

About the Therapy of Laryngotracheitis (Croup): Significance of Rectal Dosage Forms

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Key Words

Croup · Rectal prednisolone · Prednisone · Pharmacokinetic

Abstract

Glucocorticoids are drugs of choice for treatment of laryngotracheitis (croup). They may be administered orally as tablets or juice, locally as inhalation or rectally as suppository or capsule. If doctors decide to use a rectal administration for practical reasons, it is obvious from a pharmacokinetic and pharmacodynamic point of view that prednisolone capsules have an earlier and stronger anti-inflammatory effect than a prednisone suppository.

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Diagnosis and treatment of children with croup are commonly based on a history of nighttime symptoms. According to the guidelines of the German Society of Pediatric Pneumology, the severity is classified into 4 Grades: Grade 1: barking cough, hoarseness, slight inspiratory stridor after excitation. Grade 2: stridor at rest, starting dyspnea, slight jugular stricture. Grade 3: dyspnea at rest, pronounced thoracic strictures, paleness, tachycardia >160/min. Grade 4: severe dyspnea with increasing respiratory insufficiency, cyanosis, risk of asphyxia, bradycardia and somnolence. Differential diagnosis has to rule out acute epiglottitis, which comes along with high fever, aphonia, salivation and inspiratory stridor.

Therapy

There exists no causal therapy. The standard management of croup includes calming down patients and relatives and cool mist administration, that is, treatment with humidified air and rehydration. During out-patient treatment, glucocorticoids are administered. Hospitalization is necessary only if treatment remains insufficient. Distinct symptomatology (grades 3 and 4) demands hospital treatment with oxygen breathing, epinephrine and glucocorticoids.

Glucocorticoid treatment may be performed orally with tablets or juice, rectally with suppository or capsule or parenterally with injection solutions. The inhaled route of glucocorticoid administration has many advantages. But it requires the patient to master the use of an inhaler device. Poor inhaler technique and nonadherence to therapy lead to a highly variable lung dose in clinical practice with subsequent loss of clinical efficacy and wastage of economic resources [1, 2].

Glucocorticoids are the treatment of choice because of their anti-inflammatory effect for treatment of croup [3].

Prednisone and prednisolone are synthetic derivatives of glucocorticoids with an average long-lasting effect and higher affinity to type II receptors for glucocorticoids than naturally occurring cortisol. The biologically active form is prednisolone, which has to be formed from the biologically inactive form prednisone. Prednisone, on the other hand, is the inactive metabolite of prednisolone. The en-

zyme involved is the 11 β -hydroxysteroid dehydrogenase. Only free prednisolone is able to pass cell membranes and therefore able to cause a pharmacological effect [4].

Rectally administered dosage forms reveal several advantages compared with parenteral dosage forms that need to be injected and injections may hurt; also rectally administered dosage has an advantage over orally administered tablets or capsules in patients who may have difficulties to swallow or regurgitation.

The question of how prednisolone and prednisone differ from each other in terms of their pharmacokinetics and clinical efficacy is discussed below.

Pharmacokinetics

The pharmacokinetics of prednisone and prednisolone is nonlinear due to a variable protein binding. This means, changes in plasma levels after dose adjustments are not simply predictable. The duration and intensity of the effect of glucocorticoids are determined by pharmacokinetic parameters. The previously published pharmacokinetic-pharmacodynamic models for the effects of glucocorticoids enable us to estimate the contribution of a substance to its clinical effect.

Area under the effect-curve (AUEC%) for altered lymphocyte trafficking within 24 hours evaluated by difference between AUEC without prednisolone (baseline) and AUEC after prednisolone exposure

$$AUEC \% = \frac{AUEC \text{ baseline} - AUEC \text{ treatment}}{AUEC \text{ baseline}} \times 100.$$

Maximal blood level of prednisolone (C_{max}) after administration of prednisolone is 4 times as high as after the administration of prednisone, and reached twice as fast (t_{max}). C_{max} and t_{max} are important pharmacokinetic parameters to characterize the onset of action (t_{max}) and extent of action (C_{max}).

