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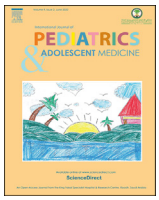

Oral enoximone allows the reduction and discontinuation of inhaled steroids and beta2 agonists in asthmatic children

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ABSTRACT

In the last two decades, improvement on asthma treatment has been merely marginal for both adults and children; inhaled corticosteroids (ICS) combined with β-2-mimetics remain the main therapy [3,4]. "New" therapies are just variations on ICS or, for children, on various other drugs that were allowed for adult asthma patients (clinicaltrials.gov). Although currently monoclonal antibodies have been introduced to the field, there is still a large therapeutic burden, given the mortality rate and widespread prevalence of uncontrolled asthma [2]. A simple and adequate way to reduce distress and costs would have great merit. PDE3 inhibitor enoximone was used earlier in successful treatment of life-threatening bronchial asthma (status asthmaticus) as well as in preoperative settings to prevent patients with severe asthma from suffering major surgery-related exacerbations; also, translational mice models showed the anti-inflammatory effects when PDE3 was targeted. Both outcomes suggested a beneficial effect of enoximone in severe chronic asthma. We hypothesized that enoximone might also be helpful in patients with severe chronic asthma; hence, we treated (and followed) > 70 patients (age 0–77, all volunteers) with personalized low doses of enoximone (orally), among them 11 minors, who are described here. Both children and adults reported improvement and/or alleviation of their asthma symptoms. All patients reported a better quality of life and greater drug compliance. The drug was well tolerated and showed no/negligible side effects. Notable bonus: asthma-related comorbidities (allergies, eczema, and rhinitis) were reported also to be less severe or even to disappear. The evaluation shows that PDE3 inhibitor enoximone is an adequate alternative for or addition to current asthma therapeutics, as add-on as well as stand-alone, considerably reducing the use of β-2-mimetics/ICS, with no or negligible side effects. Additional studies are advisable.

1. Introduction

This paper reports on 11 children who orally received low-dose (0.5–5 mg = 0.1–1.0 ml (5 mg/ml)) PDE3 inhibitor enoximone (Perfan®, Carinopharm, Germany) for asthma. The first dose was administered on all of them under the auspices of a physician and were followed closely using parameters such as dosage, results, and side effects. All of them benefited by the use of the drug and related an increase in the quality of life, as they perceived less coughing, less fatigue, better endurance, fewer sick days, and zero hospitalization. The observations indicate that enoximone meets all criteria of a novel anti-asthma drug with steroid-reducing properties and is, at the very least, a beneficial add-on in the asthma treatment of the children reviewed.

Informed consent for the treatment and anonymous publication of the results was obtained from all patients. Ethical agreements, CCMO, and METC permission do not apply as this is an investigational use application report. Youth Health Care Inspection in the Netherlands was contacted regarding the add-on use of enoximone. In the Netherlands, health care is primarily a confidential agreement between patient and physician, wherein the physician is responsible and bound by confidentiality regarding all that is agreed between both parties; patient files have to be kept.

Worldwide, between 235 and 300 million people are affected by asthma; approximately 383,000 people die from the disease per year, most of them (80%) in low-income countries [1,2]. It is the

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most common chronic disease among children. According to the Global Asthma Report 2018, asthma deaths represent the tip of the iceberg in respect to the global burden of asthma; continued surveillance of asthma mortality rates is essential to monitor progress in asthma care and as an early warning of epidemics of fatal asthma, as have occurred in the past half-century.

Asthma is an inflammatory obstructive airway disease, the treatment of which poses a challenge to both physicians and health services. In the last two decades, improvement with regard to asthma treatment has been merely marginal, for both adults and children; inhaled corticosteroids (ICS) is still the main therapy [3,4] and "new" therapies are just variations on ICS or, for children, on various other drugs that were allowed for adult asthma patients [5] (clinicaltrials.gov). Although currently monoclonal antibodies have been introduced to the field, there is still a large therapeutic burden, given the mortality rate and the still widespread prevalence of uncontrolled asthma [2]. A simple and adequate way to reduce distress and costs would have great merit.

