 mg bisacodyl suppository from Glaxo Wellcome, Poznań (Poland) to 16 volunteers each resulted in its low active metabolite (BHPM) plasma levels (10–55 $\mu g\ l^{-1}$) according to general assumptions. Its prompt laxative effect appeared within 56.6 ± 10.8 min. The calculated serum half-life time of BHPM glucuronide excretion in urine was $\sim 7.32 \pm 0.99$ h. BHPM was excreted in urine in only $3.36 \pm 0.52\%$ if compared with the above bisacodyl rectal dose administered. Any relationship between BHPM plasma and/or urine levels and its laxative action does not occur. These results confirm the thesis that the laxative action of bisacodyl suppositories is initiated through a direct interaction of the drug in the rectum.

Keywords: Bisacodyl; Metabolite BHPM; Laxative effect; HPLC; Plasma; Urine; Levels; Volunteers

1. Introduction

Bisacodyl (BIS), 4,4′-(2-pyridylmethylene)-bis(phenyl acetate), is a stimulant laxative used for the treatment of constipation and for bowel evacuation before examination procedures in surgery. Its action is usually effective within 15–60 min following rectal administration. It is rapidly converted to the active metabolite bis(*p*-hydroxyphenyl)pyridyl-2-methane (BHPM) (Reynolds, 1993). The main glucuronidation process of laxative BHPM takes place in the gut wall, i.e. extrahepatically. The exposure of the target cells, i.e. the large intestine enterocytes to the above active metabolite, and hence its laxative effect depends on the balance between the rates of five main processes: (1) supply of laxative conjugates and free BHPM to the large intestine; (2) intraluminal deconjugation; (3) uptake of free diphenol by the epithelial cells; (4) net intracellular conjugation; and (5) the active conjugates efflux from the cells (Bredo and Hillestad, 1982). Only up to 9.2 ± 3.3 or $3.1 \pm 1.2\%$ of the dose is excreted in urine in man after the administration of an oral enteric-coated tablet or of a suppository, respectively. The urinary excretion reaches

* Corresponding author. Tel./fax: +48-61-8657005.

E-mail address: hermann@eucalyptus.usoms.poznan.pl (T.W. Hermann)

0378-5173/00/$ - see front matter
PII: S0378-5173(99)00385-3

43.4 ± 15.0% as a result of BIS oral equivalent solution administration (Roth and Beschke, 1988). About 50% of a dose are eliminated in the faeces as unconjugated BHPM (Moffat, 1986).

The purpose of this publication was to follow the plasma level profile, the urinary excretion kinetics and time of bowel movement in volunteers after administration of a single dose (10 mg) of BIS suppository, Glaxo Wellcome, Poznań, Poland. The analytical assay developed for free BHPM in plasma and urine is based on an isocratic HPLC procedure (Bradshaw et al., 1995) after prior hydrolysis of BHPM glucuronides with β-glucuronidase and its selective liquid–liquid extraction (Fullinfaw et al., 1988).

2. Materials and methods

2.1. Materials

Product sample identified as bisacodyl suppositories (BIS), lot number C 005001 was obtained from Glaxo Wellcome. A BHPM authentic sample, lot number PL 314 was received free of charge from Boehringer Ingelheim Pharma KG, Biberach an der Riss, Germany. β-Glucuronidase, IX-A from *Escherichia coli* of activity 1 330 000 U g^{-1} was purchased from Sigma, St. Louis, MO. Chemicals were of either HPLC or reagent grade. Double distilled water was obtained from an apparatus made of silica glass.

2.2. Apparatus

HP 1100 Series automated quaternary LC 3D system (Hewlett® Packard Company) including quaternary pump, vacuum degasser, automatic sampler, variable wavelength detector with standard flow cell, control module and check-out sample, column temperature regulator compartment and 3D ChemStation was used for quantification of BHPM in plasma and urine. Five micrometres LiChrospher 100 RP 18 pre-packed column (250 × 4 mm) was protected by a 5 μm guard column (4 × 4 mm) and ordered from Merck, Darmstadt, Germany.

2.3. Subject selection

Sixteen each normal adult, non-smoking, male and female volunteers between 18 and 32 years (mean 24.1 ± 4.8) weighing on average 74.8 ± 6.7 kg of height 179.4 ± 7.0 cm were selected for participation in the investigations. The volunteer subjects were selected after completing a thorough history and physical examination, and after a normal laboratory examination. The laboratory tests consisted of the following: haematology, serum chemistry and urinalysis. All subjects were presented with full details of the investigation, both verbally and in written form, prior to providing written informed consent. The investigation was approved by Human Investigations Ethical Committee at the Karol Marcinkowski University of Medical Sciences.

