Camphor: risks and benefits of a widely used natural product

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ABSTRACT

This study analyzes the main aspects of the non-clinical profile of D-Camphor, a natural product widely used as a common remedy for several symptoms. The pharmacology, pharmacokinetics and toxicity of this substance are analyzed, with regard to all the literature available, in order to assess a risk profile and better understand the positive and negative aspects connected with its use. The general conclusion is that the main risks of camphor as a medicinal product are mainly due to a somehow diffused attitude of considering it as “not a real medicine”, and to its consequent sometimes not sufficiently careful administration. JASEM

Camphor is a natural product derived from the wood of the camphor laurel (Cinnamomum camphora L.) trees through steam distillation and purification by sublimation; the trees used should have at least 50 years old, and it also occurs in some other related trees in the laurel family, notably Octoea usambarensis Engl., and can also be obtained from the plant Lippia dulcis Trev., but this is not a major industrial source (Compardè et al., 1988). A major source of camphor in Asia is Osimum kiiilmanscharicum Baler ex Gurke. Camphor can also be produced synthetically from vinyl chloride and cyclopentadiene, passing through the intermediate dehydromonorormyl chloride. The naturally occurring form is dextrorotary and the synthetic form is optically inactive (Budavari, 1989; Reynolds, 1989). Camphor has a counter-irritant, rubefacient and mild analgesic action, and is a major component of iniments for relief of fibrositis, neuralgia and similar conditions. It can be used as a mild expectorant; when ingested camphor has irritant and carcimative properties. Camphorated oil, in a solution oil given through intramuscular or subcutaneous way, can be used as a circulatory and respiratory stimulant, but this use is considered hazardous. When in combination with menthol and chenododecyclic acid it has been used to aid dispersal of bile duct stones, although this is no longer recommended (Reynolds, 1989). Aim of the present work is to provide an overview over pharmacological, pharmacokinetic and toxicological aspects of camphor, in order to assess its safety profile and evaluate the eventual level of risk connected with its use.

PHARMACOLOGY

Camphor, a natural product derived from the wood of the tree Cinnamomum camphora, has a long history of use as antiseptic, analgesic, antipruritic, counterirritant and rubefacient (Elenin and barceloues, 1998; Liebtt and Shannom, 1993). Its success and wide medical use, especially in topical preparations, is connected to its mild local anesthetizing effect and to the production of a circumscribed sensation of cool, together with its characteristic penetrating odor that is of most of people associated to the idea of a strong and effective medicine (Gibson et al., 1989). Camphor is today mostly used in the form of inhalants and of camphorated oil, a preparation of 19% or 20% camphor in a carrier oil, for the home treatment of colds (Jochen and Theis, 1995) and as a major active ingredient of liniments and balms used as topical analgesics (Xu et al., 2005). The antitussive, nasal decongestant and expectorant action of camphor and of its derivatives was one of the first ones to be systematically investigated (Inoue and Takeuchi, 1969). Its nasal decongesting activity seems to be not purely mechanic, but connected with the stimulation of cold receptors in the nose. The inhalation of camphor vapours (so as the one of eucalyptus and menthol vapours) on a sample of volunteers increased the nasal sensation of airflow through the induction of cold sensation in the nose, despite of actually not affecting nasal resistance to airflow (Buroow et al., 1993). Camphor was administered in the form of aromatic vapor, at the concentrations of 50, 133 and 500 µg l⁻¹, to guinea pigs subject to chemically induced cough. No effect were registered at the lowest concentrations, but 500 µg l⁻¹ camphor gave a 33% reduction of cough frequency, to which an increase in cough latency coincided (Laudie et al., 1994). The analgesic proprieties of camphor are largely known and applied, but little is known about the molecular mechanisms that are at their basis. (Xu et al., 2005). Moiritch et al. (2005) demonstrated that camphor activates TRPV1, a member of transient receptor channel superfamily, leading to excitation and desensitization of sensory nerves. The notorious effect of generation of a sensation of heat associated with topical application of camphor (Green, 1990) is a consequence of this activation. Anyway excessive and repeated application of camphor can lead to sensibilization of TRPV1, in apparent contrast with its analgesic role (Moqrich et al., 2005; Peier et al., 2002). The antinociceptive, analgesic and counterirritant activity of camphor is instead associated with its capacity of activating TRPV1- another member of TRP channel superfamily -at the level of dorsal root gangliar (DRG) neurons and inhibiting TRPV1 activity (Mochizuki et al., 2000; Nagata et al., 2000), action that is in common with other TRPV1 agonists (Koptas et al., 1997; Dhare et al., 2002). Carboxic shares the same action with camphor, but performs it more slowly and less completely; on the other side camphor efficacy is lower, since higher concentrations are required (Xu et al., 2005). Studies on rats demonstrated that the actions of capsaicin and camphor are segregated [8], i.e. they are mediated by distinct channel regions, and camphor did not activate TRPV1 in capsaicinensitive chickens (Xu et al., 2005, Jordi and Julius, 2002). Camphor also inhibits other related TRP channels such as anakin-repeat TRP (TRPA1), which is a further evidence underlying its analgesic effects (Xu et al., 2005). Camphor can modulate the activities of hepatic enzymes involved in phase I and phase II drug metabolism. 50, 150 and 300 mg Kg⁻¹ of camphor dissolved in 0.1 ml of olive oil was administered daily to female Swiss Albino mice during 20 days. At its highest concentration it caused a significant increase in the activities of cytochrome P-450, cytochrome bo-1, cytochrome S-transferase, significantly elevating the level of reduced glutathione in the liver (Banezjere et al., 1995). Camphor was shown to inhibit mitochondrial respiration. Administration of up to 8 µM of camphor inhibited respiration rate in rat-liver mitochondria, nearly halving the oxygen consumption; this suggests that camphor may be used in oxygenating tumors prior to radiotherapy (Guilland-Cumming and Smith, 1979; 1982). Camphor can also be a potential radiosensitizing agent in radiotherapy. Treatment with camphor (0.5 pmol - body wt⁻¹) 45 minutes before local xirradiation at the dose levels of 30, 80, 100 or 120 Gy was performed to C3H/HeJ mice bearing transplanted mammary tumours. Sequential measurement of the tumour volumes during 45 days after the irradiation revealed a 4.8 delay of the maximum enhancement ratios in tumour growth (Goel and Roa, 1988). D-camphor (1100 µg ml⁻¹) inhibited oxidative metabolism in E.coli (Cardullo and Gilroy, 1975). Succinic, lactic and NADH-oxidase activities were inhibited, while NADH and succinic DCPIP oxidoredox enzymes were unaffected. The restoration of succinic oxide activity by ubiquinone (Q10) but not by vitamin K1 indicates that D-camphor may operate this inhibition by affecting quinone functions.