Drug prescription is based on clinical trials through the use of standard doses. On the other hand, personalized medicine means prescribing a dose with the optimal fit regarding the patients' genetics and phenotype; in the context of asthma this is rather fitting, as patients often practice self-dosing on a personalized "if-needed" basis. Presently, in diseases such as asthma, patient-reported outcome and the use of/reduction in ICS and β-mimetics are regarded the most important parameters, accentuating subjectivity over numerical standardization [6].

A bolus of the phosphodiesterase 3 (PDE3) inhibitor enoximone proved to have an immediate and positive effect in 8 near fatal cases of status asthmaticus, including one child [7]. Egyptian research confirmed this observation in a proof-of-concept study using the PDE3 inhibitor milrinone [8]. PDE3 is highly expressed in the structural cells of the airways (endothelium, epithelium, and smooth muscle cells) and immune cells. PDE3 inhibitors primarily target the airways and serve as a topical action drug, even if administered systemically. In the UK, oral enoximone is being used in children suffering from pulmonary arterial hypertension [9,10]. Enoximone is anti-inflammatory and clinically available (as injectable) in Europe [11].

One of the 8 status asthmaticus cases was a 16-year-old-boy [7]. At admission to the Emergency Department, the boy suffered from functional respiratory arrest for his high PaCO2 and low pH, was extremely hypercapnic and acidotic, was unable to speak, and was in and out of consciousness. All guidelines with regard to asthma had been followed, to no avail. He received an initial bolus of 100 mg enoximone IV, whereupon the respiratory arrest was countered almost immediately, within seconds, i.e., one circulation time from arm to lungs. Although he could speak in full sentences after that, in his panic, he still felt dyspneic; hence, he received a second bolus of 100 mg within 5 min. The dyspnea symptoms resolved within 15 min. [7], He was transferred to the pediatric ward, skipping (P)ICU. He did not need nebulization or oxygen. No rebound was seen during hospital stay and he was discharged after one day, after renewed proper setting of his medication. When compared to the treatment of status asthmaticus with a loading dose of salbutamol [12], enoximon seems a valid alternative, with the bonus of not being troubled by tachycardia and/or arrhythmias. The above mentioned case led to more children (i.e., their parents) seeking treatment through word of mouth.

2. Patients subdivided in 4 groups

The children could be subdivided into 4 different groups based on traditional medication cutback:

1. Patients using enoximone as an add-on, and still using their traditional medication (no cutback, n = 2)
2. Patients using enoximone and having been able to reduce their traditional medication (partial cutback, n = 1)
3. Patients having been able to discontinue their traditional medication and use only enoximone (complete cutback, n = 6)
4. Patients who, after having used enoximone for some time, saw their symptoms disappear and now use no medication at all, not even enoximone (total discontinuation of therapy, n = 2)

The initial effect of enoximone (bronchodilation) occurred in all patients within minutes after the first administration. In the following days, they all experienced improvement in their well-being, even if they could not phase down their traditional medication; observations varied from more stamina, more air, and easier breathing, to living a fuller life, including "normal" every-day activities, sports, social functions, and work/school.

It is remarkable that particularly the use of steroids (ICS) could be drastically reduced or even discontinued altogether; this was the largest group (6 out of 12 children) (Fig. 1). An unexpected secondary effect was that several of the patients noticed a decrease in asthma comorbidities such as allergic rhinitis and atopic eczema.

Seasonal influences (autumn and winter, including flu season and common colds) were seen to increase the severity and frequency of the asthma symptoms. This could be counterbalanced by slightly increasing the dosage or spreading the dose over several moments of administration per day.

