J. Pharm. Pharmacol. 1994, 46: 606–607
Received October 25, 1993
Accepted January 17, 1994

COMMUNICATIONS

Decreased cyclosporin A absorption after treatment with GoLytely lavage solution in rats

TOMOFUMI SANTA, KAZUYO NISHIHARA, SHIGEO HORIE*, HAJIME KOTAKI, YASUFUMI SAWADA, KAZUKI KAWABE*, TATSUJI IGA,
*Department of Pharmacy and *Department of Urology, University of Tokyo Hospital, Faculty of Medicine, University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan*

Abstract—Recently we observed a case in which the cyclosporin A absorption decreased after treatment with GoLytely lavage solution in a kidney transplant patient. In this study, we confirmed the decrease of the blood concentration of cyclosporin A after oral administration by GoLytely (Macrogol 3350) based on experiments with rats. The peak blood cyclosporin A concentration, and the area under the blood drug concentration-time curve from 0 to 24 h in the GoLytely-administered group were significantly lower than the control group. In the case of gastrointestinal dysfunction such as diarrhoea, or in treatment with laxatives such as GoLytely lavage solution, whole blood cyclosporin levels must be carefully monitored, and intravenous cyclosporin A may be more suitable for providing adequate immunosuppression.

Cyclosporin A is a neutral, lipophilic, undecapeptide and a potent immunosuppressant, widely used in organ transplantation and various autoimmune diseases (Kahan 1989). It has a narrow therapeutic range and various toxic effects, which are mostly concentration dependent, and it is necessary to keep the blood concentration of cyclosporin A within the therapeutic range for providing adequate immunosuppression. Recently we observed that whole blood cyclosporin A levels in a kidney transplant patient, during oral administration of cyclosporin A, decreased (from 238 to 55 ng mL^{-1}) within only four days in spite of almost the same dose of cyclosporin A (Santa et al 1993). In this period, GoLytely lavage solution (Macrogol 3350, GoLytely) was administered to relieve persistent constipation. GoLytely has been often used as the method for lavage of the colon before colonoscopy or colon surgery (Davis et al 1980; Thomas et al 1982). It was suspected that lavage of the gastrointestinal tract by GoLytely led to poor cyclosporin A absorption. In this paper, we report the influence of administration of GoLytely on absorption of cyclosporin A from the gastrointestinal tract in rats.

Materials and methods

Animal preparation. Male Wistar rats, 330–360 g, were fasted overnight and a polyethylene cannulae was surgically introduced into the left femoral artery to obtain blood specimens at various times. To maintain patency of the femoral cannulae between the blood samples, they were filled with heparinized saline. All experiments were conducted in conscious rats.

Drug preparation. Cyclosporin A was provided by Sandoz Ltd, Basel, Switzerland. Olive oil, sodium heparin and EDTA · 2Na were purchased from commercial sources. GoLytely (Niflec) was purchased from Morishita-Ruseru Ltd (Osaka, Japan). A stock solution of cyclosporin A for oral administration of rats at a concentration of 20 mg mL^{-1} was prepared in a 92:8 mixture of olive oil and ethyl alcohol. GoLytely was prepared by dissolving one pack of Niflec in 2 L water.

Correspondence: T. Santa, Department of Pharmacy, The University of Tokyo Hospital, Faculty of Medicine, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan.

Drug administration and blood collection. Cyclosporin A (20 mg kg^{-1}) was given in olive oil solution with an intragastric feeding tube attached with syringe (Ueda et al 1984). Blood specimens of about 250 μL for the analysis of cyclosporin A, were obtained via the femoral cannula in heparinized tubes before administration and at 0·5, 1, 2, 4, 6, 8, 10, 12, 18 and 24 h after administration.

In the GoLytely administered group, GoLytely (20 mL kg^{-1}) was given with the intragastric feeding tube from 1 h after cyclosporin A administration, and every 10 min thereafter (Kimura et al 1989).

All blood samples were stored at −10°C until assayed.

