Senna

Species (Family)

(i) *Cassia senna* L.
(ii) *Cassia angustifolia* Vahl. (Leguminosae)

Synonym(s)

(i) Alexandrian Senna, *Cassia acutifolia* Delite, Khartoum Senna
(ii) Indian Senna, Tinnevelly Senna

Part(s) Used

Fruit (pod), leaf

Pharmacopoeial and Other Monographs

BHC 1992[G6]
BHP 1996[G9]
BP 2001[G15]
Complete German Commission E[G3]
ESCOP 1997[G52]
Martindale 32nd edition[G43]
PDR for Herbal Medicines 2nd edition[G36]
Ph Eur 2002[G28]
WHO volume 1 1999[G63]

Legal Category (Licensed Products)

GSL[G37]

Constituents[G2,G6,G7,G8,G20,G22,G41,G48,G52,G62,G64]

Hydroxyanthracenes Pharmacopoeial standards not less than 2.5% for leaf, 3.5% for *C. senna* fruit and 2.2% for *C. angustifolia* fruit.[G15,G28] Dianthrone glycosides (1.5–3% leaf; 2–5% fruit), primarily sennosides A and B (rhein dianthrones) with sennosides C and D (rhein aloe-emodin heterodianthrones), aloe-emodin dianthrone. Sennosides A and B yield sennidin A and B respectively. Free anthraquinones including aloe-emodin, chrysophanol and rhein with their glycosides.

Carbohydrates Polysaccharides (about 2.5%)[1] including mucilage (arabinose, galactose, galacturonic acid, rhamnose) and a galactomannan (galactose, mannose);[2] free sugars (e.g. fructose, glucose, pinitol, sucrose).

Flavonoids Flavonols including isorhamnetin and kaempferol.

Glycosides 6-Hydroxymusizin and tinnevellin glycosides.

Other constituents Chrysophanic acid, salicylic acid, saponin, resin, volatile oil (trace).

Food Use

Senna is listed by the Council of Europe as a natural source of food flavouring (Tinnevelly category N2, Alexandrian category N3). Category N2 indicates that senna can be added to foodstuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product. Category N3 indicates that there is insufficient information available about Alexandrian senna, for an adequate assessment of potential toxicity.[G16] In the USA, senna is permitted for food use.

Herbal Use[G2,G4,G6,G7,G8,G32,G43,G52,G54,G56,G64]

Senna is stated to possess cathartic properties (leaf greater than fruit) and has been used traditionally for constipation. The German Commission E approved use for constipation.[G3] Senna is also used in combination with ispaghula for constipation.[G3] The Committee on Proprietary Medicinal Products (CPMP) has adopted core SPCs (Summary of Product Characteristics) for senna leaf and senna fruit (*C. angustifolia* and *C. acutifolia*) with indications for short-term use in cases of occasional constipation.[3].

Dosage

Dried pods 3–6 pods (Alexandrian) or 4–12 pods (Tinnevelly) steeped in 150 mL warm water for 6–12 hours;[G6,G7] 0.6–0.2 g (equivalent to 20–30 mg hydroxyanthracene glycosides calculated as sennosides B).[G52]

Dried leaflets 0.5–2.0 g[G6,G7] (equivalent to 20–30 mg hydroxyanthracene glycosides calculated as sennoside B).[G52]

Leaf, liquid extract 0.5–2.0 mL (1:1 in 25% alcohol).[G6,G7]

Senna Liquid Extract (BPC 1973) 0.5–2.0 mL.

Herbal drug preparations Equivalent to 15–30 mg hydroxyanthracene derivatives (calculated as sennoside B) to be taken at night.[3]

Pharmacological Actions

The cathartic action of hydroxyanthracene-containing drugs is well recognised and they have been used as laxatives for many years. However, there is still some uncertainty as to the exact mode of action of the hydroxyanthracenes.