Interactions

Very few studies of pharmacological interactions between camphor and other compounds are present in literature. In a study combining the administration of D-camphor and an extract from fresh crataegus berries, a synergic action of the two preparations emerged in ameliorating cardiac performances. Both D-camphor and the extract contributed in an increase in heart rate and cardiac output (Belz and Loew, 2003).

PHARMACOKINETICS

Camphor is readily absorbed from all the sites of administration, after inhalation, ingestion or dermal exposure (Baselt and Cravey, 1990). Peak plasma levels were reached by 3 hours after oral administration of 0.5 mg Kg⁻¹ of camphor in the plasma were assayed with selective gaschromatography (Martin et al., 2004; Valdez et al., 1999). Maximum camphor plasma concentration resulted in a range between 35.2 and 46.8 ng ml⁻¹ in the case of 8 patches, between 19.6 and 34 ng ml⁻¹ for the patches with almost undetectable concentrations were observed when only 2 patches had been applied, showing that dermal absorption is prompt but not massive. Camphor is distributed throughout the whole body, and can permeate the placenta; for this reason it must be recommended that the use of this product is avoided during pregnancy and lactation (Sweedman, 2005). Its volume of distribution is 2-4 Lkg⁻¹ (Koppel et al., 1988); plasma protein binding has been estimated as 61% (Koppel et al., 1982). After its absorption and distribution, camphor undergoes hepatic metabolism: it is hydroxylated in the liver into hydroxycamphor metabolites (Sweedman, 2005). Anahira and lshidate (1933; 1934; 1935) isolated cis- and trans-hydroxyacamphor and camphor- methylene carboxylic acid from the urine of dogs that had been fed with camphor; Shimamoto obtained 3-hydroxyacamphor (15%), 5-hydroxyacamphor (55%) and trans-hydroxyacamphor (20%) from the urine of dogs, and 5-hydroxyacamphor [as major metabolite] and 3-hydroxyacamphor from the urine of rabbits (Shimamoto, 1934). Robertson and Hussain (1969) observed that (+)-camphor and (+)-camphor increase the content of glucuronide in the urine of rabbits. (+)-camphor was moreover reduced to (+)-borneol as well as being hydroxylated to (+)-endo-hydroxyacamphor [major product] and (+)-3-endo-hydroxyacamphor. Hydrolyation of camphor, as well as noncamphor, periclyclocamphene and 5,5-diluurocamphor, is mainly
performed by Cytochrome P-450 (Collins and Loew, 1988), a class of heme-containing monoxygenases that are distributed in the whole body (Boxenbaum, 1984), by hydrogen abstraction (Wand and Thompson, 1986). Cytochrome P-450 is responsible for camphor conversion into 3-hydroxycamphor (Geb et al., 1982), while 3-hydroxycamphor is the primary component of nonenzymatic hydroxylation of camphor (Land and Swalow, 1979). Camphor hydroxylation by cytochrome P-450 occurs with a different regiospecificity for camphor and its related compounds (Collins and Loew, 1988). Hydroxylated metabolites are then conjugated with glucuronic acid and excreted in the urine (Sweetman, 2005). The half-life of 200 mg of camphor was 167 minutes when ingested alone, and 93 minutes when ingested with a solvent (Teewen 80) (Koppel et al., 1989).

