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Evaluation of the Clinical Efficacy of Prednisolone in the Treatment of Inflammatory Bowel Diseases with Different Dosage Methods

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Aim: to investigate the clinical efficacy of two methods of oral dosing of prednisolone (in mg and mg/kg) for the induction of remission for patients with ulcerative colitis (UC) and Crohn's disease (CD) using the technology of constructing and evaluating the effectiveness function (dose-effect relationship).
Material and methods. In this study were included 86 patients aged from 18 to 65 years with moderate or severe active inflammatory bowel disease (61 — UC, 25 — CD). All patients were treated with prednisolone at an initial daily dose from 30 to 60 mg with a subsequent tapering of dose. The clinical response to treatment was evaluated at the time of complete withdrawal of prednisolone using the generally accepted criteria. Two efficiency functions were constructed, compared and analyzed: the first — at the initial dosage of prednisolone in mg and the second calculating the dose in mg/kg of patient weight. The patients' body weight ranged from 41 to 98 kg. The "dose-effect" relationship for prednisolone was constructed with statistical transformation of the baseline clinical data and a quantitative expression of the actual doses and alternative responses into a graph of the effectiveness function. The mean value at each point was estimated based on the regression kernel scoring method.
Results. Two graphs of the "dose-effect" of prednisolone in mg and mg/kg of patient weight were constructed. The optimal clinically effective dose (OCED) when calculated in mg/kg of weight was 0.70 ± 0.01 (0.68 ÷ 0.72) mg/kg with the corresponding effect 79.25 ± 6.26 (66.62 ÷ 91.88) %. When two graphs in mg and mg / kg of weight were superimposed, it is shown that when an initial dose of 40 mg is prescribed without taking into account the patient's weight, the effect of therapy will be 25 % lower. Prescribing a dose of 60 mg per day without weight will be optimal for patients with a body weight of 85–90 kg. With a lower body weight, the clinical effect will not decrease, but the likelihood of recognized side effects of prednisolone should be expected in proportion to the decrease in body weight.
Conclusion. The clinical efficacy of two methods of prednisolone dosing (mg and mg/kg) for patients with IBD during the first induction course was compared.
Using a new technology for constructing and evaluating the effectiveness function (dose-effect relationship) allowed us to prove a reliable relationship between the body weight of patients with the clinical effect of prednisolone in patients with UC and CD. Based on the analysis of the dose-effect relationship, the optimal clinically effective dose of prednisolone for patients with UC and CD during the first induction course was established, equal to 0.70 mg/kg, which can be recommended for use in clinical practice for calculating individual doses.
Key words: ulcerative colitis, Crohn's disease, prednisolone, efficiency function, dose calculation
Conflict of interest: the authors declare of no conflict of interest.

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Оценка клинической эффективности преднизолона в лечении воспалительных заболеваний кишечника при разных способах дозирования

