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Excessive sleepiness in an 5-year-old child being treated with dextromethorphan. Case report and literature review

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Summary

Background. Dextromethorphan (DXM), a synthetic analog of codeine, is a widely used antitussive, available in many over-the-counter (OTC) cough and cold preparations. The drug relieves cough by acting directly on the cough center in the brain. Although dextromethorphan is considered efficacious and safe, it may induce several adverse reactions of undefined frequency. ***Material and methods.*** We describe a case report of a 5-year-old patient who experienced adverse reaction of excessive sleepiness during the day after administration of antitussive syrup with dextromethorphan. ***Results.*** After consulting the doctor, the drug was discontinued. Saline inhalations, essential oils, and butamirate were used. The treatment modification resulted in clinical improvement after three days. ***Conclusions.*** The described case confirms the risk of excessive daytime drowsiness as an adverse reaction in a child following the administration of dextromethorphan. The use of OTC medications containing dextromethorphan in children should be well counselled by healthcare providers. *(Farm Współ 2022; 15: 232-236) doi: 10.53139/FW.20221526*

Keywords: dextromethorphan, antitussives, adverse drug reactions, drowsiness

Introduction

Cough belongs to the most common and troublesome symptoms of respiratory tract infections in children. It can affect a child's activity level and sleep, willingness to play, and school attendance, and thus, is often a source of parental anxiety. It represents the most prevalent symptom in primary care settings in many countries- a persistent, irritating cough is often the reason to refer a child to a pediatrician or respiratory physician [1-3]. However, cough is a natural reflex to protect the airways against unwanted substances. Stimulation of the pharyngeal area and irritation of cough receptors in the respiratory tract (located from the larynx to the segmental bronchi) can be triggered by infection, a presence of mucus, or foreign material [3,4]. Therefore, cough facilitates mucociliary function and helps the clearance of excessive secretions and debris from the airways. Cough can be elicited with mechanical stimulation in 10% of 27-week gestational-age preterm infants and up to 90% of full-term infants [4]. An average healthy child may cough about 11 times (range 1–34) per day, but during the autumn--winter season, when upper respiratory tract infections (URTI) are more common, the frequency and severity of cough increases.

Cough can be defined based on suggested etiology, duration of presentation, and sound quality [3]. Based on the residual mucus or the sound of mucus in the airway, a cough is characterized as wet, while a non-productive cough is considered dry. The sound of cough originates from the sudden release of air compressed by a previously closed glottis (following inspiration and glottic closure, the pressure is built, and then the rapid release of the air takes place) and can vary in pitch, timbre, or loudness [5]. When cough continues daily for more than eight weeks in adults and four weeks in children, it is considered chronic [1,5]. Cough in children lasting 3 to 8 weeks has been termed prolonged acute cough [6]. The global prevalence of chronic cough in the general adult population is around 10%. However, no studies have systematically compared the worldwide prevalence of chronic cough in children so far [6,7]. Based on the duration of the presentation, cough classification in children relies on the available data on coughs related to URTI. Around 10% of preschool children continue to cough 25 days after a respiratory tract infection, and about 50% of school-age children continue to cough ten days after the onset of a common cold. Predominantly, acute/sub-acute cough in children is associated with viral/

post-viral upper respiratory tract infections and does not require specific diagnostic evaluation. Around 10% of children with a viral URTI continue to cough for 25 days [1,3,4]. URTI is very frequent as school children suffer from 7 to 10 episodes per year and can cough for up to 140 days per year. Moreover, children are almost four times more likely to experience URTI-associated acute cough than adults; also, females are more frequently affected than males [8]. The definition of cough duration is vital in the context of individual patient presentations, as some severe cough etiologies require early attention and intervention [1,9]. In terms of duration, presentation, etiology, and management, cough in children varies from that in adults as there are differences in the airway morphology, a higher degree of vulnerability to toxic insults, reduced control of the cough reflex, and differences in the maturation of the neurological and immunological system in the different pediatric age groups [3,6]. In pediatric patients, acute cough is usually the result of a viral upper respiratory tract infection or from bronchospasm induced by allergens, illness, or physical effort [4]. The most commonly recognized etiologies for chronic cough in children apart from viral UTRI are also asthma and protracted bacterial bronchitis (PBB) [6]. Although chronic cough is less common than a recurrent acute cough, it is responsible for significant morbidity in affected children and their families. According to epidemiological studies, there is a substantial and frequently unrecognized burden of morbidity regarding chronic cough in childhood, with prevalence reaching around 10% [1].

