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Review

Potential Safety Issues Surrounding the Use of Benzoate Preservatives

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Abstract: Sodium benzoate (E211) and potassium sorbate (E202) have long been used for large-scale beverage preservation, yet it is potassium sorbate that is now the preferred option for most soft drink manufacturers. Partly this is a reaction to the discovery that benzoate can cause drinks to contain traces of the carcinogen benzene. This benzene is thought to have its origins in a free-radical catalysed reaction of the benzoate with ascorbic acid. However, there may be additional benefits to using potassium sorbate rather than the benzoate preservatives in beverages. In children, a high dietary intake of sodium benzoate may be associated with asthma, allergy, or attention deficit–hyperactivity disorder. Benzoate is now known to influence cognitive functioning. By acting as a competitive inhibitor of the enzyme D-amino acid oxidase (DAAO), thereby reducing the DAAO-catalysed degradation of D-serine, it can upregulate the activity of the *N*-methyl-D-aspartate receptors in the brain. A high benzoate intake might also generate glycine deficiency, lack of glycine generally exerting a negative impact on brain neurochemistry. There are therefore strong grounds for suspecting that dietary benzoate can have neuromodulatory (mood, learning, and personality) effects and influence child hyperactivity disorders.

Keywords: preservatives; sodium benzoate; potassium sorbate; hippuric acid; benzene; urea cycle disorder therapy; cognitive functioning; hypoglycinemia

1. Introduction

Sodium benzoate (E211) and potassium sorbate (E202) are invaluable preservatives. European regulations also allow for the use of benzoic acid (E210), potassium benzoate (E212), calcium benzoate (E213) and derivatives of *p*-hydroxybenzoic acid. These compounds have been used for large-scale food, beverage, and cosmetic preservation over many decades [1,2], a number of bodies—amongst them the U.S. Food and Drug Administration and the European Union—having formulated clear legal provisions regulating their use. In the body, benzoate readily undergoes conjugation with glycine in the liver and kidney, this conversion to hippurate increasing its water solubility in order that it can be efficiently removed from the body by the kidneys [3,4]. Dietary sorbic acid can be metabolized by the same oxidation pathway as short-chain fatty acids.

This short article seeks to inform the beverage community about the rapidly expanding interest in sodium benzoate from the perspective of the existing and potential future uses of this compound in medicine. As outlined below, it now appears that clinical administration of this compound may be a promising therapy for the treatment of a number of neurological conditions, in addition to its established use in the treatment of urea cycle disease (UCD). Recent studies in this area have furthered our understanding of how this agent may impact on human physiology. Above all, they have flagged up some potentially detrimental effects of a high benzoate intake, effects which the beverage industry should take into account when making choices as to the formulation of its products.

2. The Potential of Benzoate to Generate Benzene

In 1993, Gardner and Lawrence reported that certain beverages containing benzoate salts and ascorbic or erythorbic acids contain low (ng/g) levels of the carcinogen benzene [5]. This benzene is thought to form during storage through a hydroxyl radical-catalysed decarboxylation of the benzoic acid—a reaction promoted by elevated temperatures and ultraviolet light, yet potentially inhibited by free radical scavengers and metal ion-chelating agents.

It is important to see this contamination of beverages, by traces of benzene, in perspective. This benzene formation can occur naturally in a number of fruits, such as mangoes, cranberries, greengages, and cloudberries; as well as fruit juices with naturally-occurring levels of benzoic and ascorbic acids. In addition, should individuals consume soft drinks which contain these low levels of benzene, the resulting increase in their exposure to this chemical will generally be miniscule, as compared to their normal exposure to benzene from the atmosphere. It has been estimated that it is common for each of us to inhale, on average, 220 μg benzene every day from exhaust emissions; while cigarette smokers may be exposed to up to 7900 μg benzene per day [6,7]. Benzene exposure is a hazard often faced by workers in the chemical industry. As a result, the harmful biological effects of this agent have been extensively studied, and are very well documented [8]. We should always endeavour to minimise our exposure to this chemical. It is therefore appropriate that many soft drink manufacturers have responded to the problem of trace benzene formation in soft drinks by reformulating products to contain potassium sorbate rather than sodium benzoate.

