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Pharmacokinetics of oral *vs.* intravenous dexamethasone in patients hospitalized with community-acquired pneumonia

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The use of corticosteroids as adjunctive therapy might be effective in patients with community-acquired pneumonia.
- All available data are based on intravenous therapy, while oral administration is a more practical alternative.
- The systemic exposure of oral dexamethasone in patients with severe illness is unknown.

WHAT THIS STUDY ADDS

- Despite patients' severe illness the bioavailability of oral administration of dexamethasone is good.
- This makes oral administration an appropriate and safer alternative to the intravenous route.

AIM

The use of corticosteroids as adjunctive therapy might be effective in patients with community-acquired pneumonia (CAP). Oral administration of dexamethasone is a practical and safer alternative to the intravenous route. Since patients hospitalized with pneumonia might have delayed gastric emptying, this study explored systemic exposure in terms of area under the concentration–time curve (AUC) of oral dexamethasone in patients hospitalized with CAP.

METHODS

In this randomized, open label study, 30 patients admitted with CAP were randomized to receive either 4 mg intravenous or 6 mg oral dexamethasone for 4 consecutive days. Serial blood samples were obtained before and after drug administration.

RESULTS

Median AUC to infinity was 626 μg l^{-1} h (IQR 401–1161) for the intravenous group and 774 μg l^{-1} h (IQR 618–1146) for the oral group. The AUC ratio of 6 mg oral and 4 mg intravenous dexamethasone was 1.22 (95% confidence interval (CI) 0.81, 1.82), which represents a bioavailability of 81% (95% CI 54, 121) after correction for differences in dexamethasone dose.

CONCLUSIONS

Bioavailability of oral dexamethasone in patients hospitalized with pneumonia is sufficient. This makes oral dexamethasone an appropriate alternative for intravenous administration in these patients.

Introduction

Dexamethasone is a corticoid substance used for a variety of indications, including diagnosing Cushing's disease [1], as therapy for brain oedema [2], and as adjunctive treatment in bacterial meningitis [3] for more than 40 years. Corticosteroids may also have a role as adjunctive therapy in community-acquired pneumonia (CAP) [4, 5]. An extended systemic inflammatory response may be involved in organ dysfunction and consequently result in high morbidity and mortality in CAP patients [6]. Therefore, modulation of this inflammatory response by corticosteroids may lead to better outcome [7]. To date, studies exploring the role of corticosteroids as adjunctive therapy in CAP have provided conflicting results, although the only study conducted with dexamethasone showed positive results [8].

So far, all studies have reported on the subject applied intravenous administration of corticosteroids. However, oral administration might be a valuable alternative because it provides less patient discomfort since there is no risk of phlebitis, easier application reducing administration costs, and utilization on an outpatient basis would be conceivable. Before deciding on oral administration, the bioavailability of oral dexamethasone in patients admitted with CAP needs to be established. In healthy individuals, bioavailability of oral dexamethasone has been reported to be between 70% and 78% [9, 10]. However, extrapolation of bioavailability established in healthy individuals to patients hospitalized with pneumonia might be inaccurate due to potentially impaired absorption caused by delayed gastric emptying or altered first pass metabolism [11, 12].

Our study was conducted to assess whether oral administration of dexamethasone is an alternative to the intravenous route. Given that the bioavailability of oral dexamethasone is regarded to be between 70–78% in healthy individuals, we hypothesized that a proportionally higher oral dose would be required to obtain a systemic exposure in terms of area under the concentration–time curve (AUC) similar to the intravenous dose. Therefore, we planned an open label, randomized study with parallel groups to compare systemic exposure of 6 mg oral dexamethasone with 4 mg of intravenous dexamethasone, which is the dose that reduced the length of hospital stay in patients with pneumonia [8].

Methods

Study design and patients

Patients of 18 years and older with confirmed CAP, who were hospitalized at the St Antonius Hospital in Nieuwegein (the Netherlands) between September 2011 and October 2012, were enrolled. Patients were included <24 h after admission. CAP was defined as a new infiltrate on the chest radiograph for patients with at least two of the following clinical symptoms: cough, sputum production, temperature >38.0°C or <36.0°C, signs on chest auscultation compatible with pneumonia, leukocytosis or leukopenia (white blood cell count $>10 \times 10^9\ l^{-1}$, $<4 \times 10^9\ l^{-1}$, respectively, or >10% rods in leukocyte differentiation), or C-reactive protein (CRP) >15 mg l^{-1}. Patients were excluded if they had a known congenital or acquired immunodeficiency, a haematological malignancy, or received chemotherapy, any dose of oral corticosteroids, or immunosuppressive medication in the previous 6 weeks. Other exclusion criteria were admission to the intensive care unit immediately after presentation, pregnancy or breastfeeding, moribund state (patients expected to die within 24 h after admission), and known dexamethasone allergy. Eligible patients provided written informed consent. The study was approved by the institutional Medical Ethics Committee of the St Antonius Hospital and registered at Clinicaltrials.gov (NCT01390012).

