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ASSESSMENT REPORT

**RHAMNUS PURSHIANUS D.C.; RHAMNI PURSHIANAE CORTEX; CASCARA AND
HERBAL PREPARATION(S) THEREOF WITH WELL-ESTABLISHED USE AND
TRADITIONAL USE**

Cascara (Rhamni purshianae cortex)

Herbal Substance (scientific name of the plant)	<i>Rhamnus purshianus</i> D.C. (<i>Frangula purshiana</i> (D.C.) A. Gray ex J.C. Cooper), cortex
Herbal Preparation(s)	Dried, whole or fragmented bark
Pharmaceutical forms	Herbal substance for oral preparation
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Superseded

1 INTRODUCTION

This assessment report reviews the scientific data available for cascara which consists of the dried, whole or fragmented bark of *Rhamnus purshianus* D.C. (*Frangula purshiana* (D.C.) A. Gray ex J. C. Cooper) in consideration of the German monograph of the Commission E “Rhamni purshianae cortex” (1) and the German pharmacovigilance actions for anthranoid-containing laxatives of 21 June 1996 (2). We also take into account the literature presented by the ESCOP to the monograph “RHAMNI PURSHIANI CORTEX (Cascara)” (3).

Constipation is a common complaint in 1-6% middle-aged and 20 – 80 % of the elderly people, which is treated by laxatives. Constipation also tends to be more prevalent among women. The functional constipation is the most common type without any specific aetiology (4). Among the most commonly used laxatives are either preparations containing stimulating anthracenic derivatives or lubricating laxatives (vegetable or mineral oils) or bulk forming agents.

Cascara preparations of the dried bark belong to the stimulating laxatives containing hydroxyanthracene derivatives and are intended “for short term use in cases of occasional constipation”.

This indication is substantiated by empirical data (stemming from research into the constituents and their pharmacology and other anthranoid-containing herbal substances). There are only poor clinical data available.

Cascara preparations have to be regarded as herbal medicinal products with „well established medicinal use“ in this indication according to the COMMISSION DIRECTIVE 2003/63/EC of June 2003 amending Directive 2001/83/EC of the Parliament and of the Council on the Community code relating to medicinal products for human use.

Anthraquinone laxatives such as senna, aloe dried juice, frangula bark and cascara share a tricyclic anthracene nucleus modified with hydroxyl, methyl, or carboxyl groups to form monoanthrones (5). Therefore we also refer to the assessment report for senna leaves and fruits and to the assessment report for aloe and frangula bark to assess cascara.

2 NON-CLINICAL DATA

2.1 Pharmacokinetics

2.1.1 Phytochemical characterisation

Cascara consists of the dried, whole or fragmented bark of *Rhamnus purshianus* D.C. (*Frangula purshiana* (D.C.) A. Gray ex J.C. Cooper). It contains not less than 8.0 per cent of hydroxyanthracene glycosides of which not less than 60 per cent consists of cascariosides, both expressed as cascariosides A ($C_{27}H_{32}O_{14}$; M_r 580.5) and calculated with reference to the dried herbal substance. This complies with the European Pharmacopeia.

The constituents with known therapeutic activity of cascara are cascariosides A, B, C, D, E and F. Cascariosides A and B are mixed anthrone-C- and O-glycosides, being the 8-O- β -D-glucosides of 10-(S)-desoxyglucosyl aloe-emodin anthrone and 10-(R)-desoxyglucosyl aloe-emodin anthrone (aloins A and B) respectively. They are diastereoisomers. Cascariosides C and D are the 8-O- β -D-glucosides of 10-(R)(S)-desoxyglucosyl chrysophanol anthrone (chrysaloins A and B). Cascariosides E and F are the 8-O- β -D-glucosides of 10-(R)(S)-desoxyglucosyl emodin anthrone. The total hydroxyanthracene complex of the dried bark consists of 60 - 70 % cascariosides, 10 – 30 % aloins A and B together with chrysaloins A and B and 10 – 20 % of a mixture of hydroxyanthracene O-glycosides including the monoglucosides of aloe-emodin, chrysophanol, emodin and physcion together with the corresponding aglyka (3, 6).

The fresh bark contains mono-anthrone-O-glycosides, dianthrone, C-glycosides, aloe-emodin-O-glycosides and free anthrones. 80 – 90 % of the free anthrones are bound as C-glycosides and 10 – 20 % are bound as O-monoanthrone glycosides. During the drying procedure the mono-anthrone and their O-glycosides, which cause undesirable emetic effects, are oxidized to dianthrone- and anthraquinone-O-glycosides. These forms are free of these unwanted effects (10, 11).

2.1.2 Absorption, Metabolism, Elimination

We also refer to the assessment report of “*Sennae folium*”, “*Aloe barbadensis* and *Aloe capensis*” and “*Frangula bark*”.

No pharmacokinetic data obtained with cascara or its preparations are available.

According to Witte P and Lemli L 1990 (19) anthrone-glycosides are carried, unabsorbed, to the large intestine, where the active aglykon is released by bacterial hydrolysis of the sugar. The intestinal bacterial flora also accounts for the reduction of anthraquinone aglyka to the corresponding anthrones. After absorption, the anthranoids are transformed mainly to their corresponding glucuronide and sulfate derivatives, which appear in urine and bile.

It is not known to what extent aloe-emodin-9-anthrone is absorbed. In the case of senna, animal experiments with radio-labeled rhein-anthrone administered directly into the caecum demonstrated absorption < 10 % (79).

Experiments with radiochemical anthranoids showed a significant clearance of tissue-bound activity of all organs, except the kidneys, which exhibited a pronounced retention of anthranoid equivalents.

After oral administration of 4.5 mg/kg ¹⁴C-aloe-emodin (AE) to rats 20 – 30 % of the dose was excreted in urine and the rest in faeces. Aloe-emodin was quickly metabolised to rhein, to an unknown metabolite and to conjugates of all three. In the plasma about 10% of ¹⁴C-activity was identified as free aloe-emodin. Maximum plasma values were reached 1.5 – 3 h p.a. with 248 (male) and 441 (female) ng equivalents aloe-emodin/ml. Maximum concentrations in plasma were about 3 times higher than those in ovaries and 10 times higher than those in testes. Because of the low activity concentrations in the reproductive organs TLC analysis was not possible. But if the metabolic profile of these organs is assumed to be the same as in plasma, concentrations of free aloe emodin can be calculated to be maximally about 2-4 ng/g in testes and 8-10 ng/g in ovaries after an oral dose of 4.5 mg/kg. Only liver, kidney and intestinal tract showed higher concentrations than plasma. Terminal half-life (for radioactivity) in blood was about 50 h (12).

Emodin was administered to rabbits by i.v. bolus. The AUC of emodin was 518 µg.min/ml, clearance was 72.3 ml/min, and elimination half life was 227 min. Oral administration at 10 mg/kg b.w. resulted in a very low serum concentration (approximately 2.5 µg/ml). Emodin was found to be highly bound (99.6%) to serum protein, investigated by the equilibrium dialysis method (13).

Müller SO et al. 1998 (20) presented studies which were designed to elucidate the enzymes involved in the biotransformation of naturally occurring 1,8-dihydroxyanthraquinones and to investigate whether biotransformation of 1,8 dihydroxyanthraquinones may represent a bioactivation pathway. First the metabolism of emodin was studied. With rat liver microsomes, the formation of two emodin metabolites, omega-hydroxyemodin and 2-hydroxyemodin, was observed. The rates of formation of omega-hydroxyemodin were not different with microsomes from rats that had been pretreated with inducers for different cytochrome P450 enzymes. Thus, the formation of omega-hydroxyemodin seems to be catalysed by several cytochrome P450 enzymes at low rates. The formation of 2-hydroxyemodin was increased in liver microsomes from 3-methylcholanthracene-pretreated rats and was inhibited by alpha-naphthoflavone, by an anti-rat cytochrome P450 1A1/2 antibody, and to a lesser degree, by anti-rat cytochrome P450 1A1 antibody. These data suggest the involvement of cytochrome P450 1A2 in the formation of this metabolite. However, other cytochrome P450 enzymes also seem to catalyse this reaction. The anthraquinone chrysophanol is transformed, in a cytochrome

P450-dependent oxidation, to aloe-emodin as the major product formed. Further on Müller SO et al. compared the mutagenicity of the parent dihydroxyanthraquinones and their metabolites in the in vitro micronucleus test in mouse lymphoma L5178Y cells. 2-hydroxyemodin induced much higher micronucleus frequencies, compared with emodin. Omega-hydroxyemodin induced lower micronucleus frequencies, compared with emodin. Aloe-emodin induced significantly higher micronucleus frequencies than did chrysophanol. These data indicate that the cytochrome P450-dependent biotransformation of emodin and chrysophanol may represent bioactivation pathways for these compounds.

2.2 Pharmacodynamics

2.2.1 Mode of action

We also refer to the assessment report of “*Sennae folium*”, “*Aloe barbadensis* and *Aloe capensis*” and “*Frangula bark*”.

Laxative effect

Cascara belongs to the stimulating laxatives. Emodin-9-anthrone and chrysophanol anthrone are the most important metabolites, which are produced by the bacteria of the large intestine (3).

The role of intestinal bacteria in formation active metabolites of the cascariosides and their derivatives has been investigated in vitro by Dreessen M and Lemli J 1988 (18). When incubated with caecal extract from germ free (GF) rats cascariosides A and B or C and D were not metabolised. For animals having conventional (CVL) gut microflora there was a distinction between rats and guinea pigs. The incubates from guinea pigs produced the C-glycosides barbaloin and desoxyaloin, while these from rats were able to further metabolise the C-glycosides into aloe-emodinanthrone or chrysophanolanthrone and small amounts of aloe-emodin or chrysophanol. After 48 hours incubation no unchanged cascariosides were recovered. When incubated with the *Streptococcus* species, the cascariosides were hydrolysed to barbaloin or desoxyaloin, respectively, but no further reduction took place.

1991 Che QM et al. (37) isolated a strictly anaerobic bacterium, *Eubacterium* sp. BAR, from human faeces as one of the intestinal bacteria capable of metabolising barbaloin.