3. What Have We Learned from Patients on Prolonged Administration with High Levels of Benzoate?

We can be reasonably confident that a substantial intake of sodium benzoate over long periods is associated with a relatively low risk of harm, since the administration of high doses of this compound has been the gold-standard clinical treatment of UCD for nearly 40 years [4]. UCDs are inborn errors of metabolism that usually manifest themselves initially as life-threatening emergencies in newborn babies [9]. Amino acid breakdown in the body generates ammonia. In normal individuals, this ammonia is rapidly metabolised through the urea cycle to urea, this urea then being excreted in the urine. In UCD patients, this conversion to urea is compromised, causing an accumulation of ammonia and glutamine. This build-up of ammonia (hyperammonemia) is highly toxic to nerve cells, causing a wide spectrum of neuropsychiatric abnormalities and motor disturbances. If not diagnosed rapidly in neonates, the condition is generally fatal. Sodium benzoate therapy effectively counteracts this. Benzoate, as it undergoes conjugation with the most abundant amino acid in the liver (glycine), produces the readily-excreted hippurate, thereby effectively removing excess nitrogen from the body and lowering serum ammonia levels [4]. Increasingly, this use of sodium benzoate in UCD treatment is being replaced by treatments with the proprietary drugs sodium phenylbutyrate or sodium phenylbutyrate glyceryl tri(4-phenylbutyrate), compounds that are rather more effective at lowering serum ammonia levels or which reduce the dose-dependent sodium content of the therapy [4,10,11].

UCD patients have now been administered with high levels of sodium benzoate over many years. Monitoring of these individuals has revealed this therapy to be a highly beneficial treatment of their metabolic disorder [9,10,12–14]. Even though high sodium benzoate has been reported to cause necrotic and cirrhotic changes in the livers of mice [15], such damages have yet to be reported in UCD patients on prolonged benzoate therapy. Nevertheless, a high administration of sodium benzoate is not without potential risks. The significant sodium content of this therapy means it may not be appropriate for patients with significant fluid retention or kidney dysfunction [11]. In addition, hippurate might potentially accumulate to dangerously high levels in patients with renal insufficiency, since this metabolite—the product of benzoate conjugation with glycine in the liver—is renally cleared.

4. Benzoate Has the Potential to Exert both Positive and Negative Effects on Brain Neurochemistry

Evidence has been steadily accumulating that our emotional responses, thought processing, and behaviour are strongly influenced by the levels of two key amino acids in the brain; D-serine and L-glycine. It is here that benzoate can have an impact. Not only does benzoate rapidly traverse the blood–brain barrier, but it also acts as a competitive inhibitor of the enzyme D-amino acid oxidase (DAAO). By reducing the DAAO-catalysed degradation of D-serine, it can increase D-serine levels. When glutamate is released from nerve synapses, it triggers the release of D-serine from non-*N*-methyl-D-aspartate glutamate receptors, this D-serine then acting as the endogenous agonist for the glycine modulatory binding site on *N*-methyl-D-aspartate (NMDA) receptors [16]. Not only is the binding of D-serine more potent than that of glycine at this site, but glycine is also is required for physiologic NMDA receptor-mediated neurotransmission (glutamate cannot activate the NMDA receptor in the absence of glycine) [16]. By acting to increase the levels of D-serine in various brain areas benzoate is thought to increase NMDA receptor activity. Because of this ability to upregulate NMDA receptors, sodium benzoate is now attracting attention as a potential alternative to D-serine as a cognitive enhancer [8]. Amongst its attractions are its long history of relatively safe use for food, beverage, and cosmetic preservation; its ready oral administration, and its existing approval for the clinical treatment of UCD.

NMDA receptor-mediated neurotransmission is vital for learning and memory. NMDA receptor dysfunction is implicated in both the positive (psychotic) and negative (impaired emotional responses, thought processes, and behaviour) symptoms of schizophrenia. Increased levels of DAAO expression and enzyme activity have been found in post mortem brain tissue samples from patients with schizophrenia as compared to healthy controls, while D-serine levels appear to be decreased in these patients compared to healthy controls [17]. Sodium benzoate, through its ability to inhibit the DAAO-induced degradation of D-serine, may provide a promising alternative to the administration of D-serine in increasing the function of NMDA receptors during schizophrenia treatment [18–21]. There are a number of reports that it significantly enhances NMDA receptor-mediated neurotransmission and cognitive functioning in patients with chronic schizophrenia [22–25].

