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What is low-dose corticosteroid therapy in juvenile idiopathic arthritis?

A worldwide, questionnaire-based survey*

Was versteht man unter „Low-dose"-Kortikosteroidtherapie bei juveniler idiopathischer Arthritis? Ergebnisse einer weltweiten Umfrage.

Zusammenfassung *Fragestellung:* Es sollte herausgefunden werden, was Kinderrheumatologen unter einer niedrigdosierten Kortikosteroid-Langzeittherapie (low-dose, long-term corticosteroid therapy) verstehen.

Methoden: Kinderrheumatologen aus Amerika, Australien, Israel und Europa wurden mit Hilfe eines standardisierten Fragebogens nach ihrer persönlichen Definition für eine „ low-dose, long-term corticosteroid therapy" gefragt.

Resultate: Von 99 zurückgeschickten Fragebogen waren 92 auswertbar. Die im Rahmen einer Langzeittherapie noch als niedrig angesehene Kortikosteroiddosis betrug im Mittel 0,26 ± 0,14 mg Prednisolon/kgKG/d (min-max = 0,04–0,50 mg, n = 92). Dabei waren die Mittelwerte aus Nordeuropa (0,29 ± 0,12, n = 9), Westeuropa (0,42 ± 0,14, n = 7), Südeuropa (0,30 ± 0,14, n = 9), Osteuropa (0,25 ± 0.14, n = 6) und Nordamerika (0,33 ± 0,17, n = 16) höher als aus Mitteleuropa (0,19 ± 0,09, n = 43).

Schlussfolgerung: Die Vorstellungen der Kinderrheumatologen, was unter einer niedrigdosierten Kortikosteroid-Langzeittherapie zu verstehen sei, unterscheiden sich im internationalen Vergleich um den Faktor zehn. Die Ursache dieser bemerkenswerten Differenz und die Auswirkungen der unterschiedlichen Behandlung auf den Langzeitverlauf sollten untersucht werden. Eine international akzeptierte Definition einer „low-dose, long-term corticosteroid therapy" sollte entwickelt und dann in prospektiven Studien überprüft werden.

Schlüsselwörter Juvenile idiopathische Arthritis – Therapie – Kortikosteroide – Dosierung

Summary *Objective:* To determine pediatric rheumatologists' personal definitions of systemic low-dose, long-term (> 4 weeks) corticosteroid therapy of juvenile idiopathic arthritis (JIA).

Methods: Pediatric rheumatologists from America, the Near East (Israel), Australia and Europe were asked for their personal definition of a low-dose long-term corticosteroid therapy of JIA with the aid a standardized questionnaire.

Results: Of 99 questionnaires returned, 92 were evaluable. The dosage still considered low turned out to be 0.26 ± 0.14 mg prednisolone/kgBW/day (min-max = 0.04–0.50 mg, n = 92). Higher dosages were indicated from Northern Europe (0.29 ± 0.12, n = 9), Western Europe (0.42 ± 0.14, n = 7), Southern Europe (0.30 ± 0.14, n = 9), Eastern Europe (0.25 ± 0.14, n = 6) and North America (0.33 ± 0.17, n = 16) than from Central Europe (0.19 ± 0.09, n = 43).

Conclusion: Pediatric rheumatologists' personal definitions of low-dose, long-term corticosteroid therapy vary within a wide range. The reason for these differences and the impact on patients should be investigated. In addition, a generally accepted definition for low-dose, long-term corticosteroid therapy should be developed and subsequently examined in studies.

Key words Juvenile idiopathic arthritis – therapy – corticosteroids – dosage

Dedication:
Dedicated to Frau Prof. Dr. med. Elisabeth Stoeber on the occasion of her 90th birthday.

* Instead of the old terms "juvenile rheumatoid arthritis" or "juvenile chronic arthritis", the new ILAR-WHO nomenclature "juvenile idiopathic arthritis" is used throughout the paper.

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Introduction

For the systemic, long-term treatment of juvenile idiopathic arthritis (JIA), corticosteroids are only being used in a rather restricted manner because of their various adverse effects, including in part irreversible growth suppression (5, 6, 8, 10). While higher dosages are mandatory in critical situations, like severe myocarditis, only a low-dose regimen is acceptable for long-term anti-arthritic therapy.