Yagi T et al. 1999 (38) investigated the purgative effects of intracaecally administered rhein anthrone and anthraquinones such as aloin-emodin and chrysophanol (isolated from rhubarb), emodin and rhein, and the possible synergistic effects of the anthraquinones with rhein in mice. The anthraquinones were less potent purgatives than rhein anthrone, but the equimolar mixture of aloe-emodin and rhein anthrone had synergistic potentiating effects. An equimolar mixture of other anthraquinones and rhein anthrone tended to potentiate the purgative action.

The mode of action is based on two mechanisms. Firstly, colonic motility is increased leading to a reduced transit time and reduced fluid absorption, and secondly, an influence on secretion processes by two concomitant mechanisms viz. inhibition of absorption of water and electrolytes (Na⁺, Cl⁻) into the colonic epithelial cells (antiabsorptive effect) and increase of the leakiness of the tight junctions and stimulation of secretion of water and electrolytes into the lumen of the colon (secretagogue effect) resulting in enhanced concentrations of fluid and electrolytes in the lumen of the colon.

These findings are based on investigations with different anthrones deriving also from other anthranoid-containing herbal substances, but the results of these investigations are not always consistent.

Investigations of D'Angelo L 1993 (49) suggest that the laxative effect is to be ascribed to qualitative rather than quantitative changes in colonic motility. He developed a computerised method for quantitative analysis of colonic motility in the conscious dog and applied it to the study of the motor effects of cascariosides and their metabolites administered directly into the colonic lumen.

Dose-reponse studies were carried out with a standardised cascara extract (ldB 1401; containing 40% of cascarosides A, B, C and D), aloin, aloe-emodin and aloin-emodin anthrone. All the compounds in the 30 – 60 mg/kg dose-range induced defaecation with the exception of ldB 1401, which was active only at 60 mg/kg. The defaecation was usually accompanied by the occurrence of propagating spike bursts. However, overall colonic spike activity was not affected by any of the compounds tested in the 10-60 mg/kg dose-range. The latency of ldB 1401- and aloin-induced defaecation was significantly longer than the latency of the other compounds. The difference in the latency for induction of defaecation is probably to be ascribed to pharmacokinetic factors, since ldB 1401 and aloin are pro-drugs and require hydrolysis by bacterial glycosidases in order to be active on the colon, while aloe-emodin and aloe-emodin anthrone are the active metabolites.

Results of investigations of Capasso F et al. 1983 (14) in rat isolated colon suggest that the laxative properties of aloin and 1,8-dioxyanthraquinone may depend, at least in part, on increased prostaglandin synthesis by the intestinal tissue.

Cohen MM 1982 (15) dosed rats with the cathartics cascara, phenolphthalein, senna or ricinoleic acid with or without a 3 day pretreatment with indomethacin. Jejunum, proximal and distal ileum and colon were assayed for prostaglandin E (PGE) content by RIA. Without pretreatment the mean concentration of PGE-like material was higher than control in the proximal ileum (with phenolphthalein), in the jejunum, proximal and distal ileum (with ricinoleic acid), and in the colon (with senna), although only in the latter case was this statistically significant. Cascara did not show any noteworthy increase. Indomethacin significantly reduced the PGE content of all tissue in all treatment groups, but it did not completely prevent the increase in PGE content induced by phenolphthalein, senna and ricinoleic acid and also cascara now showed a significant increase in the colon. The author concludes that the contact cathartics increase PGE-synthesis by the gastro-intestinal tract and this could in part explain their action.

Investigations of Izzo AA et al. 1996 (16) and 1997 (17) suggest that NO is a possible mediator for the laxatives effect of anthranoid-containing products.

Senna (60 mg/kg p.o.) and cascara (800 mg/kg p.o.) *ex vivo* significantly increased Ca(2+)-dependent constitutive NO synthase activity in the rat colon. Induction of NO synthase (12% of the total NO synthase) was associated with cascara, but not senna, administration. Dexamethasone, which inhibits the expression of the inducible NO synthase, significantly and dose-dependently reduced cascara- (but not senna-) induced diarrhoea and colonic fluid secretion. The authors conclude that senna probably exerts its laxative effect through stimulation of the constitutive isoform of NO synthase, while the inducible isoform of NO synthase also seems to be involved in the laxative effect of cascara (17).

Tavares IA et al. 1996 (33) compared the effect of rhein and aloe-emodin with ricinoleic acid and calcium ionophore A23187 on platelet-activating factor (PAF) release by human gastrointestinal mucosal pieces *in vitro*. Ricinoleic acid and calcium ionophore stimulated release of PAF from human stomach, ileum or colon mucosa. Aloe-emodin (100µg/ml) stimulated a small release of PAF in ileum and colon mucosa. Rhein had no effect. 5-Aminosalicylic acid (100µg/ml) inhibited PAF release induced by the drugs. The authors concluded that rhein exerted its laxative effects by a mechanism that did not involve PAF release, and that aloe-emodin may act partly via PAF release.

Izzo AA et al. 1998 (34) reviewed the kind of involvement of NO and PAF in the action of laxatives. PAF is a phospholipid mediator of inflammation and stimulates anion secretion in animals and in isolated preparations of human colon. NO, synthesised from the amino acid L-arginine, is an important enteric inhibitory neurotransmitter. In addition, NO-donating compounds stimulate anion secretion in rat and guinea-pig colon.

Recapitulating, biological factors such as platelet activating factor (PAF) and nitric oxide (NO) may play a role on the action of the stimulus on the colon, but it has to be considered that the investigations mentioned above are only experimental ones.

Cascara acts within 6 to 12 hours due to the time taken for transport to the colon and metabolisation into the active compounds (3).

Other effects

Aloe-emodin and emodin were subjects of several investigations. We refer to the assessment report of “Aloe barbadensis and Aloe capensis” and “Frangula bark”

2.2.2 Interactions with other medicinal products

There are no special investigations available.

Chronic use or abuse of cascara preparations may lead to hypokalaemia like the abuse of all anthranoid-containing laxatives. This hypokalaemia and the increased loss of potassium may increase the activity of cardiac glycosides and interfere with the action of antiarrhythmic agents (interaction with antiarrhythmic medicinal products, which induce reversion to sinus rhythm, e.g. quinidine) and medicinal products inducing QT-prolongation. Concomitant use with medicinal products inducing hypokalaemia (e.g. diuretics, corticosteroids and liquorice root) may aggravate electrolyte imbalance.

2.3 Toxicology

1955 Schmidt L (77) conducted some toxicological studies in rats with cascara sagrada among other substances. He failed to determine a LD 50 because the values showed a large variation. Instead of this he identified a tolerance dose of 6 g/kg for cascara sagrada defined as such dose which did not cause death in 50 rats. The amount of hydroxyanthracene derivatives is not known.

Chronic toxicity was tested in rats by administration of 600 mg/kg KG cascara sagrada daily for 3 months. Eosinophilic precipitations were found in the renal tubules, and the rats developed a fatty liver. Laboratory tests showed negative results.

No recent specific data are available for cascara or the cascarosides with the exception of carcinogenic activity. There exist some data for emodin, aloe-emodin and aloin. We mention the more recent studies. We also refer to the assessment report of the other anthranoid-containing herbal substances.

Emodin

2001 the National Toxicology Programm (NTP) of the U.S. Department of Health and Human Services published a technical report on toxicology and carcinogenesis studies of emodin (21; see also assessment report on frangula bark).

16-day study in F344/N rats

Groups of 5 male and 5 female rats were fed diets containing 0, 600, 2000, 5,500, 17,000, or 50,000 ppm emodin. This corresponds in males to average daily doses of approximately 50, 170, 480, 1,400, or 3,700 mg emodin/kg bw and in females to 50, 160, 460, 1,250, or 2,000 mg/kg bw. 3 female rats died before the end of the study. Mean body weights of males and females exposed to 5,500 ppm and greater were significantly less than those of the controls. Feed consumption by males and females receiving 17,000 or 50,000 ppm was decreased throughout the study. Macroscopic lesions were present in the kidney of rats exposed to 17,000 or 50,000 ppm.

16-day study in B6C3F1 mice

The size of the groups and the administered concentrations were the same as described above. The concentrations correspond in males to average daily doses of approximately 120, 400, 1,200 or 3,800 mg/kg bw and in females to 140, 530, 1,600 or 5,000 mg/kg bw. 50,000 ppm equivalents were not calculated due to high mortality. All mice exposed to 50,000 ppm died before the end of the study.

Mice in the 17,000 ppm groups lost weight during the study. Feed consumption by 5,500 ppm was greater than by the controls. Macroscopic lesions were present in the gallbladder and kidney exposed to 17,000 ppm.

14-week study in rats

Groups of 10 male and 10 female rats were fed diets with 0, 312.5, 625, 1,250, 2,500 or 5,000 ppm emodin. This corresponds to average daily doses of approximately 20, 40, 80, 170, or 300 mg/kg bw in males and females. Among others relative kidney weights of rats exposed to 1,250 ppm or greater and relative lung weights of rats exposed to 625 ppm or greater were significantly increased compared to the control groups. Relative liver weights were increased in females exposed to 625 ppm or greater. The estrous cycle length was significantly increased in females exposed to 1,250 or 5,000 ppm. All male rats exposed to 1,250 ppm or greater and all exposed female rats had pigment in the renal tubules; and the severity of pigmentation generally increased with increasing exposure concentration. The incidences of hyaline droplets in the cortical epithelial cytoplasm were increased in all groups of exposed males and in females exposed to 312.5, 625, or 1,250 ppm.

14-week study in mice

The size of the groups and the administered concentrations were the same as described above. This corresponds to average daily doses of approximately 50, 100, 190, 400, or 800 mg/kg to males and 60, 130, 240, 500, or 1,100 mg/kg to females. Relative kidney weights of male mice exposed to 1,250 ppm or greater, relative lung weights of males exposed to 625 ppm or greater, and relative liver weights of female mice exposed to 625 ppm or greater were increased. The incidences and severities of nephropathy were increased in males and females exposed to 1,250 ppm or greater. The incidences of renal tubule pigmentation were significantly increased in males exposed to 1,250 ppm or greater.

2-year (105 weeks) study in rats

Groups of 65 male and 65 female rats were fed diets containing 0, 280, 830, or 2,500 ppm emodin (equivalent to average daily doses of approximately 110, 320, or 1,000 mg/kg to males and 120, 370, or 1,100 mg/kg to females).