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Цель исследования: исследовать клиническую эффективность двух способов дозирования преднизолона (в мг и мг/кг) для индукции ремиссии у больных язвенным колитом (ЯК) и болезнью Крона (БК) с использованием технологии построения и оценки функции эффективности (зависимости «доза — эффект»).
Материалы и методы. В исследование включены 86 больных с активным заболеванием средней и тяжелой степени (61 — с ЯК, 25 — с БК) в возрасте от 18 до 65 лет. Для индукции ремиссии в качестве первого курса терапии всем пациентам назначали преднизолон в начальной дозе от 30 до 60 мг/сутки с последующим снижением. Эффект терапии оценивали на момент полной отмены преднизолона с использованием общепринятых критериев оценки клинической ремиссии. Проводили анализ двух функций эффективности: первая — при дозировании преднизолона в мг и вторая при расчете дозы в мг/кг веса пациента. Масса тела пациентов колебалась от 41 до 98 кг. Построение функции эффективности (зависимости «доза — эффект») для преднизолона проводилось по оригинальной методике, смысл которой заключается в адекватном статистическом преобразовании исходных клинических данных, получаемых в виде количественного выражения примененной совокупности доз и зарегистрированных альтернативных ответов, установленных по критериям конечной точки, в наглядный график, по которому возможно проведение аналитических оценок. Оценка среднего значения в каждой точке определялась на основе метода ядерной оценки регрессии. Достоверность различий вычислялась на основе *t*-критерия Стьюдента.
Результаты. Построены два графика «доза — эффект» преднизолона в мг и в мг/кг массы тела. Оптимальная клинически эффективная доза (ОКЭД) при расчете в мг/кг составила 0,70 ± 0,01 (0,68 ÷ 0,72) мг/кг с соответствующим эффектом 79,25 ± 6,26 (66,62 ÷ 91,88) %. При наложении двух графиков в мг и в мг/кг веса показано, что при назначении начальной дозы 40 мг без учета массы тела пациента эффект терапии будет на 25 % ниже. Назначение дозы 60 мг в сутки без учета массы будет оптимальным для пациентов с массой тела 85–90 кг. При более низкой массе тела клинический эффект не уменьшится, однако вероятность появления побочных эффектов преднизолона следует ожидать пропорциональной уменьшению массы тела.
Заключение. Проведено сравнение клинической эффективности двух способов дозирования преднизолона (в мг и в мг/кг) у больных ЯК и БК при первом индукционном курсе. Анализ зависимости «доза — эффект» позволил доказать достоверную связь массы тела пациентов с клиническим эффектом преднизолона у больных ЯК и БК. Установлена оптимальная клинически эффективная доза преднизолона у больных ЯК и БК при первом индукционном курсе, равная 0,70 мг/кг, которая может быть рекомендована к применению в клинической практике для назначения индивидуальных доз.
Ключевые слова: язвенный колит, болезнь Крона, преднизолон, функция эффективности, расчет дозы
Конфликт интересов: авторы заявляют об отсутствии конфликта интересов.

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Introduction

Short-acting systemic corticosteroids, prednisolone and methylprednisolone (CS), remain the recommended therapy for inducing remission for patients with active inflammatory bowel diseases (IBD) — ulcerative colitis (UC) and Crohn's disease (CD) — of moderate severity, which do not respond to treatment with 5-ASA drugs, and for rapid relief of symptoms for severe patients [1–4].

In the Clinical Practice Guidelines on the Management of UC and CD, various approaches were used to calculate the dose of CS. The variability of practical recommendations for calculating the dose of CS presents difficulties for choosing the right solution in practice.

Thus, the UK guidelines recommend taking oral corticosteroids at an initial fixed dose of 40 mg of prednisolone per day for patients with moderate and severe UC and for patients with mild and moderate CD who did not respond to mesalazine for 2–4 weeks, followed by a decrease of 5 mg at weekly intervals, which corresponds to an 8-week course [2, 5].

The European Clinical guidelines [1] and the recommendations of the American Gastroenterological Association [6] indicate the same initial dose of prednisolone for orally administration for patients with moderate active UC. It is emphasized that the appointment of CS should be in the minimum effective dosage with a gradual decrease of 5 mg per week for the required period. A rapid reduction in the prescribed dose, too short a course of treatment (<3 weeks) and the appointment of an ineffective dose of prednisolone (<15 mg per day) should be avoided.

The clinical guidelines of the American College of Gastroenterologists recommend orally prednisolone doses of 40–60 mg per day for patients with active UC and CD. Doses of 1 mg/kg of the patient's weight may also be prescribed, but no more than 60 mg per day [7, 8].

An Update on Current Pharmacotherapeutic Options for the Treatment of Ulcerative Colitis of the Italian Group for the Study of Inflammatory Bowel Diseases, traditional orally corticosteroids

are considered for use in cases of ineffectiveness or intolerance to treatment with topical CS or to achieve rapid relief of symptoms with active left-sided and total UC of moderate severity at a dose of 40–60 mg prednisolone. With mild to moderate CD ileocecal localization, prednisolone is prescribed at a dose of 40–60 mg per day or 1 mg/kg of patient weight as the first line of therapy. In severe UC and CD, treatment is recommended to begin with intravenous administration of CS — methylprednisorone at a dose of 0.75–1 mg/kg with a transition to orally administration of 48 mg per day (60 mg of prednisolone) and a decrease of 4–8 mg per week until complete withdrawal [4].

