Improvement of Renal Function in Transplanted Kidneys With a New Immunosuppressive Drug, 15-Deoxyspergualin: Treatment of Chronic Rejection

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15-DEOXYSPERGUALIN (DSG) is a drug discovered by Takeuchi et al[1] in 1981 as an antibiotic, extracted from *Bacillus laterosporus*. Thereafter, this drug was shown to have immunosuppressive activity by Umezawa et al[2] and Dickneit et al.[3] In animal experiments, DSG was useful as an immunosuppressant for kidney, liver, heart, and pancreas transplantation. In clinical cases of renal transplantations, DSG also was effective for the treatment of rejection as rescue therapy.[4]

In this study, we examine the effects of DSG on transplant kidney function in chronic rejection.

MATERIALS AND METHODS

Six renal transplant recipients whose serum creatinine (SCr) levels were chronically elevated (mean SCr 3.7 ± 1.6 mg/dL) were treated with 5 mg/kg of DSG IV, given daily for 5 days. Biopsy findings were compatible with chronic rejection; in some cases, cyclosporine (CyA) nephrotoxicity coexisted. The transplanted kidneys were all obtained from living donors, and the starting time of treatment ranged from 6 months to 5 years after renal transplantations.

SCr and urine creatinine, urea, and electrolyte concentrations were measured before and after treatment. Arterial blood gases were also monitored. Maintenance immunosuppression with prednisone (5 to 10 mg/d) and CyA (3 to 5 mg/kg/d) was continued. During DSG administration, azathioprine (25 to 75 mg/d) was discontinued, because DSG is known to cause leukopenia.

RESULTS

SCr and urea nitrogen levels did not change significantly. The fractional Na excretion rate (FEna) changed from 1.7 ± 0.9 to 1.3 ± 0.6, although the serum Na concentration was not altered. Urinary phosphate excretion was diminished (Up/cr), from 44 ± 12.3 to 34.7 ± 12.7 ($P < .05$). Urinary Ca excretion was decreased after the administration of DSG. The fractional tubular absorption of phosphorus (percent TRP) was significantly increased, from 55.5 ± 12.2 to 70.0 ± 10.3% ($P < .05$), although the plasma C-PTH and midportion PTH were unaffected (Fig 1).

Three of the six patients needed granulocyte colony-stimulating factor (G-CSF) for treatment of leukopenia, and recovered with this treatment.

DISCUSSION

In the present study, we find that although DSG has no effect on SCr levels and blood urea nitrogen (BUN) in chronic renal impairment after renal transplantation, this drug may improve tubular function, in terms of phosphate and sodium absorption. The most prominent change in electrolyte transport was phosphate transport, which was demonstrated by the increase in %TRP. From these results, we speculate that DSG may improve renal proximal tubular function, where phosphate transport was regulated.[5]

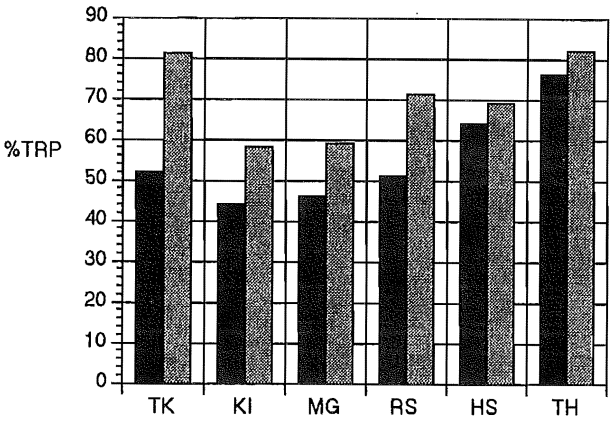

Fig 1. Change in percent TRP after DSG. Black bar, before DSG treatment; speckled bar, after DSG treatment.

There are three possibilities for an explanation of the changes produced by DSG. First, renal blood flow may affect tubular electrolyte absorption. This is not the case here, since DSG did not produce changes in the glomerular filtration rate (GFR). Another possibility is that DSG may directly improve renal tubular function. There is no evidence, however, that DSG can affect electrolyte transport, membrane enzymes, or carriers. Third, DSG may elicit these effects through improvement of chronic rejection by better suppression of immune responses. Dickneit et al[3] showed that prolongations of skin graft survival occur after the use of DSG in rats. Also, in humans, DSG is the drug

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of choice for rescue therapy in acute rejection of renal transplants.[4]

In summary, the administration of DSG has increased tubular sodium and phosphate transport, and it is speculated that these changes may be due to a modulation of immune responses by DSG, improving changes in the kidney interstitium after chronic rejection. DSG may be a useful drug, not only in acute rejection, but in chronic impairment of the transplanted kidney.

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