Respiratory infections affecting children are generally mild viral infections that can be treated at home without any medicines. However, medicinal support is sometimes required to relieve cough, fever, and pain accompanying the infection. A commonly used OTC cough suppressant is dextromethorphan (DXM). Here we describe a case report of a child who experienced an adverse reaction to a dextromethorphan medicine.

Case report

A 5-year-old boy (vaccinated according to the vaccination schedule), who is not chronically ill, was treated with a syrup containing dextromethorphan hydrobromide due to a dry cough intensifying at night and early morning and lime blossom extract to soothe irritations. The syrup was dosed according to the manufacturer's recommendations - 2.5 ml of syrup three times a day (9.375 mg dextromethorphan/day). On the second day of using the syrup, parents observed excessive sleepiness during the day in the child. This symptom occurred also on the next day of treatment. Temperature measurements showed no values above 36.8°C. The patient did not complain of sore throat and runny nose. After consulting the doctor, the syrup was discontinued. Saline inhalations, essential oils, and butamirate were used. The treatment modification did not induce drowsiness and resulted in clinical improvement after three days. There were no adverse effects in the patient's history; the last antibiotic therapy ended two weeks earlier.

Discussion

Indications for the use of antitussive drugs are minimal and concern only dry, persistent cough. With the significant intensity of dry, unproductive cough in the course of respiratory tract infections, the effectiveness of known substances with potential antitussive effects is moderate [9].

Dextromethorphan (3-methoxy-N-methylmorphinan; also known as d-methor-phan) is a synthetic analog of codeine that has been used as an antitussive agent for more than 60 years and is available in many over-the-counter cough and cold preparations [10]. It is a widely used cough suppressant, and due to its availability, efficacy, and safety profile, it has overtaken codeine [11]. Though DXM is a codeine analog, it does not have analgesic effects or cause respiratory depression at therapeutic doses [4]. In the USA, OTC preparations containing DXM comprised up to 90% of all medications with a cough suppressant that were sold in 2015 in a total of 235 million packages [12]. However, DXM may also have other medical uses, including pain management, treatment of pseudobulbar affect, and psychological applications [13]. Over the past few decades, DXM has been re-purposed several times. Initially, it was applied as a cough suppressant, then as a compounded formulation with quinidine to treat pseudobulbar affect, and most recently, it received an indication for treatment of major depressive disorder as a compounded formulation with bupropion [14]. Due to its activity on numerous channels and receptors, DXM has a wide range of pharmacodynamic effects [11]. It is a lipophilic molecule with an ionizable amine at one end. DXM is structurally related to alkaloid opioids such as morphine but does not interact with the mu receptor [10]. The primary mechanism of the antitus-

sive effect of this drug is not entirely understood. It is thought that DXM stimulates sigma-1 receptors (σ_1R) and acts as an NMDA antagonist in the nucleus tractus solitarius, the estimated site where the pulmonary vagal afferent fibers synapse in the central nervous system, that functions as a gate for the cough reflex [10,11]. The onset of action of DXM is observed 10-30 minutes following administration and lasts for 5-6 hours in adults and 6-9 hours in children [15]. DXM undergoes rapid metabolism upon initial absorption. It is primarily metabolized by cytochrome P450 (CYP2D6) into a major O-demethylated active metabolite, dextrorphan (DXO) (nonetheless, DXM is also a pharmacologically active compound). Dextrorphan is further glucuronidated by uridine diphosphate-glucuronosyltransferase to form dextrorphan-o-glucuronide, representing the most prevalent form (98%) of this drug present in the plasma. The latter substance is permanently charged and has less permeability to the blood-brain barrier. DXM is also metabolized into 3-methoxymorphinan via cytochrome P450 3A4 [10,11]. It is worth mentioning that the polymorphism of CYP2D6 contributes to variability in drug response and toxicity, which is essential since dextromethorphan is widely consumed, including a combination with other drugs, or illicit mixtures of uncertain composition [11]. The elimination half-life of DXM is approximately 1.5-4 hours, while in case of dextrorphan it is 3.5-5.5 hours [15]. Unmetabolized dextromethorphan is excreted in the urine as unchanged drug along with three of its demethylated morphinan metabolites- dextrorphan, 3 hydroxymorphinan and 3-methoxymorphinan (80–90%) [15,16].