In the Russian clinical guidelines for the treatment of UC and CD, published in 2017, the dose of systemic corticosteroids ranges from 40 to 75 mg orally, depending on the localization and severity. In severe cases, it is recommended to start with intravenous administration of 75 mg with a transition in clinical response to equivalent orally [9, 10]. In the Russian clinical guidelines of 2020, prednisolone is prescribed at a dose of 1 mg/kg of patient weight for left-sided and total UC of moderate degree and inefficiency of mesalazine, systemic inflammation. In severe UC of any localization, the dose increases to 1.5–2 mg/kg [11]. In CD proposed the calculation of the prednisolone dose for the patient's body weight from 0.75 to 2 mg/kg. In severe cases, it is recommended to start with intravenous administration with a transition to orally administration [12].

Comparison of the effectiveness of orally CS in mg and in mg/kg of body weight has never been carried out.

Aim

To investigate the clinical efficacy of two methods of prednisolone dosing (in mg and in mg/kg) for the induction of remission for patients with ulcerative colitis and Crohn's disease using the technology of constructing and evaluating the effectiveness function (dose-effect relationship).

Material and methods

In this study were included 86 patients (61 of them with UC and 25 with CD) aged from 18 to 65 years, 44 men and 42 women who were prescribed prednisolone as the first course of therapy in connection with an active disease. 43 patients (50 %) with an acute course of the disease were prescribed prednisolone without previous therapy, 43 patients (50 %) received CS due to the ineffectiveness of mesalazine. The patients were a complete clinical examination and treatment in the Regional clinical Hospital named after N.A. Semashko, Nizhny Novgorod and followed by outpatient observation. The diagnosis of ulcerative colitis and Crohn's disease was made in accordance with international and Russian recommendations for the examination of patients [4–6, 11, 12]. The severity of the attack of ulcerative colitis was assessed by the index of clinical activity Mayo. The severity of Crohn's disease was determined using the Crohn's disease Activity Index (CDAI). This assessment of the severity of IBD is generally accepted in clinical trials [13, 14]. 48 (78.7 %) patients with UC had total colon, 13 (21.3 %) had left-sided. In CD, 10 (40.0 %) patients were observed with terminal ileitis, 8 (32.0 %) — with colitis, 7 (28.0 %) — with ileocolitis. The study included patients with only an inflammatory form of CD and an uncomplicated course of the disease.

The majority of patients had an acute course of the disease: UC — 24 (39.3 %) and CD — 19 (76.0 %). Severe forms prevailed among UC patients — 46 (75.4 %), 15 (24.5 %) — they had a moderate disease. 21 patients CD (84.0 %) were diagnosed moderate disease, 4 patients were severe. The assessment of the disease activity, clinical response, and clinical remission were carried out at the time of the start of taking CS, after two weeks of admission and after the end of the course of therapy. Prednisolone was prescribed in doses from 30 to 60 mg orally. The choice of dose was carried out by the physicians in accordance with their clinical practice.

For severe patients, CS treatment was started with intravenous administration with the transition to orally administration at the same dose. In the presence of a clinical response after two weeks, the dose of prednisolone was reduced by 5 mg per week until complete withdrawal. In Crohn's disease, prednisolone was prescribed together with azathioprine 2 mg/kg of patient weight. When clinical remission was achieved at the time of completion of the course of treatment, patients with UC were prescribed mesalazine 2 grams per day as maintenance therapy. CD patients continued taking azathioprine 2 mg/kg of body weight per day. The effect of CS treatment was evaluated after 12 weeks according to generally accepted criteria by analogy with the endpoints of a standard clinical trial. The end point was the achievement of clinical remission [15].

