Patient Preference and Adherence

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REVIEW

Averting the foul taste of pediatric medicines improves adherence and can be lifesaving – Pheburane® (sodium phenylbutyrate)

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Background: Children's aversions to poor and mostly bitter tastes and their inability to swallow tablets and capsules are major challenges in pediatric medicine. Sodium phenylbutyrate (NaPB) is a lifesaving waste nitrogen, alternative to urea nitrogen, for individuals suffering from urea cycle disorders. A major issue in the use of NaPB is its highly foul taste, which often leads to children being unable to consume it, resulting in ineffective treatment, or alternatively, necessitating the application of the drug through a nasogastric tube or gastrostomy.

Methods: This study reviews the published data on a novel formulation of NaPB, Pheburane® granules, which begin to release their NaPB after a lag time of ~10 seconds followed by a slow release over several minutes.

Results: The taste-masked granule formulation of NaPB dramatically improves the acceptability of the drug by children and appears in initial studies to be both safe and effective.

Conclusion: While more studies are needed to substantiate and enrich these initial trials, the available data provide a telling example where masking the drug taste of medicine for children can sometimes be the difference between life and death.

Keywords: sodium phenylbutyrate, adherence, urea cycle disorders, Pheburane®, taste, children

Background

Children's ability to consume drugs orally is often challenging due to their aversions to bitter tastes and their inability to swallow tablets and capsules. In general, the foul taste of drugs has been estimated to be a major hurdle to adherence for 91% of patients with acute illness and 84% of patients with chronic illness.[1]

Finding solutions for this issue is critical for children in early years, before they are able to swallow the whole tablet/capsule.

Palatability of medications is dictated to a large extent by taste; however, despite the fact that a large percentage of active pharmaceutical ingredients (APIs) have foul or unpleasant taste, this is not considered to be a major issue in the design of oral drugs aimed at adults as they can typically be film coated or sugar coated, thereby masking the taste of the API.[2] Young children, not being able to swallow a tablet/capsule, often need to receive liquids and (oro-)dispersible and chewable tablets, making taste masking a major challenge.

In a recent pragmatic study among hospitalized children, nearly one-third of the participants reported medicine refusal, which correlated significantly with child's age, drug taste, texture, and volume or quantity of the medicine.[3]

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Sodium phenylbutyrate (NaPB) is an effective waste nitrogen and an alternative to urea nitrogen for individuals suffering from urea cycle disorders (UCD).[4–6] Without such therapy, these patents develop liver damage and may succumb to hepatic encephalopathy at a young age.[5] A major issue in the therapeutic use of NaPB is its extremely foul taste, often leading children not to be able to consume it, resulting in ineffective treatment, or alternatively, necessitating delivery of the drug through a nasogastric tube (NGT) or gastrostomy. The development of a tasteless taste-masked granule formulation of NaPB that can be swallowed before taste receptors are stimulated is an example of a therapeutic victory achieved through technological solutions.

The urea cycle and nitrogen scavengers

Normally, nitrogen produced by protein breakdown is removed by the liver and, to a lesser extent, by the kidney, through a cycle of five biochemical reactions collectively called the urea cycle (UC) (or ornithine cycle). Inherited inborn deficiencies of UC enzymes, or certain cases of chronic liver failure, can lead to accumulation of ammonia and result in hepatic encephalopathy. Deficiencies of *N*-acetylglutamate synthase, carbamoyl phosphate synthetase, ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinic acid lipase, and arginase are all very rare conditions. The lack of effective early treatment results in accumulation of ammonia and irreversible brain damage.[6]