3 Zymbal's gland carcinomas were observed in female rats exposed to 2,500 ppm. This incidence exceeded the range observed for current historical controls and was considered an equivocal finding. At the 6- and 12-month interim evaluations and at 2 years, emodin-related increases in the incidences of renal tubule hyaline droplets occurred in all exposed groups. The incidences of renal tubule pigmentation were significantly increased of all exposed groups of males at 2 years. There were negative trends in the incidences of mononuclear cell leukaemia in male and female rats, and the incidences in the 2,500 ppm groups were significantly decreased. In females exposed to 2,500 ppm, the incidence was below the historical control range; the incidence in males exposed to 2,500 ppm was at the lower end of the historical control range.

2-year study in mice

Groups Of 60 male mice were fed diets containing 0, 160, 312, or 625 ppm emodin (equivalent to average daily doses of approximately 15, 35, or 70 mg/kg) and groups of 60 female mice were fed diets containing 0, 312, 625, or 1,250 ppm emodin (equivalent to average daily doses of approximately 30, 60, or 120 mg/kg). Low incidences of renal tubule adenoma and carcinoma occurred in exposed male mice; these incidences included one carcinoma each in the 312 and 625 ppm groups. Renal tubule neoplasms are rare in male mice, and their presence in these groups suggested a possible association with emodin exposure. At the 12-month interim evaluation, the severity of nephropathy was slightly increased in males exposed to 625 ppm. Also at 12 months, the severity of nephropathy increased from minimal in the lower exposure groups to mild in females exposed to 1,250 ppm; the incidence in this group was significantly increased compared to the control group. At 2 years, the severities of nephropathy were slightly increased in males exposed to 625 ppm and females exposed to 1,250 ppm. The incidences of nephropathy were significantly increased in all exposed groups of females. At the 12-month interim evaluation, the incidences of renal tubule pigmentation were significantly increased in all exposed groups of males and in females exposed to 625 or 1,250 ppm. The severities increased with increasing concentration of exposure. At 2-years, the

incidences of renal tubule pigmentation were significantly increased in all exposed groups; severities also gained with increasing concentration of exposure.

Genetic toxicology

Emodin was mutagenic in *Salmonella typhimurium* strain TA100 in the presence of S9 activation; no mutagenicity was detected in strain TA98, with or without S9. Chromosomal aberrations were induced in cultured Chinese hamster ovary cells treated with emodin, with and without S9. Three separate in vivo micronucleus tests were performed with emodin. A male rat bone marrow micronucleus test, with emodin administered by 3 intraperitoneal injections, gave negative results. Results of acute-exposure (intraperitoneal injection) micronucleus tests in bone marrow and peripheral blood erythrocytes of male and female mice were negative. In a peripheral blood micronucleus test on mice from the 14-week study, negative results were seen in male mice, but a weekly positive response was observed in similarly exposed females.

Conclusion by the “National Toxicology Program’s Board of Scientific Counselors’ Technical Reports Review Subcommittee”:

- The studies give no evidence of carcinogenic activity for male rats and female mice, and equivocal evidence for female rats and male mice.
- In view of conflicting results on genotoxicity, it was noted the first pass effect and need for metabolic activation suggesting a metabolite as the genotoxic form. The metabolite 2-hydroxyemodin acts as the genotoxin (22).

2002 the American Herbal Products Association submitted a review of the data from the National Toxicology Program and relevant to the status of Cascara sagrada ingredients (11). All of the NTP oral feeding studies were of durations which exceed the duration of human exposure. The studies that are nearest the human exposure are the 16 day studies in mice and rats. The most conservative no adverse level (NOAEL) reported for these studies, is 160 mg/kg in female rats and 400 mg/kg in male mice. Assuming that an adult of 70 kg body weight consumes 21 – 100 mg hydroxanthracenes daily (0.3 – 1.43 mg per kg body weight), the association calculated a standard conservative 100-fold margin of safety.

Based on the maximal daily dose of 30 mg hydroxyanthracene recommended in the HMPC monograph of cascara (0.43 mg per kg body weight) a standard conservative 370-fold margin of safety can be calculated.

Concerning the evaluation of carcinogenicity the association concluded that the equivocal evidence of carcinogenicity in female rats in the 2-year feed study is clearly not relevant to humans because humans do not have a Zymbal’s gland and there was no additional data on which the finding of equivocal evidence was made. The equivocal evidence of carcinogenic activity of emodin in male mice based on a single occurrence of uncommon renal tubule neoplasm in each of the highest doses (i.e., at 35 and at 70 mg/kg body weight) but not in the low dose (15 mg/kg body weight). Because of the short-term duration of exposure to cascara this finding would be of questionable relevance to human exposure, just as the sex-specific differences.

Westendorf et al. 1990 (80) reported on the genotoxicity of several structurally related hydroxyanthraquinones. In the *Salmonella* /microsome assay emodin, chrysophanol and physcion were weakly mutagenic in strain TA1537 in the presence of S9 mix only. Chrysophanol was also weakly mutagenic in strain T102 without and with exogenous metabolic activation for induction of mutagenicity. No mutagenic effects were observed in the V79-HGPRT mutation assay and in the unscheduled DNA synthesis (UDS) assay for chrysophanol and physcion. Emodin was highly mutagenic in the V79-HGPRT mutation assay. In the UDS assay emodin was a strong inducer of UDS in primary hepatocytes. Emodin was also tested with respect to its transforming activity in C3H/M2 mouse fibroblasts in vitro. Emodin was clearly active in this in this assay.

Helmholz H et al. 1993 (81) investigated the mutagenic and genotoxic activities of the glycosides emodin and frangulin, and of an alcoholic extract of "*Rhamnus frangula*", and of a commercial frangula bark preparation Sanurtin N® with the aid of the in vitro salmonella/microsome mutagen test and the deoxyribonucleic acid (DNA) repair test of primary rat hepatocytes. 1 g of the alcoholic extract contained 50.76 mg glucofrangulin, 86.84 mg frangulin, 30.88 mg emodin, 10.3 mg pycsion, and 14.32 mg chrysophanol. One coated tablet of Sanurtin N® contained 8.28 mg glucofrangulin, 0.21 mg frangulin, <0.1 mg emodin, and pycsion and chrysophanol only in traces. The tests provided evidence of a dose-dependent increase in the mutation rate or the induction of DNA repair, for the glycosides, the extract of the crude herbal substance and the commercial preparation. The mutagenic potency was larger for emodin than for the alcoholic extract than for frangulin than for Sanurtin N®.

Mengs U et al. 1997 (23) investigated the potential of emodin to induce micronuclei in polychromatic erythrocytes (PCEs). Mice of both genders received a single oral dose of 2000 mg emodin/kg and were killed 24 and 48 h later. Bone marrow cells were collected from 5 males and 5 females and 2000 PCEs per animal were scored for the presence of micronuclei. There was no enhancement in the frequency of micronuclei at both preparation intervals when compared to the negative controls. Blood level examination confirmed the systemic availability of emodin. Plasma levels of up to 190 µg emodin/ml represented concentrations being in the concentration range that induced positive responses in several genotoxicity cell culture assays.

Jahnke GD et al. 2004 (24) evaluated emodin for potential effects on pregnancy outcome. Emodin was administered in feed to timed-mated Sprague-Dawley (CD) rats (0, 425, 850, and 1700 ppm; gestational day (GD) 6-20), and Swiss Albino (CD-1) mice (0, 600, 2500 or 6000 ppm; GD 6-17). Ingested dose was 0, 31, 57, and ~80-144 mg emodin/kg/day (rats) and 0, 94, 391, and 1005 mg emodin/kg/day (mice). Timed-mated animals (23-25/group) were monitored for body weight, feed/water consumption, and clinical signs. At termination (rats: GD 20; mice: GD 17), confirmed pregnant dams (21-25/group) were evaluated for clinical signs: body, liver, kidney, and gravid uterine weights, uterine contents, and number of corpora lutea. Fetuses were weighed, sexed, and examined for external, visceral, and skeletal malformations/variations. There were no maternal deaths. In rats, maternal body weight, weight gain during treatment, and corrected weight exhibited a decreasing trend. Maternal body weight gain during treatment was significantly reduced at the high dose. In mice, maternal body weight and weight gain was decreased at the high dose. Prenatal mortality, live litter size, fetal sex ratio, and morphological development were unaffected in both rats and mice. At the high dose, rat average fetal body weight per litter was unaffected, but was significantly reduced in mice.

The rat maternal lowest observed adverse effect level (LOAEL) was 1700 ppm; the no observed adverse effect level (NOAEL) was 850 ppm. The rat developmental toxicity NOAEL was +/- 1700 ppm. A LOAEL was not established.

In mice, the maternal toxicity LOAEL was 6000 ppm and the NOAEL was 2500 ppm. The developmental toxicity LOAEL was 6000 ppm (reduced fetal body weight) and the NOAEL was 2500 ppm.

The NOAELs for emodin defined by Jahnke GD are twice the decimal power and above the maximum daily dose of hydroxyanthracene derivatives (30 mg). A minimal standard conservative 132-fold margin of safety can be calculated.

Aloe-emodin

Westendorf et al. 1990 (80) also investigated aloe-emodin. In the Ames Test aloe-emodin was mutagenic in *S. typhimurium* strain TA1537 and furthermore active against TA98, TA1538 and TA97 (all frameshift mutant sites). The activity was independent of metabolic activations; in fact, the addition of S9 mix tend to suppress the mutagenicity. In the Mammalian Cell Mutation Test Westendorf et al. reported that aloe-emodin was mutagenic to V79 cells. However, other scientists question this conclusion. The highest concentration employed was 30 µg/ml and did not show much, if any toxicity (see publication). This indicates the possibility of a problem, since mutagenic effects in this assay are typically associated with toxicity. The apparent positive response was based on a very

low spontaneous mutant frequency. Numerous laboratories have recognised that the spontaneous background for HGPRT-mutants (hypoxanthine-guanine phosphoribosyl transferase) is quite variable and increase of at least 3-5 fold are required in duplicate tests to confirm an effect. In the in vitro UDS assay, also conducted by Westendorf et al. 1990, aloe-emodin was associated with a significant increase in net grains/nucleus. 2 trials were reported. The concentrations range in both covered 6.3 µg/ml to 100 µg/ml. At a concentration of 25 µg/ml the net grains/nucleus reached the criteria to call the response positive.