The construction of the dose-effect relationship or the function of the effectiveness of CS for patients was carried out according to the technology developed by S.V. Kryshtopenko et al. [16]. The estimation of the average value at each point of the efficiency function is determined by the nuclear regression estimation method as a weighted

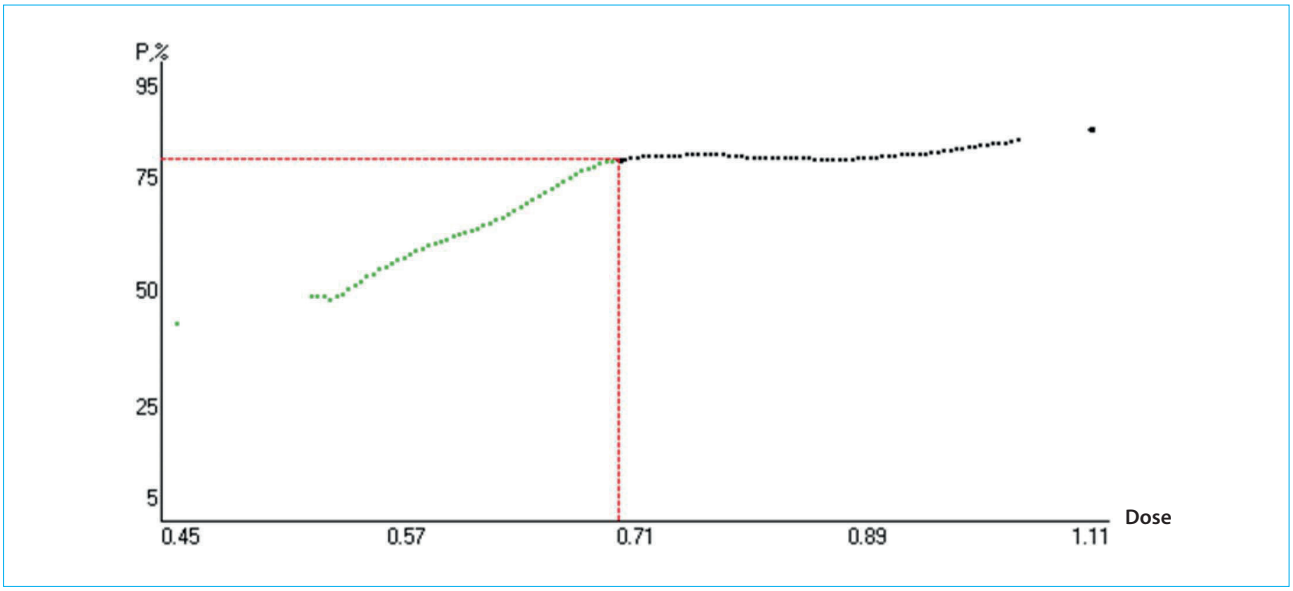

Fig. 1. The function of the effectiveness of prednisolone in patients with UC and CD at the end of the first course of treatment with dosing in mg/kg (along the abscissa axis — dose in mg/kg; maximum dose error of 25 %)

average of response variables in a fixed neighborhood of a point according to the k-nearest neighbors principle based on the Epanechkov kernel known in nonparametric statistics [17]. The reliability of the differences was calculated based on the Student's t-test [18]. The meaning of constructing the effectiveness function is an adequate statistical transformation of the initial clinical data in the form of a really applied set of doses and registered alternative responses (0 or 1) into a visual graph, according to which analytical assessments can be carried out. An important feature of this technology is the quantitative assessment of the final error of the study, which is based on two leading factors: the individual sensitivity of the organism to the drug and adequate selection with subsequent evaluation of the parameters of the endpoint.

Based on the results of the studies performed, two efficiency functions (dose-effect relationships) were compared: the first is when dosing prednisolone in mg and the second when dosing in mg/kg of patient weight. The patients' body weight ranged from 41 to 98 kg.

Results

Which mode should we choose? The dose of systemic CS in mg or in mg/kg of the patient's body weight? To answer on this question, two prednisolone efficacy functions were constructed.

The construction of the efficiency function with the calculation of the prednisolone dose in mg/kg of body weight is shown in Figure 1.