Drug assay. The blood concentration of cyclosporin A was determined with a fluorescence polarization immunoassay with a monoclonal antibody (m-FPIA) and TDX analyser (Dinabot) (Tada et al 1992).

Pharmacokinetic analysis. The maximum whole blood concentration (C_{max}) and the time of their occurrence (t_{max}) were derived from the raw data. The areas under the blood drug concentration–time curve (AUC) up to 24 h were calculated by the linear trapezoidal rule.

Statistical analysis. Statistical analysis was performed by paired analysis of variance with $P < 0.05$ as the minimal level of significance. Results are reported as the mean ± s.d.

Results

Blood cyclosporin A concentration–time profiles after oral administration are shown in Fig. 1, and pharmacokinetic parameters for oral administration are shown in Table 1.

In the GoLytely-administered group, defecation was induced after 6–8 times repeated administration of the solution at a dose

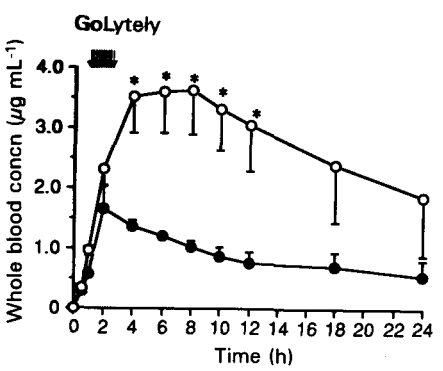

FIG. 1. Whole blood cyclosporin A concentration–time course in rats after oral administration of 20 mg kg^{-1} cyclosporin A in the GoLytely group (●), and the control group (○) (mean ± s.d., n= 3, *$P < 0.05$).

Table 1. Pharmacokinetic parameters in rats after oral administration of cyclosporin A (20 mg kg^{-1}).

	t_{max} (h)	C_{max} ($\mu g\,mL^{-1}$)	AUC_{0-24} ($\mu g\,h\,mL^{-1}$)
GoLytely	2·0 ± 0·0*	1·7 ± 0·43*	21·2 ± 4·9*
Control	6·7 ± 2·3	4·0 ± 0·37	64·6 ± 19·7

t_{max}, time to the peak concentration; C_{max}, the peak concentration. AUC_{0-24}, the area under the blood concentration–time curve up to 24 h. Data are expressed as the mean ± s.d. of three rats. *$P < 0·05$ compared with the control group.

of 20 mL kg^{-1} every 10 min, and the blood cyclosporin A concentration began to decrease at the start of defecation.

Discussion

Factors that affect the oral absorption of cyclosporin A include the elapsed time after surgery, the dose of cyclosporin A, external bile drainage, liver disease, food, and gastrointestinal dysfunction (Rodighiero 1989). Several cases have been reported on the influence of diarrhoea on the oral absorption of cyclosporin A. It has been reported that bone marrow transplant recipients with diarrhoea due to enteritis secondary to pretransplant chemoradiation therapy, acute graft-vs-host disease of the gut or infectious enteritis, absorb cyclosporin A poorly, showing greatly decreased AUC and trough concentrations (Atkinson et al 1983, 1984). In paediatric liver-transplant patients the onset of diarrhoea a few days after transplant led to poor absorption and required intravenous administration of the drug (Burckart et al 1985; Andrew et al 1987).

In our experiments with rats, cyclosporin A absorption was poor and the blood concentrations, C_{max} and AUC_{0-24} were significantly low in the GoLytely-administered group as compared with the control group. In the GoLytely group, the blood cyclosporin A concentration began to decrease at the start of defecation. These results suggest that the defecation caused by administration of GoLytely led to decrease in cyclosporin A absorption and the blood cyclosporin A level in man. Cyclosporin A is absorbed predominantly in the small intestine (Drewe et al 1992) and the extent of bioavailability is usually 20–50%. We suspected that the decrease of cyclosporin A absorption was due to a shortening of the residence time in the small intestine.