2.4. Study design

The study was a non-blinded, open-label, single dose design. All subjects were randomly assigned a drug assignment number from 1 to 16, which was used throughout the study period. The subjects were required to fast for at least 10 h prior to the timing of the rectal dose. On the treatment day, the subjects were instructed to present in the study facility. At 'hour zero' the subjects were assigned to a phlebotomist for the purpose of collecting a 5-ml blood sample. The assigned suppository was inserted in their rectum. All subjects abstained from food until the 4-h blood specimen was obtained when a standardised low fat lunch was provided. Regular meals were resumed after the 12-h blood sample was obtained. Following drug administration, venous blood samples (5 ml) obtained (in Serum Gel tubes, S/4.7 ml, Sarstedt Manovette, Germany) from the subject's right or left antecubital fossa at the following times: immediately before administration of BIS and 0.25, 0.50, 0.75, 1.00, 2.00, 3.00, 6.00, 12.00 and 24.00 h after administration. The time of bowel movement was recorded for each subject. Within 30 min following blood withdrawal, the samples were centrifuged. The separated plasma was frozen in plastic vials at −20°C and labelled with the subject I.D. number, treatment day and time of

sampling. The red blood cells were discarded. Urine samples were collected at the following time intervals: 0–2; 2–4; 4–6; 6–8; 8–10 and 10–24 h and their volume was recorded as well as 5 ml samples only were frozen in plastic vials until analysed for BHPM and remaining urine was discarded.

2.5. BHPM plasma and urine quantification procedure

2.5.1. Chromatographic conditions

A mixture: 0.01 mol l^{-1} phosphate buffer pH 5.0–acetonitrile (70:30 v/v) was filtered through a 0.45 μm nylon membrane filter (Schleicher-Schuell, Kassel, Germany) and pumped at the rate of 0.7 ml min^{-1} at 25°C and was used for determination of BHPM. However, the above mobile phase composition was changed for 50:50 (v/v) in order to shorten the retention time of BIS, but was not used for BHPM determination in serum and urine specimens, which did not contain any amount of parent drug — BIS. Absorbances of effluents were monitored at 225 nm (BHPM λ_{max}). Twenty-five microliters of fixed loop injections of analysed plasma or urine extracts were made.

2.5.2. Stock solutions and standards

Stock solutions in methanol containing 0.2 g l^{-1} and subsequently 20 mg l^{-1}BHPM were prepared. Then, aqueous standard solutions from the latter stock solutions were made containing 0.05, 0.10, 0.20, 0.40, 0.80, 1.60 and 3.20 mg l^{-1} BHPM. Hundred μl of each standard solution were transferred to a 16 mm screwed cap culture tubes containing 0.5 ml of either plasma or urine (collected at 'zero time'). The resulting either plasma or urine based standards containing 10, 20, 40, 80, 160, 320 and 640 μg l^{-1} BHPM were further processed according to the procedures described below.

2.5.3. Procedures

To each 0.5 ml of serum or urine were added: 50 μl β-glucuronidase 5000 U ml^{-1} in 0.1 mol l^{-1}phosphate buffer pH 6.8 and 50 μl 2.2 mol l^{-1} acetate buffer pH 5.0. After shaking the above solution was incubated for 12 h at 37°C to hydrolyse glucuronides to free BHPM.

BHPM was extracted with 5 ml 10% isopropanol in chloroform for 15 min and centrifuged at 2000 rev. per min for 5 min. Four milliliters of the lower organic layer was aspirated with a pipette and subsequently extracted again with 5 ml of 0.1 mol l^{-1} disodium phosphate pH 7.5. The mixture was shaken and centrifuged as previously. The 3.5 ml of the lower organic layer was again aspirated and transferred to dry culture tubes and evaporated to dryness under gentle nitrogen flow at 37°C in a water bath. The residue was reconstituted in 100 μl of 50% acetonitrile solution in 0.01 mol l^{-1} phosphate buffer pH 5.0 and transferred to micro-vials in HPLC automatic sampler.

2.5.4. BIS hydrolysis procedure to BHPM

BIS stock solutions in methanol containing first 0.4 g l^{-1} and subsequently of 20 mg l^{-1} were prepared. Then, aqueous BIS standard solutions from the latter stock solution were made containing 4, 400 and 800 μg l^{-1} BIS, which were injected (100 μl) onto the HPLC column.

In order to obtain BHPM from BIS 5 ml of the former compound stock solution was heated with 25 μl of 6 mol l^{-1} sodium hydroxide for 1 h in a screwed cap culture tube. The solution was cooled and next neutralised with 25 μl of 6 mol l^{-1} hydrochloric acid. The BHPM obtained standard solutions containing its 4, 400 and 800 μg l^{-1} concentrations were prepared from the last hydrolysed solutions, which were injected onto the column.

2.5.5. Pharmacokinetic analysis

The analytical results of serum specimens were used to calculate: apparent first-order slow (λ_2^S, h^{-1}), and fast (λ_1^S, h^{-1}) disposition rate constants, biological half-life time ($t_{0.5}$, h), time to peak serum concentration (t_{max}, h), peak serum concentration (C_{max}, μg l^{-1}) and $AUC_{0\rightarrow\infty}$ (μg h l^{-1}). From the urine data were calculated: BHPM amount excreted at time t (X_{U_t}) and ∞ (X_{U_∞}), the slow (λ_2^U, h^{-1}) and fast disposition rate constants (λ_1^U, h^{-1}), and percent BIS dose eliminated in urine (A, %). TOPFIT 2.0 software (Gustav Fis-

cher, Stuttgart, 1993) was used for calculation of the above pharmacokinetic parameters and EXCEL 4.0 program for regression statistical analysis.