Heidemann A et al. 1996 (25) undertook in vitro and in vivo experiments to clarify the genotoxic potential of the hydroxyanthraquinone aloe-emodin. The results confirmed that aloe-emodin is able to induce mutagenic effects in vitro. In in vivo studies (micronucleus assay in bone marrow cells of NMRI mice; chromosome aberration assay in bone marrow cells of Wistar rats; mouse spot test [DBA/2J x NMRI]) no indication of a mutagenic activity of aloe emodin was found. Information about a possible reaction of aloe-emodin with DNA was derived from an in vivo unscheduled DNA synthesis (UDS) assay. Hepatocytes of aloe-emodin treated male Wistar rats did not show DNA damage via repair synthesis. These data suggest that aloe-emodin is able to interact with DNA under certain in vitro conditions. However, in vivo the results did not indicate a genotoxic potential. Therefore the authors assume that a genotoxic risk for man might be unlikely.

The aim of the study of Schörkhuber M et al. 1998 (26) was to demonstrate the effect of the 1,8-dihydroxyanthraquinone (DHA)-laxatives, danthron, rheim, aloe-emodin and sennidine, on colorectal tumour cells because the available information is still inconclusive. In SW480 carcinoma cultures, dose-dependent induction of urokinase secretion into the medium was the predominant effect. Simultaneously, cell numbers were decreased by DHA-aglyka, but not by sennoside or the biphenylic laxative bisacodyl. DNA synthesis was not similarly reduced: 0.4-4 microM danthron and sennidine even stimulated 5-bromo-2'-deoxyuridine (BrdU) uptake into DNA. When uptake was normalised to cell number, danthron and sennidine doubled BrdU uptake/10(6) cells, 18 microM rheim and 0.7 microM aloe-emodin induced increases of 37 and 50%, respectively. This may at least partially be due to selective resistance of S-phase cells to DHA-caused cell loss. In VACO235 adenoma cells, sennidine and aloe-emodin did not affect urokinase secretion, but stimulated growth. Both cell numbers and DNA synthesis were increased. In contrast to SW480 carcinoma cells, VACO235 cells were also sensitive to sennoside and bisacodyl. No effects of DHA were observed in normal colorectal epithelial cells. The biological effects were preceded by specific phosphorylation of cellular proteins with molecular weights of 110, 78, 63, 57 kCa, indicating the specific induction of a cellular signalling cascade by the laxatives.

Aloin

Studies with aloin showed low acute and subchronic toxicity in rats and mice. Aloin at doses up to 60 mg/kg daily for 20 weeks showed no specific toxic effects in mice (3).

Aloin A at doses of up to 200 mg/kg body weight showed no evidence of any embryolethal, teratogenic or foetotoxic effects in rats (3).

In a model of dimethylhydrazine(DMH)-induced colorectal tumours in male mice neither aloin- nor sennoside-enriched diets (0.03% corresponding to 100 mg/kg/day) did promote incidence and growth of adenomas and carcinomas after 20 weeks as evidenced by different endpoint parameters, based on a macroscopic evaluation and microscopic examination. In the DMH-induced tumour model a tumour incidence appeared which allowed an increasing or decreasing effect to be detected after additional treatment, i.e. a 50% incidence of tumour-bearing animals. With regard to hepatotoxic and nephrotoxic effects, DMH itself enhanced plasma levels of GPT and SDH which were further significantly increased by coadministration of aloin. The anthranoids alone had no effect. No effects on serum electrolyte concentrations were observed after any of the treatments (27).

Cascara

Mereto E et al. 1996 (28) investigated anthraquinone glycosides of senna and cascara for their ability to induce aberrant crypt foci (ACF) in the rat colon mucosa, which are considered putative preneoplastic lesions. Dietary exposure to high doses of these glycosides for 56 successive days did not cause appearance of ACF or increase of incidence of ACF induced by 1,2-dimethyl-hydrazine (DMH). However, in rats treated with both DMH and the highest dose of glycosides, the average number of aberrant crypts per focus, considered a consistent predictor of tumour outcome, was higher than in rats given DMH alone. These findings suggest that senna and cascara glycoside might behave as weak promoters in rat carcinogenesis.

Borelli F et al. 2001 (29) investigated the effects of bisacodyl (4.3 and 43 mg/kg) and cascara (140 and 420 mg/kg) on azoxymethane (AOM)-induced aberrant crypt foci (ACF) and tumours. Rats, divided in 10 groups were treated with AOM and laxatives (alone or in combination) for 13 weeks. At the end of treatment animals were killed and the colon removed and examined. Cascara did not induce the development of colonic ACF and tumours and did not modify the number of AOM-induced ACF and tumours in both doses. Bisacodyl given alone, did not induce the development of colonic ACF and tumours in both doses, too. However, bisacodyl (4.3 mg/kg) coupled with AOM increased the number of crypt per focus, but not the number of tumours. Bisacodyl (43 mg/kg) significantly increased the number of crypt per focus and tumours. The results of this study indicate the absence of any promoting or initiating activity of a laxative and diarrhoeal dose of cascara.

Assessor's Overall Conclusions on Toxicology

Experimental data, mainly in vitro tests showed a genotoxic risk of several anthranoids. Most of the in-vivo studies showed no effect or only equivocal effects.

Mueller SO et al. 1999 concluded in their publication "Occurrence of emodin, chrysophanol and physcion in vegetables, herbs and liquors. Genotoxicity and anti-genotoxicity of the anthraquinones and of whole plants" (36), although three common vegetables have been shown to contain anthraquinones, data on their genotoxicity alone should not be used to derive a human risk. The authors analysed vegetables, herbs and herbal-flavoured liquids for the quantitative determination of the content of the aglycosidic anthraquinones emodin, chrysophanol and physcion. For example emodin, chrysophanol and physcion were found in lettuce and beans, and emodin and physcion in peas. For emodin the authors had shown unequivocal genotoxic potency in mammalian cells. On the contrary, chrysophanol and physcion showed borderline effects, and physcion was cytotoxic at higher concentrations. The lyophilisates of these vegetables were tested in the micronucleus test in lymphoma cells, alone and in combination with the known genotoxic and carcinogenic anthraquinone danthrone. None of the lyophilisates increased the frequency of micronuclei. Surprisingly, the genotoxicity of danthrone was reduced significantly by addition of the vegetables lyophilisates. The authors concluded that the vegetables as a whole contain numerous other constituents some of which might also have protective effects and therefore for evaluation of a putative human health risk from dietary mutagens, the assessment should not be based on measured concentrations of mutagens.

This is also to be considered in anthranoid-containing herbal substances like cascara which also are combinations of numerous constituents.

3 CLINICAL DATA

3.1 Clinical Pharmacology

3.1.1 Pharmacokinetics

Cascara

Vyth A et al. 1979 (30) isolated aloe-emodin, emodin and chrysophanol from a powdered cascara extract after oxidative hydrolysis. After oral administration of 60 mg or 100 mg of a powdered cascara extract in 2 volunteers, rhein and traces of chrysophanol were found in human urine. Because rhein was not present in the administered extract the authors suggested a process in the body in which for example chrysophanol is oxidised to rhein.

Other anthranoids

The ESCOP monograph of RHAMNI PURSHIANI CORTEX (31 in 3) mentioned an unpublished research report of a human pharmacokinetic study in 6 healthy volunteers. After oral administration of aloes (equivalent to 16.4 mg of hydroxyanthracene derivatives) for 7 days, aloe-emodin was detected as a metabolite in the plasma only sporadically and with maximum concentrations of less than 2 ng/ml. In the same study rhein was detected in the plasma in concentrations ranging from 6-28 ng/ml after single dose administration. In 7-day administration there was no evidence of accumulation of rhein.

3.1.2 Pharmacodynamics

Laxative effects

There are no pharmacodynamic data with cascara or its preparations in humans available.

Constipation is said to be present when the stools passed are of hard consistency and when evacuation of the faeces is too difficult, too infrequent and irregular. The physiological range for frequency of bowel movements is wide, extending from defaecation three times daily to once only every 2 to 3 days. In the pathogenesis of constipation the colon plays a key role because this is where the contents of the gut remain for 24 – 48 hours. During this period the liquid contents from the small intestine are converted into faeces by the absorption of water and electrolytes in response to the action of bacteria. These functions are dependent on the interplay of peristaltic processes which mix the contents and the normal coordination of the anorectal muscles during defaecation. A disturbance involving any of these individual areas may lead to constipation. In this context, functional disturbances are far more common than those of an organic variety. In addition, assessment is problematic because the symptoms are perceived differently by the individuals affected (31, 32), due to different concepts of toilet training.

Based on animals experiments and experiences with other anthranoid-containing herbal substances the laxative effect in humans is also caused by the two mechanisms described in chapter 2.2.1.

Koch A 1995 (35) evaluated the laxative effect of aloin in experiments on herself. Neither a dose of 20 mg aloin nor an increase to 60 mg aloin caused a laxative effect. Aloin was found in the faeces.

Koch A 1995 (35) gave 50 mg aloin in a gelatine capsule to 3 patients in the evening at 8 p.m. Test person A (female) fed upon vegetable and animal products, test person E (female) predominantly fed upon fish and meat and test person H (male) was a vegetarian. Test person A experienced soft stools once at day 1 and 2 and normal stools at day 3. Test person E experienced soft stools at day 1 for four times. Test person H experienced soft stools once at day 1, 2 and 3. These different results corresponded to the cleavage of aloin and appearance of aloin-emodin in the faeces. Test person E consumed an oral ferric product additionally. This product seemed to support the cleavage of aloin. This was confirmed when test person A received a ferric product to. The author concluded that the laxative effect depends on the cleavage of aloin in aloin-emodin.

Cascara acts within 6 to 12 hours due to the time taken for transport to the colon and metabolism into the active compounds (3).

Other effects

Foert E et al.1994 (42) conducted a study to evaluate if a fluid extract of cascara leads to a reduction of gallbladder volume in healthy human subjects. Sufficient gallbladder-motor function was documented by a more than 50% reduction of gallbladder-volume after a test-meal. Gallbladder-emptying was compared to placebo by ultrasonography using the ellipsoid method. Gallbladder-volume was measured in intervals of 10 min for a time period of 120 min. On day 1 all subjects had the test meal. On day 2 and 3 cascara extract or placebo were given in random order. 20 volunteers received 2 ml, 20 received 3 ml containing 36 mg or 54 mg Cascaroside A, respectively. 54 mg Cascarosid A cause a significant gallbladder-contraction. This effect is more rapid but less intense than after the test meal.