3. Side effects

In the official literature for enoximone, there are several side effects mentioned [13,14] (extrasystoles, supraventricular arrhythmia, ventricular tachyarrhythmia, hypotension, headache, sleeplessness, gastrointestinal complaints such as nausea,

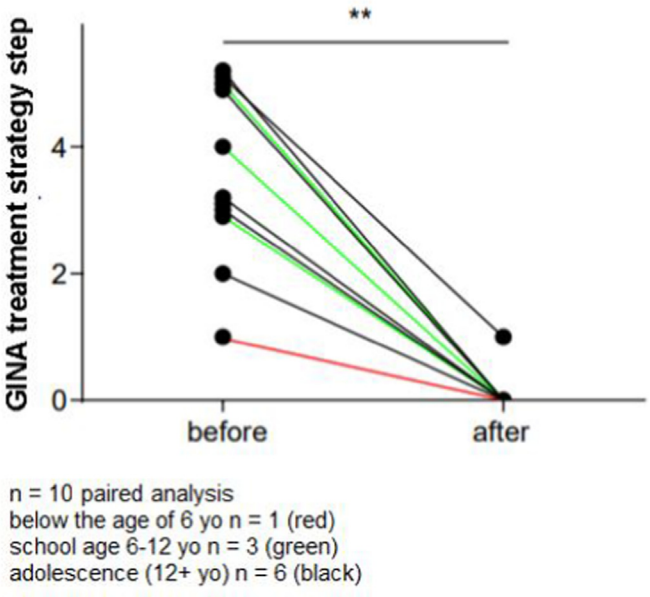

Fig. 1. Reduction/discontinuation of ICS/LABAs/SABAs.

vomiting, diarrhea, mild thrombocytopenia, and a reversible increase of liver enzymes). Rare side effects are cold shivers, oliguria, urine retention, and muscle pain in the extremities. One patient in Table 1, (#02) stated having trouble sleeping and feeling restless and agitated. All other side effects have been specifically asked after, but were not found or reported. In contrast, beneficial effects were mentioned as the traditional medication [3,4] could be phased down or discontinued; agitation, tachycardia and a rushed feeling caused by e.g., salbutamol or salmeterol disappeared when enoximone took their place. As this paper describes the investigational use of enoximone in asthma, no measuring of blood values was involved.

4. Specific patient experience with enoximone add-on therapy

More specific observations show one child (Table 1, #5) transforming from a skinny, tired, and lethargic boy who could not keep

Table 1
Patient Groups.

Group 1: patients who use enoximone as add-on and still use their traditional medication

Nr.	Age - Sex	Medication before starting enoximone	Medication after starting enoximone	Dosage enoximone	Comments
01	16 - M	Flixotide 50 mcg 4 x p/w Salbutamol 100 2 x p/w Desloratadine 5 mg 1 dd Mometasone furoate 50 mcg prn (nasal spray) Azelastine 1 mg/ml prn (nose drops)	Idem Idem Idem Idem Idem	2.5–5 mg dd	Uses slightly more enox. in cold season.
02*	13 - M	Seretide 25/50 2 dd	Idem	4 mg dd	Sleeping poorly, felt restless Stopped enox. because of that.

Both patients from this group, even #02, immediately felt better using enoximone; they could breathe better and deeper and eventually were able to do more everyday activities, like shopping, climbing stairs, partaking in sports and games, etc.
*- #02 suffers from a form of autism, including sleeping poorly and feeling restless during the night; this intensified during enoximone therapy.

Group 2: patients who use enoximone and were able to reduce their traditional medication

Nr.	Age - Sex	Medication before starting enoximone	Medication after starting enoximone	Dosage enoximone	Comments
03	16 - M	Beclomethasone 50 mcg 2 dd Montelukast 10 mg 1 dd Aerius 2.5 mg 1 dd Salbutamol 100 mcg prn Foster 100/6 4 dd	Idem Idem Stopped Idem 2 dd	15 mg dd	Grew several centimeters and gained weight. Spirometry May 2019 was excellent. Was able to do 5 out of 6 Cooper tests in school (2019).

The patient in this group had the same experiences as the patients in Group 1.