TOXICITY

Camphor occurs in nature in its dehydrorotatory form (D-camphor), while the laevorotatory form (L-camphor) exists only as a synthetic product. The two enantiomers present different profiles of toxicity. The natural form of camphor and their racemic mixture were tested for toxicity in mice. At 100 mg / Kg b.w. the natural form was non-toxic, while the synthetic form induced different kinds of toxic and behavioural effects such as body jerks and hunched posture; the racemic mixture showed similar effects to the L-form (Chatterjee and Alexander, 1986). The oral administration of acute doses of D-camphor to rats and rabbits caused pronounced signs of toxicity. In rats, the consumption of food was reduced proportionally to the administered dose, starting from 464 mg / Kg b.w. 1 day, and at 1000 mg / Kg b.w. 1 day convulsions and piloerection were observed, connected with a reduction of mobility and weight gain. The camphor dose with the highest consumption in rabbits was 681 mg / Kg b.w. 1 day, while convulsions were noted at 848 mg / Kg b.w. on the 10th day (Leuschner, 1997). Camphor showed spastic activity and a tendency to tremor in the primary cultures of chick embryo - liver cells, with enhanced porphyrin accumulation ranging from 9 to 20-fold (Bokovsky, et al., 1992). The main problems about camphor toxicity in humans are connected more to the large availability of camphor-containing products and their diffused perception as unahazardous medicines rather than to the intrinsic toxicity of camphor itself. A human therapeutic ratio in fact approximately 1:43 (Kg) -1, which corresponds to a therapeutically safe margin of more than 450 for the endpoint toxicity, reflecting a wide margin of safety (Leuschner, 1997). On the other side, as mentioned above, camphor is present in several over-the-counter products, its use as a familiar remedy is commonly accepted, but still some lack of information persists among the consumers. Cases of camphor intoxication in humans, especially children, are relatively frequent, mostly because of accidental ingestion (Siegel and Wason, 1986). More than 10000 cases of ingestion exposures to camphor-containing products were registered between 1990-2006 (Manoguerra et al., 2006), causing a range of symptoms that comprises convulsion, lethargy, ataxia, severe nausea, vomiting and coma (Koppel et al., 1988; Manoguerra et al., 2006).

Reproduction toxicity

D-camphor was orally administered to pregnant rats and rabbits during the period of organogenesis to test its embryotoxicity. Doses up to 1000 mg / Kg b.w. 1 day to rats and up to 681 mg / Kg b.w. 1 day to rabbits showed no teratogenic effects, and in none of the animals were observed higher rates of mutations or malformations (Leuschner, 1997).

Mutagenicity and carcinogenicity

In a Salmonella/microsome assay, the upper limit of the dose interval tested for (+/-) camphor resulted to be the highest non-toxic dose, suggesting that the compound is not mutagenic in the Ames test (Gomes-Camelo et al., 1998). A single dose of camphor (0.5 µM · g -1) administered 30, 45 or 60 minutes before gamma irradiation significantly reduced the frequency of sisterchromatid exchanges in mouse bone marrow, showing therefore a radiomodifying effect (Goel et al., 1999).

CONCLUSIONS

Camphor is familiar to many people as a principal ingredient in topical home remedies for a wide range of symptoms, and its use is well consolidated among the population of the whole world, having a long tradition of use as antiseptic, antipruritic, rubefacient, abortifacient, aphrodisiac, contraceptive and lactation suppressant. This compound has also a long history of scientific studies, with the way the camphor has been studied and metabolized in the organisms of both humans and animals, due to the general interest that it has always arisen among people.

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