The graph shows the initial point of the efficiency function reaching a plateau, statistically reflecting the saturation level of the trait, and clinically — the magnitude of the maximum possible effect of the drug (in %). This point is called the optimal clinically effective dose (OCED).

The OCED was 0.70 ± 0.01 (0.68 ÷ 0.72) mg/kg with the corresponding effect 79.25 ± 6.26 (66.62 ÷ 91.88) %. A further increase the dose in mg/kg does not lead to an increase the effect, which indicates a kind of saturation of the sign of the clinical effect of CS at this point at the level of 80 % with further output of the efficiency function on the plateau.

The clinical interpretation of the results obtained consists in the proven optimality of prescribing therapeutic doses of prednisolone to patients with UC and CD, taking into account the found indicator of 0.70 mg/kg. For example, patients with a body weight of 55–60 kg are recommended an individual dose of prednisolone 40 mg (0.70 mg/kg × 56 kg), and patients with a weight of 85–90 kg — a dose of 60 mg (0.70 mg/kg × 86 kg) for the first induction course.

To demonstrate clinical differences in the dosage of prednisolone for patients with UC and CD in mg and in mg/kg of body weight, Figure 2 shows the overlap of two efficiency functions with a dose offset coefficient in mg/kg 56.6 along the abscissa axis in order to compare effects at specified points on the ordinate axis.

The analysis of the two efficiency functions at the compared points of 40 mg for function (2) and 0.70 mg/kg × 56.6 = 40 mg/kg (by displacement coefficient) for function (1) indicates that when

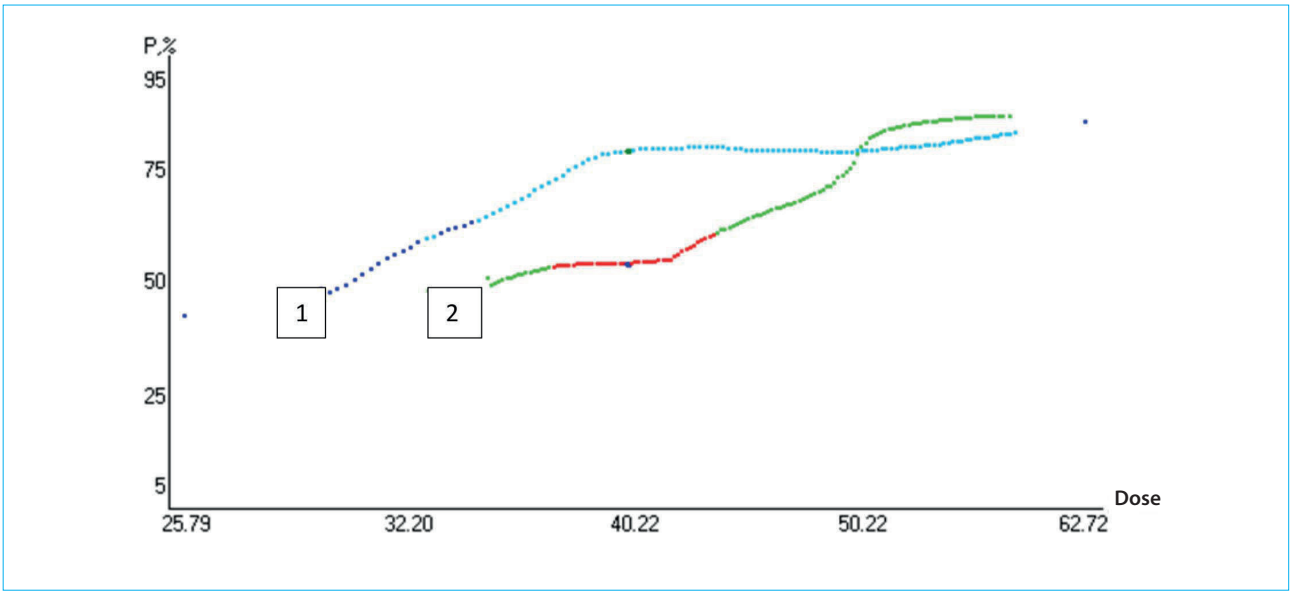

Fig. 2. Prednisolone efficacy functions in patients with UC and CD at the end of the first course of treatment with dosing in mg/kg (1) and mg (2) (along the abscissa axis — dose in mg for function (2) and in mg/kg × 56.6 for function (1); maximum the dose error is 25 %)