Group 3: Patients who were able to discontinue their traditional medication and use only enoximone

Nr.	Age - Sex	Medication before starting enoximone	Medication after starting enoximone	Dosage enoximone	Comments
05	15 -M	Ventolin 100 mcg, 2–8 dd Atrovent 20 mcg, 2–8 dd Qvar 50 2 dd	Stopped Stopped Stopped	5 mg d or 2 × 3.75 mg dd	Stopped trad. med. after ca. 1.5 yrs. Grew 10 cm and gained 7 kg in 6 months; nail clubbing disappeared. Can now partake in social activities and sports. Sleeps well (no more nightly coughing), so does not fall asleep in school anymore and gets better grades.
06	8 –F	Ventolin 100 mcg 4 dd Fluticasone 50 mcg 2 dd	Stopped Stopped	2.5 mg dd	Stopped trad. med. after 3 days. More socially active, can do sports now. Suffered from mood changes due to steroids; after starting enox. she returned to her own true cheerful character.
07	15 –M	Ventolin 100 mcg 4 dd Atrovent 20 mcg 2 dd Seretide 25/125 2 dd	Stopped Stopped Stopped	5 mg dd	Stopped trad. med. after 6 months. Feels much better on enox. Can do sports and social activities on a larger scale.
08	15 - M	Mometasone furoate 50 mcg 1 dd (nasal spray) Emadine eyedrops 2 dd	Stopped Stopped	5 mg dd prn	Stopped trad. med. immediately. Hay fever under control.
09	11 - F	Prednisone 5 mg 1 dd Qvar 100 2 dd Ventolin 100 mcg ≤ 10 dd	Stopped Stopped Stopped	5 mg dd	Stopped trad. med. after 1 month. In 2014 alone 7 prednisone treatments, next to atomizing Ventolin up to 10 dd to prevent hospitalization. No more hospitalization since starting enoximone.

The findings in Group 1 and 2 also apply to Group 3.

Group 4: patients who, after having used enoximone for some time, saw their symptoms disappear and now use no medication at all, not even enoximone.

Nr.	Age - Sex	Medication before starting enoximone	Medication after starting enoximone	Dosage enoximone	Comments
10	10 - F	Qvar 100 2 dd Salbutamol 100 2x dd 2 puffs	Stopped Stopped	5 mg eod	Stopped trad. med. after 1 month; stopped enox. after ca. 2 yrs. Was once hospitalized after forgetting Qvar just once. No more hospitalizations since starting enoximone.
11	4 - M	Salbutamol 100 with spacer	Stopped	0.5 mg dd	Stopped trad. med. after 2 months; stopped enox. after ca. 3 months. First seen at 13 months of age – had spent 6 of them in hospital. After starting enox. no more hospitalizations; released from treatment by pediatrician after one year.

Again, the same results apply to group 4.
All children (n = 11) felt better using enoximone; they could breathe freely and deeply and were able to engage more in everyday activities, including sports and games. Only one of them (#02, group 1) experienced a side effect, having trouble sleeping and feeling restless and agitated. This might be due to an increase in problems connected to an already existent form of autism, or possibly to a heightened sensitivity for the diluent (propylene glycol (43%), a non-toxic solvent and antifreeze agent that is often used, in low concentrations, in food (wine), cosmetics, and medicines) in which enoximone is dissolved in its current, liquid form.

up with school, sports, games, and other social activities, who did not eat properly, and who was ignored and scoffed at by his classmates, into a healthy young sportsman, who eats like a normal adolescent, has a busy social life, does well at school, gained several kilos and centimeters in the process, and can control his asthma with only enoximone. Even his nail clubbing, a sign that may indicate an underlying, not yet diagnosed lung disease (as this is not a common symptom in asthma) disappeared. Two other boys (Table 1, #03 and #07) experienced similar improvements in their overall condition and social life. All three boys had lung function tests performed after having used enoximone for some time, and were proud to report that these were the best tests they had ever completed. Yet another little boy was only 13 months old (Table 1, #11) when receiving his first dose of enoximone (0.5 mg in a glass of fruit juice); all his life he had been in and out of hospital because of pulmonary problems, always being short of breath, tired, and apathetic. After starting enoximone his energy increased, he started to walk, eat, and play and has not been hospitalized since (he is 4 years old now). Eventually, he was able to stop all treatment, even enoximone, and was discharged by his pulmonologist. One girl (11 years old; Table 1, #09) had been prescribed 7 prednisone treatments over one year's time to avoid hospitalization and needed 2 salbutamol puffs every two hours. After starting enoximone she needed no more traditional medication, has not been hospitalized, functions well, and uses only enoximone, interspersed with total medication-free periods. Another girl (8 years old; Table 1, #06) had been seen by a pulmonologist since her premature birth, but was still suffering from uncontrollable asthma. She was prescribed fluticasone, which turned her into a genuine mini she-devil, throwing anger tantrums, and being very hostile and aggressive in school and at home. After starting enoximone, she was able to discard the fluticasone and changed back into the pleasant and socially skilled girl she had been before.

