

The lowest dose of corticosteroids, which stops the episodes of PFAPA syndrome

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RESEARCH

Please cite this paper as: Nasser NH, Nasir NN, Habib MG, Samra NG. The lowest dose of corticosteroids, which stops the episodes of PFAPA syndrome. AMJ 2017;10(4):322–328. <https://doi.org/10.21767/AMJ.2017.2899>

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ABSTRACT

Background

The episodes of PFAPA syndrome with their exhausting periodic fever, annoying oral aphthae and sore throat, warrant treatment. Corticosteroids are the most efficacious.

Aims

Providing evidence that a weight-independent minimal dose of betamethasone the least ever used can resolve symptoms of PFAPA syndrome within few hours.

Methods

In a retrospective case-series analysis study, approved by the relevant ethical committees of Clalit Health Organization, we collected analysed and interpreted data from medical files of children who suffered from PFAPA syndrome, during 1998 until 2015, concerning the lowest effective betamethasone dose, they received and which had abated fever within few hours.

Results

We had diagnosed 132 children of our 2300 children community, as suffering from PFAPA syndrome (rate 6 per

cent). Ninety eight per cent of the patients satisfactorily responded, within two-to-twelve hours, to treatment with a minimal one-time weight-independent dose of betamethasone in every flare. The rest of patients (2 per cent) needed an equal second dose to end their first flare during the following twelve hours. Three patients who were four to five-months-old at time of diagnosis, had received 0.1mg dose.

Conclusion

A dose of 0.5mg of betamethasone for children under 5 years of age and a dose of 1.0mg was prescribed for children >5, were effective for prompt resolution of PFAPA flares. We believe that as long as there is an effective lowest dose for treating PFAPA episodes, a great reduction of corticosteroid consumption will be exercisable globally.

Key Words

PFAPA treatment, periodic fevers, inflammatory diseases, corticosteroids, aphthae stomatitis

What this study adds:

1. What is known about this subject?

Steroids are the first choice ambulatory one-time treatment for resolution of every PFAPA flare. The usual dose of prednisolone is weight-dependent, 0.16–2.0mg/kg/dose.

2. What new information is offered in this study?

A prove that a minimal steroid weight-independent dose of 0.5mg betamethasone for under five-years-old patients, or 1.0mg for patients over six-years-old, can successfully abort every PFAPA episode.

3. What are the implications for research, policy, or practice?

Effective minimal steroid dose for abating flares may curb steroid intake at a global scale. Efficacy of such dose for other steroid-responsive diseases needs proof.

Background

Flares of 'Periodic fever, aphthae stomatitis, pharyngitis and adenitis' (PFAPA) syndrome disappear spontaneously, in the majority of cases, within three to ten days, without any medical intervention. Thus, some researchers take into consideration that this is truly a transient periodic endogenous inflammation, which behaves, in fact, as a normal inflammatory process intended for healing of injured tissues, causing, adversely, various clinical features, namely fever and pain, etc., of PFAPA, though is not a true sickness.¹⁻⁴

However, the exhausting periodic fever, followed by chills, and the annoying oral aphthae and sore throat, resistant to oral, parenteral antibiotics or antiviral therapies, and the additional other complaints, such as headache and abdominal pain, bring about enormous anxiety for parents concerning the child's health, periodic absences from school, and regarding mishaps at their work. Such a situation warrants an effective ambulatory treatment, which can induce rapid remissions of PFAPA episodes.^{2,5-8}

The diagnosis of PFAPA was made when a child had at least five bouts of fever associated with one or more of the clinical markers of the disease.

Moreover, the presence of features, such as quick response to steroid therapy, being non-contagious, and a normal neutrophil count before giving the steroid, make the diagnosis solid.^{1,2,5,6,9,10-13}

Wurster et al. observed that nine patients in their group of PFAPA syndrome have maintained typical markers of the syndrome, but without fever in their flares.¹⁴

According to some experts, whenever the course of the disease in a certain patient, is consistent with the diagnosis of PFAPA, a physician can prescribe a single dose of prednisolone, as high as 2mg/kg-body-weight, at onset of fever, and expect then resolution of fever, and loosening of the associated symptoms, during two to twelve hours. Otherwise, he must consider other diagnoses.^{2,8,9,15-20}

Among the treatments suggested to alleviate the PFAPA flare-ups, the glucocorticoids are the most rewarding.^{1,2} Practically, the quick response to steroid therapy is characteristic for PFAPA more than any other periodic fever disorders, i.e., FMF, Behcet disease, etc.^{1,8-10,16-19,20-22}

On the other side of the coin, evidence has accumulated regarding the fact that physiological levels of these

hormones are enough to temper inflammation or immune reactions.