DXM is considered a safe drug when taken at recommended doses. Cold and cough medications containing DXM may induce minor adverse reactions such as nausea, vomiting, constipation, somnolence, dizziness, and allergic reactions (pruritus, rash, urticaria, angioedema, bronchospasm); however, their frequency has not been precisely defined [16,17]. Even though dextromethorphan has been used as a nonprescription drug since 1958 and is not physically addictive when taken in recommended doses, its recreational use (because of its alleged euphoric, hallucinogenic, and dissociative properties) in doses well above those considered therapeutic has become more frequent and wide-spread (especially in adolescents) since the 1990s, and cases of abuse have been described [11,18,19]. DXM in doses above 100–200 mg can produce clinical signs and symptoms resembling those of phencyclidine and ketamine, such as euphoria and dissociative hallucinations, which are probably mediated by a rather nonselective action on serotonin reuptake inhibition and σ_1 opioid, α3β4 nicotinic, and NMDA receptors. DXM also is a serotonergic drug that may exert a potential risk for serotonin syndrome and enhances the analgesic action of morphine and presumably other μ-receptor agonists [11].

DXM overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, lethargy, somnolence, slurred speech, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG with prolonged QTc interval), ataxia, toxic psychosis with visual hallucinations, hyperexcitability, and coma [4,16,20]. However, the optimistic news is that DXM abuse has fallen by nearly half during the past decade [21]. In case of overdose, children may experience severe adverse effects, including neurological disorders [16,22]. Cases of unintentional taking of medicines by children (e.g., left unsupervised, with easy access to medicines) may pose a significant threat. LoVecchio et al. performed a study evaluating the clinical presentation of accidental DXM ingestions in the pediatric patient (<5 years old) from two consecutive years. They identified a total of 304 cases with a mean age of 28.2 months (72% were ≥23 months); all of them co-ingested other products of OTC cough and cold medications (i.e., acetaminophen, pseudoephedrine, guaifenesin, ibuprofen, various H1 receptor antagonists, and very infrequently ethanol). Patients ingested DXM in a mean dose of 35 mg (2.64 mg/kg). Sixty-two patients (20.4%) experienced lethargy as the sole neurological sign; no patient had any cardiovascular abnormalities. Only one 13-month-old patient was hospitalized due to ingestion of 3.2 mg/kg of DXM but was subsequently discharged 14 hours later. No deaths were recorded. The authors concluded that accidental ingestions of DXM in children did well with supportive care alone and, in most cases, rarely required inpatient treatment [23]. Hotha et al. described case reports of altered levels of consciousness in three children with a therapeutic dose of DXM. In all cases, taking the first dose of syrup with dextromethorphan was related to the development of an altered level of consciousness. Those patients were unresponsive to any verbal commands and pain stimuli. Other systemic, cardiovascular, abdominal, respiratory, and nervous system examinations were normal, and their medical history had no pre-existing comorbidities. DXM was

discontinued, and all children recovered as they were then hospitalized and managed with symptomatic and supportive care. The causality assessment was performed based on the World Health Organization Uppsala Monitoring Centre causality scale, which was probable/likely in all three cases [24]. Due to concerns about the efficacy and need for DXM to treat cough in children, a clinical trial was conducted by Paul et al. The research aimed to compare DXM, diphenhydramine, and placebo for the treatment of 100 children diagnosed with an upper respiratory infection (URI), yielded that diphenhydramine and DXM were not superior to placebo in providing nocturnal symptom relief for children with cough and sleep difficulty due to URI [25]. Few pediatric studies provided similar results [4].

The over-the-counter symptomatic and supportive medicines are approved, but cough and cold medicines are not recommended, as these drugs may induce adverse effects in under-school-aged children. Research-based evidence for the effectiveness of cough medicines is lacking. Therefore, in 2008 the Food and Drug Administration (FDA) stated that children younger than two years should not use OTC cough and cold medicines because of concerns about their efficacy and safety. Consequently, manufacturers relabeled cough and cold medicines, only allowing children older than four years. Moreover, according to the recommendations of the American Academy of Pediatrics, cough and cold medicines should be avoided in children younger than six years [26].

Summary

There is a misconception among patients and health professionals that over-the-counter medications are often safer than prescription products. Limited regulations and ease of access may drive some of these beliefs. Many cough medicines, including DXM, are available without a prescription. DXM is a centrally acting non-opioid drug. Due to the complex mechanism of antitussive action, this compound can cause several adverse effects on the nervous system - from the deterioration of psychomotor efficiency, excessive sedation, and memory disorders to anxiety attacks, disorientation, and psychotic symptoms. DXM can be used in children from two years of age. OTC antitussive medications should not be routinely used in children under two years of age. It is crucial to take all precautions when administering medications with DXM to children. Antitussives with minimal adverse profile and some evidence of benefit may be recommended in some instances after informed counseling. Given this drug's high popularity and consumption in many countries, it is essential to inform patients about its potential adverse reactions.

Conflict of interest
None

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