5. Dose finding: identifying the lowest possible effective dose

Literature provides ample data regarding effects and side effects of enoximone in (extremely) high doses in the treatment of heart failure [13,14]. In the UK, children with post-cardiosurgical heart failure have been treated for over 20 years with a daily dose (dd) of oral enoximone 3 0.5 mg/kg for an average duration of 1 year, which did not lead to serious side effects or adverse results.9,10.

As enoximone for asthma is a new indication, which has not been described in medical literature up to now, an algorithm was formed for optimal dosage finding, based on the above-mentioned literature, on experiences with status, asthmaticus patients in the ER,7 and on perioperative treatment of severe asthma patients. In addition, extensive research on mice was performed [11]. Eventually, a specific dosage could be determined. The premise was to search for the lowest effective dose, the frequency of administration ideally being 1 dd or in the absence of complaints, even less. The algorithm yielded 0.0625–0.125 mg/kg bodyweight, which transfers to an average dosage of 5–10 mg dd for adults and 1.25–6.5 mg for children. For safety's sake, we would like to provide a caveat of a maximum dose of 20 mg dd or if the frequency is 2–3 times a week, a maximum of 25 mg per administration; it is to be noted that the study by Metra et al. indicates a safe maximum of 150 mg dd [13]. Based on the above, there was little hesitation to administer low-dose enoximone (less than 0.25 mg/kg 1 dd) to minors, although of course we proceeded very carefully, always under the auspices of a physician. When personalized dose finding was settled, the children proceeded with that particular dose.

Most asthma/hay fever/allergy patients are familiar with various traditional medications for their condition and turn out to be surprisingly good at handling their dosage, meaning that they can estimate quite adequately their need for less/more medication. This can depend on, for example, the season (pollen, heat, and cold) or exercise (sports and games). This applies to children as well, particularly when they grew up with asthma. Of course, supervision, from parents and physician both, is advisable, if not necessary. Therefore, we asked to be contacted in all cases when a patient contemplated to (temporarily) increase or reduce the dose, so that we could do a proper follow up. Thus, we discovered that time and frequency of intake had some impact on the efficiency of the working mechanism. Administration of 2.5 mg twice a day, morning and evening, appeared to have more effect in some children than 5 mg once a day. It also emerged that most asthmatic children, when having contracted a (mostly viral) respiratory infection, appeared to benefit from an increased frequency or dosage. For children who experienced a "normal" asthma pattern, it did not seem to matter whether the dd was 0.5, 1.5, or 10 mg. Also, the severity of asthma seemed not always a parameter: in most cases, severe uncontrollable asthma responded just as well to 10 mg dd as mild asthma. It is therefore advisable to always go with the lowest possible effective dose. On that basis, an increase in dosage and/or frequency of administration can be considered in case of exacerbations and/or additional disorders (colds, respiratory tract infections, pneumonia, and hay fever).