3.2 Clinical Efficacy Studies

3.2.1 Dose response studies

There are no dose response studies available.

The recommended dosage as a laxative for adults, elderly and adolescents over 12 years (10 – 30 mg hydroxyanthracene derivatives only once daily at night) is supported by experts' opinions and by clinical investigations with other anthranoid-containing laxatives like senna preparations. We refer to the assessment report of Cassia senna L. et Cassia angustifolia Vahl, folium.

The German monograph of Rhamni purshianae cortex (1) indicates a daily dose of 20 – 30 mg hydroxyanthracene derivatives calculated as cascarioside A, but recommends that the pharmaceutical form must allow lower dosages than the usual daily dose.

The ESCOP monograph for "RHAMNI PURSHIANI CORTEX", 2nd edition, (3) also recommends 20 – 30 mg hydroxyanthracene derivatives.

The recommendation in the German pharmacovigilance actions for anthranoid-containing laxatives of 21 June 1996 (2) only determines a daily maximum limit of 30 mg hydroxyanthracene derivatives in consideration of the toxicological data.

The patient has to be informed that the correct individual dose is the smallest required to produce a comfortable soft-formed motion. Therefore we prefer to recommend a larger range of 10 – 30 mg hydroxyanthracene derivatives daily.

Normally it is sufficient to take an anthranoid-containing laxative up to two to three times a week (78).

3.2.2 Clinical studies (Case studies and Clinical trials)

Laxative effect

Stern FH 1966 (39) investigated the effect of a preparation containing 162 mg of prune concentrate and 162 mg of cascarin/tablet in functional constipation in a randomised double-blind study. 25 elderly institutionalised patients of private nursing home (59 to 86 years, median: 70.7 years), refractory to other laxatives, were treated with 2 tablets before breakfast and 2 tablets one hour before bedtime, for three days. Then the dosage was reduced to a maintenance level (2 x 1) for 18 days. The same procedure was followed with a placebo. Consistency of stool, control of defaecatory pattern, lack of side effects other than mild cramps due to overdosage, and acceptance of the medication by patient were monitored. In 22 of the 25 patients (88%) the test preparation fulfilled all four of the criteria. In 1 patient (4%), it caused watery or loose stools even when the dosage was reduced to 1 tablet daily. In 2 patients (8%) it did not fulfill any of the criteria. Placebo did not have any effect.

Mauracher E et al. 1976 (40) compared 15 mg glucofrangulin (purified extract from frangula bark) with 5 mg bisacodyl (Dulcolax®) and 0.1 g of a water soluble glucoside extract from cascara (Peristaltin®, the amount of anthranoides is not specified) in a randomised double-blind crossover trial. Within a period of 3 weeks, 47 patients (most of them older than 70 years) with chronic constipation were treated consecutively for 5 days with each laxative. Each treatment phase was followed by a placebo phase of 2 days. Glucofrangulin was shown to be most effective in cases of severe constipation; in moderate cases, the effectiveness of the three test preparations did not differ significantly. Concerning the number of defaecation or number of days with defaecation, respectively, per 10 dragées, glucofrangulin showed a significant superiority. Amount of faeces, consistency and colour did not show any considerable differences. All preparations were about equally well tolerated with a slightly lower frequency of meteorism during the treatment with glucofrangulin.

Borgia M et al. 1985 (41) carried out a double-blind double-controlled trial in 4 centers. 359 patients with slight or moderate functional disorders of the gastrointestinal tract were included. The effect of a combination of herbs with rhubarb, gentian, boldus and cascara (91 patients) was compared with the effect of placebo (90 patients), the effect of a combination with rhubarb and gentian (90 patients), and the effect of a combination with boldus and cascara (88 patients). The amount of anthranoides is not specified. The test preparation with rhubarb, gentian, boldus and cascara was more effective than the inert control excluding the disturbances not related to the pharmacological activities of the components. Combinations of the components “rhubarb + gentian” and “boldus + cascara” tested as active controls, showed significant favourable effects on disturbances of appetite and digestion and on constipation respectively.

Bowel cleansing effect

Wicke L 1981 (43) investigated the cleansing effect of Cascara® and Salax® on the colon as preparatory to barium enemas. The amount of anthranoides in Cascara® is not defined. Salax® is a saline cathartic (magnesium sulphate, citric acid, bicarbonate of potassium). 67 patients (22 – 88 years old) were treated with 2 tablets Cascara® and 1 sachet Salax® at 12 o'clock a.m. and between 5 and 7 o'clock p.m. 2 hours after having supper. The patients had to intake at least 1 ½ l fluid after each administration. If there were less than 4 defaecation after administration an enema with Klyx-MagnumN® was performed 1 to 1 ½ hour before examination. The method showed very good results with very less side-effects. 41 patients (54.6 %) showed an excellent cleansing effect, 21 patients (28 %) a very good effect, 8 patients (10.6 %) a good effect, and 5 patients (6.6 %) a poor effect. 6 patients complained of dizziness, and 6 patients of abdominal pain before the examination.

Novetsky GJ et al. 1981 (44) tested different modes of colon cleansing regimes prior to gallium-67 scintigrams to investigate colonic accumulation of gallium-67, which frequently complicates the interpretation of the scintigrams. 309 patients were randomly assigned to one of 4 cleansing regimes: (1) 78 patients undertook a high fiber diet (minimum of 11.2 g fiber and 6 to 8 cups of fluid each day 3 consecutive days prior to scintigram); (2) 76 patients took 30 ml of castor oil each night for 2 consecutive nights before scintigram; (3) 76 patients took 30 ml of milk of magnesia (no further information is given) and 5 ml of cascara (the amount of anthranoides is not defined) each night for 3 consecutive nights before scintigram; (4) 79 patients did not undertake any preparation. Patient compliance rates for the 4 regimes were 17%, 32%, 36%, and 46%, respectively. Gallium-67 scintigrams were graded for colonic activity on a scale of 0-3 by 3 independent observers. 3 represents a bowel with the highest gallium-67 activity. Gallium-67 activity in the colon was significantly less after administration of castor oil than after no preparation ($p=0.047$). A high fiber diet also resulted in a substantial reduction in colonic activity when compared with no preparation but without statistical significance ($p=0.083$). Regimen 3 did not produce significantly better results than regimen 4 ($p=0.42$).

Fork FT et al. 1982 (45) conducted a three-part trial in 1200 patients to study the purgative effect of different colon cleansing regimes. The cleansing effect was scored with regard to retained faecal residue evident on double-contrast studies of the colon (1=excellent: no retained faecal material visible on double-contrast enema (DCE) film on the colon; 2=good: minimal faecal material not interfering with interpretation of DCE; 3=fair: moderate faecal debris – small polyps up to 5 mm could not be excluded; 4=poor: considerable faecal residue, sufficient to compromise the examination). The radiologist, departmental personnel, and the patient were not informed about the type of colon preparation. The films were interpreted separately and judged with regard to colon cleansing by 2 independent radiologists. Part 1 of the investigation compared 2 standard bowel cleansing systems, bisacodyl and Cascara-Salax (cascara and magnesium sulphate; the amount of anthranoides is not defined), with combinations of sodium picosulfate and magnesium citrate. An increase in salt content by 30% due to addition of saline laxative to bisacodyl (part 2) significantly increased cleansing efficacy (good cleansing effect in 52% - 80% of the patients. With an additional water enema 1 hour before the colon examination, the results were still better (part 3). 96% of the colons were clean. The taste and the effects of the cleansing systems were tolerated favourably by more than 90% of the patients.

Hangartner PJ et al. 1989 (46) compared the efficacy (by colonoscopy) and patient acceptance of 3 cleansing regimes in a randomized clinical trial. 300 consecutive outpatients undergoing colonoscopy were randomly divided into 3 groups receiving one of 3 cleansing regimes: 1: Golytely (polyethylene glycol electrolyte solution) 4 liters, 2: Golytely 2 liters with Cascara-Salax (the amount of anthranoides is not defined) and 3: X-Prep (150 mg sennosides A and B) with enema. The cleanliness of the colon was assessed on the basis of the following criteria: a) no stool residue, b) stool-liquid mixture that was readily suctioned off, c) solid stool, and d) frequency of endoscope blockage. All patients were questioned about side effects and overall acceptance. X-Prep caused significantly more abdominal cramps than 4 liters of Golytely or 2 liters Golytely with Cascara-Salax ($p < 0.001$). Vomiting was most frequent in group 1 ($p < 0.05$ vs. group 3). The cleanest colon was obtained with 4 liters of Golytely, while 2 liters of Golytely with Cascara-Salax was least efficacious. The quality of the examination was equal in groups 1 and 3, and clearly better than in group 2 ($p < 0.01$).

Looking at clinical side-effects, effectiveness and tolerability **Phillip J et al. 1990** (47) compared 2 bowel cleansing regimes: the saline solution Golytely vs. a conventional preparatory procedure (Cascara-Salax) in a prospective study including 28 patients with macroscopic normal mucosa. The performing doctor's evaluation of the colonic cleaning effect and examination conditions showed Golytely significantly ahead of Cascara-Salax. There was no significant difference concerning weight, blood pressure, pulse rate, body temperature or essential laboratory findings. Whereas preparation using Cascara-Salax was less molesting stated by the patients, there was no difference in the way colonoscopy itself was tolerated in both groups. Histologically, colonic mucous layers depicted changes in the Cascara-Salax group in 63% vs. 40% in the Golytely group without statistical significance.

