PHENOL IN PROLOTHERAPY

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Prolotherapy, the introduction of proliferant solutions into dysfunctional ligaments to reinitiate healing, relies on a mix of chemical compounds to achieve the desired result. One of the compounds which has found its way into the mix is phenol. What is phenol and why is it included in proliferant solutions? Is this substance safe for use in this setting? The following may help to answer these questions.

PHENOL

Phenol is an organic crystalline solid which can be isolated from coal tar and other distillates derived from petrified organic material. While it was originally isolated from coal on a commercial scale, phenol is now largely produced as an industrial chemical from petroleum derived starting materials, benzene and propylene, via the oxygenation of cumene. In this process phenol is produced in equimolar amounts with acetone (Kirk-Othmer).

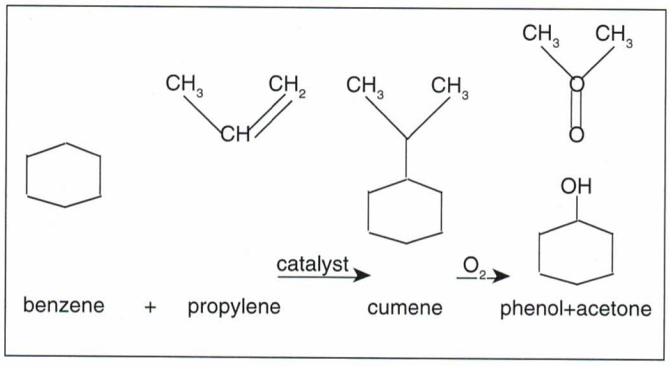

Figure 1
Production of phenol from benzene and propylene

Perhaps most importantly, for the purposes of this discussion, phenol is found in the human chemical environment both as a naturally occurring substance and as an introduced compound in many commercially available products (Gosselin et al, 1984). Phenol is produced metabolically in many animals. Certain insects produce phenol enzymatically and store it in glands from which it is released it when the animal is attacked. Phenol is used in a number of man-made products. Phenol finds use as a starting material for a number of important plastics and resins. It is used as a disinfectant and, being a hydroxylated benzene derivative, it is distinctly aromatic with an odour which is reminiscent of Lysol, certain deodorant soaps and dandruff shampoos.

Significantly, phenol is produced in vivo by the enzymatic degradation of the common amino acid tyrosine (Bernhart and Zilliken, 1959; Brancato, 1982; Wengle and Hellstrom, 1972; Docter and Zielhuis, 1967; Baselt and Cravey, 1989). This process can result in relatively high concentrations of phenol occurring naturally during digestion.

BIOCHEMISTRY OF PHENOL

As it is found in the human chemical environment in relative high concentration naturally, it is not surprising that the human body has powerful and rapid metabolic methods of removing phenol when it is encountered. The liver is thought to be the major organ involved in the metabolic conversion of phenol to either of two esters, sulfate or glucuronate, which have greatly reduced chemical and biological reactivity compared to phenol itself. These esters, called conjugates of phenol, are then rapidly and efficiently concentrated by the kidney and excreted in urine. Following a protein containing meal, phenol is released in the digestive tract and transported rapidly into the blood, where it is subsequently metabolized as above to both the sulfate and glucuronate esters (Bernhart and Zilliken, 1959). As humans are routinely exposed to phenol during the process of digestion of protein, the detoxification pathway for phenol is both rapid and efficient. The half-life of phenol has been variously estimated to be somewhere between 1 and 4.5 hours with complete clearance occurring within 24 hours (Baselt and Cravey, 1989). In fact, it is difficult to find much free phenol in exposed individuals; phenol is usually isolated as the glucuronate or sulfate esters from which it must be hydrolytically released for analysis by various instrumental methods, chiefly gas-liquid chromatography.

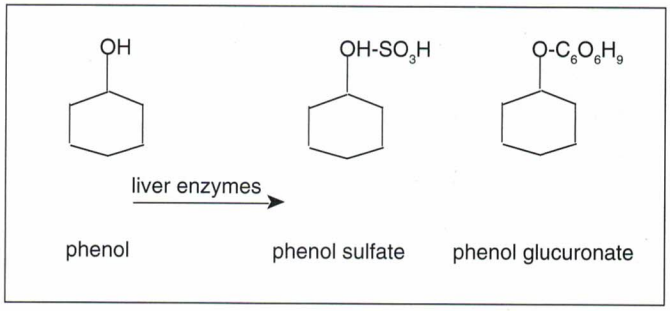

Figure 2
Detoxification of phenol by formation of conjugates

TOXICITY OF PHENOL

Clinical toxicity may occur when the metabolic detoxification system, described above, becomes overloaded, as for example by artificial exposure to phenol. Because of the chemical nature of phenol, it is freely soluble both in organic (lipid, cell membrane phospholipid, fat) and aqueous (cytosol, blood, intercellular fluids) phases. Phenol can enter the human body either by ingestion, by absorption through the skin or by injection (Gosselin et al, 1984; Sittig, 1991; Kirk-Othmer). Once phenol is introduced