Randomisation and study drugs

Patients were randomly allocated to receive intravenous or oral dexamethasone once a day. Randomization was done by a one-to-one allocation of pre-numbered containers based on a randomization table. Each container consisted of either four ampoules of 4 mg dexamethasone for intravenous administration (1 ampoule = 1 ml = 5.26 mg dexamethasone disodiumphosphate = 4 mg dexamethasone; Centrafarm BV, the Netherlands, RVG 107717), or 16 tablets of 1.5 mg dexamethasone for oral administration (for each day four tablets of 1.5 mg, Pharmachemie, the Netherlands, RVG 56080). Intravenous administration was performed by bolus injection in an intravenous cannula.

Data collection

Serial blood samples (9 ml) were drawn into Vacuette® tubes (ref 455092; Greiner Bio One, Alphen aan de Rijn, the Netherlands) from a second Teflon intravenous cannula at day 1 pre-dose (time point zero) and at 20, 40 and 60 min, and 2, 3, 4, 8 and 12 h after the first dexamethasone administration. Blood samples on days 2, 3 and 4 were collected immediately before the next dexamethasone administration by venepuncture. Serum of samples taken pre-dose (four samples per patient) was separated within 2 h and 2 ml was stored at –80°C for serum interleukin (IL)-6 measurement. These IL-6 concentrations were measured by Human IL-6 ELISA Ready-SET-Go (eBioscience). Remaining serum was stored at –20°C. Other blood samples (nine per patient) were centrifuged within 8 h after sampling and serum was stored at –20°C.

Dexamethasone serum concentrations were determined by a reversed phase HPLC method, with ultraviolet detection at 240 nm, according to the method described by Harahap *et al.* [13] Using 1 ml of serum the limit of quantification was 2.5 μg l^{-1}. The within run precision expressed as the relative standard deviation varied between 2.6% and 1.5% at concentrations between 15 and

85 μg l^{-1}. Between run precision varied between 7.9% and 7.1% at these concentrations. Accuracy calculated as the measured concentrations as percentage of the actual concentrations varied between 98.3% and 106.3%. The method was selective for the determination of dexamethasone serum concentrations in the presence of commonly used drugs, such as antibiotics, in patients with pneumonia.

Serum C-reactive protein (CRP) and white blood cell count, used types of antibiotics, and standard clinical microbiology tests were collected as part of the clinical care. The Pneumonia Severity Index (PSI) score was determined on admission [14].

Pharmacokinetic analyses

Pharmacokinetic parameters were evaluated using MWPharm 3.60, Kinfit software (Mediware, a.s., Prague, Czech Republic). Areas under the concentration–time curve to infinity (AUC(0,∞)) were calculated by using a non-compartmental, trapezoidal method. The elimination rate constant (k_e) was assessed by linear regression analysis of the concentrations in the final log-linear period. MWPharm extrapolated maximum intravenous concentration using dexamethasone concentrations measured 20 and 40 min after administration, and assessed terminal half-life and mean residence time. Clearance of the drug was calculated as the dose/AUC(0,∞) and volume of distribution was calculated as the clearance/k_e. Maximum serum concentration (C_{max}) and time until C_{max} of oral dexamethasone administration were determined from actual measured data points. The AUC ratio between the two routes of administration was calculated based on the geometric means. Bioavailability was calculated by correcting the AUC ratio for differences in dexamethasone dose. Corresponding 95% confidence intervals (CI) for the ratios were constructed by back-exponentiating the 95% CI for the mean difference on the log scale.

Statistical analyses

Overall, descriptive data were stated as number (%), mean (standard deviation (SD)) or median (interquartile range (IQR)), where appropriate. For calculation of length of hospital stay, patients who died in hospital were excluded, because this would count as having a short length of hospital stay. Differences in pharmacokinetic parameters and dexamethasone trough concentrations were calculated using the Mann–Whitney U test or Kruskall–Wallis test. All data were analyzed with SPSS statistical software for Windows, version 21.0. For all analyses, a P value of <0.05 was considered statistically significant.

Results

Thirty patients admitted with CAP were included, of which 15 received oral and 15 received intravenous dexamethasone. Mean age ± SD of the patients was 69 ± 13 years in the oral group and 74 ± 13 years in the intravenous group, with a male : female ratio of 6.5:1 (Table 1). Patients in the intravenous group were more severely ill with higher PSI scores, CRP concentrations, and leukocyte concentrations compared with the oral group. The most prevalent isolated pathogen was *Streptococcus pneumoniae*, identified in five (17%) patients. Two patients in the intravenous group were admitted to the intensive care unit compared with no patients in the oral group. One patient in the oral group and two patients in the intravenous group died in hospital. No adverse drug events were reported.