Børkje B et al. 1991 (48) compared the effectiveness and acceptability of 3 colon cleansing regimens for colonoscopy in a prospective study in 271 in- and out-patients. Regimen I (88 patients): during the last 3 days before examination only a liquid diet was allowed. On each of these days a senna preparation (X-Prep, the amount of anthranoides is not defined), and on the day of the examination a 1-l isotonic sodium chloride enema were given. Regimen II (90 patients): the day before examination only a liquid diet was allowed. In the afternoon the patients were asked to drink 4 l of the Golytely formulation during 4 h. Regimen III (93 patients): after breakfast the day before examination a Cascara-Salax laxative (PicoSalax, the amount of anthranoides is not defined) was taken; thereafter only a liquid diet was allowed. The laxative was repeated in the afternoon, after which a 1.5-l Golytely formulation was drunk during ½ h. The overall impression of palatability and convenience and the completeness of the preparation, respectively, were measured on 0- to 10-cm visual analogue scales. No differences were found concerning impression of palatability or convenience. A significantly cleaner colon was obtained with regimen II in outpatients than with regimen I ($p = 0.02$), whereas no

differences were found either between regimens I and III or between regimens II and III. With regimen I, II, and III, 14%, 8%, and 12% of the patients, respectively, had scores indicating inadequate preparation. In hospitalised patients the 3 regimens had practically equal cleansing effects. Outpatients had a significantly cleaner colon than inpatients. The authors concluded that no clinically important differences were found between the 3 regimens.

3.2.3 Clinical studies in special populations (such as elderly and children)

Use in children

First of all change of nutrition is recommended in constipated children with an increase in daily fibre intake. It is recommended that children older than 2 years of age should increase their intake of dietary fibre to an amount equal or greater than their age plus 5 g (50). The behaviour has to modify additionally, e.g. increased physical exercise.

There are no systematic clinical data available which evaluate the use of cascara as a laxative in children.

There are several reports of local intolerance of a high dose senna preparation on skin in children wearing napkins. These skin irritations were bullous and comparable with skin irritations caused by scalds (54).

According to the ESCOP and WHO monographs the use for children under 10 years cannot be recommended. According to the “NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE PAEDIATRIC POPULATION” (CPMP/ICH/2711/99) of 27 July 2000 and other monographs age limit for children should be determined to “12 years of age”.

Use in elderly

When cascara preparations are administered to incontinent adults, pads should be changed more frequently to prevent extended skin contact with faeces because of the experiences in children wearing napkins.

3.2.4 Assessor’s Overall Conclusions on Clinical Efficacy

There is only one randomised double-blind crossover trial available which assessed the laxative effect of a monopreparation of cascara. The amount of anthranoides is not given. In moderate cases of constipation, the effectiveness of the cascara preparation was equal to the effectiveness of glucofrangulin or bisacodyl. Glucofrangulin was shown to be most effective in cases of severe constipation.

The postulated laxative effect is mainly based on the pharmacological data, experts’ opinions (German monograph, ESCOP monograph) and clinical experiences. Clinical and pharmacological data obtained from other anthranoid-containing laxatives (we refer to the assessment report of SENNAE FOLIUM) and investigations with combination preparations support the efficacy of this also anthranoid-containing herbal substance for short term use in cases of occasional constipation. The current level of evidence for “the short term use of occasional constipation” can be identified as III although there exist one randomised cross over study but with some shortcomings (e.g. no definite dosis, a very short wash out phase of 2 days).

All investigations to assess the bowel cleansing effect of cascara were conducted with a combination of a cascara preparation and a saline cathartic (magnesium sulphate). Therefore the effectiveness of cascara alone cannot be assessed. Anyway the combination preparation with cascara was inferior to a Golytely regimen.

3.3 Clinical Safety

3.3.1 Contraindications

Cascara preparations should not be used by patients with known hypersensitivity to cascara.

Furthermore cascara containing medicinal products should not be used in cases of intestinal obstructions and stenosis, atony, appendicitis, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis); abdominal pain of unknown origin; severe dehydration states with water and electrolyte depletion like all anthranoid-containing laxatives.

3.3.2 Special warning/precautions for use

Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, corticosteroids or liquorice root, have to consult a doctor before taking cascara preparations concomitantly.

Like all laxatives, cascara containing medicinal products should not be taken by patients suffering from faecal impaction and undiagnosed, acute or persistent gastro-intestinal complaints, e.g. abdominal pain, nausea and vomiting unless advised by a doctor because these symptoms can be signs of potential or existing intestinal blockage (ileus).

If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of stimulating laxatives should be avoided.

Use for more than 1 - 2 weeks requires medical supervision. Cascara preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.

See also point 3.3.5 drug abuse.

3.3.3 Adverse events

In the study of Mauracher E et al. 1976 (40) glucofrangulin (purified extract from frangula bark), bisacodyl, and a water soluble glucoside extract from cascara were about equally well tolerated with a slightly lower frequency of meteorism during the treatment with glucofrangulin.

Like all anthranoid-containing laxatives cascara preparations may produce abdominal pain and colicky gastrointestinal symptoms and passage of liquid stools, in particular in patients with irritable colon. However, these symptoms may also occur generally as a consequence of individual overdosage. In such cases dose reduction is necessary. The correct individual dose is the smallest required to produce a comfortable soft-formed motion (2).

Like mentioned above hypersensitive reactions may occur.

Chronic use may lead to disorders in water equilibrium and electrolyte metabolism.

Chronic use may result in albuminuria and haematuria.

Furthermore, use over a long period may lead to pigmentation of the intestinal mucosa (pseudomelanosis coli), which usually recedes when the patient stops taking the preparation.

Yellow or red-brown (pH dependent) discolouration of urine by metabolites, which is not clinically significant, may occur during the treatment.

The German Health Authority has received 2 reports of adverse events.

Melanosis coli was detected in a 42-year old woman after administration of a mono-preparation of cascara for 4 years.

Another patient has developed urticaria taking a combination of cascara and a saline agent. He has concomitantly used mebeverine, but cascara was designed to be suspected.

Giavina-Bianchi Jr PF et al. 1997 (76) reported a case of a 30-year-old man, who had been working for 2 years in a pharmacy where he weighed and prepared chemical products without using a mask, gloves, or other protective materials. This man started to experience episodes of sneezing, coryza, and nasal pruritus and congestion after 6 months of work. Later he developed a dry cough, chest pain, sensations of chest tightening, dyspnea, and wheezing. The symptoms worsened when he entered the pharmacy, and when he manipulated capsules containing cascara sagrada and passion flower preparations. Laboratory tests showed 14% eosinophilia with 8,000 leukocytes per μ l and total IgE levels of 1130 IU/ml. The prick test was positive for cascara sagrada and passion flower at all dilutions tested.

Adesunloye BM 2003 (68) described a case of a 52-year-old woman with hemoglobin SC disease, who developed acute tubulointerstitial nephritis after 5-day administration of the herbal remedy CKLS. Following hemodialysis, the renal function improved. CKLS comprises a mixture of ingredients, among which are aloe vera, chamomile, cascara sagrada, chaparral (creosote bush), mullein (*Verbascum thapsus*), uva ursi, fenugreek, cayenne, dandelion, and eucalyptus. It is supposed to be a colon, kidney, liver, and spleen purifier. The authors concluded that the nephrotoxicity observed was most likely caused by aloe vera and cascara sagrada. However, uva ursi has been associated with albuminuria, hematuria, and urine cast, and chaparral with cystic renal disease and cystic renal cell carcinoma. There is no detailed information available concerning the exact preparation and amount of anthranoids. The causality cannot be assessed.

3.3.4 Overdose

Like for all anthranoid-containing laxatives the major symptoms of overdose / abuse are griping and severe diarrhoea with consequent losses of fluid and electrolyte, which should be replaced. Diarrhoea may cause potassium depletion, in particular. Potassium depletion may lead to cardiac disorders and muscular asthenia, particularly where cardiac glycosides, diuretics or corticosteroids are being taken at the same time.

Treatment should be supportive with generous amounts of fluid. Electrolytes, especially potassium, should be monitored. This is especially important in the elderly. Furthermore chronic ingested overdoses of anthranoid containing medicinal products may lead to toxic hepatitis (see below).

Hepatitis

Nadir A et al. 2000 (67) reported a case of a severe cholestatic hepatitis in a 48-year-old Mexican male, who developed right upper quadrant pain, nausea, anorexia, abdominal bloating, and yellowing of his skin with increase of the liver enzymes 3 days after using cascara sagrada, one capsule three times a day for 3 days. Each of these capsules contained 425 mg of aged cascara sagrada bark, having a reported 5 % cascarioide potency (21,25 mg). He concomitantly used amitriptyline 25 mg at bedtime, cimetidine 400 mg, and baclofen 10 mg twice a day. With exception of cascara sagrada, these medications were continued. The patient was known to use alcohol in moderate amounts for up to 3 years prior to this event. One week later, he was known to have ascites. Over the next 3 months, the patient experienced resolution of both his ascites and jaundice.

To assess this case of liver impairment we have used the Roussel UCLAF causality assessment method. In 1993, an international group of experts published the so-called RUCAM Score to evaluate cases of hepatotoxicity (Danan et al 1993 (65)). The score was validated and the results published (Benihou et al. 1993 (66)).

Assessment

Rucam Score +2 unlikely: The liver injury in this case is classified as a mixed liver injury. ALT increased to 999 U/L (normal range 7-56 U/L) and alkaline phosphatase to 309 U/L (normal range 43-122 U/L). No information is given of the course of these parameters. The time to onset was less than 5 days. Moderate use of alcohol is known. Baclofen and amitriptyline are known to cause increase of liver enzymes. No rechallenge took place. The ingested dose of cascara sagrada was twice the recommended.

Beuers U et al. 1991 (55) reported a case of toxic hepatitis related to abuse of senna glycosides in a 26-year-old female who had taken an extract of senna fruits corresponding to 100 mg of sennoside B daily in addition to the usual dose of 10g senna leaves twice a week in a laxative tea. When the patient stopped taking senna, aminotransferases fell by 70% within a week and ranged from 20 – 40 U/l subsequently. When the patient took senna alkaloids again, 2 months later, liver function rapidly deteriorated and improved once more when the product was stopped.

Vanderperren B et al. 2005 (56) reported a case of a 52-year-old woman who had ingested, for more than 3 years, one litre of an herbal tea each day made from a bag containing 70 g of dry senna fruits. She developed renal impairment and acute hepatic failure with increase in prothrombin time (international normalised ratio > 7) and development of encephalopathy. The patient recovered with supportive therapy. Surprisingly, large amounts of cadmium were transiently recovered in the urine.

According to the Rucam score these two hepatotoxic cases are related to the chronic ingested overdoses. Rhamni purshiana, cortex, is also an anthranoid containing herbal substance and therefore we also point out the possibility of toxic hepatic reactions in this chapter for cascara.