Loss of NMDA receptor-mediated neurotransmission is also thought to play an important role in the pathophysiology of Alzheimer's disease. Alzheimer's patients have elevated serum DAAO levels, consistent with hypofunction of NMDA receptors [26]. Administration of sodium benzoate has been reported to improve cognitive and overall functions in patients with early-stage Alzheimer's disease [27], and also, to protect memory and learning in an animal model of Alzheimer's disease [28]. In addition, it may induce functional improvements in patients with Parkinson's disease [29]. There are other clinical situations where it is normally desirable to downregulate NMDA receptor activity, as in the treatment of stroke, during withdrawal from benzodiazepine, and in anaesthesia. Agents that act this way (NMDA receptor antagonists) include several of the synthetic opioid anaesthetics (e.g., pethidine, methadone, tramadol), popular recreational drugs (e.g., ketamine, dextrorphan (a metabolite of the common cough suppressant dextromethorphan), phencyclidine) and nitrous oxide (N_2O). Through its ability to elevate D-serine levels, benzoate in the brain would be expected to counteract the suppressive effects of these latter agents on NMDA receptor activity.

While the medical research community is increasingly interested in these potential neuromodulatory uses of sodium benzoate, it is approaching application of the latter in the clinic with caution. A high benzoate administration could potentially have a negative influence on brain neurochemistry, should the conjugation of this benzoate with glycine generate shortages of glycine (hypoglycinemia) in nerve tissues [30]. Hypoglycinemia is one of the consequences of aspirin (acetylsalicylic acid) overdose, since salicylates, like benzoic acid, are substantially metabolized through their conjugation with glycine (thus forming salicylglycine, or salicyluric acid, compounds that are largely eliminated from the body in the urine). The impact on NMDA receptors of this conjugation causing a low level of glycine in the central nervous system has long been suspected as the

underlying basis of the psychosis of aspirin intoxication [4]. Despite this, certain medical treatments do seek to induce such a condition of a low brain glycine level, as when the glycine transporter inhibitors bitopertin or sarcosine are administered to patients with persistent negative symptoms of schizophrenia [31].

5. Conclusions

Even if we do not consume foods and drinks that contain benzoate or sorbate, we may still be exposed to small amounts of these compounds through our diet. These organic acids occur naturally at a high level in many berries. Benzoate can arise from the hippuric acid occurring naturally at concentrations of up to 50 mg/kg in milk and milk products [32–34]. It also forms during cheese ripening [35]. The benzoate originating from dietary hippuric acid is generated mainly through the actions of our gut microbes [4]. Benzoic acid is also one of the metabolites of cinnamon, the oral feeding of cinnamon powder having been found to generate benzoate in the blood and brain of mice [29,36].

The central issue is whether a much higher dietary intake of benzoate has the potential to exert detrimental effects (many beverages contain levels of sodium benzoate just under the regulatory level of 150 mg/L [34]). In mice, short-term consumption of sodium benzoate impairs memory performance [37]. In addition there are indications that a high intake of sodium benzoate may be linked to attention deficit–hyperactivity disorder in children [38]. This latter possibility merits serious consideration since, as mentioned above, benzoate can increase the activity of the NMDA receptors the brain and—at high levels—might even cause abnormally low levels of glycine in the central nervous system. Furthermore, a small number of children are reported to develop asthma [39] or allergy [40] in response to dietary sodium benzoate.

To date, these detrimental effects have not been described for dietary potassium sorbate. This does not mean that potassium sorbate should necessarily be regarded as completely safe. Benzoate and sorbate are both disruptive to the structure of biological membranes [41,42], a property that allows them to impact on mitochondrial energy coupling in living cells. In model organisms, they cause appreciable increases in oxidative stress, the associated damage to mitochondria possibly contributing to the pathophysiology of mitochondrial disease [37,43]. Both additives are reported to contribute to the activation of inflammatory pathways in liver tissue [44]. Potentially, therefore, these preservatives might be risk factors in the development of several chronic diseases. Nevertheless there is no evidence to indicate that the benzoate or sorbate preservatives in beverages are a risk factor in diabetes [8]. It should be noted however that studies on yet another small monocarboxylic acid—the antiepileptic drug sodium valproate—have revealed that certain individuals can be rendered particularly susceptible to the harmful effects of this kind of agent through genetic disease or chronic medical conditions. These medical conditions might also sensitise individuals to any harmful effects of a high benzoate or sorbate intake (reviewed in [8]). To counteract this latter possibility, it may soon be possible to use DNA profiling to advise individuals on whether they might potentially be at risk from these—and other—dietary additives.

It is the relatively high resistance of spoilage yeasts to growth inhibition by benzoate and sorbate that imposes the need for relatively high levels of these preservatives in many beverages [42,45]. It is to be hoped that industry will support research into furthering our understanding of this resistance, thus providing the knowledge base that will allow them to use the lowest levels of preservative in their products that still ensure a long shelf life.

Conflicts of Interest: The author declares no conflicts of interest.

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