Dexamethasone serum concentrations

A total of 300 samples were planned for calculation of the pharmacokinetic parameters; 12/300 (4.0%) in the oral group and 8/300 (2.7%) in the intravenous group were missing due to absent samples or measurement disturbances.

In the oral group, a median C_{max} of 64.4 μg l^{-1} (IQR 38.7–77.8) was reached after 2 h. Other pharmacokinetic parameters for the two routes of administration are shown in Table 2. None of these parameters was significantly different. Figure 1 shows the composite serum profiles for oral and intravenous dexamethasone. The median intravenous

Table 1

Characteristics of 30 patients hospitalized with community-acquired pneumonia who received oral or intravenous dexamethasone treatment

Characteristics	Oral (n = 15)	Intravenous (n = 15)
Age (years) (SD)	68.5 (13.3)	73.7 (12.6)
Male gender (%)	13 (86.7)	13 (86.7)
Body mass index (kg m^{-2}) (IQR)	27.5 (25.2–30.4)	23.0 (21.9–27.2)
Comorbidities (%)		
COPD	6 (40.0)	4 (26.7)
Congestive heart failure	5 (33.3)	2 (13.3)
Chronic renal failure	0	0
Diabetes mellitus	1 (6.7)	2 (13.3)
Liver disease	0	0
PSI score (SD)	83 [27]	100 [32]
PSI classes I–III (%)	10 (66.7)	7 (46.7)
PSI classes IV–V (%)	5 (33.3)	8 (53.3)
Temperature at admission (°C) (SD)	38.3 (1.1)	38.6 (0.9)
Laboratory parameters at admission		
C-reactive protein (mg l^{-1}) (SD)	132 [79]	235 [176]
White blood cell count (× 10^9 l^{-1}) (SD)	13.2 (4.9)	14.7 (5.3)
Creatinine (μmol l^{-1}) (IQR)	83 [67–102]	87 [76–97]
Microbiological aetiology (%)		
Streptococcus pneumoniae	2 (13.3)	3 (20.0)
Haemophilus influenzae	1 (6.7)	0
Staphylococcus aureus	1 (6.7)	0
Klebsiella pneumoniae	0	1 (6.7)
No pathogen identified	11 (73.3)	11 (73.3)

Data are presented as number (%), mean (SD) or median (IQR). COPD, chronic obstructive pulmonary disease; IQR interquartile range; PSI, Pneumonia Severity Index.

Table 2

Pharmacokinetic parameters of 6 mg oral dexamethasone and 4 mg intravenous dexamethasone

	6 mg oral dexamethasone (n = 15)	4 mg intravenous dexamethasone (n = 15)	P value
AUC(0.∞) (μg l^{-1} h)	774 [146]	626 [161]	0.37
$t_{1/2}$ (h)	6.9 (6.4–8.6)	9.0 (6.2–12.4)	0.37
Volume of distribution (l kg^{-1})	1.09 (0.86–1.42)	0.94 (0.72–1.22)	0.47
Mean residence time (h)	12.4 (9.7–17.1)	10.3 (8.2–12.3)	0.13
Clearance (l h^{-1})	7.7 (5.2–9.7)	6.4 (3.4–10.0)	0.27

All data are listed as median with interquartile range. AUC(0,∞), area under the concentration–time curve to infinity; $t_{1/2}$, terminal half-life.

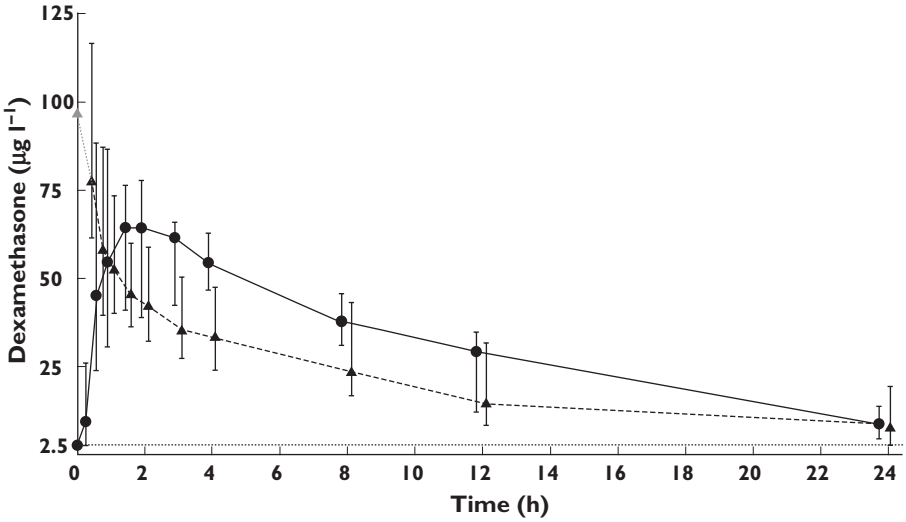

Figure 1

Median dexamethasone concentrations at each time point in μg l^{-1} with interquartile range. (–●–) Oral, (-▲-) intravenous, (···▲···) extrapolated intravenous maximum, (· · ·) detection limit