3.3.5 Drug abuse

It cannot be assessed definitely, if a longer than a brief period of treatment with stimulating laxatives leads to dependence requiring increasing quantities of the medicinal product, an atonic colon with impaired function and aggravation of the constipation.

Müller-Lissner 2005 (57) concludes that the arguments in favour of laxative-induced damage to the autonomous nervous system of the colon are based on poorly documented experiments and that the investigations that do not support such damage are well done. The cited references (Smith B 1968 (58); Riemann JF et al. 1980 (59) and 1982 (60); Berkelhammer C et al. 2002 (61); Meisel JL et al. 1977 (62); Pockros PJ et al. 1985 (63)) show abnormalities observed in humans (damage to enteric nerves, smooth muscle atrophy; distension or ballooning of axons, reduction of nerv-specific cell structures and increase in lysosomes, and sometimes a total degeneration of whole nerve fibers; short-lived superficial damage to the mucosa). They are uncontrolled observations and therefore the author concludes that the cause of these damages can also be the constipation itself or pre-existing changes of unknown etiology.

The only study comparing the morphology of the autonomous nervous system of constipated patients taking anthraquinones (aloe) to that of an appropriate control group of constipated patients without laxative intake (Riecken EO et al. 1990 (64)) does not support the hypothesis that anthraquinone containing laxatives are able to provoke relevant degenerative changes in the colonic nerve tissue. But this investigation was only conducted in 11 matched pairs only.

For safety concerns we inform the patients that if stimulating laxatives are taken for longer than a brief period of treatment, this may lead to impaired function of the intestine and dependence on laxatives.

Controversial discussion is done whether chronic use of anthranoid-containing laxatives promotes the development of colorectal carcinomas.

Siegers C-P et al. 1993 (83) reported about a retrospective study of 3,049 patients who underwent diagnostic colorectal endoscopy. The incidence of pseudomelanosis coli was 3.13% in patients without pathological changes. In those with colorectal adenomas, the incidence increased to 8.64% ($p < 0.01$), and in those with colorectal carcinomas it was 3.29%. This lower rate was probably caused by incomplete documentation of pseudomelanosis coli in those with carcinoma. In a prospective study of 1,095 patients, the incidence of pseudomelanosis coli was 6.9% in patients with no abnormality seen on endoscopy, 9.8% ($p = 0.068$) in patients with adenomas and 18.6% in patients with colorectal carcinomas. From these data a relative risk of 3.04 (1.18, 4.9; 95% confidence interval) can be calculated for colorectal cancer as a result of anthranoid laxative abuse if the pseudomelanosis coli in patients with no abnormality is calculated with 1 %.

Kune GA et al. 1988 (84) and Kune GA 1993 (85) reported of the “Melbourne Colorectal Cancer Study”. Commercial laxative use as a risk factor in colorectal cancer was investigated as one part of

this large population based epidemiological study of colorectal incidence, aetiology and survival. Commercial laxative use was similar in 685 colorectal cancer patients and 723 age/sex matched community based controls. Also, when laxatives were subdivided into various groups containing anthraquinones, phenolphthalein, mineral salts and others, previous laxative intake was similar between cases and controls. Previous use of anthraquinone laxatives and of phenolphthalein containing laxatives was not associated with the risk of colorectal cancer. Furthermore the results of this study suggest that chronic constipation, diarrhoea, and the frequency and consistency of bowel motions are unlikely to be aetiologic factors in the development of colorectal cancer. They indicate that it is the diet and not the constipation that is associated with the risk of large-bowel cancer. Additionally, a highly statistically significant association ($p=0.02$) was found with the risk of colorectal cancer in those who reported constipation and also had a high fat intake.

In a retrospective study a cohort of 2,277 patients was defined by colonoscopy. Among other factors Nusko G et al. 1993 (86) tested whether in these patients laxative use or the endoscopically diagnosed presence of melanosis coli were risk factors related to colorectal neoplasm. In comparison to patients taking no laxatives there was no significant increase in colorectal cancer rate either in laxatives users or in patients with melanosis coli. However, there was a statistically significant association between the occurrence of colorectal adenomas and laxative use (relative risk of all patients exposed to laxatives = 1.72; of patients exposed to laxatives without melanosis coli = 1.47). The relative risk of adenoma development in patients with melanosis coli was 2.19. Taking into account that polyps can be diagnosed in the dark mucosa of melanosis coli patients more easily, the authors concluded that even this relative risk of 2.19 seems to be related to a generally enhanced risk of laxative intake rather than to a special group of (anthranoid containing) laxatives.

Sonnenberg A and Muller AD 1993 (87) performed a meta-analysis, since individual case-control studies have failed to resolve the question whether constipation and use of cathartics represent significant risk factors of colorectal cancer. The analysis of 14 previously (from 1954 to 1988) published case-control studies revealed statistically significant risks for colorectal cancer associated with both constipation and use of cathartics, the pooled odds ratios and their 95 percent confidence intervals being 1.48 (1.32-1.66) and 1.46 (1.33-1.61), respectively. The increased risk applied similarly to both sexes, it was higher in cancer of the colon than rectum. Since constipation and cathartics are associated with much lower odds ratio than various dietary components, such as fat, meat, alcohol, and low-vegetable or low-residue diets, the authors concluded that their risks reflects the confounding influence of underlying dietary habits.

Loew D et al. 1994 (88) conducted a comparative study involving 423 patients with colorectal neoplasms and 522 patients with benign proctologic disorders who were regular users of laxatives for bowel regulation. A pseudomelanosis coli (PMC) test was used as an indicator of exposure to anthranoid-containing laxatives to determine if these preparations were potential colorectal carcinogenics. Results indicated no significant difference of the PMC rates between carcinoma (6.1%) and the control groups (4.2%) ($p<=0.197$).

Jacobs EJ et White E 1998 (89) examined the associations of colon cancer with constipation and use of commercial laxatives in a case-control study (424 incident cases and 414 random-digital-dial controls). Constipation was defined by "feeling constipated to the point of having to take something". The adjusted relative risk (RR) was 2.0 [95% confidence interval (CI) = 1.2-3.6] for constipation 12-51 times per year, and 4.4 (95%CI = 2.1-8.9) for constipation 52 or more times a year. Cumulative lifetime use of commercial laxatives was also associated with increased risk of colon cancer. When adjusted for constipation, commercial laxative use was no longer associated with increased risk (RR = 0.3, 95%CI = 0.1-0.9 for less than 350 uses; RR = 0.9, 95% CI = 0.4-2.3 for 350 or more uses). The association with constipation remained. In this study no subject reported use of anthranoid-containing laxatives.

Nusko G et al. 2000 (90) performed a prospective case control study at the University of Erlangen to investigate the risk of anthranoid-containing laxative use for the development of colorectal adenomas or carcinomas. A total of 202 patients with newly diagnosed colorectal carcinomas, 114 patients with adenomatous polyp, and 238 patients (controls) with no colorectal neoplasm who had been referred

for total colonoscopy were studied. The use of anthranoid preparations was assessed by standardised interview, and endoscopically visible or microscopic melanosis coli was studied by histopathological examination. There was no statistically significant risk of anthranoid use for the development of colorectal adenomas (unadjusted odds ratio 1.0; 95% CI 0.5-1.9) or carcinomas (unadjusted odds ratio 1.0; 95% CI 0.6-1.8). Even after adjustment for the risk factors age, sex, and blood in the stools by logistic regression analysis the odds ratio for adenomas was 0.84 (95% CI 0.4-1.7) and for carcinomas 0.93 (95% CI 0.5-1.7). Also, there were no differences between the patient and control groups for duration of intake. Macroscopic and high grade microscopic melanosis coli were not significant risk factors for the development of adenomas or carcinomas.

Willems M et al. 2003 (95) describe a case of melanosis coli, which occurred in a 39-year-old liver transplant patient who took an over-the-counter product containing aloe, rheum and frangula. The typical brownish pigmentation of the colonic mucosa developed in a period of ten months. The anthranoid medication was stopped and follow-up colonoscopy one year later showed normal looking mucosa once more. However, in contrast to previous examinations, a sessile polypoid lesion was found in the transverse colon. Histology showed tubulovillous adenoma with extensive low-grade dysplasia. From a practical point of view, the authors discourage from use of anthranoid-containing laxatives, although they stated that “the role of the short-term use of the laxative in the development of this patient’s adenoma is highly speculative” because he clearly was at risk for developing colonic neoplasm considering his long-standing ulcerative colitis in association with primary sclerosing cholangitis and the use of immunosuppressive medication after liver transplantation. Furthermore it would remain controversial whether melanosis coli is associated with an increased risk for colorectal cancer because of controversial results of several investigations.

Roberts MC et al. 2003 (91) conducted a population-based, case-control study with equal representation by blacks. Constipation, defined as fewer than three reported bowel movements per week, was associated with a greater than two-fold risk for colon cancer (OR 2.36; 95% CI = 1.41-3.93) adjusted for age, race, sex, and relevant confounders. The OR for constipation was slightly higher for distal than for proximal colon cancers. There was no association with laxative use (OR 0.88; 95% CI = 0.69-1.11). The authors do not explicitly mention anthraquinone-containing laxatives. They mentioned the group “stimulants, fibers, natural remedies, stool softeners, oils, osmotic agents, enemas, suppositories, and unknown”. In particular they mention phenolphthalein and magnesium.

Nilsson SE et al. 2004 (92) examined the impact of constipation and laxative treatment on the blood levels of homocysteine, folate and cobalamine in a population-based sample of aged people. Elevated plasma homocysteine might indicate an increased risk of cancer, and cardiovascular and neurological diseases. The homocysteine level depends on the supply of folate and cobalamine, and constipation and/or laxative treatment might compromise this supply. The study was based on biochemical tests in 341 females and 183 males aged 82 years and older. The concentrations of homocysteine (plasma), folate, cobalamine and urea (serum) were measured in subjects with and without ongoing treatment with laxative products. Values were adjusted for age, gender and frailty, as well as for clinical diagnoses and medicinal therapies known to affect homocysteine levels. Homocysteine levels were increased and those of folate reduced in aged subjects on laxatives. Homocysteine remained elevated after adjusting for frailty and various neurological disorders. There was no significant effect on homocysteine and folate in constipated subjects without laxatives.