Tasher et al.,⁵ for example, had reported that a small dose of as low as 0.15mg prednisolone per kg body weight, given during the PFAPA episode, reduces fever within few hours.^{4,5,20,22,23}

Anyhow, the period of time until reduction of temperature in PFAPA episodes, was not significantly shorter after using higher dose, compared to that after giving a low dose of steroid.^{3,5,24}

Our objective is to consolidate the feeling of many community physicians, that a minimal corticosteroid dose, independent of body weight, is enough for aborting every PFAPA flare, within few hours. Other researchers obtained the same outcome after treatment with two to threefold higher dose of steroid.^{1,2,5,7,9,16,25-27}

Method

In a retrospective case-series analysis study, approved by the relevant ethical committees of Clalit Health Organization, the initiator-investigator collected relevant data from 132 medical files of patients with PFAPA syndrome, dated from 1 September 1998, to 1 October 2014.

A case report file (CRF), which accurately presents the study protocol was made for the collected data.

Included in the study were: a) Children who suffered from PFAPA based on criteria known for this disease, including those who had past regular childhood illnesses, and who were not consuming any continuous medications, b) Patients who responded to the provision of one standard dose of steroid, c) Patients who needed a second dose to reduce fever within few hours.

Excluded from the study were: a) Patients suspected of PFAPA who did not improve after treatment with two equal minor doses of steroids. b) Children who grew a positive throat swab, or those whom we knew they were neutropenic before ingestion of the steroid, and c) In case of any contraindication for treatment with steroids.

Patients under six years old were treated with a single pill of 0.5mg betamethasone sodium phosphate during PFAPA flares. Patients over six-years-old received two pills (1.0mg) of betamethasone.

Retrieved data included the parents' reports about adherence to therapy, satisfaction and time until defervescence.

We had built a table of the results, to help making a comparison between the outcome of treatment with a minimal weight-independent dose of betamethasone, and the outcome, which was obtained by other researchers who had prescribed a weight-based dose, of an equivalently potent steroid, namely, prednisone or its active metabolite, the prednisolone.

The efficacy of the Betamethasone was determined according to the time, in hours, which was required for reduction of fever.

Familial and atopic tendencies of PFAPA patients were calculated.

Results

The first case of a child with PFAPA disease in our series was recorded in 1998. From that time, the calculated rate of disease, in our community, had risen to six per cent of population of children, (132 patients out of 2,300 children), compared to other cohorts.^{3,5}

At the time, we recommended 0.03–0.37mg of betamethasone per kg of body weight for the first patients suspected to suffer from PFAPA syndrome. Those doses were equal to the range of dosage of prednisolone prescribed by other researchers, i.e., 0.16mg–2mg per kg per dose, knowing that Betamethasone is a fivefold more potent than prednisone. We instructed parents to dissolve the pill into 2ml of drinking water, in every flare of PFAPA. However, it turned out soon that several parents gave to their sick children a reduced dose, at their own decision, of one or two tablet of betamethasone (0.5mg and 1mg), with no regard to the child's weight. The parents explained that reducing the dose was due to their concerns of side effects of steroids.

The parents' satisfaction was reported when reducing their child's fever, (the most worrying symptom of the attack), and improvement of feeling, within few hours.

Motivated by the will of parents, we started prescribing 0.5mg Betamethasone for children under six-years-old, and 1.0mg for children over six years of age. Satisfactory results were obtained.

One hundred twenty-nine patients from our group responded satisfactorily after taking a reduced but fixed dose of Betamethasone. This minimal dose, independent-of-weight, was able to abate fever and improve the wellbeing within a minimum of two to a maximum of twelve hours, of the present flare, and of all the following episodes of PFAPA (Table 1).

The remaining three patients out of 132 (two per cent), who were under six years old and did not respond to the treatment by 0.5mg of Betamethasone, well responded to a once more dose of 0.5mg betamethasone during the next twelve hours. Parents were advised to give the doubled dose, still in the minimal range of dosage, during the coming episodes of PFAPA, successfully.

The youngest three infants, who suffered from PFAPA, out of 132, were four to five-months-old at time of diagnosis. They received 0.1mg betamethasone, and satisfactorily improved within few hours.

Few transient side effects were recorded. Two children had pallor together with sweating, which started within three hours following betamethasone treatment, and disappeared spontaneously within few hours later.

We observed mild transient hyperglycaemia in one out of twenty-three patients, after six hours of taking the dose of betamethasone. There were no blood pressure fluctuations in any of fifteen patients during twelve hours from taking the treatment.

All parents were adherent to corticosteroid treatment in the majority of subsequent attacks of PFAPA. We recorded that in following attacks, some parents gave the same dose of betamethasone at home, as we directed them by a phone call, other parents were instructed to take betamethasone only at actual visits, as a step to prevent misunderstandings.

We observed that in the decade before our study began, about thirty-two per cent of our group of patients, the treatment with steroids was first prescribed as late as six years after the first presumed PFAPA episode.

Whereas, later before writing this paper, the gap of delay got shorter than two years in 42 per cent of patients. The gap of late diagnosis was even shortened to less than six-months after the presumed first flare, presumably, because of better acquaintance with the disease.

Table 2 shows the rate of history of atopy in our group, including atopic dermatitis, asthma and allergic rhinitis.

Unlike other studies of Padeh and Feder, we found a relatively high incidence of familial cases of PFAPA. The incidence of PFAPA within males and females was equal.

We had no records of shortening of intervals between flares after treatment with betamethasone.