AUC(0,∞) was 626 μg l^{-1} h (IQR 401–1161) and oral AUC(0,∞) 774 μg l^{-1} h (IQR 618–1146) with a P value for the difference between medians of 0.37. The AUC ratio or oral *vs.* intravenous dexamethasone was 1.22, 95% CI 0.81, 1.82 which results in a bioavailability of oral dexamethasone of 81% (95% CI 54%, 121%). The coefficient of variation for AUC(0,∞) was 60% in the intravenous group and 43% in the oral group. Trough median dexamethasone concentrations 24 h after consecutive drug administrations are presented in Table 3. No differences were found between successive measurements per group or between administration groups.

Inflammation parameters

Figures of IL-6 and CRP concentrations on day of admission and subsequent days can be found in the Web Appendix (Figure S1 and Figure S2).

Discussion

The present study showed that oral dexamethasone is well absorbed in patients with CAP. This result is in contrast with our *a priori* hypothesis that illness in pneumonia patients would lead to a reduced bioavailability. In the present study, bioavailability of oral dexamethasone was 81%, which is comparable with the bioavailability in healthy individuals in other studies, reporting a bioavailability of 70% and 78% [9, 10]. The lack of decreased bioavailability in patients with pneumonia suggests that dexamethasone absorption may not be affected by delayed gastric emptying [15]. Indications for this can be found in literature where smoking, known to affect gastric emptying, also had no effect on bioavailability of oral dexamethasone [16–18]. Another explanation could be the fact that, despite the randomization procedure, there was some imbalance between the two study arms. The

Table 3

Trough median dexamethasone concentrations with interquartile ranges after consecutive drug administrations in 30 patients admitted with community-acquired pneumonia

	Dexamethasone concentration (μg l^{-1}) 24 h after:			
	First dose	Second dose	Third dose	*P* value*
6 mg oral	8.6 (4.4–13.7) *n* = 13	7.9 (2.6–15.0) *n* = 9	8.4 (3.9–10.2) *n* = 5	0.93
4 mg intravenous	7.8 (2.5–19.3) *n* = 15	2.5 (2.5–9.2) *n* = 13	3.2 (2.5–6.5) *n* = 8	0.31
***P* value†**	0.82	0.25	0.18	

Data are presented in median with interquartile range. *Difference between dexamethasone concentrations after consecutive dose administrations calculated using Kruskall–Wallis test. †Differences between the two administration groups using Mann–Whitney U test.

patients in the intravenous group were more severely ill and the patients in the oral group had a significantly higher body mass index (BMI). However, the fact that the coefficient of variation for the AUC was larger in the intravenous group suggests that disease severity is more likely to affect distribution and elimination than absorption of dexamethasone.

Some limitations of this study must also be mentioned. As indicated above, despite randomization there was some imbalance between the groups. Due to the small sample size of 30 patients it was not feasible to examine further the possible effects of these factors on the pharmacokinetics of dexamethasone. A false negative result cannot be ruled out with this small sample size. Nevertheless, the total study population can be considered representative for CAP patients in general and confirms a good bioavailability of oral dexamethasone.

In conclusion, the AUC of 6 mg oral dexamethasone in patients hospitalized with pneumonia is not significantly different from the AUC of 4 mg intravenous dexamethasone. This makes oral dexamethasone an appropriate alternative to intravenous administration in these patients.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare the department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, has received unrestricted research funding from the Netherlands Organization for Health Research and Development (ZonMW), the Dutch Health Care Insurance Board (CVZ), the Royal Dutch Pharmacists Association (KNMP), the private-public funded Top Institute Pharma (http://www.tipharma.nl, includes co-funding from universities, government, and industry), the EU Innovative Medicines Initiative (IMI), EU 7th Framework Program (FP7), the Dutch Medicines Evaluation Board, the Dutch Ministry of Health and industry (including GlaxoSmithKline, Pfizer and others). Vera Deneer and Ewoudt van de Garde have received unrestricted research funding from the Netherlands Organization for Health Research and Development (ZonMW). There was no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1
Serum interleukin-6 concentrations with interquartile range for the 3 days following admission, categorized by dexamethasone administration route. *Levels were immeasurably low

Figure S2
C-reactive protein with standard deviation for the 3 days following admission, categorized by dexamethasone administration route