3. Results and discussion

3.1. BHPM plasma and urine quantification procedure

The mobile phase from the literature (Fullinfaw et al., 1988) was modified if its composition is concerned (70:30 v/v), because the isocratic mode instead of a gradient one was used. The flow rate of the mobile phase was increased from 0.5 to 0.7 ml min^{-1}. The other procedure conditions were taken from the above literature for urine and were adjusted for BHPM determination in plasma with the exception of plasma or urine volume which was decreased from 2 to 0.5 ml and therefore the lower limit of quantification was decreased.

As shown in a HPLC chromatogram for an aqueous mixture of BIS and its metabolite BHPM

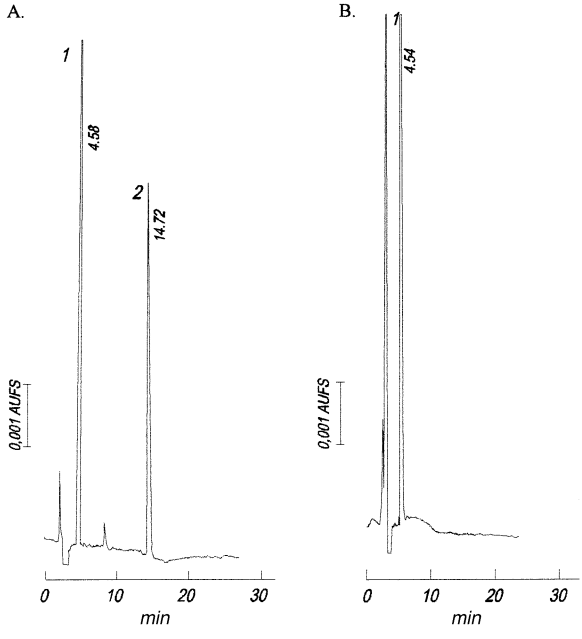

Fig. 1. HPLC chromatograms of a standard mixture containing 200 $\mu g \cdot l^{-1}$ BHPM and 200 $\mu g\, l^{-1}$ BIS obtained from their authentic samples (A) and of BHPM obtained on hydrolysis of authentic BIS sample in 6 $mol \cdot l^{-1}$ NaOH (B). Mobile phase: 0.01 $mol \cdot l^{-1}$ phosphate buffer pH 5.0–acetonitrile (50:50 v/v). Peak identification: (1) BHPM; (2) BIS.

(Fig. 1A), retention times for BIS and BHPM — its product of hydrolysis are 14.7 and 4.6 min, respectively if the latter mobile phase composition is applied. BIS in 6 mol l^{-1} sodium hydroxide is completely hydrolysed to BHPM at 60°C for 1 h, because only one peak of the retention time 4.6 min appears in a chromatogram presented (Fig. 1B). When the former mobile phase composition (70:30 v/v) was applied the retention times for BIS and BHPM were 36.8 and 14.7, respectively (Fig. 2A). BIS was not observed at all in drug administered volunteers serum and urine samples processed according to the above procedure (Fig. 2B), because it was metabolised in rectum to BHPM whose retention times were 14.4 min (Fig. 3) or 13.8 min (Fig. 4) in serum and urine samples. It was adequately separated from endogenous serum or urine components.

The proposed methods were also assessed for linearity, precision, accuracy and stability. A summary of the data obtained is shown in Table 1. Linearity was checked by chromatographing BHPM standard solutions obtained from its authentic sample as well as on BIS hydrolysis. The linearity of the two plots of peak area against concentration was assessed by linear regression. The correlation coefficients, r, were in both cases between 0.9885 and 0.9999. The calibration curves parameters are shown in Table 2.

The calibration curves covered the concentration range from 10 to 640 $\mu g\, l^{-1}$. The limit of quantification for BHPM was thus $\sim 10\ \mu g\, l^{-1}$. The linearity of the two plots of peak area against concentration for authentic BHPM and obtained on BIS hydrolysis in 6.0 mol l^{-1} sodium hydroxide solution are superimposable within accepted limits (Table 2). It means that BHPM standard can also be produced on BIS hydrolysis in suitable conditions specified above. BHPM calibration curve was always constructed prior to its determination in serum and urine specimens.

The system precision was determined by chromatographing five BHPM standard solutions of the concentration 640.0 $\mu g\, l^{-1}$each and calculating the relative standard deviation (RSD) of the peak area and retention time (RT). The calculated RSD values were well within accepted limits (Table 1).