It is thought that hydroxyanthracene glycosides are absorbed from the gastrointestinal tract, the aglycones liberated during metabolism and excreted into the colon resulting in stimulation and an increase in peristalsis. However, it has also been suggested that the purgative action of senna is due to the action of intestinal bacteria.[4] Using human intestinal flora, it was found that sennoside A is reduced to 8-glucosylrheinanthrone, hydrolysed to rheinanthrone and oxidised to sennidin A. The active principle causing peristaltic movements of the large intestine was thought to be rheinanthrone.[4]

In vitro and animal studies

Sennosides A and B, and their natural metabolites sennidins A and B, have been reported to act specifically on the large intestine in the rat with the acceleration of colonic transport the major component of their laxative effect.[5] Sennosides A and B have also been reported to induce fluid secretion exclusively in the colon, following oral administration of the glycosides to rats.[6]

It has been suggested that the laxative action of the sennosides involves prostaglandins. Indomethacin has been found to partly inhibit the action of sennosides A and B, although a bolus injection of prostaglandins into the caecal lumen was stated to neither influence transit time nor to induce diarrhoea.[5] Pretreatment of mice with indomethacin and a prostaglandin E (PGE) antagonist has been documented to prevent diarrhoea caused by intracaecal administration of rhein, which stimulates the production of PGE-like material specifically in the colon.[7] Indomethacin was found to depress the large intestinal propulsive activity of rhein, but did not suppress PGE_2-induced diarrhoea. The authors suggest that the action of rhein is mediated by prostaglandin biosynthesis and release.[7]

Antihepatotoxic activity has been documented for naphtho-α-pyrone and naphtho-γ-pyrone glycosides, and for the hydroxyanthracene glycosides isolated from a related species *Cassia tora*.[8] Greatest activity was documented for the naphtho-γ-pyrone glycosides.

Significant inhibitory activity in mice against leukaemia P388 has been documented for aloe-emodin.[G41]

Clinical studies

In a randomised, controlled trial, 91 patients with terminal received senna 12 mg daily, or lactulose, for 27 days.[9] At the end of the study, no differences were found between the two groups in defecation-free intervals, or in days with defecation. The general health of each group was also reported to be similar.

A randomised, double-blind, double-dummy, multicentre, controlled, crossover study involving 77 hospitalised elderly patients with a history of chronic constipation compared the effects of a senna–fibre combination (senna 12.4%, ispaghula 54.2%, 10 mL daily) and lactulose (15 mL twice daily) for two 14-day periods with a three- to five-day wash-out period.[10] Assessments included stool frequency and consistency, ease of evacuation, adverse effects and costs of treatment. The senna–fibre combination was reported to be significantly more effective than lactulose.[10]

Commercial preparations containing senna and ispaghula have been reported to be equally effective for the treatment of constipation in small clinical studies involving elderly hospitalised patients and/or residents in nursing homes.[11]

Side-effects, Toxicity[G20]

Senna may cause mild abdominal discomfort such as colic or cramps. Prolonged use or overdosage can result in diarrhoea with excessive loss of potassium, albuminuria and haematuria.[G3] Potassium deficiency may lead to disorders of the heart and muscular weakness especially with concurrent use of cardiac glycosides, diuretics or corticosteroids. An atonic non-functioning colon may also develop.[G45] Excessive use and abuse of senna has been associated with finger clubbing and with the development of cachexia and reduced serum globulin concentrations.[12]

Sennosides A and B are reported to be most potent with respect to laxative action, but to be the least toxic compared with other hydroxyanthracene fractions in senna. Similarly, fractions with a low laxative activity (e.g. rhein-8-glucoside) are reported to have the highest acute toxicity.[13] LD_{50} values in mice following intravenous injection of sennosides A and B and of rhein-8-glycoside are reported to be 4.1 g/kg and 400 g/kg, respectively.[13] The acute oral toxicity of all senna fractions in mice has been reported to be

greater than 5 g/kg, although all of the animals were stated to have died by the following week. The toxicity of total senna extracts is greater than that of the individual sennosides and it has been proposed that the laxative and toxic components of senna could be separated.[7]