prescribing a dose of 40 mg per day without taking into account the body weight of patients, the effect can decrease by up to 25 %. At the same time, the administration of a dose of 60 mg per day without weight will be adequate only for patients with a body weight of 85–90 kg. When prescribing an individual dose of 60 mg to patients with a body weight below 85 kg, the clinical effect, of course, will not decrease, but the appearance of side effects of prednisolone should be expected in proportion to the decrease in body weight.

Discussion

Orally doses of systemic corticosteroids recommended in CD were obtained from population studies [19, 20] and extrapolated to use in UC. At the same time, a regression meta-analysis of 32 studies did not demonstrate a response to methylprednisolone therapy at a dose exceeding 60 mg per day [21]. In the National American Cooperative Research by R.W. Summers et al. in CD [19] prednisolone was used at an initial dose of 0.5–0.75 mg/kg/day, which corresponded to doses of 40–60 mg/day in a European study by H. Malchow et al. [20], where methylprednisolone was used at a dose of 48 mg per day (equivalent to 60 mg of prednisolone). It is believed that a dose of 1 mg/kg of body weight is more effective than 40–60 mg orally in terms of prednisolone. But, for example, in a population study by W.A. Faubion et al. [22] also used a dose of 60 mg of prednisolone orally. At the same time, remission rates after 30 days (58 %) were higher than when using a dose of 1 mg/kg/day used in the Copenhagen cohort (48 %) [23]. One early study showed that prednisolone at a dose of 40 mg/day was as effective as 60 mg/day in achieving clinical remission in UC, while causing fewer side effects [24]. The variability of practical recommendations is a barrier to choosing the optimal therapeutic treatment.

The dosage methods of drugs are determined based on the conducted studies of the characteristics of their pharmacokinetics and pharmacodynamics. In cases where the relationship of body weight with the clinical effect is proven, the method of dosing in mg per kg of body weight is used.

For example, traditionally, the calculation of orally medications in mg / kg is used in pediatrics. This is primarily due to the fact that the weight of children of different ages varies dramatically and one dose or a narrow range of doses cannot be recommended. In addition, the characteristics of the body of children differ significantly from adults, primarily in the ratio between extracellular and intracellular fluid. Therefore, extracellular fluid in newborns is 45 %, and in adults — 15 % of body weight. For adult patients, some medications are still prescribed orally in doses calculated per kg of body weight. In severe forms of UC and CD, short-acting systemic corticosteroids are recommended to be administered intravenously with a dose calculation per kg of body weight [4, 11, 12]. Intravenous dosing of systemic CS in mg/kg is justified due to well-studied pharmacokinetics [25], as well as an individual approach to the patient.

Due to the relatively high bioavailability of short-acting systemic corticosteroids (70–90 %),

the calculation of doses in mg/kg used in clinical studies with intravenous administration was extrapolated to orally prednisolone.

According to the literature studies of different methods of oral dosing of prednisolone taking into account body weight in patients with UC and CD have not yet been conducted [26].

Conclusions

1. The use of technology for constructing and evaluating the effectiveness function (dose-effect relationship) allowed us to prove a reliable relationship between the body weight of patients with the clinical effect of different doses of prednisolone for patients with UC and CD.

2. Based on the analysis of the dose-effect relationship, the optimal clinically effective dose of prednisolone for patients with UC and CD at the first induction course was established, equal to 0.70 mg/kg, which can be recommended for use in clinical practice for calculating individual doses.

3. A comparison of the clinical efficacy of two methods of dosing prednisolone (in mg and in mg/kg) for patients with UC and CD during the first induction course proved the possibility of avoiding both a decrease in clinical efficacy up to 25 % and the probability of side effects when dosing taking into account body weight.

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