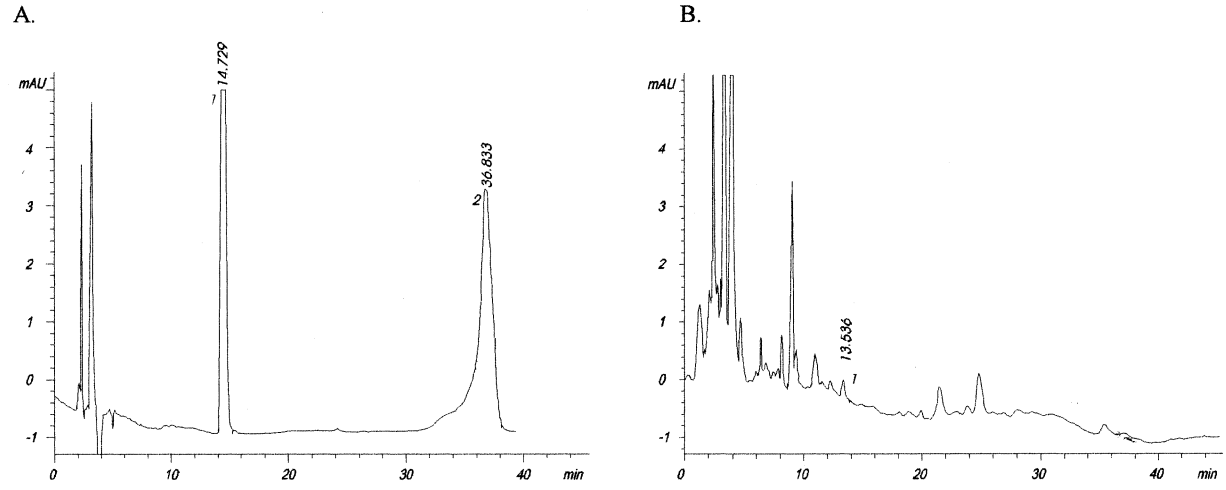

Fig. 2. HPLC chromatograms: (A) an aqueous mixture containing 200 μg l^{-1} BHPM and 200 μg l^{-1} (B) BIS; a human volunteer's serum following rectal administration of a single 10 mg BIS suppository at 1 h elapsed. Mobile phase: 0.01 mol·l^{-1} phosphate buffer pH 5.0–acetonitrile (70:30 v/v). Peak identification: (1) BHPM; (2) BIS.

The accuracy of averaged determinations was calculated as the percent difference of the mean concentration from fixed concentration. The values obtained were below 10.32 and 7.89% for urine and serum specimens, respectively (Table 1).

The mean assay recovery for BHPM was determined. The peak area obtained first on extraction of BHPM from its two samples each of serum and urine and second from direct injections of the same amount of BHPM in the mobile phase were compared. The calculated recoveries were less satisfactory for urine samples (52.37%) than for serum samples (70.55%) (Table 1).

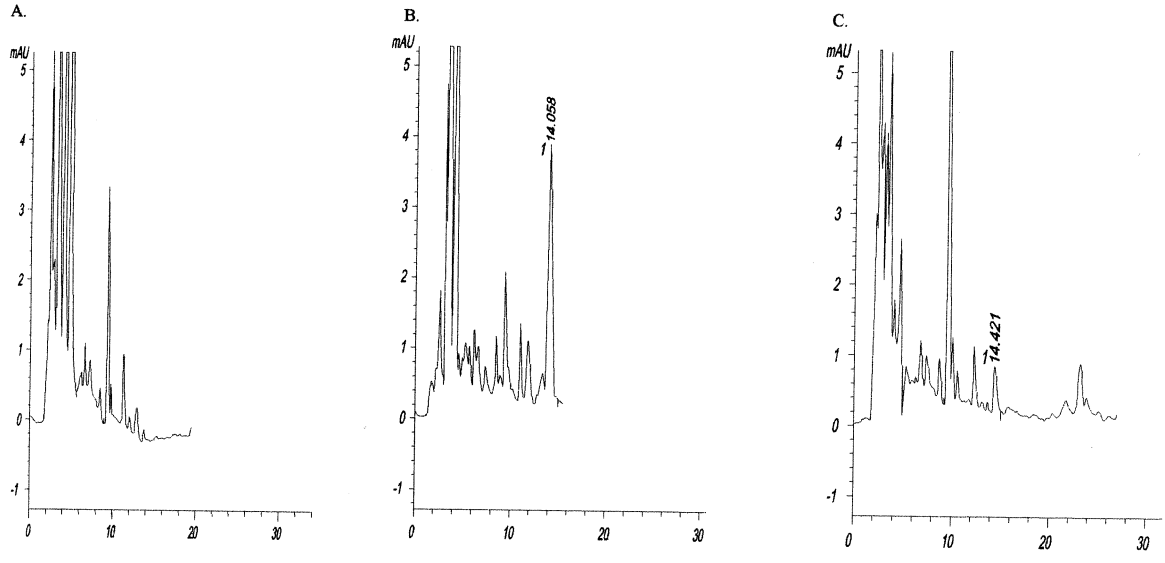

Fig. 3. Chromatograms of BHPM in human serum: (A) blank human serum; (B) human serum spiked with BHPM 320 μg·l^{-1}; (C) human voluteer's serum following rectal administration of 10 mg BIS suppository at 0.75 h elapsed. Mobile phase: 0.01 mol·l^{-1} phosphate buffer pH 5.0–acetonitrile (70:30 v/v). Peak identification: (1) BHPM.