Discussion

There are no medications, which can heal children from PFAPA syndrome forever.

However, our results unequivocally show that steroids can truly improve the patient's condition, prevent factitious empiric use of other therapies, and alleviate anxiety of parents, and reduce, in addition, absences from school.

Since the publication of Hench et al.,²² in 1949, until recently, scientists believed that anti-inflammation influence of glucocorticoids occurs only with supra-physiologic doses, as happened with his Cushingoid patients who suffered also from rheumatism.

Clinicians believed that, because the anti-inflammatory mechanism of steroids is time-consuming, thus, giving lesser amounts of glucocorticoids, for clinical purposes, account for a more delayed onset of therapeutic influence of over six to eight hours.¹²

On the other hand, observations had shown, *in vitro*, that the corticosteroid receptors are saturable at low steroid concentrations, and have a great affinity to corticosteroids, even though; their connections to those receptors are reversible.^{9,17,21,22,24,26}

They showed also that higher concentrations of steroid switch the activation of only ten to hundred responsive target genes, including few anti-inflammatory genes that regulate synthesis of inflammatory autacoids and immune-related cytokines.^{7,12,13,20-23,26}

At this work, we provide the, *in vivo*, proof about the efficacy of a weight-independent minimal dose of betamethasone for stopping PFAPA flares.

The time elapsed from swallowing the steroid until reduction of fever; the so-called index of deffervescence was similar to the results of other researchers, (Tasher et al,⁵ Feder et al,¹⁶ Padeh, et al,^{2,6} and others). Those

researchers has provided nearly a twofold higher dose than we had used, namely, a dose of 0.16–1.6mg of prednisolone per kg of body weight.^{7,19}

Conclusion

Our conclusions are consistent with scientific works, concerning the mechanism of action of corticosteroid, with regard to their switching of a small number of anti-inflammatory genes inside the cells.

Accordingly, the use of high concentrations of steroids, to activate transcription of so small number of anti-inflammatory genes could be an unsuitable therapy.

We can confidently announce that physicians can successfully handle every PFAPA episode, by giving one-time dose of only 0.5mg effervescent betamethasone, for the sick children under six-years-old, or a 1.0mg for patients who are over six-years-old, with the option of giving, only rarely, an additional equal dose, within twenty-four hours, to abate fever.

The fact that our group's recommended dose is the least, does not mean it is homeopathy, in any circumstances, in the sense that it is a steroid substance of a measurable concentration, and in the sense that it relieves fever and bad feeling, in every single flare of PFAPA, within few hours. We believe that our confirmation of the effectiveness of the lowest steroid dose, for the ambulatory resolution of PFAPA flares, will reduce to a good grade the corticosteroid registration and consumption, in a global scale.

We might be provocative by stating that we have arrived to our unequivocal and conclusive results concerning the action of minimum corticosteroids doses. Nevertheless, we do not pretend to claim that it is true about all steroid responsive diseases. Still we hope that future courageous works might bring to the same conclusions, as ours, concerning effective minimal steroid dosage in other glucocorticosteroids responsive illnesses.

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ACKNOWLEDGEMENTS

Thank to Mrs. Cohan Orli, manager of Research foundation of the Clalit Health Organization, for her support and patience in presenting the protocol of the research for the Helsinki committee and other Clalit foundations. Thanks for the support of Dr Saeed Z. the medical Head of Haifa district of Clalit Organization for his unlimited moral support. Thanks to Dr Saab A. medical manager of Asher administration for his kindest support in approval of the work.

Thank to my colleagues and co-authors; Dr Nadra, Dr Mona and Dr Nadir for reviewing the article and their important amendments and exclusive remarks, and that without their help, this paper cannot see light. We declare that we have nothing to disclose.

My gratitude to Miss Hanadi Nasser, University of Szeged, Hungary, for her commitment to find the most appropriate articles concerning the mechanism of action of corticosteroid, as a fruitful help to perform this research.

PEER REVIEW

Not commissioned. Externally peer reviewed.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

FUNDING

None

ETHICS COMMITTEE APPROVAL

The committee and approval reference number: 0026-16-COM2.

Tables

Table 1: The outcome of treatment with steroids of the PFAPA flares. Betamethasone was prescribed by us due to its higher potency and its preferred flavour compared to prednisolone. The interval between attacks had a range of 19 days to 90 days. (Nasser et al. January 2017)

Time elapsed until stopping attack (hours)	Mean interval between attacks (days)	Mean age of first steroid effective treatment	Dose of betamethasone per attack
02-Dec	42.5	2-6 (about 59%) 6-13 (about 23%)	0.5 mg/dose for <6 yrs. old 1.0 mg/dose for >6 yrs. old

Table 2: Male/female ratio, incidence of consanguinity and rate of allergic features in PFAPA syndrome. Taking into account that the study was done in rural community where consanguinity is very common can explain our results with high familial tendency of PFAPA. (Nasser et al. January 2017)

Male/female ratio	% consanguinity within PFAPA patients	History of atopy
83/49=2:1	26/132=20%	39/132=30%

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