Pharmacodynamics

Glucocorticoids counteract acute symptoms of inflammation by inhibiting vascular dilatation, edema formation and migration of leukocytes [5]. Good evidence now exists to support routine corticosteroid therapy in all children with croup [6]. Glucocorticoids alleviate respiratory distress due to the inflammation of the larynx and are therefore drugs of choice for croup [3]. Comparison of prednisolone with dexamethasone demonstrated sim-

Table 1. Pharmacokinetic parameters of prednisolone and prednisone

Parameter/unit	Prednisolone		Prednisone ^b
	40 mg p.o. ^a	100 mg rectal-capsule ^c	100 mg suppository ^d
C_{max} , $\mu\text{g/l}$	466	490	126
t_{max} , h	1.5	2.55	5
$t_{1/2 \text{ el}}$, h	2.7	2–4	–
AUC, ng/ml*h	–	3,955	1,744
F, %	–	48	29
AUEC, %	–	33	25

Data after oral administration of prednisolone, 40 mg, after rectal administration of capsules with 100 mg prednisolone and after rectal administration of a suppository with 100 mg prednisone (data from the concerning SPC). C_{max} = Highest concentration in plasma; t_{max} = time to reach C_{max} ; $t_{1/2 \text{ el}}$ = terminal elimination half life; F = fraction of dose that reaches the systemic circulation; bioavailability in %.

^a Decaprednil[®], according to [7]. ^b Data calculated as prednisolone. ^c Klismacort[®] [8]. ^d Rectodelt[®] 100.

ilar efficacy but for dexamethasone, no rectal dosage form is available [6, 9].

Prednisone has to be converted to prednisolone in the liver, which delays the onset of action for about one hour [10]. Therefore, to treat inflammation or to obtain immunosuppressive properties, prednisolone may be preferably used. A comparative study of t_{max} values after rectal administration (table 1) suggests that onset of action may even be more delayed with prednisone (5 h).

Prednisolone and prednisone show remarkable differences in their pharmacokinetic parameters, calculated for the active metabolite prednisolone. To estimate whether these differences consequently result in pharmacodynamic differences and finally in clinical consequences, the efficacy has to be investigated in a clinical trial. In a prospective placebo-controlled study, the effect of prednisolone was measured on two clinical endpoints – the duration of intubation and the need for reintubation. Steroid therapy reduces the duration of intubation and the need for reintubation in children intubated for croup significantly better than placebo [11].

In a meta-analysis of 24 randomized controlled trials, glucocorticoid treatment was associated with an improvement in the croup severity score at 6 h [12]. Nebulized budesonide, or dexamethasone given either orally or intramuscularly, were effective in treating croup. With regard to the inhalation of drugs, it has been observed that

up to 75% of patients do not use a successful inhalation technique [13, 14]. Using inhalation devices, therefore, seems to be a problem for treating children.

Due to the marked variations in the clinical efficacy parameters in the therapy of croup, it is not suitable to draw direct conclusions about the effect of glucocorticoids from their blood levels or compare one drug with the other.

To quantify the biological effect of glucocorticoids from plasma levels is possible by observing alterations of lymphocyte trafficking in blood and to analyze changes with mathematical models [15]. Lymphocyte trafficking is an early event during the development of inflammation like reddening, increase in temperature and swelling, and therefore a suitable tool to estimate the efficacy of glucocorticoids. The method uses AUEC% to compare effects of prednisolone with control conditions. The higher the difference between effect and control, the higher is the effect on lymphocyte trafficking. Using this method, the concentration of 48 mg prednisolone (that is, 48% bio-availability after administration of 100 mg prednisolone, F in table 1) results in an AUEC% of 33%. A concentration of 29 mg prednisolone (that is, 29% prednisolone bio-availability after administration of 100 mg predni-

son) reaches only an AUEC% of 25% (table 1). This means that administration of prednisolone rectally with a capsule or suppository induces a better anti-inflammatory effect than a suppository with prednisone.

Summary

Glucocorticoids are drugs of choice for treatment of laryngotracheitis (croup). They may be administered orally as tablets or juice, locally as inhalation or rectally as suppository or capsule. If doctors decide to use a rectal administration for practical reasons, the considerations outlined above lead to a preference of prednisolone compared with prednisone. It is obvious from a pharmacokinetic and pharmacodynamic point of view that using prednisolone capsules enables the possibility of an earlier and stronger anti-inflammatory effect than using a prednisone suppository.

Disclosure statement

The authors have no conflicts of interest to disclose.

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