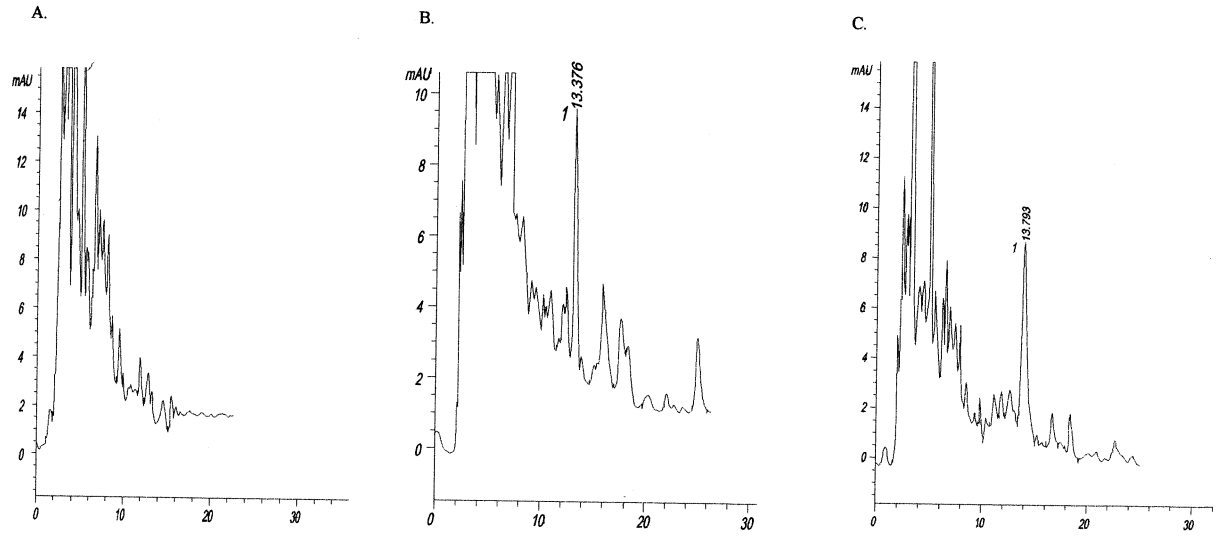

Fig. 4. Chromatograms of BHPM in human urine: (A) blank human urine; (B) human urine spiked with BHPM 640 $\mu g \cdot l^{-1}$; (C) human volunteer's urine at 8 h elapsed from the rectal administration of a 10 mg single BIS suppository. Mobile phase: 0.01 $mol \cdot l^{-1}$ phosphate buffer pH 5.0–acetonitrile (70:30 v/v). Peak identification: (1) BHPM.

Table 1
Method validation data of BHPM

Precision system % RSD[a]		Precision method % RSD	% Recovery	Accuracy % error
Peak area	Retention time			
8.19 ($n = 5$)	1.82 ($n = 5$)	2.79 ($n = 5$)	52.37 (urine) 70.55 (serum)	$\leq$10.32 (urine) $\leq$7.89 (serum)

[a] RSD, relative standard deviation.

Table 2
Averaged calibration curve parameters of BHPM obtained either on hydrolysis of bisacodyl (BIS) or from its authentic sample (BHPM)

	Calibration curve number n		Linear range ($\mu g \cdot l^{-1}$)		Regression line equation[a]		Correlation coefficient	
	Serum	Urine	Serum	Urine	Serum	Urine	Serum	Urine
BIS	3	3	10–640	20–640	$y = (0.2068 \pm 0.0180)x$	$y = (0.2035 \pm 0.0140)x$	0.9999	0.9885
BHPM	3	3	10–640	20–640	$y = (0.2345 \pm 0.0230)x$	$y = (0.2071 \pm 0.0110)x$	0.9923	0.9998

[a] y, BHPM peak area; x, BHPM concentration ($\mu g \cdot l^{-1}$).

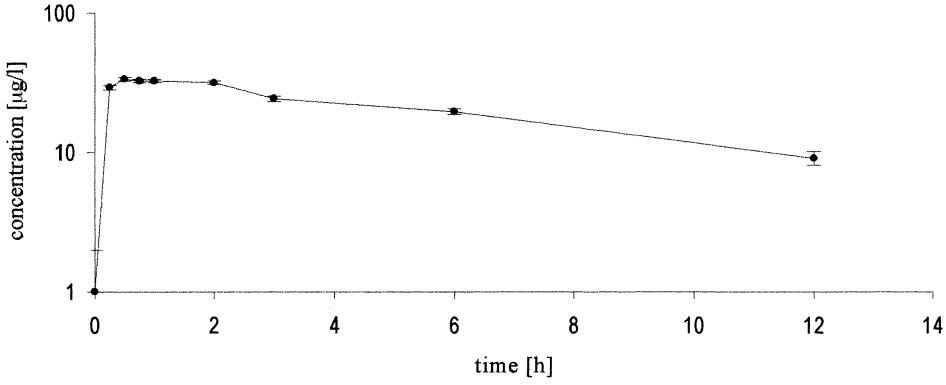

Fig. 5. Mean serum concentrations of BHPM (± S.E.M.) vs. time from 16 volunteers after rectal single dose administration of bisacodyl suppositories.