Decrease of the blood cyclosporin A concentration increases the risk of graft-vs-host disease (Yee et al 1988). In the case of the gastrointestinal dysfunction such as diarrhoea, or treatment with laxatives such as GoLytely, the whole blood cyclosporin A must be carefully monitored, and intravenous cyclosporin A may be more suitable for providing adequate immunosuppression.

References

Andrew, W., Fyock, B., Gray, S., Hendrickse, W., Siegel, J., Belknap, B., Hogge, A., Benser, M., Kennard, B., Stewart, S., Albertson, N. (1987) Pediatric liver transplantation: the Dallas experience. Transplant Proc. 19: 3267–3276

Atkinson, K., Britton, K., Paull, P., Farrell, C., Concannon, A., Dodds, A., Biggs, J. (1983) Detrimental effect of intestinal disease on absorption of orally administered cyclosporin. Transplant Proc. 15 (Suppl. 1): 2446–2449

Atkinson, K., Biggs, J. C., Britton, K., Short, R., Mrongovius, R., Concannon, A., Dodds, A. (1984) Oral administration of cyclosporin A for recipients of allogeneic marrow transplants: implications of clinical gut dysfunction. Br. J. Haematol. 56: 223–231

Burckart, G., Starzl, T., Williams, L., Sanghvi Jr, A., Venkataramanan, R., Zitelli, B., Malatack, J., Urbach, A., Diven, W., Ptachcinski, R., Shaw, B., Iwasaki, S. (1985) Cyclosporin monitoring of pharmacokinetics in pediatric liver transplant patients. Transplant Proc. 17: 1172–1175

Davis, G. R., Santa Ana, C. A., Morawski, S. G., Fordtran, J. S. (1980) Development of a lavage solution associated with minimal water and electrolyte absorption or secretion. Gastroenterology 78: 991–995

Drewe, J., Beglinger, C., Kissel, T. (1992) The absorption site of cyclosporin in the human gastrointestinal tract. Br. J. Clin. Pharmacol. 33: 39–43

Kahan, B. D. (1989) Cyclosporin. N. Engl. J. Med. 321: 1725–1738

Kimura, I., Furuta, K., Kamiya, K., Arioka, T., Sato, M. (1989) Cleaning effect and influence on electrolyte balance of MVG-5, a new bowel lavage solution. Ouyouyakuri (Japan) 38: 63–70

Rodighiero, V. (1989) Therapeutic drug monitoring of cyclosporin practical application and limitation. Clin. Pharmacokin. 16: 27–37

Santa, T., Nishihara, K., Ito, K., Yamamoto, K., Kotaki, H., Shibuya, H., Sawada, Y., Iga, T., Horie, S. (1993) Decreased cyclosporin absorption after treatment with GoLytely lavage solution in a kidney transplant patient. In: Kanaoka, Y. (ed.) The 113th Annual Meeting of The Pharmaceutical Society of Japan (Abstract 4). Pharmaceutical Society of Japan: Tokyo, Japan, p. 228

Tada, A., Tsubouchi, S., Zenda, H., Ishisone, S., Kitahara, S., Makuuchi, M. (1992) Evaluation of fluorescence polarization immunoassay with monoclonal antibody for determination of cyclosporin in whole blood of partial liver transplant recipients. Jpn. J. Hosp. Pharm. (Japan) 18: 132–138

Thomas, G., Brozinsky, S., Isenberg, J. I. (1982) Patient acceptance and effectiveness of a balanced lavage solution (GoLytely) versus the standard preparation for colonoscopy. Gastroenterology 82: 435–437

Ueda, C. T., Lemaire, M., Gsell, G., Misslin, P., Nussbaumer, K. (1984) Apparent dose-dependent oral absorption of cyclosporin A in rats. Biopharm. Drug. Dispos. 5: 141–151

Yee, G. C., Self, S. G., McGuire, T. R., Carlin, J., Sanders, J. E., Deeg, H. J. (1988) Serum cyclosporin concentration and risk of acute graft-versus-host disease after allogeneic marrow transplantation. N. Engl. J. Med. 319: 65–70