6. Administration method

Enoximone is usually administered through IV injection, in a hospital setting, under the supervision of a physician. This is not an option for asthma patients, who have to use the drug on a regular (daily) basis, and certainly not for children. Moreover, we aim to increase drug compliance by offering an easy way of asthma control, contrary to inhalers (that are socially very embarrassing for many children) and corticosteroids and/or β-2-mimetics that often have unpleasant side effects. Inspired by Ancke Furck in the Royal Brompton Hospital, UK, 9 we chose to offer the enoximone added to a beverage such as fruit juice, soda, tea, or milk. Water is an option, but is, due to somewhat bitter taste of enoximone, not recommended. The speed of the effect does not differ significantly from IV administration [15]. Both ways showed an effect within minutes.

7. Discussion

To our knowledge, this is the first report that identifies the beneficiary effects of the use of enoximone (add-on) therapy on asthma patients. As this is an investigational use report, we backtracked and recorded the medication the asthma patients used at the moment they presented themselves to the physician. Retrospectively, we observed that patients were able to phase down or discontinue altogether their traditional medicine (mainly a combination of ICS and beta-2 mimetics), and thus avert the associated side effects. Sparing children the hassle, nuisance, and invalidation springing from asthma (and, consequently, avoiding them becoming diseased adults) is obviously essential. This patient experience report illustrates the need for and the availability of alternatives for ICS and beta-2 mimetics for asthma patients who are not helped by and/or satisfied with traditional therapy. Enoximone fits in a steroid-reducing therapy.

PDE3 inhibition supports the normal healthy function of cells, including the improvement of cilia function [16] and mucosal barrier function [17]. In addition to the inflammation of the airways, asthma patients also suffer from increased production of mucus, decreased tissue compliance, and difficult clearance because of impaired cilia function. Therapeutic options should target all of these symptoms, aiming at the prevention of mucosal leakage and tissue edema by targeting epithelial and endothelial

cells to improve mucosal barrier function, mucus clearance through improved cilia function, and the reduction of viscoelasticity by making the mucus more liquid [16–18]. The latter is also due to PDE3 inhibition as this activates the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), pumping chloride and water out of the epithelial cells to make mucus more liquid [18,19].

Because this paper describes about the investigational use, no objective parameters were applied; control questions involved the use of medication, quality of life, and side effects. The most relevant observations are the immediate bronchodilatory effect and the drop of medication use during (add-on) the use of enoximone. Another observation is that patients and their parents were highly motivated to continue enoximone add-on therapy because of its immediate effect. An additional benefit is that the use of oral enoximone will reduce pollutants, HFA134a and 227ea, the propellants in metered dose inhalers [20]. A similar paper concerning the treatment with enoximone of 60+ adults suffering from asthma, showing overall the same results, is in preparation.

From the children's perspective, the social aspects of having asthma often include not being able to partake in child activities (games and sports), not being able to sleep well at night, and therefore not functioning well during daytime, affecting, among other things, school and social performances; they are lagging behind in growth and general development, are challenged with frequent hospitalization or internalization in special asthma clinics, and are often stigmatized because of their poor performance and frequent, obvious, and visible (due to inhalers and spacers) drug use. Targeting these phenomena early may save them (in youth and in later life) considerable strife, stress, and struggle.

The use of PDE3 inhibitors like enoximone in asthma can achieve significant results in medical as well as in social terms, and can generate large economic benefits. It is essential to make medication more effective, affordable, and available, relieving the physical and financial claim asthma poses on its sufferers, on health authorities, and on society. We believe that treatment with oral enoximone of children (and adults) suffering from severe asthma is a logical and essential step; side effects of enoximone are minimal even in high doses [8].

Ethical statement

Informed consent for the treatment and anonymous publication of the results was obtained from all patients. Ethical agreements, CCMO, and METC permission do not apply as this is an investigational use application report. Youth Health Care Inspection in the Netherlands was contacted regarding the add-on use of enoximone. In the Netherlands, health care is primarily a confidential agreement between patient and physician, wherein the physician is responsible and bound by confidentiality with regard to all that is agreed between both parties; patient files have to be kept.

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Declaration of competing interest

J.B. has a patent PCT/NL2015/050246, P6054704PCT pending and is the shareholder and owner of BMR b.v. Relatives of AKJ are shareholders of BMR b.v.

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