3.2. Pharmacokinetic analysis

The serum BHPM concentrations (C) following the administration of a suppository to each volunteer were well characterised by the difference in two exponentials (Fig. 5):

$$C = B \cdot e^{-\lambda_2^S \cdot t} - A \cdot e^{-\lambda_1^S \cdot t} \quad (1)$$

In Eq. (1), A and B are the corresponding zero-time intercepts, λ_1 and λ_2 are the apparent first-order: fast and slow disposition rate constants, respectively and t is the time.

The individual and averaged BHPM serum concentrations and their S.E.M.s are given in Table 3 and the above mentioned pharmacokinetic parameters in Tables 4 and 5.

Table 3
Serum concentrations of BHPM from 16 subjects after rectal single dose administration of bisacodyl suppositories

Time (h)	0.25	0.50	0.75	1.00	2.00	3.00	6.00	12.00	24.00
Subject	Concentration ($\mu g \cdot l^{-1}$)								
I	12.6	35.4	34.8	23.2	19.5	13.6	14.4	<10	<10
II	12.2	13.9	27.4	34.8	15.6	26.5	16.6	<10	<10
III	34.3	32.7	30.6	38.1	40.6	20.1	21.6	16.7	14.6
IV	29.1	22.2	12.9	20.1	16.6	17.6	16.8	<10	<10
V	49.5	51.7	44.6	25.0	47.4	23.7	22.1	20.6	14.6
VI	25.4	28.7	41.7	28.9	25.9	21.6	15.3	<10	<10
VII	18.2	26.3	21.7	20.2	20.2	16.8	23.8	11.9	<10
VIII	20.1	27.5	26.6	41.4	51.0	34.0	20.9	12.9	<10
IX	11.2	30.2	23.2	27.1	40.3	19.2	24.0	13.7	<10
X	<10	35.9	12.8	14.1	12.8	11.9	13.3	<10	<10
XI	50.7	30.3	55.4	54.7	50.7	48.9	12.8	<10	<10
XII	47.4	32.1	25.2	25.7	17.8	17.7	17.3	14.9	<10
XIII	49.3	44.3	42.5	46.9	43.8	27.7	23.3	13.7	<10
XIV	52.9	50.5	46.1	49.3	38.6	38.1	32.5	22.8	<10
XV	34.7	30.8	43.1	41.2	36.2	22.2	13.7	<10	<10
XVI	19.3	43.2	32.6	30.3	28.7	27.4	24.8	17.9	<10
Mean	29.2	33.5	32.6	32.6	31.6	24.2	19.6	9.1	<10
S.E.M.[a]	4.2	2.5	3.1	2.9	3.4	2.4	1.7	2.2	<10

[a] S.E.M., standard error mean.

Table 4
Pharmacokinetic and bioavailability parameters of BHPM as well as its laxative effect from 16 subjects after rectal single dose administration of bisacodyl suppositories

Parameter[a]	Subject															
	I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	XIII	XIV	XV	XVI
C_{max}	30.7	26.0	34.1	21.2	43.0	33.4	22.6	43.3	30.5	22.1	56.5	32.1	47.3	49.4	40.8	34.6
t_{max}	0.50	1.20	0.37	0.38	0.37	0.71	0.54	1.76	1.20	0.31	1.01	0.33	0.33	0.36	0.75	0.57
λ_1^S	15.0	3.5	15.0	14.3	14.3	5.2	14.7	1.4	3.8	14.3	2.5	14.6	14.6	14.6	4.1	14.4
λ_2^S	0.23	0.09	0.06	0.07	0.08	0.18	0.04	0.17	0.07	0.19	0.23	0.13	0.12	0.08	0.23	0.07
$t_{0.5}$	3.1	7.9	12.4	10.4	9.1	3.9	16.4	4.1	9.6	3.7	3.0	5.2	5.6	9.1	3.1	10.5
AUC	145	325	624	326	581	211	544	344	456	125	313	251	399	663	213	535
$X_{U_{0-2}}$	35.2	12.9	83.7	19.6	85.8	74.3	139.3	241.1	91.7	59.4	113.0	23.9	97.9	324.2	54.3	37.5
$X_{U_{2-4}}$	8.7	5.7	68.6	32.5	51.5	38.5	6.8	163.7	86.7	120.6	61.7	71.1	215.9	392.7	59.8	43.2
$X_{U_{4-6}}$	7.7	44.1	25.9	27.8	96.2	39.7	55.1	100.8	151.8	138.4	7.9	125.2	205.1	–	82.2	30.1
$X_{U_{6-8}}$	–	5.8	9.9	42.1	–	111.6	67.9	–	8.1	64.5	14.4	–	154.1	110.8	46.1	7.6
$X_{U_{8-10}}$	10.8	7.2	22.4	19.0	33.7	22.3	42.5	47.9	23.2	69.8	94.3	–	13.5	22.9	30.1	8.6
$X_{U_{10-24}}$	16.8	28.1	41.1	33.9	27.7	0	0	0	0	0	34.5	25.3	0	0	0	0
X_{U_∞}	79.2	103.8	251.6	174.9	294.9	286.4	311.6	553.5	361.5	452.7	325.8	245.5	686.5	850.6	272.5	127.0
λ_1^U	15.00	0.49	15.00	0.29	0.88	0.36	15.00	1.83	0.48	0.48	14.99	0.75	0.44	3.37	0.33	0.57
λ_2^U	0.22	0.21	0.21	0.29	0.15	0.35	0.13	0.37	0.13	0.34	0.16	0.74	0.44	0.70	0.33	0.54
A	0.8	1.1	2.5	1.8	2.9	2.8	3.1	5.5	3.6	4.5	3.3	2.5	6.8	8.5	2.7	1.3
t_{lax}	25.2	55.2	105.0	40.2	190.2	40.2	19.8	85.2	33.0	25.2	49.8	25.2	100.2	45.0	45.0	34.8