In vitro carcinogenicity testing has reported certain anthraquinones, including aloe-emodin, to be active in more than one strain of *Salmonella typhimurium*.[14] Aglycones were documented to exhibit genotoxic activity in a mammalian cell assay.[14]

Sensitising properties have been documented for emodin (*see* Aloes).[G51]

The CPMP core SPCs for senna include the following information.[3] There are no new, systematic preclinical tests for senna leaf or preparations thereof. Most data refer to extracts of senna fruit containing 1.4–3.5% of hydroxyanthacenes, corresponding to 0.9–2.35% of potential rhein, 0.05–0.15% potential aloe-emodin and 0.001–0.006% of potential emodin, or to isolated active constituents, e.g. rhein or sennosides A and B. The acute toxicity of senna fruit and specified extracts thereof, as well as of sennosides in rats and mice was low after oral treatment. As a result of investigations with parenteral application in mice, extracts are supposed to possess a higher toxicity than purified glucosides, possibly due to the content of aglycones.

Sennosides displayed no specific toxicity when tested at doses up to 500 g/kg in dogs for four weeks and up to 100 g/kg in rats for six months. Data for herbal drug preparations are not available. There was no evidence of any embryolethal, teratogenic or fetotoxic actions in rats or rabbits after oral treatment with sennosides. Furthermore, there was no effect on the postnatal development of young rats, on rearing behaviour of dams or on male and female fertility in rats. Data on herbal drug preparations are not available.

An extract and aloe-emodin were mutagenic in *in vitro* tests; sennosides A and B and rhein gave negative results. *In vivo* examinations of a defined extract of senna pods were negative. A specified senna extract given orally for two years was not carcinogenic in male or female rats. The extract investigated contained approximately 40.8% of hydroxyanthracenes from which 35% were sennosides, corresponding to about 25.2% of potential rhein, 2.3% of potential aloe-emodin and 0.007% of potential emodin, and 142 ppm free aloe-emodin and 9 ppm free emodin.

Contra-indications, Warnings

It is recommended that senna should not be given to patients with intestinal obstruction and stenosis, atony, inflammatory colon diseases (e.g. Crohn's disease, ulcerative colitis), appendicitis, with undiagnosed abdominal symptoms; severe dehydration states with water and electrolyte depletion. Prolonged use should be avoided.[3,G20,G45,G52]

The CPMP core SPCs for senna include the following information.[3]

As with all laxatives, senna should not be given when any undiagnosed acute or persistent abdominal symptoms are present. If laxatives are needed every day the cause of the constipation should be investigated. Long-term use of laxatives should be avoided. Use for more than two weeks requires medical supervision. Chronic use may cause pigmentation of the colon (pseudomelanosis coli) which is harmless and reversible after drug discontinuation.

Abuse, with diarrhoea and consequent fluid and electrolyte losses, may cause dependence, with possible need for increased dosages, disturbance of water and electrolyte (mainly hypokalaemia) balance, atonic colon with impaired function. Intake of anthranoid containing laxatives exceeding short-term use may result in an aggravation of constipation.

Hypokalaemia can result in cardiac and neuromuscular dysfunction, especially if cardiac glycosides, diuretics or corticosteroids are also taken. Chronic use may result in albuminuria and haematuria.

In chronic constipation, stimulant laxatives are not an acceptable alternative to a changed diet.

Interaction with other medicaments and other forms of interaction[3] Hypokalaemia (resulting from long-term use of senna) may potentiate the action of cardiac glycosides and interacts with antiarrhythmic drugs, with drugs which induce reversion to sinus rhythm (e.g. quinidine). Concomitant use with other drugs inducing hypokalaemia (e.g. thiazide diuretics, adrenocorticosteroids and liquorice root) may enhance electrolyte imbalance. Abdominal spasms and pain may occur, in particular in patients with irritable colon.[3]

Anthraquinones cause discoloration of the urine which may interfere with diagnostic tests.[G45]

Pregnancy and lactation Non-standardised hydoxyanthracene containing laxative preparations should not be taken during pregnancy or lactation since their pharmacological action is unpredictable. Although hydroxyanthracene derivatives may be excreted in the breast milk, following normal dosage their concentration is usually insufficient to affect the nursing infant.[G45]

