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*Short communication*

# Pharmacokinetics of prednisolone in children with acute lymphoblastic leukaemia

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**Summary.** The pharmacokinetics of soluble oral prednisolone were studied during induction therapy in six children with acute lymphoblastic leukaemia. There was a three- to four-fold variation in the pharmacokinetics of total and free prednisolone. For total prednisolone, the mean elimination half-life was relatively short (1.37 h) and the total clearance, relatively high (15.1 ml $min^{-1}$ $kg^{-1}$). The mean free fraction was high (0.37).

## Introduction

Prednisolone is used as an inducing agent in children with newly diagnosed acute lymphoblastic leukaemia. A standardised dose (40 mg $m^{-2}$ $day^{-1}$) is used for all children, being given in three divided doses each day. Considerable inter-individual variation in urinary steroid excretion has previously been reported in children with lymphoblastic leukaemia receiving oral prednisolone [10]. However, no formal studies of the pharmacokinetics of prednisolone have been carried out in children with acute lymphoblastic leukaemia. The aim of this study was to determine the extent of inter-individual variation in prednisolone pharmacokinetics during the induction phase of chemotherapy in children with acute lymphoblastic leukaemia.

## Methods

*Plan of study.* Six children (two male, patients 1 and 5) hospitalised with acute lymphoblastic leukaemia were studied during the initial 2 weeks of the induction phase of their therapy. The clinical details of the patients are given in Table 1. One child (patient 1) had undergone a relapse of his leukaemia; the others were all newly diagnosed cases. All of the children had been afebrile for at least 48 h prior to the study. Informed consent was obtained from the parents and, where appropriate, the child, and the study was approved by the local ethics committee. All of the children had an indwelling intravenous cannula, from which blood samples were collected to minimise venepunctures. A single oral dose of soluble prednisolone (10–20 mg; 13.0–16.9 mg $m^{-2}$) was given between 8 and 9 a.m. None of the children fasted. Blood samples were collected at 0, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5 and 6 h following the prednisolone.

*Analytical methods.* The free prednisolone fraction was separated by ultrafiltration [11], and total and free prednisolone plasma concentrations were determined by high-performance liquid chromatography [8]; the limit of sensitivity for the assay was 10 ng $ml^{-1}$.

*Calculations.* The area under the plasma concentration-time curve (AUC) for prednisolone was determined by trapezoidal approximation up to the last observation, then extrapolated by dividing the final concentration by the elimination rate constant ($\lambda_z$). Linear regression was used to obtain the elimination rate constant and the terminal half-life ($t_{½}$). Total plasma clearance (CL) was determined by dividing the dose by the respective AUC value, assuming complete absorption, which has been documented in children [1, 12]. The volume of distribution (V) was calculated from

$$V = \frac{CL}{\lambda_z}.$$

The free fraction was calculated from

$$\frac{\text{free prednisolone AUC}}{\text{total prednisolone AUC}}$$

and the free fraction range, from the ratios of the plasma concentrations at each point. All data is presented as the mean ± SEM.

## Results

There was a 3-fold variation in the $t_{½}$ of prednisolone (mean, 1.37 ± 0.23 h). A 4-fold variation occurred in both the maximal plasma concentration ($C_p$max) (138–541 ng $ml^{-1}$) and AUC (324–1,351 ng $ml^{-1}$h). A 4-fold variation was observed in CL (mean, 15.1 ± 3.2 ml $min^{-1}$ $kg^{-1}$), and a 3-fold variation took place in V (mean, 1.60 ± 0.22 l $kg^{-1}$).

The mean $t_{½}$ of free prednisolone (1.28 ± 0.19 h) was similar to that for total prednisolone. A 4-fold variation was observed in the $C_p$max for free prednisolone (54–200 ng $ml^{-1}$), and a 3-fold variation occurred in the AUC for free prednisolone (138–456 ng $ml^{-1}$ h). There was considerable inter-individual (mean, 0.37 ± 0.04) and intra-

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**Table 1.** Clinical details of children with acute lymphoblastic leukaemia

| Patient | Age (years) | Weight (kg) | Surface area ($m^2$) | Dose of prednisolone (mg) | Prednisolone (mg)/surface area ($m^2$) | Albumin ($g\ l^{-1}$) | Other drugs during study | Other drugs within last 24 h |
|---|---|---|---|---|---|---|---|---|
| 1 | 2.8 | 14.3 | 0.59 | 10 | 16.9 | 47 | – | Asparaginase, piperacillin, gentamicin, vincristine |
| 2 | 4.5 | 19.5 | 0.77 | 10 | 13.0 | 41 | Piperacillin, gentamicin | – |
| 3 | 4.6 | 15.5 | 0.67 | 10 | 14.9 | 35 | – | Allopurinol, asparaginase |
| 4 | 4.9 | 26.1 | 0.92 | 15 | 16.3 | 33 | Allopurinol, vitamin $K_1$ | – |
| 5 | 5.7 | 18.0 | 0.75 | 10 | 13.3 | 37 | Gentamicin | Piperacillin, asparaginase |
| 6 | 12.4 | 39.0 | 1.30 | 20 | 15.4 | 36 | – | Allopurinol, cefuroxime, paracetamol, daunorubicin |