The basis of therapy for this condition, in addition to a very restricted protein diet to decrease nitrogen burden, is through the use of nitrogen scavengers that utilize alternative scavenging pathways, such that hippurate and phenylacetyl-glutamine, the metabolites of benzoate and NaPB, take the role naturally played by urea to excrete waste nitrogen.[5–8] NaPB is a prodrug, which is rapidly metabolized to phenylacetate. Phenylacetate is a metabolically active compound that conjugates with glutamine via acetylation to form phenylacetylglutamine, which is then excreted by the kidneys. On a molar basis, phenylacetylglutamine is comparable to urea (each containing 2 mol of nitrogen) and therefore provides an alternate vehicle for the excretion of waste nitrogen. Based on studies of phenylacetylglutamine excretion in patients with UCD, it is estimated that, for each gram of NaPB administered, between 0.12 g and 0.15 g of phenylacetylglutamine nitrogen are produced, thus addressing the elevated plasma ammonia and glutamine levels.[7,8] Because the needed doses are proportional to protein intake, this translates into large amounts of foul taste drug to be optimally taken during meals.

NaPB was introduced experimentally in 1987 and was approved for UCD by the US Food and Drug Administration in 1996 and by the European Medicines Agency in Europe in 1999.[8] The major issue with the clinical use of this very effective scavenger has been its notoriously foul taste.[8] As young children with inborn errors in the UC are a significant group of patients for this therapy, the offensive odor is a major cause for poor adherence and, therefore, can lead to irreversible brain damage secondary to hyperammonemia. Due to this serious challenge in drug administration, children are often given NaPB through NGT or gastrostomy.[9]

As many APIs are poorly palatable, there are common practical attempts used by parents and medical staff to either dilute the drug, and hence its foul taste, or try to obscure the taste by mixing or sprinkling it with foods or drinks.[2] These approaches may lead to impaired efficacy due to incomplete drug dosing, if the mixture is not fully consumed, and may also cause the child to develop aversion to the foods used in the masking process. The use of milk for this purpose in young children, who consume mostly milk, is a classical example of this challenge.

The sciences involved in taste masking are rapidly evolving to present clinical solutions for important medications, especially for young children who cannot yet swallow whole tablets or capsules. An excellent recent review by the European Formulation Initiative is highly worth reading.[2] It appears that >25 different bitter taste receptors have been identified to date. Bitter receptor antagonists can bind to bitter receptor sites and hence render the drug tasteless. However, presently no bitter receptor antagonists are already in clinical pediatric use, except for sodium chloride.

Methods

The published literature was reviewed through Medline and EMBASE for publications on NaPB and the taste-masked granule formulation of NaPB. Relevant articles were reviewed and evaluated as to the efficacy and safety in individuals treated for UCD.

Results and discussion

The taste-masked granule formulation of NaPB initial experience

To overcome the serious issue of foul bitter taste of NaPB, a French manufacturer developed a taste-masked granule formulation of the chemical. Over the years, attempts to mask this bitter and extremely unpleasant taste in food and drink have failed, causing these children to be undertreated, with the resultant poor metabolic control. The taste-masked

granule formulation of NaPB begins to release their NaPB after a lag time of ~10 seconds followed by a slow release over several minutes. In contrast, the market-licensed NaPB releases the active drug fully and immediately, leading to immediate release of the foul taste. Hence, the taste-masked granule formulation of NaPB creates a window of opportunity to completely swallow the formulation before its taste and odor become apparent.[10]

In the taste-masked granule formulation of NaPB granules in 13 adult volunteers, 5 g of granules were bioequivalent to the licensed product, while showing significantly higher acceptance, less bitterness, and less saltiness ($P<0.01$).[11,12]

These results led the investigators to initiate the first French nationwide 1-year cohort study on 25 patients, of whom 21 were children.[13] All of them suffered from UCD, and prior to introducing the taste-masked granule formulation of NaPB, all were maintained on another nitrous scavenger, either NaPB or sodium benzoate. Five patients eventually did not participate in the trial and 20 patients had analyzable results. The majority (n=15) of them suffered from ornithine transcarbamylase deficiency, and five patients suffered from arginosuccinate synthase type 1 deficiency. Clinically, 11 patients exhibited developmental delay, seven patients had epilepsy or neurological impairment, and six patients suffered from liver impairment. Importantly, 10 patients had hyperammonemic episodes in the 6 months prior to trying the granules (ranging between 1 and 3 episodes). The taste-masked granule formulation of NaPB was given orally in a total dose ranging from 1.5 g/d to 15 g/d (mean [standard deviation], 5.2 [3.3], or 211 [112] mg/kg/d). Overall, the cohort was treated for a period between 1 month and 11 months.