Kirwan et al. have demonstrated that low-dose corticosteroid therapy can slow down the radiologic progression of rheumatoid arthritis (3, 4). However, there is still no proof that this holds true for the corticosteroid therapy of JIA as well. Moreover, there is no generally accepted definition to date for "low-dose" during a systemic, long-term corticosteroid therapy of JIA.

This paper presents the results of a worldwide questionnaire survey. The personal definitions of 92 pediatric rheumatologists of "low-dose corticosteroid therapy" for JIA differ by a factor of ten.

Methods

By means of a questionnaire, pediatric rheumatologists were asked, "Which doses do you consider low, average or high during systemic, long-term treatment (> 4 weeks) of juvenile chronic/rheumatoid arthritis (mg prednisolone/kg body weight/24h)?" The questionnaire survey was initiated on the occasion of a lecture on the corticosteroid therapy of JIA given at the "5th European Conference on Pediatric Rheumatology", held in Garmisch-Partenkirchen on October 15–19, 1997 (6). The questionnaire contained the following three additional questions; the results thereof are not reported here: 1) Indications? 2) Which preparations do you prefer? 3) Do you use a pulse therapy? If yes, what is your method?

The participants were additionally asked whether they would agree to the anonymous publication of data and whether their names may or should be listed in a publication. Only questionnaires with the agreement of the participant were used for the evaluation presented here.

The questionnaires were sent to pediatric rheumatologists in Europe, America, Australia and Israel. Selected were pediatric rheumatologists who were known to be leading experts of their particular country from publications and from international meetings (ACR, EULAR, European conferences on pediatric rheumatology). In Germany, the questionnaire was sent to all members of the "Arbeitsgemeinschaft für Kinder- und Jugendrheumatologie" who are known to treat children with JIA on a regular basis.

Results

From the 125 questionnaires, 99 (79 %) were returned and 92 (93 %) of these were analyzable. In seven out of the 99 questionnaires returned, no prednisolone dosages per kg body weight were listed, but only daily total dosages with no relation to body weight. The participants were free to name a single figure or a range as being "low dose". Seventy-two participants listed a single figure while 20 provided a range. In case a range was given, the upper figure was used for the calculation of the mean value, standard deviation, minimal and maximal values, median and spread (Table 1).

The mean for "low dose" of the 92 questionnaires was 0.26 ± 0.14 mg of prednisolone/kgBW/day (Table 1). The data vary

Table 1 Results of a questionnaire-based survey with the question "Which doses do you consider low during systemic, long-term treatment of juvenile chronic/rheumatoid arthritis (mg prednisolone/kg body weight/24h)?".
(*n* number of participants; *x* mean value; *s* standard deviation; *Min* minimal value; *Max* maximal value).

Geographical Region	n	x	s	Min	Max	Median	Spread
Central Europe[a]	43	0.19	0.09	0.09	0.50	0.20	0.07
Northern Europe[b]	9	0.29	0.12	0.20	0.50	0.24	0.10
Western Europe[c]	7	0.42	0.14	0.20	0.50	0.49	0.26
Southern Europe[d]	9	0.30	0.14	0.10	0.50	0.29	0.20
Eastern Europe[e]	6	0.27	0.14	0.09	0.50	0.25	0.10
North America[f]	16	0.33	0.17	0.04	0.50	0.28	0.28
South America[g]	2	0.23	0.04	0.20	0.25	0.23	0.05
Σ	92	0.26	0.14	0.04	0.50	0.20	0.11

a Austria, Germany, Switzerland
b Denmark, Finland, Norway, Sweden
c France, Netherlands, UK
d Bulgaria, Italy, Greece, Portugal, Spain, Turkey
e The Czech Republic, Hungary, Lithuania, Poland, Russia
f Canada, USA
g Brazil, Chile

up to a factor of ten (see "Min", "Max", Table 1). Certain differences between the geographical regions can be observed as well, whereby the minimum of 0.19 ± 0.09 mg prednisolone/kgBW/day was recorded for Central Europe while the data of Western Europe was the highest with 0.42 ± 0.14 mg prednisolone/kgBW/day.