[a] C_{max} (μg·l^{-1}), t_{max} (h), λ (h^{-1}), $t_{0.5}$ (h), AUC (μg·h l^{-1}), $X_{U_{t1-t2}}$ (μg), A (%), $X_{U\infty}$ (μg), t_{lax} (min).

Table 5
Mean pharmacokinetic and bioavailability parameters of BHPM as well as its laxative effect from 16 subjects after rectal single dose administration of bisacodyl suppositories

Parameter	$\bar{X}$	±S.E.M.[a]
C_{max} (μg·l^{-1})	35.48	2.60
t_{max} (h)	0.67	0.11
λ_1^S (h^{-1})	10.4	1.4
λ_2^S (h^{-1})	0.13	0.02
$t_{0.5}$ (h)	7.32	0.99
$AUC_{0\rightarrow\infty}$ (μg·h·l^{-1})	378.4	42.9
$X_{U_{0-2}}$ (μg)	93.36	20.82
$X_{U_{2-4}}$ (μg)	89.24	24.72
$X_{U_{4-6}}$ (μg)	75.87	15.24
$X_{U_{6-8}}$ (μg)	53.58	14.35
$X_{U_{8-10}}$ (μg)	31.21	6.23
$X_{U_{10-24}}$ (μg)	12.96	3.99
X_{U_∞} (μg)	336.1	52.6
λ_1^U (h^{-1})	4.38	1.59
λ_2^U (h^{-1})	0.33	0.05
A (%)	3.36	0.52
t_{lax} (min)	57.6	10.8

[a] S.E.M., standard error mean.

The BHPM serum concentrations were low and ranged from 10 to 55 μg l^{-1} (Table 3) as a function of time (Fig. 5) according to Eq. (1). The above concentrations are similar to other data provided in the literature (Roth and Beschke, 1988) produced on administration of a single dose Dulcolax®–Suppositorium (10 mg) (12–64 μg l^{-1}).

Serum mean BHPM biological half-life time and t_{max} were equal 7.32 ± 0.99 h and 0.67 ± 0.11 h, respectively (Table 5), which are not provided in the literature.

Pharmacokinetic evaluation of urinary excretion data obtained after extravascular administration (e.g. rectal) according to one compartment body model yields Eq. (2):

$$X_u = \frac{k_e \cdot \lambda_1^U \cdot F \cdot X_0}{\lambda_2^U}\left[\frac{1}{\lambda_1^U} + \frac{e^{-\lambda_2^U \cdot t}}{\lambda_2^U - \lambda_1^U} - \frac{\lambda_2^U \cdot e^{-\lambda_1^U \cdot t}}{\lambda_1^U \cdot (\lambda_2^U - \lambda_1^U)}\right] \quad (2)$$

In Eq. (2), k_e is first-order excretion rate constant and λ_1^U and λ_2^U are apparent: fast and slow disposition rate constants of BHPM in urine, respectively, F is the fraction of BHPM absorbed, and X_0 is the BIS dose administered. Eq. (2) describes the time course of the cumulative amount of intact drug (its active BHPM) in the urine (Fig. 6). At time infinity, Eq. (2), reduces to (Gibaldi and Perrier, 1982):

$$X_u^\infty - X_u = \frac{X_u^\infty}{\lambda_1^U - \lambda_2^U}(\lambda_1^U \cdot e^{-\lambda_2^U \cdot t} - \lambda_2^U \cdot e^{-\lambda_1^U \cdot t}) \quad (3)$$

Because λ_1^U is larger than λ_2^U, the slope of terminal linear segment of the curve yields an estimate of λ_2^U and the initial segment λ_1^U of BHPM on so called subtraction technique applied (Table 5). There are approximately over 2.5-fold differences between λ_1 and λ_2 rate constants calculated from serum and urine data (Table 5). The reason for them could be different levels of BIS metabolites in serum and urine. It should be