Most patients joined the study due to major issues with the taste of the marketed NaPB. The results of comparing taste and overall acceptability mirrored those shown in the healthy volunteers, with significantly less bitterness and dramatically improved visual analog scale scores of acceptance with the taste-masked granule formulation of NaPB. Prior to receiving the granules, some patients received the marketed product by NGT, one patient received through gastrostomy, and the rest were marked as "impossible to take the marketed product", "difficult", "need for reformulation", and "need to be treated with benzoate". With the taste-masked granule formulation of NaPB, all 20 treated patients were marked as "normal per os". The study did not follow formal measurements of adherence beyond these descriptors, and such data will be important to generate in future studies, both for short-term use and long-term use. Probably, the most important clinical outcome was the change in the episodes of hyperammonemia, with 10 patients experiencing between 1 and 3 episodes over 6 months prior to the taste-masked granule formulation of NaPB and none of them experiencing it in the 3–11 months after starting the taste-masked granule formulation of NaPB. With the lack of formal measurements of adherence, this dramatic clinical effect can serve as a surrogate of patients taking their medication regularly.

In January 2016, the authors reported the results of further follow-up of part of the original cohort.[14] Patients were followed up every 6–12 months at one reference center. Unlike the original cohort, the follow-up was not compulsory and participants had to have at least 6 more months of treatment over the original cohort described earlier.

From the original cohort of 25 patients, this review includes seven patients who continued and used granules, for over 1 year in one center, and one new patient from the same center who was exposed to the taste-masked granule formulation of NaPB for 8 months. Eight patients suffered from ornithine transcarbamylase deficiency (3), arginosuccinate synthase deficiency (3), carbamoyl phosphate synthase type 1 deficiency (1), and hyperornithinemia–hyperammonemia–homocitrullinuria (1). The granules given in a range of 2–9 g/d (mean [standard deviation], 5.6 [2.7]). The mean duration of exposure was 1.85 (0.5) years.

While there were five children requiring cognitive and social-educational support, neurological examination was either improved or stayed stable. There was a slow but steady growth in weight, height, and body surface area in the six children with available data.

In terms of number of hyperammonemic episodes, there were no such episodes among the eight followed up patients during the extended 8–30 months of the taste-masked granule formulation of NaPB. In a similar manner, the median (interquartile range) values of maximal plasma ammonia continued to decrease from 115 (75–185 μM) to 45 (30–76 μM) ($P=0.039$) and levels of glutamine stayed unchanged. However, while the authors state that "in a representative subset of this cohort, the protective effect of the taste-masked granules against metabolic decompensations was sustained", it is impossible to know whether a similar effect was achieved in the rest of the patients who were not followed up. In other words, it is not necessarily clear that this subcohort was representative of the whole initial cohort.

Conclusion

While more studies are needed to substantiate and enrich these initial trials, this experience provides a telling example where masking the drug taste in children can sometimes

be the difference between life and death. This approach can be adopted to other important pediatric drugs with foul taste (eg, cefuroxime).

Abbreviations

APIs, active pharmaceutical ingredients; NaPB, sodium phenylbutyrate; NGT, nasogastric tube; UCD, urea cycle disorders.

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Author contributions

GK conceptualized and designed the review and drafted the initial manuscript. YA, a pediatric toxicologist, contributed to the toxicological aspects of the review and reviewed and revised the manuscript. MJR, a pediatric pharmacologist, supervised the pharmacological aspects of the manuscript and critically reviewed the manuscript. All authors contributed toward data analysis, drafting and critically revising the paper, and agree to be accountable for all aspects of the work.

Disclosure

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