**Table 2.** Pharmacokinetics of prednisolone

| Patient | Total | | | | | Free | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | $t_{1/2}$ (h) | $C_P$ max ($ng\ ml^{-1}$) | AUC ($ng\ ml^{-1}\ h$) | CL ($ml\ min^{-1}\ kg^{-1}$) | V ($l\ kg^{-1}$) | $t_{1/2}$ (h) | $C_P$ max ($ng\ ml^{-1}$) | AUC ($ng\ ml^{-1}\ h$) | Free fraction | Free fraction (range) |
| 1 | 0.89 | 327 | 958 | 12.16 | 0.94 | 1.00 | 157 | 456 | 0.47 | 0.40–0.52 |
| 2 | 1.41 | 541 | 857 | 9.97 | 1.22 | [a] | 200 | 245 | 0.28 | 0.21–0.40 |
| 3 | 2.47 | 350 | 1,351 | 7.96 | 1.68 | 2.03 | 143 | 396 | 0.29 | 0.26–0.41 |
| 4 | 1.00 | 138 | 324 | 29.56 | 2.55 | 0.99 | 86 | 179 | 0.55 | 0.44–0.65 |
| 5 | 1.46 | 472 | 709 | 13.06 | 1.65 | 1.11 | 180 | 271 | 0.38 | 0.32–0.50 |
| 6 | 1.02 | 172 | 473 | 18.05 | 1.59 | 1.28 | 54 | 138 | 0.29 | 0.29–0.31 |
| Mean | 1.37 | 333 | 779 | 15.1 | 1.60 | 1.28 | 137 | 281 | 0.37 | – |
| SEM | 0.23 | 65 | 137 | 3.2 | 0.22 | 0.19 | 23 | 50 | 0.04 | – |

[a] Insufficient data available for the calculation of $t_{1/2}$

individual (ranges are given in Table 2) variation in the free fraction. There was no apparent relationship between the free fraction and the plasma concentration. The individual and mean data for the pharmacokinetics of both total and free prednisolone are shown in Table 2. Maximal plasma concentrations were observed at 0.5 h in four patients and at 1 and 1.5 h in patients 4 and 6, respectively. All six children went into remission as determined by the 28-day bone marrow examination; however, the long-term outcome cannot be related to prednisolone pharmacokinetics in such a small group.

## Discussion

The mean $t_{½}$ obtained in the present study (1.37 h) was shorter than that reported in previous studies of children (range, 1.68–3.51 h) [5, 6, 12, 15, 16], three of which examined clearance and the volume of distribution. The mean total clearance in the present study ($15.13\ ml\ min^{-1}\ kg^{-1}$) was similar to that reported by Rocci et al. [15] in a group of children (age range, 2–8 years) with nephrotic syndrome ($16.2\ ml\ min^{-1}\ kg^{-1}$ in relapse, and $13.2\ ml\ min^{-1}\ kg^{-1}$ in remission). The total clearance was considerably higher than that previously reported in two studies involving older children (age range, 5–15 years) with asthma ($3–7\ ml\ min^{-1}\ kg^{-1}$) [16] and inflammatory bowel disease ($3.72\ ml\ min^{-1}\ kg^{-1}$) [12]. The volumes of distribution in all of these studies were similar ($1–2\ l\ kg^{-1}$), except in children with nephrotic syndrome in relapse, who, as expected, showed a large volume of distribution ($3.4\ l\ kg^{-1}$) [15].

The differences in clearance and half-life between the present study and previous reports could be age-related. Older children usually have a slower rate of drug metabolism than younger children [9]. Five of the six children in the present study were 5 years old or younger, whereas the age ranges in other studies were 8–12 [16], 4–15 [5] and 5–15 years [12]; only the study by Rocci et al. [15] involved children of a similar age (2–8 years), and their findings are similar to ours.

There was no evidence of malabsorption or diarrhoea in any of the six children studied. Three of the patients received other medications on the day of the study, and the other three had received other medication within 24 h of the study. Allopurinol and daunorubicin have been shown to inhibit drug metabolism, whereas vincristine has been

shown to cause an increase in sulphate formation [3, 7, 18]. The mean free fraction obtained in the present study (0.37) was higher than the previously reported values of 0.21 [16] and 0.22 [5]. Drug displacement from albumin and corticosteroid-binding globulin could have occurred as a result of the administration of other drugs. The plasma albumin concentration was low in patient 4, who also had the highest free fraction (0.55). The high free fraction documented in these patients may have been responsible for the increased clearance of the drug.