into the human body, it is distributed widely due to its free solubility in virtually all tissues and fluids (Beeson and McDermott, 1975; Dukes, 1992; Goodman and Gilman, 1990). This, in part, is the source of phenol's toxicity: its ability to freely invade susceptible tissues and organs, where it can react chemically. In contrast, the less chemically reactive phenol conjugates produced in the liver are freely soluble only in the aqueous phase, from which they are rapidly eliminated.

Phenol toxicity may occur either acutely, by exposure to such an amount as is impossible for the liver to esterify immediately, or chronically, by dosing continuously with amounts which are large enough to prevent regeneration of the enzymatic esterification pool. While the level of phenol required to produce an overload condition probably varies among individuals, there are some guidelines which may help us analyze the question of phenol toxicity, namely the levels routinely experienced by normal individuals; that is, to assume that the levels experienced in the course of natural digestion are safe. Phenol concentrations have been measured in both artificially exposed subjects and in naturally exposed subjects (Docter and Zielhuis, 1967).

PHENOL IS FOUND IN NORMAL SUBJECTS

In normal subjects the phenol levels fluctuate depending upon the diet. Those eating a high protein diet have the highest levels of circulating phenol while fasting individuals have relatively lower levels of phenol. This is due to microbial action in the intestinal tract releasing phenol from tyrosine, one of the amino acids present in protein, and perhaps also from phenylalanine or tryptophan, the other two aromatic amino acids which can be enzymatically converted to phenol (Bernhart and Zilliken, 1959). Phenol levels in the blood, and especially those in the urine, can thus be used as an indicator for the nutritional state of the subject. Fasting results in very low but measurable levels of phenol.

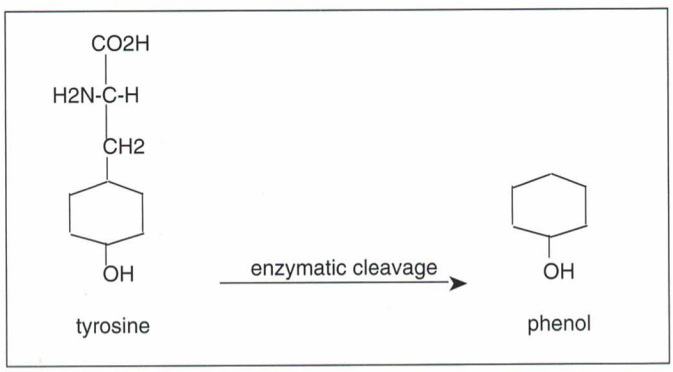

Figure 3
Microbial action produces phenol from tyrosine.

Patients with renal insufficiency have relatively higher levels of phenol in serum than do normal subjects (Wengle and Hellstrom, 1972). Urinary levels of phenol are higher than in blood as we would expect from the detoxification mechanism outlined above because both phenol and its conjugates are concentrated by the kidney. If we include the common methyl-substituted phenols, such as ortho-cresol, meta-cresol or para- cresol (naturally occurring phenols found in urine), then the levels of total phenol which might contribute to the toxic load can be as high as 200 mg/liter in urine of normal non-exposed subjects (Docter and Zielhuis, 1967). Cresol or methyl phenol is considered to be equally toxic as phenol itself. Generally speaking, the amount of phenol proper (phenol or phenol conjugates excluding the isomeric cresols) excreted by non-exposed normal persons is on the order of 5 to 10 mg/liter of urine. The amounts measured in serum of normal persons is about 0.1 mg/liter. Based upon the measurement of as much as 200 mg/liter of phenols found in the urine of unexposed individuals and assuming a daily urinary output of 1500 ml/day, a normal daily excretion rate of as much as 300 mg phenol and phenol conjugates can be extrapolated for normal individuals.