The CPMP core SPCs for senna include the following information.[3]

Pregnancy Not recommended during pregnancy. There are no reports of undesirable or damaging effects during pregnancy and on the fetus when used at the recommended dosage schedule. However, experimental data concerning a genotoxic risk of several anthranoids (e.g. emodine and physcione) and senna are not counterbalanced by sufficient studies to eliminate a possible risk.[3]

Lactation Breastfeeding is not recommended as there are insufficient data on the excretion of metabolites in breast milk. Excretion of active principles in breast milk has not been investigated. However, small amounts of active metabolites (e.g. rhein) from other anthranoids are known to be excreted in breast milk. A laxative effect in breastfed babies has not been reported.[3]

Pharmaceutical Comment

The chemistry of senna is characterised by the hydroxyanthracene derivatives. The laxative action of these compounds is well recognised and supports the herbal use of senna as a laxative for the treatment of constipation. However, the use of non-standardised hydroxyanthracene-containing preparations should be avoided since their pharmacological effect will be variable and unpredictable. The sennoside content of many licensed senna products is standardised and generally calculated as sennoside B. Clinical investigations have concluded that senna with ispaghula is more effective than lactulose as a laxative (*see* Clinical studies).

References

See also General References G2, G3, G6, G9, G12, G15, G16, G18, G20, G22, G28, G29, G31, G32, G36, G37, G41, G43, G48, G51, G52, G54, G56, G62, G63 and G64.

1 Müller BM *et al.* Isolation and structural investigation of a polysaccharide from *Cassia angustifolia* leaves. *Planta Med* 1989; 55: 99.

2 Alam N, Gupta PC. Structure of a water-soluble polysaccharide from the seeds of *Cassia angustifolia*. *Planta Med* 1986; 52: 308–310.

3 European Commission, CPMP Guidelines on Information on Medical Products: Core SPCs for Sennae Fructus Angustifolia, Sennae Fructus Acutifolia, Sennae Folium, February 1994.

4 Kobashi K *et al.* Metabolism of sennosides by human intestinal bacteria. *Planta Med* 1980; 40: 225–236.

5 Leng-Peschlow E. Acceleration of large intestine transit time in rats by sennosides and related compounds. *J Pharm Pharmacol* 1986; 38: 369–373.

6 Leng-Peschlow E. Dual effect orally administered sennosides on large intestine transit and fluid absorption in the rat. *J Pharm Pharmacol* 1986; 38: 606–610.

7 Yagi T *et al.* Involvement of prostaglandin E-like material in the purgative action of rhein anthrone, the intraluminal active metabolite of sennosides A and B in mice. *J Pharm Pharmacol* 1988; 40: 27–30.

8 Wong SM *et al.* Isolation and structural elucidation of new antihepatotoxic naphtho-gamma-pyrone glycosides, naphtho-α-pyrone glycoside and anthraquinone glycosides from the seeds of *Cassia tora*. *Planta Med* 1989; 55: 112.

9 Agra Y *et al.* Efficacy of senna versus lactulose in terminal cancer patients treated with opioids. *J Pain Symptom Management* 1998; 15: 1–7.

10 Passmore AP *et al.* Chronic constipation in long stay elderly patients: a comparison of lactulose and a senna-fibre combination. *BMJ* 1993; 307: 769–771.

11 Petticrew M *et al.* Epidemiology of constipation in the general adult population. *Health Technol Assess* 1997; 1: 1–52.

12 Senna *Lawrence Review of Natural Products*. Levittown, Pennsylvania: Pharmaceutical Information Associates Ltd, 1989.

13 Hietala P *et al.* Laxative potency and acute toxicity of some anthraquinone derivatives, senna extracts and fractions of senna extracts. *Pharmacol Toxicol* 1987; 61: 153–156.

14 Westendorf J *et al.* Possible carcinogenicity of anthraquinone-containing medical plants. *Planta Med* 1988; 54: 562.