Studies of drug metabolism in children with acute leukaemia have mainly involved cytotoxic agents. Comparative studies of drug metabolism are not available, as the clinical use of these drugs is restricted to children with malignancies. However, studies in mice with leukaemia [13] have shown a reduction in drug metabolism. A study in children with acute lymphoblastic leukaemia [14] has documented a decrease in the clearance of antipyrine and lorazepam in the 1st week of induction therapy. These authors postulate that leukaemic infiltration of the liver may impair drug metabolism. The metabolism of prednisolone is complex, involving conversion to prednisone by 11-β-hydroxysteroid dehydrogenase as well as 6-β-hydroxylation, reduction at the 20 keto-position and glucuronidation [1, 17]. The results shown in the present study show a more rapid total clearance of prednisolone than previous studies, but we cannot determine which of the several possible factors might be responsible or which metabolic pathway might be involved.

In conclusion, we documented a 4-fold inter-individual variation in the pharmacokinetics of free and total prednisolone. The extent of inter-individual variation was similar to that previously described in children with other diseases. Further studies of the pharmacokinetics of prednisolone during the 2-year course of chemotherapy in children with acute lymphoblastic leukaemia are required to see whether a subsequent decrease in the clearance of prednisolone occurs. The mode of action of prednisolone in leukaemia has not been established, although lymphoblasts are known to have steroid receptors, which may influence the prognosis [2]. Further studies are required to determine whether a relationship exists between the clearance of prednisolone and the relapse rate, as has been documented for methotrexate [4].

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## References

1. Bartoszek M, Brenner AM, Szefler SJ (1987) Prednisolone and methylprednisolone kinetics in children receiving anticonvulsant therapy. Clin Pharmacol Ther 42: 424–432
2. Costlow ME, Pui C-H, Dahl GV (1982) Glucocorticoid receptors in childhood acute lymphocyte leukaemia. Cancer Res 42: 4801–4806
3. Donelli MG, Franchi G, Rosso R (1970) The effect of cytotoxic agents on drug metabolism. Eur J Cancer 6: 125–126
4. Evans WE, Crom WR, Stewart CF, Bowman WP, Chen C-H, Abromowitch M, Simone JB (1984) Methotrexate systemic clearance influences probability of relapse in children with standard-risk acute lymphoblastic leukaemia. Lancet I: 359–362
5. Gatti G, Perucca E, Frigo GM, Notarangelo LD, Barberis L, Martini A (1984) Pharmacokinetics of prednisone and its metabolite prednisolone in children with nephrotic syndrome during the active phase and in remission. Br J Clin Pharmacol 7: 423–431
6. Green OC, Winter RJ, Kawahara FS, Phillips LS, Lewy PR, Hart RL, Pachman LM (1978) Pharmacokinetic studies of prednisolone in children. J Pediatr 93: 299–303
7. Gurtoo HL, Gessner T, Culliton P (1976) Studies of the effects of cyclophosphamide, vincristine and prednisolone on some hepatic oxidations and conjugations. Cancer Treat Rep 60: 1285–1294
8. Hartley R, Brocklebank JT (1982) Determination of prednisolone in plasma by high-performance liquid chromatography. J Chromatogr 232: 406–412
9. Lambert GH, Schoeller DA, Kotake AN, Flores C, Hay D (1986) The effect of age, gender and sexual maturation on the caffeine breath test. Dev Pharmacol Ther 9: 375–388
10. Lilleyman JS, French AJ, Young IP (1981) Variation in 17 oxygenic steroid excretion following oral prednisolone in children with lymphoblastic leukaemia. Oncology 38: 274–276
11. Miller PFW, Wheeldon J, Brocklebank JT (1987) The separation of unbound prednisolone by centrifugal ultrafiltration. J Pharm Pharmacol 39: 939–941
12. Olivesi A (1985) Normal absorption of oral prednisolone in children with active inflammatory bowel disease, including cases with proximal to distal small bowel involvement. Gastroenterol Clin Biol 9: 564–571
13. Powis G, Harris RN, Bassecher PJ, Santone KS (1986) Effects of advanced leukaemia on hepatic drug metabolising activity in the mouse. Cancer Chemother Pharmacol 16: 43–49
14. Relling MV, Crom WR, Pieper JA, Cupit GC, Rivera GK, Evans WE (1987) Hepatic drug clearance in children with leukaemia: changes in clearance of model substances during remission-induction therapy. Clin Pharmacol Ther 41: 651–660
15. Rocci ML Jr, Assael BM, Appiani AC, Edefonti A, Jusko WJ (1982) Effect of nephrotic syndrome on absorption and disposition of prednisolone in children. Int J Paediatr Nephrol 3: 161–166
16. Rose JQ, Nickelsen JA, Ellis EF, Middleton E Jr, Jusko WJ (1981) Prednisolone disposition in steroid dependent asthmatic children. J Allergy Clin Immunol 67: 188–193
17. Vermeulen A (1959) The metabolism of 4-$^{14}$C prednisolone. J Endocrinol 18: 278–291
18. Vesell ES, Passananti GT, Greene FE (1970) Impairment of drug metabolism in man by allopurinol and nortriptyline. New Engl J Med 283: 1484–1488

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