Jae Sik Joo et al. 1998 (93) investigated changes occurring on barium enema in patients ingesting stimulant laxatives. The study consisted of two parts. In part 1, a retrospective review of consecutive barium enemas performed on two groups of patients with chronic constipation (group 1, stimulant laxative use (n=29); group 2, no stimulant laxative use (n=26)) was presented to a radiologist who was blinded to the patient group. A data sheet containing classic descriptions of cathartic colon (historic term for the anatomic alteration of the colon secondary to chronic stimulant laxative use) was completed for each study. Chronic stimulant laxative use was defined as stimulant ingestion more than three times per week for 1 year or longer. To confirm the findings of the retrospective study, 18 consecutive patients who were chronic stimulant laxative users underwent barium enema examination, and data sheets for cathartic colon were completed by another radiologist (part 2).

Colonic redundancy (group 1, 34.5%; group 2, 19.2%) and dilatation (group 1, 44.8%; group 2, 23.1 %) were frequent radiographic findings in both patient groups and were not significantly different in the two groups. Loss of haustral folds, however, was a common finding in group 1 (27.6%) but was not seen in group 2 ($p < 0.005$). Loss of haustral markings occurred in 15 (40.5%) of the total stimulant laxative users in the two parts of the study and was seen in the left colon of 6 (40%) patients, in the right colon of 2 (13.3%) patients, in the transverse colon of 5 (33.3%) patients, and in the entire colon of 2 (13.3%) patients. Loss of haustra was seen in patients chronically ingesting bisacodyl, phenolphthalein, senna, and casanthranol. The authors conclude that long-term stimulant laxative use results in anatomic changes in the colon characterised by loss of haustral folds, a finding that suggests neuronal injury or damage to colonic longitudinal musculature caused by these agents.

3.3.6 Safety in special populations and situations

Like all laxatives, cascara containing medicinal products should not be taken by patients suffering from faecal impaction and undiagnosed, acute or persistent gastro-intestinal complaints, e.g. abdominal pain, nausea and vomiting unless advised by a doctor because these symptoms can be signs of potential or existing intestinal blockage (ileus).

If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of stimulating laxatives should be avoided.

Use for more than 1 - 2 weeks requires medical supervision. Cascara preparations should only be used if a therapeutic effect cannot be achieved by a change of diet or the administration of bulk forming agents.

Patients with kidney disorders should be aware of possible electrolyte balance.

3.3.7 Drug Interactions

Patients taking cardiac glycosides, antiarrhythmic medicinal products, medicinal products inducing QT-prolongation, diuretics, corticosteroids or liquorice root, have to consult a doctor before taking cascara preparations concomitantly.

3.3.8 Use in Pregnancy and Lactation

There are no recent investigations available.

In theory, it is possible that reflex stimulation might occur, involving not only the colon but also uterine muscles and then might lead to the development of hyperaemia in the pelvic region and to miscarriage as a result of neuromuscular stimulation of uterine muscles. Therefore this herbal substance was misused as an abortifacient agent (51).

Experimental data, mainly in vitro tests showed a genotoxic risk of several anthranoids (e.g. emodin, chrysophanol, and physcion).

In vitro assays overestimate the potential hazard from exposure and must be reevaluated by in vivo experiments.

The NOAELs for emodin defined by Jahnke GD are twice the decimal power and above the maximum daily dose of hydroxyanthracene derivatives (30 mg).

In vivo studies of the crude senna herbal substance in rat hepatocytes (chromosome aberration test, mouse spot test, in vivo/in vitro UDS (unscheduled DNA synthesis); showed no evidence of any genetic effects (Heidemann 1993 (53)). There exist older preclinical data which refer to extracts of senna pods containing 1.4 to 3.5 % of anthranoids, corresponding to 0.9 to 2.3 % of potential rhein, 0.05 to 0.15% of potential aloe-emodin and 0.001 to 0.006% of potential emodin or to isolated active constituents, rhein or sennosides A and B. No cytotoxic, toxic, embryotoxic or genotoxic effect could

be found in Chromosome Aberration Assay in Bone Marrow Cells of the Rat, Micronucleus Test in Rats, Mouse Spot Test.

Therefore the monographs on senna recommend for such a specified senna extract that the use is to be avoided just during the first trimester but with the advice that the further use during pregnancy should only be an intermittent and just if other actions like behavioural modification, dietary changes and use of bulk forming agents fail. Use in pregnancy cannot be recommended for all other senna preparations (we refer to the senna assessment report).

Whereas senna and also rhubarb mainly contain dianthron-glycosides, cascara and also frangula and aloe mainly contain 10-glycosyl-anthrone, anthrachinon- and anthron-glycosides. The risk of hydrolysis in aglycones and consequently systemic absorption in the gastrointestinal tract is higher for the anthrachinon- and anthron-glycosides than for the dianthron-glycosides due to the different chemical structures. The amount of aglycones represents the possible genotoxic risk. Even for this reason cascara, frangula and aloe seem to be less appropriate for sensitive patient groups like pregnant women than senna and rhubarb (82).

In addition there are no data for cascara and its preparations available. Therefore use during pregnancy cannot be recommended. Furthermore other actions like behavioural modification, dietary changes and use of bulk forming agents should be the first actions taken during pregnancy to treat constipation.

Use during lactation is not recommended, as there are insufficient data on the excretion of metabolites in breast milk, too. Investigations with a “standardised senna laxative” (Agiolax®), which also contains *Plantago ovata* seeds/husks as bulk substances, showed that small amounts of active metabolites (rhein) are excreted in breast milk. A laxative effect in breast fed babies has not been reported (52).

4 TRADITIONAL USE

The medicinal use of cascara as a purgative or laxative is known in Europe since 1880 (69). The British Pharmaceutical Codex, 1911 (70), “Hagers Handbuch der Pharmazeutischen Praxis” 1927 (72), and Martindale, 25th edition 1967 (73) already indicate such a use

Harvey Wickes Felter, 1922 (71) also propagates the use in case of sick headache due to atonic sluggishness of the bowels. Cascara was also used in gastric and duodenal catarrh, with jaundice, and in chronic diarrhea when accompanied by hepatic torpor.

Madaus 1938 (69) reports that Clarke(1853 - 1931) also indicated the use for rheumatic complaints in his material medica, published 1900 - 1902.

Martindale, 25th edition 1967 (73) also describes the action of cascara as a bitter stomachic given in small dose before meals.

Dragendorff 1967 (74) compares the use of cascara with the use of frangula bark. Fresh bark has an emetic effect and dried bark a laxative effect. Additionally the bark is externally used for scabies. He did not specify the preparation used or the underlying pharmacological action.

The dispensatory of the United States of America, 1918 (75), also describes the use of cascara as vegetable cathartic.

Conclusion

The use of cascara as a laxative is mentioned in nearly all references. In consequence of the laxative properties the herbal substance was also used as a purgative. The use as a laxative is accepted as a well established use.

In former times purification often was the first step to treat a lot of diseases. Such a procedure is obsolete now. Furthermore there are no plausible pharmacological data for the purification of other organs than the bowel.

Rarely the external use of the fresh bark is mentioned, but without explanation of the underlying pharmacological action. The use in skin affections is surprising because other anthranoid-containing herbal substances, e.g. senna can cause skin irritations by themselves.

Furthermore the possible risks as described above have to take into account.

None of these indications can be adopted in the traditional list as a traditional one.

5 ASSESSOR'S OVERALL CONCLUSIONS

The short term use of occasional constipation

There is only one randomised double-blind crossover trial available which assessed the laxative effect of a monopreparation of cascara. The amount of anthranoides is not given. In moderate cases of constipation, the effectiveness of the cascara preparation was equal to the effectiveness of glucofrangulin or bisacodyl.

The postulated laxative effect is mainly based on the pharmacological data, experts' opinions (German monograph, ESCOP monograph) and clinical experiences. Clinical and pharmacological data obtained from other anthranoid-containing laxatives (we refer to the assessment report of SENNAE FOLIUM) and investigations with combination preparations support the efficacy of this also anthranoid-containing herbal substance for short term use in cases of occasional constipation. The current level of evidence for "the short term use of occasional constipation" can be identified as III although there exist one randomised cross over study but with some shortcomings (e.g. no definite dosis, a very short wash out phase of 2 days).

Use for bowel cleansing

All investigations to assess the bowel cleansing effect of cascara were conducted with a combination of a cascara preparation and a saline cathartic (magnesium sulphate). Therefore the effectiveness of cascara alone cannot be assessed. Anyway the combination preparation with cascara was inferior to a Golytely regimen.

Traditional use

The use of cascara as a laxative is mentioned in nearly all references. The use as a laxative is accepted as a well established use.

Rarely the external use of the fresh bark is mentioned, but without explanation of the underlying pharmacological action.

Furthermore the possible risks as described above have to take into account.

None of these indications can be adopted in the traditional list as a traditional one.

Because of the possible genotoxic or tumourigenic risk in experimental investigations and the results of Siegers 1993 (83) a pharmacovigilance actions for anthranoid-containing laxatives were initiated in Germany 1996. The daily dose and the duration of administration were limited. Children, pregnant women and nursing mothers were excluded from the application of cascara containing laxatives.

The results of the more recent studies are inconsistent and the possibility of a carcinogenic risk of long-term use of anthranoid-containing laxatives cannot be assessed definitely. Some studies revealed a risk for colorectal cancer associated with the use of anthraquinone-containing laxatives, some studies did not. However, a risk was also revealed for constipation itself and underlying dietary habits. Further investigations are needed to assess the carcinogenic risk definitely.

In his review article van Gorkom BA 1999 (94) concluded that although the short-term use of anthranoid laxatives is generally safe, long-term use cannot be recommended.

In “Goodman & Gilman’s The Pharmacological Basis of Therapeutics” (11th edition 2006) (5) the following conclusion is drawn: “Regardless of whether a definitive causal relationship can be demonstrated between the use of anthraquinone laxatives and colonic pathology, these agents should not be recommended for chronic or long-term use.”

Taking all available data in consideration, the conditions determined in the German pharmacovigilance actions for anthranoid-containing laxatives have to be maintained for the moment.

In consideration of the recommendations in the monograph the benefit-risk-ratio is positive and the short term use of occasional constipation can be regarded as safe.

6 LITERATURE REFERENCES

See annex

7 PROPOSED COMMUNITY MONOGRAPH FOR CASCARA (RHAMNI PURSHIANAE CORTEX)

See annex