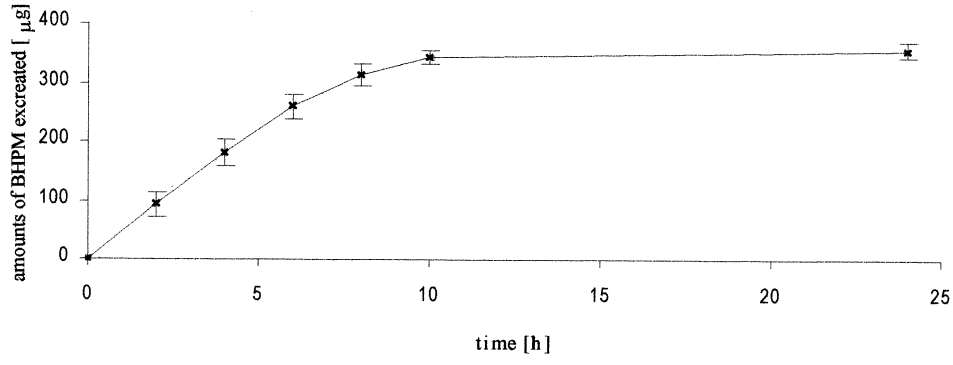

Fig. 6. Cumulative renal extraction curve of BHPM (± S.E.M.) from 16 subjects after rectal single dose administration of bisacodyl suppositories.

mentioned also that BIS monoacetate as a BIS metabolite could also appear in serum and urine (Fullinfaw et al., 1988). However, we did not observe and follow that metabolite in serum and urine, but it could be too absorbed from rectum and hydrolysed in liver to BHPM.

Mean percent amount of BHPM excreted in the urine if compared with the BIS dose administered is very low ($3.36 \pm 0.52\%$) (Table 5) and ranges from 0.8 to 8.5% (Table 4). That data are typical for a BIS suppository, and are similar to a reference $3.1 \pm 0.3\%$ (Roth and Beschke, 1988).

3.3. Time of bowel movement

The time of bowel movement was recorded according to every volunteer report and is presented in Table 4. Mean time of bowel movement is equal 57.6 ± 10.8 min (Table 5) and ranges from 25.2 to 190.2 min (Table 4). According to references the above time ranges from either 15 to 60 min (Reynolds, 1993) or 9.6 to 45 min (mean 18.0 ± 10.2 min) (Roth and Beschke, 1988). It can be learnt from the above data that the laxative effect of Dulcolax®–Suppositorium (10 mg) appears earlier (~ 20 min) than on Bisacodyl® Glaxo Wellcome, Poland suppository administration. However, the averaged time of bowel movement of the latter suppositories still meets the requirements (Reynolds, 1993).

4. Conclusions

Suppositories Bisacodyl® Glaxo Wellcome, meet the requirements for classic laxative preparations of diphenyl methane derivatives (Reynolds, 1993). Their time of bowel movement is prompt enough (57.6 ± 10.8 min) and their active agent (BHPM) is only slightly absorbed from rectum ($3.4 \pm 0.5\%$). BHPM exerts its laxative effect within large intestine. Its mean peak serum concentration (35.5 ± 2.6 μg l^{-1}) and amounts excreted at time ∞ (336.1 μg) are low according to general rules. As far as the pharmacotherapeutic data are concerned, the 'grandfather' drugs like BIS should be verified on the onset of modern analytical technology used for assays in biological fluids. They allow us to conclude that a common believe about completely non-absorbable BIS from large intestine is exaggerated. Fortunately, its absorption is low, especially from rectum but it depends on the route of administration. Therefore, eventual side effects produced should be minimal on the rectal route.

Acknowledgements

The authors wish to appreciate the financial support from Glaxo Wellcome S.A., Poznań, Poland and the gift of BHPM authentic samples from Dr W. Roth, Boehringer Ingelheim Pharma KG, Biberach an der Riss, Germany.

References

Bradshaw, K.M., Burnett, J., Sidhu, A.S., 1995. High-performance liquid chromatographic determination of bisacodyl in pharmaceutical dosage forms marketed in Australia. J. Pharm. Biomed. Anal. 13, 1355–1362.

Bredo, R., Hillestad, B., 1982. Uptake, conjugation and transport of laxative diphenols by everted sacs of the rat jejunum and stripped colon. Acta Pharm. Toxicol. 51, 377–387.

Fullinfaw, R.O., Bury, R.W., Moulds, R.F.W., 1988. Screening procedure for stimulant laxatives in urine using high-performance liquid chromatography with diode array detection. J. Chromatogr. 433, 131–140.

Gibaldi, M., Perrier, D., 1982. Pharmacokinetics. Marcel Dekker, New York, p. 39.

Moffat, A.C. (Ed.), 1986. Clarke's Isolation and Identification of Drugs in Pharmaceuticals, Body Fluids and Post-Mortem Materials. The Pharmaceutical Press, London, p. 397.

Reynolds, J., 1993. Martindale: The Extra Pharmacopoeia XXX. The Pharmaceutical Press, London, p. 871.

Roth, W., Beschke, K., 1988. Pharmakokinetik und laxierende Wirkung von Bisacodyl nach Gabe verschiedener Zubereitungsformen. Arzneim.-Forsch. Drug Res. 38, 570–574.