PHENOL TOXICITY IN EXPOSED SUBJECTS

Individuals exposed to either phenol or benzene, which is largely metabolized to phenol, excrete high amounts of conjugated phenol in the urine. Urine phenol concentrations of 100 to 400 mg/liter have been measured in occupationally exposed workers breathing 4.2 to 12.5 mg/cubic meter of either phenol or benzene vapors. Patients receiving phenol for nerve blockade demonstrated a maximal serum phenol concentration of 3 mg/liter at 19 minutes for unconjugated phenol and 4.2 mg/liter for conjugated phenol at 55 minutes (Baselt and Cravey, 1989). Generally speaking, a fatal dose of phenol is in the range of 2 to 3 grams in the acutely exposed individual.

Phenol is used topically for various clinical dermatologic indications. In addition to its antiseptic properties, phenol has anaesthetic properties; one of the effects upon dermal exposure to phenol is local numbness. Phenol promotes the growth of orderly arrays of collagen and elastin and is in current use by plastic surgeons for `face peels' for removal of facial wrinkles (Kligman et al, 1985). This increased deposition of orderly arrays of collagen and elastin, which also occurs at the site of prolotherapy injections, partially explains the inclusion of phenol in the protocol used currently (Hackett et al, 1991; Dorman and Ravin, 1991). Because phenol passes readily through the skin, care must exercised when working with large quantities of it. Plastic surgeons using phenol for facial wrinkle removal must protect their hands with gloves and the patient must limit exposure by having only small sections of the face exposed to the phenol solution every few minutes, thereby allowing time for the body to metabolize the phenol before applying more.

Fairly large amounts of phenol can be tolerated without apparent illness. In one case an elderly patient, confused about what to do with a topical phenol/saline in oil preparation prescribed for scalp itch, drank the material contain ing approximately 650 mg of phenol without apparent ill effect, except for the ulcerogenic effects on his nervous physicians.

Phenol can be quite toxic due to its neurolytic effects as well as its ability to interfere with oxygen transport. Acute toxic exposure occurs when phenol is absorbed in such an amount that the normal metabolic detoxification mechanism is overwhelmed. Acute exposure leading to death of the patient has resulted in

varying blood and urine phenol concentrations (Baselt and Cravey, 1989). A workman who fell into a vat of phenol up to his thighs died within a half hour and exhibited a blood phenol concentration of 90 mg/liter. A badly burned ten year old boy who was treated with a phenol containing disinfecting solution over a period of 2.5 days died of apparent phenol poisoning. He exhibited phenol levels in his urine of 220 mg/liter; his blood levels were not reported. In two other cases of dermal exposure to phenol, blood concentrations of 4.7 and 56 mg/liter were measured. A man who drank Lysol in a suicidal gesture exhibited a blood level of phenol of 46 mg/liter.

Chronic exposure to phenol resulting in fatality has not occured commonly since the end of the last century. In the 1800s several cases of `phenol marasmus' were described in individuals who cleaned hospitals with phenol disinfectant solutions containing 5 to 10% phenol. Chronic transdermal exposure led to a wasting phenomenon with symptoms of starvation. As a result of these incidents, the practice of using relatively concentrated phenol solutions for disinfection of operating rooms was abandoned.

SAFETY OF PHENOL IN PROLOTHERAPY

In ordinary practice, a solution containing no more than 1% phenol in combination with other substances is injected into dysfunctional ligaments for the purpose of treating ligamentous laxity. In the course of a single treatment session, as much as 20 cc of a 1% phenol solution might be injected containing a total of 200 mg of phenol. This amount is well below the amount known to be toxic in humans as discussed above. In fact, quantities of phenol excreted in the urine of normal non artificially exposed humans are higher than the amount injected in a single prolotherapy treatment. In other words the amount of phenol injected per treatment session is less than would be expected to be found naturally in the urine of normal untreated individuals. The quantity of phenol injected is less than the amount of phenol excreted in urine per 24 hours as a part of normal metabolism following digestion.

Based upon this analysis, acute phenol toxicity due to prolotherapy injections, even with the protocol as described above, is not possible for a patient with normal liver function. Further, because phenol is completely cleared within 24 hours, chronic phenol toxicity is likewise impossible in the normal course of prolotherapy where the interval between treatments is usually at least one week. This is because continuous exposure is required to chronically impair the normal detoxification mechanism and allow unconjugated phenol to chemically react with vital structures. Thus phenol, as used in prolotherapy, is safe as a component of the proliferating solution when used in the accepted technique of injection as outlined in current practice.

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❒ **PHYSIATRIC PROCEDURES IN CLINICAL PRACTICE**
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