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 be at least 50 years old. It also occurs in some other related trees in the laurel family, notably Ocotea usambarenensis Eng., and can also be obtained from the plant Lippia dulcis Trev., but this is not a major industrial source (Compadre et al., 1986). A major source of camphor in Asia is Ocimum kilimandscharicum Baker ex Gurke. Camphor can also be produced synthetically from vinyl chloride and cyclopentadiene, passing through the intermediate dehydronorbornyl chloride. The naturally occurring form is dextrorotatory and the intermediate dehydronorbornyl chloride. 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 (Burrow 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 (Laude et al., 1994).

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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). Moqrich et al. (2005) demonstrated that camphor activates TRPV3, 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 topic application of camphor (Green, 1990) is a consequence of this activation. Anyway excessive and repeated application of camphor can lead to sensibilization of TRPV3, in apparent contrast with its analgesic role (Moqrich et al., 2005; Peier et al., 2002). The antipruritic, 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 TRPA1 channels (Moqrich et al., 2005; Nagata et al., 2005), action

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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 post-ingestion when 200 mg camphor was taken alone, and 1 hour post-ingestion when it was ingested with a solvent (Tweed 80) (Koppel et al., 1988). In case of dermal application, the volume of the absorption is relatively low in comparison with the speed of the process. After application of different numbers of commercial patches (2, 4 or 8) to the skin of human subjects during 8 hours, the levels of camphor in the plasma were assayed with selective gas chromatography (Maetin 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 4 patches while 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 (Sweetman, 2005). Its volume of distribution is 2-4 L/kg (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 (Sweetman, 2005). Asahina and Ishidate (1933; 1934; 1935) isolated cis- and trans-α-hydroxycamphor and camphor-α-carboxylic acid from the urine of dogs that had been fed with camphor; Shimamoto obtained 3-hydroxycamphor (15%), 5-hydroxycamphor (55%) and trans-α-hydroxycamphor (20%) from the urine of dogs, and 5-hydroxycamphor [as major metabolite] and 3-hydroxycamphor 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 (+)-5-endohydroxycamphor [major product] and (+)-3-endohydroxycamphor. Hydroxylation of camphor, as well as norcamphor, pericyclocamphanone and 5,5-difluorocamphor, 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 resistance induced by an increase tone of the arterioles, and while the former appeared to be the main factor in inducing the rapid initial effect, the former added a long-lasting effect (Belz and Loew, 2003).

**PHARMACOKINETICS**

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is responsible for camphor conversion into 5-hydroxycamphor (Gelb et al., 1982), while 3-hydroxycamphor is the primary product of non-enzymatic hydroxylation of camphor (Land and Swallow, 1979). Camphor hydroxylation by cytochrome P-450 occurs with a different region-specificity for camphor and its related compounds (Collins and Loew, 1986). 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 (Tween 80) (Koppel et al., 1988).

TOXICITY
Camphor occurs in nature in its dextrorotatory form (D-camphor), while the laevo rotatory form (L-camphor) exists only as a synthetic form. The two enantiomers present different profiles of toxicity. D-camphor, L-camphor and their racemic mixture were tested for toxicity in mice. At 100 mg · Kg b.w.⁻¹ 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 (Chatterjie and Alexander, 1986).

The oral administration of acute doses of D-camphor to rats and rabbits caused pronounced signs of toxicity. In rats, the consume of food was reduced proportionally to the administered dose, starting from 464 mg · Kg b.w.⁻¹ · day⁻¹, and at 1000 mg · Kg b.w.⁻¹ · day⁻¹ convulsions and pilo-erection were observed, connected with a reduction of motility and weight gain. Reduced body weight gain and food consumption were observed in rabbits treated with 681 mg · Kg b.w.⁻¹ · day⁻¹ (Leuschner, 1997).

Camphor showed porphyrogenic activity in primary cultures of chick embryo - liver cells, with enhanced porphyrin accumulation ranging from 5- to 20-fold (Bonkovsky 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 unhazardous medicines rather than in the intrinsic toxicity of camphor. The daily maximum human therapeutic dose is in fact approximately 1.43 mg · Kg⁻¹, which corresponds to a therapeutic ratio 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 100000 cases of ingestion exposures to camphor-containing products were registered between 1990 and 2003 (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⁻¹ cause no teratogenic effects, and in none of the animals were observed higher rates of mutations or malformations (Leuschner, 1997).

Mutagenicity and cancerogenicity
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-Carneiro 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 sister-chromatid exchanges in mouse bone marrow, showing therefore a radiomodifying influence (Goel et al., 1989).

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 on its action and on the way through which it is metabolized in the organisms of both humans and animals, due to the general interest that it has always arisen among common people and scientists. Already in 1879, Schmiedeberg and Meyer were analyzing the metabolites isolated from the urine of dogs that had been fed with (+/-) camphor (Schmiedeberg and Meyer, 1879), and during the first half of the twentieth century the number of studies focused on its pharmacology and pharmacokinetics has been remarkable. The bibliographic search that was performed for the compilation of this toxico-pharmacological overview revealed a rich literature existing on camphor, and put in evidence the large amount of works focused on toxic aspects of camphor that were published during the last 30 years; a great number of reports concerning cases of camphor intoxication were also collected. In most cases camphor intoxication occurred following accidental ingestion of camphor-containing product, and sometimes lethal episodes of intoxication of infants

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due to application of camphor to their nostrils were collected. As it emerges from all the observed data the toxic risks of camphor-containing products in general, and of camphorated oil in particular, are connected essentially with its improper uses, e.g. accidental ingestion, but camphor does not represent a threat for safety when used on the target patients, following the indicated dosages and the contraindications. Special care must be taken during pregnancy, due to the fact that camphor crosses the placental barrier, and camphor and camphor containing products should be avoided in children who have a history of febrile convulsions or other predisposing factors for convulsions (Galland et al., 1992).

In the past, when camphor was used medicinally, the oral doses ranged from 120-300 mg (Wade, 1977), and the parenteral dose range was from 60-200 mg (not recommended any more). Camphorated oil can be used with no risks for safety when following the prescriptions. The relatively diffused tendency to the improper use of camphor [high dosages, accidental ingestion, use on infants] is connected with the perception of the product, by many consumers, as a sort of “panacea” with no contraindication. More and more accessible information is therefore necessary to bring to a “responsabilization” of the consume of this product, in order to avoid hazardous situations.

All the above considerations allow the conclusion that camphor in its form of camphorated oil can be safely used at the proposed dosages, on the indicated patients target, for topical application.

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