Discussion

When using corticosteroids systemically in pediatric rheumatic diseases, we should differentiate between interventional therapy of critical situations and long-term antirheumatic treatment. The concept of low-dose corticosteroid therapy is related to long-term antirheumatic treatment. For adult patients with rheumatoid arthritis, a daily dosage of 10 mg of prednisolone or less has been recommended as a low-dose therapy (1). However, there are more restrictive recommendations suggesting a definition of not more than 5 mg per day as a low-dose therapy (2). Extrapolated to childhood, these recommendations would mean a daily dose of about 0.10–0.18 mg of prednisolone per kg body weight.

In pediatric rheumatology, no internationally recognized definition has been made to date for the term "low dose". As is obvious from the results of this survey, considerable differences between pediatric rheumatologists exist in the personal definition of a low-dose therapy. About 20 % of the answers consider 0.5 mg prednisolone per kg BW to be a "low-dose therapy", a dosage which, at least according to the German experience, produces severe adverse reactions when administered as a long-term therapy.

The aim of the "low-dose concept" is to have a dosage of corticosteroids which guarantees the desired effect in the absence of more severe adverse reactions. It is obvious from the mechanism of action of corticosteroids, however, that the desired effects and the adverse reactions appear together and that a threshold of the dosage under which only the desired effects appear in the absence of adverse reactions does not exist. Thus, the attempt to achieve the desired effects always means having to accept adverse effects as well. In the case of low-dose therapy, the adverse reactions must be negligible, or at least of a minor degree.

The enormous variation of the personal definitions of low-dose, long-term corticosteroid therapy in JIA may indicate that it is problematic to give only a bare figure as a definition. Some patients develop a specific adverse reaction at lower doses while others exhibit the same side effect only at higher doses. The number of patients who develop a certain non-allergic, adverse reaction presumably follow a dose-dependent Gaussian-like curve. This may be one of the reasons that many of the participants of this questionnaire-based survey gave a range of dosages rather than a fixed figure. Furthermore, for some adverse reactions, like growth disturbances, more sensitive and less sensitive phases, in addition to the interindividual differences, are seen to exist in the same individual. Therefore, it might be reasonable to look for a different approach to define low-dose, long-term corticosteroid therapy. A reasonable method could be the inclusion of adverse effects of a corticosteroid therapy in such a definition, similar to the way the clinicians used to find the proper dose of aspirin. They increased the aspirin dose until tinnitus developed and then slightly decreased it. In the case of corticosteroid therapy the inclusion of growth inhibition which is specific for childhood would seem to be a suitable way to properly define low-dose therapy for JIA, thus, also considering that growth retardation is among one of the most severe adverse effects of corticosteroids in childhood. Moreover, low-dose, long-term corticosteroid therapy will only be accepted by the patients and their parents as an anti-arthritic treatment if it does not cause growth retardation. Measuring the height can easily be performed in daily practice, in contrast, for instance, to measuring bone mineral density. Therefore, the following definition is suggested as a kind of primer for a discussion: "Low dose is that dosage of corticosteroids which entails no significant inhibition of net growth velocity". A prerequisite of this definition is the availability of a growth curve from at least four to six months before the onset of corticosteroid therapy. This definition would provide neither fixed starting nor fixed maintenance dosages, but would lead to an individual dosage tailored to the individual patient. However, it would at best be available no earlier than after about four to six months. The fact that the disease itself, as well as nutritional factors, also have growth retarding effects is considered in this definition by the preobservation of the growth curve before beginning corticosteroid therapy. In highly active cases, corticosteroids may even produce growth-promoting effects by inhibiting inflammation. In cases of severe growth retardation below the 3rd percentile, however, the corticosteroid therapy is mostly the essential factor and not the disease itself (7, 9).

In conclusion, we should ponder the reason why we use the corticosteroid therapy so differently. The impact of the different usage of corticosteroids for the patients should be investigated. In a next step, the questionnaire information could stimulate pediatric rheumatologists to agree on a standardization of systemic corticosteroid therapy, especially on a definition of "low dose" for the treatment of JIA. Such a definition is a prerequisite for studies on the long-term effects of low-dose corticosteroid treatment on radiologic progression as well as on growth velocity.

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